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ORIGINAL RESEARCH

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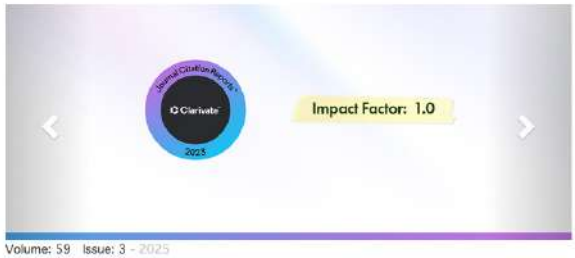

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Review

What Has Changed in the 2025 American Thyroid Association Management Guidelines for Adult Patients with Differentiated Thyroid Cancer? Part 1: Preoperative Evaluation, Diagnosis and Surgery

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Abstract

The guidelines for the management of thyroid nodules and differentiated thyroid cancer were first published by the American Thyroid Association in 1996 and subsequently updated in 2006, 2009, and 2015. In light of advances in technology and the accumulation of new scientific evidence, the guidelines were revised once again in 2025. The most notable change in the 2025 version is the exclusion of thyroid nodules, with the focus placed solely on differentiated thyroid cancer. This review aims to provide an overview of the major recommendation level changes introduced in the 2025 ATA guidelines compared with the previous version. This part specifically addresses the updates regarding the diagnosis and surgical management of differentiated thyroid cancer.

Keywords: ATA guidelines, diagnosis, differentiated thyroid cancer, papillary thyroid cancer, thyroidectomy

Please cite this article as "Uludag M, Unlu MT, Isik C, Caliskan O, Aygun N. What Has Changed in the 2025 American Thyroid Association Management Guidelines for Adult Patients with Differentiated Thyroid Cancer? Part 1: Preoperative Evaluation, Diagnosis and Surgery. Med Bull Sisli Etfal Hosp 2025;59(3):263-272".

American Thyroid Association (ATA) first published the guideline on the management of thyroid nodules and differentiated thyroid cancer (DTC) in 1996, with subsequent revisions published in 2006, 2009 and 2015.[1–4]

In light of recent advances in the management of thyroid nodules and DTC in the literature, ATA has decided to divide the subjects into two distinct sets of guidelines. After reviewing the available evidence, the first guideline was published on the management of DTC in adult patients.[5]

This guideline highlights several differences compared with the one published in 2015. In this study, we aimed to evaluate the changes introduced since the 2015 guideline. The 2015 guideline included a total of 101 recommendations: 31 related to thyroid nodules and 70 related to DTC.[4] However, the recent guideline includes 84 recommendations concerning DTC.[5]

As the first part of our review series, the updates regarding the diagnosis and surgical management of differentiated thyroid cancer are evaluated in this part.

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Phone: +90 539 211 32 36 **E-mail:** m.taner.unlu@gmail.com

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Methods

Due to the growing body of knowledge regarding the management of thyroid nodules and DTC, it was decided to divide the topics into two separate updated guidelines. Task force chairs were appointed by the ATA President with approval from the Board of Directors. A committee was formed comprising experts with complementary specializations in Endocrinology, Surgery (endocrine surgery and otolaryngology–head and neck surgery), Nuclear Medicine, Pathology, Medical Oncology, Cancer Genetics, and Medical Informatics/Clinical Epidemiology. For the first time, a patient advocate was also included in the process. In accordance with ATA's policy to ensure broad specialty and geographic representation with fresh perspectives, at least one-third of the task force consisted of new members who had not participated in the development of previous ATA guidelines.

Systematic review methods

A series of systematic reviews were conducted using the PICO framework (Population, Interventions, Comparisons, Outcomes) to guide the guideline development. The population was patients with DTC. Outcomes were prioritized by consensus, with survival and mortality given the highest priority, followed by oncologic (metastasis, progression, recurrence) and clinical outcomes (quality of life, function, adverse events), while intermediate outcomes were of lower priority.

For key questions on active surveillance versus immediate surgery and on the diagnostic accuracy of serum thyroglobulin (Tg) after thyroidectomy without radioactive iodine (RAI), systematic reviews were commissioned from the Pacific Northwest Evidence-based Practice Center.[6,7] Searches were performed in MEDLINE, Embase, and Cochrane Central, supplemented by reference list review, and limited to English-language studies. Two investigators independently screened and selected studies, extracted data, and assessed study quality (risk of bias). The overall evidence quality was evaluated using an approach adapted from the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) Working Group, considering factors such as risk of bias, consistency, directness, precision, and potential reporting bias. Evidence was classified as having "high," "moderate," "low," or "very low" certainty, reflecting the level of confidence in the results. Following the modified GRADE methodology developed by the Clinical Guidelines Committee of the American College of Physicians; evidence deemed too limited to allow reliable conclusions was rated as "insufficient".[8]

For other key questions, task force members conducted their own literature searches with information specialist support, selected studies based on predefined criteria, and assessed evidence quality using GRADE-based methods.

Guideline development methods

Recommendations were created by subgroups using systematic review findings, then reviewed and revised by the full committee. Final approval was based on group discussion and majority consensus of non-conflicted members. The quality of included studies was assessed using criteria adapted from the U.S. Preventive Services Task Force and the Cochrane Collaboration.[9, 10] Each recommendation was graded as strong or conditional.[11]

Strong recommendations apply to all or nearly all people or situations, and are indicated when the benefits clearly outweigh the harms with at least moderate certainty. Other factors supporting strong recommendations include insensitivity to values/preferences regarding outcomes, high feasibility and acceptability, low or efficient cost and resource use, and anticipated positive impacts on equity. When certainty is low, strong recommendations require a strong rationale for benefit despite uncertainty in the evidence, along with supporting considerations (e.g., low cost, high feasibility, high acceptability, and/or likely positive impacts on equity). Conditional recommendations apply to most people or situations, but alternative approaches may be appropriate under certain circumstances. Conditional recommendations are indicated when the balance of benefits and harms is relatively close, when certainty regarding benefits and/or harms is lower, when decisions are preference-sensitive, or when there are important concerns regarding feasibility, acceptability, resource use, or equity impact.

When evidence was low or insufficient, a Good Practice Statement (GPS) was used as an alternative to a graded recommendation.[12] A GPS functions like a strong recommendation, applying to nearly all situations, and not following it would be considered outside of usual clinical practice. Benefits must be clear and highly certain, even without direct evidence, often inferred from indirect evidence. GPS required a unanimous consensus from the guideline group.

After recommendations were drafted, a final literature review was conducted up to July 1, 2024, with a single exception for the 2025 WHO tumor classification update by all panel members, until no further revisions were needed, ensuring full consensus. Patient representatives participated fully in all discussions.

The guidelines were reviewed and approved by the ATA Clinical Practice Guidelines and Statements Committee and the ATA Board of Directors, then shared with ATA members for feedback in Fall 2024. Feedback was incorporated before journal submission. The organization of recommendations is detailed in the table of contents.

2025 RECOMMENDATIONS

Low-risk neoplasms

The World Health Organization defined endocrine and neuroendocrine tumors in its 5th edition. In this edition, non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), follicular tumor of uncertain malignant potential, and hyalinizing trabecular tumor were classified as low-risk neoplasms.[13]

There was no recommendation regarding the management of these tumors in the 2015 guideline. The first recommendation of the current guideline addresses these tumors and is presented as a good practice statement. Recommendation 1 states that NIFTP and other tumors of uncertain malignant potential [follicular tumor of uncertain malignant potential, hyalinising trabecular tumor) can be diagnosed pathologically. The malignant potential of these tumors is minimal, and in fact lower than that observed in the lowest-risk DTC. Completion thyroidectomy, lymphadenectomy, and/or RAI are not routinely recommended as additional treatments. There is still uncertainty on the best postoperative follow-up strategy for these tumors.[5]

Screening in individuals with familial follicular cell–derived DTC

In the ATA guideline, the issue of screening for familial follicular cell–derived DTC was first addressed in Recommendation 1 within the section on thyroid nodules in the 2015 revision. This recommendation stated that screening of individuals with familial follicular cell–derived DTC may lead to earlier detection of thyroid cancer. But still there is no advice either in favour of or against ultrasound screening, due to the lack of evidence to suggest a decrease in morbidity or mortality.[4]

In the 2025 guideline, new recommendations on genetic predisposition to follicular-derived thyroid cancers and related genetic testing were introduced, grouped under four recommendations (Recommendations 2, 3, 4, and 5). Recommendation 2 states that germline genetic testing may be considered when there is suspicion of a syndrome associated with DTC. These scenarios include:[5]

A. Suspected Cowden/PTEN hamartoma tumor syndrome [PHTS) based on the combination of DTC and associated extra-thyroidal malignancies, tumors, or characteristic features.

(Conditional recommendation, Moderate certainty of evidence)

B. In patients diagnosed with FNMTC during childhood, clinical and family history should be evaluated for features of DICER1 tumor predisposition. Germline DICER1 testing may be considered in patients from families with paediatric DTC.

(Conditional recommendation, Very low certainty of evidence)

C. Pathological diagnosis of cribriform-morular thyroid carcinoma associated with the APC gene.

(Conditional recommendation, Moderate certainty of evidence)

D. The occurrence of other tumor and/or cancer combinations in a patient and/or family members, including rare conditions such as Carney complex or Werner syndrome, may raise concern for an inherited predisposition. In such cases, genetic counselling and testing may be suggested.

(Conditional recommendation, Moderate certainty of evidence)

The issue of whether patients with non-syndromic FNMTC should undergo genetic testing is addressed in Recommendation 3. Recommendation 3 states that there is insufficient evidence to support the clinical use of germline genetic testing in non-syndromic FNMTC. In such cases, the presence of extra-thyroidal malignancies within the family may influence the decision regarding genetic testing.[5]

(Conditional recommendation, Moderate certainty of evidence)

Thyroid cancer screening in family members of patients with FNMTC

This issue is addressed in Recommendation 4. It states that individuals with a family history of FNMTC should undergo a careful history taking and direct neck examination as part of routine health care. When three or more affected relatives (first- or second-degree) fulfill the clinical definition for FNMTC, ultrasound screening may be taken into consideration for first-degree relatives of such persons. If there are additional worrisome features (especially young age at diagnosis) or if the family structure is limited, ultrasound screening may also be considered in families with only two affected members. More research is needed to determine the ideal age for such screening to begin, and should be considered cautiously against the risk of overtreatment.[5]

(Conditional recommendation, Very low certainty of evidence)

The advice to consider germline genetic testing in patients with DTC in whom somatic alterations are detected in tumor samples is addressed in Recommendation 5.

Genomic analysis of tumor tissue undertaken for clinical purposes may reveal not only somatic but also germline variants. If a variant is identified that could indicate a clinically significant predisposition to cancer, it is recommended that the patient and their family history be reviewed for clinical correlation, and referral for genetic counselling with potential germline testing should be made.[5]

(Conditional recommendation, Moderate certainty of evidence)

Impact of surgical experience on thyroidectomy complications

Although surgical complications were discussed in the 2015 revision, the effect of surgeon experience on complication rates is specifically addressed in the 2025 guideline. Recommendation 6 states that patients with thyroid cancer, especially those requiring more complex procedures, should be referred to high-volume thyroid surgeons (performing >25–50 thyroidectomies annually), as they have lower complication rates and overall better outcomes.[5]

(Strong recommendation, Moderate certainty of evidence)

Role of Diagnostic Imaging and Laboratory Tests in Preoperative Staging

Use of ultrasonography

Although recommendations regarding preoperative imaging and testing remain in the new revision, some minor changes are noteworthy. Preoperative ultrasonography was addressed in Recommendation 32 of the 2015 revision and is now included as Recommendation 7 in the 2025 revision. The ultrasonography recommendation consists of three components:[5]

A. Preoperative neck ultrasonography is recommended to assess both central and lateral lymph nodes, as well as for the detection of gross extrathyroidal extension in all patients scheduled for surgery with malignancy confirmed by cytology or molecular findings. The addition of "gross extrathyroidal extension" is a new element in this recommendation.

B and C recommendations remain the same with 2015 edition.

B. For lymph nodes appearing suspicious on US and measuring greater than 8–10 mm in the smallest dimension, fine-needle aspiration (FNA) is recommended to confirm malignancy if the result might influence the treatment strategy.

(Strong recommendation, Moderate certainty of evidence)

C. In selected patients, FNA with Tg washout may be added for the assessment of suspicious cervical lymph nodes. However, interpretation may be challenging in patients with an intact thyroid gland.

(Conditional recommendation, Low certainty of evidence)

Cross-sectional Imaging and 18F-Fluorodeoxyglucose PET Imaging

In the 2015 revision, Recommendation 33 included two items: one on cross-sectional imaging and one on PET. In the 2025 revision, these recommendations were combined into Recommendation 8, now presented in three sections. The cross-sectional imaging recommendations are detailed in two sections and have been expanded compared with the 2015 guideline.

In the 2015 revision, preoperative intravenous (IV) contrast-enhanced cross-sectional imaging (CT or MRI) was recommended in addition to ultrasound for patients with clinically suspected advanced disease, including invasive primary tumors or clinically apparent multiple or large lymph node metastases.

(Strong recommendation, Low-quality evidence)

The 2025 revision expands this recommendation, advising preoperative IV contrast-enhanced cross-sectional imaging of the neck and mediastinum (CT or MRI) for patients with clinical suspicion of advanced or invasive disease. This includes primary tumors with gross extrathyroidal extension, extensive (e.g., large or invasive) adenopathy, or involvement of the aerodigestive tract and/or thoracic structures. Imaging should be performed in addition to physical examination and ultrasound.

(Strong recommendation, Moderate certainty of evidence)

In addition, the 2025 guideline introduces a new recommendation not present in 2015 regarding distant metastasis evaluation. It suggests preoperative cross-sectional imaging of the chest, abdomen, and pelvis when the results are expected to change the surgical plan.

(Good Practice Statement)

Regarding preoperative PET imaging, the recommendation remains largely unchanged from 2015: routine use of preoperative 18F-fluorodeoxyglucose (FDG)-PET/CT is not advised.

(Strong recommendation, Moderate certainty of evidence)

In the 2025 revision, the phrase "prior to surgery" was added to specify the timing.[5]

Serum thyroglobulin measurement

This recommendation remains unchanged in the 2025 revision compared with 2015 and is presented as Recommendation 9. Preoperative assessment of serum Tg or thyroglobulin antibodies (TgAb) is not advised regularly.[5]

(Conditional recommendation, Low certainty of evidence)

Should preoperative somatic genomic testing be performed to guide the extent of surgery?

Genomic testing was not included in the 2015 revision; however, the 2025 revision addresses the use of preoperative genomic tests in Recommendation 10. Routine genomic testing of histologically confirmed DTC before surgery is not advised. Nevertheless, when the genomic profile is available, the presence or lack of specific alterations may be assessed in relation to clinical, radiographic, and cytopathological findings when determining the extent of surgery.[5]

(Conditional recommendation, Low certainty of evidence)

Are there patients for whom active surveillance or percutaneous ablation are appropriate treatment options?

In the ATA guideline, active surveillance and percutaneous therapies as primary treatment were included for the first time in the 2025 revision under Recommendation 11. Following Recommendations 12, 13, and 14 also present new guidance regarding active surveillance.

Part A of the Recommendation 11 indicates that active surveillance may be an appropriate treatment strategy for selected patients with cT1aN0M0 papillary thyroid cancer (PTC). The guideline emphasises the importance of shared decision-making between the patient and the clinical team, carefully weighing the potential risks and benefits.

(Conditional recommendation, Low certainty of evidence)

Additionally Part B states that, in certain patients with cT1aN0M0 PTC, ultrasound-guided percutaneous ablation may be an alternative to surgery or active surveillance, with the same emphasis on collaborative decision-making and careful assessment of risks and benefits.[5]

(Conditional recommendation, Low certainty of evidence)

Optimal approach for patients under active surveillance

According to Recommendation 12, disease progression in patients under active surveillance should be followed up using neck ultrasound.[5]

(Good Practice Statement)

Recommendation 13 states that routine measurement of serum Tg and/or TgAb is not indicated in patients on active surveillance.[5]

(Good Practice Statement)

Are there clear indications for when surgery is required in patients under active surveillance?

Recommendation 14 provides guidance on surgical indications for patients undergoing active surveillance. Surgery is considered in cases of newly detected lymph node metastases confirmed by biopsy, primary tumor growth exceeding 3 mm, presence of distant metastases, documentation of extrathyroidal extension, posterior tumor growth, patient concern, failure to continue follow-up, and/or patient preference for surgery.[5]

(Good Practice Statement)

What is the optimal operative approach in DTC?

Surgery remains the primary treatment for differentiated thyroid cancer (DTC). Compared with the 2015 revision, the 2025 update includes notable changes and new recommendations regarding the surgical approach. The section previously titled "Operative Approach for Biopsy Diagnostic for Follicular Cell-Derived Malignancy" in the 2015 guideline has been revised in 2025 to "Optimal Operative Approach in DTC."

In the 2015 revision, surgical interventions for the thyroid were presented in Recommendation 35 under three main categories.[5]

A. If there are no contraindications, the primary surgery for patients with thyroid cancer larger than 4 cm, or with gross extrathyroidal extension (clinical T4), or with clinically detectable lymph node metastases (clinical N1) or distant metastases (clinical M1) should be a near-total or total thyroidectomy, including complete removal of all gross primary tumor.

(Strong recommendation, Moderate-quality evidence)

B. In patients with thyroid cancer between 1 cm and 4 cm without extrathyroidal extension and with no clinical evidence of lymph node metastasis (cN0), both a bilateral operation (near-total or total thyroidectomy) or a unilateral operation (lobectomy) can be preferred as the initial surgical approach. In cases of low-risk papillary or follicular carcinoma, a lobectomy alone may be adequate as first-line therapy, although total thyroidectomy may be chosen by the treatment team to facilitate radioactive iodine (RAI) treatment or improve surveillance, depending on tumor characteristics and patient preference.

(Strong recommendation, Moderate-quality evidence)

C. In patients with thyroid cancer smaller than 1 cm, without extrathyroidal extension and clinically negative lymph nodes (cN0), if surgery is indicated, the initial surgery should be a lobectomy. This is relevant only if there is no reason to intervene the contralateral lobe. Lobectomy alone is considered adequate for small, unifocal, intrathyroidal carcinomas in patients without a history of prior head and neck radiation, familial thyroid cancer, or clinically detectable cervical lymph node metastases.

(Strong recommendation, Moderate-quality evidence)

In the 2025 revision, recommendations regarding surgical interventions for the thyroid are presented in Recommendation 15 under three main categories. In this recommendation:

A. In patients with thyroid cancer smaller than 2 cm (cT1N0M0), without gross extrathyroidal extension or metastases, surgery can be performed, when surgery is indicated, lobectomy should be the first treatment of choice, provided there are no bilateral tumors or other reasons to remove the contralateral lobe.

(Strong recommendation, Moderate certainty of evidence)

B. Given its lower risk profile and side effects, lobectomy may be the recommended initial surgical strategy for patients with low-risk, unilateral thyroid tumors measuring 2–4 cm (cT2N0M0). But, in cases where worrisome contralateral nodules are present or based on patient preference, the medical team and patient may decide to perform a total thyroidectomy in order to facilitate RAI therapy and/or better follow-up. When lobectomy is selected as the first course of treatment, patients should be informed that they may need to have a completion thyroidectomy if higher-risk features are found after surgery, or that they may need to convert to a total thyroidectomy intraoperatively.

(Conditional recommendation, Low-to-moderate certainty of evidence)

C. Total thyroidectomy with lymph node dissection should be preferred as the initial surgical treatment in patients with thyroid cancer larger than 4 cm (cT3a), any tumor of any size with gross extrathyroidal extension (cT3b or cT4), or those with clinically evident nodal (cN1) or distant metastatic disease (cM1), if there are no contraindications.

(Strong recommendation, Moderate certainty of evidence)

Differences in thyroidectomy recommendations

Significant differences in surgical recommendations can be observed between the two revisions. In the 2015 guidelines, for intrathyroidal tumors smaller than 1 cm without metastases, lobectomy was recommended as the initial surgical approach if there was no indication to remove the contralateral lobe. In the 2025 revision, however, this recommendation has been extended to include tumors smaller than 2 cm, with lobectomy now proposed as the preferred initial procedure in such cases.

In 2015 edition, for thyroid cancers >1 cm and <4 cm without extrathyroidal extension or clinical evidence of lymph node metastasis (cN0), either bilateral surgery (near-total or total thyroidectomy) or unilateral surgery (lobectomy) was considered appropriate. By contrast, the 2025 guidelines specify that in patients with low-risk, unilateral thyroid cancer measuring >2 cm but <4 cm (cT2N0M0), lobectomy may be preferred as the initial operation due to its lower risk and morbidity profile. Importantly, patients should be informed about the possibility of conversion to total thyroidectomy intraoperatively or the need for completion thyroidectomy postoperatively if higher-risk features are discovered. Nonetheless, similar to the 2015 revision, the 2025 guidelines still acknowledge that total thyroidectomy may be selected for tumors in the 2–4 cm range, either to facilitate RAI therapy, improve follow-up, or in the presence of suspicious contralateral nodularity or based on patient preference.

For tumors larger than 4 cm, those with gross extrathyroidal extension, or with lymph node or distant metastases, the 2015 guidelines recommended total thyroidectomy with complete removal of the primary tumor. The 2025 revision expands on this by recommending total thyroidectomy with lymph node dissection in such cases. Depending on the clinical scenario, this may involve either prophylactic or therapeutic lymph node dissection. Thus, while the 2025 guidelines adopt a more conservative surgical approach for smaller tumors, they simultaneously advocate for a more extensive operation in patients with advanced disease compared to the 2015 recommendations.

Lymph node dissection

In the 2015 revision, recommendations regarding central lymph node dissection were presented in Recommendation 36 under three subcategories:[4]

A. To ensure clearance of disease from the central neck, a therapeutic central compartment (level VI) neck dissection and a total thyroidectomy should be performed in patients with clinically affected central lymph nodes.

(Strong recommendation, Moderate-quality evidence)

B. In patients without clinically evident central neck lymph node involvement (cN0) but with advanced primary tumors (T3 or T4), or with papillary thyroid carcinoma presenting with clinically apparent lateral neck node metastases (cN1b), or where the information would guide subsequent therapy, prophylactic central compartment neck dissection (ipsilateral or bilateral) may be considered.

(Weak recommendation, Low-quality evidence)

C. For small (T1 or T2), non-invasive, clinically node-negative papillary thyroid carcinoma (cN0), as well as for most follicular thyroid cancers, thyroidectomy without prophylactic central neck dissection is considered appropriate.

(Strong recommendation, Moderate-quality evidence)

Recommendation 37 addressed therapeutic lateral neck dissection. It stated that in patients with biopsy-proven metastatic lateral cervical lymphadenopathy, a therapeutic lateral compartment neck dissection should be performed.

(Strong recommendation, Moderate-quality evidence)

In the 2025 revision, prophylactic lymph node dissection is addressed separately in Recommendation 19, while therapeutic lymph node dissection is covered in Recommendation 20. Unlike the 2015 revision, which defined the central neck dissection field as level VI, the 2025 revision specifies that the relevant compartment includes both levels VI and VII.

In Recommendation 19;

A. For the majority of patients with FTC or small, non-invasive, clinically node-negative PTC (cT1–T2, cN0), prophylactic central compartment lymph node dissection is not recommended.

(Strong recommendation, Moderate certainty evidence)

B. For patients with more advanced thyroid cancer (T3 or T4) who are clinically node-negative (cN0), or in cases where nodal status would inform subsequent therapeutic decisions, prophylactic central compartment dissection may be considered. However, the potential benefits of this approach should be balanced against the surgical risks of thyroidectomy.

(Conditional recommendation, Low certainty evidence)

What is the best approach for therapeutic central and lateral compartment lymph node dissections?

In the 2025 revision, Recommendation 20 states:

A. In patients with clinically involved central lymph nodes (cN1a), a therapeutic central compartment (Level VI and upper Level VII) neck dissection with thyroidectomy should be performed for the disease clearance from the central neck.

(Strong recommendation, Moderate certainty evidence)

B. For patients presenting with clinically positive lateral neck lymph nodes (cN1b), it is advised that therapeutic central lymph node dissection of the ipsilateral central compartment be performed alongside lateral neck dissection and thyroidectomy.

(Conditional recommendation, Low-certainty evidence)

C. In cases where biopsy confirms, or clinical examination reveals, metastatic involvement of the lateral neck compartment, an initial surgical approach should include therapeutic dissection of the lateral neck lymph nodes, generally encompassing Levels IIa, III, IV, and Vb.

(Strong recommendation, Moderate-certainty evidence)

Differences in neck lymph node dissection

In the 2015 revision, prophylactic and therapeutic neck dissections were addressed within a single recommendation and presented in three sections. In contrast, the 2025 revision separates these into two distinct recommendations: prophylactic central neck dissection is addressed in a two-point recommendation (Recommendation 19), while therapeutic neck dissection is presented in a separate three-point recommendation. A notable trend between the two revisions is a shift away from routine prophylactic central neck dissection.

Although the 2015 revision suggested that prophylactic central neck dissection could be omitted during thyroidectomy in most small, non-invasive, clinically node-negative PTCs (cT1–T2, cN0) and most FTCs, the 2025 revision explicitly states that prophylactic central neck dissection should not be performed in these tumors, with a strong recommendation.

In 2015 edition, prophylactic central compartment neck dissection (ipsilateral or bilateral) should be considered for patients with clinically node-negative advanced primary tumors (T3 or T4), patients with clinically involved lateral neck nodes (cN1b), or patients with PTC in whom the information may be used to guide further treatment (Weak recommendation). In the 2025 revision, this was downgraded to may be considered for patients with advanced (T3–T4) PTC who are clinically node-negative (cN0) or when the information may guide further treatment, but it is recommended that this approach be weighed against the risks associated with thyroidectomy (Conditional recommendation, Low-certainty evidence). The key difference is the addition of a risk–benefit consideration of lymph node dissection relative to thyroidectomy while weakening the recommendation.

However, in Recommendation 15 of the 2025 revision, total thyroidectomy, in which the primary tumor is removed completely, and lymph node dissection are recommended as part of initial treatment for T3–T4 tumors (regardless of lymph node metastasis) if there are no contraindications related to the surgery. (Strong recommendation, Moderate-certainty evidence) This implies that lymph node dissection (prophylactic or therapeutic) is routinely recommended for all patients. Therefore, Recommendation 15C and Recommendation 19B are not fully aligned regarding prophylactic central neck dissection.

For patients with lateral neck metastases but no central compartment involvement, central neck dissection was defined as prophylactic in the 2015 revision. In contrast, the 2025 revision recommends ipsilateral central neck dissection in lateral metastasis regardless of central compartment involvement, defining it as therapeutic central neck dissection.

For clinically involved central neck nodes, the recommendation for therapeutic central neck dissection in addition to total thyroidectomy remains similar in both revisions. The most notable difference is the definition of the central compartment: Level VI in 2015, and Levels VI and VII in 2025.

Regarding therapeutic lateral neck dissection, the 2015 revision recommended it for patients with biopsy-proven metastatic lateral cervical lymphadenopathy. The 2025 revision expands this recommendation to include pa-

tients with clinically apparent metastatic lateral compartment cervical lymphadenopathy and emphasizes that this should be part of the initial surgical treatment. The extent of dissection is specified as typically including Levels IIa, III, IV, and Vb.

Completion Thyroidectomy

In the 2015 revision, Recommendation 38, Part A states that completion thyroidectomy should be performed in patients who, if diagnosed prior to the first operation, would have been offered a total thyroidectomy. When lymph nodes are clinically involved, a therapeutic central neck dissection should also be performed. For low-risk papillary and follicular thyroid carcinomas, a lobectomy alone may provide adequate treatment. (Strong recommendation, Moderate-quality evidence)

In Part B of the same recommendation, routine use of RAI ablation instead of completion thyroidectomy is not recommended; but, in certain cases, RAI may be used for the ablation of the remaining lobe. (Weak recommendation, Low-quality evidence).[4]

In the 2025 revision, the recommendation for completion of thyroidectomy is provided in Recommendation 16. Although specific indications are described, the strength of the recommendation is weaker compared to previous guidelines.

In Part A, completion thyroidectomy may be offered after an initial lobectomy to refer persistent primary malignancy, allow for RAI therapy, and/or improve follow-up based on a greater estimated risk of recurrence detected postoperatively, while taking recurrent laryngeal nerve function into account. (Conditional recommendation, Low–Moderate certainty evidence)

Part B stated that, similar to other histologic types of differentiated thyroid carcinoma (DTC), completion thyroidectomy may be considered for the remaining lobe (OTC) based on appropriate indications. (Conditional recommendation, Very low-certainty evidence).[5]

Surgical approach in thyroglossal duct carcinoma

Thyroglossal duct cysts are the most common congenital neck lesions, and malignancy can arise from the tissue of a thyroglossal duct cyst. The reported incidence of malignancy ranges from 1% to 7% in clinical series, with over 95% of cases originating from thyroid tissue.[14-16]

The management of carcinomas arising from thyroglossal duct tissue remains controversial. In the 2025 revision, recommendations regarding the surgical approach for thyroid cancers originating from thyroglossal duct tissue are provided in Recommendations 17 and 18.

In Recommendation 17, Part A, it is suggested that the first surgical treatment for thyroid cancer originating from a thyroglossal duct cyst (TGDCa) should involve the total excision of the tumor or cyst and the central part of the hyoid bone (Sistrunk procedure). *(Conditional recommendation, Low-certainty evidence)*

In Part B, for TGDCa with significant or suspicious thyroid nodularity, Sistrunk procedure along with thyroidectomy may be offered to achieve a total removal of potential multicentric disease, facilitate RAI therapy for larger tumors—particularly in older patients—and/or improve follow-up. *(Conditional recommendation, Low-certainty evidence)*

In Part C, for TGDCa patients who have signs of more advanced disease (such as widespread local invasion, involvement of lymph nodes, or distant metastasis), Sistrunk procedure combined with total thyroidectomy is recommended. *(Strong recommendation, Moderate-certainty evidence)*.[5]

In the 2025 revision, Recommendation 18 provides guidance on when completion thyroidectomy should be performed following a Sistrunk procedure.

In Part A of this recommendation, it is suggested that completion (total) thyroidectomy may be performed in patients who have shown metastases to Delphian/prelaryngeal lymph node(s) or after resection of a TGDCa with higher-risk features (much like a completion thyroidectomy following lobectomy). *(Conditional recommendation, Moderate-certainty evidence)*

In Part B, completion thyroidectomy may be offered after removal of TGDCa with lower risk factors in the presence of significant or suspicious thyroid nodularity to guarantee total removal of potential multicentric disease, facilitate RAI therapy—especially in older patients or those with larger tumors—and/or improve follow-up. *(Conditional recommendation, Low-certainty evidence)*.[5]

The recommendations on preoperative management are similar in both guidelines: Recommendation 39 in the 2015 revision and Recommendation 21 in the 2025 revision.

These state that, prior to surgery, the surgeon should review surgical risks with the patient through the informed consent process, including the possibility of nerve injury and parathyroid damage. In addition, the surgeon should communicate any significant findings from the preoperative evaluation with relevant colleagues, including anaesthesiologists. *(Good Practice Statement)*.[5]

Preoperative voice or laryngeal examination

The recommendations for preoperative voice and laryngeal assessment are nearly identical in the two revisions. In the 2015 revision, these were presented as Recommendations 40 and 41, whereas in the 2025 revision they are consolidated into Recommendation 22.

In the updated guideline, Part A states that all patients undergoing thyroid surgery should have their voice evaluated as part of the routine preoperative physical examination. Both the patient's own description of any voice changes and the physician's clinical evaluation should be included in this assessment. *(Strong recommendation, Moderate-certainty evidence)*

Part B of the 2025 recommendation specifies that preoperative laryngeal examination is required in certain following situations:

a. Presence of preoperative dysphonia (note: in the 2025 revision, the term "voice disorder" was replaced with "dysphonia"). *(Strong recommendation, Moderate-certainty evidence)*

b. Those with a history of cervical or upper thoracic surgery that could have endangered the recurrent laryngeal nerve or vagus nerve. *(Strong recommendation, Moderate-certainty evidence)*

c. Patients with thyroid cancer demonstrating extensive central compartment involvement or posterior extrathyroidal extension or metastases to jugular chain lymph nodes (in the 2025 revision, lateral metastasis has been added to this criterion). *(Strong recommendation, Low-certainty evidence)*.[5]

Intraoperative assessment of the laryngeal nerves

In the 2015 revision, Recommendation 42 emphasized two key points. First, the recurrent laryngeal nerve (RLN) should be visually identified in all cases during dissection. In addition, specific care should be taken to preserve the external branch of the superior laryngeal nerve (EBSLN) during upper pole dissection of the thyroid gland. *(Strong recommendation, Moderate quality evidence)*

Part B stated that intraoperative nerve stimulation, with or without formal monitoring, may be used to aid in identifying the nerve and verifying its functional integrity. *(Weak recommendation, Low quality evidence)*.[4]

In the 2025 revision, the evaluation of the laryngeal nerves is addressed in Recommendation 23, with greater detail than in 2015. In section A, the 2015 statement is expanded to specify that during thyroidectomy and/or paratracheal lymph node dissection (the latter newly added), the recurrent laryngeal nerve (RLN) should be visually detected to maintain its integrity and function. *(Good Practice Statement)*

What was presented as section B in 2015 has now been elaborated into three separate parts (B, C, and D). Section B advises that intraoperative neurophysiological monitoring of the RLN may be used during thyroidectomy for malignancy, especially in total or repeat procedures, as a means of lowering the risk of nerve injury. *(Conditional recommendation, Low to moderate certainty evidence)*

Section C notes that during thyroidectomy for malignancy, intraoperative detection and neurophysiological monitoring of the external branch of the superior laryngeal nerve (EBSLN) may be used to ensure the accurate recognition of the nerve and optimize voice outcomes. *(Conditional recommendation, Moderate to high certainty evidence)*

Finally, section D recommends that, in order to prevent potential bilateral nerve injury, the integrity and function of the RLN should be assessed following the first lobectomy—before proceeding with contralateral resection—through intraoperative stimulation of the vagus nerve or proximal RLN, either with monitoring or via laryngeal palpation. *(Good Practice Statement)*[5]

Intraoperative and perioperative management of the parathyroid glands

In the 2015 revision, intraoperative management of the parathyroid glands is addressed in Recommendation 43. This recommendation states that in the course of thyroid surgery, the parathyroid glands and their blood supply should be secured. *(Strong recommendation, Moderate-quality evidence)*.[4]

In the 2025 revision, Recommendation 24 provides detailed guidance on both intraoperative and postoperative management of the parathyroid glands.

In Part A, to reduce the risk of hypoparathyroidism during thyroid surgery, the parathyroid glands and their blood supply should be preserved. If a parathyroid gland becomes devascularized or is inadvertently removed, it should be auto-transplanted into adjacent muscle tissue after frozen section confirmation of benign parathyroid tissue (even partial). *(Good Practice Statement)*

In Part B, following total thyroidectomy, central lymph node dissection, or unilateral procedures after prior contralateral thyroid surgery, calcium and vitamin D supplementation (either routine or selective) should be administered, directed by parathyroid hormone levels. This approach decreases the incidence of hypocalcemia and shortens hospital stay compared with relying solely on serial calcium measurements. *(Strong recommendation, Moderate-certainty evidence)*.[5]

Should the thyroidectomy bed be drained?

In the 2025 revision, Recommendation 25 introduces guidance on drainage, stating that routine drainage of the thyroidectomy bed is generally not recommended, since it is linked to longer hospital stays, may increase infection risk, and does not decrease the likelihood of hematoma. *(Conditional recommendation, High-certainty evidence)*.[5]

How should the surgeon manage postoperative voice changes and symptoms?

In the 2015 revision, this was presented in two recommendations (44 and 45), while in the 2025 revision, it is presented as Recommendation 26 in three parts. Parts A and B of Recommendation 26 are the same as in the 2015 revision, and a new Part C has been added in this update. In Part A of Recommendation 26, patients' voices should be evaluated postoperatively. If the voice is abnormal, a formal laryngeal examination is recommended. *(Good Practice Statement)*

In Part B, it is recommended that significant findings during surgery and details of postoperative care be communicated by the surgeon to the patient and to other physicians involved in the patient's postoperative management. *(Good Practice Statement)*

Part C, newly added section in this revision, advises that patients with a documented recurrent laryngeal nerve injury resulting from surgery be promptly referred to a speech-language pathologist and a voice specialist. *(Good Practice Statement)*.[5]

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Review

What Has Changed in the 2025 American Thyroid Association Management Guidelines for Adult Patients with Differentiated Thyroid Cancer? Part 2: Postoperative Initial Treatment

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Abstract

American Thyroid Association (ATA) guidelines for the management of thyroid nodules and differentiated thyroid cancer (DTC) were first published in 1996 and subsequently updated in 2006, 2009, and 2015. In 2025, the ATA released a revised version focusing exclusively on DTC and excluding thyroid nodules from its scope. In our previous review, we summarized the updates regarding preoperative evaluation, diagnosis, and surgical management of DTC. In this second part of the series, we aimed to compare the 2015 and 2025 ATA guidelines in terms of initial postoperative management. The main changes are evaluated at the level of recommendations, with a particular emphasis on recurrence risk stratification, postoperative risk-adapted surveillance, adjuvant radioactive iodine (RAI) use, postoperative imaging, and radiation safety. This review provides a comprehensive comparison of the 2015 and 2025 ATA guidelines, outlining the key changes in early postoperative management of DTC and highlighting their potential impact on individualized patient care.

Keywords: ATA risk stratification system, differentiated thyroid cancer, papillary thyroid cancer, postoperative management, radioactive iodine therapy

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The American Thyroid Association (ATA) first issued clinical practice guidelines for the management of thyroid nodules and differentiated thyroid cancer (DTC) in 1996, with major revisions published in 2006, 2009, and 2015.[1–4]

In response to the growing body of evidence and emerging advances in diagnosis and treatment, the ATA elected to publish two distinct guideline documents. Following an extensive review of the literature, the first of these, addressing the management of DTC in adult patients, was released.[5]

This latest guideline introduces several significant changes compared with the 2015 edition. In the present study, we aimed to compare, at the level of recommendations, the differences between the 2015 and 2025 ATA guidelines regarding initial postoperative management, as a continuation of our prior review that focused on preoperative evaluation, diagnosis, and surgical management. As highlighted in our previous work, the 2015 guideline contained 101 recommendations, 31 of which were related to thyroid

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nodules and 70 to DTC,[4] whereas the most recent guideline comprises 84 recommendations exclusively dedicated to DTC.[5]

This paper represents the second part of our review series and focuses specifically on the updates related to the initial postoperative management of DTC.

Methods

Given the expanding literature on thyroid nodules and DTC, the ATA divided the guideline development into two separate documents. The ATA President, with approval from the Board of Directors, appointed task force chairs, who subsequently formed a multidisciplinary committee. This group consisted of experts from endocrinology, endocrine and otolaryngology–head and neck surgery, nuclear medicine, pathology, medical oncology, cancer genetics, and medical informatics/clinical epidemiology. Notably, for the first time, a patient advocate participated in the process. To ensure diversity of expertise, geography, and perspective, at least one-third of the task force members were newly appointed and had not contributed to earlier ATA guidelines.

Systematic review methods

A structured series of systematic reviews was conducted, guided by the PICO framework (Population, Interventions, Comparisons, Outcomes). The target population was patients diagnosed with DTC. Outcomes were prioritized by consensus, with survival and mortality considered primary, followed by oncologic endpoints such as metastasis, progression, and recurrence, and then clinical outcomes including quality of life, functional status, and treatment-related adverse events. Intermediate outcomes were given lower priority.

For selected key topics, such as active surveillance versus upfront surgery and the diagnostic utility of serum thyroglobulin (Tg) measurement after thyroidectomy without radioactive iodine (RAI), systematic reviews were performed by the Pacific Northwest Evidence-based Practice Center.[6,7] Searches were executed in MEDLINE, Embase and Cochrane Central, supplemented by reference screening, and restricted to English language studies. Study selection, data extraction, and risk of bias assessments were independently performed by two reviewers. The certainty of evidence was graded using a methodology adapted from the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) Working Group, accounting for bias, consistency, directness, precision, and potential publication bias. Evidence was rated as "high," "moderate," "low," or "very low" certainty, reflecting confidence in the findings. When evidence was inadequate for reliable conclusions, it was categorized as "insufficient" following the modified GRADE methodology of the American College of Physicians.[8]

For other key questions, task force members undertook independent literature searches with support from information specialists and used GRADE-based methods to evaluate study quality.

Guideline development methods

Draft recommendations were developed within subgroups based on the systematic review findings and then refined through full-committee review. Final approval required a majority consensus of members without conflicts of interest. Study quality was evaluated using criteria derived from the U.S. Preventive Services Task Force and Cochrane Collaboration.[9,10] Each recommendation was classified as either strong or conditional.[11]

Strong recommendations were issued when benefits clearly outweighed harms with at least moderate certainty, and they were intended to apply to nearly all patients or settings. Additional factors justifying strong recommendations included minimal variability in patient values, high feasibility, acceptability, cost-effectiveness, and anticipated improvements in equity. When certainty of evidence was low, a strong recommendation required compelling justification for anticipated benefit. Conditional recommendations were used when benefits and harms were more closely balanced, when evidence certainty was limited, or when patient preferences and contextual factors might lead to different decisions.

Where evidence was insufficient but clinical consensus deemed guidance necessary, Good Practice Statements (GPS) were issued.[12] GPS function similarly to strong recommendations and represent actions considered standard of care, supported by indirect but compelling evidence. GPS issuance required the unanimous agreement of the task force.

A final literature update was conducted through July 1, 2024, with inclusion of the 2025 WHO tumor classification update as the only exception. Recommendations were revised until full consensus was achieved. Patient representatives were actively involved in all deliberations.

The final guideline was subsequently reviewed and approved by the ATA Clinical Practice Guidelines and Statements Committee and the ATA Board of Directors, and ATA members provided feedback during Fall 2024 prior to journal submission. The complete organization of recommendations is presented in the table of contents.

2025 RECOMMENDATIONS

Basic principles of histopathological evaluation of thyroidectomy specimens

The basic principles for histopathological evaluation were presented in three sections in Recommendation 46 of the 2015 revision, and in three sections in Recommendation 27 of the 2025 revision.

In the first section of Recommendation 27, it is stated that, in addition to the fundamental histopathological characteristics needed for AJCC staging (such as the condition of resection margins), data that assist with risk assessment should also be included in the pathology report. These include the presence of vascular invasion and the number of invaded vessels, the number of examined and tumor-involved lymph nodes, the size of the largest metastatic focus in the lymph nodes, and the presence or absence of extranodal extension. (Good Practice Statement) This recommendation is almost the same as the 2015 edition.

In the second section, it is advised that histopathological subtypes of DTC associated with adverse outcomes (prognosis) (e.g., tall cell, columnar cell, hobnail variants of papillary thyroid carcinoma, widely invasive follicular thyroid carcinoma [FTC], oncocytic thyroid carcinoma [OTC], and high-grade follicular cell-derived non-anaplastic thyroid carcinoma) or subtypes associated with favourable prognosis (e.g., minimally invasive encapsulated follicular variant of papillary thyroid carcinoma [IEFVPTC] and minimally invasive FTC) should be identified and reported in histopathological examination (Good Practice Statement).[5]

Although the basis of the recommendation is the same as in the 2015 revision, it is noteworthy that there are differences in the subtypes listed as examples. The main reason for this is that the 2015 revision was based on the 4th edition of the World Health Organization (WHO) classification of endocrine tumors published in 2004, whereas the 2025 revision took into account the most recent edition (5th edition), published in 2022.

Accordingly, in the 2015 revision, the entities included in the 4th edition—such as poorly differentiated thyroid carcinoma and non-invasive encapsulated follicular variant papillary thyroid carcinoma—were removed. In line with the changes introduced in the 2022 classification, the following were added: widely invasive follicular thyroid carcinoma, OTC, high-grade follicular cell-derived non-anaplastic thyroid carcinoma and IEFVPTC.[13]

In the third section it is stated that, histopathological subtypes linked to familial syndromes (cribriform-morular carcinoma, which may be associated with familial adenomatous polyposis; PTEN hamartoma tumor syndrome [PHTS], which is associated with FTC or PTC) should be recognized and reported. (Good Practice Statement) This recommendation is the same as the 2015 revision.

In the 2025 revision, the discussion under the recommendation aims to strengthen standardization and international comparability by suggesting the use of standardized, structured reporting templates for pathology developed by the College of American Pathologists (CAP).[14]

Assessment of Recurrence Risk and Initial Evaluation

In the 2025 revision, assessment of recurrence risk and initial evaluation recommendations are provided in Recommendation 28, organized into two items.

A. The 2025 ATA Risk Stratification System is advised for assessing the risk of structural persistent/recurrence (locoregional and/or distant) and survival in patients with DTC. It takes into account the tumor's histopathological characteristics, the number of cervical lymph nodes, the AJCC staging system, postoperative imaging modalities, and (where applicable) serum Tg and TgAb measurements. (Strong recommendation, moderate-quality evidence)

B. Routine postoperative molecular profiling of histological specimens is not advised. However, the 2025 ATA Risk Stratification System indicates that if such information is available, it might be utilized to further refine the recurrence risk (Conditional recommendation, low-quality evidence.[5]

In addition, the prognostic use of molecular testing was previously discussed only within a limited framework, mainly in the preoperative evaluation of nodules.

The 2025 ATA Risk Stratification System has been newly developed. This system estimates the clinical outcomes of patients with DTC (PTC, FTC/IEFVPTC, OTC) at the time of initial diagnosis and after surgery, generally within the first 3 months postoperatively. Risk prediction in this system is based not only on the initial pathology report but also on biochemical and radiological data obtained within the first few months after surgery.

In this revision, recurrence risk has been provided separately for PTC, FTC, and OTC, and classified into four categories: low, low-intermediate, high-intermediate, and high.

In the 2015 revision, mortality prediction was addressed in Recommendation 47, while recurrence and persistent disease were covered in Recommendation 48, presented in three items. In Recommendation 47, AJCC/UICC staging was recommended for all patients with DTC because of its utility in predicting disease-specific mortality and the necessity for cancer registries.[4]

In Recommendation 49, for patients with DTC treated with thyroidectomy, the 2009 ATA Initial Risk Stratification Sys-

tem was recommended, based on its usefulness in predicting the risk of recurrent and/or persistent disease (Strong recommendation, Moderate-quality evidence).

In another section, it was suggested that a modified version of the 2009 ATA Initial Risk Stratification System, incorporating additional prognostic variables not included in the original system (e.g., extent of lymph node involvement, mutation status, and/or degree of vascular invasion in FTC), may be used to further improve risk classification for DTC. Yet, the 2009 Initial Risk Stratification System's additional advantage from incorporating these particular prognostic indicators has not yet been determined (Weak recommendation, Low-quality evidence).

In the final section, although not routinely advised for initial postoperative risk stratification in DTC, the BRAF mutation status—and potentially other mutations such as TERT—was reported to have the potential to refine risk prediction when interpreted in the context of other clinicopathologic risk factors (Weak recommendation, Moderate-quality evidence).[4]

In the 2015 ATA guidelines, risk assessment was carried out using a three-tiered system (low, intermediate, high risk), based on key histopathological and clinical features such as tumor size, extrathyroidal extension, and lymph node metastasis. Although postoperative serum Tg and imaging findings were considered important for diagnosis and follow-up, they were not central to the risk classification.[4]

In both revisions, molecular testing is not routinely recommended for risk assessment; however, in the 2025 revision, it is stated that if molecular testing has been performed, it may provide additional value in risk evaluation.[4,5]

Assessment of clinical response after surgery

In the 2015 revision, Recommendation 49 stated that the initial recurrence risk estimates should be constantly adjusted during follow-up, since the risk of recurrence and disease-specific mortality may vary over time depending on the clinical course of the disease and the response to therapy (Strong recommendation, Low-quality evidence).[4]

In the 2025 revision, this recommendation has been revised. In Recommendation 29, it is stated that ATA Response to Therapy Criteria should be used in the assessment of clinical response after surgery, and these criteria should be applied together with ATA Recurrence Risk Estimates to guide decisions regarding additional therapy or the intensity of surveillance (Strong recommendation, Moderate-quality evidence).[5]

The 2025 revision has advanced the concept of dynamic risk stratification introduced in the 2015 revision to an earlier timeframe and strengthened its integration into clinical practice. The most notable innovation is the timing of the first postoperative assessment; response categories are now recommended to be applied not only during long-term follow-up but also within the first 3 months after surgery. The scope of the response categories (excellent, indeterminate, biochemical incomplete, structural incomplete) has been expanded, and it is stated that this classification can be used at every stage of the postoperative period following tumor resection. This approach represents a critical innovation, particularly for individualizing the indications and dosing of radioactive iodine (RAI) therapy. As a result, the 2025 ATA guideline, through Recommendation 29, has shifted the assessment of treatment response to an earlier period and transformed it into a dynamic tool that guides therapeutic decisions.[5]

Measurement of postoperative Tg levels

In the 2025 revision, Recommendation 30 provides guidance on the timing of Tg measurement after total thyroidectomy and lobectomy.

The section A states that after total thyroidectomy, a postoperative serum Tg measurement is recommended at 6–12 weeks, either during thyroid hormone therapy or after TSH stimulation. These measurements can assist in making additional decisions related to clinical management. (Strong recommendation, Low-quality evidence)

According to the Section B, after lobectomy, a single serum Tg measurement at 6–12 weeks, with normal TSH levels, may be useful to confirm the absence of unexpected increases; however, no specific cutoff value has been established for this scenario (Good Practice Statement).[5]

In the 2015 revision, Recommendation 50 addressed the prediction of postoperative disease status, with three sections related to thyroglobulin and one section related to postoperative whole-body scintigraphy.

The section A indicates that postoperative disease status (e.g., presence or absence of persistent disease) should be taken into account when deciding whether additional therapy (e.g., RAI, surgery, or other treatments) is needed. (Strong recommendation, Low-quality evidence)

According to the Section B, postoperative serum Tg (during thyroid hormone therapy or following TSH stimulation) can be used to evaluate persistent disease or residual thyroid tissue and predict disease recurrence in the future. Most patients see their lowest Tg levels 3-4 weeks after surgery. (Strong recommendation, Moderate-quality evidence)

The section C states that, the ideal cutoff value for postoperative serum Tg, or the optimal timing of its measurement (during thyroid hormone therapy or after TSH stimulation) can guide decisions regarding RAI therapy, is unknown. Therefore, no recommendation can be provided (No rec-

ommendation, Insufficient evidence).[4]

In the 2015 revision, postoperative Tg measurement was recommended, although no specific timing was provided; it was emphasized that in most patients, Tg reaches its nadir within 3–4 weeks. No recommendations were given regarding the circumstances for measurement. In contrast, the 2025 revision specifies a 6–12 week timeframe for Tg measurement. The most notable update is the inclusion of Tg measurement after lobectomy, with a single measurement at 6–12 weeks potentially revealing unexpectedly high values, although no reliable cutoff has been established for this group.

Role of Postoperative ultrasound and other imaging modalities after primary resection (CT, MRI, and 18FDG-PET-CT)

The 2025 revision, in Recommendation 31, provides guidance on postoperative imaging in seven sections. Section A states that for assessing the thyroid bed as well as the central and lateral cervical lymph node compartments, ultrasonography is the preferred modality for follow-up in most DTC patients (Strong recommendation, Moderate-quality evidence).

Section B recommends performing cervical ultrasonography and/or cross-sectional imaging before RAI therapy if the postoperative serum Tg exceeds the excellent response range or if TgAb is present (Good Practice Statement).

Section C advises performing cervical ultrasonography within 6–12 months after completion of initial therapy to evaluate the thyroid bed and cervical lymph node compartments; further timing and frequency should be determined based on residual/recurrent disease risk and response to therapy (Good Practice Statement).

Section D notes that small (<8–10 mm) suspicious lymph nodes or lesions can be monitored without fine-needle aspiration (FNA) if they don't exhibit growth or pose a threat to critical structures (recurrent laryngeal nerve, trachea, esophagus, or major vessels) (Conditional recommendation, Low-quality evidence).

Section E recommends FNA with Tg measurement in needle washout when suspicious lymph nodes or lesions are ≥8–10 mm and when cytologic confirmation would influence treatment decisions (Good Practice Statement).

Section F suggests additional cross-sectional imaging to evaluate common metastatic sites (lung, bone) if Tg or TgAb rises after total thyroidectomy but cervical ultrasonography shows no or minimal structural disease (Good Practice Statement).

Finally, Section G indicates that in cases of OTC or poorly differentiated thyroid carcinoma (PDTC), 18FDG-PET/CT may be considered when Tg or TgAb rises postoperatively, yet cervical ultrasonography shows no or minimal structural disease (Conditional recommendation, Low-quality evidence).[5]

In the 2025 revision, postoperative imaging recommendations are provided in Recommendation 31, organized into seven items. In comparison, the 2015 ATA guidelines addressed postoperative imaging in Recommendations 65, 68, and 69. The 2025 revision emphasizes that ultrasonography (US) is the preferred imaging modality for follow-up in most patients with DTC. Many of the US-related recommendations in the 2025 revision align with the 2015 guidelines, including performing US after initial therapy, defining follow-up intervals, performing biopsies for suspicious lymph nodes >8–10 mm, and measuring thyroglobulin in needle washouts.

The 2025 revision clarifies follow-up of suspicious lymph nodes or lesions with a short-axis diameter <8–10 mm, stating that these can be monitored without FNA unless they show growth or threaten vital structures. A new recommendation in 2025 advises performing cervical US and/or cross-sectional imaging before RAI therapy if the postoperative serum Tg exceeds the excellent response range or if TgAb is present.

Regarding cross-sectional imaging, the 2015 revision's Recommendation 69 included three detailed points. Section A recommends contrast-enhanced cross-sectional imaging (CT or MRI) of the neck and upper thorax in cases where (i) US cannot fully delineate extensive recurrent lymph node disease, (ii) invasive recurrent disease may require complete evaluation of aerodigestive tract invasion, or (iii) US may not adequately visualize cervical lymph node disease (e.g., high Tg with negative neck US) (Strong recommendation, Moderate-quality evidence). Section B advises considering contrast-free chest CT (for lung parenchyma) or contrast-enhanced chest CT (including mediastinum) in high-risk DTC patients with high serum Tg (generally >10 ng/mL) or rising Tg antibodies, regardless of negative RAI imaging (Strong recommendation, Moderate-quality evidence). Section C states that in high-risk DTC patients with elevated serum Tg (generally >10 ng/mL), negative neck and chest imaging, and symptoms related to other organs—or in patients preparing for TSH-stimulated RAI therapy and at risk of tumor swelling complications—imaging of other organs (including brain MRI, skeletal MRI, and/or abdominal CT or MRI) should be considered (Strong recommendation, Low-quality evidence).[4]

In the 2025 revision, cross-sectional imaging is summarized in two items, with Section B already discussed in the previous ultrasonography-related paragraph. Section F states that after total thyroidectomy for DTC, if Tg (or TgAb) levels

rise but cervical ultrasonography shows no structural disease or only minimal tumor burden, additional cross-sectional imaging is recommended to assess common metastatic sites such as the lungs and bones.

In the 2015 ATA guidelines, the use of 18FDG-PET was addressed in two items under Recommendation 68, which is summarized in a single item in Recommendation 31 of the 2025 revision. In the 2015 revision, Section A recommended considering 18FDG-PET scanning in high-risk DTC patients with elevated serum Tg (generally >10 ng/mL) and negative RAI imaging (Strong recommendation, Moderate-quality evidence). Section B further stated that 18FDG-PET may also be considered (i) as part of initial staging for poorly differentiated thyroid cancers and invasive Hurthle cell carcinoma, especially when other disease findings are present on imaging or serum Tg levels are high, (ii) as a prognostic tool to detect lesions and patients at highest risk of rapid disease progression and disease-specific mortality in metastatic cases, and (iii) for assessing treatment response following systemic or local therapy of metastatic or locally invasive disease.[4]

In the 2025 revision, it is recommended that in cases of OTC and poorly differentiated thyroid carcinoma (PDTC), 18FDG-PET/CT may be considered when Tg (or TgAb) levels rise after total thyroidectomy, even if cervical ultrasonography shows no structural disease or only minimal tumor burden.[5]

Radioactive iodine therapy after thyroidectomy in the primary Treatment of DTC

In the 2015 revision, RAI recommendations were based on the 2015 risk classification. In contrast, the 2025 revision aligns RAI recommendations with the newly developed 2025 ATA Risk Stratification System. The 2025 RAI recommendations have also been adapted from the Martinique guidelines.[15]

Key definitions related to RAI therapy

Remnant Ablation: The elimination of residual benign thyroid tissue in the thyroid bed to facilitate follow-up of the disease.

Adjuvant Therapy: The administration of additional RAI to decrease the risk of recurrence.

Treatment of Known Disease: The administration of RAI to treat areas of known residual or metastatic disease.

RAI therapy after total thyroidectomy According to 2025 ATA risk stratification

For ATA low-risk DTC patients, routine remnant ablation after total thyroidectomy is not recommended (Strong recommendation, High-quality evidence).

For patients with low-intermediate or intermediate-high risk DTC, adjuvant RAI therapy after total thyroidectomy may be considered to reduce the risk of recurrence (Conditional recommendation, Low-quality evidence).

For ATA high-risk DTC patients, adjuvant RAI therapy after total thyroidectomy is routinely recommended (Strong recommendation, Moderate-quality evidence).

In patients diagnosed with DTC who have distant metastases, RAI therapy after total thyroidectomy is routinely recommended (Strong recommendation, Moderate-quality evidence).[5]

In the 2015 revision, RAI recommendations were provided in five items.

RAI Therapy after Thyroidectomy According to the 2015 ATA Guidelines (Recommendation 51, details in Table 14)

In ATA low-risk DTC patients, routine RAI remnant ablation after thyroidectomy is not recommended. Individual patient factors that may affect recurrence risk, follow-up outcomes, and patient preferences should be considered in the decision-making process (Weak recommendation, Low-quality evidence).

For patients with unifocal papillary microcarcinoma, in the absence of other adverse features, routine RAI remnant ablation after lobectomy or total thyroidectomy is not recommended (Strong recommendation, Moderate-quality evidence).

For patients with multifocal papillary microcarcinoma, in the absence of other adverse features, routine RAI remnant ablation after thyroidectomy is not recommended. Individual patient factors that could influence recurrence risk, follow-up outcomes, and patient preferences should be taken into account in the RAI decision-making process (Weak recommendation, Low-quality evidence).

For ATA intermediate-risk DTC patients, adjuvant RAI therapy after total thyroidectomy may be considered (Weak recommendation, Low-quality evidence).

For ATA high-risk DTC patients, adjuvant RAI therapy after total thyroidectomy is routinely recommended (Strong recommendation, Moderate-quality evidence).[4]

In the 2015 revision, RAI therapy was addressed in Recommendation 51, which included five items, whereas in the 2025 revision, RAI therapy is provided in Recommendation 32, summarized in four items.

In the 2015 revision, routine RAI remnant ablation after thyroidectomy was not recommended for ATA low-risk DTC patients. In addition, the recommendation emphasized that individual patient factors that could influence

recurrence risk, follow-up outcomes, and patient preferences should be considered in the RAI decision-making process (Weak recommendation, Low-quality evidence). Furthermore, two other items addressed patients with unifocal or multifocal papillary microcarcinoma: in the absence of other adverse features, routine RAI remnant ablation after thyroidectomy was not recommended. It is noteworthy that the additional caution about individual patient factors was included only for multifocal papillary microcarcinoma, not for unifocal cases. The recommendation for low-risk and multifocal papillary microcarcinoma is based on weak recommendation and low-quality evidence, whereas for unifocal papillary microcarcinoma it is a strong recommendation supported by moderate-quality evidence.

In the 2025 revision, routine remnant ablation after total thyroidectomy is also not recommended for ATA low-risk DTC patients. However, the recommendation level is strong, supported by high-quality evidence.

For intermediate-risk DTC patients, the 2015 revision suggested that adjuvant RAI therapy may be considered after total thyroidectomy (Weak recommendation, Low-quality evidence). In the 2025 revision, the intermediate-risk group has been subdivided into "low-intermediate" and "intermediate-high" risk categories. In both subgroups, RAI may be considered as adjuvant therapy, with a conditional recommendation based on low-quality evidence.

For high-risk DTC patients, routine adjuvant RAI therapy after total thyroidectomy is recommended in both 2015 and 2025 revisions, with a strong recommendation supported by moderate-quality evidence.

A new recommendation added in the 2025 revision is that for patients with distant metastases at diagnosis, routine RAI therapy after total thyroidectomy is recommended.

RAI therapy in oncocytic thyroid carcinoma

In the 2025 revision, Recommendation 32 states that, due to limited outcome data in OTC, no definitive recommendation can be made about RAI therapy. If RAI is not applied empirically, diagnostic whole-body scintigraphy (WBS) may be considered to assess iodine avidity (Conditional recommendation, Very low-quality evidence).[5]

In the 2015 revision, no separate recommendation existed for OTC (Hurthle cell/oncocytic thyroid carcinoma). In the 2025 revision, an independent recommendation for OTC has been introduced. Although no definitive recommendation can be made, this guidance effectively removes routine RAI use in OTC and emphasizes individualized decision-making.

Preparation for RAI Therapy

The 2025 revision provides recommendations for preparing patients for RAI therapy in Recommendation 34.

Section A states that for DTC patients scheduled for RAI remnant ablation or adjuvant therapy, rhTSH stimulation is preferred over thyroid hormone withdrawal for preparation (Strong recommendation, High-quality evidence).

Section B recommends considering rhTSH stimulation in DTC patients of any risk level who have serious comorbidities that make thyroid hormone withdrawal contraindicated (Good Practice Statement).

Section C notes that if thyroid hormone withdrawal is planned before RAI therapy or diagnostic testing, LT4 should be discontinued for at least 3–4 weeks. If LT4 withdrawal will exceed four weeks, initial replacement with liothyronine (LT3) should be considered, which must be discontinued at least 2 weeks before RAI. TSH levels should be checked prior to radioisotope administration (Good Practice Statement).

Section D recommends a TSH target >30 mIU/L for preparation prior to RAI therapy or diagnostic testing (Good Practice Statement).

Section E states that in DTC patients with known distant metastases, preparation can involve either LT4 withdrawal or rhTSH stimulation (Conditional recommendation, Low-quality evidence).[5]

In the 2015 revision, preparation for RAI therapy through thyroid hormone withdrawal was addressed in Recommendation 53 (two items), and rhTSH stimulation was addressed in Recommendation 54.

Section A states that if thyroid hormone withdrawal is planned prior to RAI therapy or diagnostic testing, LT4 should be discontinued for 3–4 weeks. If LT4 withdrawal is planned for 4 weeks or longer, liothyronine (LT3) may be used during the initial weeks, and LT3 must be discontinued at least 2 weeks before RAI. Serum TSH should be measured prior to radioisotope administration to assess the degree of TSH elevation (Strong recommendation, Moderate-quality evidence).

Section B notes that a TSH target >30 mIU/L is generally adopted for preparation before RAI therapy or diagnostic testing. However, the optimal TSH level associated with long-term outcomes remains uncertain (Weak recommendation, Low-quality evidence).[4]

Recommendation 54 – rhTSH Preparation for RAI Therapy (2015 ATA Guidelines): Section A states that rhTSH stimulation is a suitable alternative to thyroid hormone withdrawal for patients scheduled for RAI remnant ablation or adjuvant therapy, in ATA low- and intermediate-risk DTC patients

without extensive lymph node involvement (i.e., T1–T3, N0/Nx/N1a, M0). This recommendation is supported by multiple consistent observations showing superior short-term quality of life, no reduction in ablation efficacy, and no significant difference in long-term outcomes (Strong recommendation, Moderate-quality evidence).

Section B notes that rhTSH stimulation may be taken into consideration as an alternative to thyroid hormone withdrawal before adjuvant RAI therapy in ATA intermediate-risk DTC patients with widespread lymph node disease (clinically numerous LNs) but no distant metastases (Weak recommendation, Low-quality evidence).

Section C states that in ATA high-risk DTC patients, who have higher disease-related mortality and morbidity risks, more controlled long-term outcome data are needed before rhTSH preparation can be recommended for adjuvant RAI therapy (No recommendation, Insufficient evidence).

According to Section D, rhTSH preparation should be considered for DTC patients of any risk level who have serious comorbidities that might make thyroid hormone withdrawal impossible. The inability to produce a sufficient endogenous TSH response following thyroid hormone withdrawal or serious physical or mental health issues that could rapidly worsen with hypothyroidism and cause serious side effects are examples of significant comorbidities (Strong recommendation, Low-quality evidence.)

In the 2015 revision, Recommendation 53, Section A, which addresses LT4 withdrawal, and Section B, which sets the TSH target, are similarly included in the 2025 revision. In Recommendation 54, Sections A and B propose rhTSH stimulation as an alternative to thyroid hormone withdrawal in low- and intermediate-risk DTC patients. However, no recommendation regarding rhTSH use was provided for high-risk DTC patients. Additionally, Section D of Recommendation 54 states that in DTC patients of any risk level who have comorbidities that could cause serious complications if thyroid hormone withdrawal is performed, rhTSH should be considered for preparation prior to RAI therapy.[4]

In the 2025 ATA guideline, Recommendation 34, Section A, clearly states that rhTSH stimulation should be preferred over LT4 withdrawal in DTC patients prior to RAI therapy (Strong recommendation, High-quality evidence). Notably, the 2025 revision does not differentiate preparation strategies based on risk category. It emphasizes that TSH must be measured and a target of >30 mIU/L should be achieved.

In addition to the 2015 guideline, the 2025 revision introduces a recommendation for DTC patients with distant metastases, stating that either LT4 withdrawal or rhTSH stimulation may be used for preparation (Conditional recommendation, Low-quality evidence).[5]

Low-Iodine Diet before RAI Therapy

In patients scheduled for RAI remnant ablation or therapy, a low-iodine diet should be implemented for approximately 1–2 weeks prior to treatment (Good Practice Statement).

In the 2015 revision, Recommendation 57 regarding the implementation of a low-iodine diet has remained largely unchanged in the 2025 revision.

Diagnostic Radioactive Iodine Whole-Body Scan (WBS): Timing and Indications

In the 2025 revision, Recommendation 36 addresses diagnostic RAI WBS. It states that in patients scheduled for RAI therapy after total thyroidectomy, a diagnostic 123I or low-dose 131I WBS may be considered before the therapeutic administration (ablation, adjuvant, or treatment purposes) to guide treatment schedule (Conditional recommendation, Low-quality evidence).

In the 2015 ATA guideline, diagnostic WBS was addressed in Recommendation 50, Section D. This recommendation states that postoperative diagnostic RAI WBS may be helpful in situations where the surgical report or neck ultrasonography cannot reliably assess the extent of thyroid remnant or residual illness, and where the results may change treatment decisions or the RAI activity. Simultaneous single-photon emission computed tomography (SPECT/CT) can improve the localization and identification of uptake foci. The therapeutic activity should ideally be provided within 72 hours following the diagnostic scan, which should use either low-dose 131I (1–3 mCi) or 123I (1.5–3 mCi). (Weak recommendation, Low-quality evidence).

In the 2015 revision, routine use of diagnostic WBS was not recommended, although it was noted to be potentially useful in selected cases. In the 2025 revision, it is suggested that diagnostic WBS may be beneficial if performed prior to RAI treatment planning.

Post-therapy radioactive ıodine whole-body scan (WBS) and SPECT/CT

In the 2025 revision, Recommendation 37 states that post-therapy scans should be conducted after following RAI treatment (Strong recommendation, Moderate-quality evidence).

In the 2025 revision, Recommendation 38 states that single-photon emission computed tomography (SPECT/CT) may be performed in conjunction with diagnostic or post-therapy WBS if available (Conditional recommendation, Low-certainty evidence).

In order to document RAI uptake in any structural disease and to inform disease staging, post-treatment WBS (with or without SPECT/CT) is advised following RAI remnant abla-

tion or therapy, according to Recommendation 58 in the 2015 revision (Strong recommendation, Low-quality evidence).

In the 2015 revision, a single recommendation (Recommendation 58) addressed post-therapy WBS, stating that it could be performed with or without SPECT/CT. The 2025 revision combines these into a single recommendation, suggesting that if available, WBS should be performed in conjunction with SPECT/CT.

Radiation safety and risks for patients

Before starting RAI preparation, patients should be given both verbal and written instructions to minimize radiation exposure to family members and the public. These instructions should comply with local regulations in the country where the treatment is performed (e.g., Nuclear Regulatory Commission guidelines in the United States) (Good Practice Statement).

In the 2015 ATA guideline, there was no separate recommendation regarding radiation safety education.[4]

In the 2025 ATA guideline, it is recommended that patients be informed with both verbal and written instructions before starting RAI preparation, and that this education comply with the regulatory guidelines of the country where the treatment is performed. This approach is stated as a Good Practice Statement.[5]

How to Counsel Patients on RAI-Related Salivary Gland and Lacrimal Duct Side Effects, and How to Reduce Risks?

This subject is explained under the recommendation 40 as four items.

A. Patients should be informed that RAI therapy may increase the risk of secondary malignancy, lacrimal duct stenosis, and acute and chronic salivary gland morbidity (Good Practice Statement).

B. General measures, such as hydration, are recommended to prevent salivary gland side effects after RAI (Good Practice Statement).

C. Patients with xerostomia have an increased risk of dental caries; therefore, they are advised to consult their dentist for preventive strategies (Good Practice Statement).

D. Nasolacrimal duct obstruction should be considered to be treated surgically since it can cause excessive tearing (epiphora) and increased susceptibility to infection (Good Practice Statement).[4]

In the 2015 revision, Recommendation 83 did not provide guidance on routine preventive measures for salivary gland injury after RAI due to insufficient evidence.

The 2025 ATA guideline, however, modified this approach compared to Recommendation 83 in the previous guideline. Recommendation 40 in the 2025 revision states that patients should be counseled about the potential acute and chronic salivary gland morbidity, lacrimal duct stenosis, and secondary malignancy risks associated with RAI therapy (Section A). Section B specifically recommends general preventive measures, such as hydration, to protect the salivary glands.[5]

In the 2025 revision, the recommendations regarding patients with xerostomia and nasolacrimal duct obstruction were similar to Recommendations 83 and 84 in the 2015 revision.

How to counsel patients on the risk of second primary malignancy (SPM) After RAI therapy

In the 2025 revision, Recommendation 41 states that patients who receive RAI treatment for DTC should be made aware of their risk of developing a second primary malignancy (SPM). No further health screening is advised because the absolute risk increase associated with RAI seems to be minimal. (Good Practice Statement).[5]

In the 2015 revision, Recommendation 86 stated that patients should be informed about the possibility of developing a second primary malignancy (SPM. RAI-related risk increases are, nevertheless, thought to be minimal, and it is not sufficient to justify additional screening beyond age-appropriate general population health examinations.[4]

The counseling and screening recommendations regarding the risk of secondary malignancy after RAI in the 2025 revision are similar to those in the 2015 revision.

Other Tests to perform in patients receiving RAI therapy

In the 2025 revision, Recommendation 42 states that in patients who will receive therapeutic RAI, baseline evaluations should include a complete blood count and assessment of kidney function (Good Practice Statement).[5]

Also in the 2015 revision, it was recommended that patients receiving therapeutic doses of RAI should have a baseline complete blood count and assessment of kidney function (Weak recommendation, Low-quality evidence).[4]

The 2025 revision Recommendation 43 addresses counselling patients about RAI therapy, pregnancy, breastfeeding, and gonadal function.

A. In women of reproductive age, a negative pregnancy test should be confirmed before RAI therapy, and pregnancy should be avoided for at least 6 months after treatment (Good Practice Statement).

B. RAI should not be administered to breastfeeding women. Based on the clinical situation, treatment should be postponed until at least 3 months after cessation of breastfeeding or milk expression. In women with a recent history of breastfeeding, diagnostic 123I scanning may be considered to evaluate potential breast involvement (Good Practice Statement).

C. Male patients who have received a cumulative RAI dose exceeding 14.8 GBq (400 mCi) should be informed about the potential risk of infertility (Good Practice Statement).

D. Women should be informed that RAI therapy has not been shown to have a long-term adverse effect on fertility (Good Practice Statement).

The 2015 ATA recommendations on RAI, pregnancy, breastfeeding, and gonadal function were as follows:

Recommendation 88: Pregnancy should be avoided for 6-12 months following treatment, and women of reproductive age undergoing RAI therapy should have a negative pregnancy test before beginning treatment.

Recommendation 89: RAI should not be administered to breastfeeding women. Treatment might be delayed until the mother has stopped nursing or expressing milk for at least 3 months, depending on the clinical circumstances. To assess possible breast involvement in women who have recently breastfed, a diagnostic 123I or low-dose 131I scan may be taken into consideration.

Recommendation 90: Counseling regarding the possible risk of infertility should be given to male patients who have received cumulative RAI doses more than 400 mCi.[4]

In the 2025 revision, Recommendation 43 regarding RAI therapy and reproductive considerations largely mirrors the 2015 recommendations 88–90. Key points include: women of reproductive age should have a negative pregnancy test before RAI and avoid pregnancy for at least 6 months (revised from 6–12 months in 2015), breastfeeding women should not receive RAI, and men receiving a cumulative dose >400 mCi should be counselled regarding potential infertility. Additionally, the 2025 update adds that RAI has not been shown to have long-term adverse effects on female fertility.

The role of radiotherapy (alone or in combination with chemotherapy) in patients with differentiated thyroid cancer (DTC)

Regarding the role of radiotherapy in DTC, Recommendation 44 in the 2025 revision provides two points:

A. Adjuvant external beam radiotherapy (EBRT) may be considered in patients with high-risk features for locoregional disease progression (e.g., aggressive histologic subtype, gross extrathyroidal extension, positive surgical margins, visceral or soft tissue invasion), particularly when anticipated progression is not amenable to salvage surgery. EBRT may improve locoregional recurrence-free survival, though evidence for improved overall survival is lacking, and significant toxicity risks must be considered (Conditional recommendation, low-level evidence).

B. In patients with macroscopic residual disease or locally advanced, unresectable DTC, EBRT—either alone or combined with chemotherapy—may improve locoregional control, but this approach may also cause acute and long-term treatment-related toxicity (Conditional recommendation, low-level evidence).

In the 2015 revision, Recommendation 60 states that in patients with DTC, routine adjuvant EBRT to the neck after initial complete surgical resection has no established role (Strong recommendation, Low-quality evidence).

Recommendation 61 indicates that in DTC patients, routine systemic adjuvant therapy beyond TSH-suppressive therapy with RAI and/or LT4 has no established role (Strong recommendation, Low-quality evidence).[4]

In the 2015 revision, it was stated that adjuvant radiotherapy and chemotherapy have no established benefit after initial surgical treatment. In the 2025 revision, this recommendation is no longer included; instead, adjuvant EBRT is limited to selected patients with high-risk features in whom salvage surgery is not feasible. The guideline frames EBRT use by balancing potential benefits (local-regional control) against harms (toxicity and lack of survival benefit). Additionally, it notes that in selected cases, EBRT can be administered concurrently with chemotherapy.[4,5]

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Review

What Has Changed in the 2025 American Thyroid Association Management Guidelines for Adult Patients with Differentiated Thyroid Cancer? Part 3: Long-Term Surveillance, Advanced and Novel Treatments

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Abstract

American Thyroid Association (ATA) guidelines for the management of thyroid nodules and differentiated thyroid cancer (DTC) were first published in 1996 and updated in 2006, 2009, and 2015. In 2025, the ATA released a revised version that, for the first time, focuses exclusively on DTC. In our previous reviews, we summarized the updates on preoperative, diagnostic, surgical, and early postoperative management of DTC. In this third and final part, we compare the 2015 and 2025 ATA guidelines with respect to long-term follow-up, TSH suppression strategies, thyroglobulin monitoring, follow-up of low-risk patients. Diagnostic radioiodine whole-body scanning, FDG-PET/CT, dynamic risk stratification, and the management of recurrent or metastatic disease, including local therapies, radioiodine preparation and dosing, and systemic treatments were also highlighted in this part. Particular emphasis is placed on the expanded recommendations for kinase inhibitor therapy, sequencing of systemic agents, targeted therapies (NTRK, RET, ALK, BRAF), redifferentiation approaches, immunotherapy, and supportive care strategies addressing bone and brain metastases, financial toxicity and psychosocial needs. This review provides a comprehensive synthesis of these updates and discusses their implications for individualized long-term management of DTC.

Keywords: Advanced treatment strategies, ATA guidelines, differentiated thyroid cancer, long-term surveillance, papillary thyroid cancer

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The American Thyroid Association (ATA) first issued clinical practice guidelines for the management of thyroid nodules and differentiated thyroid cancer (DTC) in 1996, with major revisions subsequently published in 2006, 2009, and 2015.[1–4]

In response to evolving evidence and therapeutic advances, the ATA for the first time divided the guideline development into two separate documents and released the first, focused on the management of DTC in adult patients.[5]

Building upon the updates presented in the 2015 guideline, the most recent version introduces important changes regarding long-term surveillance, adjuvant therapies, and advanced treatment strategies. In this paper, we aim to systematically compare the recommendations of the 2015

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and 2025 ATA guidelines in the context of long-term follow-up, monitoring of disease recurrence, metastatic DTC and the role of novel systemic and targeted therapeutic approaches.

This article represents the third and final part of our review series and concentrates specifically on the guideline updates related to long-term management and advanced treatment modalities for DTC.

The methodology for evidence synthesis, recommendation development, and grading of evidence certainty has been detailed in the first two parts of this review series (Parts 1 and 2). As the methodology is identical, it is not restated here.

2025 RECOMMODATIONS

In patients treated for Differentiated Thyroid Cancer (DTC), the appropriate degree of TSH suppression

In the 2025 revision, Recommendation 45 states that the decision to reduce TSH levels below the reference range should be individualized. This decision should be made by weighing the potential benefits and risks. It is suggested that high-risk patients are likely to benefit more from subnormal TSH levels compared to low-risk patients (see Table 9). (Conditional recommendation, Low-certainty evidence).[5]

In the 2015 revision, this recommendation was provided as Recommendation 59 in five subsections.

In subsection A, it was recommended that, for high-risk thyroid cancer patients, initial TSH suppression should be reduced to below 0.1 mU/L (Strong recommendation, Moderate-quality evidence).

In subsection B, for intermediate-risk thyroid cancer patients, initial TSH suppression was recommended at 0.1–0.5 mU/L (Weak recommendation, Low-quality evidence).

Subsection C states that, TSH could be maintained within the lower part of the reference range (0.5–2 mU/L) during ongoing surveillance for recurrence in low-risk individuals who had undergone remnant ablation and had undetectable serum Tg levels. Similar recommendations were given for low-risk patients without remnant ablation who also had undetectable serum Tg levels (Weak recommendation, Low-quality evidence).

Subsection D indicates that, for low-risk patients who had undergone remnant ablation and had low serum Tg levels, TSH could be maintained at or slightly below the lower limit of normal (0.1–0.5 mU/L) during continued surveillance for recurrence. Comparable guidance applied to low-risk patients without remnant ablation; however, in this group, serum Tg levels might be measurably higher, and ongoing surveillance for recurrence was recommended (Weak recommendation, Low-quality evidence).

Finally, in subsection E, for low-risk patients who had undergone lobectomy, TSH could be maintained in the mid- to lower reference range (0.5–2 mU/L) during ongoing surveillance for recurrence. In such cases, if patients were able to maintain TSH levels within this target range, thyroid hormone therapy might not be necessary (Weak recommendation, Low-quality evidence).[4]

The 2015 ATA guidelines, in Recommendation 59, adopted a risk-based and stepwise approach to TSH suppression in the early management of DTC, stratifying recommendations across high-, intermediate-, and low-risk groups while also taking into account Tg and anti-Tg levels as well as the type of surgical procedure (lobectomy vs. total thyroidectomy).[4] In the new guideline, the decision to reduce TSH below the reference range is recommended on the basis of a potential benefit–risk balance, and it is stated that this should be applied with reference to Table 9, which has been structured similarly to Table 13 of the 2015 guideline. Table 9 specifies TSH targets according to the response-to-therapy categories following initial treatment: excellent response, indeterminate response, biochemical incomplete response, and structural incomplete response. Accordingly, in patients with an excellent response, TSH is recommended to be maintained within the normal reference range. In those with an indeterminate response, TSH is likewise recommended to be kept within the reference range; however, the evidence regarding specific target levels is noted to be inconclusive. In patients with biochemical or structural incomplete response, TSH suppression below the reference range is recommended, although, again, the data regarding optimal target levels are considered inconclusive.[5]

Duration of TSH suppression below the reference range

In the 2025 revision, Recommendation 45 specifies the following: In subsection A, long-term TSH suppression is not recommended in low- or intermediate-risk patients without biochemical or structural evidence of recurrence (Conditional recommendation, Low-certainty evidence). In subsection B, the balance of benefits and risks of TSH suppression, as well as the TSH targets, should be reassessed over time (Good Practice Statement).[5]

In the 2015 revision, the role of TSH suppression during thyroid hormone therapy in the long-term follow-up of DTC, according to the clinical situation at any point, was addressed in Recommendation 70 across five subsections.

In subsection A, it was recommended that in patients with a structural incomplete response to therapy, the serum TSH

level should be maintained indefinitely below 0.1 mU/L, provided there are no specific contraindications (Strong recommendation, Moderate-quality evidence).

In subsection B, considering the initial ATA risk classification, Tg level, Tg trend over time, and the risks associated with TSH suppression, serum TSH levels for patients with a biochemical incomplete response should be kept between 0.1 and 0.5 mU/L (Weak recommendation, Low-quality evidence).

In subsection C, in patients who initially presented with high-risk disease but who demonstrate either an excellent (clinically and biochemically disease-free) or indeterminate response to therapy, thyroid hormone therapy aiming for serum TSH levels of 0.1–0.5 mU/L may be considered for up to five years; thereafter, the degree of TSH suppression may be reduced with continued surveillance for recurrence (Weak recommendation, Low-quality evidence).

In subsection D, in patients with an excellent or indeterminate response to therapy, particularly those at low risk of recurrence, serum TSH may be maintained within the lower reference range (0.5–2 mU/L) (Strong recommendation, Moderate-quality evidence).

Finally, in subsection E, in patients with an excellent or indeterminate response who have not undergone remnant ablation or adjuvant therapy, with a normal neck ultrasound, low or undetectable suppressed serum Tg, and stable or declining Tg or anti-Tg antibody levels, serum TSH may be allowed to rise into the lower reference range (0.5–2 mU/L) (Weak recommendation, Low-quality evidence).[4]

In the 2015 guideline, Recommendation 70 outlined TSH targets in five subsections, stratified according to the response-to-therapy classification at any point during follow-up. In contrast, the 2025 revision has simplified this to two subsections under Recommendation 46.

In the 2025 guideline, long-term TSH suppression is not recommended in low- or intermediate-risk patients or in those without evidence of recurrence; moreover, the risks and benefits of TSH suppression, as well as the target levels, are advised to be reassessed over time. Overall, the 2025 revision emphasizes a more individualized approach to TSH suppression, with a notable tendency toward reducing the degree of suppression compared to the 2015 guideline.[5]

The role of serum Tg measurement in the follow-up of differentiated thyroid cancer

In the 2025 revision, this topic is addressed in Recommendation 47, structured into five subsections. In subsection A, it is stated that serum Tg should be measured using an assay calibrated against the BCR-457 standard, and Tg antibodies should be quantitatively assessed with every Tg measurement (Good Practice Statement).

In subsection B, in patients who have undergone total thyroidectomy, with or without RAI, serum thyroglobulin (measured while on thyroid hormone therapy) should be used to monitor response to therapy and to detect recurrence—although its predictive value is higher in those treated with radioactive iodine (RAI) (Strong recommendation, Moderate-certainty evidence).

In subsection C, during the initial follow-up period, serum Tg should be measured every 6–12 months while the patient is on thyroxine therapy, with more frequent testing being appropriate in ATA intermediate- to high-risk patients (Good Practice Statement).

Subsection D states that, in patients who have undergone lobectomy, routine serum Tg measurement during the initial follow-up period while on thyroid hormone therapy is not recommended (see Recommendation 30) (Conditional recommendation, Very low-certainty evidence).

Finally, in subsection E, in patients with circulating Tg antibodies, serial measurement of TgAb levels using the same assay may be useful for disease monitoring. Current Tg immunometric assays and radioimmunoassays are generally affected by TgAb, and Tg measurement by liquid chromatography–tandem mass spectrometry (LC-MS/MS) has low sensitivity. Therefore, Tg measurements alone should not be relied upon in this population; imaging remains the primary modality for surveillance (Conditional recommendation, Low-certainty evidence).[5]

In the 2015 guideline, Recommendation 62 addressed serum Tg measurement across five points.

In point A, it was recommended that serum Tg should be measured using an assay calibrated against the CRM-457 international standard, and Tg antibodies should be quantitatively assessed with each Tg measurement. Ideally, both serum Tg and anti-Tg antibodies should be measured in the same laboratory and by the same method for consistent longitudinal evaluation in a given patient (Strong recommendation, High-quality evidence).

In point B, during initial follow-up, serum Tg should be measured every 6–12 months while the patient is on thyroxine therapy, with more frequent testing considered suitable for ATA high-risk patients (Strong recommendation, Moderate-quality evidence).

The point C states that, in ATA low- and intermediate-risk patients with an excellent response to therapy, the utility of subsequent Tg testing is uncertain, and the interval between serum Tg measurements may be extended to at least 12–24 months (Weak recommendation, Low-quality evidence).

In point D, it was recommended that serum TSH be assessed at least annually in all patients receiving thyroid hormone therapy (Strong recommendation, Low-quality evidence).

Finally, in point E, for ATA high-risk patients (regardless of response to therapy) and for all patients with a biochemical incomplete, structural incomplete, or indeterminate response, serum Tg should be monitored at least every 6–12 months for several years (Weak recommendation, Low-quality evidence).[4]

In the 2015 guideline, Recommendation 63;

A. In ATA low- and intermediate-risk individuals who have undergone remnant ablation or adjuvant therapy and have a negative cervical ultrasound, serum Tg should be assessed during months 6–18 of thyroxine therapy using a sensitive Tg assay (<0.2 ng/mL) or following TSH stimulation to confirm the absence of disease (excellent response) (Strong recommendation, Moderate-quality evidence).

B. In low- and intermediate-risk patients with an excellent response to therapy, repeat TSH-stimulated Tg testing is not recommended (Weak recommendation, Low-quality evidence).

C. In patients showing indeterminate, biochemical incomplete, or structural incomplete responses after additional treatments or spontaneous declines in Tg levels during thyroid hormone therapy, TSH-stimulated Tg testing may be considered later to reassess the response to therapy (Weak recommendation, Low-quality evidence).[4]

In the 2015 guideline, Recommendation 64;

Regular serum Tg measurements during thyroid hormone therapy should be taken into account in the follow-up of DTC patients who have undergone less than total thyroidectomy and in those who have undergone total thyroidectomy but not RAI ablation. Although specific Tg threshold values that effectively differentiate normal remnant thyroid tissue from persistent thyroid cancer are not known, increasing Tg values over time are suggestive of developing thyroid tissue or cancer (Strong recommendation, Low-quality evidence).[4]

In the 2015 revision, Recommendation 62 section A recommended that serum Tg measurement be calibrated according to the CRM-457 international standard, whereas in the 2025 revision, calibration is recommended using the BCR-457 standard (European Commission Institute for Reference Materials). In the 2015 ATA guideline, serum Tg monitoring under thyroid hormone therapy was recommended in RAI-treated patients in Recommendation 62 section E and Recommendation 63 section A, and in non-RAI patients in Recommendation 64. In contrast, the 2025 guideline, in Recommendation 47 section B, recommends in a single point that serum Tg measurement under thyroid hormone therapy should be performed to detect recurrence in all patients, regardless of whether RAI was administered.

In the 2025 revision, Recommendation 47 section C corresponds to 2015 Recommendation 62 section B, updating the initial follow-up schedule: serum Tg should be measured every 6–12 months during thyroxine therapy, with more frequent testing appropriate for ATA intermediate- to high-risk or high-risk patients.

In the 2015 Recommendation 63, in low- and intermediate-risk patients who had received RAI and had a negative cervical ultrasound, Tg measurement was recommended at 6–18 months under thyroxine therapy or after TSH stimulation. In patients with an excellent response, TSH-stimulated Tg testing was not recommended, whereas it was suggested for patients with indeterminate or incomplete responses. Furthermore, in low- and intermediate-risk patients with an excellent response, repeat TSH-stimulated Tg testing was not recommended. In patients showing indeterminate, biochemical incomplete, or structural incomplete responses after additional treatments or spontaneous Tg declines during thyroid hormone therapy, TSH-stimulated Tg testing could later be considered to reassess therapy response.

In the 2015 Recommendation 64, Tg monitoring was recommended in patients who underwent more conservative surgery than total thyroidectomy. Although specific Tg thresholds to reliably distinguish normal remnant thyroid tissue from persistent thyroid cancer were not defined, rising Tg values over time were considered suspicious for growing thyroid tissue or cancer. However, in the 2025 guideline, Recommendation 47 point D newly states that routine serum Tg measurement is not recommended in patients after lobectomy during the initial follow-up period under thyroid hormone therapy. Additionally, in Recommendation 30 point B of the 2025 guideline, a single serum Tg measurement at 6–12 weeks in lobectomy patients, when TSH is within the normal range, may be useful to confirm that Tg is not unexpectedly elevated, although no specific cut-off value is defined.

Finally, in the 2025 ATA guideline, Recommendation 47 point E explicitly notes that circulating anti-Tg antibodies can affect Tg results, whereas in the 2015 guideline, this was mentioned in Recommendation 62 point A.[5]

Can follow-up be reduced or discontinued in low-risk DTC patients?

In the 2025 revision, six recommendations are provided regarding the follow-up and discontinuation of follow-up in low-risk patients.

1. In low-risk DTC patients treated with total thyroidectomy and RAI who demonstrate a sustained excellent response 5–8 years after initial therapy, routine ultrasound may be discontinued; these patients can subsequently be monitored every 1–2 years using only biochemical markers (Conditional recommendation, Low-certainty evidence).
2. In low-risk DTC patients treated with total thyroidectomy and RAI who demonstrate a sustained excellent response for 10–15 years, routine biochemical follow-up for thyroid cancer is not required; these patients can be considered in complete remission (Good Practice Statement).
3. In low-risk DTC patients treated with total thyroidectomy alone who demonstrate a sustained excellent response 5–8 years after initial therapy, routine ultrasound may be discontinued; subsequent follow-up can be performed every 1–2 years using only biochemical markers (Conditional recommendation, Low-certainty evidence).
4. In low-risk DTC patients treated with total thyroidectomy alone who demonstrate a sustained excellent response for 10–15 years, routine biochemical follow-up for thyroid cancer is not required; these patients can be considered in complete remission (Good Practice Statement).
5. In low-risk DTC patients treated with lobectomy, if the initial ultrasound is negative, subsequent ultrasounds should be performed every 1–3 years for 5–8 years after initial therapy. Nodules in the residual lobe should be monitored according to the ATA thyroid nodule guidelines (Good Practice Statement).
6. In low-risk DTC patients treated with lobectomy, if postoperative Tg is not significantly elevated, additional Tg testing is not routinely recommended (Good Practice Statement).

In the 2015 ATA guideline, Recommendation 70 points D and E emphasized that aggressive TSH suppression is not necessary in low-risk patients with excellent or indeterminate response, and that maintaining TSH between 0.5–2 mU/L is sufficient. However, no recommendations regarding the duration of follow-up were provided.

In contrast, the 2025 ATA guideline has a separate, more detailed recommendation (Recommendation 48) specifically for follow-up of low-risk DTC patients. In patients who underwent total thyroidectomy, whether or not they received RAI, those with a sustained excellent response can discontinue ultrasound monitoring 5–8 years after initial therapy, and those with a sustained excellent response for 10–15 years can be considered in complete remission and removed from follow-up.

In low-risk patients after lobectomy, if the ultrasound is negative, follow-up should be performed every 1–3 years for 5–8 years. In the 2025 revision, Recommendation 47 does not recommend routine Tg measurement under thyroxine therapy, and Recommendation 48 specifies that in low-risk patients after lobectomy, if Tg is not significantly elevated, additional Tg testing is not recommended.[5]

Diagnostic RAI WBS

In the 2025 guideline, Recommendation 49 addressed diagnostic RAI WBS across four points.

A. In patients who have undergone lobectomy or total thyroidectomy without RAI, whole-body radioiodine scintigraphy (WBS) should not be performed for follow-up purposes (Good Practice Statement).

B. In DTC individuals with low or low–intermediate risk of recurrence who demonstrate an excellent response to therapy, routine diagnostic radioiodine WBS is not necessary during follow-up (Conditional recommendation, Low-certainty evidence).

C. In DTC patients with intermediate–high or high risk of recurrence, diagnostic radioiodine WBS may be performed if there is suspicion of recurrence in order to evaluate the presence of iodine-avid disease. If performed, it should be done using 123I or low-activity 131I (Conditional recommendation, Low- certainty evidence).

D. SPECT-CT radioiodine imaging may be applied in addition to planar imaging to better determine the anatomical localization of radioiodine uptake and to differentiate between potential cancer foci and nonspecific uptake (Conditional recommendation, Low- certainty evidence).[5]

In the 2015 revision, Recommendations 66 and 67 addressed WBS.

In Recommendation 66, following RAI remnant ablation or adjuvant therapy, in low- and intermediate-risk patients who demonstrate an excellent response to therapy—defined as undetectable Tg under thyroid hormone therapy, negative anti-Tg antibodies, and negative ultrasound—routine diagnostic WBS during follow-up is not necessary.

In Recommendation 67, section A, diagnostic WBS performed 6–12 months after adjuvant RAI therapy, following thyroid hormone withdrawal or rhTSH administration, may be used in the follow-up of patients at high or intermediate risk (with higher-risk features) for persistent disease (see risk classification system, section [B19]) and should be performed using 123I or low-activity 131I (Strong recommendation, Low-quality evidence).

In section B, in patients with uptake on planar imaging, SPECT/CT RAI imaging is preferred over planar imaging to better localize RAI uptake anatomically and to distinguish possible tumors from nonspecific uptake (Weak recommendation, Moderate-quality evidence).[4]

In the 2015 revision, following RAI remnant ablation or adjuvant therapy, in low- and intermediate-risk patients who demonstrated an excellent response to therapy—defined as undetectable Tg under thyroid hormone therapy, negative anti-Tg antibodies, and negative ultrasound—routine diagnostic WBS during follow-up was not considered necessary. For high- or intermediate-risk patients, WBS was recommended 6–12 months after RAI therapy, and in patients with uptake on planar imaging, SPECT/CT was recommended to better localize the uptake and differentiate tumors from nonspecific uptake.

In the 2025 revision, WBS is not recommended in low-risk, RAI-untreated total thyroidectomy patients or lobectomy patients who are low–intermediate risk and demonstrate an excellent response to therapy. In intermediate–high and high-risk patients, WBS is recommended only if there is suspicion of recurrence, rather than routinely. SPECT/CT continues to be recommended to differentiate nonspecific tissue from cancer.

18FDG-PET/CT Imaging

In the 2025 revision, Recommendation 50 addresses 18FDG-PET/CT in two points.

In point A, 18FDG-PET/CT may be performed in DTC patients with high serum Tg levels and high risk of recurrence, especially in oncocytic thyroid carcinoma or aggressive histology, and in patients with a prior negative RAI imaging history (Conditional recommendation, Moderate- certainty evidence).

In point B, 18FDG-PET/CT may also be used:

(i) As a prognostic tool in individuals at highest risk for fast disease progression and disease-specific mortality, and

(ii) To assess response to therapy after systemic or local treatment of invasive disease (Conditional recommendation, Low-certainty evidence).[5]

In the 2015 revision, Recommendation 68 states:

A. In high-risk DTC patients with negative RAI imaging and higher serum Tg (often >10 ng/mL), 18FDG-PET screening should be taken into consideration (Strong recommendation, Moderate-quality evidence).

B. 18FDG-PET scanning can also be used for the following purposes: (i) initial staging of poorly differentiated thyroid cancers, especially in patients with high serum Tg levels or other imaging findings, such as invasive Hurthle cell carcinoma; (ii) prognostication to identify lesions and patients at highest risk of rapid disease progression and disease-specific mortality in metastatic disease; and (iii) assessing response to treatment following systemic or local therapy in metastatic or locally invasive disease. (Weak recommendation, Low-quality evidence).[4]

Although the recommendations in the two revisions are generally similar, several details are noteworthy. In the 2015 revision, section A was a strong recommendation, whereas in the 2025 revision this point has been downgraded to a conditional recommendation. The 2015 edition addressed patients with rising Tg despite negative imaging, while the 2025 revision includes high-risk DTC patients, particularly those with oncocytic thyroid carcinoma (OTC) or aggressive histology. The recommendation added in point A of the 2025 revision was included in point B of the 2015 revision. In point B of the 2025 revision, the use of 18FDG-PET/CT as a prognostic tool in patients at highest risk for rapid disease progression and disease-specific mortality, and for evaluating response after systemic or local treatment of invasive disease, remains similar to the 2015 revision. Additionally, the term "Hurthle cell carcinoma" used in the 2015 revision has been replaced in the 2025 revision with "Oncocytic thyroid carcinoma" in accordance with the 2022 WHO classification.[6,7]

Is continuous risk stratification (assessment of response to therapy) useful for long-term disease follow-up and treatment management decisions?

In the 2025 revision, Recommendation 51 addresses this issue. It states that continuous risk stratification (dynamic risk assessment), when used alongside the initial recurrence risk, allows the clinician to provide individualized management recommendations based on changing risk estimates over time and should be used to guide the timing and type of imaging (Good practice statement).[5]

In the 2015 revision, specific details on how surveillance and treatment strategies should be modified over time based on reclassification of response to therapy within the ATA risk categories were not yet defined. In the 2025 revision, it is emphasized as a good practice statement that dynamic risk stratification can directly guide which imaging to perform and when, based on evolving risk assessments.

When and what type of treatment should be applied for local, regional residual, clinically recurrent, or progressive DTC?

2025 Revision addresses Recommendation 52 subdivided into three sections.

1. A number of considerations should be addressed when deciding whether to do focused central and/or lateral

neck surgery or therapeutic regional neck surgery as part of reoperative therapy. These include the extent of previous surgery(ies), the size and anatomical location of the new disease, its growth rate, patient characteristics and preferences, and the context of overall disease management (Good Practice Statement).

2. For patients with recurrent or residual thyroid cancer, percutaneous ethanol ablation may be a viable alternative therapeutic option, especially if they are at a high risk of reoperation-related complications. (Conditional recommendation, Low-certainty evidence).
3. Radiofrequency ablation (RFA) may be an alternative treatment in recurrent or residual thyroid cancer, particularly in patients at high risk of complications from reoperation (Conditional recommendation, Low-certainty evidence).

In the 2015 guideline, Recommendation 71 strongly recommended therapeutic compartmental central and/or lateral neck dissection in patients with persistent or recurrent disease confirmed by biopsy, where anatomically localized central neck lymph nodes were ≥8 mm and lateral neck nodes were ≥10 mm, performed within previously operated compartments while preserving uninvolved vital structures.

In the 2025 revision, Recommendation 52 point 1 emphasizes that the decision for reoperation should consider multiple factors—including prior surgical extent, lesion size and anatomical location, growth rate, patient-specific factors/preferences, and overall disease context—rather than relying solely on lymph node size criteria.

Additionally, ethanol ablation and RFA were not mentioned in the 2015 guidelines, but in the 2025 revision, they are suggested as conditional, low-certainty alternative therapies for recurrent or residual thyroid cancer.[5]

Should RAI therapy be used in the treatment of isolated cervical lymph node metastases?

In the 2025 revision, Recommendation 53 addresses this point. It states that for defined isolated cervical lymph node metastases, additional RAI therapy may be considered in cases where local therapy is not feasible, or following local treatment (Conditional recommendation, Low certainty of evidence).[5]

In the 2025 revision, the use of RAI in the treatment of isolated cervical lymph node metastases is presented as a formal recommendation. In the 2015 revision, although the text emphasized that "for regional nodal metastases detected on diagnostic WBS, RAI could be used in patients with low-volume disease or in combination with surgery," it was not included among the official recommendations.[4]

Should external beam radiotherapy (EBRT) be used in isolated cervical lymph node metastases?

In the 2025 revision, Recommendation 54 addresses EBRT in cervical lymph node metastases:

EBRT delivered with modern techniques such as IMRT or stereotactic radiotherapy may be considered in cases of unresectable locoregional recurrence or when there is extranodal extension or soft tissue involvement (Conditional recommendation, Low certainty of evidence).[5]

In the 2015 guidelines, no recommendation was provided regarding external radiotherapy for locoregional lymph node metastases. In the 2025 revision, however, it is suggested—albeit with low certainty of evidence—that external neck radiotherapy may be considered in cases where locoregional disease is unresectable or when there is extranodal extension and soft tissue involvement.[4]

Preparation and dosage strategies for RAI therapy in regional and/or distant metastases

In the 2025 revision, Recommendation 55 outlines three points regarding preparation and dosing strategies for RAI therapy in patients with regional and/or distant metastases:

The Section A states that, in patients with renal insufficiency or those over 70 years of age, empirical administration of >5.5 GBq (150 mCi) of ^{131}I should be avoided due to the increased likelihood of exceeding toxicity thresholds. If doses above this level are being considered, dosimetry should be performed before RAI administration to confirm safety (Strong recommendation, Moderate-certainty evidence).

According to section B, dosimetry-guided RAI administration (either lesion-based or based on the maximal tolerated activity) may be taken into consideration for patients with locoregional or metastatic disease for whom doses greater than 5.5 GBq (150 mCi) are being considered (Conditional recommendation, Moderate-certainty evidence).

Section C indicates that for patients with distant metastatic disease treated with RAI, preparation may be achieved either through rhTSH-mediated TSH stimulation or by LT4 withdrawal (Conditional recommendation, Low-certainty evidence).

It should be noted that in the 2025 revision, point C is presented as a conditional recommendation with a low level of evidence.[5]

In the 2015 revision, Recommendation 73 stated that although dosimetric approaches to the treatment of locoregional or metastatic disease have theoretical advantages, no recommendation could be made regarding the superiority of one method of RAI administration [empirical high activity, blood and/or body dosimetry, or lesional dosim-

etry) over another. In subsection B of the same recommendation, it was emphasized that in patients over the age of 70, empirically administered doses of 131-I exceeding 150 mCi, which could potentially surpass the maximum tolerable tissue dose, should be avoided [Strong recommendation, Moderate-quality evidence).

In the 2025 revision, however, it is specifically recommended that in patients with renal impairment or those over 70 years of age, when doses above 5.5 GBq [150 mCi) are considered, empirical administration should be avoided and treatment should instead be guided by dosimetric assessment.

In the 2015 guideline, Recommendation 74 stated that for patients with distant metastatic disease treated with 131-I, there was insufficient outcome data to recommend routine use of rhTSH-stimulated therapy in all patients. Furthermore, Recommendation 75 noted that recombinant human TSH [rhTSH)–stimulated therapy may be recommended for certain patients who have underlying comorbidities that make iatrogenic hypothyroidism potentially risky, for patients with pituitary disease where serum TSH cannot be elevated, or in cases where treatment delay could be harmful. The activity delivered to these individuals should be at least as high as or higher than what would have been given if the patient had been prepared by hypothyroidism or by a dosimetrically determined activity (Strong recommendation, Low-quality evidence).

In contrast, the 2025 revision provides a more inclusive recommendation, stating that for patients with regional and/or distant metastases, either rhTSH-stimulated TSH elevation or LT4 withdrawal may be used as preparation methods before RAI therapy.[4]

What RAI dose adjustment strategies should be used in patients with lung metastases?

In the 2025 revision, recommendations for RAI therapy in lung metastases are provided in three points:

A. Pulmonary micrometastases can be treated with RAI, and therapy may be repeated as long as the disease continues to take up RAI and shows a clinical response (Conditional recommendation, Low- certainty evidence).

B. For pulmonary micrometastases, RAI dosing should be either empirical (3.7–7.4 GBq [100–200 mCi]; for patients >70 years, 3.7–5.55 GBq [100–150 mCi]) or estimated using dosimetry to limit whole-body retention at 48 hours to 2.96 GBq (80 mCi) and deliver ≤200 cGy to the bone marrow (Good Practice Statement).

C. RAI can be used to treat radioiodine-avid macronodular metastases, and if an objective benefit is shown, the treatment may be repeated. RAI dosage can be empirical (3.7–7.4 GBq [100–200 mCi]; for patients older than 70 years, 3.7–5.55 GBq [100–150 mCi]) or determined by whole-body dosimetry to keep bone marrow exposure below 200 cGy and 48-hour whole-body retention at 2.96 GBq (80 mCi) (Conditional recommendation, Low-certainty evidence).[5]

In the 2015 revision, Recommendation 77 on the treatment of lung micrometastases was presented in two points, which correspond to points A and B in the 2025 revision. The 2015 guideline specified that therapy could be repeated every 6–12 months, whereas the 2025 revision no longer provides a specific interval for repeat treatment. The recommendation in 2025 is given as a conditional recommendation with low-quality evidence.

For macronodular metastases, the approach in 2015 was described in Recommendation 78, and a similar recommendation appears as point C in the 2025 revision. In 2015, it was emphasized that complete response was uncommon and overall survival was poor; this statement is not included in the 2025 revision.[4]

RAI dose adjustment strategies in patients with bone metastases

In the 2025 revision, recommendations for RAI therapy and dose adjustment in bone metastases are provided in Recommendation 57, with two points:

According to part A, RAI therapy for iodine-avid bone metastases has been associated with improved survival and is recommended (Strong recommendation, Low-certainty evidence).

Part B states that, the administered activity may be determined either empirically (3.7–7.4 GBq [100–200 mCi]) or using dosimetry (Conditional recommendation, Very low-certainty evidence).

These recommendations are essentially the same as Recommendation 79 in the 2015 revision, with only minor changes in the recommendation strength and evidence level.[5]

Timing of empirical RAI in Tg-positive, diagnostic RAI scan–negative patients

In the 2025 guideline, this is addressed in Recommendation 58:

A. Patients with stimulated serum Tg <10 ng/mL following thyroid hormone withdrawal or <5 ng/mL following rhTSH (indeterminate response) can be monitored with thyroid hormone therapy alone if there is no structurally identifiable disease. Additional treatment should be saved for situations where serum Tg increases over time or other indications of structural disease progression emerge (Conditional recommendation, Low-certainty evidence).

B. In patients with no targetable tumor on imaging (e.g., cross-sectional imaging and/or 18FDG-PET/CT) but with markedly elevated or rapidly rising serum Tg, empirical (3.7–7.4 GBq, 100–200 mCi) or dosimetry-guided RAI therapy can be considered (Conditional recommendation, Low-certainty evidence).

C. Repeat RAI therapy may be considered for persistent, unresectable disease that localizes following empirical RAI application and shows evidence of a significant tumor shrinkage until the tumor disappears or no longer responds to treatment (Conditional recommendation, Low-certainty evidence).

In the 2015 revision, Recommendations 80–82 presented similar guidance under a single heading. However, 2015 Recommendation 81 included the statement: "The risk of high cumulative RAI activity should be balanced against uncertain long-term benefits. If empirical RAI is given and post-therapy scanning is negative, the patient should be considered RAI-refractory, and further RAI should not be given." This and the corresponding caution in Recommendation 82 regarding high cumulative RAI risk are not included in the 2025 revision.[4,5]

How is radioactive iodine–refractory (RAIR) DTC classified?

In the 2025 guideline, this is addressed in Recommendation 59:

A. Patients who have not received RAI for ablation or therapy cannot be diagnosed with RAIR DTC. Ablation or therapeutic RAI should be used to assess the disease state of patients who fit the criteria for RAI (Good Practice Statement).

B. Patients with RAIR DTC should not be given additional empirical RAI therapy. Other treatment options should be considered (Good Practice Statement).[5]

In the 2015 guideline, Recommendation 91 classifies RAI-refractory structural DTC in patients who have received appropriate TSH stimulation and iodine preparation into four main categories:

1. Malignant/metastatic tissue that never shows RAI uptake (no uptake outside the thyroid bed on the first therapeutic WBS).
2. Tumor tissue that initially demonstrated RAI avidity but later lost the ability to concentrate RAI (iodine uptake).
3. Heterogeneous uptake, where some lesions show uptake while others do not.
4. Significant RAI uptake is present, but radiologic or clinical progression occurs.

Once a DTC patient is classified as RAI-refractory, there is no indication for further RAI therapy.[4]

In the 2015 revision, the four-item RAIR definition is not explicitly included in the 2025 guideline as a recommendation, although similar explanations appear in the text. In the 2025 revision, it is recommended that for establishing a RAIR diagnosis, RAI therapy should be administered at ablative or therapeutic doses. In section B, it is advised that patients diagnosed as RAIR should not receive empirical RAI therapy, and other treatment options should be considered—this is similar to the 2015 recommendation.

Which metastatic DTC patients can be monitored without additional treatment?

In the 2025 revision, this is addressed in Recommendation 60:

A. Patients with clinically severe comorbidities or those with RAIR metastatic DTC who are asymptomatic, stable, or minimally progressing can be followed up with serial radiographic imaging every three to twelve months while on TSH-suppressive thyroid hormone therapy (Conditional recommendation, Low certainty evidence).

B. Routine molecular testing is not advised for patients with residual RAIR DTC if systemic therapy or redifferentiation therapy are not planned (Conditional recommendation, Moderate certainty evidence).[5]

This recommendation in the 2025 revision is similar to Recommendation 92 in the 2015 edition.[4,5]

What is the optimal approach to select the best therapy in RAIR DTC patients considered eligible for systemic treatment?

In the 2025 revision, this is addressed in Recommendation 61:

Before starting systemic treatment for progressive disease, tissue-based biomarker testing should be performed to detect targetable oncogenic alterations (Strong recommendation, Moderate-certainty evidence).[5]

In the 2015 revision, there were no recommendations regarding biomarker testing prior to systemic therapy.

What is the recommended first-line treatment in progressive RAIR-DTC patients without an actionable oncogenic alteration when systemic therapy is indicated?

In the 2025 revision, this is addressed in Recommendation 62:

In progressive RAIR-DTC patients who do not have an FDA-approved first-line therapy based on an actionable biomarker, a multi-kinase inhibitor (MKI) such as lenvatinib or sorafenib is recommended. Lenvatinib is preferred as first-line therapy in most cases (Strong recommendation, High-certainty evidence).[5]

In the 2015 guideline, Recommendation 96 presented kinase inhibitor therapy as an option to be "considered" only for RAIR

DTC patients with rapidly progressing, symptomatic, or life-threatening disease not amenable to local control. It did not provide specific guidance on which drug to use, only suggesting FDA-approved agents or access through clinical trials.

In contrast, the 2025 guideline strengthens the language from "considered" to "recommended". MKI therapy is now recommended as first-line systemic therapy for progressive RAIR DTC patients who do not have a targetable biomarker for first-line treatment. Specifically, lenvatinib (preferred) and sorafenib are recommended as first-line MKIs.

Timing of MKI initiation in RAIR DTC patients

In the 2025 revision, this is addressed in Recommendation 63:

A. For symptomatic RAIR DTC patients in whom local therapies such as radiotherapy or surgery are not appropriate, lenvatinib or another MKI should be initiated without delay (Strong recommendation, Moderate-certainty evidence).

B. For asymptomatic RAIR DTC patients with progression over the past 12–14 months and in whom local therapy is not suitable, early initiation of lenvatinib can be considered if the main goal is efficacy. Conversely, if quality of life is the primary concern, delaying lenvatinib initiation and continuing disease monitoring may be the most appropriate approach (Good Practice Statement).[5]

In the 2015 guideline, there was no clear definition or separate recommendation regarding the optimal timing to start MKI therapy in RAIR DTC patients.

What is the optimal starting dose of lenvatinib in RAIR DTC?

This issue is provided in Recommendation 64 of the 2025 revision. Recommendation 64:

According to part A, for patients starting lenvatinib for progressive RAIR DTC, the recommended starting dose is 24 mg once daily for most patients; a lower starting dose can be considered in selected patients (Strong recommendation, High-certainty evidence).

Part B specifies that, the management of lenvatinib-related adverse events should include dose interruptions and dose reductions as key strategies (Good Practice Statement).[5]

This recommendation was also not included in the 2015 guideline.

How should adverse effects be managed in patients receiving VEGFR-targeted MKI therapy?

This issue is provided in Recommendation 65 of the 2025 revision. Recommendation 65

For patients undergoing MKI therapy, preventing, minimizing, and promptly managing side effects are crucial. During the first two months of therapy, patients starting MKI medication should be assessed and followed at least every two weeks. After that, they should typically be checked every one to two months (Good Practice Statement).[5]

There was no recommendation regarding this issue in the 2015 edition.

What is the preferred second-line therapy approach for RAIR DTC patients?

This issue is provided in Recommendation 66 of the 2025 revision. Recommendation 66

In RAIR-DTC patients who experience progression during MKI therapy or cannot tolerate the treatment, Cabozantinib is recommended as a second-line therapy if there is no contraindication to continue the treatment (Strong recommendation, High-certainty evidence).[5]

In the 2015 guideline, Recommendation 97 stated that in the event of failure of initial tyrosine kinase inhibitor therapy, re-evaluation could be considered within therapeutic clinical trials, with a weak recommendation and low-quality evidence. In the 2025 revision, it is clearly recommended that, in the absence of contraindications, Cabozantinib be used as second-line therapy with strong recommendation and high-quality evidence.

In the 2015 guideline, Recommendation 99 advised that unproven agents should primarily be used within therapeutic clinical trials. In the 2025 revision, Recommendations 67–71 more clearly emphasize these agents with low-to-moderate certainty evidence and strong recommendations.

What is the most appropriate first-line therapy for NTRK fusion–positive RAIR-DTC patients?

In Recommendation 67 of the 2025 revision, it is indicated that, in progressive RAIR-DTC patients harboring an oncogenic NTRK fusion, NTRK-targeted therapy is recommended as first-line treatment (Strong recommendation, Moderate- certainty evidence).[5]

What is the optimal first-line treatment in RET fusion–positive RAIR-DTC patients?

In the 2025 revision, Recommendation 68 states; In progressive RAIR-DTC patients with oncogenic RET fusion, first-line RET-targeted therapy is recommended (Strong recommendation, Moderate- certainty evidence).[5]

What is the optimal first-line treatment in ALK fusion–positive RAIR-DTC patients?

Anaplastic lymphoma kinase (ALK)-targeted therapy is advised as the first-line treatment for progressive RAIR-DTC patients with oncogenic ALK fusion, according to Recommendation 69 of the 2025 revision (Strong recommendation, Low- certainty evidence).[5]

What is the optimal first-line treatment in BRAF V600E–mutated RAIR-DTC patients?

In the 2025 revision, Recommendation 70 states;

A. In progressive RAIR-DTC patients with oncogenic BRAF V600E mutation who are not suitable candidates for lenvatinib, first-line BRAF-targeted therapy may be considered (Conditional recommendation, Moderate-certainty evidence).

B. In BRAF V600E–mutated RAIR-DTC patients who progress during the treatment or cannot tolerate one or more previous MKI therapies, BRAF-targeted therapy is recommended (Strong recommendation, Moderate-certainty evidence).

C. DTC patients with BRAF alterations without V600 mutation should not receive current BRAF-targeted therapies (Strong recommendation, Moderate- certainty evidence).[5]

What is the optimal first-line treatment in RAIR-DTC patients with other potentially targetable molecular alterations?

In the 2025 revision, Recommendation 71 states:

Progressive RAIR-DTC patients carrying potentially targetable alterations other than NTRK, RET, ALK, or BRAF V600E should be offered participation in a clinical trial or first-line lenvatinib therapy (Conditional recommendation, Low-certainty evidence).[5]

What is the optimal approach to addressing disease progression in gene-specific therapy for RAIR-DTC?

In the 2025 revision, Recommendation 72 states;

A. Whenever possible, perform surgical or core tumor biopsy to enable NGS testing to identify potential molecular mechanisms of acquired resistance (Good Practice Statement).

B. In patients where tumor biopsy is not feasible, surgical or core biopsy is preferred instead of ctDNA analysis (Conditional recommendation, Low-certainty evidence).

The 2015 ATA guideline did not include a clear definition or separate recommendation for gene-specific RAIR-DTC management.[5]

What is the role of immunotherapy in RAIR-DTC?

In the 2025 revision, Recommendation 73 states:

In selected patients—such as those whose tumors exhibit high tumor mutational burden or deficiencies in DNA mismatch repair—immune checkpoint inhibitors or other forms of immunotherapy may be considered (Conditional recommendation, Low- certainty evidence).[5]

In the 2015 guideline, immunotherapy was not presented as a recommendation; it was only briefly mentioned that it should be investigated in RAI-resistant thyroid cancer. In the 2025 revision, immunotherapy is presented as a conditional recommendation with low-quality evidence, indicating that it can be applied in selected cases.

What is the role of kinase inhibitor–mediated redifferentiation therapy in RAIR DTC patients?

In the 2025 revision, Recommendation 74 states:

A. In progressive RAIR DTC patients with targetable mutations, redifferentiation through MAPK pathway blockade can be considered in selected patients. Participation in clinical trials is encouraged (Conditional recommendation, Low certainty evidence).

B. In high-risk, unselected DTC patients, redifferentiation approaches in adjuvant RAI therapy are not recommended (Strong recommendation, Moderate certainty of evidence).[5]

Comparing with the 2015 edition, this appears to be a newly introduced recommendation.

What is the role of cytotoxic chemotherapy in RAIR DTC?

In the 2025 revision, Recommendation 75 states that in patients with RAIR DTC who are metastatic, rapidly progressive, symptomatic, and/or at imminent risk, and in whom other treatments cannot achieve control, cytotoxic chemotherapy can be considered. However, it is recommended that this treatment preferably be administered within the context of a therapeutic clinical trial (Conditional recommendation, Low-certainty evidence).[5]

According to the 2015 ATA guideline (Recommendation 100), cytotoxic chemotherapy in RAIR DTC patients was suggested for consideration in metastatic, rapidly progressive, symptomatic, or life-threatening disease not controlled by other treatment options (e.g., tyrosine kinase inhibitors). In the 2025 guideline, this recommendation remains unchanged, with the addition that this therapy is preferably administered within the context of a therapeutic clinical trial.[4]

What is the optimal approach for patients with oligometastatic RAIR DTC?

In the 2025 revision, Recommendation 76 states that for patients with RAIR DTC who have solitary or oligometastatic disease (two to five lesions), focal ablation therapy may be considered. The optimal treatment approach should be determined through evaluation by a multidisciplinary team (Conditional recommendation, Low-certainty evidence).[5]

In the 2015 ATA guideline, oligometastatic RAIR DTC was only briefly mentioned in Recommendation 96 in the con-

text of kinase inhibitor use and was not presented as a formal recommendation. In contrast, the 2025 ATA guideline introduces a completely new Recommendation 76 specifically for the management of patients with solitary or oligometastatic RAIR DTC.[4]

What is the optimal treatment approach for localized symptomatic RAIR DTC?

In the 2025 revision, Recommendation 77 states: Local therapy is recommended for patients with symptomatic RAIR DTC. Surgical resection, radiotherapy, or percutaneous thermal ablation techniques (e.g., RFA, MWA, cryoablation) can be applied to the disease foci causing symptoms (Conditional recommendation, Moderate-certainty evidence).[5]

In the 2015 ATA guideline, local therapies for managing symptomatic foci in patients with RAIR-DTC were mentioned briefly. Surgical resection, stereotactic body radiotherapy (SBRT), thermal ablation, and radiotherapy were discussed in explanatory text for localized RAIR-DTC, but these approaches were not clearly defined, and recommendation levels were not specified. Recommendation 93 addressed advanced thyroid cancers, noting that methods such as stereotactic radiation and thermal ablation (RFA and cryoablation) could serve as alternatives to surgery in distant metastases.

In the current guideline, Recommendation 77 explicitly includes RFA, MWA, and cryoablation as options for managing symptomatic RAIR-DTC foci, in addition to surgery and radiotherapy. Furthermore, this recommendation is classified as conditional with moderate- certainty evidence, providing a clearer statement on the strength and certainty of the evidence.[4,5]

In patients with DTC, when should bone-targeted agents be considered?

In the 2025 revision, Recommendation 78 states:

According to part A, in RAIR-DTC patients with symptomatic and/or multiple bone metastases, treatment with bone-modifying agents is advised to reduce the risk of skeletal-related events (Strong recommendation, Low- certainty evidence).

Part B states that administering bone-modifying agents every 3 months instead of monthly may reduce the risk of adverse events such as osteonecrosis of the jaw. However, this approach could increase the risk of symptomatic skeletal events (Conditional recommendation, Low- certainty evidence).[5]

In the 2015 ATA guideline, Recommendation 101, the primary approach for managing bone metastases in RAIR-DTC patients focused on symptom control using local therapies (surgery, radiotherapy) alongside systemic treatments. For widespread or symptomatic bone metastases, bisphosphonates or denosumab were recommended, with prior assessment of renal function, calcium levels, and dental evaluation. In the 2025 ATA guideline, Recommendation 78, it is similarly recommended that bone-modifying agents be used in RAIR-DTC patients with symptomatic or multiple bone metastases. New in 2025 is the additional guidance on the dosing interval of these agents.[4,5]

What is the optimal treatment in patients with brain metastases?

In the 2025 revision, Recommendation 79 indicates;

A. The primary treatment approach for central nervous system metastases is surgical resection and/or SBRT (Conditional recommendation, Low-certainty evidence).

B. If the metastases are RAI-avid, radioactive iodine may be considered. When RAI is planned, pre-treatment with SBRT and concomitant glucocorticoids is recommended to minimize the effects of TSH-stimulated tumor volume increase and RAI-related inflammatory response (Good Practice Statement).[5]

There is no major difference between the 2015 and 2025 guidelines regarding the management of brain metastases. In the 2015 guideline, Recommendation 94 addressed the approach for DTC patients with brain metastases, and the 2025 revision presents a nearly identical recommendation.[4,5]

Who should be considered for clinical trials?

In the 2025 revision, Recommendation 80 states that, patients should be informed about participation in prospective clinical trials based on the eligibility criteria of specific studies and the potential benefits of participation. Physicians considering referring patients to clinical trials should review available treatment options and eligibility criteria. This process should preferably involve direct discussions with research center staff and review of materials available at www.clinicaltrials.gov (Good Practice Statement).[5]

There is no significant difference between 2015 Recommendation 95 and 2025 Recommendation 80 regarding which patients should be included in clinical trials. In 2015, the recommendation was supported as a "strong recommendation, moderate-quality evidence," whereas in 2025, although no formal recommendation grade is given, it is presented as a Good Practice Statement.[4,5]

Management considerations for pregnant patients with DTC

A. The majority of pregnant patients can safely postpone surgery until after delivery. As an exception, surgery may be performed in the second trimester in rare cases with a

significant risk of disease progression (Conditional recommendation, Low-certainty evidence).

B. It is recommended for individuals with DTC throughout pregnancy to have at least one neck ultrasound performed in the early second trimester, and more frequently if clinically required. In some situations, MRI cross-sectional imaging may be performed. Ionizing radiation-intensive imaging techniques ought to be reserved for extremely critical situations (Conditional recommendation, Low-certainty evidence).

C. TSH targets in pregnant patients are generally the same as those set before pregnancy. If there are concerns about potential adverse effects of excessive thyroid hormone on pregnancy, the levothyroxine dose may be adjusted to allow for less TSH suppression. TSH should be monitored approximately every 4 weeks until 16–20 weeks of gestation, and at least once between 26–32 weeks (Good Practice Statement).

D. In pregnant patients with an incomplete response to therapy, follow-up with neck ultrasound and Tg is appropriate; if cross-sectional imaging is needed, MRI is preferred. Pregnant patients with an excellent or indeterminate response category should be monitored in the same way as nonpregnant patients (Conditional recommendation, Low-certainty evidence).[5]

In the 2015 revision, Recommendation 31 summarized the management of malignancy in pregnant patients in a single statement. It is advised that papillary thyroid cancer detected early in pregnancy should usually be monitored with ultrasound. If the tumor shows significant growth before 24–26 weeks of gestation or if suspicious cervical lymph nodes are detected, surgery during pregnancy may be considered. However, if the disease remains stable until mid-gestation, or if the diagnosis is made during the second half of pregnancy, surgery should be delayed until after delivery.[4]

In contrast, the 2025 revision addresses DTC management during pregnancy in more detail under Recommendation 81, divided into four subpoints. Similar to the previous guideline, it recommends delaying surgery until after delivery in the absence of significant disease progression, with the option of surgery in the second trimester if progression occurs. Different from the 2015 guideline, the 2025 update explicitly allows MRI for cross-sectional imaging when necessary during pregnancy, while emphasizing that ionizing radiation should only be used in exceptional situations. Moreover, the 2025 revision introduces clear recommendations on TSH monitoring frequency in pregnant patients with DTC.[5]

What are the long-term survivorship issues associated with thyroid cancer treatment?

In the 2025 revision, Recommendation 82 states that patients should be informed about potential long-term side effects related to the treatments they have received. In addition, these patients should be monitored during follow-up with appropriate interventions and/or referrals as needed (Good Practice Statement).

In the 2015 ATA guideline, long-term survivorship issues were discussed only within the section on long-term follow-up of DTC, but not presented as a formal recommendation. In contrast, the 2025 revision introduces this topic explicitly as a recommendation.[4,5]

How should the financial challenges caused by thyroid cancer be addressed?

In the 2025 revision;

According to the part A, patients and families struggling financially due to a thyroid cancer diagnosis should be informed about the resources available to help alleviate this burden (Good Practice Statement).

Part B states that clinicians should be aware that many patients with thyroid cancer face financial hardship arising from the costs of diagnosis, treatment, and follow-up. These issues should be discussed openly with patients and their families (Good Practice Statement).[5]

In the 2015 guideline, there was no direct recommendation regarding financial toxicity.

In contrast, the 2025 revision introduces a new recommendation, emphasizing that the financial burden experienced by patients and their families should be acknowledged and openly discussed.[4,5]

What are the critical psychosocial issues in thyroid cancer survivors?

In the 2025 revision, Recommendation 84 states:

A. The availability of resources that can assist with their psychosocial needs in relation to the cancer diagnosis should be emphasized to thyroid cancer survivors (Good Practice Statement).

B. Healthcare professionals who treat patients with thyroid cancer should be ready to help them cope with the psychological effects of the diagnosis and course of therapy (Good Practice Statement).[5]

In the 2015 ATA guideline, the psychosocial dimension was addressed only indirectly, mentioned briefly in the explanatory sections, and—similar to financial toxicity—no formal recommendation was provided.

In the 2025 revision, however, unlike the previous guideline, clinicians are now recommended to support thyroid cancer survivors in addressing their psychosocial needs.[4,5]

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Original Research

Cervical lymphadenopathies: A Retrospective Single-Center Analysis of Patients Undergoing Excisional Biopsy

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Abstract

Objectives: The aim of this retrospective study was to evaluate and compare cervical ultrasound findings, fine needle aspiration biopsy (FNAB) results and excisional biopsy results in the diagnosis of patients presenting with cervical lymphadenopathy and to reveal the most common causes.

Methods: A total of 137 patients who underwent cervical ultrasonography and FNAB before excision were included in the study. Demographic data, cervical ultrasonographic findings, FNAB pathology results and final pathology results after excisional biopsy were analysed.

Results: The pathological results indicated that reactive follicular hyperplasia was diagnosed in 33.6% (n=46) of the patients. A diagnosis of non-Hodgkin lymphoma (NHL) was made in 27.7% (n=38) of cases, while 13.1% (n=18) were diagnosed with Hodgkin lymphoma. Malignant pathology was diagnosed in 66 patients. In the FNAB results of patients diagnosed as malignant, 57 were interpreted as non-diagnostic and suspicious, while 9 were interpreted as benign. Of these, 8 had a pathological examination of lymph node excision that revealed non-Hodgkin lymphoma (NHL), and in one patient with a benign FNAB result, the result of lymph node excision was reported as malignant.

Conclusion: Especially in cervical lymphadenopathies in patients over 40 years of age, the possibility of malignancy increases significantly. In lymphoproliferative diseases and in cases accompanied by clinical suspicion, it would be rational to use the direct excisional biopsy option. Although prior fine needle aspiration biopsy may provide significant guidance in metastatic diseases, it should be kept in mind that false negative rates may increase in the diagnosis and staging of lymphoma.

Keywords: Cervical lymphadenopathies, excisional biopsy, fine needle aspiration biopsy, lymphoma, metastasis ve reactive follicular hyperplasia

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Lymphadenopathy (LAP) is a condition characterised by an enlargement and structural abnormality of lymph nodes, typically defined as nodes exceeding one centimetre in size.[1] It may be a presenting symptom of a range of diseases, including infectious, immunological, neoplastic and metabolic disorders. The prevalence of LAP is estimated to be between 0.5 and 0.6% in the general population, affecting individuals of all age groups, including children and adults.[1, 2] G. Since one-third of the lymphatic system is located in the neck, cervical lymph nodes are the most

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common site for peripheral LAP.[3] A study of a pediatric population revealed that 98% of lymph nodes were located in the cervical region.[4]

Despite its frequently benign nature, lymphadenopathy necessitates a comprehensive clinical evaluation, including detailed history-taking, physical examination, laboratory testing, and cervical ultrasonography, to accurately distinguish between benign and malignant etiologies. Although excisional lymph node biopsy (ELB) is often considered the definitive method for diagnosis, fine needle aspiration biopsy (FNAB) remains a valuable tool when combined with ultrasonographic evaluation for determining the underlying etiology. Furthermore, it is particularly effective in the assessment of various pathological conditions, including those with metastatic potential. In cases where a diagnosis cannot be reached through FNAB and clinical suspicion persists, or in instances of lymphoproliferative diseases, direct ELB may be the preferred option when larger sample sections are required for histopathological evaluation.[5,6]

Excisional lymph node biopsy (ELB) is a more invasive procedure compared to fine needle aspiration biopsy (FNAB). Excision can be performed under local anaesthesia, although general anaesthesia may be preferred, particularly in paediatric patients and in cases where the cervical LAP is deeply located.

One of the major challenges of this procedure is navigating the complex cervical anatomy, which increases the risk of adverse outcomes. Another potential issue is the formation of scars on the skin in the cervical region. Despite all these risks, ELB has the highest sensitivity especially in the diagnosis of lymphoma. The availability of sufficient tissue allows for the analysis of lymph node structure and the classification of lymphoma.[2]

The primary question in this context is which patients require ELB. In recent years, direct ELB has been recommended as an alternative to diagnosing each cervical lymph node with FNAB due to the increasing prevalence of medical-legal concerns. Consequently, the objective of this retrospective study was to evaluate and compare the diagnostic accuracy of cervical ultrasound, FNAB pathology, and excisional biopsy in patients presenting with cervical lymphadenopathy and to determine the optimal timing for surgical excision.

Methods

In this study, a total of 312 patients who underwent excisional biopsy for cervical LAP at the Istanbul Medeniyet University Goztepe Prof Dr Suleyman Yalcin City Hospital Otorhinolaryngology clinic between November 2015 and June 2024 were evaluated. A total of 137 patients who had undergone fine-needle aspiration biopsy (FNAB) at our clinic or an external centre and had undergone cervical ultrasonography prior to excision were included in the study. The study was approved by the Istanbul Medipol University Non-Interventional Ethics Committee (decision number: 768-01.08.2024). This study was conducted in accordance with the Declaration of Helsinki. Due to the retrospective nature of the study, it was not necessary to obtain patient consent. The indication for biopsy was established in cases where the lymph node was unresponsive to empirical medical treatment and presented with at least one suspicious ultrasonographic feature, such as a short-axis diameter greater than 1 cm, presence of intranodal necrosis, a round shape, absent or displaced echogenic hilum, irregular, blurred, or spiculated margins and peripheral or mixed vascularity patterns. All patients underwent lymph node excision under general or local anaesthesia according to their age and lymph node location. The largest lymph node with pathological lymph node appearance on ultrasonography was surgically excised. Histopathological evaluation of the excised lymph nodes was performed.

The data set comprised demographic information, cervical ultrasonographic findings, results of FNAB, and pathological results following ELB. The ultrasonography reports were classified according to whether they indicated a reactive or pathological finding. The results of FNAB were classified and evaluated as follows: benign, suspicious, and non-diagnostic. The final pathological results of ELB were compared with the ultrasonography and FNAB pathological results.

Statistical Analysis

SPSS (Statistical Package for the Social Sciences) 24.0 (Armonk, New York: IBM Corp.) programme was used for statistical analyses. Descriptive statistical methods (Number, Percentage) were used to evaluate the study data. Pearson Chi-Square test was used for group comparisons. Significance was evaluated at $p<0.01$ and $p<0.05$ levels.

Results

The numbers and ratios of the patients who underwent FNAB followed by LAP excision according to age ranges are given in Table 1.

In terms of gender distribution, 59.9% (n=82) and 40.1% (n=55) of the patients who underwent FNAB and subsequent LAP excision were male and female, respectively.

Table 2 presents the distribution of diagnoses according to ELB pathological results. The pathological results indicated that reactive follicular hyperplasia was diagnosed in 33.6% (n=46) of the patients. A diagnosis of non-Hodgkin lympho-

Table 1. Number of patients who underwent FNAB and LAP excision according to age distribution

Age Range	Number	%
0-20	20	14.6
21-30	22	16.1
31-40	11	8.0
41-50	19	13.9
51-60	26	19.0
61-99	39	28.5
Total	137	100.0

Table 2. Distribution of diagnoses according to pathology results

Diagnosis	Number	%
Reactive follicular hyperplasia	46	33.6
Non-Hodgkin Lymphoma	38	27.7
Hodgkin Lymphoma	18	13.1
Tuberculosis	16	11.7
Metastasis	10	7.3
Sarcoidosis	3	2.2
Cat-scratch disease	3	2.2
Ebstain-Barr Virus	2	1.5
Toxoplasma	1	0.7
Total	137	100

ma (NHL) was made in 27.7% (n=38) of cases, while 13.1% (n=18) were diagnosed with Hodgkin lymphoma. Malignant pathology was diagnosed in 66 patients. Patients diagnosed as malignant were mostly in the 41-99 age range. A statistically significant difference was found between age groups according to ELB results (p=0.001; p<0.01). Patients diagnosed as malignant were mostly in the 41-99 age range. No statistically significant difference was observed between the ELB and FNAB results (p>0.05). No statistically significant difference was observed between the ELB diagnosis results and USG results (p>0.05). Detailed comparison of ELB results with ultrasonography, FNAB pathological results and age distribution is given in Table 3.

The detailed distribution of ELB pathology results according to FNAB results is given in Table 4. In the FNAB results of patients diagnosed as malignant, 57 were interpreted as non-diagnostic and suspicious, while 9 were interpreted as benign. Of these, 8 had a pathological examination of lymph node excision that revealed non-Hodgkin lymphoma (NHL), and in one patient with a benign FNAB result, the result of lymph node excision was reported as malignant. Final pathology results did not show a statistically significant difference according to the results of FNAB (p>0.05).

Discussion

Cervical lymphadenopathy may result from either benign or malignant etiologies, and determining the appropriate diagnostic approach is essential to achieving a timely and accurate diagnosis. Upon clinical presentation, a thorough history and physical examination are conducted to assess the pathological nature of the lymph node. Patient age is an important factor, as the likelihood of malignancy increases with advancing age. In our study, the incidence of malignancy was notably higher among individuals over 40 years of age. Similarly, Al Kadah et al.[1] identified a statistically significant correlation between age and malignancy in their study of 251 cases. It was reported that malignancy was detected in 95 of the 543 patients referred to a tertiary

Table 3. Comparison of results according to final pathology findings

	Final Pathology Results				[a]p
	Malign		Benign		
	Number	%	Number	%	
Age					
0-40	13	19.7	40	56.3	0.001**
41-99	53	80.3	31	43.7	
FNAB results					
Benign	9	13.6	9	12.7	0.513
Non-Diagnostic	28	42.4	24	33.8	
Suspicious	29	43.9	38	53.5	
USG					
Benign	18	27.3	28	39.4	0.132
Pathological	48	72.7	43	60.6	

[a]Pearson Chi-Square; **p<0.01. FNAB: fine needle aspiration biopsy; USG; Ultrasonography.

Table 4. Comparison of final pathology results according to FNAB results

Diagnosis	FNAB results						[a]p
	Benign		Non-Diagnostic		Suspicious		
	N	%	N	%	N	%	
Ebstain-Barr Virus	1	5.6	0	0.0	1	1.5	0.177
Hodgkin Lymphoma	0	0.0	7	13.5	11	16.4	
Cat-scratch disease	0	0.0	2	3.8	1	1.5	
Metastasis	1	5.6	6	11.5	3	4.5	
Non-Hodgkin Lymphoma	8	44.4	15	28.8	15	22.4	
Reactive follicular hyperplasia	7	38.9	18	34.6	21	31.3	
Sarcoidosis	1	5.6	1	1.9	1	1.5	
Tuberculosis	0	0.0	3	5.8	13	19.4	
Toxoplasma	0	0.0	0	0.0	1	1.5	

FNAB: fine needle aspiration biopsy.

cancer centre in the UK with peripheral lymphadenopathy.[7] In the same study, it was reported that advanced age was a risk factor for malignancy, with each 10-year increase in the patient's age increasing the risk of malignancy by a factor of 1.64. Additionally, male gender, lymph node size, and especially lymph nodes in the supraclavicular region were identified as risk factors for malignancy. Celenk et al.[5] also reported that advanced age was associated with malignancy.

In the presence of clinically suspicious lymph nodes and pathological lymph nodes according to ultrasound findings, further investigations are required to reach a definitive diagnosis. In our study, patients who underwent both FNAB and ELB were selected. Our clinical approach is to perform ELB directly in patients who are referred especially in the presence of clinical suspicion. However, recently, especially in internal medicine, ELB has been recommended as a primary treatment for lymph nodes that have not responded to medical therapy without the need for additional examination such as FNAB. In the present study, the patients who underwent FNAB prior to ELB were evaluated. Of the 137 patients included in the study, 46 (33.6%) were diagnosed with reactive follicular hyperplasia. Of the 46 patients with reactive follicular hyperplasia, 7 had benign FNAB results, while the remaining 39 had non-diagnostic or suspicious results. The necessity of surgery in these patients is a matter of debate.

While the accuracy of FNAB diagnosing metastatic carcinoma in the lymph nodes is over 90%, this rate is approximately 70% for primary lymphoma.[8,9] Gupta et al.[10] found that when FNAB diagnosis was combined with ultrasound findings, sensitivity increased from 72.7% to 95.4% and specificity increased from 82.1% to 92.3%. In addition, Lioe et al.[11] investigated the role of FNAB in the diagnosis of superficial LAP and found the specificity of this method to be high and found false negativity in 7 patients out of 157 patients. In the same study, it was highlighted that the most challenging aspect was differentiating between reactive hyperplasia and low-grade lymphoma. Excluding lymphomatous cases resulted in a decreased false negativity rate.

The present study identified 66 patients who were diagnosed with malignant pathology as a consequence of ELB. Of the total number of patients, only 9 were determined to have a benign diagnosis following FNAB. In the remaining 57 patients, the results of FNAB were interpreted as non-diagnostic and suspicious. The final pathology of eight patients with a benign FNAB result was Non-Hodgkin's Lymphoma, while the final pathology of one patient whose ELB result was reported as metastasis was interpreted as benign. In accordance with the results of this study and the existing literature, it can be concluded that, in addition to the high rate of false negativity of FNAB, particularly in cases of lymphoproliferative malignancies, a larger sample size is required for the typing of this disease. Therefore, ELB should be preferred as the gold standard in this group of patients.

In our study, metastatic lymph node diagnosis was reported in 7.3% (n=10) of the patients. In the study conducted by Metin et al.,[12] the incidence rate was 14.2% in patients under 40 years of age. In contrast, the rate doubled in patients over 40 years of age, and lymph nodes in the fourth and fifth neck regions were identified as a significant risk factor.

In considering the aetiology of infectious LAP, the prevalence of tuberculosis, which represents the most striking pathology, is observed to vary between countries and ethnic groups. In the present study, tuberculosis was observed in 11.7% (n=16) of the patients. This rate is higher

in developing countries, reaching a prevalence of 45.45%.[13] Conversely, the prevalence of tuberculosis in developed countries is reported to range between 1.9 and 4.5% (2, 6). In our study, 13 of the FNAB results of patients with a final pathology result of tuberculosis were interpreted as suspicious, while three were interpreted as non-diagnostic. Thus, FNAB demonstrates a lower false-negative rate in cases of tuberculosis compared to lymphoproliferative conditions. Among other infectious causes, 1.5% (n=2) Epstein-Barr virus, 2.2% (n=3) cat scratch and 0.7% (n=1) toxoplasma were observed in our study. These rates were similar to the results of Ozkan et al.[14]

This study has several limitations. Firstly, retrospective and single-centre design of the study is a key limitation, as it restricts the generalisability of the findings. It is recommended that future research adopt a multi-centre approach in order to enhance the external validity and broader applicability of the results. Consequently, the participants included in this study were selected based on specific criteria, which may have resulted in a bias towards malignancy and potentially influenced the outcomes. Additionally, some FNAB procedures were performed at external centers, which limited standardization. As both ultrasonography and FNAB are operator-dependent, performing them and interpreting the results by the same experienced clinician is recommended to reduce variability and enhance diagnostic accuracy. This study investigated the comparative outcomes of FNAB and excisional biopsy. A more comprehensive assessment of the patient's characteristics, clinical features and comorbidities would enhance the validity of the findings. Future research should include larger, prospective studies to yield more definitive conclusions.

Conclusion

Cervical lymphadenopathy (LAP) is a common pathology at all ages. However, in cases of cervical LAP over 40 years of age, the possibility of malignancy increases significantly. FNAB has limited sensitivity in diagnosing lymphoproliferative diseases and in cases accompanied by clinical suspicion, the direct ELB should be preffered to obtain sufficient tissue for histological subtyping. It should be noted that FNAB has a relatively high false-negative rate, particularly in the diagnosis and classification of lymphoma. FNAB demonstrates high diagnostic accuracy for metastatic carsinoma, especially when combined with ultrasonographic evaluation. İn patient with risk factors for metastatic disease, FNAB should be the initial diagnostic approach. In cases of infectious etiologies, such as tuberculosis, FNAB may be adequate. However, in cases where there is persistent concern, histopathological confirmation through excision is recommended.The selection of the optimal modality, between FNAB and ELB, must be made by a multidisciplinary team comprising radiologists, pathologists and clinicians to ensure that clinical, radiological and cytological data are integrated for the optimum patient management.

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Original Research

The Role of Preoperative CHA2DS2-VASc Score in Predicting Late Saphenous Vein Graft Failure in Non-STEMI Patients with Prior Coronary Artery Bypass Grafting: A Retrospective Study

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Abstract

Objectives: Despite the prevalence of saphenous vein graft (SVG) failure following coronary artery bypass graft (CABG) surgery, SVGs continue to be widely used. This study aimed to investigate the value of the CHA2DS2-VASc score, originally developed for predicting thromboembolic events in atrial fibrillation, in predicting SVG failure post-CABG.

Methods: This retrospective study analyzed data from 526 patients with a history of CABG who presented with non-ST-elevation myocardial infarction between January 2017 and April 2024. SVG failure was defined as exhibiting stenosis of 70% or greater, or complete occlusion. Preoperative CHA2DS2-VASc scores were calculated for each patient. Multivariable analysis was conducted to identify independent predictors of SVG failure.

Results: Among the 526 patients, 242 (46%) experienced SVG failure. Patients with SVG failure exhibited higher CHA2DS2-VASc scores. Multivariable analysis identified the CHA2DS2-VASc score (OR: 2.203, 95% CI: 1.672-2.902, p<0.001), time interval after CABG (OR: 1.167, 95% CI: 1.081-1.259, p<0.001), and number of SVGs (OR: 2.378, 95% CI: 1.745-3.241, p<0.001) as independent predictors of SVG failure. Of those parameters, the CHA2DS2-VASc score demonstrated a higher AUC value (AUC=0.796, AUC=0.724, AUC=0.641, respectively).

Conclusion: Pre-operative CHA2DS2-VASc score may be predictive of late SVG failure after CABG.

Keywords: Cha2ds2-vasc score, coronary angiography, coronary artery bypass grafting, non-st elevation myocardial infarction, saphenous vein graft failure

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In the treatment with patients of coronary artery disease (CAD), coronary artery bypass grafting (CABG) remains essential despite improvements in percutaneous coronary intervention (PCI).[1,2] Regardless of the presence of diabetes mellitus (DM), the current European guidelines prefer CABG over PCI in a number of coronary syndromes, including left main disease and three-vessel CAD with an intermediate to high SYNTAX score (Level 1, Class A).[3,4] The great saphenous vein is still often used in CABG because of its length and accessibility, even though arterial conduits—particu-

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larly the left internal mammary artery (LIMA)—have shown better and more resilient graft results than the saphenous vein graft (SVG).[5] Worldwide, up to 95% of patients have CABG with at least one SVG in addition to the LIMA.[6] The reported patency rates for SVGs vary widely: 11-41% failure within less than 3 years, 19-33% failure within 5 to 10 years, and 39-61% failure at follow-ups exceeding 10 years.[5] SVGs are prone to progressive degeneration over time, displaying accelerated atherosclerosis even if they maintain patency. SVGs develop neointimal hyperplasia and foamy macrophages during the first year following anastomosis to the arterial system, which leads to stenotic lesions with enlarging necrotic cores.[7] This results in a high incidence of ischemia-driven events, distal embolization, and occlusive pathology. Therefore, it seems important to identify factors that contribute to graft failure in patients treated with SVG and to identify factors that predict graft failure.

A simple risk assessment method for determining the chance of stroke or thromboembolic events in people with non-valvular atrial fibrillation (AF) is the CHA2DS2-VASc score. This score method considers a number of variables, such as gender, age, diabetes mellitus, vascular disease, congestive heart failure (HF), hypertension (HT), and previous stroke history.[8] According to recent research, the CHA2DS2-VASc score may be used to forecast the severity and outcome of acute coronary syndrome.[9,10] Additionally, a study found that in patients receiving elective PCI with a drug-eluting stent, the CHA2DS2-VASc score was linked to de-novo coronary stenosis.[11] However, there are limited studies regarding the ability of this scoring system to predict SV failure in patients undergoing CABG. In order to evaluate the association between preoperative CHA2DS2-VASc score and SVG failure in patients undergoing CABG, we carried out a retrospective analysis.

Methods

Study Design and Population

Patients with a history of CABG who underwent coronary angiography after being diagnosed with non-ST-elevation myocardial infarction (NSTEMI) at a tertiary healthcare facility between January 2017 and April 2024 were included in this retrospective single-center analysis. Following the application of inclusion and exclusion criteria, 526 of the 785 patients who were initially under consideration were added to the study. The study cohort was stratified into two subgroups (SVG failure group and SVG patency group) based on the presence of atherosclerotic SVG failure, confirmed by angiography. Patients with a history of CABG with full arterial conduits, patients within the first year following CABG, patients for whom the preoperative CHA2DS2-VASc score could not be determined due to insufficient data, and patients with severe comorbidities such as advanced lung and kidney disease or cancers that were expected to cause death during the 6-month follow-up period were all excluded.

This study was approved by the Kartal Kosuyolu Research and Education Hospital Clinical Research Ethics Committee and followed the Declaration of Helsinki's guidelines. Participants' formal informed permission was acquired.

Data Collection and Determination of the CHA2DS2-VASc Score

Clinical characteristics and laboratory parameters of the patients before CABG were retrieved from the hospital's electronic health records and national database. Demographic information including age and gender, as well as data on HT, hyperlipidemia, and DM, HF, and stroke or transient ischemic attack (TIA) history were obtained. Lastly, each patient's pre-operative CHA2DS2-VASc score was calculated, with 1 point awarded for HT, DM, and HF, and 2 points for age ≥ 75 years and a history of stroke or TIA.[8]

Coronary Angiographic Evaluation

Coronary angiography was performed via the femoral artery. Intravenous heparin was administered to all patients in accordance with current guidelines.[3] Selective injections were administered to the LIMA and each aortic anastomosis. An aortic root angiography was performed in situations where graft or stump injection was unable to determine the SVG's condition. Diverse projections were employed to ensure comprehensive coverage of arterial grafts, coronary arteries, and SVGs, enabling subsequent quantitative analysis. Two experienced cardiologists independently evaluated SVG patency by meticulously analyzing coronary angiographic images. A graft was classified as failed if it exhibited stenosis of 70% or greater, or if it was entirely occluded. On the other hand, if a graft displayed less than 70% stenosis and the complete graft course could be seen, it was deemed patent.[12]

Statistical Analysis

While categorical data were presented as absolute and percentage values, continuous research data were presented as mean and standard deviation values. Pearson's chi-squared or Fisher's exact test was used to compare categorical data groups, while the independent samples t-test and Mann-Whitney U test were used to compare independent continuous data groups. The independent predictors of the dependent variable (SVG failure) were identified using crude univariate and adjusted multivariable regression analysis. The odds ratio (OR) was used to describe the

model's coefficients, and 95% was the confidence interval (CI). Based on identifying the ideal cutoff value for SVG failure predictions, the receiver operating characteristic (ROC) curve analysis was utilized to elucidate the connections between the factors under consideration and SVG failure. Statistical significance was defined as 2-tailed probability (p) values less than 0.05 for all statistical analyses. Jamovi and R 4.01 software (Vienna, Austria) with the "ggplot," "Hmisc," and "rms" packages were used for all statistical analyses.

Results

The study population consisted of 526 patients, with 242 (46%) patients with SVG failure versus 284 (54%) patients with SVG patency. Based on SVG failure, Table 1 displayed the research population's demographic and clinical characteristics. In the SVG failure group, the proportion of male patients was considerably lower than in the SVG patency group (73.1% vs. 82.4%, p=0.01). HT, DM, CKD, cerebrovascular disease and AF were more common in patients with SVG failure than patients with SVG patency (p<0.001, p<0.001, p<0.001, p=0.005, p=0.024, respectively). In addition, patients with SVG failure had substantially higher CHA2DS2-VASc scores, the number of SVGs, and the time interval following CABG than patients with SVG patency (p<0.001, for all). Furthermore, patients with SVG failure had lower ejection fractions (EF) and statin usage in contrast to another group (p<0.001, p=0.017, respectively). A box plot demonstrating the distribution of CHA2DS2-VASc values in patients with SVG failure and with SVG patency was presented in Figure 1. Table 2 presents comparisons of relevant laboratory parameters based on the SVG failure. White blood cell and hemoglobin levels were significantly lower among the patients with SVG failure (p=0.03, p=0.031, respectively). However, those with SVG failure had noticeably greater triglyceride levels (p=0.031).

The predictors associated with the risk of SVG failure were determined through a multivariable logistic regression analysis, as outlined in Table 3. The selection of covariates is based on clinical judgement, comorbidities, and statistically significant variables in univariable analysis. This model

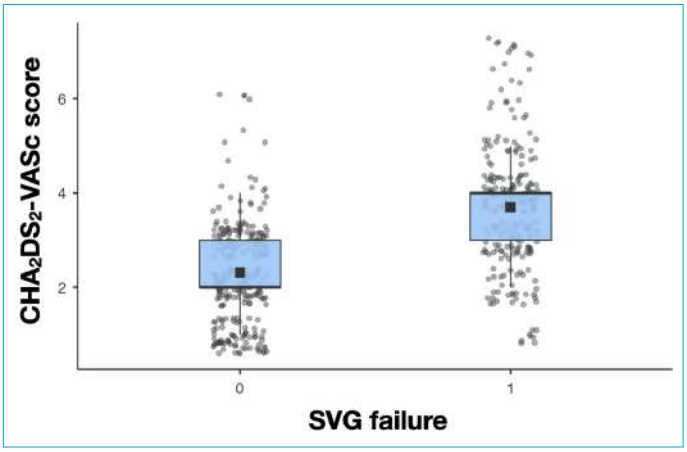

Figure 1. Box plot demonstrating the distribution of CHA2DS2-VASc values in patients with SVG failure and with SVG patency.

Table 1. Demographic and clinical characteristics of study patients based on SVG failure

Variables	Patients with SVG failure n=242 (46%)	Patients with SVG patency n=284 (54.0%)	p
Age (years)	67±9.24	65.5±8.74	0.061
Gender (male), n (%)	177 (73.1)	234 (82.4)	**0.01**
HT, n (%)	220 (91.7)	210 (73.9)	**<0.001**
DM, n (%)	128 (52.9)	92 (32.4)	**<0.001**
CKD, n (%)	56 (23.1)	34 (12)	**<0.001**
Cerebrovascular Disease, n (%)	28 (11.6)	14 (4.9)	**0.005**
EF (%)	55 (40-65)	55 (55-65)	**<0.001**
Atriyal fibrillation, n (%)	29 (12)	18 (6.3)	**0.024**
CHA2DS2-VASc score	4 (3-4)	2 (2-3)	**<0.001**
Time interval after CABG (year)	7 (5-9)	4 (2-6)	**<0.001**
The number of SVGs	3 (2-3)	2 (2-3)	**<0.001**
Beta-blocker usage, n (%)	228 (94.2)	266 (94.3)	0.956
ACEi usage, n (%)	158 (65.8)	181 (63.7)	0.616
Oral anti-diabetic usage, n (%)	61 (25.6)	62 (21.8)	0.308
Insulin usage, n (%)	25 (10.4)	19 (6.7)	0.125
Statin usage, n (%)	168 (69.4)	223 (78.5)	**0.017**

ACEi: angiotensin converting enzyme inhibitors; CABG: coronary artery bypass grafting surgery; SVGs: saphenous vein grafts; HT: hypertension; DM: diabetes mellitus; CKD: chronic kidney disease; EF: ejection fraction.

Table 2. Comparison of laboratory findings of the groups based on SVG failure

Variables	Patients with SVG failure n=218 (44%)	Patients with SVG patency n=278 (56.0%)	p
WBC (10^3/μL)	7.75 (5.80-10.37)	8.90 (6.60-10.20)	**0.03**
Hemoglobin (g/dL)	13.50 (12.20-14.20)	13.65 (12.60-14.80)	**0.031**
Platelet (10^3/μL)	240 (193-267)	227.5 (188-280)	0.823
Total Cholesterol (mg/dL)	184.2 (158.8-210.8)	189 (157.75-214.60)	0.869
Triglyceride (mg/dL)	158 (131.25-217)	145 (114-237)	**0.031**
HDL-C (mg/dL)	41 (38-44)	41 (37-49)	0.490
LDL-C (mg/dL)	107 (85-135)	108 (82-138)	0.989
eGFR (ml/min/1.73 m^2)	71.1 (38.3-105)	77 (65.8-88.2)	0.089
Creatinine (mg/dL)	1.05 (0.75-1.63)	0.98 (0.88-1.16)	0.185
Uric acid (mg/dL)	5.8 (5.4-6.7)	5.7 (5.4-6.5)	0.856
CRP (mg/L)	10 (4-35.5)	9.5 (3-40)	0.288
Albumin (g/dL)	4.0 (3.80-4.10)	3.9 (3.60-4.30)	0.413

CRP: C reactive protein; eGFR: estimated glomerular filtration rate; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein; WBC: white blood cell; SVG: saphenous vein graft.

Table 3. Multivariable analysis for prediction of SVG failure

Variables	Multivariable analysis			
	p	OR	95% Confidence Interval (CI)	
			Lower	Upper
Age (years)	0.072	0.974	0.947	1.002
Gender (male)	0.165	1.550	0.835	2.876
CHA2DS2-VASc score	**<0.001**	2.203	1.672	2.902
Time interval after CABG (year)	**<0.001**	1.167	1.081	1.259
The number of SVGs	**<0.001**	2.378	1.745	3.241
CKD	0.530	1.258	0.615	2.572
Statin usage	**0.003**	0.432	0.248	0.751
EF (%)	0.263	0.986	0.961	1.011
Atrial fibrillation	0.125	0.516	0.221	1.201
Hemoglobin	0.142	0.883	0.748	1.042

CKD: chronic kidney disease; CABG: coronary artery bypass grafting surgery; SVG: saphenous vein graft; CRP; EF, ejection fraction; OR: odds ratio; CI: confidence interval.

included covariates such as age, gender (male), CHA2DS2-VASc score, time interval after CABG, the number of SVGs, CKD, statin usage, EF, AF, and hemoglobin. In this model, statin usage, CHA2DS2-VASc score, time interval after CABG, and the number of SVG were identified as independent predictors of SVG failure (OR: 0.432, 95% CI: 0.248-0.751, p=0.003; OR: 2.203, 95% CI: 1.672-2.902, p<0.001; OR: 1.167, 95% CI: 1.081-1.259, p<0.001; OR: 2.378, 95% CI: 1.745-3.241, p<0.001; respectively). The graphs showing the relationships between the probability of SVG failure and CHA2DS2-VASc score, time interval after CABG, and the number of SVGs were demonstrated in Figure 2. Additionally, the ROC curves were constructed for CHA2DS2-VASc score, time interval after CABG, and the number of SVGs to determine the predictive values for SVG failure in Figure 3. In the ROC analysis, the CHA2DS2-VASc score exhibited an area under the curve (AUC) of 0.796, with a sensitivity of 54.96% and a specificity of 91.55% (Fig. 3). Furthermore, it had a higher AUC value compared to the time interval after CABG and the number of SVGs (AUC: 0.796 vs. AUC: 0.724 vs. AUC: 0.641, respectively), indicating its superior predictive performance. In addition, sensitivity, specificity, positive predictive value, negative predictive value and AUC values of these parameters were demonstrated in Table 4.

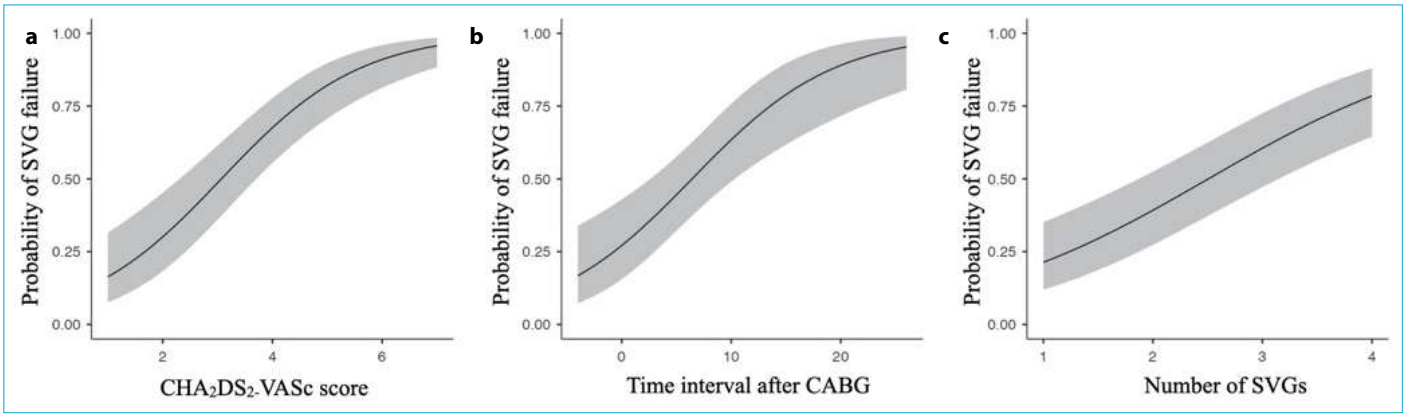

Figure 2. The marginal mean graphs showing the relationship between the probability of SVG failure and CHA2DS2-VASc score **(a)**, time interval after CABG **(b)**, and number of SVG **(c)**.

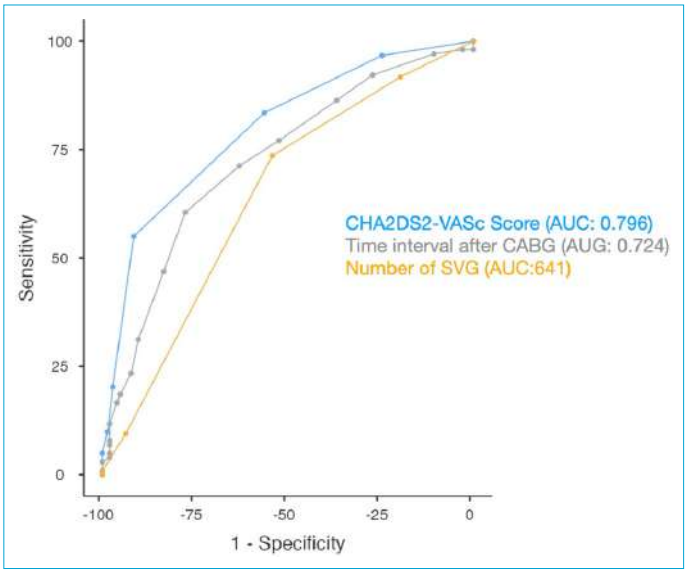

Figure 3. Receiver operating characteristic curves for CHA2DS2-VASc score (blue), time interval after CABG (gray) and number of SVG (yellow) to predict the presence of SVG failure. (AUC, area under the curve; CABG, coronary artery bypass graft; SVG, saphenous vein graft).

Discussion

In this retrospective analysis, we investigated the relationship between the preoperative CHA2DS2-VASc score and the incidence of late SVG failure in patients with NSTEMI who had previously had CABG. According to our research, the CHA2DS2-VASc score was an independent predictor of late SVG failure, as were the number of SVGs, the duration after CABG, and the usage of statins. Interestingly, we found that the CHA2DS2-VASc score had more predictive ability than the other measures evaluated.

SVG failure remains one of the most important problems restricting the advantages of CABG, even if it is still the preferred therapy for left main coronary artery and multivessel disease with an intermediate to high SYNTAX score.[13] However, the use of SVGs in the CABG procedure is still very common. There are three stages of post-CABG graft failure: early (less than one month), intermediate (one month to one year), and late (more than one year). These stages are linked to unfavorable clinical outcomes including mortality, non-fatal myocardial infarction, and the need for recurrent revascularization.[14] Our study did not investigate early graft failure commonly observed at the anastomosis site, which is often associated with technical factors, endothelial damage, and thrombosis, nor did it examine intermediate SVG failure, which is linked to neointimal hyperplasia.[14] On the other hand, atherosclerosis has been blamed in the etiology of late graft failure. Hence, risk factors related to atherosclerosis, such as age, race, gender, hypercholesterolemia, DM, HT, and CKD may contribute to late SVG dysfunction.[14]

Table 4. Assessment of parameters for predicting SVG failure: Sensitivity, specificity, predictive values, and AUC

Parameters	Cut-off value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC
CHA2DS2-VASc score	4	54.96	91.55	84.71	70.46	0.796
Time interval after CABG (year)	7	60.49	77.67	72.94	66.39	0.724
Number of SVG	3	73.55	54.23	57.70	70.64	0.641

PPV: Positive predictive value; NPV: Negative predictive value; AUC: Area under the curve; CABG: Coronary artery bypass grafting surgery; SVG: Saphenous vein graft.

The CHA2DS2-VASc score is a scoring tool that was first used in clinical practice to assess the risk of stroke or systemic thromboembolism in patients with atrial fibrillation. Previous study has demonstrated that the CHA2DS2-VASc score, which includes conventional atherosclerosis risk factors, can predict atherosclerotic diseases and be associated with their prognosis.[9–11,15] Additionally, Huan et al.[16] showed that in CAD patients, the CHA2DS2-VASc score predicts death. However, there are still few studies showing a relationship between the CHA2DS2-VASc score and late SVG failure, which has been connected to atherosclerosis.[17,18] In the study by Yarlioglues et al.,[18] which was similar to ours, only patients with stable angina were included, and SVG stenosis of 50% or more was defined as SVG failure. In addition, the study by Tasbulak et al.,[17] also similar to ours, included patients with both stable angina pectoris and ACS, whereas our study included only NSTEMI patients. Like other studies, ours clarifies the relationship between the CHA2DS2-VASc score and late SVG failure. Moreover, by encompassing a larger patient cohort compared to existing studies, our investigation broadens the scope of inquiry in this domain.

One of the most important factors predicting SVG failure is the age of the graft.[5,19] As the time interval after CABG increases, SVG failure also increases. Kulik et al.[20] demonstrated that in patients with LDL-C levels <100 mg/dL, the patency rate of SVG was higher in the first year. Additionally, the Post CABG Trial Investigators revealed that a higher dose of lovastatin was associated with less progression of SVG atherosclerosis and a lower incidence of new SVG occlusions.[21] Similarly, we discovered that the number of SVG, statin usage, and the duration following CABG were independent predictors of SVG failure. Furthermore, the CHA2DS2-VASc score in our research had a better predictive value than the period after the SVG count and CABG.

To sum up, the CHA2DS2-VASc score might be a useful instrument for determining the likelihood of late SVG complications. Particularly in patients with high CHA2DS2-VASc scores who are referred for CABG, the consideration of arterial grafts instead of SVGs could be contemplated. However, further research is needed for a better understanding of this relationship and its translation into clinical practice.

Study Limitations

There are some limitations to this study. Firstly, a retrospective design was used in the data collection process; hence there may be potential information gaps that could affect our results. Secondly, our study was conducted at a single center and had a small patient cohort, limiting the generalizability of our findings. Finally, more extensive and thorough research is required to assess the impact of additional possible clinical factors.

Conclusion

The usefulness of this score as a predictor for SVG failure has been highlighted by this study, which showed a link between the CHA2DS2-VASc scoring system and SVG failure in patients following CABG.

Disclosures

Ethics Committee Approval: The Clinical Research Ethics Committee of Kartal Kosuyolu Research and Education Hospital granted approval for this study. (date: 02/07/2024, number: 2024/12/855).

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Original Research

ChatGPT's Role in Coronary Artery Bypass Graft Information: A Critical Assessment

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Abstract

Objectives: This research evaluates the accuracy and reliability of ChatGPT's responses to inquiries concerning coronary artery bypass graft (CABG) surgery.

Methods: Between December 1, 2024, and December 15, 2024, two sets of questions were used to assess ChatGPT's performance: (1) a list of frequently asked questions (FAQs) sourced from official cardiovascular surgery websites, professional healthcare platforms, and social media, and (2) a list of scientific questions derived from the 2021 American Association for Thoracic Surgery (AATS) Guidelines for CABG in patients with ischemic cardiomyopathy and heart failure. Responses were evaluated using the modified DISCERN scoring system. To test reproducibility, each question was asked twice on separate computers within the same day. Two experienced cardiovascular surgeons independently scored the responses, and any disagreements were resolved through discussion.

Results: A total of 107 FAQs were assessed, of which 88 met the inclusion criteria. Based on the modified DISCERN scale, 71 responses (80.7%) received a score of 5, while 9 responses (10.2%) were rated as 4. The highest accuracy was observed in the preoperative preparation category, where all responses achieved a perfect score. Regarding scientific questions derived from the AATS Guidelines, 15 out of 20 (75.0%) were answered thoroughly and satisfactorily. The reproducibility rate was 92.0% for FAQs and 90.0% for guideline-based questions.

Conclusion: This study is the first to demonstrate that ChatGPT provides highly accurate and dependable responses regarding CABG surgery, particularly for frequently asked questions. Although performance declines slightly when addressing scientific questions based on guidelines, the reproducibility rate remains high. These findings indicate that AI-driven tools like ChatGPT could play a valuable role in patient education and enhancing public awareness about CABG surgery.

Keywords: Artificial intelligence, CABG, ChatGPT, DISCERN score

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Coronary artery bypass graft (CABG) surgery is one of the most commonly performed surgical procedures in cardiovascular medicine, primarily used to restore blood flow to the heart muscle in patients with severe coronary artery disease (CAD).[1] CABG involves using grafts, typically harvested from the saphenous vein or internal mammary artery, to bypass occluded coronary arteries, thereby improving myocardial perfusion and reducing ischemic symptoms. Despite its widespread application, the actual long-term outcomes and post-operative complications of

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CABG vary among patients, influenced by factors such as comorbidities, graft patency, and adherence to secondary prevention measures.[2] Given the increasing burden of CAD worldwide, enhancing patient awareness and compliance with post-CABG management strategies is crucial in reducing morbidity, mortality, and healthcare costs.[3] In the age of communication, many people use internet resources to get information about their symptoms and diseases including YouTube, Instagram, and artificial intelligence (AI) applications.[4]

ChatGPT is an AI application developed by OpenAI (San Francisco, California, United States of America), which behaves as multi-language chatbot. ChatGPT has been introduced to every part of life and business, including professional health services.[5] However, the efficiency and safety of AI in professional healthcare services is still under debate, and numerous studies are being performed to understand the capability of ChatGPT in medicine. Cakır and colleagues evaluated the knowledge of ChatGPT about urinary system stone diseases. The authors found that ChatGPT fully and adequately answered 19 out of 20 questions.[6] In another study by Cinar which analyzed ChatGPT answers about scoliosis showed that ChatGPT provided satisfactory answers to questions asked by the public.[7]

Even though numerous studies were performed about the capacity and use of ChatGPT in the field of medicine, no study has evaluated the performance of ChatGPT in CABG. In this study, the aim was to analyze the accuracy and proficiency of ChatGPT answers about CABG.

Methods

The study was conducted between December 1, 2024 and December 15, 2024. Two question lists were created according to the study design. This study did not involve any human participants or patient data; therefore, ethical approval was not required. The study was conducted in accordance with the principles of the Declaration of Helsinki. First, a frequently asked questions (FAQs) list was created by researching internet resources (official websites of cardiovascular surgery departments, charities that provide information about cardiovascular diseases, and websites of healthcare professionals working in the field of cardiovascular surgery) frequently used by patients. Moreover, hashtags related to CABG were searched in popular social media applications including YouTube, Instagram, and Facebook, etc. and an attempt was made to identify the questions frequently asked by society about CABG. Questions based on scientific data were prepared according to 2021: The American Association for Thoracic Surgery Expert Consensus Document: Coronary artery bypass grafting in patients with ischemic cardiomyopathy and heart failure. Scientific questions were grouped in another file. When preparing questions, questions associated with personal health problems and requiring personal responses, questions that contain advertising or aim to direct patients to a specific person or healthcare institution, questions with unrealistic nature, repetitive inquiries, and grammatically incorrect questions were excluded. Questions (n=88) on the FAQ list was divided into subgroups as preoperative preparation (n=16), surgery process (n=18), postoperative period (n=18), risks and complications (n=20), and daily life - long term results (n=16). Inquiries based on 2021 AATS Guideline: Coronary artery bypass grafting in patients with ischemic cardiomyopathy and heart failure included 20 scientific questions.

All FAQs and scientific questions related with CABG were answered by the free version of ChatGPT on December 10, 2024. The ChatGPT responses were scored by two experienced cardiovascular surgeon with minimum ten-year experience. The modified DISCERN scoring system was used when assigning scores to ChatGPT answers. The modified DISCERN form was developed to analyze the accuracy and reliability of medical contents, especially videos and written content. Criteria in the modified DISCERN scale can be used for the evaluation of the accuracy and proficiency of written sources. The scale includes five questions and each question is answered with yes (one point) or no (zero point). Five points indicate highest quality of ChatGPT answers [8]. When assessing the accuracy and proficiency of ChatGPT answers to scientific questions, 2021 AATS Guideline were taken into account. Each ChatGPT answer was rated by the cardiovascular surgeon separately, and, if ChatGPT' responses scored differently, the response was re-assessed, and a new score was obtained by joint decision of the two cardiovascular surgeon.

The repeatability of ChatGPT answers was evaluated by asking the same question to ChatGPT twice, on the same day, using different computers. The reproducibility of answers was accepted as positive if ChatGPT answers had the same score twice. Two ChatGPT responses with different scores according to modified DISCERN score were considered negative with regard to reproducibility. Since no patient data was used, ethics committee approval was not obtained for the present study.

Statistical Analysis

Statistical analysis was done using Excel Version 17 (Microsoft Corporation, USA). The questions were assessed separately as FAQ and questions based on 2021 AATS Guideline. The modified DISCERN scores for the ChatGPT responses are presented as percentages.

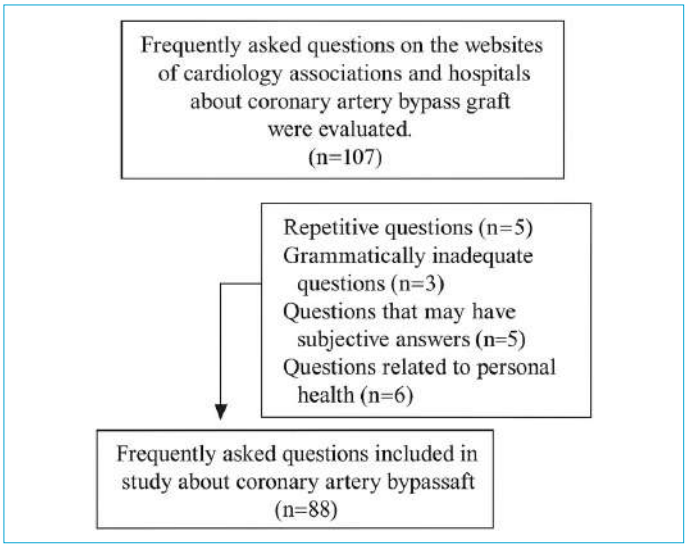

Figure 1. Flowchart of the selection process for frequently asked questions about coronary artery bypass graft (CABG) surgery.

Results

In total, 107 FAQs were evaluated in the study, and 88 questions met the study inclusion criteria. Five repetitive inquiries, 3 questions with significant grammatical errors, 5 questions requiring subjective answers, and 6 questions associated with personal health condition(s) were excluded from the study. The flowchart of the present study is documented in Figure 1.

According to the modified DISCERN scale, 71 (80.7%) of ChatGPT answers to FAQs about CABG scored 5, and 9 (10.2%) ChatGPT answers had scores of 4. In addition, 7 (7.9%) and 1 (1.1%) ChatGPT answers to FAQs about CABG obtained score 3 and score 2, respectively. None of ChatGPT responses to FAQs about CABG had score 1. When ChatGPT answers to FAQs subgroups are evaluated, ChatGPT achieved the highest accuracy rates in the preoperative preparation subgroup, and all ChatGPT answers to preoperative preperation questions scored 5 according to the modified DISCERN scale. A total 14 of 18 (77.8%) ChatGPT answers to surgery process FAQs, 13 of 18 (72.2%) ChatGPT answers to postoperative period FAQs, and 16 of 20 (80.0%) ChatGPT answers to risks and complications FAQs scored 5. Moreover, 15 of 20 (75.0%) scientific questions according to 2021 AATS Guideline were completely and satisfactorily answered by ChatGPT (Score 5). The modified DISCERN scores for ChatGPT answers to FAQs are summarized in Table 1.

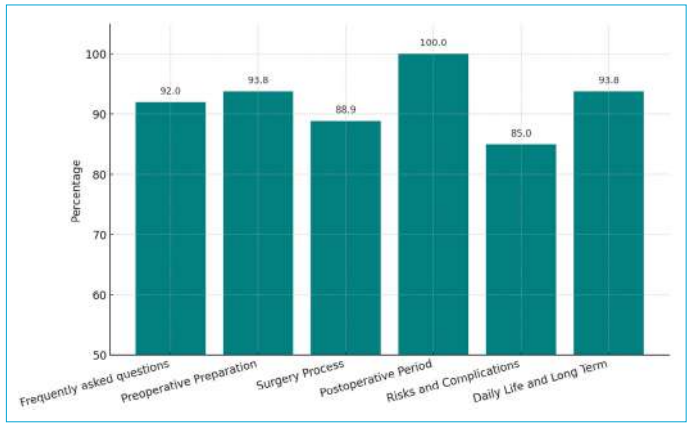

Figure 2. Distribution of selected CABG-related questions by category.

Reproducibility ratio was 92.0% for FAQs and 90.0% for 2021 AATS Guideline. Repeatability was highest (100%) for ChatGPT answers to postoperative period questions, and lowest (85.0%) for ChatGPT answers to risks and complications questions (Fig. 2).

Discussion

Due to the opportunities provided by AI, AI is increasingly used in our daily lives and professions. However, the effectiveness and reliability of AI, as well as its adequacy and impact on human life, are among frequently discussed topics.[9] Some professional health providers suggest that the introduction of AI in the medical field has increased the success of screening tests, enabled earlier disease diagnosis, reduced unnecessary blood test analysis and imaging modalities, and ensured more adequate follow-up schemes. However, the capability of ChatGPT has not been analyzed in many medical disciplines. Thus, our aim was to assess the performance of ChatGPT about CABG, which

Table 1. Modified DISCERN scores for responses by ChatGPT to questions related to coronary artery bypass graft

	Score 5, n (%)	Score 4, n (%)	Score 3, n (%)	Score 2, n (%)	Score 1, n (%)
Frequently asked questions (n=88)	71 (80.7)	9 (10.2)	7 (7.9)	1 (1.1)	-
Preoperative Preparation (n=16)	16 (100)	-	-	-	-
Surgery Process (n=18)	14 (77.8)	2 (11.1)	2 (11.1)	-	-
Postoperative Period (n=18)	13 (72.2)	3 (16.7)	1 (5.5)	1 (5.5)	-
Risks and Complications (n=20)	16 (80.0)	2 (10.0)	2 (10.0)	-	-
Daily Life and Long Term (n=16)	12 (75.0)	2 (12.5)	2 (12.5)	-	-
Guideline (n=20)	15 (75.0)	2 (10.0)	1 (5.0)	1 (5.0)	1 (5.0)

is one of the most important surgeries in cardiovascular surgery practice. This study revealed that ChatGPT gave completely accurate and satisfactory answers for 80.7% of FAQs about CABG. Though the quality of ChatGPT answers decreased, ChatGPT correctly answered 75.0% of scientific questions based on 2021 AATS Guideline. Moreover, ChatGPT achieved satisfactory reproducibility rates in answers for both FAQs and guideline questions.

Internet sources are frequently used by patients and the public due to their easily accessible and free nature; however, numerous studies emphasized the insufficiency of web sources in medicine. Also, some authors demonstrated that countless sources contained misinformation about health. In a study by Alsyouf et al.,[10] which analyzed information quality about prostate cancer in social media, the ratio of misleading information was 30 times higher than accurate information about prostate cancer in social media. In another study, Sevgili and Baytaroglu investigated the quality of YouTube videos about CAD and COVID-19. They stated that despite high view ranking of YouTube videos, YouTube videos included false information about CAD and COVID-19.[11] Conversely, Caglar and colleagues used ChatGPT to answer questions related to pediatric urological disorders, and the authors concluded that ChatGPT gave completely accurate and satisfactory answers for more than nine of ten questions.[12] In another study by Bulck and Moons, they analyzed the performance of ChatGPT in answering questions related with CAD. The authors found that ChatGPT gave completely accurate and sufficient answers for more than 85% of questions.[13] In this study, the quality of ChatGPT answers to questions about CABG was analyzed according to the modified DISCERN scale for the first time. Our results demonstrated that more than eight out of ten FAQs related with CABG were answered completely accurately and sufficiently by ChatGPT. Accessing numerous sources and the ability to review these sources may result in this high accuracy and proficiency rate of ChatGPT in answering question about CABG.

Guidelines are scientific reports with the purpose of guiding decisions and defining criteria regarding diagnosis, treatment and follow-up for a specific disease. When preparing guidelines, authors use countless medical papers including reviews, original articles, meta-analysis, and case reports.[14] ChatGPT performance for questions involving intense medical information is a matter of curiosity. Antaki and colleagues analyzed the performance of ChatGPT in an ophthalmology resident exam, and ChatGPT received 55.8 points out of 100. Antaki and colleagues stated that ChatGPT exam points were comparable with mean exam scores of ophthalmology residents.[15] Similarly, Cinar demonstrated that the accuracy and sufficiency of ChatGPT answers significantly decreased when responding to scientific questions in comparison with answering FAQs about scoliosis.[7] In contrast, Caglar et al.[12] obtained excellent outcomes with ChatGPT while answering guideline-based inquiries about pediatric urological diseases. In our study, ChatGPT gave accurate and satisfactory answers for more than 15 of 20 questions based on 2021 AATS Guideline.

Although this is the first research to evaluate the capacity of ChatGPT answers about CABG, our study involves some limitations. In the present study, only the English language, which is the most common language on the web and in the academic field, was used. It was considered that evaluating more than one language would make the analysis difficult, and be confusing for readers. We believe that use of ChatGPT to answer questions about CABG in rarer languages could be discussed in further studies. Secondly, the present study was done in a certain time period, but information about CABG is continuously shared on the internet. Lastly, the quality of ChatGPT responses was analyzed by two cardiovascular surgeon, understandability of ChatGPT answers about CABG may be the subject of further studies.

Conclusion

In conclusion, for the first time, our findings revealed that ChatGPT accurately and satisfactorily answered both FAQs about CABG and questions based on 2021 AATS Guideline. In addition, the reproducibility rate of ChatGPT responses was sufficient for both FAQs and scientific questions about CABG. The findings of the present study suggest that introducing ChatGPT in cardiology practice will provide better information about CABG for patients and public.

Disclosures

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Original Research

Immediate Video-Assisted Thoracoscopic Surgery Versus Chest Tube Drainage in the First Episode of Primary Spontaneous Pneumothorax: A Comparative Study

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Abstract

Objectives: To compare the outcomes of the patients with primary spontaneous pneumothorax (PSP) treated by immediate video-assisted thoracoscopic surgery (VATS) and chest tube placement in the first episode.

Methods: Fifty patients aged between 18 and 40 years with PSP were grouped regarding the treatment modalities as G1 (patients undergoing chest tube placement, n=25) and G2 (patients undergoing immediate VATS, n=25). VATS procedure consisted of apical blebectomy and partial pleurectomy. Early outcomes (chest tube and hospital duration, and in-hospital complications) and late outcomes (recurrence rate after 10 years) were compared.

Results: In G2, the mean duration of surgery was 40.3±14.5 min. No conversion to thoracotomy was required. The rate of complication was insignificantly higher in G1 (p>0.05). Prolonged air leak was significantly common in G1 (p=0.03). In G2, the duration of chest tube and hospital stay were significantly lower (p=0.03 and p=0.05, respectively). After a follow-up of 10 years, a significantly higher recurrence rate was recorded in G1 (p=0.02). Recurrence was insignificantly higher in smokers (p>0.05), and mostly detected in older patients (p=0.03).

Conclusion: Immediate VATS in the first episode of PSP is an effective treatment to prevent recurrence in patients with PSP. VATS is safe with a lower rate of morbidity, and lower durations of chest tube and hospital stay compared to chest tube treatment.

Keywords: Chest tube, outcomes, primary spontaneous pneumothorax, recurrence, video-assisted thoracoscopic surgery

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Primary spontaneous pneumothorax (PSP) is a significant global problem, commonly affecting young people without clinically apparent lung diseases. The annual incidence rates of PSP are 18-20/100000 in men and 1.2-6/100000 in women.[1] Nowadays, four general approaches are used for the initial management of PSP, including (a) observation only, (b) oxygen supplementation, (c) drainage through needle aspiration or tube thoracostomy, and (d) immediate operation under video-assisted thoracoscopic surgery (VATS) or thoracotomy.[2] PSP usually resolves when non-surgical treatment modalities (mostly chest tube placement) are used.[3] The main concern after the initial treatment is the high rate of recurrence (25-43%).[4] Thus preventive surgical intervention, meaning immediate operation, is offered as an alternative approach to diminish that high recurrence rate. Several systematic studies investigated the role of early surgical intervention in the first attack of PSP and reported lower recurrence rates.[2,5,6]

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In this study we compared the early (in-hospital) and late (10 years of follow-up) outcomes of the patients with PSP treated by immediate VATS and chest tube placement.

Methods

This study was conducted at a research and training hospital and the Ethics Committee of Sisli Hamidiye Etfal Training and Research Hospital endorsed the study protocol (approval date and number: 11.06.2024-4439). The written informed consent from the enrolled patients was waived, and this study was conducted in accordance with the Declaration of Helsinki. The data of all patients diagnosed to have PSP were collected. Among them, patients with previous pneumothorax and chest surgery were excluded. Patients older than 40 years old were excluded to avoid bias from underlying comorbidity. Patients with known contraindications for general anesthesia and lacking the ability to understand the information and the consequences were also excluded. Patients with a small and asymptomatic pneumothorax that was treated by either observation only or oxygen supplementation were omitted from the study. Pneumothorax was defined as small based on the guidelines after chest X-rays.[7,8] Patients presenting with severe dyspnea necessitating urgent chest tube placement were also not included in the study. Only patients without visible bullous lesions in their computed tomography of the chest were selected. A total of 50 patients (aged between 18 and 40 years) with PSP from January 2010 to January 2014 were enrolled into the study. The patients were grouped regarding the treatment modalities as G1 (patients undergoing chest tube placement) and G2 (patients undergoing immediate VATS). Each group consisted of 25 patients. Each patient was informed about the treatment options in detail and asked to choose among the treatment modalities.

In G2, VATS is done within the first 24 hours after hospital admission. The VATS procedure was done with a camera port incision (6th intercostal space at anterior axillary line) and an access incision of 5 cm over the 4th intercostal space) and included the resection of the apical blebs using endostaplers, and an apical pleurectomy extending from the 4th rib level up to the apex of the pleural cavity anteriorly, laterally, and posteriorly. No pleurodesis agents (such as talc poudrage) or staple line coverage after bleb resection were used. A chest tube was placed from the camera port. In G1, the chest tube was placed at the 4th intercostal space in the anterior axillary line. In both groups chest tubes were connected to continuous suction, and each patient received similar post-procedural chest physiotherapy. Chest tubes were removed when there was no visible air leak along with a totally expanded lung on chest X-ray, and fluid output was less than 150 ml/day.

Early outcomes included chest tube and hospital duration, and complications during the in-hospital stay. Follow-up was done at the outpatient clinic every 3 months for the first 2 years, then yearly via phone calls or WhatsApp messages to the patients for up to 10 years. Recurrences and their managements were noted. Statistical analysis was performed using the IBM SPSS version 26.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean±standard deviation (SD), median (min-max), or number and frequency, where applicable. The independent t-test was used to compare two groups. A p-value of <0.05 was considered statistically significant.

Results

Table 1 demonstrates the demographic data of the patients. There was no significant difference between both groups ($p>0.05$). All patients were symptomatic and presented with shortness in breath and chest pain. The diagnosis of PSP was confirmed by chest X-rays and computed tomography of the chest in each patient. The computed tomography of the chest demonstrated no visible bullous lesions in any lungs, either on the right or left side. For patients in G2, the mean duration of surgery was 40.3±14.5 min. No conversion to thoracotomy was required.

Table 2 shows the in-hospital outcomes. The rates of complication were 24% in G1 and 8% in G2 ($p>0.05$). Morbidi-

Table 1. Demographic data in both groups

	G1 (chest tube group)	G2 (immediate VATS group)	P
Total number	25	25	
Males (%)	23 (92)	24 (96)	NS
Females (%)	2 (8)	1 (4)	NS
Mean age (years±SD)	26.7±4.8	26.4±5.0	NS
Mean BMI (kg/m^2±SD)	18.8±3.9	19.1±4.2	NS
Smokers (n, %)	14 (56)	19 (76)	NS
Laterality of PSP (right/left) (%)	60/40	48/52	NS

VATS: video-assisted thoracoscopic surgery; SD: standard deviation; BMI: body mass index; PSP: primary spontaneous pneumothorax; NS: not significant.

Table 2. Post-intervention findings

	G1 (chest tube group)	G2 (immediate VATS group)	P
In-hospital morbidity (n, %)	6 (24)	2 (8)	0.12
Duration of chest tube (days±SD)	5.7±3.2	4.4±1.8	0.03
Hospital stay (days±SD)	6.0±3.7	4.6±2.3	0.05

VATS: Video-assisted thoracoscopic surgery; SD: Standard deviation.

ties in G1 included prolonged air leak lasting more than 5 days in 5 patients and wound infection in 1 patient, whereas those in G2 included wound infection in 2 patients. Prolonged air leak was significantly higher in G1 (p=0.03). Two patients with prolonged air leaks necessitated a second chest tube placement. In G2 the duration of chest tube and hospital stay were significantly lower (p=0.03 and p=0.05, respectively). No mortality was recorded in either groups.

After a follow-up of 10 years, a significantly higher recurrence rate was recorded in G1 (6 patients, 24%) compared with that in G2 (0%) (p=0.02). Recurrences developed at 4, 8, 12, 14, 20, and 28 months after the treatment with a chest tube. Overall recurrence rates for one, two and three years were 12%, 20%, and 24%, respectively, in patients undergoing tube thoracostomy as the initial treatment. These patients underwent VATS resection and no further recurrence developed during the follow-up in any of them. Recurrent PSP was insignificantly higher in smokers (4/6 patients, 67%) (p>0.05). Patients with recurrent PSP were significantly older than those without recurrence (30.7±4.9 years versus 25.4±4.1 years, p=0.03).

Discussion

According to the guidelines, non-surgical treatments are the first-line management for the first PSP episode, and VATS is used for recurrent pneumothorax, prolonged air leak, or for people with at-risk occupations during the first period.[9,10] However, the most major problem following non-surgical treatment in the first episode is the high rate of recurrence (25-43%).[4,9] It is traditionally known that when surgery (either thoracotomy or VATS) is performed in the treatment of PSP, the rate of recurrence is as low as 0-3.6%.[11] Thus, it was proposed that performing immediate VATS during the first period of PSP might reduce the rate of recurrence.[3,4,6,12]

In an early study dated 1996, Schramel et al.[13] used immediate VATS in the case of first PSP episode and compared their results with patients undergoing non-surgical treatment. The authors demonstrated that VATS was more effective in terms of recurrence in the treatment of the first PSP episode, and concluded that from 1991 they treated all their PSP patients using VATS at their first episode. Torresini et al.[14] demonstrated that chest tube treatment at first episode of PSP had a recurrence rate of 22.8% in the first year. Olesen et al.[4] also reported that VATS should be the standard of care in the first presentation of PSP.

Chou et al.[15] demonstrated no recurrence in patients undergoing VATS blebectomy in the first episode of PSP after a follow-up period of 38 months. In our study, each patient completed a longer follow-up period (10 years). We detected no recurrence in patients undergoing VATS, while a highly significant recurrence (24%) was recorded in patients undergoing tube thoracostomy. This rate was in accordance with other studies reporting a recurrence rate of 20 to 50% in non-surgically treated patients.[16,17] It was also reported that recurrence in non-surgically treated patients tends to occur in the first year, especially in females, and tall and thin males with a higher incidence in smokers.[16,18] In our study 3 out of 6 patients presented with recurrent PSP in within the first year after tube thoracostomy treatment. We detected that recurrence was common in active smokers insignificantly (p>0.05), and older patients significantly (p<0.05).

Although it was reported that the usage of several agents for chemical pleurodesis following blebectomy/bullectomy and partial pleurectomy lowered the recurrence of PSP,[19] several studies demonstrated that intraoperative chemical pleurodesis offers no additional advantage to surgery in deterring recurrence for patients with PSP.[20,21] Another intraoperative strategy to reduce the recurrence rate is to cover the staple line with absorbable cellulose mesh and fibrin glue.[22] In our study no chemical pleurodesis agents (such as talc poudrage) or staple line coverage after bleb resection was used.

In our study, the mean durations of the chest tube and hospital stay were significantly lower in G2 (p<0.05). Although insignificant, the morbidity rate was lower in G2 (8% versus 24%). It was reported that compared to conservative treatment, VATS had lower complication rates, and shorter durations of chest tube and hospital stay.[12,23,24,25] Olesen et al.[4] grouped their 181 patients in terms of chest tube treatment versus VATS in the first episode of PSP. They concluded that hospital stay was lower in the VATS group. Besides, 13% and 42% of the patients undergoing chest tube treatment necessitated either a second chest tube placement or suction to fully expand the lung, respectively.

Another important point to consider while comparing immediate VATS and chest tube placement in the treatment of the first episode of PSP is the economic burden. It was reported that conservative treatment of PSP in the first episode yielded a higher total cost compared to VATS.[13,25,26] We did not investigate the cost of both treatment groups in our study.

Conclusion

We concluded that immediate VATS in the first episode of PSP is an effective treatment to prevent recurrence. VATS is safe with a lower rate of morbidity, and lower durations of chest tube and hospital stay compared to chest tube treatment. However, more well-designed randomized controlled trials are needed to strengthen the current evidence.

Disclosures

Ethics Committee Approval: The study protocol was approved by the Sisli Hamidiye Etfal Training and Research Hospital Clinical Research Ethics Committee (date: 17.12.2024, number: 4668).

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Original Research

Does Grafting Matter in Surgically Treated Calcaneal Fractures? A Retrospective Analysis

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Abstract

Objectives: The role of bone grafting in the surgical treatment of displaced intra-articular calcaneal fractures (DIACFs) remains controversial. Although bone grafts are commonly used to restore joint congruity and support anatomical reduction, recent evidence favors minimally invasive approaches that may eliminate the need for routine grafting. This study aimed to evaluate the impact of bone graft use on radiological parameters and functional outcomes in Sanders Type II, III, and IV calcaneal fractures treated surgically.

Methods: This retrospective cohort study included 115 patients who underwent open reduction and internal fixation (ORIF) for DIACFs between 2016 and 2022. Fractures were classified using the Sanders classification and subgrouped as grafted (+) or non-grafted (–). Böhler and Gissane angles and calcaneal height were measured at four time points. Functional outcomes were assessed using the American Orthopaedic Foot and Ankle Society (AOFAS) hindfoot score. Intergroup and intragroup comparisons were made using appropriate statistical methods.

Results: Of the 115 patients, 38 had Type II, 43 had Type III, and 34 had Type IV fractures. Demographics and follow-up durations were comparable across groups ($p>0.05$). Both grafted and non-grafted groups demonstrated significant postoperative improvements in radiological parameters ($p<0.05$), which gradually declined over time. No statistically significant intergroup differences were observed at any time point ($p>0.05$). AOFAS scores and superficial wound infection rates were also similar.

Conclusion: Bone grafting did not yield superior radiological or functional outcomes in Sanders Type II, III and IV DIACFs treated with ORIF. These findings support a selective approach to grafting, especially in cases with significant comminution or bone loss, and align with current trends favoring biologically friendly and minimally invasive techniques.

Keywords: Bone graft, calcaneus fracture, sanders classification

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Calcaneus fractures are among the most frequently encountered tarsal bone fractures in the foot, typically resulting from high-energy trauma.[1] These fractures, accounting for approximately 1% to 2% of all skeletal fractures, lead to significant morbidity.[2] Particularly, displaced intra-articular calcaneal fractures (DIACF) are complex injuries requiring anatomical reduction and stable fixation.[3]

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According to the Sanders classification, Type 2, Type 3, and Type 4 fractures are evaluated based on the degree of posterior subtalar joint facet involvement, and treatment approaches remain a subject of debate.[4] While conservative and surgical treatment options are discussed for Type 2 and 3 fractures, surgical intervention is generally unavoidable for Type 4 fractures due to their high comminution rate.[5] However, the necessity of graft usage and its impact on long-term clinical outcomes among these surgical options are yet to be clearly defined.[6] Furthermore, bone quality itself, which is independent of fracture morphology, may also influence radiological and functional outcomes.[7]

Current literature highlights the advantages of graft use in replacing bone loss and restoring joint congruity.[8] Conversely, some studies suggest that graft use may increase infection risk and surgical morbidity.[9] Recent advancements in minimally invasive techniques have reportedly reduced the need for grafting and accelerated postoperative healing.[10, 11] Moreover, recent systematic reviews have demonstrated that percutaneous and minimally invasive approaches can achieve comparable radiological and functional outcomes to traditional open techniques, while significantly lowering the rates of soft tissue complications and postoperative infections.[12, 13] While the question of the need for grafting in calcaneal fractures has been explored, our study uniquely analyzes a large cohort with granular subgroup analysis by Sanders type, offering a fresh perspective within the existing literature.

We hypothesized that there would be no significant difference in radiological and functional outcomes between patients treated with and without bone grafting in Sanders Type II, III, and IV intra-articular calcaneal fractures treated with open reduction and internal fixation. This study aims to evaluate the effects of graft use on radiological and functional outcomes in intra-articular calcaneal fractures and to compare these findings with current literature.

Methods

This retrospective study evaluated patients who underwent surgical treatment for intra-articular calcaneal fractures at our institution between 2016 and 2022. Patient records, including radiographic images (X-ray and computed tomography[14] and operative notes, were comprehensively reviewed. Fractures were classified according to the Sanders classification into Type II (Group A), Type III (Group B), and Type IV (Group C). Each group was further subdivided based on the use of bone grafts during surgery: grafted (+) and non-grafted (–) (Table 1). In our study, we used cancellous allografts for bone grafting.

A total of 141 patients were initially screened. Following the application of exclusion criteria and the removal of patients with incomplete follow-up data, 28 patients were excluded. Thus, 115 patients were included in the final analysis. Among them, 38 had Type II fractures (15 grafted, 23 non-grafted), 43 had Type III fractures (21 grafted, 22 non-grafted), and 34 had Type IV fractures (20 grafted, 14 non-grafted). Demographic characteristics, radiographic parameters, and the American Orthopaedic Foot and Ankle Society (AOFAS) Score[15] were evaluated and compared between grafted and non-grafted subgroups within each fracture type. Radiographic parameters such as Böhler and Gissane angles, as well as calcaneal height, were measured using standard lateral radiographs in accordance with previously described methods.[16, 17]

Inclusion Criteria

- Patients with unilateral, displaced intra-articular calcaneal fractures
- Closed fractures
- Age between 16 and 65 years
- Availability of preoperative CT and X-ray images, and postoperative lateral and axial radiographs of the calcaneus

Table 1. Demographic characteristics and clinical data of grafted and non-grafted patients according to Sanders classification.

	Tip II Graft (-)	Tip II Graft (+)	Tip III Graft (-)	Tip III Graft (+)	Tip IV Graft (-)	Tip IV Graft (+)
Age (Mean±SD)	39.8±10.7	36.6±9.0	40.8±9.2	39.1±11.8	37.6±10.7	39.5±10.9
p	0.198[m]		0.584[m]		0.843[m]	
Sex (Female) n	6	3	6	7	6	3
p	0.666[X²]		0.665[X²]		0.156[X²]	
Sex (Male) n	17	12	16	14	8	17
p	0.666[X²]		0.665[X²]		0.156[X²]	
Follow-up Time (Mean±SD)	42.6±20.4	47.4±20.5	40.8±19.6	47.9±22.2	27.4±11.3	31.1±11.3
p	0.419[m]		0.295[m]		0.188[m]	
AOFAS Score (Mean±SD)	79.1±13.2	78.9±14.0	72.3±8.0	74.8±7.7	60.9±11.3	57.1±12.7
p	0.846[m]		0.261[m]		0.435[m]	

AOFAS: American Orthopaedic Foot and Ankle Society; SD: standard deviation.

- Sanders Type II, III, or IV fractures
- Undergoing open reduction and internal fixation with plates and screws via the extensile lateral approach.[1]

Exclusion Criteria

- Open fractures (n=4)
- History of previous calcaneal surgery (n=3)
- Concomitant fractures of the foot or ankle (n=5)
- Follow-up period of less than 12 months (n=7)
- Incomplete radiological or clinical follow-up data (n=9)

A total of 28 patients were excluded based on the criteria above.

This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the relevant institutional review board on February 26, 2025, with approval number: 241, meeting number: 33.

Statistical Analysis

Descriptive statistics were presented as mean±standard deviation, median (minimum–maximum), frequency, and percentage, where appropriate. The distribution of variables was assessed using the Kolmogorov-Smirnov test. For comparisons between two independent groups with non-normally distributed quantitative data, the Mann-Whitney U test was used. The Wilcoxon signed-rank test was applied to evaluate changes in paired non-normally distributed quantitative data. The Chi-square test was used for the analysis of categorical variables. A p-value of <0.05 was considered statistically significant. All statistical analyses were performed using SPSS software version 22.0 (IBM Corp., Armonk, NY, USA).

For the evaluation of radiological changes across the four time points (preoperative, early postoperative, third postoperative month, and final follow-up), the Wilcoxon signed-rank test was applied for intragroup comparisons. This allowed the assessment of temporal changes within both grafted and non-grafted groups. Intergroup comparisons at each time point were performed using the Mann–Whitney U test. The corresponding results are presented in Tables 2, 3 and 4. Future research should consider reporting effect sizes and conf*0idence intervals to improve the understanding of clinical significance.

In this manuscript, ChatGPT (OpenAI, GPT-4o version) was used solely for language editing purposes. No artificial intelligence tools were involved in data analysis or scientific content generation.

Table 2. Böhler angle measurements at four time points and intergroup/intragroup comparisons in grafted and non-grafted subgroups across Sanders fracture types

	Group A (Sanders Tip 2)				Group B (Sanders Tip 3)				Group C (Sanders Tip 4)			
	Graft (-) Mean S.D.	Graft (+) Mean S.D.	p		Graft (-) Mean S.D.	Graft (+) Mean S.D.	p		Graft (-) Mean S.D.	Graft (+) Mean S.D.	p	
Böhler Angle					**Böhler Angle**				**Böhler Angle**			
Preop	9.5±7.1	8.5±4.1	0.822[m]	Preop	6.4±7.4	6.7±5.8	0.608[m]	Preop	3.2±7.7	1.4±5.8	0.185[m]	
Early Postop	27.4±9.7	29.1±8.6	0.560[m]	Early Postop	28.5±8.1	26.5±7.5	0.318[m]	Early Postop	24.4±6.4	24.0±3.9	0.684[m]	
3. Month	28.1±7.5	26.9±6.7	0.519[m]	3. Month	25.6±7.6	26.1±6.3	0.971[m]	3. Month	19.4±6.1	18.1±7.1	0.634[m]	
Final follow-up	26.9±7.1	25.3±8.0	0.822[m]	Final follow-up	23.4±9.9	25.6±7.0	0.243[m]	Final follow-up	14.8±7.6	13.3±6.4	0.505[m]	
Change relative to the preop				Change relative to the preop				Change relative to the preop				
Early Postop	17.9±8.7	20.7±10.8	0.393[m]	Early Postop	22.1±9.8	19.9±10.4	0.661[m]	Early Postop	21.2±10.6	22.6±7.2	0.382[m]	
Intragroup change p	0.000	0.001		Intragroup change p	0.000	0.000		Intragroup change p	0.001	0.000		
3. Month	18.7±8.4	18.4±7.5	0.881[m]	3. Month	19.2±8.7	19.4±9.1	0.971[m]	3. Month	16.1±8.2	16.7±8.6	0.790[m]	
Intragroup change p	0.000	0.001		Intragroup change p	0.000	0.000		Intragroup change p	0.001	0.000		
Final follow-up	17.4±8.0	16.8±9.7	0.905[m]	Final follow-up	17.0±8.9	18.9±10.0	0.443[m]	Final follow-up	11.6±7.1	11.9±7.5	0.985[m]	
Intragroup change p	0.000	0.001		Intragroup change p	0.000	0.000		Intragroup change p	0.001	0.000		

SD: Standard deviation; Preop: preoperative; Postop: postoperative. [m]Mann-whitney u test / [w]Wilcoxon test; [m]Mann-whitney u test / [w]Wilcoxon test

Table 3. Gissane angle measurements at four time points and intergroup/intragroup comparisons in grafted and non-grafted subgroups across Sanders fracture types.

	Group A (Sanders Tip 2)			Group B (Sanders Tip 3)			Group C (Sanders Tip 4)		
	Graft (-) Mean S.D.	Graft (+) Mean S.D.	p	Graft (-) Mean S.D.	Graft (+) Mean S.D.	p	Graft (-) Mean S.D.	Graft (+) Mean S.D.	p
Gisanne Angle				**Gisanne Angle**			**Gisanne Angle**		
Preop	132.7±12.1	133.0±10.3	0.787[m]	Preop	139.5±14.0	141.7±12.6	0.381[m]	Preop	145.8±18.6	146.4±12.2	1.000[m]
Early Postop	121.8±10.2	120.7±8.7	0.881[m]	Early Postop	123.1±6.9	124.4±9.8	0.502[m]	Early Postop	126.1±9.4	126.2±7.9	0.924[m]
3. Month	123.0±9.9	122.4±7.1	0.811[m]	3. Month	127.5±9.0	125.2±6.8	0.179[m]	3. Month	129.6±10.7	132.7±8.5	0.293[m]
Final follow-up	124.5±10.1	123.5±8.0	0.881[m]	Final follow-up	129.5±9.5	127.4±7.1	0.617[m]	Final follow-up	132.3±12.7	142.0±14.8	0.059[m]
Change relative to the preop				Change relative to the preop				Change relative to the preop			
Early Postop	-10.9±13.5	-12.3±11.1	0.491[m]	Early Postop	-16.5±14.1	-17.3±11.2	0.770[m]	Early Postop	-19.6±19.5	-20.3±8.0	0.717[m]
Intragroup change p	0.002	0.004		Intragroup change p	0.000	0.000		Intragroup change p	0.005	0.000	
3. Month	-7.7±12.6	-10.6±11.2	0.288[m]	3. Month	-12.1±15.6	-16.5±10.9	0.177[m]	3. Month	-16.2±17.6	-13.7±6.5	0.834[m]
Intragroup change p	0.006	0.016		Intragroup change p	0.003	0.000		Intragroup change p	0.007	0.000	
Final follow-up	-8.3±10.2	-9.5±12.1	0.419[m]	Final follow-up	-10.0±18.8	-14.3±12.3	0.215[m]	Final follow-up	-13.5±17.4	-4.4±6.8	0.101[m]
Intragroup change p	0.001	0.016		Intragroup change p	0.042	0.000		Intragroup change p	0.012	0.024	

SD: Standard deviation; Preop: Preoperative; Postop: Postoperative. [m]Mann-whitney u test / [w]Wilcoxon test; [m]Mann-whitney u test / [w]Wilcoxon test; [m]Mann-whitney u test / [w]Wilcoxon test.

Table 4. Calcaneal height measurements at four time points and intergroup/intragroup comparisons in grafted and non-grafted subgroups across Sanders fracture types

	Group A (Sanders Tip 2)			Group B (Sanders Tip 3)			Group C (Sanders Tip 4)		
	Graft (-) Mean S.D.	Graft (+) Mean S.D.	p	Graft (-) Mean S.D.	Graft (+) Mean S.D.	p	Graft (-) Mean S.D.	Graft (+) Mean S.D.	p
Calcaneus Height				**Calcaneus Height**			**Calcaneus Height**		
Preop	37.5±3.1	36.0±3.2	0.192[m]	Preop	35.0±4.7	34.2±3.4	0.685[m]	Preop	32.1±2.6	34.4±4.0	0.155[m]
Early Postop	49.9±4.8	50.7±4.8	0.567[m]	Early Postop	48.2±4.4	48.4±3.7	0.874[m]	Early Postop	40.1±4.1	43.9±2.6	0.054[m]
3. Month	49.1±5.5	49.4±6.7	0.419[m]	3. Month	47.6±5.6	48.1±3.3	0.871[m]	3. Month	38.2±4.1	42.1±3.1	0.534[m]
Late Postop	48.7±5.0	48.6±5.0	0.881m[m]	Late Postop	45.3±5.0	46.1±3.4	0.323[m]	Late Postop	35.8±4.2	37.6±3.4	0.142[m]
Change relative to the preop				Change relative to the preop				Change relative to the preop			
Early Postop				Early Postop				Early Postop			
Intragroup change p	0.000	0.001	[m]	Intragroup change p	0.000	0.000	[m]	Intragroup change p	0.001	0.000	[m]
3. Month				3. Month				3. Month			
Intragroup change p	0.000	0.001	[m]	Intragroup change p	0.000	0.000	[m]	Intragroup change p	0.001	0.000	[m]
Final follow-up				Late Postop				Late Postop			[m]
Intragroup change p	0.000	0.001	[m]	Intragroup change p	0.000	0.000	[m]	Intragroup change p	0.003	0.009	

SD: Standard deviation; Preop: Preoperative; Postop: Postoperative. [m]Mann-whitney u test / [w]Wilcoxon test; [m]Mann-whitney u test / [w]Wilcoxon test; [m]Mann-whitney u test / [w]Wilcoxon test.

Results

A total of 115 patients (84 males, 31 females) with intra-articular calcaneal fractures were included in the study. Fractures were classified into Sanders Types II, III, and IV, and each type was further divided into grafted (+) and non-grafted (–) subgroups (Figs. 1-3). Baseline demographic characteristics, including age, sex, follow-up duration, and AOFAS scores, were similar across subgroups (p>0.05) (Table 1).

Tables 2, 3, and 4 summarize the measurements of Böhler angle, Gissane angle, and calcaneal height, respectively, across four time points—preoperative, early postoperative, 3-month follow-up, and final follow-up—for both grafted and non-grafted subgroups in each Sanders type.

Across all Sanders fracture types, intergroup comparisons revealed no significant differences between grafted and non-grafted subgroups at any time point for any of the radiographic parameters (p>0.05).

Intragroup analysis showed that both grafted and non-grafted subgroups experienced statistically significant postoperative improvements in Böhler angle and calcaneal height, as well as a significant reduction in Gissane angle when compared to preoperative values (p<0.05 for all).

However, the magnitude of change from preoperative measurements did not differ significantly between the grafted and non-grafted groups for any of the radiographic parameters across all Sanders types.

Over the course of follow-up, Böhler angle and calcaneal height exhibited a gradual decline from the early postoperative period, though values remained significantly elevated compared to baseline. Conversely, Gissane angle showed a slight increase over time following its initial

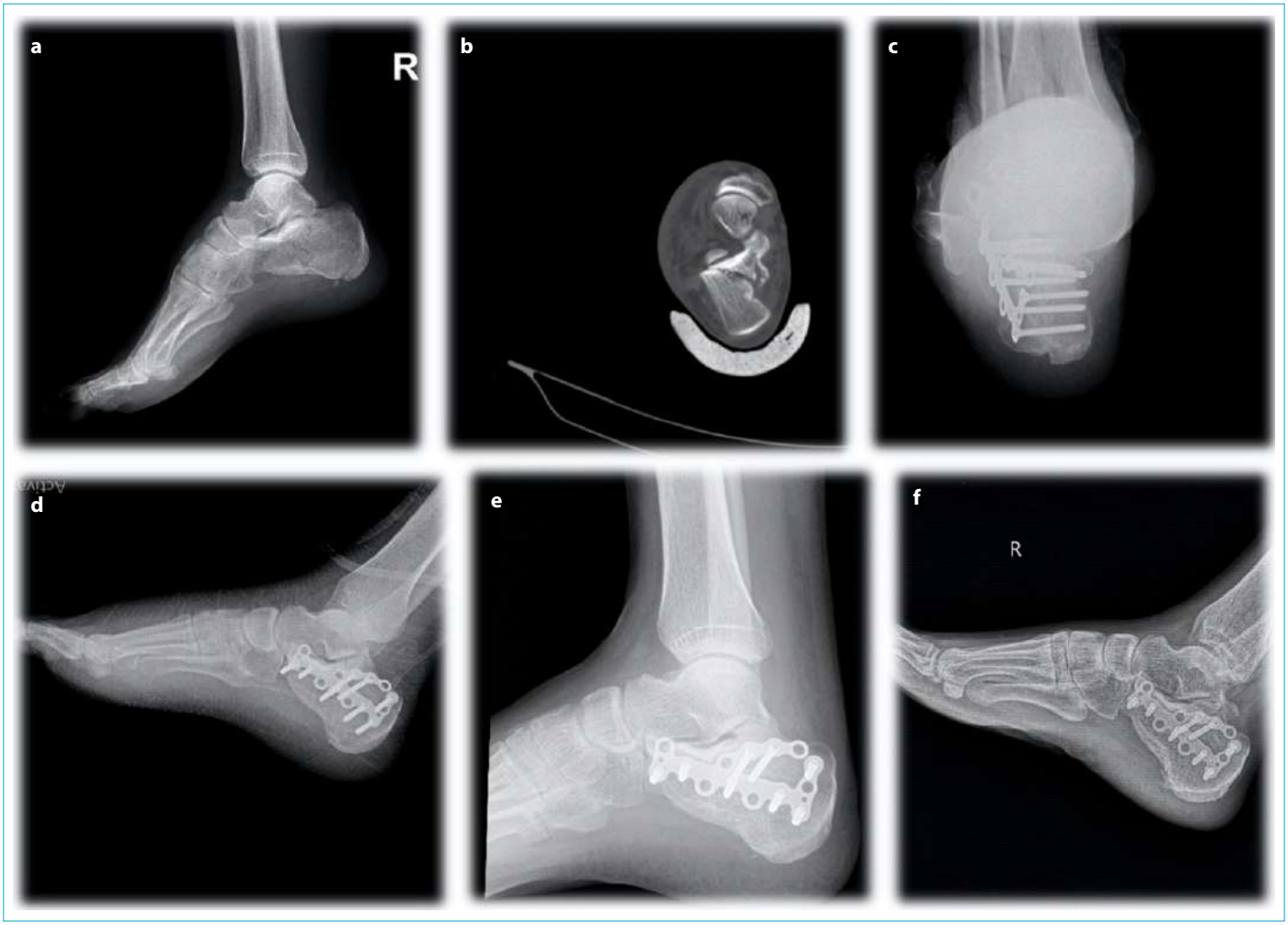

Figure 1. Representative Case of a Sanders Type II Calcaneal Fracture Treated Without Bone Grafting.

(a) Preoperative lateral X-ray; **(b)** axial CT image demonstrating the Sanders Type II classification; **(c)** postoperative axial X-ray of the calcaneus; **(d)** early postoperative lateral X-ray; **(e)** lateral X-ray at 3-month follow-up; **(f)** lateral X-ray at final follow-up.

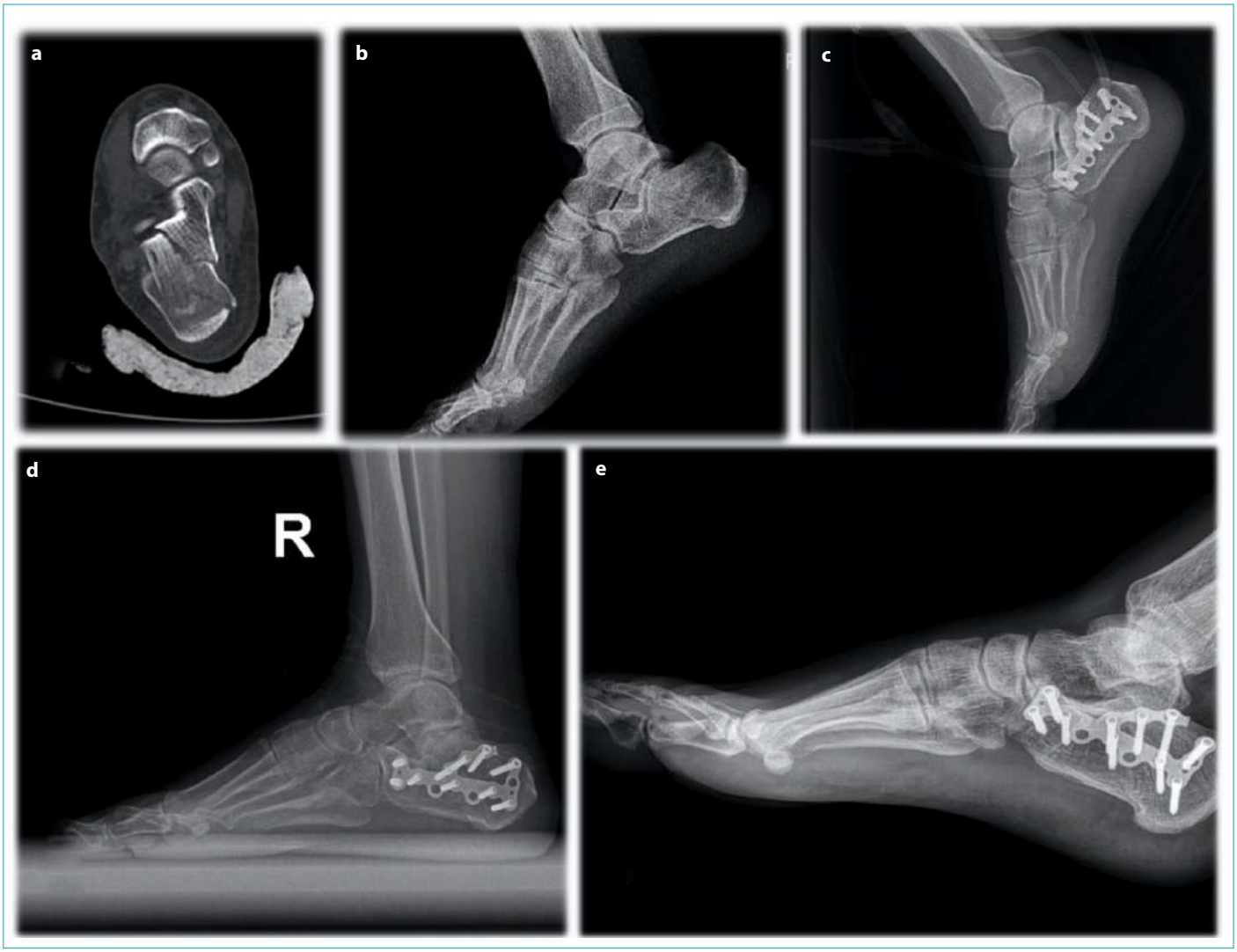

Figure 2. Sanders Type III Calcaneal Fracture Treated with Bone Grafting.

(a) Preoperative axial CT image demonstrating Sanders Type III fracture configuration; **(b)** preoperative lateral X-ray; **(c)** early postoperative lateral X-ray; **(d)** lateral X-ray at 3-month follow-up; **(e)** lateral X-ray at final follow-up.

postoperative decrease (Figs. 4-6). These temporal changes were consistent between grafted and non-grafted groups, without statistically significant intergroup differences.

Postoperative complications included superficial wound infections in 16.6% of non-grafted patients and 18.5% of grafted patients, with no statistically significant difference ($p>0.05$). All superficial infections were effectively managed with antibiotics or minor debridement. CRPS was observed in both groups and was treated successfully with conservative measures. Overall, the use of bone grafts during ORIF did not result in superior outcomes in radiological parameters or functional recovery as measured by the AOFAS score.

Discussion

In this retrospective cohort study, we assessed the impact of bone grafting on radiological and functional outcomes in patients with displaced intra-articular calcaneal fractures treated with open reduction and internal fixation. A total of 115 patients classified as Sanders Type II, III, or IV were evaluated. Bone grafting was not associated with significant improvements in radiographic parameters or AOFAS scores throughout the follow-up period. The AOFAS Ankle-Hindfoot Scale, despite its widespread use, has been reported to exhibit ceiling effects, particularly in its pain and alignment subscales, limiting its sensitivity in detecting subtle functional differences over time.[18] Complication rates, including superficial infection, were also comparable. These findings suggest that bone grafting may not provide

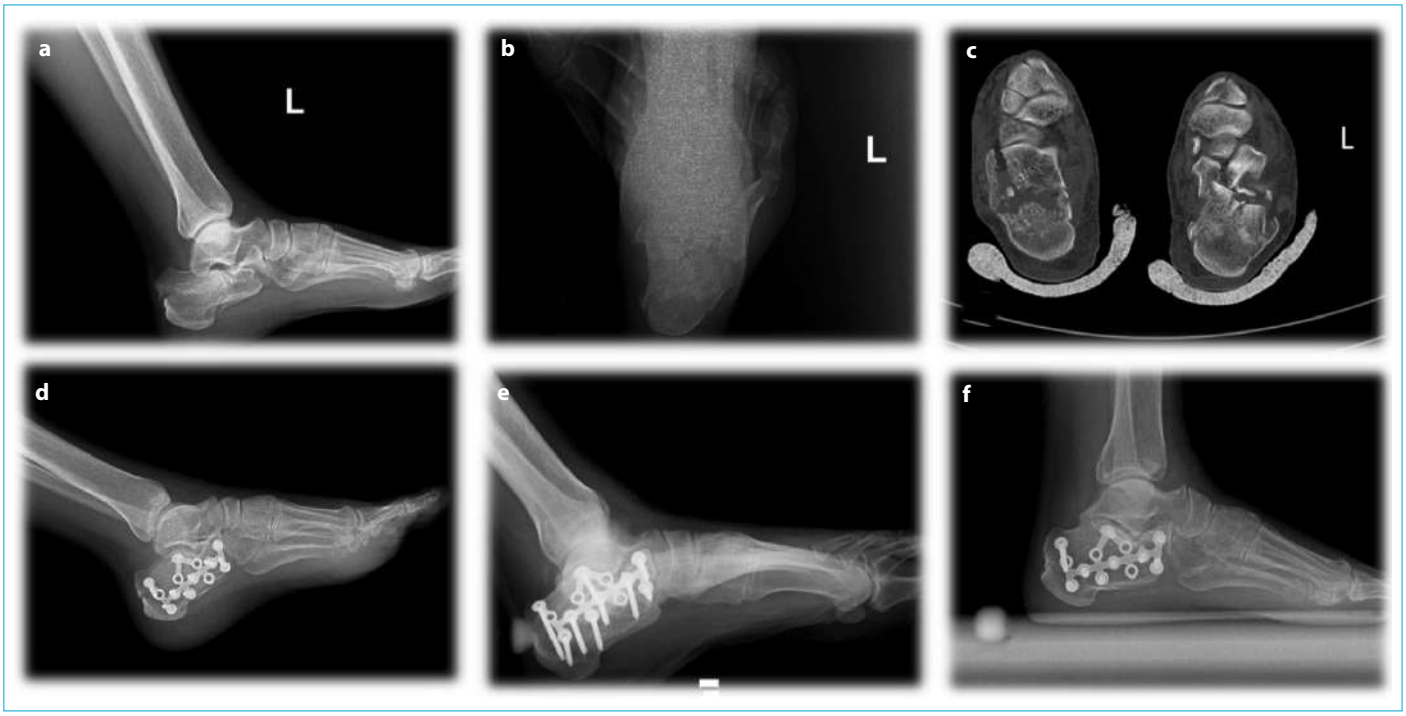

Figure 3. Sanders Type IV Calcaneal Fracture Treated with Bone Grafting

(a) Preoperative lateral X-ray; **(b)** preoperative axial calcaneal X-ray; **(c)** preoperative axial CT scan showing comminuted fracture morphology; **(d)** early postoperative lateral X-ray; **(e)** lateral X-ray at 3-month follow-up; **(f)** lateral X-ray at final follow-up.

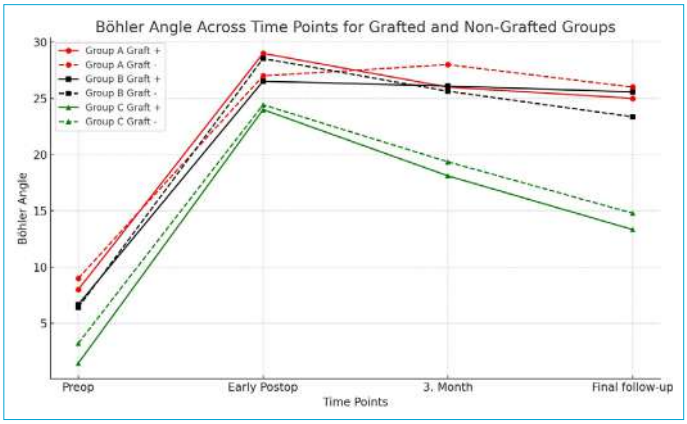

Figure 4. Böhler Angle Changes Over Time:

This graph shows Böhler angle improvements in all Sanders subgroups after surgery, with a gradual decrease over time. Solid lines represent grafted patients; dashed lines represent non-grafted.

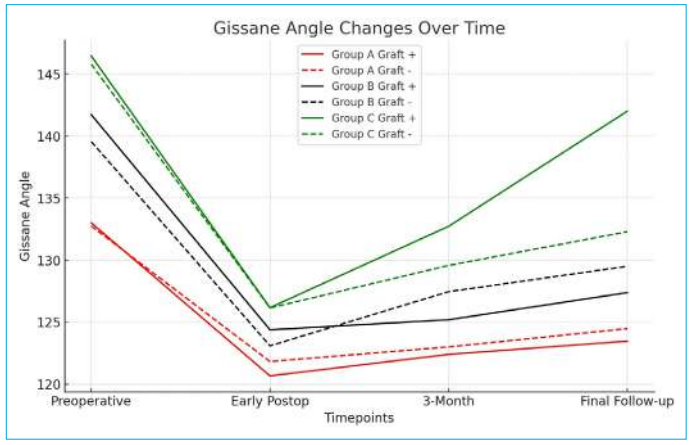

Figure 5. Gisanne Angle Changes Over Time:

This graph shows a postoperative decrease in Gissane angle across all Sanders subgroups, with a slight upward trend later. Solid lines for grafted patients; dashed lines for non-grafted.

additional clinical or radiographic benefit in the routine management of these fractures and should be considered selectively based on fracture morphology and bone loss. This approach is consistent with the broader trend in orthopedic surgery favoring biologically friendly techniques, as also demonstrated in deformity correction studies employing the Ilizarov method without bone grafting.[19]

Zheng et al.,[17] in their meta-analysis, reported a significantly higher AOFAS score in patients who received grafts, although no significant differences were found in Böhler's angle, Gissane's angle, calcaneal height, or width. In our study, no significant differences in AOFAS scores were observed between groups with and without graft usage. Another meta-analysis also found no significant difference in postoperative functional outcomes with graft usage, which is consistent with our findings.[5] In the current literature, there is no clear consensus on the optimal graft type for calcaneal fractures, and no studies explicitly compare the

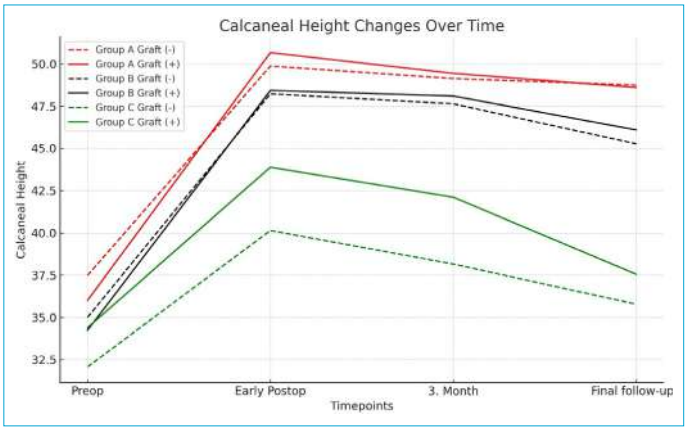

Figure 6. Calcaneal Height Changes Over Time:

This graph shows an increase in calcaneal height after surgery, with some decline during follow-up. Solid lines indicate grafted; dashed lines non-grafted patients.

outcomes of different graft types.[5, 6, 17, 20-23] In our study, the comparison between grafted and non-grafted subgroups within each Sanders classification (Type II, III, and IV) revealed no statistically significant differences in age, sex, follow-up duration, or AOFAS scores. These findings are consistent with previous studies that reported comparable functional outcomes between grafted and non-grafted patients.[20, 21] Longer follow-up studies may reveal potential differences in AOFAS scores between groups. Consistent with our data, Park et al.[2] reported that bone defects following calcaneal fracture surgery spontaneously filled within one year and functional outcomes were independent of graft usage. Wilkinson et al.[8] demonstrated that the need for grafting was reduced in patients treated with minimally invasive techniques, a finding supported by systematic reviews showing that these approaches yield favorable outcomes with less soft tissue morbidity and reduced need for bone augmentation.[13] Although open reduction is traditionally favored for restoring anatomical landmarks, evidence from meta-analyses suggests that percutaneous techniques achieve similar restoration of Böhler and Gissane angles without the increased risk of wound complications.[12] Furthermore, literature suggests that postoperative wound complications are more common in cases with extensive incisions and graft usage may increase the risk of infection.[24] Hammond and Crist[25] reported that percutaneous techniques reduced infection rates and the need for grafting. Despite the use of conventional incisions and fracture approaches in our study, no clinical or radiological differences were observed between groups. Swords et al.[26] argue that graft usage does not provide a significant contribution to postoperative functional recovery and advocate for the preference of minimally invasive techniques. From a surgical perspective, the primary rationale for bone grafting has traditionally been to fill bone voids and maintain the height of the posterior facet. However, recent evidence indicates that with modern fixation techniques—particularly locking plates and improved intraoperative imaging—adequate stabilization can often be achieved without the need for grafts.[27, 28] In line with this, our findings support the trend toward more selective use of grafts, reserving them for cases with significant bone loss or comminution. Radiologically, Böhler angle and calcaneal height increased significantly following surgery, with a gradual reduction in these gains during follow-up. In contrast, Gissane angle decreased postoperatively but exhibited a slight upward trend over time. These changes, however, were not significantly different between the grafted and non-grafted groups, suggesting that bone grafting does not influence the preservation of postoperative alignment throughout the follow-up period. Tian et al.[5] reported that Gissane's angle showed a statistically significant difference favoring the graft group in the long-term, yet emphasized that this difference was of limited clinical relevance. Similarly, Brunner et al.[27] found no measurable benefit of bone graft use on the preservation of Böhler's and Gissane's angles during follow-up, supporting our findings. Consistent with previous studies, our findings suggest that the decrease in Böhler angle and calcaneal height and the increase in Gissane angle observed over time may result from remodeling and subsidence at the fracture site during healing. These changes could influence load distribution and subtalar joint biomechanics. However, in our study, these radiographic changes did not translate into significant differences in clinical or functional outcomes between grafted and non-grafted groups.[2, 17, 22]

However, our study suggests that approaches that do not damage bone biology during surgery may not yield different results from minimally invasive procedures. Nevertheless, literature has shown that percutaneous screw fixation without grafting in Sanders Type II and III fractures provides high patient satisfaction and stability.[3] The crucial point is not graft usage, but rather appropriate stability provision, which may be a more important factor on outcomes. These findings support that graft usage does not provide additional short- and medium-term stabilization. Complications that may be associated with graft use are also important. Wei et al.,[9] in their review, reported that autologous iliac graft harvesting can cause minor complications (wound infection, hematoma, nerve damage) at a rate of 6-39% and major complications (deep infection, chronic pain, revision surgery) at a rate of 1-10%. He et al.,[21] in a prospective study, also reported a significant increase in postoperative infection rates in patients who received grafts. Furthermore, other studies have suggested that bone graft use may prolong operative time and increase the risk of

wound complications. Abidi et al.[29] identified graft usage as a factor associated with impaired wound healing, while Longino and Buckley[20] reported higher infection rates in the grafted group, though this difference was not statistically significant.

In our study, although the number of non-grafted patients was higher, the rate of superficial wound infections was comparable between the groups and did not reach statistical significance. This finding suggests that infection development is likely more influenced by surgical technique—particularly the extent of soft tissue handling—than by the use of graft material itself. These results are in line with meta-analytic evidence indicating lower complication rates associated with percutaneous approaches compared to conventional open techniques, largely due to better soft tissue preservation.[12, 13] This study is strong in terms of comprehensively evaluating the effects of graft use on radiological and functional outcomes in intra-articular calcaneal fractures and comparing it with current literature. The study is notable for including almost all calcaneal fracture types (Sanders Type II, III, and IV), covering a wide age range, and having clearly defined inclusion and exclusion criteria.

However, the retrospective design of this study, potential biases in patient selection, and the relatively small sample size should be considered as limiting factors. Although effect sizes and confidence intervals were not included in the current analysis, we recognize that incorporating these measures would strengthen the clinical interpretation of the findings. We have therefore highlighted this as a limitation and suggested the inclusion of effect sizes and confidence intervals in future research. Additionally, our study did not analyze the potential impact of different graft types on outcomes due to limited data and lack of consensus in the literature; future studies focusing on this aspect would be beneficial. Specifically, the non-grafted subgroup in Sanders Type IV fractures (n=14) may lack sufficient statistical power to detect moderate effects, thus warranting caution in generalizing the findings to all Sanders Type II, III, and IV fractures. Additionally, the variability in surgical techniques used and differences in surgeon experience should be acknowledged as potential confounding variables. Future prospective, randomized controlled trials may overcome these limitations and contribute to more definitive conclusions.

Conclusion

The findings of this study demonstrate that graft use in calcaneal fractures does not provide a significant advantage in terms of preserving Böhler's angle, calcaneal height, and functional outcomes. Due to the risk of additional morbidity and potential complications, graft use should not be routinely recommended except in selected cases.

Our results support the current shift in the literature toward more conservative and biologically friendly techniques, aligning with meta-analytic evidence that highlights the safety and efficacy of percutaneous reduction without routine grafting.[12]

Disclosures

Ethics Committee Approval: The study was approved by the of Metin Sabanci Baltalimani Bone Diseases Training and Research Hospital Ethics Committee (date: 26.02.2025, no:241).

Informed Consent: The authors declared that written informed consent was obtained from all participants before their inclusion in the study.

Conflict of Interest: The authors declared no conflict of interest.

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Authorship Contributions: Concept – B.O., H.U., K.A., M. B.K., M.M., G.P., M.K.; Design – B.O., H.U., K.A., M. B.K., M.M., G.P., M.K.; Supervision – B.O., H.U., K.A., M. B.K., M.M., G.P., M.K.; Materials – B.O., H.U., K.A.; Data Collection and/or Processing – M. B.K., M.M., G.P., M.K; Analysis and/or Interpretation – B.O., M. B.K., G.P.; Literature Review – B.O., M. B.K., G.P.; Writing – B.O., M.K.; Critical Review – B.O., H.U., M.K.

Use of AI for Writing Assistance: The authors declared that no artificial intelligence-supported technologies were used.

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Original Research

Mechanical Thrombectomy in Acute Ischemic Stroke: Do Patients Admitted During On-Hours Exhibit Better Results?

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Abstract

Objectives: Mechanical thrombectomy (MT) has revolutionized stroke care over the past decade. Thus, we aimed to assess whether presenting during off-hours affects workflow times, clinical outcomes, and mortality of patients with acute ischemic stroke (AIS) undergoing MT at our center and, if there is an impact, to identify areas for improvement in the treatment of acute stroke.

Methods: A total of 263 consecutive patients who underwent MT between January 2020 and April 2023 were included in the study. The patients were categorized into two groups: those who presented during on-hours (Group 1) and those who presented during off-hours (Group 2).

Results: Among the 263 patients enrolled in the study (131 men and 132 women; mean age: 69.49±12.22 years; age range: 25–95 years), 74 (28.14%) were admitted to the hospital during on-hours, and 189 (71.86%) were admitted during off-hours. Of these patients, 30 (40.54%) and 68 (35.98%) from Groups 1 and 2, respectively, had good outcomes in the third month. The groups showed similar demographics, treatment-related characteristics, and outcomes, with no significant differences detected. The only notable difference was that the percentage of Diffusion-Weighted Magnetic Resonance Imaging (DW-MRI) was notably greater in the off-hours group (p=0.044).

Conclusion: The results indicate that MT performed on patients presenting during off-hours yielded similar workflow times, successful recanalization, and clinical outcomes to MT performed on patients presenting during on-hours.

Keywords: Acute ischemic stroke, mechanical thrombectomy, off-hours, on-hours, outcomes

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In Türkiye, the burden of strokes is particularly profound. It ranks among the top causes of mortality and functional impairment, resulting in serious social, economic, and healthcare consequences.[1] Beyond the immediate health impact, stroke leads to high direct treatment costs and substantial indirect expenses due to the loss of productivity and long-term care needs.[2,3]

Mechanical thrombectomy (MT) has revolutionized stroke care over the past decade. It is now considered the standard of care for eligible patients with proximal large-vessel occlusion (LVO), offering significantly better outcomes than medical management alone when performed within the recommended time windows.[4] Numerous randomized controlled trials and real-world data have demonstrated

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that MT can improve functional independence, reduce disability, and enhance the long-term quality of life in acute ischemic stroke (AIS) patients. However, the effectiveness of MT is highly time-sensitive. Several studies have shown that delays in reperfusion significantly reduce the likelihood of favorable neurological outcomes.[5,6]

Wang et al.[7] reported that a majority of ischemic stroke patients presenting to the emergency department with known admission times arrived during off-hours. Meta-analyses, systematic reviews, and large-scale observational studies have reported associations between off-hours presentation and increased morbidity, worse functional outcomes, and higher mortality in AIS.[8–10] Among patients undergoing MT, the results regarding the effect of interventions during off-hours are conflicting in terms of time parameters and clinical outcomes.[11–16] Thus, in this study, we aimed to assess whether presenting during off-hours affects workflow times, clinical outcomes, and mortality among patients with AIS undergoing MT at our center and, if there is an impact, to identify areas for improvement in the treatment of AIS.

Methods

Patients who underwent MT at Bursa City Hospital for LVO during the period of January 2020 to April 2023 were included in this study. Of these patients, those who had incomplete data, were under 18 years of age, had had a stroke in the hospital, had received intravenous tissue plasminogen activator (IV tPA) from an external center and were then referred to our hospital for MT, or had received only IV tPA were excluded from the study. During the study period, 479 patients with AIS underwent reperfusion therapy, of which 263 met the eligibility criteria (Fig. 1). The study was approved by the ethics committee of Bursa City hospital (approved on September 27, 2023; Decision No: 2023-16/9) and was performed in accordance with the principles of the Declaration of Helsinki.

Our hospital is located in Bursa Province, one of Türkiye's largest provinces in the Marmara Region, which has a population of 3,250,000. Our hospital is one of the few major centers in South Marmara that provide MT services off-hours.

In this study, "during on-hours" was defined as weekdays from 8:00 to 16:00, while "off-hours" referred to all other times, including weekdays outside of 8:00–16:00, weekends, and public holidays (including religious holidays). Patients were categorized into two groups based on when they arrived at the emergency department: Group 1 included those who arrived during on-hours, while Group 2 consisted of those who arrived off-hours.

The severity of AIS was classified by the National Institutes of Health Stroke Scale (NIHSS) score.[17] The etiology of ischemic stroke was classified according to the Trial of Org 10172 in Acute Stroke Treatment criteria.[18] All patients underwent a control brain Computed Tomography (CT) scan 24 h after the MT procedure. Functional outcomes were assessed using the Modified Rankin Scale (mRS) at three months. An mRS score of ≤ 2 indicated a good clinical outcome, while a score of 3–6 corresponded to a poor clinical outcome. The efficacy of MT was assessed using the Modified Thrombolysis in Cerebral Infarction (mTICI) scale.[19] An mTICI score of ≥2b was considered a successful MT according to the American Heart Association/American Stroke Association (AHA/ASA) guidelines.[4,19]

We compared Group 1 and Group 2 in terms of demographics, comorbidities, stroke etiologies, Alberta Stroke Program Early CT score (ASPECT), initial NIHSS, NIHSS at 24 h, change in NIHSS at 24 h, symptomatic intracranial hemorrhage, discharge mRS, in-hospital mortality, mRS at three months, good outcome at three months (mRS ≤2), and mortality at three months. Time intervals were defined as door-to-neurologist assessment time, door-to-needle time, door-to-groin time, symptom-to-door time, symptom-to-needle time, and door-to-imaging time.

All AIS patients in our hospital are evaluated by the same neurology team. Neurologists, nurses, anesthesiologists, and anesthesia technicians provide uninterrupted healthcare services by working night shifts. The interventional neuroradiology team, consisting of five members, shares shifts equally and is called to the hospital outside regular working hours for patients requiring MT.

We evaluated whether diffusion-weighted MRI (DW-MRI) was performed in addition to CT as an imaging protocol. In our study, the off-hours group showed a significantly higher DW-MRI percentage than the on-hours group. Therefore, the patient groups were compared to examine the effect of DW-MRI acquisition on time parameters, such as clinical

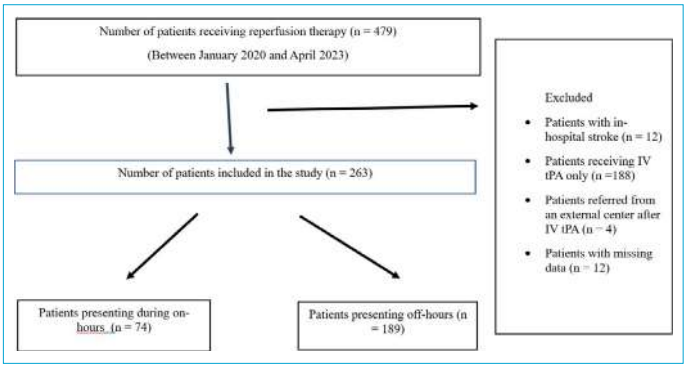

Figure 1. Flowchart: Inclusion and exclusion criteria.

outcomes and treatment initiation times, in AIS patients. Patients eligible for IV tPA treatment received 0.9 mg/kg within 4.5 h from the onset of stroke before undergoing MT. MT was conducted using a stent retriever, aspiration, or a combined strategy of both methods. The Solitaire flow restoration stent (ev3/Covidien, Irvine, CA, USA) or the Trevo NXT stent (Stryker, Kalamazoo, MI, USA) device was used as a stent retriever during thrombectomy.

Statistical Analysis

IBM SPSS Statistics for Windows version 25.0 (IBM Corp., Armonk, NY, USA) was used. We examined histograms and Q-Q plots to assess whether the data followed a normal distribution. Depending on the type of data, we applied the appropriate statistical analysis. We presented continuous variables as means with standard deviations for normally distributed data and as medians with interquartile ranges for non-normal data. Categorical variables were described using frequencies and percentages. Depending on the distribution, the continuous variables were compared using either the Student's t-test (for normal data) or the Mann–Whitney U test (for non-normal data). For the categorical variables, we applied the chi-square, Fisher's exact, and Fisher–Freeman–Halton tests where appropriate. A p-value under 0.05 was used as the threshold for statistical significance.

Results

A total of 263 patients (131 men and 132 women) were included in the study. The mean age was 69.5 years, with a range of 25–95. Among these patients, 74 (28.1%) were admitted during on-hours, while 189 (71.9%) presented outside of those hours. Moreover, 169 patients (64.26%) presented at our hospital, while 94 patients (35.74%) were referred from other hospitals. A total of 241 patients (91.63%) received only MT treatment, while 22 patients (8.37%) received both IV tPA and MT treatments.

Recanalization was successful for 67 patients (90.54%) in the on-hours group and 165 patients (87.30%) in the off-hours group. Fifteen patients (20.27%) in the on-hours group and 45 patients (24.59%) in the off-hours group died in hospital. Thirty patients (40.54%) in the on-hours group and 68 patients (35.98%) in the off-hours group had a good outcome in the third month. Seventeen cases (22.97%) in the on-hours group and 59 cases (31.22%) in the off-hours group were mortal in the third month. The off-hours group showed a significantly higher DW-MRI percentage than the on-hours group (p =0.044). As shown in Table 1, the demographics, disease and treatment characteristics, and outcomes were similar.

The patients who underwent DW-MRI experienced significantly longer door-to-groin times than those who did not (p=0.017). We observed similar outcomes across the DW-MRI groups in terms of hemorrhage, time of door-to-neurologist, mRS at discharge, good outcome at discharge, mortality in hospital, mRS at the third month, time of door-to-needle, good outcome at the third month, and mortality at the third month (Table 2).

Discussion

In the present study, no significant differences were found in the demographic characteristics, comorbidities, workflow times, or clinical outcomes between patients who presented during on-hours and those who presented off-hours. The only notable difference was that the percentage of DW-MRI was notably greater in Group 2 than in Group 1. It was observed that presentation off-hours did not affect workflow times, clinical outcomes, or mortality in patients with AIS undergoing MT at our center.

The data in the reviewed literature indicate that a greater share of ischemic stroke patients was admitted to hospitals off-hours[7] and that the majority of patients who underwent MT were reported to present off-hours.[13, 20, 21] In our study, a greater proportion of patients (71.86%) presented to the emergency department off-hours.

Studies investigating the effect of being admitted to hospital off-hours or on weekends on patients with AIS undergoing MT have reported varied results. Several investigations reported that clinical outcomes following stroke interventions were comparable in terms of whether the procedures were performed during standard hours or outside of them.[13–15] Other studies reported a tendency toward worse clinical outcomes among patients presenting off-hours,[11,12] whereas some studies revealed better clinical outcomes among patients admitted to hospital off-hours.[16]

Benali et al.[16] (2021) observed that 90-day functional results significantly improved in patients treated during nighttime hours compared with those treated in the daytime. In the current study, no differences were observed in discharge and three-month good outcomes, in-hospital and three-month mortalities, or discharge and three-month mRS between patients undergoing MT who presented on-hours and those who presented off-hours.

One recent meta-analysis covering 26 studies and about 82,850 patients and examining the effect of being admitted to hospital off-hours for MT treatment on AIS outcomes found that off-hours stroke treatments had a significantly lower likelihood of achieving successful recanalization compared with treatments during routine hours.[11] Similarly, another meta-analysis of 19 studies (approximately

Table 1. Summary of variables by group

	Groups			
	All patients (n=263)	**On-hours (n=74)**	**Off-hours (n=189)**	**p**
Age (n=263)	69.49±12.22	70.50±12.32	69.09±12.20	0.401
Sex (n=263), %				
Male	131 (49.81)	38 (51.35)	93 (49.21)	0.754
Female	132 (50.19)	36 (48.65)	96 (50.79)	
Comorbidities (n=263), %				
Heart diseases	142 (53.99)	47 (63.51)	95 (50.26)	0.053
Diabetes mellitus	81 (30.80)	18 (24.32)	63 (33.33)	0.202
Prior cerebrovascular disease	47 (17.87)	13 (17.57)	34 (17.99)	1.000
Prior transient ischemic attack	9 (3.42)	1 (1.35)	8 (4.23)	0.452
Hypertension	178 (67.68)	56 (75.68)	122 (64.55)	0.112
Hyperlipidemia	33 (12.55)	10 (13.51)	23 (12.17)	0.929
Smoking (n=263), %	49 (18.63)	11 (14.86)	38 (20.11)	0.421
Alcohol use (n=263), %	10 (3.80)	2 (2.70)	8 (4.23)	0.730
First application (n=263), %				
Another hospital	94 (35.74)	27 (36.49)	67 (35.45)	0.875
Our hospital	169 (64.26)	47 (63.51)	122 (64.55)	
Etiology (n=257), %				
Large artery atherosclerosis	96 (37.35)	26 (35.14)	70 (38.25)	0.338
Cardio embolism	99 (38.52)	34 (45.95)	65 (35.52)	
Other determined reasons	3 (1.17)	1 (1.35)	1 (1.10)	
Undetermined reasons	59 (22.96)	13 (17.57)	46 (25.14)	
ASPECT (n=263), %	10 (10 - 10)	10 (10 - 10)	10 (10 - 10)	0.068
≤ 9	55 (20.91)	10 (13.51)	45 (23.81)	0.093
10	208 (79.09)	64 (86.49)	144 (76.19)	
Circulation (n=263), %				
Posterior	31 (11.79)	5 (6.76)	26 (13.76)	0.171
Anterior	232 (88.21)	69 (93.24)	163 (86.24)	
DW-MRI (n=263), %	174 (66.16)	42 (56.76)	132 (69.84)	0.044
Intervention (n=263), %				
Only MT	241 (91.63)	68 (91.89)	173 (91.53)	1.000
IV tPA + MT	22 (8.37)	6 (8.11)	16 (8.47)	
NIHSS, %				
Admission (n=263)	14 (10–18)	14.5 (10–18)	14 (10–18)	0.917
24th hour (n=254)	11 (4–18)	11 (5–16)	11 (4–19)	0.926
Change (n=254)	−2 (−6–0)	−2 (−7–0)	−1 (−6–0)	0.618
Door-to-neurologist time, min (n=263)	20 (10–42)	22.5 (10–42)	20 (10–44)	0.940
Door-to-needle time, min (n=22)	71 (55–90)	73.5 (67–81)	71 (48.5–91)	0.606
Door-to-groin time, min (n=263)	100 (70–140)	90 (70–125)	101 (72–148)	0.082
Symptom-to-door time, min (n=263)	120 (58–196)	110 (51–196)	120 (60– 193)	0.442
Symptom-to-needle time, min (n=22)	145 (120–180)	133.5 (100–201)	146 (123–178.5)	0.825
Door-to-CT time, min (n=228)	18 (10–26)	19 (10–27)	18 (10–25)	0.696
Door-to-CT angiography time, min (n=243)	27 (16–53)	25 (15–43)	27.5 (18–58)	0.074
Door-to-DW-MRI time, min (n=142)	29 (13–48)	22 (7–59)	30.5 (17.5–47.5)	0.272
TICI (n=263), %				
TICI 0	15 (5.70)	1 (1.35)	14 (7.41)	0.052
TICI 1	13 (4.94)	3 (4.05)	10 (5.29)	
TICI 2A	3 (1.14)	3 (4.05)	0 (0.00)	
TICI 2B	52 (19.77)	15 (20.27)	37 (19.58)	
TICI 2C	6 (2.28)	1 (1.35)	5 (2.65)	
TICI 3	174 (66.16)	51 (68.92)	123 (65.08)	

Table 1. Summary of variables by group (Cont.)

	Groups			
	All patients (n=263)	**On-hours (n=74)**	**Off-hours (n=189)**	**p**
Successful recanalization, mTICI ≥ 2b (n=263), %	232 (88.21)	67 (90.54)	165 (87.30)	0.603
Hemorrhage (n=255), %	84 (32.94)	24 (32.43)	60 (33.15)	1.000
Symptomatic	27 (10.59)	7 (9.46)	20 (11.05)	0.929
Asymptomatic	57 (22.35)	17 (22.97)	40 (22.10)	
APACHE score (n=254)	11.18±6.37	10.74±6.66	11.35±6.26	0.488
Intubation (n=257), %	94 (36.58)	24 (32.43)	70 (38.25)	0.463
Duration of intubation, days (n=257)	0 (0–6)	0 (0–6)	0 (0–7)	0.410
Length of stay in hospital, days (n=257)	6 (3–15)	6.5 (3–14)	6 (3–16)	0.810
mRS, discharge (n=257)	4 (2– 5)	4 (2–5)	5 (2– 5)	0.315
Good outcome, mRS ≤ 2, discharge (n=257), %	78 (30.35)	24 (32.43)	54 (29.51)	0.755
Mortality, in hospital (n=257), %	60 (23.35)	15 (20.27)	45 (24.59)	0.563
mRS, 3rd month (n=263)	4 (1–6)	3 (1–5)	4 (1–6)	0.230
Good outcome, mRS ≤ 2, 3rd month (n=263), %	98 (37.26)	30 (40.54)	68 (35.98)	0.491
Mortality, 3rd month (n=263), %	76 (28.90)	17 (22.97)	59 (31.22)	0.240

Descriptive statistics were presented using mean±standard deviation for normally distributed continuous variables, median (25^{th}–75^{th} percentile) for non-normally distributed continuous variables, and frequency (percentage) for categorical variables. ASPECTS: Alberta Stroke Program Early CT Score; DW-MRI: Diffusion-weighted MRI; CT: Computed tomography; IV tPA: Intravenous tissue plasminogen activator; MT: Mechanical thrombectomy; NIHSS: National Institutes of Health Stroke Scale; m TICI: Modified Thrombolysis in Cerebral Infarction; APACHE II: Acute Physiology and Chronic Health Evaluation II; mRS: Modified Rankin Scale.

Table 2. Summary of variables with regard to DW-MRI

	Diffusion MR		p
	No (n=89)	**Yes (n=174)**	
Door-to-neurologist time, min (n=263)	20 (10–35)	22 (10–48)	0.099
Door-to-needle time, min (n=22)	63.5 (49–90)	74.5 (65–88)	0.575
Door-to-groin time, min (n=263)	90 (67–121)	105.5 (75–150)	0.017
Hemorrhage (n=255), %	33 (38.37)	51 (30.18)	0.188
Symptomatic	13 (15.12)	14 (8.28)	0.209
Asymptomatic	20 (23.26)	37 (21.89)	
mRS, discharge (n=257)	4 (2–6)	4 (2–5)	0.982
Good outcome, mRS, discharge (n=257), %	25 (28.74)	53 (31.18)	0.687
Mortality, in hospital (n=257), %	23 (26.44)	37 (21.76)	0.495
mRS, 3rd month (n=263)	3 (1–6)	4 (1–6)	0.489
Good outcome, mRS, 3rd month (n=263), %	36 (40.45)	62 (35.63)	0.445
Mortality, 3rd month (n=263), %	27 (30.34)	49 (28.16)	0.713

Descriptive statistics were presented using median (25th–75th percentile) for non-normally distributed continuous variables and frequency (percentage) for categorical variables. mRS: Modified Rankin Scale.

14,185 patients) reported reduced successful recanalization rates for patients who presented off-hours versus those who presented on-hours.[12] Conversely, a large registry paper by Ding et al.[13] found no difference in recanalization success between off-hours and on-hours thrombectomy cases. In our study, no statistically significant difference was found in the mTICI classification between patients who underwent MT during off-hours and those treated during on-hours. The successful recanalization rate was 87% for the off-hours group and 91% for the on-hours group.

Several clinical studies have reported that although there were delays in workflow times for patients presenting off-hours, these did not affect the clinical outcomes. A study conducted in China involving 111 comprehensive stroke

centers and over 1,700 patients found that onset-to-door time and onset-to-reperfusion time were significantly longer in patients presenting off-hours than in those presenting during on-hours. Regardless of whether patients presented during on- or off-hours, their clinical outcomes and mortality rates were similar.[13]

Hinsenveld et al.[14] reported that delays in workflow times for patients admitted off-hours did not affect the clinical outcomes. Löwhagen Hendén et al.[22] found that among patients with AIS undergoing MT, those who arrived off-hours experienced a longer time from CT scan to recanalization. However, the time from stroke onset to CT was similar, regardless of when the patients arrived. Notably, this delay did not translate into worse clinical outcomes, as patients who came in after hours fared just as well as those treated during the day. Similarly, Weddell et al.[15] observed that patients presenting off-hours had a longer door-to-groin puncture time. Nevertheless, this did not seem to affect how well the patients recovered, as clinical outcomes were comparable between both groups.

In some studies, delays in workflow times for patients presenting off-hours and undergoing MT were linked to lower rates of functional independence. The 2023 meta-analysis by Ghozy et al.[11] also noted that key workflow intervals were significantly prolonged during off-hours—for example, onset-to-door and door-to-recanalization times were all for off-hour patients—and that these delays corresponded with worse clinical outcomes than those seen in on-hour cases. Likewise, a 2022 meta-analysis (Zha et al.[12]) reported that multiple time metrics (including door-to-groin puncture, imaging-to-groin, and onset-to-recanalization, among others) were significantly longer for off-hour presentations and that such prolonged timelines were linked to an overall a tendency toward poorer prognosis for those patients.

Interestingly, Zha et al.[23] found that onset-to-door time was shorter for patients presenting outside working hours. This study found that arrival or treatment off-hours did not affect the in-hospital workflow or clinical outcomes. In the present study, presentation off-hours did not affect workflow times for patients with AIS undergoing MT at our center.

Neuroradiologists performing MT being present at the hospital during on-hours but requiring them to come to the hospital when called off-hours could potentially cause delays in hospital workflows. However, we did not observe any extension in workflow times at our center, even during procedures off-hours.

Nevertheless, the percentage of patients undergoing DW-MRI was significantly higher among those presenting off-hours than among those presenting during on-hours. The door-to-groin puncture time was significantly longer for patients who underwent DW-MRI than for other patients. In our study, performing DW-MRI on patients did not affect the clinical results. DW-MRI may be preferred during off-hours, as less experienced physicians are on duty and DW-MRI can be performed quickly due to lower patient density.

Despite its contributions, our study has several limitations. First, the retrospective nature and single-center design of the current study can be considered a limitation. Second, the effects of off-hours in Türkiye may vary depending on the coordination of stroke treatment in different regions. Third,, it would have been beneficial to divide the analysis into different times of the day to assess mortality, workflow, and other clinically important measures. Fourth,, given the large number of variables tested, there remains a potential risk of type I error due to multiple comparisons, although only two variables reached statistical significance. This should be considered when interpreting isolated p-values.

Finally, there was no significant difference in stroke severity, stroke etiology, baseline NIHSS, or ASPECT scores between the patients admitted during and those admitted out of office hours, indicating that the results obtained were independent of these variables, which could affect clinical outcomes.

Conclusion

In our cohort of patients with AIS who underwent MT, we found no significant differences between those who presented during on-hours and those who arrived outside of these hours. The key parameters, namely workflow times, success rate of vessel recanalization, functional outcomes at three months, overall clinical recovery, and mortality rates, were comparable between the two groups. These findings suggest that the quality and efficiency of care were consistently maintained, regardless of the time of patient presentation.

Disclosures

Ethic Committee Approval: The study was approved by the Bursa City Hospital Clinical Research Ethics Committee (date: 27.09.2023 number: 2023-16/9).

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Original Research

Does Co-Infection with HPV 16 Have a Worse Effect on Cervical Pathology than HPV 16 Alone?

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Abstract

Objectives: The aim of this study is to evaluate whether the presence of other HPV genotypes in addition to HPV16 infection has a negative effect on pathological outcomes.

Methods: This retrospective study was conducted using data from patients followed up at the Gynaecological Oncology Clinic of Antalya Training and Research Hospital between 2017 and 2025. Patients who were HPV16-positive and also carried other genotypes in addition to HPV16 were included in the study. HPV genotyping was performed using the Hybrid Capture 2 and CLART Genomica systems.

Results: Of the total 2,700 HPV (Human Papillomavirus) -positive women, 524 were HPV16-positive only, while 358 were positive for HPV16 along with other genotypes. Histopathological results, including CIN 2/3, HSIL, and invasive cancer, did not show significant differences between the two groups (p>0.05). However, abnormal colposcopy findings were statistically more prevalent in the co-infection group (p=0.037). Cigarette smoking was associated with a 1.27-fold increased risk for co-infection (p=0.026).

Conclusion: The findings of this study indicate that HPV16 is the primary determinant in the development of high-grade cervical pathology, and the presence of other high-risk HPV types does not significantly worsen histopathological outcomes. The results support the importance of a risk-based approach in cervical cancer screening processes and emphasize the need to prioritise early diagnosis and preventive interventions in HPV16-positive individuals.

Keywords: Coinfection, HPV-16, papillomavirus infections, uterine cervical neoplasms

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Annually, more than 660,000 women globally receive a diagnosis of cervical cancer, and more than 348,000 perish from the disease.[1] The prevalence of concurrent multiple high-risk HPV (Human Papillomavirus] infections has been observed to be between 20% and 50% among patients exhibiting abnormal cervical cytology or histological findings.[2] The effect of HPV16 co-infection with other HPV types has been shown to include potential interaction with viral entry/replication, but also the ability of multiple high risk HPV types to sustain tissue oncogenic transformation in separate lesions or tissue sections.[3, 4] Recent studies have demonstrated that the transfection of other high risk HPV types into keratinocytes already infected with HPV16 can result in the suppression of HPV16 genome replication and a potential reduction in infectivity.[5] The process known as 'superinfection exclusion' is a viral mechanism that prevents a cell infected with

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one virus from becoming infected with the same or a different virus. This phenomenon has been observed in HPV16 and HPV18 co-infections, and in vitro experiments suggest that HPV16 may inhibit HPV18 infection during the early stages of infection; however, this mechanism is ineffective in persistent cell lines. It has been hypothesised that both genomes compete for transcription during the early phases of infection, yet demonstrate equivalent replication efficiency in the persistent phase. This finding demonstrates that, in the initial phases of an infection, both genomes engage in a competitive process for transcription. However, in the context of persistent infections, these genomes exhibit equivalent replication efficacy.[6] Contemporary research underscores the notion that the isolated presence of HPV16 remains the most decisive prognostic determinant in the progression of cervical lesions. In contrast, concomitant infections with additional high-risk HPV types generally do not appear to exacerbate the risk of disease advancement.[7] On the contrary, certain combinations may even exert a modulatory effect, potentially stabilizing lesions at earlier histopathological stages. Nonetheless, particular scenarios merit caution: co-infections involving other potent oncogenic HPV types or occurring in immunocompromised individuals may act as surrogate indicators of persistent infection and, consequently, carry an elevated risk for neoplastic transformation.[8]

HPV types 16 and 18 are among the types with the highest oncogenic potential for cervical cancer and are generally analysed independently of each other in ASCCP guidelines. However, the primary objective of this study is to isolate and characterise the specific pathogenic effect of HPV16 in cervical lesions and to determine whether co-infections with high-risk or other HPV types detected are alongside HPV16 in the general population, compared to HPV16 infection alone. Furthermore, the data obtained will be evaluated in comparison with existing literature, and the findings will be interpreted from clinical and epidemiological perspectives.

Methods

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Antalya Training and Research Hospital (approval no: No: 16/10 / dated 24.10.2024). This retrospective study was conducted using data from patients who presented to the Gynecological Oncology Clinic at Antalya Training and Research Hospital between 2017 and 2025. Inclusion criteria comprised women who tested positive for HPV type 16 alone or in combination with other HPV types. Patients were excluded if they were positive for HPV types other than HPV 16, had undergone hysterectomy, or had a confirmed diagnosis of any gynecological malignancy. HPV screening was performed using the Hybrid Capture 2 assay (Qiagen), a validated and widely utilized diagnostic method in clinical practice. For samples testing positive for HPV, further genotyping was carried out using the CLART HPV kit (Genomica) to determine specific viral subtypes. Relevant clinical and demographic data were extracted from electronic medical records and the hospital's database system. Data included patient age, menopausal status, and histopathological findings from colposcopy-directed cervical biopsies and endocervical curettage (ECC). ECC was indicated in cases where the squamo-columnar junction (SCJ) was partially or completely unvisualized due to factors such as bleeding, inflammation, or cervical scarring. The ECC procedure was performed using a Novak curette to obtain samples from the entire endocervical canal, which were subsequently processed for histopathological examination. Histological outcomes from cervical biopsy and ECC specimens were classified into the following categories: normal cervical tissue, cervicitis, cervical intraepithelial neoplasia (CIN 1, CIN 2, CIN 3), high-grade squamous intraepithelial lesion (HSIL), suspected invasive carcinoma, microinvasive carcinoma, and invasive cervical cancer.

Statistical Analysis

Statistical analyses were performed using SPSS 27.0 software (IBM Inc, Chicago, IL, USA). Visual summarisations were performed with Graphpad prism 10.4.0 software. Kolmogrov-Smirnov test, histogram analyses, skewness/kurtosis data and Q-Q plots were used to evaluate the conformity of numerical variables to normal distribution. Qualitative parameters were defined as frequency (N) or percentage (%). Quantitative parameters were expressed as mean±standard deviation. In quantitative parameters with normal distribution, intergroup variance analyses were performed with Levene's test. Relationships between two independent groups were analysed by independent t-test. Associations between categorical parameters were analysed using Pearson's chi-square analysis or Fisher's exact test. Binary outcomes and associated parameters were analysed using (LR) analyses. Cut-off values of quantitative parameters were determined by ROC analyses. Distributions between categorical parameters were summarised with heat maps. The analyses were performed with a 95% confidence interval, and a type-I error rate of 5% (α=0.05) was taken as a basis and $p<0.05$ was accepted as the significant limit.

Results

During the study period, 2,700 patients were admitted to the gynaecological oncology clinic with HPV positivity. The study population consisted of 524 patients (59.4%) with HPV 16 positivity, 56 patients (6.3%) with HPV 16+18 positivity, 281 patients (31.9%) with HPV 16 and other positivity, and 21 patients (2.4%) with HPV 16+18 and other positivity. In the study cohort, a to-

Table 1. Summary of the general distribution of smoking, menopause and HPV status

Feature	Frequency (N)	Percentage (%)	
Cigarette			
Nonsmoker	365	41.4	
Smoker	439	49.8	
Unknown	78	8.8	
Menopausal status			
Unknown	10	1.1	
Premenopausal	620	70.3	
Postmenopausal	252	28.6	
HPV status			
Group 1 (59.4%)			
HPV 16 (Group 1)	524	59.4	
HPV16 + 18	56	6.3	
Group 2 (40.6%)			
HPV 16 and other	281	31.9	
HPV 16+18 and other	21	2.4	
	Min	**Max**	**Mean±SD**
Age	21	68	43.7±9.1

tal of 439 patients (49.8%) were classified as smokers, while 365 patients (41.4%) were classified as non-smokers (Table 1). The smoking status of 78 patients (8.8%) remained uncertain. The mean age of the study cohort was 43.7 years (±9.1 years), and a summary of the age distribution is given in Figure 1.

The number of postmenopausal patients was 252 (28.6%), while the number of premenopausal patients was 620 (70.3%) (Table 1).

The general distribution of diagnostic approaches is summarised in Table 2. The heat map of the distribution of

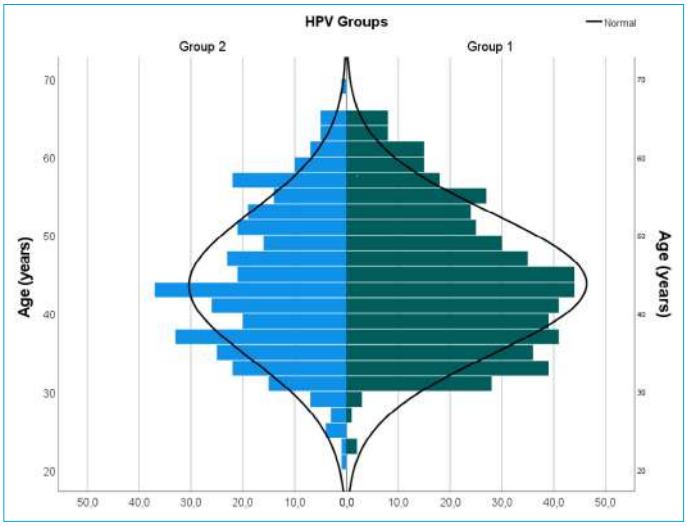

Figure 1. Group 1 and 2 age distribution summary.

Table2. General distribution of diagnostic approaches.

Diagnostic Approach	Frequency (N)	Percentage (%)
Cytology		
NILM	283	32.1
Infection	138	15.6
Inadequate	109	12.4
ASCUS	65	7.4
LSIL	74	8.4
ASC-H	13	1.5
HSIL	10	1.1
AGC	3	0.3
Invasive suspicion	0	0.0
Endometrial degenerated cells	0	0.0
Unknown	186	21.1
AIS	1	0.1
Colposcopy		
Normal	281	31.9
Abnormal	588	66.7
Inadequate	13	1.5
Did you get a pathology?		
No	1	0.1
Yes	881	99.9
Cervical biopsy		
Not done	275	31.2
Cervix tissue	90	10.2
Servisit	145	16.4
SEN	13	1.5
CIN	5	0.6
CIN 1	169	19.2
CIN 2	60	6.8
CIN 3	107	12.1
Suspicion of invasive Ca/microinvasive	5	0.6
Invasive Ca	8	0.9
HSIL	5	0.6
ECC		
Not done	141	16.0
Negative	622	70.5
SEN	6	0.7
CIN	3	0.3
CIN1	28	3.2
CIN2	21	2.4
CIN3	51	5.8
Suspicion of invasive CA	2	0.2
Invasive CA	3	0.3
HSIL	5	0.6
Pathology result		
Cervix tissue	325	36.8
Servisit	135	15.3
CIN 1	209	23.7
CIN2 - CIN3 - HSIL	194	22.0
Suspicion of invasive ca/microinvasive	6	0.7
İnvasive Ca	13	1.5

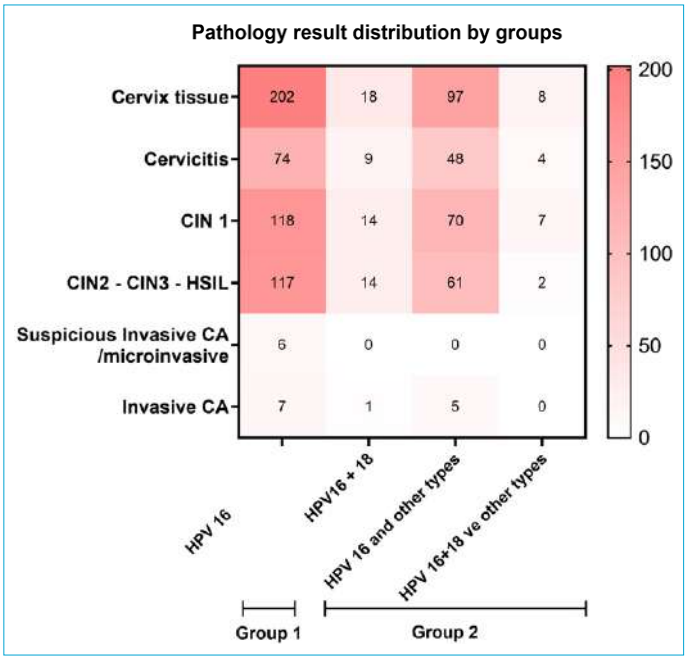

Figure 2. Heat map summary of pathology result distributions by groups according to frequency (p>0.05).

pathology results according to frequency revealed no significant difference between the groups in terms of cervical pathology results (p>0.05) (Fig. 2).

Subsequent analysis revealed that age, menopausal status and smoking did not demonstrate statistical differences between the groups (p=0.721, p=0.405, p=0.071) (Table 3).

However, a statistically significant difference was identified between the two groups with respect to cytological results (p=0.004). The study revealed that 342 cases (65.27%) in Group 1 and 246 cases (68.72%) in Group 2 exhibited ab-

Table 3. Comparison of the distribution of diagnostic approaches between groups

Diagnostic Approach	Group 1 (n=524, %59.4)	Group 2 (n=358, %40.6)	
	Distribution†		P
Age	43.7±9.0	43.5±9.4	0.721[a]
Cigarette			
Does not drink	233 (44.47)	132 (36.87)	0.071[b]
Drinking	249 (47.52)	190 (53.07)	
Unknown	42 (8.02)	36 (10.06)	
Menopausal status			
Unknown	8 (1.53)	2 (0.56)	0.405[b]
Premenopausal	368 (70.23)	252 (70.39)	
Postmenopausal	148 (28.24)	104 (29.05)	

†Data are expressed as mean±standard deviation or frequency (%) according to their distribution. [a]Independent t-test, [b]Pearson chi-square analysis.

Table 4. Comparison of the distribution of diagnostic approaches between groups

Diagnostic Approach	Group 1 (n=524, %59,4)	Group 2 (n=358, %40,6)	
	Frequency (%)		P
Cytology			
NILM §	149 (28.44)	134 (37.43)	0.004[a]
Infection	86 (16.41)	52 (14.53)	
Inadequate	56 (10.69)	53 (14.8)	
ASCUS	36 (6.87)	29 (8.1)	
LSIL §	52 (9.92)	22 (6.15)	
ASC-H	6 (1.15)	7 (1.96)	
HSIL	8 (1.53)	2 (0.56)	
AGC	2 (0.38)	1 (0.28)	
Invasive suspicion	0 (0)	0 (0)	
Endometrial degenerated cells	0 (0)	0 (0)	
Unknown §	128 (24.43)	58 (16.2)	
AIS	1 (0.19)	0 (0)	
Colposcopy			
Normal	178 (33.97)	103 (28.77)	0.037[b]
Abnormal	342 (65.27)	246 (68.72)	
Inadequate §	4 (0.76)	9 (2.51)	
Did you get a pathology?			
No	0 (0)	1 (0.28)	0.406[a]
Yes	524 (100)	357 (99.72)	
Cervical biopsy			
Not done	173 (33.02)	102 (28.49)	0.052[a]
Cervix tissue	54 (10.31)	36 (10.06)	
Servisit	84 (16.03)	61 (17.04)	
SEN	7 (1.34)	6 (1.68)	
CIN	5 (0.95)	0 (0)	
CIN 1	91 (17.37)	78 (21.79)	
CIN 2	27 (5.15)	33 (9.22)	
CIN 3	69 (13.17)	38 (10.61)	
Suspicion of invasive Ca/ microinvasive	5 (0.95)	0 (0)	
Invasive Ca	5 (0.95)	3 (0.84)	
HSIL	4 (0.76)	1 (0.28)	
ECC			
Not done	89 (16.98)	52 (14.53)	0.075[c]
Negative	357 (68.13)	265 (74.02)	
SEN	1 (0.19)	5 (1.4)	
CIN	1 (0.19)	2 (0.56)	
CIN1	19 (3.63)	9 (2.51)	
CIN2	14 (2.67)	7 (1.96)	
CIN3	36 (6.87)	15 (4.19)	
Suspicion of invasive CA	2 (0.38)	0 (0)	
invasive CA	3 (0.57)	0 (0)	
HSIL	2 (0.38)	3 (0.84)	

Table 4. Comparison of the distribution of diagnostic approaches between groups (Cont.)

Diagnostic Approach	Group 1 (n=524, %59,4)	Group 2 (n=358, %40,6)	
	Frequency (%)		P
Pathology result			
Cervix tissue	202 (38.55)	123 (34.36)	0.20[b]
Servisit	74 (14.12)	61 (17.04)	
CIN 1	118 (22.52)	91 (25.42)	
CIN2 - CIN3 - HSIL	117 (22.33)	77 (21.51)	
Suspicion of invasive Ca/ microinvasive	6 (1.15)	0 (0)	
Invasive Ca	7 (1.34)	6 (1.68)	

[§]=The subcategories that cause significance and proportional differences between the groups are marked. [a]Fisher's exact test; [b]Pearson chi-square analysis.

Table 5. Separate (univariate) investigation of the effect profiles and predictive properties of the parameters on co-infection (Group 2)

	Co-infection				
Factor	B	Nagelkerke R^2	p	OR	95%CI
Age (years)	-0.003	<0.001	0.224	0.72	0.983 - 1.012
Menopausal status	0.080	<0.001	0.583	1.08	0.815 - 1.440
Cigarette	0.243	0.008	0.026	1.27	1.030 - 1.579

Reference category: Group 1., LR: Likelihood Ratio; CI: Confidence Interval; OR=Odd ratio.

normal colposcopy results, indicating a statistically significant difference (p=0.037). However, cervical biopsy results were within the limit of statistical significance between the two groups (p=0.052) (Table 4).

Furthermore, smokers demonstrated a 1.27-fold elevated prevalence of co-infection (p=0.026, OR=1.27) (Table 5).

Notwithstanding the high prevalence of smoking observed among individuals with CIN2-CIN3, HSIL and invasive cancer, the most significant discrepancy was identified among those with invasive cancer. The observed variation in cervical tissue between these groups can be attributed to the substantial sample size of the study population (Fig. 3).

Discussion

The primary findings of our study indicated that there was no statistically significant difference between the cervical pathology results of patients with HPV 16 co-infection and individuals with HPV 16 infection only. In addition, the risk of co-infection increased 1.27-fold in patients who smoked,

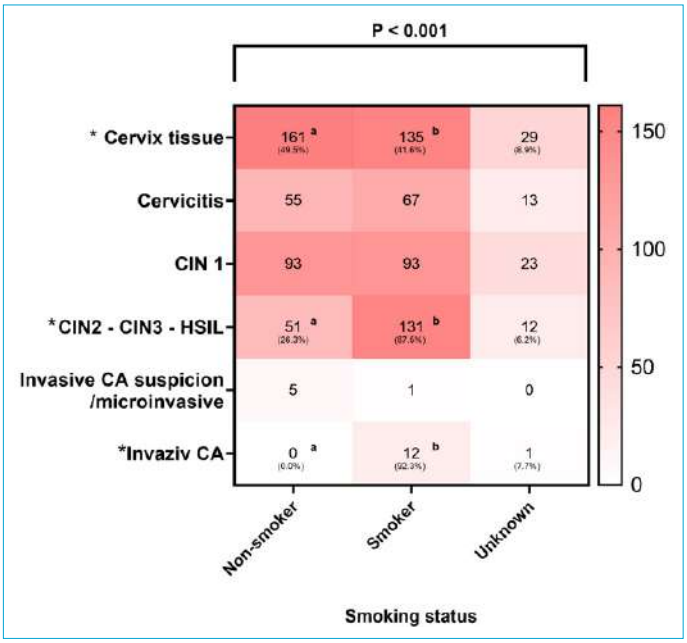

Figure 3. Visual summary of the distributional relationship between smoking and pathology and frequency values (Fisher's exact test; p<0.001) (*: Pathology subgroups that cause distributional differences are marked; (a, b): Data are divided into row percentages and those that differ in pairwise comparisons according to smoking status are marked). Cervical tissue, CIN2 - CIN3 - HSIL and invasive CA showed higher smoking rates, but the most significant difference was observed in those with invasive CA.

and it was observed that smoking rates were higher in patients diagnosed with CIN 2, CIN 3, HSIL and invasive cancer. The most significant difference was observed in patients diagnosed with invasive cancer.

In a study of 963 patients, a group infected only with HPV-16 (n=74) was compared with a group with HPV-16 positivity with high risk (n=68) and a group with HPV-16 co-infection with other types of HPV (n=27). The study found a relative risk [RR] of 1.39 with 95% confidence interval to be increased in the high risk HPV group. The discrepancy observed in our study may be attributable to numerical disparities between the groups.[9] In another study in the literature, analyses of the effect of HPV16 and HPV18 coinfection on CIN showed an odds ratio (OR) of 3.8 for this coinfection compared with HPV16 infection alone (95% CI: 2.5-5.7, p=0.004). A similar result was observed in the analysis of the association between HPV16 and HPV52 coinfection, yielding an odds ratio of 3.6 (95% CI: 2.6-5.1, p=0.009). Collectively, these findings suggest that coinfection with HPV18 and HPV52 is associated with a significantly higher risk of developing CIN (Cervical Intraepithelial Neoplasia) compared to HPV16 infection alone.[10] In contrast to the present study, the aforementioned study included all CIN lesions. In a subgroup analysis of a study conducted by Spi-

nillo et al.[10] to evaluate the clinical outcomes of co-infection with HPV 16 and other high-risk HPV types in women with a histological diagnosis of CIN or invasive cervical cancer, the odds of CIN3+ were higher in women with co-infection with HPV16 and HPV18 (OR=3.8, 95% CI 2.5-5.7, p=0.004, compared with HPV16 alone) or HPV52 co-infection (OR=3.6, 95% CI 2.6-5.1, p=0.009, compared with HPV infection alone) was higher than the odds ratio associated with single HPV infection. One of the study's findings was that multiple infections had no effect on residual disease [10]. The differences between the two studies appear reasonable given that the

diagnosis of HPV co-infection is strongly influenced by age, the type of genotyping system used, and the severity of cervical disease identified by biopsy or conisation.[11-13]

Wu et al.[14] demonstrated in a subgroup analysis of a population-based study that concurrent infection with HPV16 and other high-risk genotypes did not significantly increase the risk of CIN3+ lesions compared to HPV16 infection alone. (Odds ratio [OR]=0.637, 95% confidence interval [CI]=0.493–0.822). In the present study, HPV18 was not analysed as a separate subgroup. The primary motivation for this decision stemmed from the study's objective of isolating and characterising the specific pathogenic potential of HPV16 in cervical lesions. The analysis of HPV18 in isolation could have introduced confounding effects, which would have obscured the distinct clinical course attributable to HPV16. Furthermore, the prevalence of HPV18 infection either alone or in co-infection with HPV16 was extremely low in the present cohort, a finding that is analogous to the low rates reported in the population-based study by Wu et al.,[14] in which HPV16/18 co-infection was observed in only 1.13% of cases. This low frequency prevented the conduct of a statistically robust subgroup analysis for HPV18 within the current dataset. As a result, HPV18 was included in the general 'other high-risk HPV' category, allowing the analysis to continue focusing on determining whether co-infection alters the disease course defined by HPV16.The distribution of HPV types among the 4,933 patients who underwent colposcopy was as follows: 52.38% were infected with HPV16 alone. 23.54% were co-infected with HPV16 and at least one other high-risk HPV type. The proportion of individuals infected with both HPV16 and HPV18 was 1.13%, and co-infections involving these two types plus other high HPV types were also found at 1.13%. [14] In a subgroup analysis of a study involving 7,940 patients in China, compared to HPV 16 infection alone, the risk of CIN 3+ was significantly reduced in women infected with HPV 16 plus other high-risk HPV [OR=0.621, 95% CI=0.511–0.755], compared to HPV 16 + low-risk HPV (OR=0.620, 95% CI 0.436–0.883) and HPV 16 + low risk HPV + other hrHPV (OR=0.248, 95% CI 0.157–0.391), the risk of CIN 3+ was significantly reduced. In contrast to our study, the prevalence of CIN 3+ was associated with an increase in the severity of cytological abnormalities in HPV 16/18-positive women, peaking at cytology HSIL+ (89.9% and 82.3%), which represented a significantly higher risk compared to NILM (Negative for Intraepithelial Lesion or Malignancy) (OR=65.466, 95% CI 50.234–85.316). This difference may be attributed to the larger sample size of this study.[15] In conclusion, this study found that HPV16 co-infection, excluding HPV18, was associated with a lower or similar risk of high-grade cervical lesions compared to HPV16 alone.These findings suggest that the presence of multiple HPV types in HPV16-positive individuals may attenuate the pathogenic potential of the infection, possibly through mechanisms such as viral interference or cross-protective immune responses. Such interactions may contribute to a less aggressive clinical course in the context of co-infection.

One potential explanation for the discordant findings in the literature is based on molecular and immunological interactions between HPV genotypes. The extant literature has described a mechanism known as 'superinfection exclusion', which suggests that when a cell is already infected with one HPV, it may prevent the entry or replication of a second HPV type. This mechanism may provide a rationale for the observation of reduced pathological progression in certain co-infection scenarios.[6] Conversely, as demonstrated by Sobota et al.,[16] co-infection with HPV genotypes belonging to the same phylogenetic group may suppress the progression of viral oncogenesis due to competition for host cell resources.

When interpreting the results, it is important to consider the limitations of this study. First, the retrospective design of the study limits the establishment of cause-and-effect relationships. Second, the lack of long-term follow-up data prevents the dynamic assessment of the potential effects of concurrent infections on disease progression. Third, the biological significance of concurrent infections could not be thoroughly analysed since HPV viral load was not measured. Additionally, the immunological status of the patients was not included in the study, which may have affected the persistence or clearance of the infection in some cases. Finally, the fact that the study was conducted at a single centre may limit the generalisability of the findings to the general population. However, the study also has important strengths. The histopathological confirmation of cervical pathology and the examination of a well-defined patient group enhance the reliability of the clinical outcomes. The emphasis on the effects of HPV16 and co-infections provides important insights into their roles in disease progression. Additionally, the use of real-world data ensures that the findings are consistent with routine clinical

practice. The presence of these characteristics facilitates the development of risk-based screening and management strategies for individuals with HPV16-positive results.

In conclusion, the findings of our study emphasise the crucial role of HPV16 in the progression of clinically significant cervical pathology. In the context of co-infections with other HPV types, HPV16 remains the dominant determinant of disease severity. The absence of a significant effect of concurrent infections on histopathological outcomes suggests that the presence and persistence of HPV16 should be given greater consideration in routine clinical decision-making. The findings support the prioritisation of early diagnosis and preventive strategies for individuals testing positive for HPV16, thereby improving patient risk classification and guiding more targeted clinical management.

Disclosures

Ethics Committee Approval: The study was approved by Antalya Training and Research Hospital Clinical Research Ethics Committee (No: 6/25, dated 09.05.2024).

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Original Research

Evaluation of Patients Diagnosed with Inherited Metabolic Diseases in Adulthood

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Abstract

Objectives: Inherited metabolic diseases (IMDs) arise due to deficiencies in enzymes involved in metabolic pathways or other dysfunctions within these pathways, leading to a deficiency of specific end products or the toxic accumulation of intermediate metabolites. These diseases may present at any age with varying clinical courses. With advances in treatment options and increased awareness, IMDs are increasingly being diagnosed and managed in adulthood. This study aims to understand the clinical features and diagnostic processes of patients diagnosed with IMDs during adulthood and to raise awareness regarding these conditions.

Methods: Medical records of adult patients diagnosed with IMDs between June 2022 and June 2024 were retrospectively reviewed. Patients were included if they were diagnosed with an IMD at or above the age of 18. Those diagnosed during childhood but transitioning to adulthood were excluded.

Results: Twenty patients, aged 19–72 years (11 males, 9 females), were diagnosed with IMDs. The mean age of symptom onset was 30 years (range: 15–70 years), and the mean age of diagnosis was 37 years (range: 18–72 years). Diagnoses included Fabry disease (n=10, 20%), familial hypobetalipoproteinemia (FHBL) (n=3, 15%), and alkaptonuria (AKU) (n=2, 10%). Other diagnoses included Gaucher disease, Niemann-Pick disease type B, glycogen storage disease type IIIa (GSD IIIa), glycogen storage disease type XV (GSD XV), and cerebrotendinous xanthomatosis (CTX). Sixty-five percent of patients were identified via family screening, while 35% were diagnosed based on clinical findings supported by biochemical tests. Misdiagnoses before definitive IMD diagnosis included osteoarthritis, psoriatic arthritis, renal failure, heart failure, proteinuria, interstitial lung disease, hepatosteatosis, and nephrolithiasis. Disease-specific treatments were initiated and follow-ups were conducted.

Conclusion: Chronic and mild phenotypes of certain IMDs may pose diagnostic challenges. Increased awareness among healthcare professionals and further studies focusing on differential diagnoses are critical to improving the detection and management of IMDs.

Keywords: Adult, disease awareness, inherited metabolic disease, treatment

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Inherited metabolic diseases (IMDs) are a group of genetic disorders caused by the deficiency or absence of an enzyme or cofactor involved in a metabolic pathway. This results in either the lack of a specific end product or the excessive accumulation of a potentially toxic intermediate substrate.[1] The term "IMD" was first introduced by Sir Archibald Garrod in reference to alkaptonuria.[2] IMDs are exclusively monogenic disorders, most commonly inherited in an autosomal recessive manner. To date, more than 1,450 IMDs have been identified, and this number continues to grow with advancements in genetic diagnostic methods.[3] Although individually rare, IMDs collectively have an incidence of 1:800 to 1:2.500 live births.[4] Compared to developed countries, the prevalence of IMDs is higher in Türkiye due to the increased rate of consanguineous marriages.

Due to the success of newborn screening programs in treating pediatric patients, many individuals with inherited metabolic diseases (IMDs) now reach adulthood. However, the exact prevalence of these diseases in the adult population remains unclear, as late-onset forms that manifest during adulthood are often underrecognized. It is estimated that 50% of individuals with IMDs are adults.[5,6] Studies have shown that 23–40% of IMD cases are diagnosed in adulthood.[7,8] Diagnosing IMDs in adult patients is challenging due to phenotypic differences from pediatric cases, the influence of factors such as obesity and smoking on clinical presentations, the variability of symptoms across different ages, and the resolution of certain symptoms with supportive therapies.[9] Adult patients with IMDs may present with diverse symptoms or findings, leading them to seek care from specialists in various fields, including neurology, cardiology, gastroenterology, nephrology, and ophthalmology.[10] Awareness of IMDs among clinicians in adult specialties is crucial for early diagnosis and treatment initiation, as well as for providing genetic counseling during pregnancy and protecting at-risk fetuses.[11] Given the increasing recognition of IMDs in adulthood, it is essential for clinicians across specialties, in addition to pediatric metabolic specialists, to acquire more knowledge about this patient population and to identify their characteristic features.

This study aims to document the clinical characteristics of patients diagnosed with IMDs who presented to different specialties in a tertiary care center. Additionally, it seeks to improve understanding of the prognoses of these patients and to raise awareness of IMDs in adult clinical practice.

Methods

A retrospective review was conducted on the medical records of 20 patients diagnosed with IMDs between June 2022 and June 2024 at the Pediatric Metabolic Diseases Clinic of Şişli Hamidiye Etfal Training and Research Hospital, University of Health Sciences. The collected data included demographic and clinical characteristics such as age, sex, diagnosis, age of symptom onset, presenting complaints, initial clinical consultations, physical examination findings, laboratory results, diagnostic tests, and treatments (both disease-specific and symptomatic). Only patients aged 18 years or older at the time of diagnosis were included in the study, while individuals diagnosed during childhood and transitioning to adulthood were excluded.

For Fabry disease, the diagnosis was established through enzymatic analysis, Lyso-Gb3 levels, and genetic testing in males, while Lyso-Gb3 levels and genetic testing were used in females. Glycogen storage diseases were diagnosed using genetic analyses, while Niemann-Pick type B and Gaucher diseases were confirmed through enzyme activity levels and genetic testing. Homogentisic acid in urine was used for diagnosing alkaptonuria (AKU), while low levels of LDL cholesterol and ApoB confirmed familial hypobetalipoproteinemia (FHBL). Elevated cholestanol and 7-dehydrocholesterol levels were used for diagnosing cerebrotendinous xanthomatosis (CTX). Genetic analyses included single-gene sequencing or genetic panels for symptomatic index cases and mutation analysis for family screening.

The data analysis was performed using SPSS version 22.0 (Statistical Package for Social Science, IBM Corp, Armonk, NY, USA). Descriptive statistics were presented as means, minimums, and maximums for continuous variables, and as counts and percentages for categorical variables.

Ethics Committee Approval

Ethics committee approval for the study was obtained from the Non-Interventional Research Ethics Committee of Şişli Hamidiye Etfal Training and Research Hospital, University of Health Sciences, on 19/11/2024, with the decision number 4623/2024. All study procedures were in compliance with the principles of the Helsinki Declaration.

Results

During the study period, 20 patients diagnosed with IMDs were included, of whom 11 (55%) were male and 9 (45%) were female. Consanguinity between parents was present in 19 patients (95%). The mean age of the patients was 38 years (range: 19–72 years). The mean age of symptom onset was 30 years (range: 15–70 years), and the mean age at diagnosis was 37 years (range: 18–72 years). Among the cases, 10 (20%) were diagnosed with Fabry disease, 3 (15%) with familial hypobetalipoproteinemia (FHBL), and 2 (10%) with alkaptonuria (AKU). One case each of Gaucher disease, Niemann-Pick disease type B, glycogen storage disease type IIIa (GSD type IIIa), glycogen storage disease type XV (GSD type XV), and cerebrotendinous xanthomatosis (CTX) were also identified. The clinical and demographic characteristics of the patients are shown in Table 1.

Table 1. The clinical and demographic characteristics of the patients in the study

Patient No	Age/ Gender	Symptoms/Findings	Mode of Diagnosis	Diagnostic Approach (Biochemical/ Genetic)	Genetic	Diagnosis	Treatment
1	49/F	Osteoarthritis	Clinical	Urine organic acid (↑Homogentisic acid)	*HGD* Homozygous	Alkaptonuria	Nitisinone + Tyrosine-restricted diet
2	36/M	Joint pain, Kidney stones	Family screening	Urine organic acid (↑Homogentisic acid)	*HGD* Homozygous	Alkaptonuria	Nitisinone + Tyrosine-restricted diet
3	51/M	Renal failure, Kidney transplant, Hypertrophic cardiomyopathy Hearing loss	Clinical	↓Alpha-galactosidase, ↑Lyso Gb3	*GLA* Hemizygous	Fabry Disease	Declined enzyme replacement therapy due to surgeries
4	72/F	Heart failure	Family screening	Genetic analysis	*GLA* Heterozygous	Fabry Disease	Declined enzyme replacement therapy due to old age
5	46/M	Hypertension, Hypertrophic cardiomyopathy, Proteinuria	Family screening	↓Alpha-galactosidase, ↑Lyso Gb3	*GLA* Hemizygous	Fabry Disease	Enzyme replacement therapy (ERT)
6	40/M	Renal failure, Hearing loss, Angiokeratoma	Family screening	↓Alpha-galactosidase, ↑Lyso Gb3	*GLA* Hemizygous	Fabry Disease	Enzyme replacement therapy (ERT)
7	33/M	Proteinuria, Acroparesthesia	Family screening	↓Alpha-galactosidase, ↑Lyso Gb3	*GLA* Hemizygous	Fabry Disease	Enzyme replacement therapy (ERT)
8	37/M	Angiokeratoma, Acroparesthesia, Increased vascular tortuosity in eyes	Family screening	↓Alpha-galactosidase, ↑Lyso Gb3	*GLA* Hemizygous	Fabry Disease	Enzyme replacement therapy (ERT)
9	45/F	Renal failure, Heart failure, Acroparesthesia	Family screening	Genetic analysis	*GLA* Heterozygous	Fabry Disease	Enzyme replacement therapy (ERT)
10	19/M	Proteinuria, Hypertrophic cardiomyopathy	Family screening	↓Alpha-galactosidase, ↑Lyso Gb3	*GLA* Hemizygous	Fabry Disease	Enzyme replacement therapy (ERT)
11	48/F	Hypohidrosis, Hypertrophic cardiomyopathy, Increased vascular tortuosity in eyes	Family screening	Genetic analysis	*GLA* Heterozygous	Fabry Disease	Enzyme replacement therapy (ERT)
12	22/M	Hypertrophic cardiomyopathy, Difficulty gaining weight	Family screening	↓Alpha-galactosidase, ↑Lyso Gb3	*GLA* Hemizygous	Fabry Disease	Enzyme replacement therapy (ERT)
13	34/F	Abdominal swelling, Joint pain	Family screening	↓Beta-glucosidase, ↑Lyso Gb1	*GLA* Compound Heterozygous	Gaucher Disease	Enzyme replacement therapy (ERT) + Vitamin D supplementation
14	43/F	Joint pain, Iron deficiency anemia, Hepatosplenomegaly, Interstitial lung disease	Clinical	↓Sphingomyelinase, ↑Lyso SM, Lyso SM-509	*SMPD* Homozygous	Niemann-Pick Disease Type B	Applied for enzyme replacement therapy
15	31/M	Chest pain, Hypertrophic cardiomyopathy	Clinical	Genetic analysis	*GYG1* Homozygous	Glycogen Storage Disease Type XV	Symptomatic treatment
16	55/F	Xanthomas, Depression	Clinical	↑Cholestanol, ↑7-dehydrocholesterol	*CYP27A1* Homozygous	Cerebrotendinous Xanthomatosis	Chenodeoxycholic acid therapy
17	38/F	Ataxia, Hepatosteatosis	Clinical	↓Apo B, ↓LDL Cholesterol, ↓Vitamin E	*APOB* Homozygous	Hypobetalipoproteinemia	MCT-supported fat-restricted diet + Fat-soluble vitamins

Table 1. The clinical and demographic characteristics of the patients in the study (Cont.)

Patient No	Age/ Gender	Symptoms/Findings	Mode of Diagnosis	Diagnostic Approach (Biochemical/ Genetic)	Genetic	Diagnosis	Treatment
18	19/F	Asymptomatic, Hepatosteatosis	Family screening	↓Apo B, ↓LDL Cholesterol	*APOB* Heterozygous	Hypobetalipoproteinemia	Fat-soluble vitamins
19	21/M	Asymptomatic, Hepatosteatosis	Family screening	↓Apo B, ↓LDL Cholesterol	*APOB* Heterozygous	Hypobetalipoproteinemia	Fat-soluble vitamins
20	27/M	Fatigue, Hypoglycemia, Muscle weakness	Clinical	↓Glucose, ↑ALT, ↑AST, ↑Triglycerides, ↑Creatine Kinase	*AGL* Homozygous	Glycogen Storage Disease Type IIIa	Modified Atkins diet

M: Male; F: Female; Glu: Glucose; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; Tg: Triglyceride; CK: Creatine kinase; Apo B: Apolipoprotein B.

In our cohort includes 8 unrelated families. 65% of patients (13 cases from four families; 9 Fabry, 2 FHBL, 1 AKU, 1 Gaucher) were diagnosed through family screening. The remaining 7 patients (35%) were diagnosed based on clinical findings supported by biochemical and genetic tests. These included 1 case each of Niemann-Pick disease type B, CTX, FHBL, GSD type IIIa, GSD type XV, Fabry disease, and AKU. The index case of Fabry disease was diagnosed through selective screening in the cardiology department, while one GSD type XV patient, who could not be diagnosed biochemically, was identified through clinical exome sequencing. Some phenotypic features of adult patients diagnosed with inherited metabolic diseases are presented in Figure 1 (a-d).

Symptomatic patients primarily presented to internal medicine (30%), gastroenterology (10%), nephrology (10%), cardiology (10%), and orthopedics (10%), as well as hematology and physical therapy departments. Prior to diagnosis, these patients had been misdiagnosed with conditions such as osteoarthritis, psoriatic arthritis, renal failure, heart failure, proteinuria, interstitial lung disease, hepatosteatosis, and nephrolithiasis. Among Fabry disease patients, organ screenings revealed ocular and cardiac involvement in asymptomatic women. In men, hypertrophic cardiomyopathy was detected in three cases, while two cases showed ocular involvement and proteinuria. A total of 11 patients (60%) presented with involvement of two or more organs at the time of diagnosis. This group included 8 Fabry patients, and one patient each with AKU, Niemann-Pick disease type B, CTX, and GSD type IIIa.

Disease-specific treatments were initiated for the IMD patients. Two Fabry patients declined treatment (one due to advanced age and social reasons, and the other due to surgical considerations). Enzyme replacement therapy was administered to 8 Fabry and 1 Gaucher patient. Additionally, 2 AKU patients received nitisinone (NTBC) and a specialized diet, while the CTX patient was treated with chenodeoxycholic acid. A patient with GSD type IIIa was managed with a modified Atkins diet, and the homozygous FHBL patient was treated with fat-soluble vitamin supplementation and a fat-restricted diet. Heterozygous FHBL patients were also managed with fat-restricted diets.

Discussion

Inherited metabolic diseases (IMDs) are a group of genetic disorders that typically present acutely in childhood or, more commonly, progress insidiously in adulthood.[12] Diagnosing IMDs in adults is rare, and these conditions are often overlooked in clinical practice.[7] This study presents the clinical

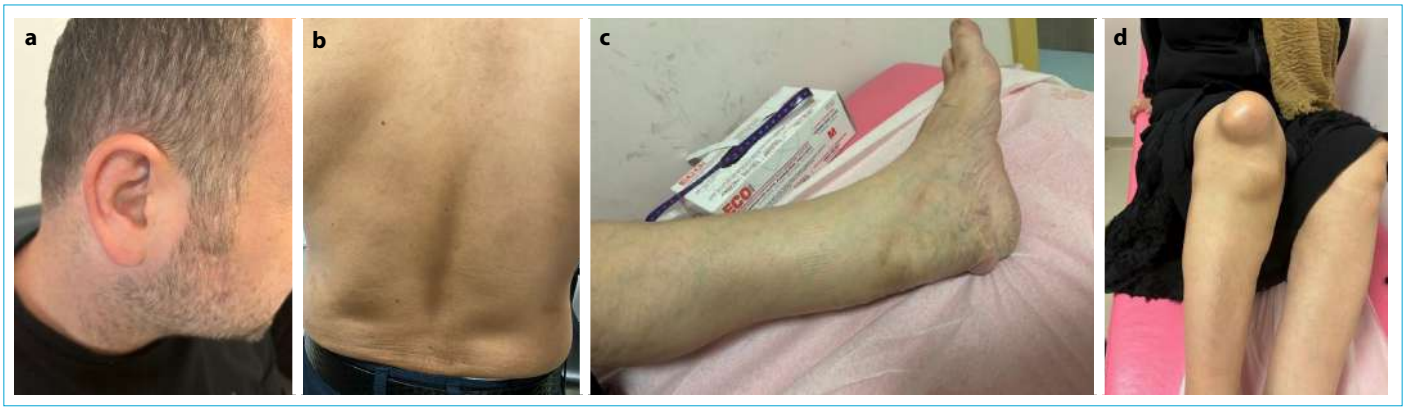

Figure 1. Images of cases. **(a)** Patient no 2- Ear ochronosis. **(b)** Patient no 6- Anjiokeratoma of Fabry disease. **(c)** Patient no 16- Xanthoma in the left achilles tendon. **(d)** Patient no 16- Xanthoma in the right knee.

features, diagnostic processes, and treatment pathways of 20 adult patients diagnosed with IMDs. It aims to increase awareness of these conditions among healthcare professionals.

Timely diagnosis of IMDs is essential for initiating treatment, determining prognosis, and conducting family screening. A study conducted in Spain reported that the average age of diagnosis in adult patients was 39 years, with a mean diagnostic delay of 8.6 years from the onset of symptoms.[8] Similarly, one study found that adult patients were diagnosed, on average, 15 years after the appearance of their initial symptoms.[9] In our cohort, the mean age of the patients was 38 years, and the average diagnostic delay was 7 years. This delay may be attributed to insufficient recognition of the chronic and mild phenotypes of IMDs by adult specialists and limited access to biochemical tests necessary for diagnosis.

A study from Saudi Arabia showed that the most frequent specialties visited before IMD diagnosis were neurology, ophthalmology, nephrology, pulmonology, and gastroenterology.[10] Similarly, in our study, the most common specialties patients consulted were internal medicine, gastroenterology, nephrology, cardiology, and orthopedics. Until receiving a definitive diagnosis, these patients were often misdiagnosed with conditions such as osteoarthritis, psoriatic arthritis, renal and heart failure, proteinuria, interstitial lung disease, and hepatosteatosis. Given the broad clinical heterogeneity of IMDs and their multisystemic nature, it is essential to recognize that patients may present to a variety of medical specialties. Clinicians should be vigilant for symptoms or findings suggestive of disorders outside their primary specialty and refer patients for further metabolic and genetic testing when necessary.

In our study, Fabry disease was the most frequently diagnosed condition (20%). Reports indicate that Fabry disease and mitochondrial disorders are commonly diagnosed in adulthood.[5] A five-year study from Italy identified Fabry disease, urea cycle defects, and glycogen metabolism disorders as the most common IMDs diagnosed after the age of 16.[13] Similarly, a study conducted in Türkiye reported that Fabry disease, along with citrullinemia type 2, multiple acyl-CoA dehydrogenase deficiency, alkaptonuria, and adrenoleukodystrophy, were the most frequent diagnoses in adult IMD patients.[14] These findings align with our results.

Conclusion

In conclusion, the significant increase in the number of adults diagnosed with IMDs suggests that many adult IMD patients remain undiagnosed. To establish the most effective diagnostic approach for adults presenting with diverse symptoms and suspected IMDs, it is crucial to first identify the clinical and biochemical phenotypes of patients and then select and sequence appropriate metabolic and genetic tests. Clinicians should recognize that the majority of IMDs are treatable, and early diagnosis allows some patients to live unaffected or minimally affected by their condition and its complications. While the chronic and mild phenotypes of certain IMDs may pose diagnostic challenges, increasing awareness among healthcare professionals and conducting further research are critical steps toward improving detection and management.

Disclosures

Ethics Committee Approval: The Non-Interventional Research Ethics Committee of Şişli Hamidiye Etfal Training and Research Hospital, University of Health Sciences Ethics Committee granted approval for this study (date: 19/11/2024, number: 4623/2024).

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Original Research

Evaluation of Our Paediatric Patients Hospitalised with Covid-19 Diagnosis: Single Centre Experience

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Abstract

Objectives: We analyses separate age groups for in-hospital COVID pediatric patients clinical symptoms, lab tests, and treatment efforts. We also wanted to see if having another illness or a patient's nutritional condition could change the way the disease unfolds.

Methods: Between July 2020 and September 2021, 90 pediatric patients (aged 1 month-18 years) with positive PCR and/or antibody tests who were hospitalised in our hospital were included in the study. Patients were classified according to age groups (0-2, 2-5, 5-12, >12 years), disease severity and presence of comorbidities. Demographic characteristics, clinical findings, laboratory parameters and radiological imaging were evaluated.

Results: The disease had a mild course in 73.3% of the patients with a mean age of 87 months. In the youngest age group (0-2 years), fever (53.3%) and respiratory distress (26.7%) were more common and hospital stay was longer (median 7 days). Comorbidity rate (47.4%) was significantly higher in the moderate to severe disease group ($p<0.001$). The rates of elevated CRP (54.5%) and pathological chest radiography (36.4%) were higher in obese children. Recovery time was significantly longer in comorbid patients (7.3±2.4 days).

Conclusion: Our study suggests that COVID-19 does not affect all children in the same way—it appears to vary notably with age. In our observations, younger children and those with existing health conditions seem to require a bit more care and close monitoring to ensure the best outcomes.

Keywords: Paediatric COVID-19, clinical features, comorbidities, nutritional status, hospitalisation outcomes

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The COVID-19 pandemic has become a major public health crisis, profoundly affecting global health, economy and social life. Although SARS-CoV-2 infection is considered a mild disease, especially among children, there is still limited information on how children can be protected against the long-term consequences of COVID-19.[1, 2] Although low morbidity rates have been observed among children, cases with a severe course have been reported to be mostly associated with comorbidities. This requires a better understanding of the clinical and laboratory characteristics of the paediatric population and optimisation of treatment approaches.[3, 4]

The existing literature on the effects of COVID-19 on children focuses on the mild course of the disease in children. However, most of these studies are based on general findings and do not address the relationships between age groups, clinical symptoms and laboratory results in sufficient detail. In particular, studies describing the effects of

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children with comorbidities on treatment outcomes are limited.[1] In addition, it has been reported that COVID-19 is not limited to mild symptoms in children, and some patients may develop post-infectious hyperinflammatory syndromes such as Multisystem Inflammatory Syndrome (MIS-C).[5] This study aims to fill the knowledge gap in this field by detailing the clinical features of COVID-19 cases in childhood and the impact of comorbidity on the disease course.

There are still significant gaps in knowledge about the clinical course and treatment approaches of COVID-19 in childhood. In our study, we hypothesised that clinical differences, laboratory findings and treatment responses will vary between age groups in pediatric patients hospitalised with a diagnosis of COVID-19. It was predicted that the disease would be more severe especially in younger age groups, the clinical picture would be more serious in the presence of comorbidities, and the duration of treatment would be prolonged. According to this hypothesis, our research goal was to analyze and compare the clinical particulars, laboratory results, radiological imaging, and treatment responses of children hospitalized due to COVID-19 by age groups, while also assessing the impact of comorbidities and nutritional status on the progression of the disease. The information we expect to gather, we believe, will aid in the formulation of age-specific management protocols and risk factor determination in cases of childhood COVID-19 infection.

Methods

Study Design and Patient Selection

This study is a retrospective, single-centre study conducted at a tertiary care hospital between 1 July 2020 and 30 September 2021. The study included hospitalised paediatric patients aged between 1 month and 18 years, whose COVID-19 diagnosis was confirmed by PCR and/or antibody tests. Nasopharyngeal and oropharyngeal swab samples were taken for PCR testing, and the samples were analysed by the real-time RT-PCR method. Suspected COVID-19 cases with negative PCR and antibody tests were excluded from the study.

Data Collection and Clinical Evaluation

Demographic characteristics, clinical findings, laboratory results and radiological imaging were obtained from patient files and electronic records. Age, gender, body mass index, underlying diseases, presenting complaints, contact history and duration of hospitalisation were recorded on a case follow-up form specially prepared for each patient. Laboratory tests included complete blood count parameters (haemoglobin, leukocyte, neutrophil, lymphocyte, platelet), inflammatory markers (CRP, sedimentation, procalcitonin, ferritin, fibrinogen), D-dimer, liver function tests (AST, ALT), cardiac markers (troponin, CK-MB), LDH and other biochemical parameters.

Radiological Evaluation

Chest radiographs of all patients were taken and evaluated for the presence of pathological findings. Thorax computed tomography (CT) examination was performed in the presence of a clinical indication. Thorax CT findings were classified as stage 1 (minimal involvement), stage 2 (moderate involvement) and stage 3 (extensive involvement) according to the extent of infiltration. All chest radiographs were retrospectively reviewed and evaluated by a board-certified pediatric radiologist who was blinded to the clinical data.

Treatment and Follow-up

Patients were followed up with antibiotic-free follow-up, antiviral treatment (Favipiravir), antibiotic treatment, anticoagulant treatment or combinations of these treatments according to clinical findings. Complications (bacterial superinfection, MIS-C) and the need for oxygen therapy were recorded.

Statistical Analysis

In our study, statistical analyses were performed using IBM SPSS Statistics for Windows, Version 26.0 (Armonk, NY: IBM Corp.). In descriptive statistics, number and percentage values for categorical variables, mean, standard deviation, minimum and maximum values for numerical variables were given. In the comparison of independent groups, Student t-test was used when the normal distribution condition was met, and Mann Whitney U test was used when it was not met. Chi-square test was used to compare categorical variables. Determinant factors were analysed by logistic regression analysis. Statistical significance level was accepted as $p<0.05$.

Ethics Committee Approval

The study protocol was approved by Prof. Dr. Cemil Taşcıoğlu City Hospital Ethics Committee (Approval Date: 08.11.2021, Number: 390). All stages of the study were conducted in accordance with the principles of the Declaration of Helsinki.

Results

In retrospective analyses of pediatric patients who were hospitalised with a diagnosis of COVID-19 since the beginning of the pandemic, differences according to age groups

are noteworthy. In 90 paediatric patients evaluated, the mean age was 87 months (minimum 1 month, maximum 384 months). When the patients were divided into age groups, symptoms such as fever and respiratory distress were observed more frequently in the youngest age group (0-2 years) and the hospital stay was longer. In this group, the proportion of patients treated without antibiotics was lower and the proportion of patients treated with antiviral therapy was higher. As we moved towards the older age groups (5-12 years and 12+ years), the disease showed a milder course and complications decreased. In addition, the rate of avoiding antibiotic use increased in these groups. In terms of laboratory findings, significant differences were found in white blood cell and CRP values according to age groups; these findings were associated with the severity of the disease. In treatment approaches, the need for oxygen therapy was observed more frequently in younger age groups, whereas this rate decreased in older children. In general, the duration of hospitalisation shortened with increasing age, with the longest in the 0-2 age group and the shortest in the 12+ age group (Table 1) (Fig. 1).

In our study, laboratory and radiological findings of 90 pediatric patients hospitalised with the diagnosis of COVID-19 were evaluated. Haemoglobin values were generally normal or slightly low. White blood cell counts varied in a wide range and were found below or above normal limits in some patients. Lymphocyte counts were significantly decreased in severe cases. Platelet counts were mostly within the normal range. Inflammatory markers (CRP, ferritin and D-dimer) evaluated according to age groups tended to increase with increasing age. In particular, CRP levels were found to be low in the youngest age group, but increased significantly in the group older than 12 years. Ferritin and D-dimer values similarly showed an age-related increase. When the risk classification of the patients was made, it was observed that children in the high-risk group had elevated levels of at least two markers and required close follow-up. In the medium-risk group, there were patients with single marker elevation, while all markers were normal in the low-risk group. Radiological examinations showed that pathological findings were detected more frequently in chest radiographs in young children. While pathological findings were 40% in the 0-2 age group, this rate decreased to 25%

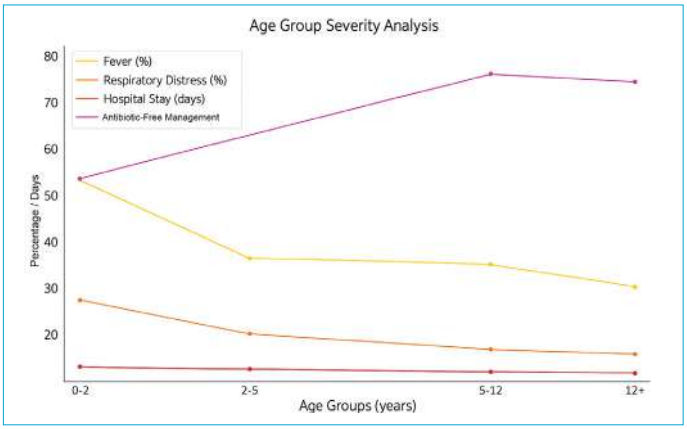

Figure 1. Age Group Severity Analysis: The figure illustrates the severity of COVID-19 across different pediatric age groups based on key clinical parameters. It presents trends for fever (%), respiratory distress (%), hospital stay (days), and antibiotic-free management (%), showing variations in disease severity and treatment approaches across age groups.

Table 1. Key demographic and clinical characteristics of paediatric COVID-19 patients (n=90)

Characteristics	Overall (n=90)	0-2 years (n=15)	2-5 years (n=18)	5-12 years (n=32)	12+ years (n=25)	p
Age (months), median (min-max)	87 (1-384)	-	-	-	-	<0.001
Gender (F/M), n	42/48	7/8	9/9	15/17	11/14	0.532
BMI (kg/m^2), mean±SD	19.1±6.8	16.8±2.1	17.4±2.3	19.3±4.2	22.1±5.8	<0.001
Presenting symptoms, n (%)						
Fever	35 (38.9)	8 (53.3)	7 (38.9)	12 (37.5)	8 (32.0)	0.003
Respiratory distress	12 (13.3)	4 (26.7)	3 (16.7)	3 (9.4)	2 (8.0)	0.001
Lab findings						
WBC (×10^3/μL), mean±SD	-	8.2±3.1	7.8±2.9	7.3±2.8	6.9±2.7	0.042
CRP (mg/L), median	-	3.8	3.2	2.6	2.1	0.038
Treatment, n (%)						
Antibiotic-free management	-	8 (53.3)	12 (66.7)	26 (81.3)	20 (80.0)	<0.001
Antiviral therapy	-	4 (26.7)	3 (16.7)	4 (12.5)	3 (12.0)	0.008
Oxygen requirement	-	3 (20.0)	2 (11.1)	2 (6.3)	1 (4.0)	0.002
Hospital stay, median days (min-max)	5 (1-21)	7 (2-21)	6 (1-15)	4 (1-12)	4 (1-10)	<0.001

Statistical Analysis: Mann-Whitney U test/Kruskal-Wallis test for continuous variables; Chi-square test for categorical variables.

in the 5-12 age group. Computed tomography was performed only in severe cases and pathological findings were observed in most of these patients. Radiological examinations support that the disease has a more severe course especially in young children (Table 2).

In our study, treatment approaches, symptom profiles, recovery times and complications of paediatric patients hospitalised due to COVID-19 were evaluated in detail. In the majority of patients (73.3%), the disease showed a mild course and was treated with conservative methods. In this group, hospitalisation was generally short (median 4 days) and treatment was limited to symptomatic monitoring. In moderate disease, antiviral therapy (e.g. Favipiravir) was used and hospitalisation was longer on average (median 6 days). In more severe cases, combined treatment approaches (including antibiotics, low molecular weight heparin or supportive therapies) were required, with a median length of stay of up to 8 days. When symptom patterns were analysed, 27.8% of patients had fever only, and this group generally had a mild course. Cases with cough (16.7%) usually had a mild to moderate course, while cases with respiratory symptoms (30%) had a more severe course. The combination of respiratory and systemic symptoms indicated a more severe disease picture requiring antiviral and oxygen therapy. Similarly, the need for treatment increased in cases where respiratory and gastrointestinal symptoms were combined. In 4.4% of the cases, gastrointestinal symptoms such as diarrhea and vomiting were observed in combination with respiratory symptoms. Isolated gastrointestinal symptoms were not reported in this cohort. Although these combined symptoms were more frequently seen in the younger age group, no statistically significant difference was found between age groups ($p>0.05$) (Table 3). 6.7% of patients were considered asymptomatic and were kept under observation only. When recovery times were evaluated according to age groups, the shortest recovery time was observed in the 5-12 age group (mean 4.9 days), while the longest recovery time was recorded in the 0-2 age group (mean 6.2 days). The recovery time was significantly prolonged in children with comorbidities (mean 7.3 days), whereas children without comorbidities recovered faster (mean 4.6 days). In terms of complications, bacterial superinfection was detected in 7.8% of patients and these patients required antibiotic treatment. Multisystem inflammatory syndrome (MIS-C) was observed in 3.3% of cases and these patients were treated with intravenous immune globulin (IVIG) and steroids. Myocarditis was observed in 2.2% and required close follow-up. Intensive care or oxygen therapy was required in 8.9% of patients (Table 3).

Table 2. Laboratory and radiological findings in paediatric COVID-19 (n=90)

Category	Parameter	Value/Range	Reference Range
Key Laboratory Parameters	Haemoglobin (g/dL)	11.8±1.9	11.5-15.5
	WBC (/μL)	7350 (1830-18600)	4500-11000
	Lymphocytes (/μL)	2510 (330-11790)	1500-7000
	Platelets (/μL)	287000±98000	150000-450000
Inflammatory Markers by Age Group	CRP (mg/L)	See below	<5.0
	Ferritin (ng/mL)	See below	7-140
	D-dimer (ng/mL)	See below	<500
Age-Specific Inflammatory Marker Values	0-2 years	CRP: 1.98±1.2, Ferritin: 75.6±45.3, D-dimer: 425±180	-
	2-5 years	CRP: 2.45±1.8, Ferritin: 82.4±52.1, D-dimer: 445±195	-
	5-12 years	CRP: 3.15±2.1, Ferritin: 95.8±58.4, D-dimer: 465±210	-
	>12 years	CRP: 3.85±2.4, Ferritin: 108.2±62.7, D-dimer: 485±225	-
Disease Severity Classification	High Risk (n, %)	22 (24.4%)	≥2 elevated markers
	Moderate Risk (n, %)	35 (38.9%)	1 elevated marker
	Low Risk (n, %)	33 (36.7%)	Normal markers
Imaging Findings	Chest X-ray (Normal)	63 (70.0%)	-
	Chest X-ray (Pathological)	27 (30.0%)	-
	CT Findings (Normal)	5 (21.7%)	-
	CT Findings (Pathological)	18	78.3%) -

All values are expressed as mean±SD or median (range). Statistical significance is set at $p<0.05$. CT imaging was performed only in selected severe cases.

Table 3. Treatment approaches, symptom patterns, recovery, and complications

Category	Parameter	Value/Details
Treatment Approaches	Conservative Management (n, %)	66 (73.3)
	Antiviral Therapy - Favipiravir (n, %)	11 (12.2)
	Combination Therapy* (n, %)	13 (14.5)
	*Includes combinations with antibiotics, LMWH, or other supportive treatments	-
Symptom Patterns and Outcomes	Isolated Fever (n, %)	25 (27.8)
	Isolated Cough (n, %)	15 (16.7)
	Respiratory Symptoms† (n, %)	27 (30.0)
	Combined Symptoms: Resp + Systemic	8 (8.9)
	Combined Symptoms: Resp + GI	4 (4.4)
	Combined Symptoms: Fever + Fatigue	10 (11.1)
	Asymptomatic (n, %)	6 (6.7)
	†Includes dyspnoea and other respiratory symptoms	-
Recovery Patterns	Mean Recovery Time (days) by Age Group	-
	0-2 years	6.2±2.1
	2-5 years	5.8±1.9
	5-12 years	4.9±1.7
	>12 years	5.4±2.0
	Recovery Time by Comorbidity Status	-
	Present	7.3±2.4
	Absent	4.6±1.5
Complications and Special Care Needs	Bacterial Superinfection (n, %)	7 (7.8)
	MIS-C (n, %)	3 (3.3)
	Myocarditis (n, %)	2 (2.2)
	ICU/Oxygen Need (n, %)	8 (8.9)

Values are expressed as mean±SD or median (range). Statistical significance is set at $p<0.05$. Treatment escalation is based on disease severity.

In our study, clinical characteristics, laboratory findings, treatment approaches and the effects of comorbidities were analysed in paediatric patients hospitalised with a diagnosis of COVID-19. While the median age of the patients in the mild disease group was 73 months, the median age in the moderate-severe disease group was 156 months. The rate of comorbidities was significantly higher in the moderate-severe disease group (47.4%) compared to the mild disease group (21.1%). Patients with a body mass index over 25 kg/m^2 were more common in the moderate-severe disease group (26.3% vs. 8.5%). Laboratory findings played an important role in the determination of disease severity. Lymphopenia, CRP >5 mg/L and D-dimer >500 ng/mL were frequently observed in the moderate-severe disease group, and elevated values of these parameters showed a strong correlation with disease severity. In the mild disease group, conservative treatment methods were generally applied and the median duration of treatment was determined as 4 days. In the moderate-severe disease group, antiviral therapy or combined therapy (antiviral, antibiotic and oxygen support) was more commonly used, and the median duration of treatment in these patients was prolonged up to 7 days. The impact of comorbidities on disease severity and length of hospital stay is striking. Respiratory diseases were generally of moderate severity, with a median length of hospitalisation of 4 days. Cardiac problems were associated with a higher severity of illness and the median length of stay was 12 days. Patients with neurological and metabolic-endocrine diseases showed a moderate disease severity, with median length of stay of 5 and 6 days, respectively. Patients with haematological or oncological diseases had the most unfavourable prognosis in terms of disease severity and risk of complications, with a median length of stay of 10 days (Table 4) (Fig. 2).

In our study, nutritional status, clinical course, laboratory and imaging findings, and contact history of paediatric patients hospitalised due to COVID-19 were investigated. As a result of the classification of patients according to body mass index (BMI), it was observed that the severity of the disease was higher, laboratory abnormalities and complication rates were higher in obese or overweight children. This group stayed longer in the hospital (median 6 days) and had

Table 4. Clinical characteristics, laboratory findings, treatments, and comorbidity impacts

Category	Parameter	Mild Disease (n=71)	Moderate-Severe (n=19)	p
Demographics & Risk Factors	Median Age (months)	73 (2-214)	156 (3-384)	0.024
	Presence of Comorbidity (%)	15 (21.1)	9 (47.4)	<0.001
	BMI >25 kg/m^2 (%)	6 (8.5)	5 (26.3)	0.018
Laboratory Findings	Lymphopenia (<1500/μL)	-	28 (31.1)	-
	CRP >5 mg/L	-	31 (34.4)	-
	D-dimer >500 ng/mL	-	34 (37.8)	-
Treatment Categories	Conservative Management (%)	66 (73.3)	Median Duration: 4 (1-8)	-
	Antiviral Therapy (%)	15 (16.7)	Median Duration: 5 (5-10)	-
	Combination Therapy* (%)	9 (10.0)	Median Duration: 7 (5-21)	-
Comorbidity Impacts	Respiratory (%)	8 (8.9)	Moderate severity risk	Median Stay: 4 days
	Cardiac (%)	2 (2.2)	High severity risk	Median Stay: 12 days
	Neurological (%)	6 (6.7)	Moderate severity risk	Median Stay: 5 days
	Haematologic/Oncologic (%)	3 (3.3)	High severity risk	Median Stay: 10 days
	Metabolic/Endocrine (%)	6 (6.7)	Moderate severity risk	Median Stay: 6 days

All p-values for severity associations are <0.05. Treatment duration varies significantly based on disease severity and complications. Comorbidities significantly impact both disease severity and length of stay. Statistical tests: Chi-square, Fisher's exact test, Mann-Whitney U test. OR = Odds Ratio, CI = Confidence Interval, AB = Antibiotic, O_2 = Oxygen therapy.

a slower response to treatment. In normal weight children, the disease showed a more stable course and the median length of hospitalisation was 5 days. Patients categorised as underweight generally had a milder disease course, shorter hospitalisation (median 4 days) and fewer complications. Laboratory and imaging findings varied according to BMI. Among obese or overweight patients, 54.5% had elevated CRP and 36.4% had abnormal chest radiographs. These rates were 36.6% and 34.1% in normal weight patients and 26.3% and 23.7% in lean patients, respectively. These findings suggest that BMI is directly related to disease severity. In the contact history analysis, a milder disease course was generally observed in patients who were infected from the same household. Patients in this group were hospitalised for a shorter period (median 4 days) and had lower complication rates (7.7%). Patients infected outside the same household had a more severe disease course, longer hospitalisation (median 6 days) and higher complication rates (15.8%). In patients without a history of contact, the most severe disease presentations and the highest treatment requirements were recorded (Table 5) (Fig. 2).

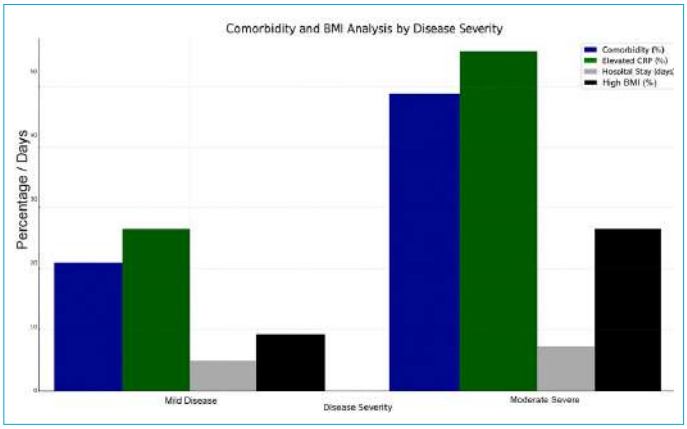

Figure 2. Comorbidity and BMI Analysis by Disease Severity: This figure illustrates the relationship between comorbidities, elevated CRP levels, hospital stay duration, and high BMI (%) across mild and moderate-severe COVID-19 cases in pediatric patients. It highlights the increased prevalence of comorbidities, inflammatory markers, and prolonged hospitalization in more severe cases.

Discussion

Our investigation showed that the clinical progression of COVID-19 in children varies greatly between different age categories. Observation showed that younger children are more vulnerable to the infection and need more aggressive treatment approaches while with increasing age, children become less ill and require less treatment in fact, it is more likely that the disease will take a milder course. In addition to respiratory involvement, gastrointestinal symptoms such as diarrhea and vomiting have also been reported in pediatric patients, especially in younger age groups, and should be considered during clinical assessment.[6] This suggests that the clinical picture of COVID-19 infection in children is likely to be age specific and that management strategies should be developed bearing such differences in mind. The results of the study also, like many others, from evidence point out that children at the age of infanthood should be monitored very carefully and that the management plan to guide them should be age oriented.

Table 5. Nutritional status, clinical course, laboratory/imaging, and contact analysis

Category	Parameter	Underweight (n=38)	Normal (n=41)	Overweight/Obese (n=11)	p
BMI Characteristics	Mean BMI±SD	16.2±1.8	21.3±1.9	29.3±4.1	<0.001
	Height-for-age Normal (%)	89.5	92.7	90.9	0.042
Clinical Course	Mild Disease (%)	78.9	70.7	63.6	-
	Moderate-Severe Disease (%)	21.1	29.3	36.4	-
	Median Hospital Stay (days)	4 (1-12)	5 (1-15)	6 (2-21)	-
Laboratory/Imaging	Elevated CRP (%)	26.3	36.6	54.5	-
	Abnormal Chest X-ray (%)	23.7	34.1	36.4	-
Contact Analysis	Mild Disease (%)	76.9 (Household)	68.4 (Non-household)	-	0.028
	Complications (%)	7.7 (Household)	15.8 (Non-household)	-	0.008
	Median Stay (days)	4 (1-15) (Household)	6 (2-21) (Non-household)	-	0.002
Treatment Needs	Conservative Management (%)	76.9 (Household)	65.8 (Non-household)	-	-
	Additional Therapy* (%)	23.1 (Household)	34.2 (Non-household)	-	-

All p-values <0.05 are considered significant. Overweight and obese categories were combined due to small numbers. Contact categories were simplified to highlight key differences.

The data we obtained in this study clearly reveal the differences in the clinical course and treatment of COVID-19 among paediatric age groups. Especially in the 0-2 age group, fever and respiratory distress were the most common symptoms. Antibiotic and antiviral use rates are higher in this age group and hospitalisation periods are significantly longer than other age groups. Similarly, a systematic review by Patel et al.[7] reported that 27% of children hospitalised due to COVID-19 were infants under one year of age and this group required respiratory support at a higher rate.[7] In older age groups (5-12 and 12+ years), the disease generally has a milder course. Swann et al.[8] in a large cohort study conducted in the United Kingdom, it was found that COVID-19 had a milder course and hospitalisation rates were lower in children over 10 years of age.[8] In addition, the increase in the rate of antibiotic-free treatment with increasing age suggests that the immune response to infection in this age group may be more effective. Irfan et al.[9] also emphasised that the rates of severe clinical picture decreased with increasing age and treatment requirements were lower.[9] Our findings show that younger age groups are more vulnerable to COVID-19 infection and require more medical intervention. Interestingly, some studies have suggested a bimodal distribution in disease severity, with both infants (<1 year) and adolescents being at higher risk for severe illness.[10] This situation reveals that the management of infection and treatment strategies should be planned more carefully, especially in the 0-2 age group.

In our study, lymphopenia was frequently observed in severe COVID-19 cases. This observation has been reported in the literature quite extensively. In particular, low lymphocyte levels have been shown to be strongly associated with disease severity and activation of the inflammatory process.[11] In addition, it has been previously reported that C-reactive protein (CRP), ferritin and D-dimer levels tend to increase with increasing age and these parameters correlate with the severity of the disease.[12] From our analysis, it was noted that inflammation markers were elevated in patients above the age of 12. This supports the progressive inflammatory response mechanisms of COVID-19.[13] In our patients in the high-risk group, elevated levels of at least two inflammatory markers were observed. Similarly, it has been emphasised that ferritin levels exceeding 1000 ng/mL is an important marker for predicting severe respiratory distress and other complications.[14] The inclusion of inflammatory markers such as ferritin might be helpful in the diagnosis process and treatment as suggested by the result. In addition, it has been widely supported in the literature that high D-dimer levels are associated with thrombotic complications and increase the risk of mortality.[11, 13] Our study outcomes underscore the need to pay attention to tracking laboratory indicators, particularly with regard to their use in the control of complicated cases. Both in estimating the prognosis and devising personalised treatment plans, these parameters serve as useful indicators.

In our study, it was found that obese or overweight children had more severe disease, hospital stay was longer in this group, and the rates of elevated CRP (54.5%) and abnormal chest radiography (36.4%) were higher. In addition, it was observed that the disease had a milder course in normal or underweight children. The relationship between obesity and the clinical severity of COVID-19 is widely sup-

ported in the literature. According to the meta-analysis of Singh et al.,[15] obesity increases the risk of severe disease by 52% in COVID-19 patients (RR=1.52, 95% CI 1.41-1.63). Likewise, in the systematic review of Nour and Altintas,[16] it was stated that the prevalence of obesity increased significantly due to the quarantine conditions in the pandemic, which increased the complications associated with COVID-19. Elevated CRP levels and high rates of abnormal chest radiographs suggest that the inflammatory response may be more intense in obese individuals. In the study by Choi et al.,[17] it was stated that inflammatory markers were higher in obese patients and this increased the risk of worsening of the disease. In addition, weakening of the immune system and increased inflammatory response in obese children may prolong hospitalisation and lead to more serious consequences of the disease.[14] The milder symptoms in normal or underweight individuals may be due to the metabolic and immunological advantages of these individuals.[18] This finding suggests that maintaining a healthy BMI, especially in children, may favourably affect the clinical course of COVID-19.

In our study, the rate of comorbidities was high in the moderate to severe disease group (47.4%). It was observed that cardiac diseases prolonged the hospital stay (12 days) and haematological or oncological comorbidities negatively affected the prognosis. In addition, recovery time was longer in comorbid patients (mean 7.3 days). These findings are consistent with previous studies in the literature. For example, Zhang et al.[19] reported that patients with comorbidities had a poor prognosis and increased disease severity after COVID-19 infection. In the same study, it was emphasised that especially cardiovascular diseases were associated with high mortality rates.[19] Similarly, Notarte et al.[20] reported that infection was more severe in individuals with haematological malignancy and immune response was suppressed in this group.[20] In a large-scale study conducted by Woodruff et al.[21] in a paediatric patient population, it was reported that children with comorbidities had higher intensive care needs and increased mortality rates.[21] Martin et al.[22] showed that haematological comorbidities increased the severity of COVID-19 disease in children and the recovery time of these patients was significantly prolonged.[22] These findings emphasise the significant effect of the presence of comorbidities on the clinical course of COVID-19 infection. We find literature that supports this claim, plus it illustrates once more the impact various forms of comorbidities have on clinical results.

Our study has some limitations. The single centre and relatively limited number of patients may affect the generalisability of our findings. In addition, there may have been difficulties in accessing some clinical data due to its retrospective design. However, our study also has strengths. Considerable understanding of the progression of COVID-19 disease in children was obtained from a meticulous assessment of the patient's clinical details, laboratory tests, and imaging studies. In particular age group specific analyses have been instrumental in appreciating the differing features of the disease in varies age categories. Targeted multicenter research focusing on a larger sample set is imperative for confirming the data in the future. Simultaneously, the prolonged consequences of the sickness and the potential developable late-stage problems ought to be addressed in follow-up studies. In more focused terms, future work may study in more details the risk determinants as well as compare the treatment modalities for their effectiveness.

Conclusion

Our study revealed that the course of COVID-19 in children shows significant differences between age groups. The fact that the disease is more severe and requires more intensive treatment especially in younger age groups emphasises the necessity of special approaches for this age group. Moreover, the existence of comorbidities and nutritional elements seem to have considerable impact on the disease's progression. Based on the information presented, age-tailored management protocols and risk assessment during COVID-19 treatment in pediatric patients is necessary. In-depth studies will at some point be able to validate these conclusions and enhance the transitions towards different suppositions. In this way, more effective management of COVID-19 infection in the pediatric age group can be achieved and the negative consequences of the disease can be minimised.

Disclosures

Ethics Committee Approval: The study protocol was approved by the Ethics Committee of Prof. Dr. Cemil Taşcıoğlu City Hospital (Approval Date: 08.11.2021, Number: 390).

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Original Research

Comparative Analysis of Girls With Slowly Progressive Central Precocious Puberty Vs. Rapidly Progressive Central Precocious Puberty: Single-Center Experience

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Abstract

Objectives: Central precocious puberty (CPP) can present as either slowly progressing CPP (SP-CPP) or rapidly progressing CPP (RP-CPP). The speed of progression is critical in determining treatment decisions. This study aims to compare the clinical data between patients who received treatment and those who did not, and to identify factors that may influence the progression in cases of RP-CPP.

Methods: This single-center retrospective observational study includes 406 female patients aged 5-8 years who were followed for CPP at the pediatric endocrinology clinic between 2021 and 2023. The patients were categorized into two groups: those with SP-CPP who did not receive gonadotropin-releasing hormone agonist (GnRHa) treatment (n=252) and those with RP-CPP who did receive GnRHa treatment (n=154). Patients were analyzed according to clinical, laboratory, and radiological findings.

Results: The median age at onset of pubertal signs were 7.2 years (Range 5-8) for the SP-CPP group and 7 (5-8) years for the RP-CPP group (p=0.352). In univariate analysis, Tanner breast stage, luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, peak LH levels, and bone age/chronological age ratios were significantly higher in the RP-CPP group. In multivariate logistic regression analysis, Tanner breast stage (p=0.001) and the bone age/chronological age ratio (p<0.001) were found to be a significant parameter, while other variables were not significant (p>0.05).

Conclusion: In this cohort, the bone age/chronological age ratio is a significant parameter for early detection of rapidly progressing precocious puberty cases. It is crucial to classify early puberty cases by evaluating clinical, laboratory, and radiological findings collectively and to make treatment decisions based on individual assessments.

Keywords: Bone age, chronological age, GnRHa treatment, precocious puberty

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Central precocious puberty (CPP) is characterized by the early activation of the hypothalamic-pituitary-gonadal (HPG) axis, resulting in the early onset of pubertal signs in children. This condition is defined by the onset of pubertal development before age 8 in girls and before age 9 in boys.[1, 2] Central precocious puberty can be classified based on the clinical course, progression of puberty, and growth rate into slowly progressing CPP (SP-CPP) and rapidly progressing precocious puberty (RP-CPP). In SP-CPP, pubertal signs and hormone levels increase gradually, whereas RP-CPP may exhibit an aggressive course, where monitoring alone is insufficient and early diagnosis and treatment are crucial for preserving final height.[2, 3]

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This study aims to: (1) examine the anthropometric measurements and hormonal values of girls aged 5-8 years presenting with pubertal signs; (2) compare the presenting features, anthropometric, and pubertal findings of treated and untreated patient groups; and (3) highlight the importance of these data in making treatment decisions.

Methods

A total of 406 girls diagnosed with CPP and followed up in the pediatric endocrinology unit between 2021-2023 were included in this single-center, retrospective observational study.

Girls with a starting age of pubertal signs ≤8 years and those who started idiopathic puberty without menarche were included. Cases of peripheral precocious puberty, patients with organic lesions detected on cranial magnetic resonance imaging, secondary precocious puberty caused by cerebral palsy or hydrocephalus, accompanying systemic diseases, history of medications potentially affecting the HPG axis, growth hormone deficiency, uncontrolled thyroid disease, or adrenal-gonadal pathology, any metabolic or genetic diseases that causes CPP were excluded from the study.

The patients were divided into two groups by evaluating their clinical findings during a minimum 6-month follow-up period: RP-CPP group, also receiving gonadotropin releasing hormone agonist (GnRHa) treatment (n=154), and the SP-CPP group, not receiving GnRHa treatment (n=252). The criteria for CPP included the onset of secondary sexual characteristics before age 8, increased double wall thickness of the endometrium, a uterus long axis >35 mm on pelvic ultrasonography (USG), a basal Luteinizing Hormone (LH) value>0.2 mIU/L, and bone age (BA) equal to or greater than chronological age (CA). Inclusion criteria for the RP-CPP group included breast development progressing through stages within 6 months, rapidly advancing BA and growth rate exceeding that of healthy children. Patients not meeting these criteria were classified as SP-CPP.[3]

Patient Data and Anthropometric Measurements

Patient anamnesis, the duration of pubertal signs, and pubertal stages according to Tanner classification were obtained from electronic system records. Birth weight, gestational age, and identification of patients born small for gestational age (SGA) were noted. Patients born before 37 weeks of gestation were considered preterm. Birth weight was expressed as a standard deviation score (SDS) according to gestational age. Children with a birth weight SDS below 2 were classified as SGA.

For anthropometric measurements, a calibrated wall-mounted Harpenden Stadiometer (Holtain Ltd, Crymych, UK) was used. Body mass index (BMI) was calculated by dividing weight in kilograms by height in square meters. All measurements were expressed as SDS according to national standards. Patients were categorized based on BMI SDS according to World Health Organization criteria. Thus, those with BMI SDS between 1.3 and 1.8 SDS were considered overweight, and those with BMI SDS ≥1.8 SDS were considered obese.[4]

Laboratory Examinations and Radiological Imaging

Luteinizing hormone, follicle-stimulating hormone (FSH), and estradiol (E2) levels of all cases were evaluated. Cases with a basal serum LH level>0.2 mIU/L were considered to have an activated HPG axis based on clinical findings. A standard stimulation test with Gonadotropin-releasing hormone (GnRH) (Gonadorelin Acetate, LH-FSH 0.1 mg/mL; Ferring, Istanbul, Turkey) was administered intravenously at 100 mg in the morning, and serum LH and FSH levels were measured at 0, 30, 60, and 90 minutes. A peak LH of ≥5.0 mIU/L was considered indicative of HPG axis activation. Bone age was assessed using the Greulich and Pyle method.[5]

Pelvic USG was performed by an experienced radiologist to measure the long axis of the uterus and the double thickness of the endometrium. Cases with a uterine long axis >35 mm were evaluated as CPP based on clinical findings.[5]

Ethical Approval

The research has complied with all the relevant national regulations and institutional policies, is in accordance with the tenets of the Helsinki Declaration and has been approved by the Sisli Hamidiye Etfal Training and Research Hospital Clinical Research Ethics Committee (2024/4316). Written informed consent was obtained for all participant's legal guardians.

Statistical Analysis

Analyses were performed using SPSS version 24.0 (IBM Corp, Armonk, NY). Numbers, percentages, means, medians, etc., were used to summarize the results. The normal distribution of numerical data was assessed using the Shapiro-Wilk test. For normally distributed data, mean and standard deviation (SD) were reported, while median and interquartile range (IQR) were used for non-normally distributed data. Differences between groups and parametric data were compared using the Student's t-test. Non-parametric data were compared using the Mann-Whitney U test. Categorical data were compared using the chi-square test or Fisher's exact test. Variables found significant in univariate analysis ($p<0.05$) were included in multivariate logistic regression analysis to identify independent effective

factors. The diagnostic performance of factors significant in multivariate analysis were further evaluated using receiver operating characteristic (ROC) curves. The Youden index were calculated as sensitivity - (1-specificity) from the coordinates of the curve. All p-values were evaluated bidirectionally, with p<0.05 considered significant.

Results

The median age was 7.1 years (range 5-8 years). The median birth weight was 3100 grams (IQR 2750-3406), and 61 patients (15%) were classified as SGA. At the time of presentation, the median weight was 0.9 SDS, the median height was 0.8 SDS, and the median BMI was 0.96 SDS. Obesity was observed in 19.4% of the cases (n=79). Among the patients, 252 were classified as SP-CPP, and 154 as RP-CPP. There were no significant differences in demographic and anthropometric data between these two groups (Table 1).

When the pubertal examinations at the initial presentation were evaluated, the median stage of thelarche was 2 (IQR 2-3), and the median stage of pubarche was 2 (IQR 1-2). The laboratory and radiological features showed that the LH, FSH, E2, and peak LH values in the SP-CPP group were 0.6 (IQR 0.4-0.9) mIU/L, 2 (IQR 1.2-3) mIU/L, 5 (IQR 5-14.9) pg/mL, and 4.1 (IQR 3.4-5.9) mIU/L, respectively. In the RP-CPP group, these values were 0.8 (IQR 0.5-2.2) mIU/L, 2.5 (IQR 1.6-4.6) mIU/L, 10 (IQR 5-23.8) pg/mL, and 5 (IQR 3.6-7.5) mIU/L, respectively. All hormone levels in the RP-CPP group were statistically significantly higher than those in the SP-CPP group (p<0.001, p<0.001, p=0.003, and p=0.002, respectively) (Table 2).

Table 1. Demographic and clinical features of the participants

Variables	All patients (n=406)	SP-CPP (n=252)	RP-CPP (n=154)	p
Age (years, median, range)	7.1 (5-8)	7.2 (5-8)	7 (5-8)	0.352[a]
Birth weight (gr, median, IQR)	3100 (2750-3406)	3100 (2747-3400)	3075 (2787-3425)	0.769[a]
Presence of SGA (n, %)				
Absent	345 (85)	217 (86.2)	128 (83.2)	0.412[b]
Present	61 (15)	35 (13.8)	26 (16.8)	
Weight SDS (median, IQR)	0.9 (0.3-1.5)	0.9 (0.29-1.55)	0.9 (0.3-1.5)	0.855[a]
Height SDS (median, IQR)	0.8 (0.23-1.4)	0.79 (0.24-1.49)	0.83 (0.22-1.37)	0.792[a]
BMI SDS (median, IQR)	0.96 (0.28-1.76)	1 (0.32-1.82)	0.91 (0.22-1.66)	0.432[a]
Presence of obesity (n, %)				
Absent	327 (80.6)	202 (80.2)	125 (81.2)	0.803[b]
Present	79 (19.4)	50 (19.8)	29 (18.8)	

[a]Mann-Whitney U-test; [b]Chi-square test; BMI: Body mass index; GnRH: Gonadotropin Release Hormone; IQR: Interquartile range; N/A: Non-applicable; RP-CPP: Rapidly progressive central precocious puberty; SDS: Standart deviation score; SGA: Small for Gestational Age; SP-CPP: Slowly progressive central precocious puberty.

Table 2. Puberty stage, laboratory and radiologic findings

Variables	All patients (n=406)	SP-CPP (n=252)	RP-CPP (n=154)	p
Tanner puberty stage (median, IQR)				
Thelarche	2 (2-3)	2(2-2)	3(2-3)	**0.001[a]**
Pubarche	2 (1-2)	2(1-2)	2(1-3)	0.488[a]
LH (mIU/L, median, IQR)	0.7 (0.4-1.4)	0.6 (0.4-0.9)	0.8 (0.5-2.2)	**<0.001[a]**
FSH (mIU/L, median, IQR)	2.2 (1.3-3.9)	2 (1.2-3)	2.5 (1.6-4.6)	**<0.001[a]**
Estradiol (pg/mL, median, IQR)	6.5 (5-20.3)	5 (5-14.9)	10 (5-23.8)	**0.003[a]**
Peak LH value (mIU/L, median, IQR)	4.5 (3.5-5.9)	4.1 (3.4-5.9)	5.7 (5-7.5)	**0.002[a]**
BA/CA (median, IQR)	1.14 (1-1.28)	1.12 (1-1.22)	1.25 (1.14-1.4)	**<0.001[a]**
Uterine length (cm, median, IQR)	34 (30-38.3)	33 (30.6-38.2)	35.1 (34-39.7)	0.442[a]
Endometrium thickness (mm, median, IQR)	1.75 (0.75-2.3)	1.6 (0.7-2.3)	1.8 (0.8-2.3)	0.813[a]
Height velocity SDS (median, IQR)	1.04 (0.16-2.51)	0.56 (-0.29-1.58)	1.46 (0.4-3.22)	**0.006[a]**

[a]Mann-Whitney U-test; BA/CA: Bone Age/Chronological Age; BMI: Body mass index; FSH: Follicle stimulating hormone; GnRH: Gonadotropin Release Hormone; IQR: Interquartile range; LH: Luteinizing hormone; N/A: Non-applicable; RP-CPP: Rapidly progressive central precocious puberty; SDS: Standart deviation score; SGA: Small for Gestational Age; SP-CPP: Slowly progressive central precocious puberty; All p-values less than 0.05 was bold.

The BA/CA ratio was a median of 1.12 (IQR 1-1.22) in the SP-CPP group and a median of 1.25 (IQR 1.14-1.4) in the RP-CPP group, showing a statistically significant higher ratio in the RP-CPP group (p<0.001). The pelvic USG measured the median uterine length for all patients at 34 mm (IQR 30-38.3), and the median endometrial thickness at 1.75 mm (IQR 0.75-2.3), with no significant differences between the two groups (p=0.442 and p=0.813, respectively) (Table 2).

There was a significant difference in the height velocity standard deviation (HVSD) between RP-CPP and SP-CPP groups, with SP-CPP having a lower HVSD compared to the RP-CPP group (p=0.006) (Table 2).

When the effects of being SGA or AGA on Tanner pubertal stage, LH, FSH, and estradiol levels, BA/CA ratio, and growth velocity were evaluated, no statistically significantly differences were observed between the two groups (Table 3). Among patients with SGA, those classified as RP-CPP had significantly higher LH and FSH levels and BA/CA ratios compared to those with SP-CPP (Table 4).

Tanner telarche stage, Luteinizing hormone, FSH, E2, peak LH value and BA/CA, which were significant in univariate analysis, were included in a binomial logistic regression analysis. In the multivariate analysis, Telarche stage (Odds ratio [OR]: 3.855, 95%-Confidence Interval [CI]: 1.704-8.719, p=0.001) and the BA/CA ratio remained significant (OR: 141.138, 95%-CI: 32.884-605.761, p<0.001), while the other parameters were loses their significance (Table 5).

Table 3. Distribution of laboratory and radiological parameters according to SGA or AGA status

Variables	All Patients (n=406)	SGA (n=61)	AGA (n=345)	p
Puberty stage (median, IQR)				
Breast	2 (2-3)	2 (2-3)	2 (2-3)	0.475[a]
Pubic	2 (1-2)	2 (1-2)	2 (1-2)	0.494[a]
LH (mIU/L, median, IQR)	0.7 (0.4-1.4)	0.7 (0.4-1.4)	0.7 (0.4-1.4)	0.514[a]
FSH (mIU/L, median, IQR)	2.2 (1.3-3.9)	2.2 (1.2-2.9)	2.2 (1.3-3.9)	0.055[a]
E2 (pg/ml) (median,IQR)	6.5 (5-20.3)	5 (5-14.8)	7.6 (5-21.2)	0.184[a]
BA/CA (median, IQR)	1.14 (1-1.28)	1.13 (1-1.25)	1.14 (1-1.29)	0.777[a]
Height Velocity SDS (median, IQR)	1.04 (0.16-2.51)	1 (0.14-2.3)	1.1 (0.2-2.72)	0.749[a]

[a]Mann Whitney U test; AGA: Appropriate for gestational age; BA/CA: Bone age/Chronological age; E2: Estradiol; FSH: Follicle stimulating hormone; IQR: Interquartile range; IU: International unit; LH: Luteinizing hormone; SDS: Standart derivation scores; SGA: Small for gestational age; All p-values less than 0.05 was bold.

Table 4. Distribution of Laboratory and Radiological Parameters in SGA Cases According to Rapid and Slow Puberty

Variables	SP-CPP (n=35)	RP-CPP (n=26)	p
Puberty Stage (Median, IQR)			
Breast	2 (1-2)	2 (2-3)	0.080[a]
Pubic	2 (1-2)	2 (1-2)	0.285[a]
LH (mIU/L, Median, IQR)	0.62 (0.4-1.2)	0.95 (0.64-1.97)	**0.047[a]**
FSH (mIU/L, Median, IQR)	1.73 (0.99-2.67)	3.13 (1.78-5.62)	**0.014[a]**
E2 (pg/ml) (Median,IQR)	5 (5-10)	6.3 (5-23.9)	0.184[a]
BA/CA (Median, IQR)	1.1 (1-1.16)	1.21 (1-1.37)	**0.016[a]**
HV SDS (Median, IQR)	0.42 (0.22-1.5)	0.91 (0.06-2.63)	0.425[a]

[a]Mann Whitney U test; BA/CA: Bone age/Chronological age; E2: Estradiol; FSH: Follicle stimulating hormone; HV: Height velocity; IQR: Interquartile range; IU: International unit; LH: Luteinizing hormone; RP-CPP: Rapidly progressive central precocious puberty; SDS: Standart derivation scores; SP-CPP: Slowly progressive central precocious puberty; All p-values less than 0.05 was bold

Table 5. Multivariate Analysis of Factors Influencing progression rate of precocious puberty

Variables	Odds ratio	Lower (95%-CI)	Upper (95%-CI)	p
Tanner puberty stage (telarche)	3.855	1.704	8.719	**0.001**
LH	1.085	0.909	1.294	0.368
FSH	1.058	0.952	1.174	0.295
Estradiol	1.007	0.993	1.021	0.312
Peak LH value	1.001	0.990	1.012	0.858
BA/CA	141.138	32.884	605.761	**<0.001**

Binomial logistic regression analysis; Ref: Reference, 95%-CI: 95% Confidence interval; All p-values less than 0.05 was bold.

The effect of BA/CA, identified as an independent variable, in evaluating the speed of precocious puberty development was assessed using a receiver operating characteristic (ROC) curve. A BA/CA higher than the 1.18 cut-off value predicted RP-CPP with 69.5% sensitivity and 69.4% specificity (Area under the curve: 0.727, p=0.001) (Fig. 1).

Discussion

Central precocious puberty can exhibit either slow or rapid progression patterns. The rapidly progressing form often necessitates GnRHa therapy due to the potential for accelerated bone maturation, physical maturation, and early menarche.

In this cohort, when comparing the RP-CPP group receiving GnRHa treatment to the SP-CPP cases, the treatment group

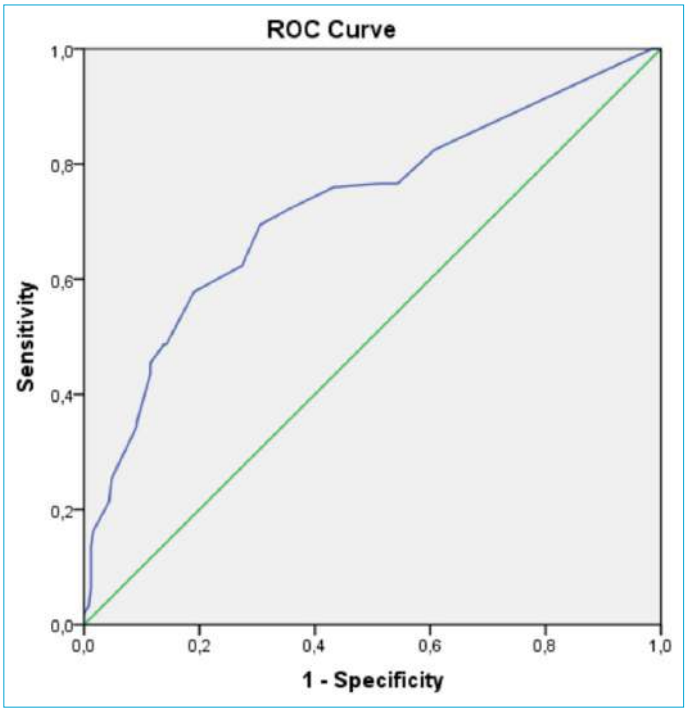

Figure 1. Receiver operating characteristic curve analysis for prediction of precocious puberty based on bone age/chronological age.

exhibited more advanced pubertal findings. Demirkale et al.'s study also observed that the RP-CPP group had more advanced breast development, although the pubic hair stage was similar between the two groups.[3] In this cohort, the thelarche stage in the SP-CPP group was significantly lower compared to the RP-CPP group, whereas there was no significant difference in pubic hair stages.

Nutritional habits, sedentary lifestyle, increased use of digital devices, and the resultant rise in obesity prevalence are factors influencing the development of CPP.[6] Chen et al. (2017) found a correlation between obesity and precocious puberty, identifying obesity as a contributing factor to CPP development.[7] Zeng et al. reported higher BA/CA in obese and overweight CPP children compared to those with normal weight, although laboratory parameters were similar.[8] In this cohort, 19.4% of CPP cases were obese, with obesity rates being comparable between the SP-CPP and RP-CPP groups.

It is known that SGA individuals have an increased risk of developing CPP compared to AGA individuals.[9] SGA individuals experience faster pubertal progression and may achieve a shorter final height.[10] Persson et al. highlighted that intrauterine exposures influence the onset of puberty, with SGA girls experiencing puberty and menarche approximately 5 months earlier than AGA girls.[11] Demirkale et al. reported similar menarche onset ages between SGA and AGA groups in SP-CPP cases.[3] Yu et al. found no differences in LH, FSH, and E2 levels between SGA and AGA CPP cases.[12] Our study, in line with the literature, found that 15% of CPP cases were SGA. Although laboratory variables were similar between the SGA and AGA groups, significant differences in LH, FSH, and BA/CA were observed between SGA-born SP-CPP and RP-CPP groups, with higher values in the SGA RP-CPP group.

Previous studies have indicated that GnRHa treatment provides no height benefits for girls with SP-CPP, consistent with the expectation that potential height gain is lost when bone age matures rapidly.[13] By definition, girls with a lower BA/CA ratio experience slower pubertal progression. Klein et al. demonstrated that a decrease in BA/CA is associated with delayed menarche onset and serves as a good indicator of pubertal suppression in treated girls.[14] Klein et al. showed a significant reduction in BA/CA in CPP cases receiving GnRHa treatment.[15] Some authors suggest making height-based treatment decisions for CPP girls undergoing GnRHa therapy. Adan et al. proposed treatment criteria based on predicting adult height (PAH) <155 cm and/or a LH/FSH peak ratio>0.6, observing greater breast development, advanced BA (2.0±0.2 years), and higher plasma E2 concentrations in the treatment group.[16] Léger et al. based treatment decisions on BA and peak LH, not treating those with less than 2 years of BA advancement and peak LH <6 mIU/mL, but initiating treatment if PAH declined and a final height exceeding PAH and TH was achievable.[17] Thus, BA advancement and its close association with PAH are critical determinants for GnRHa therapy decisions. Varimo et al. emphasized the importance of closely monitoring growth velocity and BA.[18] Kutlu et al. classified cases with a BA/CA>1.2 as rapidly progressing.[19] Demirkale et al. demonstrated in their study on final height that the BA/CA ratio in RP-CPP cases is higher compared to those with slower progression.[3] Our study suggests that a BA/CA ratio above 1.18 may serve as a predictive value for rapidly progressing puberty. While our study does not explicitly address the benefits of GnRHa therapy on final height and menarche age for children with a BA/CA ratio at this threshold, we believe early identification of RCPP can provide clinical benefits.

The main limitations of our study include its retrospective design and the relatively small sample size. Moreover, the lack of follow-up until final height represents a major limitation in assessing the long-term efficacy of GnRHa treatment. Furthermore, the comparable proportion of obese patients in both groups limits the ability to assess the impact of obesity. Another limitation of our study is the inability to evaluate family history and maternal or sibling age at menarche due to incomplete records.

Conclusion

The slow and rapidly progressing forms of CPP can be distinguished through clinical, laboratory, and bone age assessments. While SCPP generally follows a milder clinical course, RCPP requires more aggressive treatment. It is crucial to classify early puberty cases by their progression patterns through a combined evaluation of clinical, laboratory, and radiological findings, and to make individualized therapeutic decisions regarding GnRHa therapy. Understanding the tempo of puberty progression is vital in treatment decisions, and we believe that the BA/CA ratio can serve as a valuable guide in this context.

Disclosures

Ethic Committee Approval: The study was approved by the Sisli Hamidiye Etfal Training and Research Hospital Clinical Research Ethics Committee (date: 27.02.2024 number:4316).

Informed Consent: Written informed consent was obtained for all participant's legal guardians.

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Original Research

Therapeutic Plasma Exchange in Pediatric Intensive Care and Brief Overview of the Literature

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Abstract

Objectives: This study aimed to evaluate the therapeutic plasma exchange (TPE) procedures performed in our pediatric intensive care unit (PICU) and to review the relevant literature.

Methods: This retrospective study was conducted between 2020 and 2024. Forty-nine patients who received TPE at any point during their PICU stay were included. The groups were categorized as survivors and non-survivors.

Results: Of the 49 cases, 71.4% were male, with a median age of 54 months (range 20–135 months). A total of 274 TPE sessions were performed. The three most common indications for TPE were sepsis, trauma induced multiple organ dysfunction syndrome/disseminated intravascular coagulation, and neurological diseases. The non-survivor group had higher rates of chronic illness ($p<0.001$), pediatric risk of mortality score III, and pre- and post-procedure vasoactive inotropic scores ($p=0.005$, $p<0.001$, and $p<0.001$, respectively). The use of invasive mechanical ventilation and continuous renal replacement therapy ($p=0.005$, $p<0.001$, respectively), as well as TPE in cases with sepsis ($p<0.001$), were more frequent in non-survivors. The most common complication during the procedures was hypotension (9.9%).

Conclusion: Sepsis remains the most frequent indication for TPE in PICUs. Although the most common complication of TPE in our study was hypotension, there were no life-threatening complications, suggesting it is a safe treatment modality.

Keywords: Critical care, encephalitis, multiple organ failure, multiple trauma, sepsis

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Therapeutic plasma exchange (TPE) is an extracorporeal treatment modality used in critically ill adult and pediatric patients requiring intensive care management.[1] In pediatric patients, challenges such as difficulty in establishing a well-functioning vascular access, the risk of circuit clotting due to slow blood flow, fluid overload or anemia resulting from issues in returning circulated blood, and hypothermia pose significant barriers to its feasibility.[2] The use of TPE in critically ill patients in pediatric intensive care units (PICUs) is further limited by existing hemodynamic instability.[2, 3] Nevertheless, there are reports in the literature of TPE procedures being performed even in neonates.[4]

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TPE exerts its therapeutic effects by removing pathogenic autoantibodies, immune complexes, cytokines, and toxins or by replacing deficient A Disintegrin and Metalloproteinase with Thrombospondin Motifs 13 (ADAMTS-13) in various neurological, inflammatory, renal, and hematological conditions.[5] The American Society for Apheresis (ASFA) provides guidelines with recommendations for numerous indications at varying levels of evidence; however, most of the supporting evidence is derived from adult studies.[6] Consequently, the role of apheresis in critically ill pediatric patients remains uncertain and is categorized under category III, where clinical decision-making relies on the clinician's expertise and experience. This also highlights the limited number of publications on TPE in critically ill pediatric populations, most of which are confined to case reports and retrospective studies.[7]

In this study, we aimed to evaluate the application methods, indications, complications, and effects on prognosis of TPE procedures performed in our PICU, while reviewing the current literature and comparing our findings with contemporary PICU studies.

Methods

Study Design

This single-center retrospective cohort study was conducted between January 2020 and August 2024 in our eight-bed tertiary-level PICU. Ethical approval was obtained from the University of Health Sciences Turkey, Bagcilar Training and Researh Hospital's Clinical Research Ethics Committee prior to the study (date: September 19, 2024; approval number: 2024/09/07/073). The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Informed consent was obtained from the parents of the patients before hospitalization in the pediatric intensive care unit and all interventional procedures.

Inclusion criteria were defined as: 1) being between 1 month and 18 years of age, 2) admission to the PICU, and 3) undergoing TPE at any point during their PICU stay.

Therapeutic Plasma Exchange (TPE)

Although no written protocol exists in our unit, TPE is generally performed using the following approach: Double-lumen dialysis catheters appropriate for the patient's age and weight are used for vascular access. Catheter placement is prioritized based on the patient's age and weight in the following order: internal jugular vein, subclavian vein, and femoral vein. In our unit, the Prismaflex® (Baxter, USA) TPE 1000 and TPE 2000 sets are utilized, and the procedure is performed using the centrifugal filtration method.

The plasma volume to be exchanged (in liters) is calculated using the formula:

Plasma volume=0.070 × body weight (kg) × (1 - hematocrit).

The first session typically involves exchanging 1.5 times the calculated plasma volume, while subsequent sessions use the calculated plasma volume, adjusted based on the patient's clinical condition. Fresh frozen plasma (FFP) serves as the replacement fluid.

Prior to each procedure, the circuit is primed with blood or 0.9% NaCl, depending on the patient's age, weight, and hemodynamic status. Anticoagulation is achieved with an initial bolus of heparin (10–30 IU/kg), followed by a continuous infusion at a rate of 10 IU/kg/h, tailored to the patient's bleeding risk. Blood flow rates are adjusted according to the patient's age, weight, and hemodynamic status, ranging between 2–6 mL/kg/min.

Each procedure is completed within approximately 3–4 hours, during which heart rate, respiratory rate, peripheral oxygen saturation, and systolic/diastolic blood pressure are closely monitored. Sedation infusions are administered as needed for patients who do not tolerate the procedure well. Pre- and post-procedure blood samples, including serum electrolytes and coagulation tests, are obtained, and any necessary corrections are made accordingly.

Data Collection

Medical records of the patients were retrospectively reviewed, and the following demographic and clinical data were collected: age, sex, presence of chronic illness, PICU length of stay, Pediatric Risk of Mortality Score III (PRISM III), pre- and post-procedure Vasoactive Inotropic Score (VIS), need for invasive mechanical ventilation (IMV) and duration of IMV, central venous catheter placement site, need for continuous renal replacement therapy (CRRT), number of failing organs, indications for TPE and their categorization based on ASFA recommendations, number of TPE sessions, complications directly related to TPE, and mortality/morbidity status.

New-onset mental or motor retardation, epilepsy, tracheostomy requirement, and limb loss at the time of PICU discharge were defined as morbidity. Patients were categorized into two groups: survivors and non-survivors, and comparisons were made between these two groups.

Data analysis and Brief Literature Overview

A brief literature review was conducted to provide context and compare our findings with existing studies. PubMed and Google Scholar databases were searched for studies on TPE procedures performed in PICUs between 2020 and 2024. The search terms included 'apheresis, children, intensive care, pediatric, plasmapheresis, therapeutic plasma exchange,' and only studies published in English were included.

Statistical Analysis

All statistical analyses were performed using SPSS version 29.0 (IBM Corp., Armonk, NY, USA). The Mann-Whitney U test was used to compare non-normally distributed continuous variables between the two groups, while the Pearson chi-square test was applied to assess the relationships between categorical variables. Results were evaluated at a 95% confidence interval, and a p-value of less than 0.05 was considered statistically significant.

Results

A total of 274 TPE sessions were performed on 49 patients included in the study. Of the patients, 71.4% were male, and the median age of all patients was 54 months (range: 20 – 135 months). The general characteristics and PICU follow-up data of all patients are shown in Table 1.

The most common indication for TPE was sepsis with multi-organ dysfunction syndrome (MODS) (53%), followed by trauma induced MODS/disseminated intravascular coagulation (DIC) at 20.4%. The most frequently observed complication during TPE procedures was hypotension (9.9%) (Table 2).

Table 1. Demographic and clinical characteristics of pediatric patients in intensive care

Characteristics	Values
Age (month), median (IQR)	54 (20 – 135)
Gender, % (n)	
Female	28.6% (14/49)
Male	71.4% (35/49)
Chronic illness, % (n)	49% (24/49)
PICU stay (day), median (IQR)	18 (9 – 27)
PRISM III, median (IQR)	13 (9 – 22)
VIS, pre-procedure, median (IQR)	10 (0 – 35)
VIS, post-procedure, median (IQR)	0 (0 – 35)
Respiratory support	
IMV, % (n)	65.3 (32/49)
IMV stay (day), median (IQR)	5 (0 – 18)
Central venous catheter location, % (n)	
Internal jugular vein	51 (25/49)
Subclavian vein	42.9 (21/49)
Femoral vein	8.1 (4/49)
CRRT, % (n)	49 (24/49)
Number of organ dysfunction, median (IQR)	2 (1 – 3)
0-1 organ, n (%)	34.7 (17/49)
Multiple organs (≥2), n (%)	65.3 (32/49)
Mortality, % (n)	38.8 (19/49)
Morbidity, % (n)	34 (16/49)

CRRT: Continuous renal replacement treatment; IMV: Invasive mechanical ventilation; PICU: Pediatric intensive care unit; PRISM: Pediatric risk of mortality score; VIS: Vasoactive inotropic score.

Patients were divided into two groups: survivors and non-survivors, and comparisons were made between these groups (Table 3). The prevalence of chronic illness was significantly higher in the non-survivor group ($p<0.001$). There were significant differences between the survivors and non-survivors in terms of PRISM-III scores and pre- and post-procedure VIS values ($p=0.005$, $p<0.001$, $p<0.001$, respectively). The non-survivor group had higher rates of IMV and CRRT use ($p=0.005$, $p<0.001$, respectively). In the survivor group, the total number of procedures and the number of sessions per patient were significantly higher ($p=0.032$, $p=0.032$, respectively). The non-survivor group also showed a higher rate of TPE use in cases of sepsis with MODS ($p<0.001$).

Table 4 summarizes the literature on the use of TPE in critically ill pediatric patients.[3, 8-22]

Discussion

The ASFA recently published a systematic review of apheresis indications, introducing new recommendations and updates. In the 2022 ASFA Ninth Guidelines, 27 category I, 44 category II, 91 category III, and 4 category IV indications were identified following the updated recommendations.[6] In our study, 2% of patients fell under category II, 69.4% under category III, and 28.6% were non-categorized (NC). Consistent with previous reports, category III indications were the most common among critically ill pediatric patients undergoing TPE, with sepsis with MODS being the leading indication (Table 4).

TPE remains a category III treatment for sepsis with MODS. Previous studies report TPE use in 24–44.4% of pediatric sepsis with MODS cases (Table 4). Although a systematic review found no mortality benefit of TPE in severe pediatric sepsis overall, benefits were observed in cases associated with TAMOF.[23] A large retrospective study also linked TPE to reduced mortality in pediatric sepsis, though the proportion involving thrombocytopenia-associated multiple organ failure (TAMOF) was unclear.[24] Similarly, a 2014 study showed higher survival in TAMOF patients treated with TPE.[25] In our cohort, sepsis with MODS was the most common TPE indication (53%), all involving TAMOF. The mortality rate in this subgroup was 61.5% (16/26). TPE may contribute to survival by clearing endotoxins and inflammatory cytokines and restoring hemostatic balance via FFP replacement.[5, 23, 24] Although we did not specifically assess the impact of TPE on mortality, non-survivors had higher chronic disease rates, PRISM III scores, and VIS values, as well as more frequent IMV and CRRT use. Survivors underwent more TPE sessions, possibly reflecting longer treatment courses. Thus our findings should be interpreted cautiously.

Table 2. Therapeutic plasma exchange indications, asfa categories, and procedural complications in pediatric patients

Indications and Complications	% (n/49)	Number of sessions	ASFA category
TPE Indications, % (n)			
Sepsis with MODS	53 (26/49)	114	III
Trauma induced MODS/DIC	20.4 (10/49)	47	NC
Neurologic diseases			
Encephalitis of unknown origin	4.1 (2/49)	12	NC
Transverse myelitis	4.1 (2/49)	22	NC
ADEM	2 (1/49)	31	II
Acute hepatic failure	6.1 (3/49)	15	III
Drug poisoning	4.1 (2/49)	8	III
Toxic epidermal necrolysis	4.1 (2/49)	15	III
Idiopathic dilated cardiomyopathy	2 (1/49)	10	III
Total procedures of TPE, n	274		
TPE procedure number per patient, mean	5.6±4.5		
TPE procedural complications (per procedure), % (n)			
Hypotension	9.9 (27/274)		
Hypocalcemia	9.5 (26/274)		
Catheter occlusion	5.1 (14/274)		
Bleeding	4 (11/274)		
Occlusion of filter	3.3 (9/274)		
Vomiting and nausea	2.6 (7/274)		
Signs of infection at catheter site	1.8 (5/274)		
Anaphylaxis	0.4 (1/274)		
Total	36.5 (100/274)		

ADEM: Acute disseminated encephalomyelitis; ASFA: American Society for Apheresis; DIC: Disseminated intravascular coagulation; MODS: Multiple organ dysfunction syndrome; TPE: Therapeutic plasma exchange.

Table 3. Comparison between survivors and non-survivors

Parameter	Survivors (n=30)	Non-Survivors (n=19)	p
Age (month), median (IQR)	113 (21-154)	38 (17-93)	0.142
Gender, % (n)			0.277
Female	36.7 (11/30)	15.8 (3/19)	
Male	63.3 (19/30)	84.2 (16/19)	
Chronic illness, % (n)	26.7 (8/30)	84.2 (16/19)	<0.001**
PICU stay (day), median (IQR)	20 (11-31)	16 (5-22)	0.103
PRISM III, median (IQR)	12 (6-18)	22 (12-35)	0.005*
VIS, pre-procedure, median (IQR)	0 (0-20)	35 (20-50)	<0.001*
VIS, post-procedure, median (IQR)	0 (0-0)	40 (10-50)	<0.001*
IMV, % (n)	50 (15/30)	89.5 (17/19)	0.005**
CRRT, % (n)	30 (9/30)	78.9 (15/19)	<0.001**
Total procedures of TPE	201	73	0.032↑
TPE procedure number per patient, mean	6.7±5.2	3.9±2.2	0.032↑
Indications for TPE, % (n)			
Sepsis with MODS	10 (33.3)	16 (84.2)	<0.001**
Trauma induced MODS/DIC	7 (23.3)	3 (15.8)	0.523

*Mann-Whitney U test; **Pearson chi-square test; ↑Independent-samples t-test. CRRT: Continuous renal replacement treatment; DIC: Disseminated intravascular coagulation; IMV: Invasive mechanical ventilation; MODS: Multiple organ dysfunction syndrome; NC: Non-categorized; PICU: Pediatric intensive care unit; PRISM III: Pediatric risk of mortality score III; VIS: Vasoactive inotropic score.

Table 4. Review of published studies on therapeutic plasma exchange in pediatric critical care

Author (year)	Age (months), median	Gender female (%)	No of Pts.	Total procedure	RRT rate, %	Replacement solution, FFP (%)	Mortality %	PRISM III, median	Indications, (%)	ASFA Category, %	Complications per procedure, %	Complications
Atay (2020)[3]	80	51.3	39	172	30.7	87.2	-	9	MAS (28.2)	III (56.4)	7.6	Catheter
Balasubramanian (2023)[8]	128.4	29.4	24	115	41.6	58.3	12.5	-	Acute hepatic failure (25)	III (41.7)	10.4	Hypocalcemia
Bustos (2021)[9]	72	-	36	167	25	58.3c	8	11	Autoimmune encephalitis (16.6)	III (50)	17.4	Hypotension
Dalkiran (2022)[10]	59.6	48	25	128		80d	20	-	Sepsis with MODS (20)	III (40)	8	Tachycardia, pruritus, shivering
Durak (2023)[11]	122	54.9	102	672	25.3	98a	13.7	-	COVID-19-related conditions (46.1)	NC (46.1)	23.5	Hypotension
Duyu (2020)[12]	47	50.7	75	249	26.6	95.2a	26.6	15	Sepsis with MODS (29.3)	III (45.3)	19.2	Circuit
Ekinci (2024)[13]	80.4	51.8	328	1528	38.1	61.2	28.4	10	Sepsis with MODS (33.2)	III (64.3)	28.3	Hypotension
Fateen (2023)[14]	91	54.2	24	125	-	-	-	-	GBS (62.5)	I (70.8)	55.2	Hypotension
Holt (2024)[15]	168	54.2	25	118	52	-	12	-	Sepsis with MODS (24)	I (48)	27.1	Hypocalcemia
Mazahir (2021)[16]	96	34.7	46	293	-	-b	4.3	-	Atypical HUS (34.7)	I (78.2)	7.1	Hypotension
Ozsoylu (2021)[17]	84	40	25	105	-	70d	-	27	Sepsis with MODS (28)	III (44)	30.4	Nausea and vomiting
Ozturk (2022)[18]	84.8	43	84	463	52.3	100	50	-	Sepsis with MODS (40.4)	III (77.3)	0	-
Shamarao (2023)[19]	96	45.45	33	122	72.7	85.2	39.3	-	Acute hepatic failure (48.48)	I (57)	9.1	Hypotension
Sık (2020)[20]	34	47	135	635	26.1	90.4a	21.4	17	Sepsis with MODS (44.4)	III (71.1)	16.3	Circuit
Talay (2024)[21]	93	43.9	41	119	14.6	100	26.8	15	HUS (22)	I (46.3)	56 (per person)	Fever
Yazici Ozkaya (2024)[22]	72	50	154	486	48	99	27.3	12	Acute hepatic failure (28)	III (79.9)	13.9	Hypotension

ASFA: The American society for apheresis; GBS: Guillain-Barré syndrome; HUS: Hemolytic uremic syndrome; FFP: Fresh frozen plasma; MAS: Macrophage activation syndrome; MODS: Multiple organ dysfunction syndrome; NC: Non-categorized; PRISM: Pediatric risc of mortality score; RRT: Renal replacement therapy. [a]In cases of allergic reactions to plasma, 5% albumin was used for replacement. [b]For replacement, 34.8% albumin + FFP and 65.8% only albumin were used. [c]In neurological diseases and intoxications, 5% albumin was preferred as the replacement solution. [d]In neurological diseases, 5% albumin was preferred as the replacement solution.

Our center's location likely explains the relatively high rate (20.4%) of TPE for trauma-induced MODS/DIC compared to other studies (Table 4). Among 10 patients treated for this indication, three died. TPE was typically administered for at least three days, guided by thrombocytopenia resolution and MODS improvement. Disseminated intravascular coagulation (DIC) represents a severe hemostatic challenge, particularly in critically ill pediatric patients with trauma or sepsis. It is characterized by the activation of the coagulation cascade, leading to the excessive consumption of coagulation factors and platelets. In trauma-induced DIC, suppression of the anticoagulant pathway, impaired fibrinolysis, and excessive clotting activity result in microvascular thromboses, contributing to MODS.[26] Furthermore, a sustained systemic inflammatory response, driven by neutrophil activation and endothelial damage, plays a significant role in the progression to MODS in trauma-induced DIC patients.[27] Recent studies have demonstrated that, similar to sepsis, severe trauma can lead to endothelial injury and ADAMTS13-von Willebrand factor imbalance. TPE has been shown to restore ADAMTS13 activity, improve platelet levels, and enhance renal function, among other parameters, in these patients.[28]

Neurological diseases are the most common pediatric TPE indications. While Bustos et al.[9] reported autoimmune encephalitis as the leading cause, Fateen et al.[14] found Guillain-Barré syndrome most frequent. In our cohort, TPE was performed for five cases of neurological diseases: two cases of transverse myelitis, two cases of encephalitis of unknown etiology, and one case of acute disseminated encephalomyelitis (ADEM), which is classified as an ASFA category II indication. The encephalitis cases were refractory to intravenous immunoglobulin (IVIG) and steroid treatment, presenting with progressive neurological deficits before TPE initiation. Following TPE, both patients were discharged with only mild neurological deficits.

We also encountered two rare cases of toxic epidermal necrolysis (TEN), both resistant to IVIG and steroids. One recovered fully, while the other required amniotic membrane transplantation.

There remains limited evidence supporting TPE in many critical illnesses, and many indications are off-label. Durak et al.[11] reported 27.4% of TPE cases as MIS-C, but its role remains inconclusive due to the retrospective study design. MIS-C was reclassified under vasculitis in the 2022 ASFA guidelines.[6] Other off-label uses included Henoch-Schönlein purpura nephritis[30] and Crimean-Congo hemorrhagic fever.[17] Randomized controlled trials are needed to clarify TPE's role in such contexts.

TPE complications are relatively rare. In adults, allergic reactions to FFP, bleeding, and hypocalcemia are most common.[31] In Türkiye, FFP is often used due to albumin's cost. In our study, the only major complication was FFP-related anaphylaxis. Hypotension remains the most common complication in the literature (Table 4).[9, 11, 13, 14, 16, 19, 22]

This study's limitations include its retrospective, single-center design, lack of standardized TPE timing and session numbers, small sample size, and absence of dedicated subspecialists, possibly underrepresenting some TPE indications.

Conclusion

Our findings align with the literature, showing that sepsis is the most common indication for TPE in the PICU. The presence of rare indications, such as trauma-induced MODS/DIC and TEN, in our study supports the idea that patients with these conditions may also benefit from TPE. Given the lack of life-threatening complications observed, we believe that our study demonstrates TPE to be an effective and safe extracorporeal treatment modality in critically ill pediatric patients when managed by experienced personnel.

Disclosures

Ethics Committee Approval: The study was approved by the University of Health Sciences Turkey, Bagcilar Training and Researh Hospital's Clinical Research Ethics Committee in September 19, 2024 (approval number: 2024/09/07/073).

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Original Research

The Exclusively Breastfeeding Rate and Related Factors Among Preterm Infants at Discharge and Postnatal 6th Months of Age

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Abstract

Objectives: Breastfeeding is accepted to be the optimum nutrition for term and preterm newborns. The objective of our study was to investigate the rates of exclusive breastfeeding (EBF) at discharge among infants less than 34 weeks of gestation (GWs), followed up in neonatal intensive care unit (NICU) and to analyze the factors influencing EBF practices at discharge and 6th months of age.

Methods: In this study, we retrospectively evaluated the medical records of neonates <34 GWs admitted to NICU within the first postnatal 24 hours of life between January 2022 and June 2023. The maternal and neonatal demographic data and the related medical and nutritional factors, morbidities were recorded. Data regarding the duration of exclusive breastfeeding, and the maintenance of breastfeeding were retrieved from the follow-up records of the high-risk newborn outpatient clinic post-discharge. The rate of breastfeeding at discharge and the factors influencing breastfeeding practices were analyzed.

Results: The study cohort comprised 114 neonates, of whom 44.8% were female and 55.2% were male. The mean gestational age was 29.8±2.6 weeks and the mean birth weight was 1365±474 grams. The exclusive breastfeeding rate was 57.8% at discharge and declined to 45.6% at six months. The mean duration of breastfeeding was 15.7±6.5 months. Maternal ethnicity and the language barrier were found to be statistically significantly associated with exclusive breastfeeding at discharge, respectively (p=0.04, p=0.05). Infants who were exclusively breastfed at six months had significantly higher gestational age and shorter duration of hospital stay, respectively (p=0.029, p=0.02). Exclusive breastfeeding at six months was statistically significantly associated with a reduced incidence of extrauterine growth retardation (EUGR) (p=0.04). Among exclusively breastfed infants at discharge, 96.9% (n=64) received breast milk as their first feed, significantly more than mixed-fed infants (p=0.005). Time to reach full enteral feeding was also statistically significantly shorter in the exclusively breastfed group (p=0.017). Infants with a shorter duration of feeding via orogastric/nasogastric tube had a significantly higher rate of exclusive breastfeeding at six months compared to the mixed-fed group (p=0.043).

Conclusion: To improve exclusive breastfeeding rates at discharge and six months postnatally, and to reduce the incidence of EUGR, feeding preterm infants with their mother's own milk from birth should be actively promoted. In addition, comprehensive and consistent maternal support should be provided in the NICU to facilitate both the initiation and continuation of breastfeeding under all circumstances from birth.

Keywords: Discharge, exclusively breastfeeding, extrauterine growth retardation, preterm

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Breastfeeding represents the gold standard mode of nutrition during the neonatal period and the initial six months of life, optimizing infant growth and development. Human milk exhibits easy digestibility, high bioavailability, and encompasses all essential nutrients required by the infant. Furthermore, the bioactive components and beneficial microorganisms in human milk confer protection against infections, rendering it an ideal and infant-specific nutritional source. Beyond its fundamental role in healthy infant nutrition, human milk is also the most efficacious dietary intervention, with established benefits for both term and preterm infants receiving care and treatment within the neonatal intensive care unit (NICU).[1-4] Notably, breastfeeding infants admitted to the NICU holds critical significance due to its association with reduced mortality and morbidity rates, the prevention of illness and readmission within the first year of life, and the promotion of improved long-term neurodevelopmental outcomes.

The initiation of breastfeeding and the maintenance of exclusive breastfeeding (EBF) are influenced by a multitude of maternal and infant-related factors. The immediate postpartum hours are of paramount importance for the commencement and continuation of breastfeeding. This is particularly challenging and significant for extremely preterm infants in the intensive care setting who are confronted with many morbidities affecting multi-organ systems. Admission to the NICU, delayed mother-infant contact, and the physical and emotional adversities experienced by the mother throughout gestation can exert a negative impact on maternal-infant interaction and breastfeeding practices.[5-7] In this context, the expression of breast milk and the provision of optimal lactation support to the mother are crucial for enabling preterm infants to receive their mother's own milk.

The objective of our study was to investigate the rates of EBF at discharge among preterm infants followed up in NICU, to analyze the factors influencing breastfeeding practices.

Methods

This study was conducted retrospectively and included neonates who were admitted to the neonatal intensive care unit (NICU) of our hospital within the first 24 hours of life, between January 2022 and June 2023. "Ethics committee approval was obtained from the Istanbul Training and Research Hospital Clinical Research Ethics Committee (25.02.2025 Decree no: 30). Infants admitted within the first 24 hours who subsequently required inter-hospital transfer for any reason, those diagnosed with congenital metabolic disorders, neonates with congenital gastrointestinal system anomalies, and patients with incomplete data were excluded from the analysis. Maternal variables assessed included age, parity, presence of chronic medical conditions, medical complications encountered during pregnancy, prior hospitalizations during gestation, mode of delivery, language barriers, and challenges in access to healthcare. Neonatal variables included gestational age, birth weight, head circumference, the requirement for resuscitation in the delivery room, APGAR scores, primary diagnosis for NICU admission, the presence and duration of respiratory support, morbidities encountered during the NICU stay, time to initiation of enteral feeding, initial feeding modality, day of achievement of full enteral feeding, duration of orogastric or nasogastric tube feeding, type of feeding at discharge, length of hospital stay, weight and head circumference at discharge. Data regarding the duration of EBF, and the continuation of breastfeeding were retrieved from the follow-up records of the high-risk newborn outpatient clinic post-discharge. The rate of EBF at discharge and postnatal 6 months, and the factors influencing breastfeeding practices were analyzed.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 25 (IBM Corp., Armonk, NY). Descriptive statistics, including means, standard deviations, medians, interquartile ranges, frequencies, percentages, minimums, and maximums, were utilized to summarize the study data. The normality of continuous variables was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Normally distributed continuous variables were presented as Mean±Standard Deviation, while non-normally distributed continuous variables were expressed as Median [minimum-maximum] or Median [Interquartile Range]. For comparisons between two groups of normally distributed continuous variables, the Independent Samples T-test was employed. The Mann-Whitney U test was used for comparisons of two groups of non-normally distributed continuous variables. Categorical variables were compared using the Chi-Square test or Fisher's Exact Test, as appropriate. Statistical significance was defined as a p-value <0.05.

Results

The study cohort comprised 114 neonates, of whom 44.8% were female and 55.2% were male. Sixteen infants were excluded from the study due to incomplete data. The gestational age of the participants ranged from 23 to 34 weeks, with a mean gestational age of 29.8±2.6 weeks. The mean birth weight was 1365±474 grams. The mean maternal age was 28.8±5.2 years. The median of maternal parity was 2 (min-max: 1-7). A total of 36.8% (n=42) of the infants were delivered vaginally, while 63.2% (n=72) were delivered via cesarean section. The mean duration of NICU stay was 50.9±32.9 days. The mean discharge weight was 2397±486 grams (Table 1).

Table 1. Demographic data of study population

Maternal characteristics	
Age*	28.9±4.8
Gravida [median (min.-max.)]	1 (1-4)
Parity [median (min.-max.)]	2 (1-7)
Route of delivery	
NSVD n (%)	42 (36.8)
C/S n (%)	72 (63.2)
Ethnicity	
Turkish, n (%)	87 (76.3)
Other, n (%)	27 (23.7)
Hospitalization during pregnancy, n (%)	58 (50.9)
Language barrier, n (%)	12 (10.5)
Limited access to the healtcare, n (%)	31 (27.2)
Neonatal characteristics	
Gender	
Female n(%)	51(44.7)
Male n(%)	63 (55.3)
Gestational week*	29.8±2.6
Birth weight(grams)*	1365±474
Weight at discharge*	2397±486
Lenght of hospital stay (day)*	50.9±32.9

NSVD: normal spontaneous vaginal delivery; C/S. C-Section. *(mean±SD).

The rate of EBF at the time of discharge was 57.8%, and the rate of EBF at six months of age was 45.6%. The mean duration of breastfeeding was 15±6.5 months.

Maternal factors influencing EBF at discharge and six months are detailed in Table 2. Maternal ethnicity and the language barrier were found to be statistically significantly associated with EBF at discharge, respectively (p=0.04, p=0.05).

Evaluation of infant-related factors and morbidities affecting EBF at discharge did not reveal any statistically significant differences (Table 3). However, infants who were exclusively breastfed at six months demonstrated a statistically significantly higher gestational age at birth, shorter duration of hospital stay, and younger post-conceptual age at discharge compared to infants receiving mixed feeding, respectively (p=0.029, p=0.02, p=0.046). Although not statistically significant, the duration of invasive mechanical ventilation during the NICU stay was lower in the six-month exclusively breastfed group compared to the mixed-feeding group. The length of hospital stay was significantly shorter in the six-month exclusively breastfed group (p=0.043). Among the 52 infants exclusively breastfed at six months, 13 (25%) were diagnosed with EUGR, whereas 27 (43.8%) of the 62 infants not exclusively breastfed at six months received a diagnosis of EUGR. EBF at six months was statistically significantly associated with a reduced incidence of EUGR (p=0.04) (Table 3).

The median time of initiation of the first feeding in the NICU was 2 days (min–max: 1-21). The majority of infants, 91.2% (n=104), received breast milk as their initial feed. Among exclusively breastfed infants at discharge, 96.9% (n=64) re-

Table 2. Maternal factors affecting feeding at discharge and postnatal six months

Maternal factors	**NICU Discharge**			**Postnatal 6th month**		
	Exclusively breastfed n=66 (%57.8)	**Mixed feeding n=48 (%42.2)**	**p**	**Exclusively breastfed n=52 (%45.6)**	**Mixed feeding n=62 (%54.4)**	**P**
Maternal age*	28.1± 4.8	29.9±4.6	0.670	28.1± 5.1	29.5±4.5	0.603
Gravida*	2.0±1.3	1.9±1.2	0.702	2±1.3	1.98±1.1	0.550
Parity*	1.5±0.8	1.6±0.8	0.654	1.6±0.8	1.6±0.8	0.925
Route of delivery**						
NSVD	23(34.8)	19(39.5)	0.606	17(32.6)	25(40.3)	0.748
C/S	43(65.2)	29(60.5)		35(67.4)	37(59.6)	
Maternal ethnicity**						
Turkish	46(69.6)	41(85.4)	0.047	39(44.8)	48(55.2)	0.763
Other	20(30.4)	7(14.6)		13(48.1)	14(51.9)	
Language barrier**						
Present	10(15.1)	2(4.2)	0.050	6(11.5)	6(9.7)	0.748
Not present	56(84.9)	46(95.8)		46(88.5)	56(90.3)	
Hospitalization during pregnancy	3.4±4.6	3.7±4.3	0.952	3.2±4.6	3.8±4.4	0.850
Limited access to the healtcare **	23(34.8)	10(20.8)	0.195	17(32.7)	16(25.8)	0.718

NICU: neonatal intensive care; NSVD: normal spontaneous vaginal delivery; C/S: C-Section. *mean±SD; ** n (%); Statistically significant p<0.05 values are in bold.

Table 3. Neonatal factors affecting exclusive feeding at discharge and postnatal six months

Neonatal factors	NICU Discharge			Postnatal 6th month		
	Exclusively breastfed n=66 (%57.8)	Mixed feeding n=48 (%42.2)	p	Exclusively breastfed n=52 (%45.6)	Mixed feeding n=62 (%54.4)	p
Gender, n (%)						
Female	28 (42.4)	23 (47.9)	0.562	20 (38.4)	31 (50)	0.219
Male	38 (57.6)	25 (52.1)		32 (61.6)	31 (50)	
Gestational week**	29.6±2.6	30.0±2.7	0.617	29.9±2.4	29.7±2.9	0.029
Birth weight**	1365±467	1366±488	0.576	1418±463	1321±481	0.499
Weight at discharge**	2430±481	2351±495	0.951	2385±423	2407±537	0.110
Hospital stay (day)**	50.1±29.5	52.2±37.5	0.360	45.5±24.9	55.5±38.1	0.028
Ventilation duration (days)**						
Invasive	10.6±16.1	10.8±17.6	0.163	8.2±14.3	12.7±18.4	0.079
Non-invasive	12.8±11.3	14.2±13.9	0.896	13.7±12.1	13.1±12.8	0.984
Total	23.3±23.1	24.9±29.3	0.522	21.8±21.9	25.9±28.6	0.248
Respiratory distress syndrome*	54 (81.8)	39 (81.2)	0.939	44 (84.6)	49 (79)	0.446
Chronic lung Disease*	16 (24.2)	11 (22.9)	0.870	13 (25)	14 (22.6)	0.763
hs-Patent ductus arteriosus*	19 (28.7)	10 (20.8)	0.269	12 (23.1)	17 (27.5)	0.787
Necrotizing enterocolitis *						
Stage 2-3	11 (16.7)	6 (12.5)	0.539	15 (28.8)	28 (45.2)	0.055
Intraventricular hemorrhage*						
Stage 1-2	15 (22.7)	7 (14.5)	0.378	12 (23)	10 (16)	0.605
Stage 3- PVHI	2 (3)	2 (4)		1 (2)	3 (5)	
Retinopathy of prematurity*						
Stage 2-3	5 (7.5)	3 (6.2)	0.263	3 (5.8)	5 (8.1)	0.263
Extrauterine growth retardation						
Present	21 (31.8)	19 (39.6)	0.393	13 (25)	27 (43.6)	0.040
Not present	45 (68.2)	29 (60.4)		39 (75)	35 (56.4)	

NICU: neonatal intensive care; Hs: hemodynamically significant; PVHI: periventricular hemorrhagic infarct; *n (%); **mean±SD; Statistically significant p<0.05 values are in bold.

ceived breast milk as their first feed, which was significantly higher (p=0.005). Time to reach full enteral feeding was also statistically significantly shorter in the exclusively breastfed group (p=0.017). Infants with a shorter duration of feeding via orogastric/nasogastric tube had a significantly higher rate of exclusive breastfeeding at six months compared to the mixed-fed group (p=0.043) (Table 4).

Discussion

Our study revealed an EBF rate of 57.8% and 45.6% at the time of discharge from the NICU and six months of age for infants born <34 GWs, respectively. The duration of invasive mechanical ventilation, the length of hospital stay, the duration of feeding via orogastric tube, and language barrier were identified as factors influencing exclusive breastfeeding rates at six months of age. Furthermore, EUGR was observed less frequently in infants exclusively breastfed at postnatal six months.

Kutar et al.,[8] reported an EBF rate of 30% at discharge among preterm infants born <34 GWs.[8] In our study, we found a higher EBF rate of 57.8% at NICU discharge among infants born before <34 GWs. We suppose that this higher rate may be attributed to optimum lactation support provided by a dedicated nurse, the initiation of enteral feeding as early as possible, the active promotion of breastfeeding, and the timely establishment of mother-infant skin-to-skin contact. In the same study, the rates of EBF at discharge were 12.5%, 14%, and 44.8% for moderate, very preterm and extremely preterm infants, respectively. These rates were lower than those reported for preterm infants from Sweden (55%, 41%, and 64%) but comparable to findings reported from Brazil.[9, 10] Similar to latter studies, we found that the exclusive breastfeeding rates at discharge for moderate, very preterm, and extremely preterm infants were 50.0%, 64.4%, and 55.0%, respectively.

Table 4. Feeding characteristics at discharge and postnatal six months

Feeding characteristics	NICU discharge			Postnatal 6th month		
	Exclusively breastfed	Mixed feeding	p	Exclusively breastfed	Mixed feeding	p
Inititation of feeding(days)	2.2±3.5	2.3±1.9	0.88[a]	2.5±1.4	2.4±1.1	0.998[a]
Type of first feeding						
Breast milk	64 (%96.9)	40 (%83.3)	0.005[b]	49 (%94.2)	54 (%87)	0.201[b]
Formula	2 (%4.1)	8 (%16.7)		3 (%5.8)	8 (%13)	
Time of transition to FEF	19.2±11.0	25.3±19.4	0.017[a]	18.8±11.4	24.4±17.7	0.068[a]
Duration of feeding with NGT/OGT	36.8±20.9	39.1±30.4	0.183[a]	34.4±19.8	40.6±28.9	0.047[a]

NICU: neonatal intensive care; FEF: Full enteral feeding; NGT: Nasogastric tube; OGT: Orogastric tube; [a]Mann-Whitney U test; [b]chi-square test; Statistically significant $p < 0.05$ values are in bold.

In their study, Wang Y et al.[11] reported that only 22.5% of preterm infants were exclusively breastfed at six months, highlighting the challenges in breastfeeding initiation and continuation. Similarly, Sokou et al.[12] found that while 78.1% of NICU-discharged preterm infants initially received human milk, the exclusive breastfeeding rate at six months dropped to 19.4%. In contrast, we found a higher EBF rate of 45.6% at postnatal six months. This may be related to close post-discharge follow-up extending to two years for infants born <34 GWs, along with maternal education and breastfeeding support. Our cohort's exclusive breastfeeding rate at discharge was 57.8%, decreasing to 45.6% by six months. Among extremely preterm infants, this decline was more pronounced (58% to 34.6%). This reduction may be associated with prolonged hospitalization, delayed transition to oral and full enteral feeds, and the psychological burden experienced by mothers during the NICU stay. Nevertheless, the relatively higher six-month EBF rate observed in our study compared to other reports may reflect the positive impact of structured support and follow-up services.

Prior research has indicated that factors impacting EBF in term infants include insufficient lactogenesis, maternal anxiety, and factors impeding effective sucking and swallowing.[13] These risks are reported to be more prevalent in the preterm population. Preterm neonates frequently experience challenges related to enteral nutrition due to the immaturity of their gastrointestinal systems.[14] Preterm human milk is recognized as the optimal nutritional source for these infants, offering immunological protection and containing digestive enzymes and nutrients specifically tailored to their developmental needs.[15, 16] Achieving full enteral feeding with mother's milk as early as feasible is a pivotal goal of preterm infant care, crucial for optimizing growth and neurodevelopmental outcomes.[17] In the study of Bagga et al.,[18] they suggested that breastfeeding at the initial feeding was associated with a 1.5-fold increase in the odds of EBF. The most likely explanation for this association is the presence of a critical early postpartum period during which establishing and maintaining adequate milk production is essential. Achieving sufficient milk volume in these days is key to support sustained breastfeeding over time.[19-21] Similarly, in our study, 91.2% of infants had received breast milk as their initial feed and we found a statistically significantly higher EBF rate at discharge among infants who received breast milk as their first feed.

Many factors may influence EBF outcomes of preterm infants at the time of NICU discharge and postnatal six months. In the study of Kutar et al.,[8] type of delivery, delay in initiating tube feeding and establishment of oral feeds were found to be associated with a shorter duration of EBF. Similarly, in another study, the type of delivery, gestational age, and maternal family support were observed to be independent predictors of EBF at postnatal six months.[22] In our study, at the time of discharge, there were no significant differences between the exclusively breastfed and mixed-fed groups in terms of mechanical ventilation duration, length of hospital stay, or duration of orogastric feeding. However, by 6 months of age, the length of hospital stay was significantly shorter in the EBF group.

Reddy et al.,[23] reported that mothers of exclusively breastfed infants were younger, with EBF rates being 5% higher among younger mothers. In developing countries, factors such as limited access to education and insufficient familial support for the mother may affect breastfeeding practices among young mothers. This observation contrasts with findings in high-income countries, where higher maternal age is often associated with better

breastfeeding experiences and an increased rate of EBF. These discrepancies emphasize the importance of considering socioeconomic variables when evaluating the impact of maternal age on breastfeeding outcomes.[24] In our study, we could not identify any significant association between maternal age and EBF.

Language and cultural barriers are important factors which may have a negative impact on the success of EBF.[18] Previous studies also indicate that language and cultural barriers can limit access to consistent lactation support.[25-28] While some research has shown reduced breastfeeding rates among mothers with different ethnicities, others have highlighted the positive impact of culturally tailored programs.[12, 29, 30] In our study, the mothers who experienced language barriers with the health care team were less likely to exclusively breastfeed their child at NICU discharge. These results suggest that effective communication and family support contribute to improved breastfeeding rates in the NICU settings and at discharge.

Compared to formula feeding, human milk feeding in preterm infants is well-established to reduce preterm morbidities.[31] In a study evaluating risk factors for EUGR in infants with very low birth weight, the cessation of feeding and a prolonged time to achieve full enteral feeds were identified as independent risk factors. It has been reported that the avoidance of delayed feeding in the postnatal period and the prompt advancement to enteral nutrition are crucial for the prevention of EUGR in preterm infants.[32] Risk factors associated with EUGR development in preterm infants were defined as moderate-severe chronic lung disease, delay in the transition to enteral feeding, and insufficient human milk intake.[33] Non-breastfed infants are at an increased risk of growth failure, underscoring the critical importance of breastfeeding in this population. Consistent with the existing literature, in our study, we observed a lower incidence of EUGR in preterm infants exclusively breastfed at six months. We emphasize that, transition to full enteral feeding as early as possible, supporting breastfeeding, increasing caloric intake in the first week, may improve weight gain velocity and prevent EUGR.

Conclusion

In conclusion, to improve exclusive breastfeeding rates at discharge and six months postnatally, and to reduce the incidence of EUGR, feeding preterm infants with their mother's own milk from birth should be actively promoted. In addition, comprehensive and consistent maternal support should be provided in the NICU to facilitate both the initiation and continuation of breastfeeding under all circumstances from birth.

Disclosures

Ethics Committee Approval: The study was approved by the Istanbul Training and Research Hospital Clinical Ethics Committee (date: 25.02.2025, no: 30).

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Original Research

Developmental and Cognitive Outcomes in 342 Patients With Different Types of Hyperphenylalaninemia

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Abstract

Objectives: The aim of this study is to evaluate neurodevelopmental and cognitive outcomes in patients diagnosed with different types of hyperphenylalaninemia (HPA), identify the factors influencing these outcomes, and contribute to the debate regarding the thresold for initiating dietary treatment based on plasma phenylalanine (Phe) levels.

Methods: Patients with hyperphenylalaninemia (HPA) who were followed up and had developmental and/or cognitive evaluations at the Division of Pediatric Metabolism and Nutrition, Department of Pediatrics, between 1984 and 2018, were retrospectively assessed. The study included patients with mild (Phe:360-600 µmol/L), moderate (Phe:600-1200 µmol/L), or classic Phenylketonuria (PKU) (Phe ≥1200 µmol/L) treated with diet and/or tetrahydrobiopterin (BH4), along with untreated HPA patients (Phe:240-360 µmol/L). This classification was based on plasma Phe levels measured at the time of diagnosis. Denver Developmental Screening Test (DDST), Stanford-Binet test, and Wechsler Intelligence Scale for Children (WISC-R) adapted for Turkish children were applied for developmental and cognitive evaluation. Intellectual disability or developmental delay (ID/DD) was defined as a full-scale intelligence quotient (IQ) <70 on the Stanford-Binet or WISC-R, or as delay in two or more developmental domains on the DDST, with children meeting any of these criteria classified as having ID/DD. The relationships between ID/DD, age at diagnosis, diagnostic methods, plasma Phe levels, and brain MRI findings were analyzed.

Results: A total of 342 patients were included in the study, comprising 182 (53.2%) females and 160 (46.8%) males. Of these, 53 (15.5%) had mild PKU, 97 (28.4%) had moderate PKU, 102 (29.8%) had classic PKU, and 90 (26.3%) were diagnosed with HPA. A significant association was found between ID/DD and both the age at diagnosis and diagnostic method in patients treated with diet and/or BH4 ($p < 0.001$ and $p < 0.01$, respectively). In patients with ID/DD, the median plasma Phe levels at the first, third, and last years of follow-up were significantly higher compared to patients without ID/DD ($p < 0.024$). White matter abnormalities observed on brain MRI were significantly associated with PKU severity, the presence of ID/DD, and the median plasma Phe levels in the last year of follow-up ($p = 0.01$, $p < 0.001$, and $p < 0.001$, respectively). Notably, 9 (10%) of untreated HPA patients exhibited ID/DD, despite regular follow-up and the absence of known risk factors.

Conclusion: In addition to early diagnosis and treatment, lifelong adherence and regular follow-up are essential for achieving normal neurodevelopmental and cognitive outcomes in individuals with PKU. However, clinical management remains heterogeneous across centers. The presence of developmental delay in 10% of untreated HPA patients underscores the need to urgently re-evaluate current plasma Phe thresholds for treatment initiation and follow-up.

Keywords: Developmental delay, diet, early diagnosis, hyperphenylalaninemia, intellectual disability, phenylketonuria

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Phenylketonuria (PKU) is a rare autosomal recessive inherited disorder of phenylalanine (Phe) metabolism caused by mutations in the PAH gene (12.q22-24.1), which encodes the enzyme phenylalanine hydroxylase (PAH).[1] The PAH enzyme converts Phe to tyrosine using BH4 as a cofactor, along with molecular oxygen, and iron.[2] Deficiency of either the PAH enzyme or BH4 results in the accumulation of Phe in the blood and brain.

Untreated PKU is associated with irreversible intellectual disability, microcephaly, motor dysfunction, eczema like rash, seizures, developmental delay, abnormal behavioral patterns, autism spectrum features, and psychiatric symptoms.[3] Although the precise mechanisms through which elevated Phe causes neurotoxicity remain unclear, several potential mechanism have been proposed.[4] These include reduced glutamatergic synaptic activity and decreased function of enzymes such as pyruvate kinase and HMG-CoA reductase, contributing to myelin disruption and white matter abnormalities. Elevated Phe levels also inhibit tyrosine hydroxylase and tryptophan hydroxylase key enzymes involved in neurotransmitter synthesis. In addition, competitive inhibition of the large neutral amino acid transporter reduces the availability of neurotransmitter precursors in the brain, impairing neurotransmission.[4-6]

The prevalence of PKU varies globally, with higher incidence in countries such as Ireland (1:2,700) and Turkey (1:4,500), compared to much lower rates in Finland and Japan (<1:100,000).[7, 8] Since 2006, Turkey's national newborn screening program has achieved >95% coverage.[9] Despite early detection, long term neurocognitive outcomes largely depend on consistent lifelong adherence to treatment. Current guidelines recommend treatment initiation at plasma Phe levels >360 µmol/L, while levels between 120-360 µmol/L are considered safe.[4, 10] Nevertheless, the threshold for initiating treatment remains controversial. Some studies have indicated that patients with Phe levels between 240 and 360 µmol/L may still experience cognitive and attention-related difficulties. Maintaining Phe levels at or below 240 µmol/L has been associated with better neuropsychological outcomes, including improved cognitive flexibility and inhibitory control.[11, 12] At our center, treatment is initiated when plasma Phe levels exceed 360 µmol/L.

This study aims to evaluate patients with different types of HPA from a neurodevelopmental and cognitive perspective, identify factors influencing these outcomes, and contribute to the literature regarding the plasma Phe threshold for initiating phenylalanine restricted dietary treatment.

Methods

This study was approved by the Çukurova University Ethics Boards and Commisions (Approval date: December 2, 2016; Meeting number: 59; Decision number: 13) and conducted in accordance with the Declaration of Helsinki.

Study Population

This study evaluated 342 patients with HPA who were followed up at the Department of Pediatrics, Division of Pediatric Metabolism and Nutrition, between 1984 and 2018 and had formal neurocognitive and developmental assessments. Data were retrospectively collected from hospital records. The cohort included patients diagnosed with mild (Phe: 360-600 µmol/L), moderate (Phe: 600-1200 µmol/L), classic PKU (Phe ≥1200 µmol/L) who were managed with a phenylalanine restricted diet and/or BH4 therapy, along with untreated HPA patients with Phe levels between 240-360 µmol/L. Patients were classified into mild, moderate, classic PKU, or untreated HPA groups based on their plasma Phe concentrations measured at the time of diagnosis.

Neurocognitive and Laboratory Evaluation

Neurodevelopmental and cognitive outcomes were assessed using age appropriate standardized tests. The Denver Developmental Screening Test (DDST) was applied for children aged ≤2 years, the Stanford-Binet Intelligence Scale for those aged 2-6 years, and the Wechsler Intelligence Scale for Children-Revised (WISC-R) for children aged ≥7 years. Intellectual disability was defined as a full-scale intelligence quotient (IQ) score <70 on either the Stanford-Binet or WISC-R. For children assessed with the DDST, a delay in two or more developmental domains (gross motor, fine motor-adaptive, language, and personal-social) was considered indicative of developmental delay. Clinical judgment including caregiver reports, observed functional abilities, and overall clinical evaluations was used to support test findings. Based on these criteria, children were classified as having intellectual disability or developmental delay (ID/DD).[13] Since age at diagnosis and initiation of treatment are directly related to neurodevelopmental outcomes, treated patients were categorized into seven groups according to age at diagnosis (in days): group I (3-14), group II (15-29), group III (30-59), group IV (60-89), group V (90-179), group VI (180-360), and group VII (>360). In the treated group, the relationship between age at diagnosis and the outcomes of the DDST, Stanford-Binet, and WISC-R tests was analyzed. Neurodevelopmental and cognitive test results were compared between patients diagnosed through the newborn screening program and those diagnosed outside the newborn screening program. In addititon, the relationship between age of diagnosis, diagnostic method, PKU type, median plasma Phe levels during the first, second, third, and last years of follow-up, brain MRI findings, and the presence of ID/DD was investigated.

Plasma Phe levels were measured using high performance liquid chromatography (HPLC) in the Pediatric Metabolism Laboratory of the Department of Pediatric Metabolism and Nutrition. Blood samples were collected in EDTA tubes, centrifuged to separate plasma, and stored under appropriate conditions until analysis. Phe concentrations were determined by comparing the sample values with internal calibrators and validated quality control standards.

Statistical Analysis

All statistical analyses were conducted using SPSS software, version 23 (IBM Corp., Armonk, NY, USA). A p-value of <0.05 was considered statistically significant. Categorical variables were summarized as frequencies and percentages, while continuous variables were reported as medians with minimum and maximum values (median; min-max). Associations between categorical variables were analyzed using the Pearson chi-square test. Differences in plasma Phe levels, presence of ID/DD, and brain MRI findings were evaluated using the Mann-Whitney U test.

Results

Demographics

A total of 342 patients were included in the study, comprising 182 (53.2%) females and 160 (46.8%) males. Among these, 53 (15.5%) patients had mild PKU, 97 (28.4%) had moderate PKU, 102 (29.8%) had classic PKU, and 90 (26.3%) were diagnosed with HPA. Demographic and clinical characteristics including PKU subtype, gender distribution, consanguinity, family history, age and method of diagnosis, need for special education, duration of follow-up, and age and clinical status at the last follow-up are summarized in Table 1.

Table 1. Demographic characteristics and comorbidities of patients with Phenylketonuria and Hyperphenylalaninemia

Hyperphenylalaninemia (HPA) classification	Phenylketonuria (PKU)			Hyperphenylalaninemia (240 < Phe < 360 µmol/L)
	Mild PKU	Moderate PKU	Classic PKU	
Number of patients, n (%)	53 (15.5)	97 (28.4)	102 (29.8)	90 (26.3)
Sex (F), n (%)	31 (58.5)	50 (51.5)	57 (55.9)	44 (48.9)
Consangunity	16 (30.2)	65 (67)	75 (73.5)	44 (48.9)
Family History, n (%)	15 (28.3)	27 (27.8)	31 (30.4)	16 (17.8)
Age at diagnosis*	0.66 (0.17-13.2)	0.66 (0.13-268.5)	1.01 (0.17-93.3)	1 (0.33-74.1)
Diagnosis methods, n (%)				
Newborn screening	46 (86.8)	79 (81.4)	78 (76.5)	85 (94.4)
Outside newborn screening	7 (13.2)	18 (18.6)	24 (23.5)	5 (5.6)
Reason for admission (diagnosis outside of newborn screening), n (%)				
Psychomotor retardation	1 (14.2)	8 (44.4)	17 (70.8)	1 (20)
Family history	6 (85.7)	10 (55.5)	6 (25)	4 (80)
Epilepsy	0	0	1 (4.1)	0
Treatment, n (%)				
Phenylalanine restricted formula	10 (18.9)	79 (81.4)	101 (99)	No treatment
Sapropterin dihydrochloride + phenylalanine restricted formula	5 (9.4)	8 (8.2)	1 (1)	
Sapropterin dihydrochloride + unrestricted diet	38 (71.7)	10 (10.3)	0	
Comorbidities, n (%)				
Psychomotor retardation	1 (1.8)	14 (14.4)	25 (25.4)	2 (2.2)
Epilepsy	2 (3.7)	4 (4.1)	10 (9.8)	0
Malnutrition	0	12 (12.3)	7 (6.8)	1 (1.1)
Osteoporosis	0	2 (2)	3 (2.9)	0
Obesity	0	0	4 (3.9)	0
Follow-up duration*	38 (1-181)	75 (9-342)	110 (3-403)	16 (1-227)
Age at last follow-up*	39 (1-188)	76 (13-356)	112 (3-414)	17.5 (2-241)
Requires special education/Unable to attend school n (%)	2 (4.5)	10 (22.7)	30 (68.1)	2 (4.5)
Median plasma Phe levels last year of follow-up, n (%)				
Normal (<120 µmol/L)	1 (1.9)	3 (3.1)	2 (2.0)	3 (3.3)
Follow-up (120-360 µmol/L)	30 (56.6)	28 (28.9)	22 (21.6)	83 (92.2)
Poor control (>360 µmol/L)	22 (41.5)	66 (68)	78 (76.5)	4 (4.4)
Patient follow-up status, n (%)				
Actively followed	52 (98.1)	95 (97.9)	100 (98)	88 (97.8)
Lost to follow-up	1 (1.9)	2 (2.1)	2 (2)	2 (2.2)

*Months, median (min-max); Sapropterin dihydrochloride (synthetic tetrahydrobiopterin, BH4).

Developmental/Cognitive Evaluation

Neurodevelopmental and cognitive outcomes were assessed using age appropriate standardized tests: 106 (30.9%) patients were evaluated with the WISC-R, 165 (48.2%) with the Stanford-Binet test, and 71 (20.9%) with the DDST. Among the 252 patients receiving a phenylalanine restricted diet and/or BH4 therapy, a significant association was observed between age at diagnosis and the presence of ID/DD (p<0.001). Notably, ID/DD was identified in 62.5% of patients diagnosed after 90 days of age (Fig. 1). Of these 252 patients, 203 (80.6%) were diagnosed through the newborn screening program, while 49 (19.4%) were diagnosed outside the newborn screening program. In patients diagnosed through newborn screening, 23 (11.3%) had ID/DD, whereas 23 (46.9%) of those diagnosed out of the screening program had ID/DD, and this relationship was statistically significant (p<0.001) (Table 2).

A significant relationship was found between the type of HPA and the presence of ID/DD (p<0.001) (Table 2). As the phenotype progressed from HPA to classic PKU, the incidence of ID/DD increased. Among patients with ID/DD, plasma Phe levels at the first, third, and last year of follow-up were significantly higher compared to those without ID/DD (p=0.007, p=0.035, and p<0.001, respectively) (Table 3).

In the present study, the most important result was the presence of ID/DD in 9 (10%) of untreated HPA patients with plasma Phe levels between 240 µmol/L and 360 µmol/L, despite regular follow-up and the absence of other risk factors such as prematurity, hypoxic-ischemic encephalopathy, hypothyroidism, vitamin deficiencies, and epilepsy.

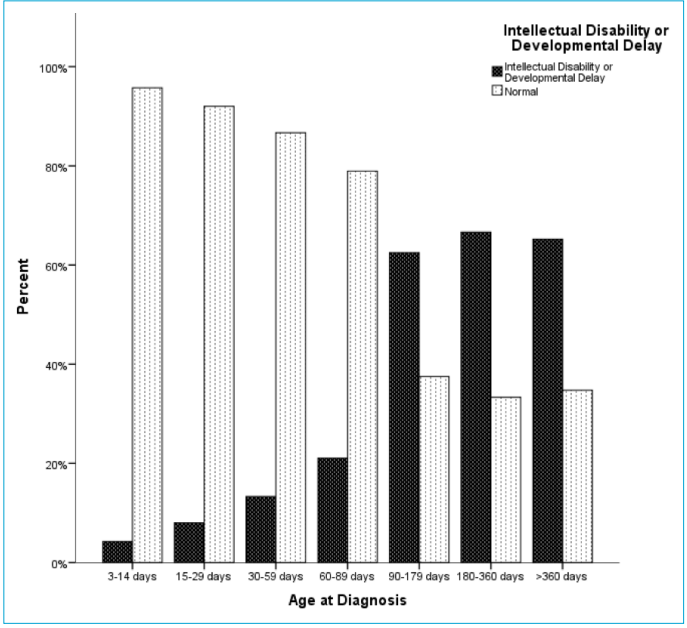

Figure 1. Intellectual disability or developmental delay results based on age of diagnosis in patients followed with treatment (p <0.001).

Brain MRI was performed in 116 patients as part of the neurological evaluation, revealing white matter involvement in 74 (63.8%) cases, including 2 (1.7%) with HPA, 2 (1.7%) with mild PKU, 23 (19.8%) with moderate PKU, and 47 (40.5%) with classic PKU. MRI findings from selected patients in our cohort are shown in Figure 2, which illustrates mild gliotic changes in the bilateral periventricular peritrigonal regions in a patient with moderate PKU, and in Figure 3, which depicts more extensive bilateral periventricular white matter hyperintensities and ventricular enlargement due to cerebral atrophy in a patient with classic PKU. A significant relationship was found between white matter abnormalities and both PKU type and the presence of ID/DD (p=0.01, p<0.001, respectively). In addition, plasma Phe levels during the last year of follow-up were significantly higher in patients with white matter involvement (p<0.001). Of the 44 patients who required special education, 34 (77.2%) had white matter abnormalities on brain MRI. Among these 44 patients, 19 (43.2%) were diagnosed through the newborn screening program.

Table 2. Intellectual disability and developmental delay according to PKU subtypes and diagnostic method

	Intellectual disability/ developmental delay		p
	Yes, n (%)	No, n (%)	
Hyperphenylalaninemia classification			
Hyperphenylalaninemia	9 (10)	81 (90)	<0.001
Mild PKU	3 (5.6)	50 (94.3)	
Moderate PKU	14 (14.4)	83 (85.5)	
Classic PKU	29 (28.4)	73 (71.5)	
Diagnostic methods			
Newborn screening	23 (11.3)	180 (88.7)	<0.001
Outside of newborn screening	23 (46.9)	26 (53.1)	

Table 3. Comparison of median plasma phenylalanine levels by presence of Intellectual disabilityand developmental delay

Post diagnosis follow-up period	Intellectual disability/ developmental delay		p
	Yes	No	
1st year *	318 (162-600)	264 (78-858)	0.007
2nd year *	300 (90-612)	294 (84-942)	0.290
3rd year *	372 (66-816)	306 (78-1200)	0.035
Last year at follow-up*	690 (168-1860)	330 (66-1410)	<0.001

* Values are expressed as median (min–max), in µmol/L.

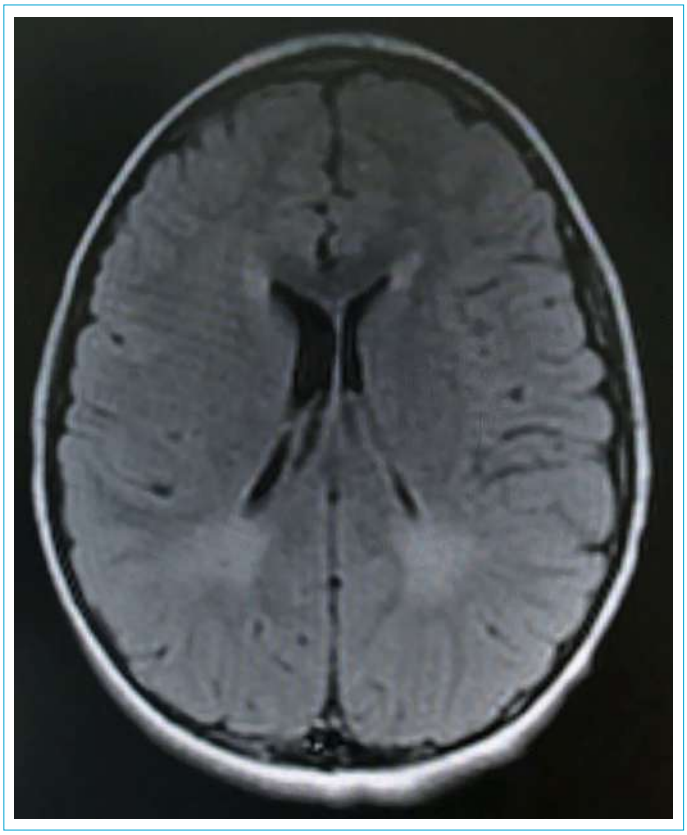

Figure 2. Axial T2-FLAIR brain MRI of a patient with moderate PKU, showing mild gliotic white matter changes in the bilateral periventricular peritrigonal regions, more prominent posteriorly.

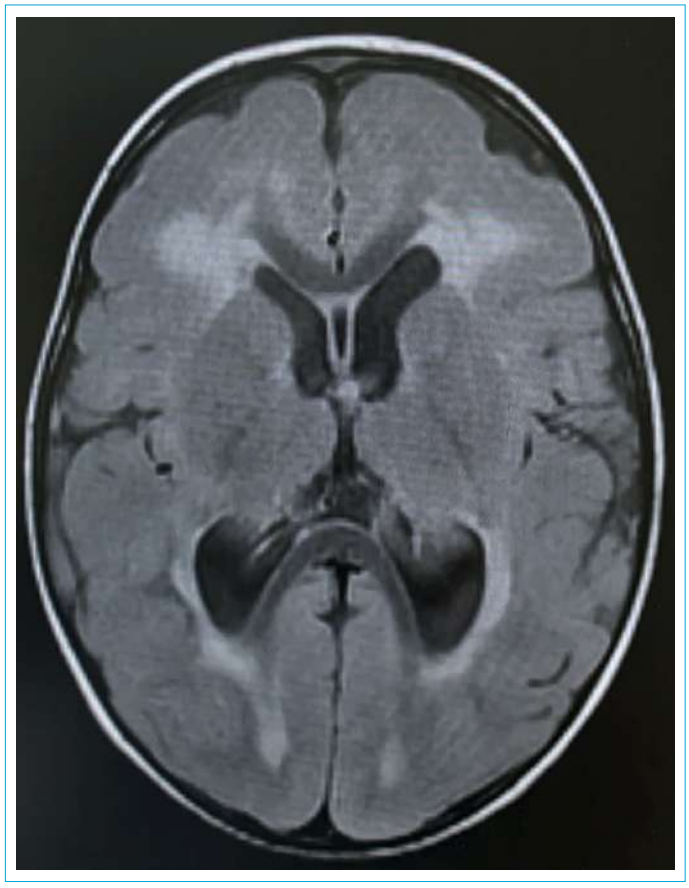

Figure 3. Axial T2-FLAIR brain MRI of a patient with classic PKU, demonstrating bilateral symmetric hyperintensities in the periventricular white matter, consistent with gliotic changes. The lateral ventricles appear enlarged, secondary to atrophy.

Discussion

Phenylketonuria is an inherited metabolic disorder in which normal cognitive and neuromotor development can be achieved through early diagnosis via newborn screening and timely initiation and maintenance of appropriate treatment.[4] In our study, normal neurocognitive outcomes were more frequently observed in individuals diagnosed via newborn screening. Among 203 PKU patients diagnosed by newborn screening programme and followed up with treatment, ID/DD was identified in 4.3% (n=2) of mild, 7.6% (n=6) of moderate, and 19.2% (n=15) of classic PKU cases. These results highlight the importance of early diagnosis and timely intervention in achieving favorable neurodevelopmental outcomes in PKU. The timing of diagnosis and initiation of treatment plays a pivotal role in neurological development, as several studies have demonstrated an inverse correlation between the timing of treatment initiation and cognitive performance, particularly IQ, in treated patients.[14, 15] One study reported that patients who began treatment within three weeks had significantly higher IQ scores compared to those who started between three and six weeks.[15] Smith et al.; found that each four week delay in initiating a phenylalanine restricted diet was associated with a 4-point decrease in IQ.[16] In our study, a significant relationship was observed between age at diagnosis and developmental/cognitive outcomes among 252 treated patients. Intellectual disability and/or developmental delay was found in 62.5% of patients diagnosed after 90 days of age, and the frequency of ID/DD increased with later diagnosis.

In the study by Yalaz et al.,[17] mental retardation was reported in 67% of patients who received early treatment and in 100% of those who remained untreated, among a cohort of 146 individuals with PKU.

The authors noted that none of the patients who initiated treatment after 12 months of age achieved normal neurodevelopmental outcomes, and a statistically significant difference in IQ scores was observed between those who began treatment within the first two months of life and those who started later. Similarly, a study evaluating neurological outcomes in 38 late diagnosed patients with classical PKU found intellectual disability in 37 cases.[18] Although early diagnosis and dietary treatment significantly reduce the risk of severe neurocognitive impairment, executive function deficits, particularly in planning and organizational

skills, have been reported even among patients treated early.[19, 20] Furthermore, within the phenotypic spectrum of PKU, cases of neurocognitive impairment have also been described in patients maintaining blood Phe levels consistently below 6 mg/dL (360 µmol/L) during follow-up.[21-23] Parra et al.[24] reported that children with mild HPA (Phe 2-6 mg/dL), diagnosed early, demonstrated average range cognitive performance, significantly higher than peers with PKU (Phe >6 mg/dL) who were also diagnosed and treated early. However, both groups showed similar difficulties in working memory and attention. In the present study, neurodevelopmental and cognitive evaluations were performed in 90 untreated patients with plasma Phe levels between 240–360 µmol/L. Notably, 9(10%) of these patients were identified as having ID/DD.

Evinc et al.[23] evaluated cognitive and behavioral profiles in 41 untreated children with HPA aged 6-16 years, with lifetime median plasma Phe levels between 240–600 µmol/L. Both the 240–360 µmol/L and 360–600 µmol/L subgroups demonstrated significantly lower full-scale IQ and verbal comprehension scores compared to healthy controls. Moreover, children in the higher Phe range exhibited more pronounced attention deficits and difficulties in inhibitory control. Based on these findings, the authors concluded that even plasma Phe levels between 240–360 µmol/L may pose a risk for neurocognitive impairment and recommended re-evaluating the current treatment initiation threshold.

We analyzed the relationship between median plasma Phe levels at the first, second, and third years following diagnosis, as well as during the last year of follow-up, and developmental or cognitive assessment outcomes. Consistent with previous studies, our findings revealed a negative association between higher plasma Phe levels and the presence of ID/DD.[12, 25] In patients with ID/DD, plasma Phe levels at the first, third, and last years of follow-up were significantly higher than in those without ID/DD. According to the study by Parra et al., patients diagnosed through newborn screening with initial Phe levels exceeding 15 mg/dL who maintained median Phe concentrations below 240 µmol/L during the first year of life demonstrated significantly higher IQ scores compared to those with levels between 240–360 µmol/L and above 360 µmol/L. The authors concluded that maintaining Phe levels above 360 µmol/L during the first year is consistently associated with impaired cognitive development.[26]

In our study, brain MRI was performed in 116 patients, and white matter abnormalities were identified in 74 (63.8%) cases, most frequently among children with classic PKU. White matter involvement has generally been associated with elevated plasma Phe levels and patient age in the literature.[27, 28] We observed a significant association between plasma Phe levels during the last year of follow-up and the presence of white matter abnormalities on MRI. Moreover, patients with white matter involvement had a significantly higher rate of ID/DD compared to those with normal MRI results. One study found no association between white matter abnormalities and neurocognitive impairment,[29] while another reported a significant relationship between brain MRI abnormalities and plasma Phe levels during the last five years of follow-up, though no significant correlation was observed with IQ scores.[30]

As demonstrated in our study, the neurocognitive and developmental outcomes observed in HPA patients, whether diagnosed through newborn screening or following symptomatic presentation, may represent only the tip of the iceberg, underscoring the need for further research to optimize long term neurological outcomes.

This study has several limitations, primarily its retrospective design. Developmental and cognitive assessments were not conducted uniformly at diagnosis or at standardized intervals but instead occurred at various points during routine follow-up. Despite these limitations, the study has notable strengths: it includes a large cohort representing all subtypes of HPA and provides formal neurodevelopmental evaluations for all participants. Importantly, it contributes to the ongoing debate regarding treatment thresholds by identifying that 10% of patients with plasma Phe levels between 240–360 µmol/L had intellectual disability or developmental delay.

Conclusion

As shown in our study although early diagnosis with newborn screening program is essential for normal mental and motor development and cognitive functions in PKU patients, but also ensuring the lifelong treatment compliance and follow-up are the other important determinants playing role for satisfactory outcomes. The most striking finding of our study is the 10% rate of ID/DD among patients with plasma Phe levels between 240-360 µmol/L. This concerning result underscores the unmet need for clearer guidance on the appropriate threshold for initiating treatment.

Disclosures

Ethics Committee Approval: The study was approved by Çukurova University Ethics Boards and Commissions (Approval date: December 2, 2016, and meeting number: 59, decision number: 13).

Informed Consent: Informed consent was obtained.

Peer-review: Externally peer-reviewed.

Conflict of Interest: The authors declare no conflict of interest.

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Authorship Contributions: Concept – S.O.Y., H.N.O.M.; Design – S.O.Y., H.N.O.M.; Supervision – H.N.O.M.; Materials – S.O.Y., H.N.O.M., D.K., F.D.B., B.S.Y., S.K.; Data Collection and/or Processing – S.O.Y., H.N.O.M., D.K., F.D.B., B.S.Y., S.K.; Analysis and/or Interpretation – D.K., G.S.; Literature Review – S.O.Y., B.S.Y..; Writing – S.O.Y., H.N.O.M.; Critical Review – H.N.O.M.

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Original Research

Intralesional Platelet-Rich Plasma Injection in Patients with Recalcitrant Alopecia Areata

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Abstract

Objectives: Alopecia areata (AA) is a common, chronic autoimmune disease that causes non-cicatricial hair loss. Its relapsing and remitting nature leads to the search for new, effective treatment options. The study aimed to evaluate the therapeutic efficacy of intralesional platelet-rich plasma (PRP) and intralesional steroid (ILS) injections in patients with AA.

Methods: A retrospective chart review was carried out from 2020-2021. A total of 75 patients with AA were included in the study. Thirty-six patients were treated with intralesional PRP, and 39 patients were treated with ILS injections for three sessions. The patients were evaluated with a hair pull test and SALT scores at months 0, 3, and 6.

Results: Of 75 patients, the mean age of the PRP group was 34.33±10.61, and the mean age of the ILS group was 33.82±13.31 years. After three PRP or ILS therapy sessions, at 3. and 6. months, SALT 3 and SALT 6 scores were statistically significantly lower in the PRP group than in the ILS group (p=0.038, p<0.001, respectively). When the treatment response was evaluated at the end of the 6th month in the PRP group, there was no response in 2 (5.5%) patients, partial response in 1 (2.7%) patient, good response in 3 (8.4%) patients, and very good response in 30 (83.4%) patients. Only 2 (5.9%) patients had a clinical relapse in a 6-month period. Side effects were seen in 16 (44.4%) patients in the PRP group and 8 (20.5%) patients in the ILS group, and the frequency of side effects in the PRP group was statistically significantly higher than in the ILS group (p=0.026). However, the side effects of both groups were minor, such as itching, pain, burning, ecchymosis, and folliculitis.

Conclusion: PRP seems to be an effective and safe treatment option for limited patchy alopecia areata, but its superiority over ILS has not been fully demonstrated, making ILS still the first-line treatment

Keywords: Alopecia, ILS, platelet-rich plasma, PRP, steroid, triamcinolone

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Alopecia areata (AA) is a common, chronic, autoimmune disease that causes non-cicatricial hair loss due to disruption of immune privilege of the hair follicles.[1] The scalp is the mainly involved area, but the disease can affect the beard, eyebrows, eyelashes, the hair follicles of the whole body, and nails.[2] The course of the disease is variable. The disease may start as a single alopecia patch on the scalp and undergo spontaneous resolution, or it may present with widespread alopecia patches with frequent relapses and even progress to alopecia universalis.[3]

Topical treatments are generally preferred over systemic therapies for the limited patchy forms of AA. Intralesional

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triamcinolone acetonide injection (TA) is the first line of treatment in adult patients with a SALT score of 0-30%.[4] Intralesional steroid injection (ILS) is a convenient, effective, and inexpensive treatment modality.[5] Relapses and treatment failures with ILS lead to the search for new effective treatment options.

Since AA is known to be an acquired autoimmune disorder, treatment strategies are always based on reducing the immune response by providing immunosuppression. However, it can be suggested that achieving hair regeneration by restoring normal hair follicle function in AA requires more than immunosuppression.[4] Platelet-rich plasma (PRP) is known to play a role in tissue regeneration and/or restoration by stimulating cell proliferation and differentiation with its rich growth factor content.[6, 7] In the literature, several studies reported the effectiveness of PRP in AA with varying success rates.

This study aimed to evaluate the therapeutic efficacy of intralesional PRP in patients with chronic alopecia areata and to compare the effectiveness of PRP and intralesional steroid injection in AA.

Methods

A retrospective chart review was conducted over 20 months, from January 2020 to August 2021. The study included 75 patients with alopecia areata who were admitted to a dermatology outpatient clinic. The Ankara Training and Research Hospital Clinical Research Ethics Committee approved the study (20.10.2021 E-93471371-514.01.02). The study was performed in accordance with the latest version of the 'Helsinki Declaration' and 'Guidelines for Good Clinical Practice'.

Inclusion criteria consisted of patients with limited patchy AA on the scalp aged 18-65 years who had not received any topical and/or systemic treatment in the last 1 month. When the SALT score is 0-30 %, and the type of AA is patchy, the disease is considered "limited patchy AA". Patients with systemic diseases that may cause platelet disorders (malignancy, hematological diseases, autoimmune diseases, HIV, hepatitis B-C) were excluded.

Demographic data such as age, gender of the patients, disease duration, family history, comorbidities, and side effects of the treatment were recorded. The study group (75 patients) consisted of patients with a duration of the disease of more than 1 year, which is defined as "chronic AA". Of the 75 patients with AA, 36 were treated with intralesional PRP injections for three sessions at 3-week intervals. PRP group included patients with chronic AA who were treated with topical steroids and/or ILS with failure and/or relapses previously. The ILS group included the remaining 39 patients with chronic AA (the patients who received topical steroids and/or ILS with failure and/or relapses previously) who were treated with ILS injections again for three sessions at 3-week intervals. Clinical photographs before and after treatment were obtained from the patient photographs archive. Clinical response was evaluated by calculating the Severity of Alopecia Tool (SALT) score. All the patients were assessed with a hair pull test at the margins of alopecia patches and SALT scores at months 0, 3, and 6 and were followed up for relapse for the next 6 months. SALT is an assessment method to measure the severity of hair loss in patients with AA. The scalp is divided into four parts to calculate the SALT score: the vertex, the right/left lateral side and the back. The percentage of hair loss in the four areas is multiplied by 0.4, 0.18, 0.18, and 0.24, respectively, and the SALT score is calculated by summing the scores in 4 regions.[3, 8] AA investigational assessment guidelines divided SALT score into subgroups: S0-S5. The S1 subgroup defines hair loss that is less than 25%.[3, 8] In the evaluation of post-treatment responses: < 25% decrease in SALT score="no response", a decrease of 25-49% in SALT score="partial response", a reduction of 50-74% in SALT score="good response", and a decrease of 75% or more in SALT score="very good response".

Treatment Technique and Protocol

PRP Group: A PRP kit (T-lab PRP Kit, T-lab Regenerative Medicine Company, Bursa, Turkiye) with a Class IIb certificate was used for the patients in the PRP group. Sixteen ml of peripheral venous blood was collected into two self-vacuumed tubes and centrifuged for 2 minutes at 2000 rpm. After centrifugation, supernatant plasma with the whole buffy coat was drawn up into 1 ml 30-gauge insulin syringes without adding any activator. The platelet concentration in PRP was increased to 3-7 times the basal serum value. Then, it was injected intradermally into the alopecia patches of the scalp in aliquots of 0.05-0.1 ml/cm^2 at 1-centimetre intervals.

ILS Group: Triamcinolone acetonide was diluted with saline solution to obtain a concentration of 5 mg/ml according to the recommendations of the AA Consensus of Experts study and drawn into 1 ml 30-gauge insulin syringes.[4] The suspension was then injected intradermally into the alopecia patches of the scalp in aliquots of 0.05-0.1 ml/cm^2 at 1-centimetre intervals.

Statistical Analysis

All analyses were carried out using IBM SPSS Statistics for Windows, Version 20.00 (Armonk, New York, USA: IBM Corp), and a p-value less than 0.05 was considered statistically significant. The normality of the data was tested by the Shapiro-

Wilk test, and it was determined that continuous variables did not show normal distribution. Continuous variables were expressed by mean±standard deviation and median, interquartile range. Categorical variables were represented by number and percentage. Mann-Whitney U and Chi-Square tests were used to compare continuous and categorical data between the groups. The Friedman test was used to determine whether the change in the SALT score was significant during the treatment process, and the post hoc Dunn test was used for pairwise comparisons. The Cochran Q test was used to compare the positivity rates according to the hair pull test results in three different periods. The Conover post-hoc test was used for pairwise comparisons.

Results

This comparative study included 75 patients with patchy AA. Thirty-six out of 75 patients were treated with PRP and 39 with ILS. The age, sex distributions, family history, medical history, and disease duration of the PRP and ILS groups are presented in Table 1. Of the 36 patients treated with PRP, 20 (55.6%) were female, 16 (44.4%) were male, and the mean age of the PRP group was 34.33±10.61 years. The median disease duration in the PRP group was 14 (min:12, max:60, IQR:4) months. Characteristics of the two groups in terms of sex, age, and disease duration were similar (p=0.416, p=0.504, p=0.071).

The patients were evaluated with SALT scores and hair pull tests at 0, 3, and 6 months. There was no statistically significant difference in the SALT 0 scores of the PRP and ILS groups at baseline (p=0.067). At 3. and 6. months, SALT 3 and SALT 6 scores were statistically significantly lower in the PRP group than in the ILS group (p=0.038, p<0.001, respectively) (Table 2). At baseline, the number of patients in the PRP group with a positive hair pull test was statistically significantly higher than in the ILS group (p=0.005). There was no statistically significant difference between the groups regarding hair pull test results at 3. and 6. months (p=0.509, p=0.669, respectively) (Table 2).

Table 1. Demographic features of the PRP and ILS groups

	PRP group (n=36)	ILS group (n=39)	p
Sex (n/%)			
Female	20 (55.6)	18 (46.2)	0.416
Male	16 (44.4)	21 (53.8)	
Age (Mean±SD, years)	34.33±10.61	33.82±13.31	0.504
Family history (n/%)			
Present	3 (8.3)	5 (12.8)	0.713
Absent	33 (91.7)	34 (87.2)	
Medical history (n/%)			
Present	6 (16.7) 1. Atopic dermatitis 2. Celiac disease 3. Gastritis 4. Gallstone 5. Depression 6. Hypertension and asthma	13 (33.3) 1. Coronary artery disease, diabetes mellitus 2. Atrial septal defect 3. Hypothyroidism 4. Epilepsy 5. Hypertension and gastritis 6. Asthma 7. Hypothyroidism 8. Hypertension 9. Hypertension 10. Hypothyroidism 11. Atopic dermatitis 12. Hypertension 13. Hypothyroidism	0.097
Absent	30 (83.3%)	26 (66.7%)	
Disease duration (median/minimum, maximum, IQR, months)	14 (min:12, max:60, IQR:4)	15 (min:12, max:72, IQR:5)	0.071

SD: Standard deviation; IQR: interquartile range; Data were expressed as mean±SD, median, minimum, maximum and IQR in continuous variables and n (%) in categorical variables, respectively. Independent samples were compared with Mann–Whitney U test and Chi Square test.

Table 2. SALT scores and hair pull test at 0, 3 and 6 months in the PRP and ILS groups

	PRP group (n=36)	ILS group (n=39)	p
SALT 0			
Median (min, max, IQR)	3.6 (min:1.2, max:22.4, IQR:2.9)	3 (min:1, max:21.5, IQR:2)	0.067
Hair pull test 0 Number/%			
Positive	28 (77.8)	18 (46.2)	0.005*
Negative	8 (22.2)	21 (53.8)	
SALT 3			
Median (min, max, IQR)	1.6 (min:0, max:16.4, IQR:2.83)	2.5 (min:1, max:20, IQR:1.8)	0.038*
Hair pull test 3 Number/%			
Positive	13 (36.1)	17 (43.6)	0.509
Negative	23 (63.9)	22 (56.4)	
SALT 6			
Median (min, max, IQR)	0 (min:0, max:8.4, IQR:1.35)	2 (min:0.8, max:18, IQR:1.7)	<0.001*
Hair pull test 6 Number/%			
Positive	6 (16.7)	8 (20.5)	0.669
Negative	30 (83.3)	31 (79.5)	
New Hair Growth Time (months)			
Median (min, max, IQR)	1 (min:1, max:2, IQR:0)	2 (min:1, max:3, IQR:2)	0.001*
Pigmentation status of the new hairs Number/%			
Pigmented	25 (69.4)	5 (12.8)	0.001*
Depigmented	11 (30.6)	34 (87.2)	

Min: Minimum; Max: Maximum; IQR: interquartile range; Data were expressed as median, minimum, maximum and IQR in continuous variables and n (%) in categorical variables, respectively. Independent samples were compared with Mann–Whitney U test and Chi Square test.

All the patients were included in the S1 (SALT score < 25%) group according to AA investigational assessment guidelines. When treatment responses were compared over three periods (months 0, 3, and 6), there was a statistically significant difference in SALT scores between the three measurement periods. The score decreased significantly until the measurement at the 6th month in the PRP group (p<0.001) (Fig. 1, Table 3). There was a statistically significant difference between the three measurements regarding hair pull test results (p<0.001). Still, there was no statistically significant difference in the PRP group's hair pull test results between the 3rd and 6th months (p=0.068) (Table 3).

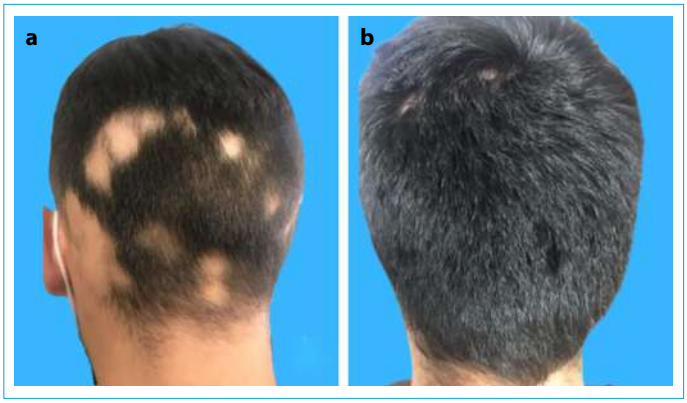

Figure 1. Before treatment **(a)** and after 3 sessions of PRP **(b)**.

When the treatment response was evaluated at the end of the 3rd month, there was no response in 5 (13.8%) patients, partial response in 7 (19.4%) patients, good response in 11 (30.5%) patients, and very good response in 13 (36.3%) patients. However, according to the evaluation at the end of the 6th month, there was no response in 2 (5.5%) patients, partial response in 1 (2.7%) patient, good response in 3 (8.4%) patients, and very good response in 30 (83.4%) patients. Thirty-four (94.5%) patients who responded to treatment were followed up for relapse for a total of 6 months after excluding 2 (5.5%) patients who were unresponsive to PRP treatment. Only 2 (5.9%) patients had a clinical relapse.

Side effects were seen in 16 (44.4%) patients in the PRP group and 8 (20.5%) patients in the ILS group, and the frequency of side effects in the PRP group was statistically significantly higher than in the ILS group (p=0.026). However, the side effects of both groups were minor, such as itching, pain, burning, ecchymosis, and folliculitis, and none of the patients experienced major side effects (Table 4).

Discussion

Alopecia areata is a common autoimmune disease with inflammation-induced patchy hair loss that is easy to diagnose with its typical clinical findings. However, the

Table 3. Change in SALT scores and hair pull test results assessed in three different periods in PRP and ILS groups

PRP group (n=36)		**p**
SALT scores		
SALT 0 Median (min, max, IQR)	3.6 (min:1.2, max:22.4, IQR:2.9)	<0.001*
SALT 3 Median (min, max, IQR)	1.6 (min:0, max:16.4, IQR:2.83)	
SALT 6 Median (min, max, IQR)	0 (min:0, max:8.4, IQR:1.35)	
Pairwise Comparisons		
SALT 0 vs SALT 3		<0.001*
SALT 0 vs SALT 6		<0.001*
SALT 3 vs SALT 6		<0.001*
Hair pull test		
Hair pull test 0 (positive, n/%)	28 (77.8%)	<0.001*
Hair pull test 3 (positive, n/%)	13 (36.1%)	
Hair pull test 6 (positive, n/%)	6 (16.7%)	
Pairwise Comparisons		
Hair pull test 0 vs Hair pull test 3		<0.001*
Hair pull test 0 vs Hair pull test 6		<0.001*
Hair pull test 3 vs Hair pull test 6		0.068
ILS group (n=39)		**p**
SALT scores		
SALT 0 Median (min, max, IQR)	3 (min:1, max:21.5, IQR:2)	<0.001*
SALT 3 Median (min, max, IQR)	2.5 (min:1, max:20, IQR:1.8)	
SALT 6 Median (min, max, IQR)	2 (min:0.8, max:1.8, IQR:1.7)	
Pairwise Comparisons		
SALT 0 vs SALT 3		<0.001*
SALT 0 vs SALT 6		<0.001*
SALT 3 vs SALT 6		0.005*
Hair pull test		
Hair pull test 0 (positive, n/%)	18 (46.2%)	0.002*
Hair pull test 3 (positive, n/%)	17 (43.6%)	
Hair pull test 6 (positive, n/%)	8 (20.5%)	
Pairwise Comparisons		
Hair pull test 0 vs Hair pull test 3		0.743
Hair pull test 0 vs Hair pull test 6		0.001*
Hair pull test 3 vs Hair pull test 6		0.003*

Min: Minimum, Max: Maximum, IQR: interquartile range; Data were expressed as median, minimum, maximum and IQR in continuous variables and n (%) in categorical variables, respectively. Continuous dependent samples were compared with Friedman test and post hoc Dunn test was used for pairwise comparisons. Categorical dependent samples were compared with Cochran Q test and Conover post-hoc test was used for pairwise comparisons.

disease poses a therapeutic challenge because no treatment is either curative or preventive. PRP is a promising treatment modality that has gained importance in managing dermatological diseases with its rich content of growth factors, cytokines, and versatile effects. PRP ensures cell proliferation and differentiation, stimulates angiogenesis, prevents apoptosis, and has a potent anti-inflammatory effect.[6, 7] Also, specifically for hair follicles, PRP was shown to induce cell proliferation in the dermal papilla, improve dermal papilla cell survival via anti-apoptotic effects, prolong the anagen phase of the hair life cycle, prevent transition to the catagen phase resulting in hair regrowth.[9] Last but not least, PRP decreases local tissue inflammation by suppressing cytokine release, which may be beneficial in treating the inflammatory component of AA.[10]

Table 4. Distribution of side effects in the PRP and ILS groups

	PRP group (n=36)	ILS group (n=39)	p
Side effects (n/%)			0.026*
Present	16 (44.4)	8 (20.5)	
Absent	20 (55.6)	31 (79.5)	
Side effect list (n/%)			
Present	16 (44.4)	8 (20.5)	
	3 (8.3) erythema	3 (7.7) erythema	
	3 (8.3) pain	3 (7.7) pain	
	2 (5.6) ecchymosis	1 (2.6) ecchymosis	
	3 (8.3) itching	1 (2.6) folliculitis	
	4 (11.1) burning sensation		
	1 (2.8) folliculitis		

Data were expressed as n (%) in categorical variables. Independent samples were compared with Chi Square test.

This study investigated the therapeutic efficacy of PRP in patchy AA patients. In our study, we evaluated the SALT scores and results of the hair pull test of the patients who received PRP (single spin, 2000 rpm for 2 minutes without activator) or ILS (5 mg/ml TA). SALT scores were similar in PRP and ILS groups at baseline evaluations. We found a statistically significant decrease in SALT scores after each of the three treatment sessions compared to baseline in both ILS and PRP groups. Besides, the SALT scores were significantly lower in the PRP group in the 3rd and 6th months compared to the ILS group.

Multiple studies in the literature have demonstrated encouraging outcomes of PRP in the treatment of AA whereas some studies could not show its superiority over ILS and even found ILS more effective. Kapoor et al.[11] compared the therapeutic efficacy of intralesional TA and PRP prospectively in 40 patients with AA. Twenty patients received ILS (10 mg/ml), and 20 patients received (single spin, 2000 rpm for 3 minutes without activator) PRP every 3 weeks for 12 weeks. They reported that the reduction in the SALT score at each visit was greater in the TA group than the PRP group and concluded that triamcinolone was more effective in AA. Albalat et al.[12] conducted a randomized, double-blind study and evaluated PRP and ILS in treating 80 patients with AA. Forty patients received ILS (5 mg/ml TA), and 40 patients received (double spin, 150g for 10 minutes, 1500-2000 g for 10 minutes with activator) PRP 3-5 sessions every 2 weeks. They found a statistically significant improvement in SALT scores after treatment compared to baseline in both ILS and PRP groups. After 3 months, 65% of the patients in the ILS group and 72.5% of the patients in the PRP group showed >70% improvement. Balakrishnan et al.[13] evaluated therapeutic response to PRP and TA in AA in a comparative study with 40 patients. Sixteen patients who completed the study received (double spin, 1500 rpm for 15 minutes, 2500 rpm for 10 minutes without activator) PRP and 16 who completed the study on the other arm received ILS (10mg/ml TA) 3 sessions every 4 weeks. They reported no statistically significant difference between the two groups at the 4th and 12th weeks. Fawzy et al.[14] used trichoscopy, SALT score, and Alopecia Areata Symptom Impact Scale to compare ILS and PRP in AA. Fourteen patients were treated with ILS (5 mg/ml TA), and 17 patients were treated with PRP (single spin, 3000 rpm for 10 minutes without activator) once monthly for 3 months. They reported a significant improvement in trichoscopy findings and SALT scores compared to baseline levels in both groups. Hegde et al.[15] conducted a randomized, placebo, and active-controlled split scalp study to evaluate the efficacy of PRP in AA. The left side of the scalp of 50 patients with AA received a placebo (intralesional normal saline), the right side of the scalp of 25 patients received intralesional PRP (double-spin 1400 rpm for 10 minutes, 2800 rpm for 10 minutes without activator), and right side of the scalp of 25 patients received ILS (5mg/ml TA) for three treatment sessions at 4 weeks intervals. The SALT score showed significant improvement from baseline in both groups. Additionally, the maximum absolute regrowth was shown by the steroid group, followed by PRP, followed by the placebo group.

On the other hand, a study also reported PRP as a more effective treatment alternative. Trink et al.[16] evaluated the efficacy and safety of PRP for the treatment of AA in a randomized, double-blind, placebo- and active-controlled, half-head, parallel-group study consisting of 45 patients. Fifteen patients received (single spin, 70 g for 8 minutes with activator) PRP, 15 patients received (2.5mg/ml TA) ILS, and 15 patients received placebo (distilled water) for one half their scalp for three sessions 1 month apart. They re-

ported that patients treated with PRP had significantly increased hair regrowth, Ki-67 levels, and decreased hair dystrophy and burning or itching sensation compared with TA or placebo groups.

In summary, Kapoor et al.[11] reported that ILS was more effective than PRP in treating patches of AA. Albalat et al.,[12] Balakrishnan et al.,[13] Hegde et al.[15] and Fawzy et al.[14] found that PRP was an effective treatment option, but they could not demonstrate its superiority over ILS. Trink et al.[16] reported that PRP was more effective than placebo and ILS in terms of increased hair regrowth, which is in line with the findings of our study. The patients in our study were patients with chronic AA who did not benefit from ILS. Given that PRP was effective in this patient group, it can be suggested that sometimes anti-inflammatory treatment is not sufficient in the treatment of AA, and the use of mechanisms effective in prolonging the anagen phase, inducing cell differentiation and promoting hair growth with PRP may provide additional benefits in the treatment AA. Besides, it should be noted that there were some differences in the materials and methods of the studies, such as PRP preparation protocols, treatment schedules, and TA concentration. In a recent meta-analysis, the aforementioned four studies investigating the effectiveness of PRP in alopecia areata were evaluated and found that pooled mean differences from the four studies did not exhibit a significant difference in the mean change in the SALT score between PRP and TA groups. Thus, it was concluded that PRP is a promising steroid-saving treatment option in the management of AA.[5] When we evaluated all the studies together, the dose of TA seemed to affect the results of the studies. While ILS was more successful at 10 mg/ml TA doses, PRP was more successful when TA was used in 2.5 mg/ml doses. Although PRP was more effective in our study, ILS seems to retain its place in the first step of treatment due to its accessibility and cost-effectiveness, and PRP will take its place as the second option in cases where ILS fails.

While the clinicians are more cautious about the cutaneous side effects of TA, interestingly, in our study, side effects related to PRP were more common significantly. In line with the reported side effects of our study, Albalat et al.[12] reported erythema and burning sensation in 20 patients (50%) in both groups after the first session, but no other serious side effects were observed. Consequently, PRP seems to be a safe alternative treatment since no side effects were reported in many studies in the literature.[15, 16]

The present study has several limitations. The main limitation is its retrospective design and small sample size, which might not be enough to determine the true prevalence of side effects and complications. SALT scores were calculated from photographs, and there was not a blind investigator. Lastly, PRP and ILS injections were only performed on different areas of the scalp but not on beards and eyebrows. Therefore, it was not possible to assess different response rates for other areas of involvement.

Conclusion

PRP seems to be an effective and safe treatment option for limited patchy alopecia areata, but its superiority over ILS has not been fully demonstrated, making ILS still the first-line treatment. Further prospective randomized controlled studies with a greater number of patients and with a standardized protocol for the preparation and administration of PRP are needed to fully address the place of PRP in the treatment algorithm of AA.

Disclosures

Ethics Committee Approval: The study was approved by the Ankara Training and Research Hospital Clinical Research Ethics Committee (date: 20.10.2021, number: E-93471371-514.01.02).

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Original Research

Knowledge and Self-Efficacy Levels of Family Physicians on Epilepsy Management in Türkiye: Pre- and Post-Education Evaluation

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Abstract

Objectives: Family physicians (FPs) are directly responsible for the care of people with epilepsy. However, their education about epilepsy may be inadequate or lacking. The aim of this study was to assess the basic knowledge and self-efficacy levels regarding epilepsy among FPs and to identify their educational needs in managing epilepsy.

Methods: The sample for this pre-test-intervention-post-test study consisted of 60 FPs. FPs attended a four-hour training on epilepsy management. The effectiveness of the training was assessed with the Epilepsy Knowledge and Self-Efficacy (EKSE) scale before and after the training. In addition, a survey was conducted to determine the problems encountered in the follow-up of epilepsy patients and their training needs.

Results: 60 physicians participated in the study [37 males (61.7%), mean age 37.97±8.92 years and professional duration 80.48±70.59 months]. While the total EKSE score of FPs was 90.23±10.97 before the training, it increased to 112.3±15.26 points after the training ($p<0.001$). After the training, significant score increases were observed in all subcomponents of the EKSE compared to before the training. After the training, there was a significant improvement in the physicians' ability to recognize diseases accompanying epilepsy, to have sufficient knowledge about antiseizure medications, and to follow up patients with epilepsy compared to before the training ($p<0.001$, $p=0.001$, and $p=0.002$, respectively).

Conclusion: This study demonstrated that FPs have need for education regarding epilepsy management and that the education provided has a positive impact.

Keywords: Epilepsy, education, family physician, primary care, health promotion

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Epilepsy is a brain disorder characterized by a predisposition to recurrent seizures, with serious cognitive, psychological, and social consequences.[1] It affects more than 50 million people worldwide, 80% of whom live in low- and lower-middle-income countries (LIMCs).[2] Nearly half of people with epilepsy living in LIMCs remain undiagnosed, and only one in five of those diagnosed receive appropriate treatment.[3] This situation is called the epilepsy diagnosis and treatment gap. A recent meta-analysis shows that the epilepsy treatment gap varies widely, from 5.6% in Norway to 100% in parts of Tibet, Togo and Uganda.[4]

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The World Health Organization (WHO) supports the inclusion of primary health care services in these processes in order to close the epilepsy diagnosis and treatment gap. [5] WHO emphasizes the importance of primary health care services in the detection of epilepsy cases, implementation of basic treatment protocols and follow-up of treatments. It also views epilepsy care as a shared responsibility between primary and secondary care providers.[5,6] The International League Against Epilepsy (ILAE) has developed a training curriculum to strengthen epilepsy diagnosis and care at the primary care level.[7] However, it has been stated that educational programs need to be developed and adapted to the needs of different environments due to differences between country income groups.[7] FPs are the first point of contact in providing medical care and social support to people with epilepsy. Despite the frequent encounters of FPs with patients with epilepsy, epilepsy management is not included in undergraduate and graduate curriculum, making it difficult for FPs to effectively help patients with epilepsy.[8]

In this study, training seminars were organized to improve the knowledge and self-efficacy perceptions of FPs regarding epilepsy management. Educational seminars have been made more functional by focusing on the difficulties and educational needs of physicians during the follow-up of epilepsy patients in a primary care setting. It has been predicted that increasing physicians' knowledge and self-efficacy levels regarding epilepsy may positively affect the care of epilepsy patients. The main aim of the study was to evaluate the basic knowledge and self-efficacy levels of FPs and general practitioners working in the eastern part of Türkiye about epilepsy. It was also aimed to determine the difficulties and training needs of physicians in epilepsy management in primary health care.

Methods

Participants

In Türkiye, primary care services are provided by family physicians or physicians who are not family physicians but have a "family physician practice authorization certificate" All of these physicians are called family physicians/general practitioners.[9] There is no postgraduate curriculum for epilepsy in Türkiye. It is also not included in the family medicine specialization curriculum.

This intervention study was conducted among FPs and general practitioners (GPs) receiving specialist training in the Department of Family Medicine at a university hospital in eastern Türkiye. Physicians were invited to attend epilepsy seminars held during regular training hours. A total of sixty physician volunteers who attended the training seminars and completed the pre-training survey were included in this study.

Intervention

Four sixty-minute educational seminars were planned, one week apart, about epilepsy, including the medical and social aspects of the disease. Participants were invited to participate in the study using a pre-test-intervention-post-test design. They were asked to fill out questionnaires before and after the training. When creating the content of the training seminar, the content described in the training curriculum developed and recommended for use by the ILAE Education Council, which is evidence-based and consensus-based for the management of epilepsy in the primary health care setting, was first reviewed. [7] The medical portion of the training consisted of a short classical lecture that included information on how physicians diagnose epilepsy, counsel people with epilepsy on a range of issues, provide treatment and follow-up for people with epilepsy, refer patients to higher care facilities as appropriate, manage epilepsy emergencies including status epilepticus, and recognize and provide basic care for psychiatric and somatic comorbidities. The social part was about psychosocial issues such as stigma, possible consequences, health reports (military service, driver's license, work permit, sports certificate) and daily life problems that patients with epilepsy may encounter. As a basis for the social aspects of epilepsy, information on the website of the Turkish chapter of the ILAE was used.[10] The training was enriched with real-life cases. All training was carried out by a neurologist (GY). The seminar content has been designed in accordance with ILAE standards, and a detailed summary of the core training content is presented in Supplemental material 1.

Data Collection Tools

Data Collection Form

This section provides information on the sociodemographic characteristics of the participants, such as age, sex, length of service, and professional status (family physician/general practitioner). In addition, additional descriptive questions were included to understand the participants' knowledge and experience of epilepsy. The questions used in this section were taken from the first section (five multiple-choice questions) measuring epilepsy knowledge of a survey evaluating the knowledge and attitudes of primary care physicians about epilepsy.[11] These questions cover topics such as the definition of epilepsy, the source of epilepsy information, first exposure to an epileptic seizure, first treatment experience, and self-assessed satisfaction with epilepsy information. The second section of the survey assessing attitudes toward epilepsy was excluded from the scope of our study.

Family Physicians' Epilepsy Knowledge and Self-Efficacy Scale

Epilepsy knowledge and self-efficacy (EKSE) scale was applied under supervision before (pre-) and after (post-test) the intervention. EKSE is a scale that questions the needs of family medicine in terms of epilepsy management from the perspective of core competencies. EKSE evaluates physicians' perceptions of some knowledge and self-efficacy regarding epilepsy management using 24 positive and 5 negative statements on a 5-point Likert scale. Positive questions are calculated as 1 point for the answer 'strongly disagree', 2 points for the answer 'disagree', 3 points for the answer 'undecided', 4 points for the answer 'agree', and 5 points for the answer 'strongly agree'. Negative statements were coded as the opposite of positive questions. The lowest and highest scores that can be obtained from the 29 statements in the survey are between 29 and 145 points. The Cronbach alpha internal consistency coefficient of the scale was reported as 0.848 (Supplemental material 2).[8]

The World Organization of Family Physicians (WONCA) European definition of the competencies expected from a family physician consists of six subcomponents including primary care management (PCM), person-centered care (PCC), holistic approach (HA), comprehensive approach (CA), specific problem-solving skills (SPSS) and community orientation (CO).[12] The items in the EKSE scale are included in the family medicine core competencies. Primary care management (questions 1-4), Person-centered care (questions 5-7), Holistic approach (questions 8-10), Comprehensive approach (questions 11-23), Specific problem solving skills (questions 24-28) and Community orientation (question 29) are listed.

Challenges and Educational Needs of Family Physicians

A questionnaire was created to obtain information about the difficulties/problems physicians encounter in managing patients with epilepsy in the primary care setting and thus to determine their training needs. After the literature review, a question pool was created by the researchers on this subject. The questions were then selected from this pool by an expert panel. A pilot application was conducted with 20 physicians before the study. The form consists of twelve yes/no questions. Frequencies and percentages of responses were calculated before and after the training (Table 1). It was thought that this questionnaire could de-

Table 1. Difficulties encountered by family physicians in the follow-up of patients with epilepsy

Questions	Answers	Pre-training (n=60)	Post-training (n=60)	p*
Lack of knowledge about epilepsy	No	37 (61.7)	45 (75.0)	0.201
	Yes	23 (38.3)	15 (25.0)	
Not knowing how to follow up an patient with epilepsy	No	22 (36.7)	32 (53.3)	0.144
	Yes	38 (63.3)	28 (46.7)	
Not knowing the diseases that accompany epilepsy	No	20 (33.3)	42 (70.0)	<0.001
	Yes	40 (66.7)	18 (30.0)	
Having difficulty prescribing anti-seizure medication	No	34 (56.7)	43 (71.7)	0.151
	Yes	26 (43.3)	17 (28.3)	
Not having enough information about drug dosage/side effects	No	11 (18.3)	31 (51.7)	0.001
	Yes	49 (81.7)	29 (48.3)	
Insisting on prescribing drugs without a report	No	27 (45.0)	46 (76.7)	0.002
	Yes	33 (55.0)	14 (23.3)	
Not being able to allocate enough time due to patient density	No	37 (61.7)	42 (70.0)	0.472
	Yes	23 (38.3)	18 (30.0)	
Difficulty managing the patient in special situations	No	38 (63.3)	43 (71.7)	0.383
	Yes	22 (36.7)	17 (28.3)	
Patient non-compliance with treatment	No	40 (66.7)	43 (71.7)	0.700
	Yes	20 (33.3)	17 (28.3)	
Difficulty in referring the patient to a specialist and consulting	No	43 (71.7)	50 (83.3)	0.210
	Yes	17 (28.3)	10 (16.7)	
I don't have any problems	No	59 (98.3)	53 (88.3)	0.070
	Yes	1 (1.7)	7 (11.7)	
Not knowing what to do with health reports	No	41 (68.3)	49 (81.7)	0.152
	Yes	19 (31.7)	11 (18.3)	

Answer categories are expressed as frequency (percent); *: McNemar's chi-square test; The p-values lower than 0.05 highlighted as bold.

termine the difficulties/problems experienced by family physicians in the management of patients with epilepsy and that training seminars prepared according to the needs on this subject could be useful.

Ethical Approval

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Inonu University Ethics Committee (date:14.11.2023, no: 2023/5240). The participants of the study signed written informed consent.

Statistical Analysis

According to the theoretical power analysis, the sample size required to find a statistically significant difference between the groups was calculated as at least 34 physicians.[13] In the study, variables were summarized appropriately according to different measurement levels. Mean±standard deviation and median (interquartile range) were used for continuous variables (Tables 2 and 3), while categorical variables were presented as frequency and percentage (Table 1). In statistical analyses, type 1 error level was set as α=0.05. Normality assumption for continuous paired measurements was checked by Shapiro-Wilk test. Paired t-test was used for variables with normal distribution, and Wilcoxon signed rank test was used for variables with non-normal distribution. In pre- and post-training comparisons, Wilcoxon signed-rank test and paired samples t-test were used in dependent groups according to the assumption of normal distribution (Table 2). Wilcoxon signed-rank test was used in subgroup analyses according to occupational groups (Table 3). McNemar chi-square test was used to compare

Table 2. Evaluation of knowledge and self-efficacy perceptions regarding epilepsy management

Subgroups	Pre-training (n=60)	Post-training (n=60)	p
PCM	8.27±2.46 | 8 (5-14)	12.68±4.58 | 11 (4-20)	<0.001*
PCC	10.07±2.11 | 10 (5-15)	12.05±1.91 | 12 (7-15)	<0.001*
HA	10.67±2.00 | 10 (7-15)	12.02±1.98 | 12 (7-15)	<0.001*
CA	38.3±7.42 | 39 (18-53)	49.58±7.39 | 50 (25-65)	<0.001*
CO	2.97±1.09 | 3 (1-5)	3.63±1.07 | 4 (2-5)	0.002*
SPSS	19.97±2.24 | 20 (15-25)	21.83±2.45 | 22 (15-25)	<0.001*
Total score	90.23±10.97 | 90 (59-119)	112.3±15.26 | 111 (72-146)	<0.001**

Subgroups are expressed as mean±std. deviation and median (interquartile range); *: Wilcoxon signed-rank test; **: Paired-samples t-test; The p-values lower than 0.05 highlighted as bold; PCM: Primary care management; PCC: Person-centred care; HA: Holistic approach; CA: Comprehensive approach; CO: Community orientation; SPSS: Specific problem-solving skills.

Table 3. Evaluation of knowledge and self-efficacy perception regarding epilepsy management (According to occupational groups)

Subgroups	Occupational group	Pre-training (n=60)	Post-training (n=60)	p*
PCM	GP	7.95±2.70 | 7 (5-14)	11.89±4.57 | 11 (7-20)	0.01
	FP	8.41±2.37 | 8 (5-14)	13.05±4.60 | 12 (4-20)	<0.001
PCC	GP	9.95±2.20 | 10 (5-14)	11.79±2.23 | 12 (7-15)	0.036
	FP	10.12±2.10 | 10 (6-15)	12.17±1.76 | 12 (7-15)	<0.001
HA	GP	10.37±2.14 | 10 (7-14)	11.74±2.28 | 12 (7-15)	0.145
	FP	10.80±1.94 | 11 (7-15)	12.15±1.84 | 12 (8-15)	<0.001
CA	GP	36.11±8.49 | 38 (18-52)	48.32±6.66 | 49 (38-61)	0.001
	FP	39.32±6.75 | 39 (25-53)	50.17±7.72 | 50 (25-65)	<0.001
CO	GP	2.74±0.99 | 3 (1-4)	3.26±1.24 | 3 (2-5)	0.217
	FP	3.07±1.13 | 3 (1-5)	3.80±0.95 | 4 (2-5)	0.005
SPSS	GP	19.63±2.31 | 20 (16-25)	21.58±2.95 | 23 (16-25)	0.044
	FP	20.12±2.22 | 20 (15-24)	21.95±2.21 | 22 (15-25)	<0.001
Total score	GP	86.74±13.10 | 89 (59-112)	108.58±14.45 | 109 (89-139)	0.002
	FP	91.85±9.57 | 92 (75-119)	114.02±15.5 | 111 (72-146)	<0.001

Subgroups are expressed as mean±std. deviation and median (interquartile range); *: Wilcoxon signed-rank test; The p-values lower than 0.05 highlighted as bold; PCM: Primary care management; PCC: Person-centred care; HA: Holistic approach; CA: Comprehensive approach; CO: Community orientation; SPSS: Specific problem-solving skills; FP: Family physician; GP: General practitioner.

categorical variables (Table 1). Statistically significant results (p<0.05) are emphasized in bold font in the tables. Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) Statistics 27.0 (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0 Armonk, NY: IBM Corp. USA)

Results

Data Collection Form Results

Sixty physicians [(37 male (61.7%); 41 family physicians (68.3%)] answered the EKSE scale before and after the training. The mean age of the participants was 37.97±8.92 years (range: 25-56 years) and professional duration was 80.48±70.59 months (range: 1- 276 months).

All 60 participants (100%) answered the question "What is epilepsy?" correctly.

According to the responses to the question "Where did you first get your information about epilepsy?", the vast majority of participants 95% (57 person) indicated medical school as their main source of information. On the other hand, 1.7% (1 person) indicated their role as a primary care physician and 3.3% (2 person) selected "other" but did not specify.

When participants were asked, "Where did you first witness a seizure?" 18.3% (11 person) reported observing the seizure in medical school, 10% (6 person) as a resident physician in a hospital, 21.7% (13 person) as a primary care physician, 11.7% (7 person) in another healthcare setting, and 30% (18 person) in "other settings." Additionally, 8.3% (5 person) of participants reported never having witnessed a seizure before.

When the participants were asked the question "Where was your first experience of epileptic seizure treatment?", the responses were as follows: 13.3% (8 person) stated that they had their first experience of treatment at medical school, 5% (3 person) as a resident physician at a hospital, 45% (27 person) as a primary care physician, and 6.7% (4 person) at another health center. It was also noted that 30% (18 person) of the participants had never treated an epileptic seizure before.

When participants were asked the question "How would you rate your level of knowledge about epilepsy?", 30% (18 person) stated that they were very satisfied with their knowledge, 43.3% (26 person) were partially satisfied, and 1.7% (1 person) were not satisfied. These findings reflect the satisfaction level of the participants with their knowledge about epilepsy according to their own assessment.

Perceptions of Knowledge and Self-Efficacy Regarding Epilepsy Management

While FPs' EKSE scores before the training were 90.23±10.97, they increased to 112.3±15.26 points after the training (p<0.001). After the training, significant score increases were observed in all subcomponents of EKSE compared to before the training (Table 2). No statistically significant relationship was found between the age, sex, and professional duration of FPs and their EKSE scores (p>0.05). When the FP and GPs' EKSE total scores were compared before and after the training, a statistically significant increase was observed in both groups (p<0.001 and p=0.002, respectively). There was no statistically significant difference in the pre- and post-training HA and CO subcomponents in GPs (p>0.05) (Table 3).

Challenges and Educational Needs of Family Physicians

Following the training seminars addressing the difficulties that FPs reported in managing patients with epilepsy, improvements in their knowledge and self-confidence levels were observed to varying degrees. These improvements demonstrate the effectiveness of training that addresses the specific challenges physicians face. After the training, a significant improvement was observed in the knowledge levels of FPs regarding not having sufficient knowledge about the interactions, dosages and side effects of ASMs (81.7% vs. 48.3%, p=0.001), not recognizing the diseases seen together with epilepsy (66.7% vs. 30%, p<0.001) and having problems in the follow-up of patients with epilepsy (55% vs. 23.3%, p=0.002) (Table 1).

Discussion

In this study, a significant increase was observed in the EKSE total scores and all subcomponent scores of the physicians after the training compared to before the training. This suggests that education on epilepsy management increases FPs' perceptions of knowledge and self-efficacy. No statistically significant relationship was found between FPs' EKSE scores and their age, sex and professional duration. There was no significant difference in the HA and CO subcomponents of the GPs after the training compared to before the training. This can be interpreted as the GPs did not lack knowledge about these subcomponents or they considered themselves more competent.

There are few studies in the literature examining the effects of educational courses aimed at improving the knowledge and practice of primary care providers regarding epilepsy.[14-19] Because these studies used different populations and methodologies, their results cannot be directly compared.

This situation limits the generalizability of the research results. In a study conducted in Bolivia, a large proportion of general practitioners stated that they felt inadequate in the field of epilepsy before the training. However, after the training, a significant increase in the knowledge and skills of physicians regarding epilepsy was observed.[14] Similarly, an online epilepsy course in Latin America has created a significant shift in the way GPs approach patients with epilepsy. At the end of the course, physicians' confidence in disease management increased from 21% at the beginning to 73%.[15] In Thailand, a significant improvement in knowledge and attitudes of physicians and nurses was found after training on epilepsy care, highlighting the importance of epilepsy education.[16] A pediatric epilepsy education program for primary care physicians has been reported to increase knowledge and confidence in epilepsy management, potentially improving the large epilepsy treatment gap in children in Zambia.[17] A study using the methodology of Project ECHO (Extension for Community Healthcare Outcomes), a telementoring program, found that it offered primary care providers an effective approach to epilepsy management, with over 98% of participants reporting greater comfort and self-efficacy in treating patients with epilepsy or neurological disorders.[18] In this context, education programs are a cost-effective way to improve the knowledge, attitudes and practices of primary health care workers regarding epilepsy. Continuing education programs are needed to improve the management of individuals with epilepsy.[19] Although the new methodologies or online trainings mentioned have reported success in terms of applicability and reaching more healthcare personnel, we think that face-to-face training and feedback from participants after the course is a more effective approach. Another important issue is that inadequate knowledge of healthcare personnel has been reported as a contributing factor to the epilepsy treatment gap.[20] Therefore, the need for continuous and effective education campaigns, especially for healthcare personnel in rural communities, has been emphasized to increase knowledge about epilepsy and close the epilepsy treatment gap.[13] In the current study, a significant increase in FPs' EKSE scores was observed after the training compared to before the training. This shows the positive effect of their training on epilepsy.

In order to plan training campaigns for healthcare professionals, basic knowledge levels need to be determined.[13] A study conducted in Türkiye found that most physicians in the primary care setting generally have sufficient knowledge about intervention during a seizure.[8] However, the same study showed that physicians need more information and support regarding the treatment and long-term follow-up of epilepsy patients. Especially in special cases such as pregnancy, breastfeeding and childhood, primary care physicians feel inadequate in prescribing ASM and experience indecisiveness in issuing documents such as driving, sports and work permits for patients with epilepsy.[8] Some studies also support the fact that physicians have difficulty in managing patients because they do not have sufficient knowledge about ASMs.[16,17] In the United States, FPs have been noted to have difficulties in stopping and starting ASM, changing ASMs, and managing patients throughout pregnancy. This suggests that FPs, who are responsible for protecting the health of patients with epilepsy and their babies, need more information and training on the use of ASM before and during pregnancy as part of a person-centered and comprehensive approach.[21] Similarly, in our study, it was observed that most of the FPs had difficulties because they did not have sufficient knowledge about ASM before the training, did not know the diseases that occur together with epilepsy, and did not know how to follow up patients with epilepsy. This situation reveals the need for training in epilepsy management in primary care in our country.

The current study revealed that a solution-oriented approach to the educational needs of FPs and the problems they encounter during the epilepsy management process is an effective way to increase their interest in education. The high level of interest and positive evaluations of the participants in the training show that this approach is successful in achieving the learning objectives. As a result, the role of physicians in the management of epilepsy in primary health care is important. It is clear that cases of complex or treatment-resistant epilepsy, especially those with initiation of ASMs, changes during pregnancy, psychiatric comorbidities or diagnostic uncertainty, should be appropriately referred to neurologists. Supporting primary care physicians in issues such as epilepsy monitoring and evaluation of comorbidities will increase clinical safety by strengthening collaborative care models. The training we have organized has increased physicians' knowledge and confidence in managing conditions that do not require a neurologist, and has also enabled them to better identify patients who need to be referred to a specialist. In the current study, the increase in self-confidence observed in the subjects that the participants stated they had difficulty with compared to before the training is an important indicator of this situation. Further studies are needed to assess whether these self-reported improvements lead to actual changes in clinical behavior.

The current study has several limitations. First, participants' knowledge and practice in the management of patients with epilepsy were based on self-reports. This may include potential bias in subjective assessments. Second, voluntary

participation may have introduced selection bias, which may affect the generalizability of our training program to the general population. Thirdly, the duration of the training seminars was limited due to the fact that the program was organized in a shorter format rather than a course or symposium. In this context, the fact that some of the participants came from family health centers caused the training hours to be limited in order to ensure their participation in all seminars and to prevent problems that may occur during the permission processes. Finally, although participants reported increased confidence in managing patients with epilepsy after the training, no review could be conducted to assess the extent to which this training was reflected in clinical practice and whether it increased patient referrals to the epilepsy center. More comprehensive research is needed in the future to observe the long-term impact of training on patient outcomes.

Conclusion

FPs, who frequently encounter patients with epilepsy, need training in epilepsy management. Training in this area will increase physicians' knowledge levels and self-efficacy perceptions. This study can form the basis for future research.

Disclosures

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Original Research

Fatigue, Insomnia, and Disability as Independent Predictors of Depressive Symptoms in Multiple Sclerosis: A Prospective Observational Study

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Abstract

Objectives: This study aimed to identify the clinical factors independently associated with depressive symptoms in patients with multiple sclerosis (MS) and to evaluate the impact of depression on health-related quality of life (QoL).

Methods: In this prospective observational study, 90 patients with MS were evaluated. Age, sex, disease duration, MS subtype, and Expanded Disability Status Scale (EDSS) scores were recorded. The Fatigue Severity Scale (FSS), Insomnia Severity Index (ISI), Epworth Sleepiness Scale (ESS), Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS) scale, and the EuroQol 5-Dimension 3-Level (EQ-5D-3L) questionnaire were administered. The presence of restless legs syndrome (RLS) was also recorded. Depression severity was measured using the Patient Health Questionnaire-9 (PHQ-9). First, univariable associations were examined, and relevant variables were subsequently entered into a multivariable linear regression model using backward elimination.

Results: Higher FSS, ISI, and EDSS scores were independently associated with higher PHQ-9 scores. FSS and ISI scores showed the strongest correlations with depression (ρ=+0.52 and +0.57; $p<0.001$). EDSS showed a modest association (ρ=+0.23, $p=0.031$). Age, sex, and disease duration were not significant predictors. S-LANSS scores, MS subtype, and RLS were significant in univariate analysis but excluded from the final model. Depression scores were significantly associated with higher EQ-5D-3L scores, indicating poorer QoL ($p<0.001$).

Conclusion: Fatigue and insomnia were the strongest independent predictors of depression in MS, surpassing traditional clinical indicators. Routine screening for these symptoms may facilitate earlier detection and treatment of depression and improve QoL in clinical practice.

Keywords: Depression, fatigue, insomnia, mood disorders, multiple sclerosis, quality of life

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Multiple sclerosis (MS) is a chronic, immune-mediated neurological disorder characterized by demyelination, axonal loss, and neurodegeneration in the central nervous system.[1,2] In addition to physical disability, MS is frequently accompanied by psychiatric comorbidities, particularly depression, which affects up to 50% of patients over the disease course.[3] Despite its high prevalence and clinical significance, depression often goes underrecognized and untreated in MS populations, partly due to overlapping symptoms such as fatigue, cognitive decline, and sleep disturbances.[4,5]

Importantly, depression in MS is not only a consequence of disease burden—it may also worsen disease outcomes. Depression can contribute to increased symptom perception,

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reduce adherence to disease-modifying therapies (DMTs), and potentially impact immune regulation through stress-related neuroendocrine pathways.[6,7] In patients with MS, depression has also been linked to cognitive impairment, disruptions in occupational functioning, increased risk of suicidal ideation, and poorer quality of life.[3,8]

The pathogenesis of depression in MS is multifactorial, involving neuroinflammatory and neurodegenerative mechanisms as well as psychological and social stressors. Demyelinating lesions affecting mood-related circuits, immune-mediated alterations in neurotransmitter systems, and the psychosocial burden of living with a chronic, unpredictable illness may all contribute to the development of depressive symptoms.[9,10]

Several studies have examined the association between depression and MS-specific clinical features, including disease duration, MS subtype, and neurological disability as assessed by the Expanded Disability Status Scale (EDSS).[5,11] However, recent research has shifted focus to patient-reported outcomes, suggesting that subjective symptoms such as fatigue, insomnia, and neuropathic pain may be stronger correlates of depression than traditional neurological markers.[12,13]

Given its high prevalence and clinical consequences, identifying the key predictors of depression in MS is critical for timely intervention. In this study, we aimed to examine the independent clinical and demographic factors associated with depressive symptoms in a cohort of patients with MS. We also aimed to assess the relationship between depression and health-related quality of life.

Methods

Study Population

This prospective study was conducted with patients diagnosed with MS who were evaluated at the MS Outpatient Clinic of the Neurology Department at Sisli Etfal Training Research Hospital over a one-month period. Patients were diagnosed according to the McDonald criteria.[14] Written informed consent was obtained from all participants, who were evaluated by a neurologist specialized in demyelinating disorders. Individuals were eligible for inclusion if they had a confirmed diagnosis of MS. Exclusion criteria included the presence of other neurological conditions, age under 18, current use of medications for depression and/or anxiety, and refusal to participate in the study. The study protocol received approval from the Ethics Committee of Sisli Etfal Training and Research (approval date and number: 20.5.2025-4865). All procedures were carried out in accordance with the principles of the Declaration of Helsinki.

Clinical and Psychological Assessments

Demographic characteristics, age at disease onset, duration of illness, disease severity, fatigue level, use of DMTs, number of relapses, types of relapses experienced, MS subtype (relapsing-remitting MS [RRMS], and secondary progressive MS [SPMS]), and the presence of restless legs syndrome (RLS) were recorded. Additionally, data on neuropathic pain and other comorbid medical conditions were collected.

The Expanded Disability Status Scale (EDSS) and the Fatigue Severity Scale (FSS)[15] were used to assess disease severity and fatigue levels, respectively. An average FSS score of 4 or above was considered indicative of clinically relevant fatigue. The self-completed Leeds Assessment of Neuropathic Symptoms and Signs pain scale (S-LANSS) was used to determine the presence of neuropathic pain, with a cut-off score of ≥12.[16] Depression was evaluated using the Patient Health Questionnaire-9 (PHQ-9) and categorized as: mild (5-9), moderate (10-14), moderately severe (15-19), or severe (≥20).[17]

Health-related quality of life was assessed using the EQ-5D-3L, a three-level instrument developed by the EuroQol Group.[18] Additionally, insomnia and excessive daytime sleepiness were questioned using Insomnia Severity Index (ISI) and Epworth Sleepiness Scale (ESS), respectively.[19,20] Patients scoring ≥15 on the ISI were classified as having moderate to severe insomnia, while those scoring >10 on the ESS were classified as having excessive daytime sleepiness.[19,20] Associations between these parameters and PHQ-9 scores were investigated.

Statistical Analysis

All analyses were performed using Python version 3.11 (open source), with the following packages: pandas 2.2 for data manipulation, SciPy 1.12 for statistical testing, statsmodels 0.15 for regression analysis, and scikit-posthocs 0.7 for post hoc comparisons. Data visualizations were generated using matplotlib 3.8. All statistical tests were two-sided, and a p value of <0.05 was considered statistically significant. Normally distributed continuous variables were summarized as mean±standard deviation (SD), and non-normally distributed variables as median with interquartile range (IQR). Categorical variables were described as counts and percentages (n, %).

The primary outcome was the PHQ-9 total score (range: 0–27), treated as a continuous measure of depressive symptom burden. Associations between continuous predictors and PHQ-9 were evaluated using Spearman rank correlation (ρ) with corresponding 95% confidence intervals (CIs). Binary predictors were assessed using Welch's t-test, with effect sizes reported as Cohen's d. Categorical variables

with more than two unordered groups were tested via the Kruskal–Wallis H test, with effect size estimated using epsilon squared (ε^2). Significant findings were further explored through Dunn's post hoc tests with Bonferroni correction.

Variables with a p-value <0.20 in univariate testing or deemed clinically relevant (e.g., age, sex, EDSS) were considered for inclusion in multivariable modelling.

To identify independent predictors of depressive symptoms (PHQ-9), an ordinary least squares (OLS) regression model was constructed with the following candidate variables: age, sex, EDSS, FSS, ISI, ESS, S-LANSS score, RLS, and alcohol use. Robust standard errors (HC3) were applied to address potential heteroscedasticity. Multicollinearity was assessed using the variance inflation factor (VIF), with variables exceeding VIF >5 marked for potential removal. A backward elimination approach was used, sequentially removing variables with p>0.10 unless clinically essential. Model fit was evaluated using adjusted R^2, and residual diagnostics included assessments for normality, linearity, and influential observations (defined as Cook's distance >4/n).

Associations between depressive symptoms (PHQ-9) and quality of life were examined using the EQ-5D-3L. Two outcomes were analyzed: EQ-5D-3L point score (higher values indicate worse health) and EQ-5D-3L percentage score (higher values indicate better perceived health status). Both were correlated with PHQ-9 using Spearman's rank correlation. Scatter plots were used to visualize the relationships, with fitted linear trend lines for illustration.

Results

Sociodemographic and Clinical Characteristics

A total of 90 patients with a median age of 36.5 years (IQR:27.0–45.0) were included in the study. There were 67 females (74.4%) and 23 (25.6%) males. Detailed baseline characteristics are presented in Table 1.

Among the participants, 81 (90%) had RRMS and 9 (10%) had SPMS. The DMTs used were as follows: dimethyl fumarate (n=34), fingolimod (n=16), natalizumab (n=16), ocrelizumab (n=8), cladribine (n=7), teriflunomide (n=6), and peginterferon beta-1a (n=1). Two patients were not receiving any treatment. A total of 50 patients (55.5%) reported fatigue, and 23 (25.5%) reported neuropathic pain. The median FSS score was 37 (IQR: 27–48), and the median S-LANSS score was 2 (IQR: 0-11.8).

The median PHQ 9 score was 8 (IQR: 5–14). Depression severity was categorized as mild in 33 patients (36.6%), moderate in 17 (18.8%), moderately severe in 19 (21.1%), and severe in 2 (2.2%). The median EQ-5D-3L point score was 7 (IQR:6-9) and the median EQ-5D-3L percentage score was 75% (IQR: 50%–90%). Additionally, the median ISI and ESS scores were 6.5 (IQR: 3-11) and 3.5 (IQR: 2-6), respectively. Nine patients (10%) were classified as having insomnia and 13 (14.4%) as having excessive daytime sleepiness.

Table 1. Baseline characteristics of the study population

Variable	Value
Age, year	36.5 (27.0 – 45.0)
Age at MS diagnosis, year	28.0 (22.0 – 38.5)
MS duration, year	4.0 (2.0 – 8.0)
Number of relapses	2.0 (1.0 – 3.0)
EDSS score	1.0 (1.0 – 2.0)
Sex	
Female	67 (74.4)
Male	23 (25.6)
Other comorbid disease	
No	61 (67.8)
Yes	29 (32.2)
Current smoker	
No	69 (76.7)
Yes	21 (23.3)
Alcohol use	
No	78 (86.7)
Yes	12 (13.3)
Restless Leg Syndrome	
No	68 (75.6)
Yes	22 (24.4)

*Data are presented as median (interquartile range) for continuous variables and as number (%) for categorical variables. EDSS: The Expanded Disability Status Scale; MS: Multiple sclerosis.

Depression and Clinical Correlates

Among all continuous variables, sleep and fatigue-related measures exhibited the strongest positive correlations with depressive symptoms. Specifically, ISI (ρ=+0.57, p<0.001) and FSS (ρ=+0.52, p<0.001) were the most prominent contributors, followed by the S-LANSS score (ρ=+0.42, p<0.001). These variables individually explained approximately 20–30% of the rank variance in PHQ-9 (Table 2).

Additional variables such as ESS (ρ=+0.31, p=0.003) and EDSS (ρ=+0.23, p=0.031) also demonstrated significant but comparatively weaker associations. In contrast, demographic and disease-specific variables such as age (ρ=–0.09, p=0.386), MS duration (ρ=–0.08, p=0.479), and age at diagnosis (ρ=–0.06, p=0.597) were not significantly correlated with PHQ-9 scores.

Binary predictors revealed a notable effect of RLS on PHQ-9 scores. Patients with RLS had significantly higher depressive symptoms compared to those without (mean difference: +3.7 points; t=2.89, p=0.007). A trend toward lower

Table 2. The associations between continuous predictors and PHQ-9 scores using Spearman's rank correlation.

Variable	ρ	p
Insomnia severity index	**+0.57**	**< 0.001**
Fatigue severity scale	**+0.52**	**< 0.001**
S LANSS pain score	+0.42	< 0.001
Epworth sleepiness scale	+0.31	0.003
EDSS	+0.23	0.031
Relapse count	+0.18	0.094
Age	−0.09	0.386
MS duration	−0.08	0.479
Age at MS diagnosis	−0.06	0.597

Bold entries remain significant after Benjamini–Hochberg control for a 10 % false discovery rate. EDSS: The Expanded Disability Status Scale; MS: Multiple sclerosis; S-LANSS: The self-completed Leeds Assessment of Neuropathic Symptoms and Signs pain scale.

PHQ-9 scores was observed in participants reporting alcohol use, though this did not reach statistical significance (p≈0.06). No meaningful differences were found for smoking status or other comorbid conditions (p>0.20 for both).

Overall, subjective symptoms—particularly insomnia and fatigue—emerged as stronger correlates of depression than MS-specific clinical metrics such as EDSS, relapse count, or disease duration (ρ values ranging from approximately 0.15 to 0.25).

Depressive symptom severity was also compared across DMTs and MS clinical subtypes using nonparametric tests due to unequal group sizes and non-normal distributions. No statistically significant difference in PHQ-9 scores was found among the different DMT categories (Kruskal–Wallis H=6.12, df=7, p=0.527; ε^2=0.07). When analyzed by MS subtype, patients with SPMS disease phenotypes had notably higher PHQ-9 scores compared to those with RRMS, with median scores of 14 (IQR: 9–18) vs. 7 (IQR: 5–13), respectively. This difference reached statistical significance (H=4.73, p=0.030; ε^2=0.05). However, due to the small size of the SPMS group and its collinearity with EDSS, MS subtype was excluded from the multivariable model to avoid overfitting.

Multivariable Modelling of Depressive Symptoms

Selection of Candidate Predictors

To identify independent predictors of depressive symptoms, all potential variables were first screened using univariate analysis. Five continuous variables met the prespecified inclusion threshold (p<0.20): FSS, ISI, ESS, and S-LANSS scores. Among binary variables, RLS (p=0.007) and alcohol use (p=0.06) were also eligible. Although not statistically significant, sex was included in all models due to its known clinical relevance.

Categorical variables with multiple levels, including DMT type and MS subtype, were excluded from multivariable analysis due to limited group sizes and lack of robust associations.

Age, sex, and EDSS were included in all models regardless of univariate significance.

Initial Model and Collinearity Diagnostics

An initial linear regression model (ordinary least squares) was constructed with 11 predictors. To ensure valid estimates, robust standard errors (HC3) were applied to adjust for heteroscedasticity. Multicollinearity was assessed using variance inflation factors (VIF), which revealed high overlap between the three sleep-related measures (VIF: 6.3–8.1).

Backward stepwise elimination was applied to remove variables with high collinearity or limited contribution (p>0.10). This resulted in the exclusion of the ESS, S-LANSS, alcohol use, and RLS from the final model.

Final Model Composition

The final model retained five predictors, explaining 57% of the variance in PHQ-9 scores (adjusted R^2=0.57). Residuals were normally distributed, with no influential outliers (Cook's distance <0.15 for all cases). All VIF values were <2.4.

- Fatigue Severity (β=+0.15, p<0.001): Each 10-point increase in FSS was associated with a 1.5-point increase in PHQ-9.
- Insomnia Severity (β=+0.24, p<0.001): Each 5-point increase in ISI was linked to a 1.2-point increase in PHQ-9.
- EDSS (β=+0.50, p=0.046): Higher disability scores were modestly associated with higher depression scores.
- Age (β=−0.03, p=0.073): A trend toward lower PHQ-9 scores with increasing age was observed, though not statistically significant.
- Sex (β=+0.52, p=0.55): No independent association was found after adjustment.

Fatigue and insomnia emerged as the strongest independent predictors of depressive symptoms in this MS cohort. Neurological disability contributed to a lesser extent, while age showed a weak inverse trend. Neither sex nor lifestyle factors (e.g., alcohol, smoking, RLS) were independently associated with depression after accounting for other variables.

Patients reporting poorer overall health status also had significantly higher depression scores, supporting the bidirectional relationship between health-related quality of life and mood in MS. Both EQ-5D-3L index and percentage scores were moderately and significantly correlated with PHQ-9 (both p<0.001) (Table 3).

Table 3. The relationship between quality of life and depression

Variable	Spearman ρ with PHQ 9	p	Direction
EQ 5D 3L point (higher = worse health)	+0.47	< 0.001	Worse health → higher PHQ 9
EQ 5D 3L % (higher = better health)	0.45	< 0.001	Better health → lower PHQ 9

EQ-5D-3L: EuroQol-5 Dimensions-3 Levels questionnaire; PHQ-9: Patient Health Questionnaire-9.

Discussion

In this prospective study of patients with MS, we found that fatigue severity, insomnia, and neurological disability were independently associated with depressive symptoms. Among these, fatigue and insomnia emerged as the most robust predictors, each contributing significantly to PHQ-9 variance. Additionally, depressive symptoms were significantly related to poorer perceived health-related quality of life. These findings underscore the central role of patient-reported outcomes in understanding and addressing depression in MS.

Fatigue was the most powerful predictor of depressive symptoms in our multivariable model. This aligns with a substantial body of literature indicating that fatigue is not only highly prevalent in MS but also closely linked to emotional well-being.[5,12,21,22] While fatigue has traditionally been conceptualized as a consequence of neurological damage or systemic inflammation, emerging evidence suggests a deeper mechanistic overlap with depression. Heitmann et al.[23] proposed that neuroinflammation in MS may disrupt reward processing pathways, particularly in the mesolimbic system, leading to anhedonic symptoms that manifest as both fatigue and depression. Similarly, Dobryakova et al.[24] have suggested that dopaminergic imbalance in the cortico-striatal circuitry plays a central role in MS-related fatigue, implicating disrupted motivation and affect regulation as common underlying mechanisms. These neurobiological models help explain why fatigue is not only prevalent in MS but also so tightly linked with depressive affect. Our findings support this interpretation and suggest that fatigue should be addressed not only as a physical complaint but also as a window into broader affective dysregulation.

Insomnia was the second strongest predictor of depression in our cohort. Sleep disturbances are increasingly recognized as core features of psychiatric comorbidity in MS, and our findings echo prior studies that report strong correlations between insomnia symptoms and depressive affect.[25,26] Neuroinflammatory processes affecting sleep-regulating brain regions, along with MS-related pain, nocturnal spasms, or bladder dysfunction, may all contribute to sleep fragmentation in MS patients.[25,26] Our results suggest that clinicians should routinely assess insomnia as part of depression screening in MS, as addressing insomnia could provide dual benefits for mood and functional status.

We also found that higher EDSS scores were modestly associated with more severe depressive symptoms. Although the strength of this relationship was weaker than fatigue or insomnia, it remains consistent with prior studies showing that physical disability, particularly reduced mobility and dependence in activities of daily living, is a psychological stressor in MS.[11,22] Notably, some earlier studies have reported stronger associations between EDSS and depression;[22] however, our data suggest that subjective experiences such as fatigue and sleep quality may play a more prominent role in patients' psychological burden than clinician-rated disability alone.

Other variables—such as disease duration, sex, age at diagnosis, MS subtype, and number of relapses—did not show significant associations with depressive symptom severity in our study. These findings are consistent with recent work suggesting that static disease variables may be less important for predicting mood outcomes than dynamic or subjective factors.[5,11,22] Although patients with SPMS had higher PHQ-9 scores in univariate analysis, MS subtype was excluded from the multivariable model due to collinearity with EDSS. Thus, we cannot confirm its independent effect. Still, this aligns with the view that disability may be more strongly linked to depression than disease course alone.[11]

We observed a moderate correlation between PHQ-9 scores and S-LANSS, a measure of neuropathic pain. Although this variable did not retain significance in the final model due to collinearity, our univariate findings are in line with prior research showing that chronic pain contributes to depressive symptoms in MS.[3,23,27] Similarly, patients with RLS had significantly higher PHQ-9 scores than those without. While RLS did not remain significant in multivariate analysis, this suggests that sleep-related movement disorders may also contribute to mood disturbances and merit clinical attention.[28]

Quality of life, as measured by the EQ-5D-3L, showed a moderate negative correlation with PHQ-9 scores. This supports existing evidence that depression significantly impairs perceived health and functional well-being in MS.[3,8] The strong link between depressive symptoms and both

EQ-5D-3L point and percentage scores highlights the importance of mood assessment not only for psychiatric care, but also as a determinant of broader health outcomes in this population.

This study has several strengths. First, it employed a comprehensive set of both clinical and patient-reported measures, allowing for a multidimensional assessment of depression in MS. The use of validated scales such as the PHQ-9, FSS, ISI, and EQ-5D-3L enhances the reliability and comparability of our findings. Second, by including a multivariable regression model with robust statistical controls, we were able to identify independent predictors of depressive symptoms beyond basic clinical descriptors. Third, the exclusion of patients receiving psychiatric medications reduced potential confounding effects of pharmacological treatment on mood assessments.

However, some limitations should also be noted. First, the cross-sectional design precludes any inference about the directionality or causality of the observed associations. Longitudinal studies are needed to clarify whether symptoms such as fatigue and insomnia contribute to the development of depression or vice versa. Second, the relatively small sample size, particularly within subgroups such as SPMS, may have limited statistical power to detect more nuanced associations. Third, the reliance on self-reported measures introduces potential reporting bias. Finally, exclusion of patients currently receiving antidepressant or anxiolytic medications may have led to underestimation of depression prevalence and potentially excluded individuals with more severe psychiatric symptoms.

Conclusion

In this study, fatigue, insomnia, and disability emerged as the strongest predictors of depressive symptoms in patients with multiple sclerosis. Among these, patient-reported symptoms—especially fatigue and insomnia—were more strongly associated with depression than traditional clinical measures. These findings highlight the importance of incorporating psychosocial symptom screening into routine MS care to better identify and manage depression. Importantly, our results also demonstrate that depressive symptoms are significantly associated with poorer health-related quality of life in this population, further underscoring the need for timely recognition and intervention.

Disclosures

Ethics Committee Approval: The study protocol was approved by the Ethics Committee of Şişli Hamidiye Etfal Training and Research Hospital (approval date and number: 20.05.2025-4865).

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Original Research

Perceptions of Patients with Respiratory Disorders About Environmental Smoke

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Abstract

Objectives: Environmental smoke exposure is a poorly understood issue and might be a potential source of long-term respiratory exposure to toxic pollutants. Both secondhand and thirdhand smoke (THS) exposure are important matters of public health. We aimed to document the knowledge about smoke exposure of vulnerable groups with respiratory diseases.

Methods: A total of 911 currently smoking patients admitted to the outpatient clinics between October 2023 - October 2024 enrolled in our study. Following a medical examination and pulmonary function assessment, individuals were asked to complete the BATHS questionnaire on thirdhand smoking exposure.

Results: Of the 911smoker participants who comprised our sample, 322 (35.3%) had COPD, 227 (24.9%) had asthma and 570 (62.5%) experienced moderate to severe secondhand exposure. Patients with COPD had the lowest BATHS total and persistence scores (3.61±0.58 and 3.77±0.69, respectively), while asthmatics had the lowest BATHS health scores (3.41±0.46) ($p<0.05$). Total and subdimension scores were significantly higher among individuals aged 18-30, university graduates, employed in the workforce, and earning exceeds minimum wage ($p <0.05$). No gender difference was noted ($p>0.05$). BATHS total scores had significant negative correlation with secondhand smoke exposure and disease duration ($p<0.05$) whereas positively correlated with better pulmonary function values, attending a smoking cessation clinic, and living at home with children under sixteen ($p<0.05$).

Conclusion: This study identifies the knowledge gap about the detrimental effects of smoke exposure in patients with respiratory diseases. It underscores the importance of focusing initiatives to reduce both active and passive smoking through educational programs targeting active smokers at risk of lung illnesses.

Keywords: Attitudes, BATHS questionnaire, COPD patients, environmental smoke exposure

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Tobacco use is a significant contributor to preventable diseases and mortality in the entire world.[1] Today, smoking causes over 8 million deaths globally each year, with over 1.2 million of those deaths occurring from passive smoke inhalation rather than direct tobacco use.[1]

Secondhand smoke exposure (SHS), generally referred to as passive smoking, poses a serious health risk, involving the inhalation of a mixture of mainstream and sidestream smoke that contaminates the air surrounding tobacco consumption areas.[2] SHS comprises harmful carcinogen compounds in either particle or vapor phases, rendering it a primary source of indoor pollution.[2]

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The other term "thirdhand smoke" (THS) is defined as the accumulated chemical residue that is left behind when the smoke dissipates, because it contains toxic particles that can be deposited on surfaces, furniture, clothing, hair, and even in the atmosphere over time.[3] These compounds may persist on indoor surfaces for days and weeks, and can be ingested, inhaled, or absorbed via the skin by individuals, potentially exhibiting carcinogenic consequences.[4,5] Thus, THS is not directly "smoke". People can protect themselves from SHS exposure by moving away from areas where smoking is prevalent, but THS pollutants are stored in the environment and nothing can be done about it them if THS is present.[4,5]

In low-income populations, the prevalence of indoor smoking is still high despite the governmental regulations of smoking bans.[6] Since SHS is the forerunner of THS accumulation, environmental smoke exposure is more likely to occur in indoor settings where populations have higher smoking rates.[7, 8]

The goal of this study was to assess the understanding of presently smoking patients with respiratory disorders about environmental smoke exposure, as well as to raise their awareness of "toxic tobacco residue".

Furthermore, we intended to determine how respondents' perspectives differ depending on their current smoking behaviors, whether or not they had children living in their houses, and whether or not they were exposed to secondhand smoke in their surroundings.

Methods

This cross-sectional, analytical study was conducted in a training and research hospital after the approval of the Institutional Ethics Committee. The participants consisted of currently smoking patients older than 18 years who were admitted to the Outpatient Clinic of the Chest Disease Department between October 2023 and October 2024. After being informed about the study's purpose, each research participant provided an oral agreement and completed the face-to-face interview.

The participants were cathegorised as: 1- healthy individuals, 2- patients with Chronic Obstructive Pulmonary Disease (COPD) who were diagnosed with Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) criteria, followed up at least for 2 years in the outpatient clinic and in a stable state 3- patients having a diagnosis of asthma according to Global Initiative for Asthma (GINA) criteria, did not have an acute attack history in the previous month and have regular follow-ups in the outpatient department for the past 2 years.[9, 10] During the outpatient visit, professional staff members performed pulmonary function tests on each participant using the Spirolab (MIR II, Rome, Italy) devices and adhering to American Thoracic Society (ATS) standardized requirements.[9] Patients either with COPD or asthma were all under maintenance treatment according to guidelines.[9, 10] Asthma Control Test (ACT) was applied for patients with asthma, COPD assessment test (CAT) for patients with COPD and their exacerbation history of the previous year were all recorded.[11,10] The sociodemographic details, comorbidities, income level, qualification, and marital status were all noted.

The Fagerström Test for Nicotine Dependence (FTND) questionnaire, is a validated tool that rates nicotine dependency on a scale of 0 to 10, with 10 being the highest level of dependence.[12]

Secondhand smoke exposure which mainly forms by inhaling environmental tobacco smoke was evaluated with an 11-point scale questionnaire comprising four ranked questions which was developed by Vardavas and his colleagues.[13] This scale asks about many exposure sites, such as daily exposure at home or in a car, weekly exposure in public spaces, and weekly exposure at work. Each response is given a specific number of points. It allows for a quantitative assessment of SHS exposure, with a maximum score of 11.[13]

People's opinions on thirdhand smoke are measured by the Beliefs About Third-Hand Smoke Scale (BATHS-T).[14] At the beginning of the study, participants were given educational materials regarding the term "thirdhand smoke", and then a face-to-face Turkish-validated questionnaire, the BATHS-T, was used to assess their knowledge and attitudes around thirdhand smoke.[15] The questionnaire was created following a thorough review of the pertinent literature.

There are nine questions total; five address the impact of third-hand smoke on health (1, 2, 3, 7, and 8), and four address the longevity of THS in the environment (4, 5, 6, and 9). The answers are arranged using the Likert type with five points.[14]

People select one among the five options: strongly disagree, disagree, agree, disagree, and remain undecided. The average score can be found by dividing the total score by the total number of questions. It's possible to receive one point at the very least and five at the most. People's levels of awareness are seen as increasing with their scores.

Statistical Analysis

The suitability of the variables in the study to normal distribution was evaluated graphically and with Shapiro Wilk's test, and the mean and standard deviation were used as descriptive statistics of the variables with normal distribution. The median (minimum; maximum) was used as descriptive statistics for variables that were determined not to have a normal distribution. The relationship between demographic characteristics and smoking-related variables and groups was examined with Pearson Chi-square. Kruskal-Wallis analysis of variance was used to compare the differences in age at smoking initiation, duration of disease, Forced Vital Capacity (FVC) %, Forced Expiratory Volume in 1st second (FEV1) %, FEV1/FVC % values, as well as scores on BATHS total (BATHSt), BATHS health (BATHSh), and BATHS persistence (BATHSp), regarding the health status of the participants. If a difference was detected between groups, Bonferroni corrected pairwise comparison results were examined. Mann Whitney U test was used to compare the differences in demographic characteristics and smoking-related variables according to scores on BATHSt, BATHSh, and BATHSp. Pearson correlation analysis was performed for the relationship between scores on BATHSt, BATHSh, and BATHSp with age at smoking initiation, duration of disease, values of FVC%, FEV1%, FEV1/FVC%.

IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp. Armonk, NY) and MS-Excel 2016 programs were used for statistical analyses and calculations. Statistical hypotheses were evaluated by taking the Type-I error level $\alpha=0.05$.

Results

A total of 911 smokers completed the surveys with all the required answers, of whom 35.3% had COPD, 24.9% had asthma and 39.7% were healthy adults. Table 1 presents a comparison of the research groups' demographics regarding their smoking-related factors.

The study group consisted of 510 (55,9%) men, and 189 (20.7%) of the individuals were over 65. The most common comorbidities among them were hypertension (16%) and cardiovascular diseases (12%), while 12% had more than one comorbidity. 57.7% of the respondents stated that their parents smoked at home when they were growing up, and 49% currently share their homes with a family member who smokes. The proportion of participants living with a child under the age of 16 at home was 50%.

69.2% of the 911 participants reported smoking at home, whereas 35% continued to smoke at work despite government policies prohibiting smoking in enclosed areas and public locations. Furthermore, 62% of the study participants noted moderate to smoke exposure at home, work, in cars, or in public places.

According to the Fagerström test, 17% of research participants had significant nicotine dependency, 45% smoked more than 20 cigarettes a day. Only 20% of the total stated that they had been admitted to a smoking cessation clinic.

Asthmatics had a significantly younger smoking start age (18.85±3.63 years) compared to healthy individuals and COPD patients ($p<0.05$).

COPD patients had longer disease duration and lower lung function test results compared to asthmatics ($p <0.05$). Asthmatics scored higher on the BATHSt and BATHSp knowledge assessment of thirdhand smoke than COPD patients, who scored lower on the BATHSt and BATHSp knowledge assessment ($p<0.05$).

The associations between patients' BATHS total and subscale scores and smoking-related characteristics were thoroughly examined. It was concluded that there is a statistically significant relationship between the third-hand tobacco smoke exposure awareness scale (BATHS) total scores and the variables of the participants, which were documented in Table 2.

The Dunn-Bonferroni test was used in a pairwise comparison of BATHS scores according to the study groups to determine which group was responsible for the variation in age, comorbidity, daily cigarette consumption, and the Fagerström dependence test (not shown).

The following instances had higher BATHS total scores: individuals who were between the ages of 18 and 30 and university graduates, patients with allergic rhinitis; those who smoke one to ten cigarettes a day and score lower on the Fagerström dependence test; those who live at home with children under the age of 16; patients who smoke at work; patients who do not smoke at home; those who seek help from a smoking cessation clinic; those who lead active lives in the workforce; and those whose income exceeds the minimum wage ($p<0.05$). The BATHS total scores of individuals with COPD were recorded as the lowest and those with asthma as the highest in the survey ($p<0.05$).

The relationship between BATHS health scores and the smoking-related variables of the groups is shown in Table 3.The BATHS health scores showed a statistically significant correlation with smoking status at home or at the workplace, having a parent who smoked when they were a child, being employed full-time, admission to a smoking cessation clinic, income level, and educational status ($p<0.05$). The Dunn-Bonferroni test was utilized to identify the group responsible for the variation between the study groups based on health status, exposure to secondhand smoke, comorbidity, and daily cigarette consumption (not shown).

The highest BATHS health scores were noted in those in-

Table 1. Comparison of the demographic characteristics and smoking related variables of the groups

	Healthy group n (%)	Patients with COPD, n (%)	Patients with asthma, n (%)	Statistics of the test	
Total	362 (39.7)	322 (35.3)	227 (24.9)		
Variables				x^2	p
Age					
18 – 30 years	52 (14.4)	0 (0.0)	56 (24.7)	342.224	< 0.001
31 – 50 years	119 (32.9)	9 (2.8)	123 (54.2)		
51 – 65 years	125 (34.5)	198 (61.5)	40	(17.6)	
>65 years	66 (18.2)	115 (35.7)	8 (3.5)		
Gender					
Female	154 (42.5)	124 (38.5)	123 (67.3)	13.808	0.001
Male	208 (57.5)	198 (61.5)	104 (32.7)		
Living with a child<16 years old					
Absent	145 (40.1)	221 (68.6)	86 (37.9)	72.317	< 0.001
Present	217 (59.9)	101 (31.4)	141 (62.1)		
Comorbidities					
-	210 (58.0)	80 (24.8)	97 (42.7)	244.524	< 0.001
Hypertension	36 (9.9)	86 (26.7)	32 (14.1)		
Cardiovascular diseases	37 (10.2)	58 (18.0)	21 (9.3)		
Diabetes	20 (5.5)	3 (0.9)	7 (3.1)		
Chronic Renal Diseases	5 (1.4)	23 (7.2)	4 (1.8)		
Allergic Rhinitis	8 (2.3)	11 (3.5)	58 (25.5)		
≥1 comorbidities	46 (12.7)	61 (18.9)	8 (3.5)		
Smokers among the household members					
Absent	203 (56.1)	122 (37.9)	131 (57.7)	29.638	< 0.001
Present	159 (43.9)	200 (62.1)	96 (42.3)		
Smoking at home					
No	72 (19.9)	77 (23.9)	131 (57.7)	104.625	< 0.001
Yes	290 (80.1)	245 (76.1)	96 (42.3)		
Having smoker parents during childhood					
No	125 (34.5)	120 (37.3)	140 (61.7)	47.216	< 0.001
Yes	237 (65.5)	202 (62.7)	87 (38.3)		
Exposure to secondhand smoke (home, car, workplace, public areas)					
-	23 (6.4)	20 (6.2)	103 (45.4)	252.161	< 0.001
Mild	80 (22.1)	52 (16.1)	63 (27.8)		
Moderate	214 (59.1)	169 (52.5)	47 (20.8)		
High	45 (12.4)	81 (25.2)	14 (6.2)		
Occupational status					
Unemployed	123 (34.0)	140 (43.5)	69 (30.4)	11.414	0.003
Active working	239 (66.0)	182 (56.5)	158 (69.6)		
Smoking at workplace					
No	217 (59.9)	198 (61.5)	176 (77.5)	21.441	< 0.001
Yes	145 (40.1)	124 (38.5)	51 (22.5)		
Marital status					
Single	133 (36.7)	106 (32.9)	137 (60.4)	46.431	< 0.001
Married	229 (63.3)	216 (67.1)	90 (39.6)		
Number of cigarettes smoked per day					
1 - 10	17 (4.7)	16 (5.0)	158 (59.6)	473.316	< 0.001
11 - 20	122 (33.7)	118 (36.6)	66 (29.1)		
>21	223 (61.6)	188 (58.4)	3 (1.3)		

Table 1. Comparison of the demographic characteristics and smoking related variables of the groups (Cont.)

	Healthy group n (%)	Patients with COPD, n (%)	Patients with asthma, n (%)	Statistics of the test	
Admission to cigarette cessation department					
No	282 (77.9)	239 (74.2)	200 (88.1)	16.107	< 0.001
Yes	80 (22.1)	83 (25.8)	27 (11.9)		
Nicotine dependency (Fagerström test)					
Mild nicotine dependence	261 (72.1)	63 (19.6)	166 (73.1)	340.442	< 0.001
Moderate nicotine dependence	97 (26.8)	110 (34.2)	51 (22.5)		
High nicotine dependence	4 (1.1)	149 (46.2)	10 (4.4)		
Educational status					
Primary or secondary school	109 (30.1)	189 (58.7)	78 (34.4)	63.409	< 0.001
University graduates	253 (69.9)	133 (41.3)	149 (65.6)		
Level of income					
Below minimum wage	169 (46.7)	260 (80.7)	153 (67.4)	87.307	< 0.001
Above minimum wage	193 (53.3)	62 (19.3)	74 (32.6)		
Having an exacerbation or attack last year for patients with COPD and asthma					
No		167 (51.9)	144 (63.4)	7.261	0.007
Yes		155 (48.1)	83 (36.6)		
	Mean±SD	**Mean±SD**	**Mean±SD**	**x^2**	**p**
Start age for smoking initiation	19.81±3.35	19.73±3.70	18.85±3.63	24.116	< 0.001
Duration of the disease (years)		14.68±7.87	11.00±5.96	29.928	< 0.001
FEV1%	86.32±11.99	51.67±12.49	84.91±12.48	582.158	< 0.001
FVC %	96.38±10.95	74.16±18.09	96.12±12.09	302.375	< 0.001
FEV1/FVC %	91.36±8.24	72.38±12.60	90.75±7.69	370.646	< 0.001
BATHS Total Scores	3.98±0.50	3.61±0.58	4.05±0.51	122.014	< 0.001
BATHS Health Scores	3.80±0.49	3.47±0.55	3.41±0.46	104.356	< 0.001
BATHS Persistence Scores	4.19±0.60	3.77±0.69	4.83±0.65	293.406	< 0.001

dividuals who had completed their university education, those who led active lives in the workforce, and those whose income exceeded the minimum wage; those who smoked at home or the workplace, had moderate levels of secondhand tobacco exposure, had grown up with a smoker parent, sought assistance from a smoking cessation clinic, had diabetes, and smoked twenty-one or more cigarettes per day ($p < 0.05$). The healthy participants had the highest BATHS health scores in the survey, while the patients with asthma recorded the lowest ($p<0.05$).

There was a statistically significant relationship between the BATHS scale persistence scores and the smoking-related variables shown in Table 4. The Dunn Bonferroni test was used to determine which group the difference originated from according to variables (not shown).

Individuals with the highest BATHS persistence scores were single, aged 18 to 30, university graduates, led active lives at work, earned more than the minimum wage every month, had allergic rhinitis, were not exposed to secondhand tobacco smoke, smoked one to ten cigarettes per day, and had the mildest nicotine dependence ($p<0.05$).

Furthermore, those individuals who did not smoke at home, did not have a family member who smoked, did not have a child under the age of sixteen living at home, did not have a parent who smoked when they were children, and were COPD or asthma patients with no exacerbation in the previous year all had higher BATHSp scores ($p<0.05$). It's interesting to notice that COPD patients scored the lowest on the BATHSp survey, while asthma patients obtained the highest scores ($p<0.05$).

Table 5 presents the correlation analysis between the patients' clinical features and their BATHS total and subscale scores. While BATHS total scores were positively correlated with visiting a smoking cessation clinic, living at home with children under sixteen, and FEV1%, FVC%, FEV1/FVC%, CAT, and ACT values ($p<0.05$). However, they showed a significant negative correlation with disease duration and secondhand smoke exposure ($p<0.05$).

Tablo 2. Relationship between BATHS total score and the variables

Variable	Median (Min., Max.)	Test Statistics	
		z	p
Gender			
Female	4.00 (2.22; 4.78)	-0.821	0.412
Male	4.00 (2.44; 4.67)		
Living with a child <16 years old			
No	4.00 (2.22; 4.67)	-2.030	0.042
Yes	4.00 (2.44; 4.78)		
Smokers among the household members			
No	4.00 (2.22; 4.78)	-1.909	0.056
Yes	4.00 (2.44; 4.78)		
Smoking at home			
No	4.00 (2.44; 4.78)	-1.981	0.048
Yes	4.00 (2.22; 4.67)		
Having smoker parents during childhood			
No	4.00 (2.22; 4.78)	-0.337	0.736
Yes	4.00 (2.22; 4.78)		
Occupational status			
Unemployed	3.89 (2.22; 4.67)	-5.448	< 0.001
Active working	4.00 (2.44; 4.78)		
Smoking at workplace			
No	4.00 (2.22; 4.78)	-2.162	0.031
Yes	4.00 (2.44; 4.78)		
Marital status			
Single	4.00 (2.22; 4.78)	-1.651	0.099
Married	4.00 (2.22; 4.67)		
Admission to cigarette cessation department			
No	4.00 (2.22; 4.78)	-2.138	0.033
Yes	4.00 (2.44; 4.67)		
Educational status			
Primary or secondary school	3.78 (2.22; 4.67)	-15.403	< 0.001
University graduates	4.00 (2.22; 4.78)		
Level of income			
Below minimum wage	3.89 (2.22; 4.78)	-6.630	< 0.001
Above minimum wage	4.00 (2.22; 4.78)		
Having an exacerbation or attack last year for patients with COPD and asthma			
No	4.00 (2.22; 4.78)	-1.722	0.085
Yes	3.89 (2.44; 4.67)		
Variables	**Median (Min.; Max.)**	**Test Statistics**	
		x^2	p
Healthy group	4.00 (2.44; 4.67)	122.014	< 0.001
COPD	3.78 (2.22; 4.67)		
Asthma	4.00 (2.44; 4.78)		
Age			
18 – 30	4.00 (2.67; 4.78)	53.268	< 0.001
31 – 50	4.00 (2.44; 4.78)		
51 – 65	4.00 (2.22; 4.78)		
≥65	3.89 (2.22; 4.67)		

Tablo 2. Relationship between BATHS total score and the variables (Cont.)

Variable	Median (Min., Max.)	Test Statistics	
		z	p
Comorbidity			
-	4.00 (2.44; 4.78)	38.320	< 0.001
Hypertension	4.00 (2.22; 4.78)		
Cardiovascular diseases	4.00 (2.44; 4.67)		
Diabetes	4.00 (2.67; 4.67)		
Chronic renal diseases	3.78 (2.22; 4.67)		
Allergic Rhinitis	4.00 (2.44; 4.67)		
Comorbidities ≥1	3.78 (2.44; 4.67)		
Exposure to secondhand smoke			
-	4.00 (2.44; 4.78)	6.082	0.108
Mild	4.00 (2.22; 4.78)		
Moderate	4.00 (2.22; 4.67)		
High	4.00 (2.44; 4.67)		
Number of cigarettes smoked per day			
1-10	4.00 (2.44; 4.78)	24.588	< 0.001
11-20	3.89 (2.22; 4.78)		
≥ 21	4.00 (2.22; 4.67)		
Nicotine dependency (Fagerström Test)			
Mild nicotine dependence	4.00 (2.22; 4.78)	39.762	< 0.001
Moderate nicotine dependence	4.00 (2.33; 4.78)		
High nicotine dependence	3.89 (2.22; 4.67)		

A positive correlation was found between BATHS health scores and FEV1%, FVC%, FEV1/FVC% values, the status of visiting a smoking cessation clinic, exposure to secondhand smoke, age of smoking initiation, and having grown up with smoking parents ($p < 0.01$). The BATHS persistence scores were positively correlated with FEV1%, FVC%, FEV1/FVC% values and living at home with children under sixteen, whereas, they were negatively correlated with disease duration, exposure to secondhand smoke, and having grown up with smoker parents ($p<0.01$).

There was a positive and significant relationship between exposure to secondhand smoke and visiting a smoking cessation clinic and having grown up with smoker parents ($p<0.01$). It was found that visiting a smoking cessation clinic among the study participants was positively correlated with having grown up with smoker parents, disease duration, and CAT scores ($p<0.05$).

S.D.: Standard Deviation, BATHS: Beliefs About Third-Hand Smoke Scale, FEV1%: Forced expiratory volume in 1. second, FVC%: Forced vital capacity, FEV1/FVC%: Forced expiratory volume in 1. second to forced vital capacity ratio, CAT: Chronic Obstructive Pulmonary Disease Assessment Test, ACT: Asthma Control Test, SHS: Second hand smoke.

Discussion

The potential health outcomes of firsthand smoke are well-recognized and research priorities have shifted to focus on secondhand and thirdhand smoke exposures, two public health concerns. Approximately 80% of tobacco products consumed worldwide are found in low- and middle-income nations.[1]

Research indicates that approximately 40% of patients with COPD or asthma persist in smoking, despite being aware of their respiratory condition and the adverse effects of smoking on their prognosis and disease progression.[16,17]

The main objective of our study was to assess current smokers' awareness of the negative effects of smoking on not only themselves but also on family members and colleagues, as well as the particular concept of THS. We intended to draw attention to the fact that these smokers should at least follow the smoking ban at home or in other enclosed spaces.

Our findings highlight a lack of awareness about thirdhand smoke among smokers with COPD who displayed the lowest scores in BATHS total and persistence scores. These scores may be associated with the individual's educational background or insufficient health literacy.

Table 3. Relationship between BATHS health scores and the variables

Variables	Median (Min., Max.)	Test Statistics	
		z	p
Gender			
Female	3.60 (2.00; 4.60)	-1.013	0.311
Male	3.60 (2.00; 5.20)		
Living with a child <16 years old			
No	3.60 (2.00; 5.20)	-0.203	0.839
Yes	3.60 (2.00; 5.20)		
Smokers among the household members			
No	3.60 (2.00; 5.20)	-0.401	0.688
Yes	3.60 (2.00; 4.60)		
Smoking at home			
No	3.60 (2.00; 4.60)	-2.562	0.010
Yes	3.60 (2.00; 5.20)		
Having smoker parents during childhood			
No	3.60 (2.00; 4.60)	-3.491	< 0.001
Yes	3.60 (2.00; 5.20)		
Occupational status			
Unemployed	3.60 (2.00; 4.60)	-4.575	< 0.001
Active working	3.60 (2.00; 5.20)		
Smoking at workplace			
No	3.60 (2.00; 5.20)	-4.414	< 0.001
Yes	3.80 (2.20; 5.20)		
Marital status			
Single	3.60 (2.00; 5.20)	-1.125	0.261
Married	3.60 (2.00; 4.80)		
Admission to cigarette cessation department			
No	3.60 (2.00; 5.20)	-4.350	< 0.001
Yes	3.80 (2.20; 5.20)		
Educational status			
Primary or secondary school	3.40 (2.00; 4.60)	-12.335	< 0.001
University graduates	3.80 (2.20; 5.20)		
Level of income			
Below minimum wage	3.60 (2.00; 5.20)	-6.191	< 0.001
Above minimum wage	3.80 (2.20; 5.20)		
Having an exacerbation or attack last year for patients with COPD and asthma			
No	3.60 (2.00; 4.40)	-0.176	0.860
Yes	3.60 (2.00; 4.40)		
Variables	**Median (Min.; Max.)**	**Test Statistics**	
		x^2	p
Healthy	3.80 (2.40; 5.20)	104.356	< 0.001
COPD	3.60 (2.00; 4.40)		
Asthma	3.40 (2.00; 4.00)		
Age			
18 – 30	3.60 (2.00; 4.60)	2.405	0.493
31 – 50	3.60 (2.00; 4.60)		
51 – 65	3.60 (2.00; 5.20)		
≥ 65	3.60 (2.00; 4.60)		

Table 3. Relationship between BATHS health scores and the variables (Cont.)

Variables	Median (Min., Max.)	Test Statistics	
		z	p
Comorbidity			
-	3.60 (2.00; 5.20)	17.131	0.009
Hypertension	3.60 (2.00; 4.60)		
Cardiovascular diseases	3.60 (2.00; 4.40)		
Diabetes	3.70 (2.60; 4.60)		
Chronic renal diseases	3.40 (2.20; 5.20)		
Allergic rhinitis	3.60 (2.40; 4.40)		
Comorbidities ≥ 1	3.60 (2.00; 4.60)		
Exposure to secondhand smoke			
-	3.60 (2.00; 4.40)	18.889	< 0.001
Mild	3.60 (2.20; 5.20)		
Moderate	3.60 (2.00; 5.20)		
High	3.60 (2.20; 4.60)		
Number of cigarettes smoked per day			
1- 10	3.60 (2.00; 4.20)	36.723	< 0.001
11- 20	3.60 (2.00; 5.20)		
≥ 21	3.80 (2.20; 5.20)		
Nicotine dependency (Fagerström test)			
Mild nicotine dependence	3.60 (2.00; 5.20)	4.961	0.084
Moderate nicotine dependence	3.60 (2.00; 4.60)		
High nicotine dependence	3.60 (2.00; 5.20)		

The prevalence of smoking among parents (62.7%), increased rates of household smokers (62.1%), moderate to high exposure to secondhand smoke (77.7%), and workplace smoking (38.5%) among patients with COPD may be regarded as influential factors in their attitudes. Tobacco addiction is a chronic disease, thus quitting smoking may be more challenging for those with COPD than for those without it due to increased nicotine dependence.[18]

Furthermore, plenty of information has pointed out that newly diagnosed COPD is increasingly prevalent in younger adults and females, proving that the illness is no longer limited to older men.[1] The tobacco industry may contribute to the rise in female smokers worldwide since it encourages women to smoke by messages as a symbol of gender equality in the media.[19]

The low scores for persistence beliefs suggested that patients with COPD believed that simply opening the windows or turning on the air conditioner in interior spaces at home or the workplace was sufficient to purify the air and that smoke particles could not remain on walls or furniture.

According to a recent study examining THS beliefs, patients with asthma or COPD had lower health domain scores and had impairments in self-awareness of their health state.[20] Despite their vulnerability to smoke exposure, which could exacerbate respiratory symptoms, those individuals have continued to smoke inside under prevailing restrictions and do not care about their family members or colleagues. WHO recommends that all individuals be educated on the health effects of tobacco, including its addictive characteristics and risk factors associated with secondhand smoke exposure.[1]

Based on their BATHS total scores, our research participants with asthma were generally aware of the adverse effects of tobacco smoke. However, they are likely to underestimate the health risks and still have some knowledge gaps because, like the previously cited study, they recorded the lowest scores in health beliefs.[20] Additionally, participants with asthma began smoking at younger ages and visited the cigarette cessation department less frequently than those in the healthy group and COPD patients.

Although the risks of environmental smoke inhalation are higher in active smokers, adult smokers with asthma may continue to smoke because they have learnt to use tobacco as a coping mechanism for stressful situations or unpleasant emotional experiences. In line with the results of our study and earlier research, younger people with higher levels of education and financial status were more likely to believe that THS components will contaminate cloth-

Tablo 4. Relationship of BATHS persistence scores in terms of variables

Variable	Median (Min., Max.)	Test statistics	
		z	p
Gender			
Female	4.25 (2.25; 6.50)	-1.368	0.171
Male	4.25 (2.00; 5.75)		
Living with a child <16 years old			
No	4.25 (2.25; 6.00)	-2.732	0.006
Yes	4.25 (2.00; 6.50)		
Smokers among the household members			
No	4.25 (2.25; 6.50)	-2.143	0.032
Yes	4.25 (2.00; 5.75)		
Smoking at home			
No	4.50 (2.50; 6.00)	-5.093	< 0.001
Yes	4.25 (2.00; 6.50)		
Having smoker parents during childhood			
No	4.25 (2.25; 6.00)	-2.276	0.023
Yes	4.25 (2.00; 6.50)		
Occupational status			
Unemployed	4.25 (2.25; 5.75)	-4.938	< 0.001
Active working	4.25 (2.00; 6.50)		
Smoking at workplace			
No	4.25 (2.25; 6.00)	-0.375	0.707
Yes	4.25 (2.00; 6.50)		
Marital status			
Single	4.50 (2.50; 6.00)	-3.383	0.001
Married	4.25 (2.00; 6.50)		
Admission to cigarette cessation department			
No	4.25 (2.00; 6.50)	-0.328	0.743
Yes	4.25 (2.50; 5.75)		
Educational status			
Primary or secondary school	4.00 (2.00; 5.75)	-12.727	< 0.001
University graduates	4.50 (2.25; 6.50)		
Level of income			
Below minimum wage	4.25 (2.00; 5.75)	-4.914	< 0.001
Above minimum wage	4.50 (2.22; 4.78)		
Having an exacerbation or attack last year for patients with COPD and asthma			
No	4.25 (2.00; 6.00)	-2.171	0.030
Yes	4.25 (2.50; 6.50)		
Variables	**Median (Min., Max.)**	**Test statistics**	
		x^2	p
Healthy group	4.25 (2.50; 5.00)	293.406	<0.001
COPD	4.00 (2.00; 5.00)		
Asthma	5.00 (3.00; 6.50)		
Age			
18 – 30	4.50 (2.50; 6.00)	120.189	< 0.001
31 – 50	4.50 (2.50; 6.50)		
51 – 65	4.25 (2.00; 6.00)		
≥ 65	4.00 (2.50; 5.00)		

Tablo 4. Relationship of BATHS persistence scores in terms of variables (Cont.)

Variable	Median (Min., Max.)	Test statistics	
		z	p
Comorbidities			
-	4.25 (2.00; 6.50)	73.035	< 0.001
Hypertension	4.25 (2.50; 5.75)		
Cardiovascular diseases	4.25 (2.50; 5.75)		
Diabetes	4.50 (2.75; 5.75)		
Chronic renal diseases	4.00 (2.25; 5.50)		
Allergic Rhinitis	5.00 (2.50; 5.75)		
Comorbidities ≥1	4.00 (2.50; 5.00)		
Exposure to secondhand smoke			
-	4.75 (2.50; 5.75)	45.615	< 0.001
Mild	4.25 (2.25; 6.00)		
Moderate	4.25 (2.50; 5.75)		
High	4.25 (2.00; 6.50)		
Number of cigarettes smoked per day			
1-10	4.75 (2.50; 6.00)	138.346	< 0.001
11- 20	4.25 (2.50; 6.50)		
≥ 21	4.25 (2.00; 5.00)		
Nicotine dependency (Fagerström test)			
Mild nicotine dependence	4.50 (2.50; 6.00)	67.481	< 0.001
Moderate nicotine dependence	4.25 (2.50; 6.50)		
High nicotine dependence	4.00 (2.00; 5.00)		

ing, hair, or furniture and harm other people's health.[20,21] Participants over 65 reported the lowest BATHS total and persistence belief scores in our survey.

Unlike previous studies, we did not find a gender difference on behalf of women in the beliefs regarding the influence of THS on health.[20,21]

Even though half of our study population were living with someone under the age of sixteen, 69% declared no smoking ban at home and 49% of them had a household member who also smokes. Another concern was that these people viewed smoking exclusively on the balcony or in the bathroom as a means to a home smoking ban or reduce exposure.

It is the indispensable duty of parents to provide a healthy and smoke-free environment for their children. Homes stand still as an important site of unintentional smoke exposure for the kids, even if the data THS may induce fetal lung injury.[22] Besides, children who are exposed to secondhand smoke may potentially mimic smoking as a result of modeling their parents or friends.[23,24]

Consistent with previous research, our study participants who had children under the age of sixteen and did not smoke at home scored higher overall on the BATHS than those without children.[5,23,25,26,27] Nonetheless, the fact that they smoked at workplaces might suggest that these parents believed passive smoking only harmed children. Another investigation showed the disparity between parents' practical approach and their awareness of THS, which may have contributed to our current finding.[28]

Furthermore, similar to the recent study, BATHS persistence scores were highest among participants without children younger than sixteen years of age. In line with previous findings, growing awareness of THS appears to have a greater impact on smoker parents' views on smoke exposure in children than SHS.[5,23]

63% of our recruited individuals were active workers, 35% reported smoking at work despite indoor smoking bans, and 62% reported moderate to severe environmental tobacco smoke exposure in their vehicles or public places. Our investigation revealed a negative correlation between BATHS scores, secondhand smoke exposure, and disease duration, which may be interpreted as a consequence of this interaction.

The majority of our participants were middle-aged and employed in furniture and textile manufacturing. It is noteworthy that the risk of patients being subjected to tobacco smoke and its harmful toxicants was rising because smoke residues were likely to be stored in a substantial amount in

Table 5. Correlation analysis findings

Variables	Mean	S.D.	1	2	3	4	5	6	7	8	9	10	11	12	13	14
BATHS total	3.86	0.57	1,00													
BATHS health	3.59	0.53	0.876**	1.00												
BATHS persistence	4.20	0.76	0.908**	0.596**	1.00											
Start age of smoking	19.54	3.57	0.031	0.095**	-0.033	1.00										
Duration of disease	13.16	7.36	-0.178**	-0.061	-0.230**	0.335**	1.00									
FEV1%	73.72	20.43	0.263**	0.127**	0.327**	-0.085*	-0.252**	1.00								
FVC%	88.46	17.64	0.210**	0.102**	0.259**	-0.092**	-0.177**	0.856**	1.00							
FEV1/FVC%	84.50	13.35	0.216**	0.100**	0.271**	-0.062	-0.240**	0.737**	0.327**	1.00						
CAT	21.49	5.21	-0.057	-0.066	-0.044	-0.245**	-0.213**	-0.614**	-0.498**	-0.268**	1.00					
ACT	21.28	1.85	-0.014	-0.037	0.008	-0.077	-0.080	0.223**	0.211**	0.072	0.001	1.00				
Exposure to SHS	1.62	0.93	-0.078*	0.115**	-0.199**	0.164**	0.072	-0.181**	-0.144**	-0.129**	0.029	-0.092	1.00			
Admission to smoking cessation department	0.21	0.41	0.071*	0.114**	-0.011	0.177	0.097*	-0.073*	-0.049	-0.116**	0.121*	-0.085	0.241**	1.00		
Having a smoker parent during childhood	0.58	0.49	0.011	0.116**	-0.075*	0.052	0.053	-0.023	0.004	-0.078*	0.144**	-0.018	0.606**	0.319**	1.00	
Living with a child<16 years old	0.50	0.50	0.067*	0.007	0.091**	-0.021	-0.271**	0.253**	0.207**	0.189**	-0.070	-0.027	-0.061	-0.069*	-0.040	1.00

** The correlation was found to be significant at the 0.01 level. * The correlation was found to be significant at the 0.05 level.

organic products such as cotton and upholstery fabric. The problem lies in the encouragement of smoking and exposure to secondhand smoke when individuals who smoke remain in situations where smoking is allowed. A previous study found that a total smoking ban in the workplace prompts individuals to also prohibit smoking among their families.[24]

Moreover, in susceptible individuals, inhaling secondhand smoke in enclosed places may increase the likelihood of developing an early onset of respiratory disorder.[25]

The current study discovered a positive correlation between overall BATHS scores and pulmonary function tests and admittance to the smoking cessation clinic based on the correlation analysis carried out concurrently.

These findings might reflect the importance of health literacy and nicotine dependence as influential factors in environmental tobacco smoke exposure. It should be kept in mind that, even after they quit smoking, THS is still present in homes of smokers. Researchers have demonstrated that, since homes are contaminated by cigarette smoke, the existence of nicotine in settled house dust before quitting smoking may increase the likelihood of relapse in people who have tried to give up tobacco usage.[8] This contamination must be adressed as a matter of consumer protection.

Unlike most other studies, we did not examine the views of nonsmokers because of the significance of widespread exposure to anti-tobacco messages as a community-level strength for current smokers.[5,20,23] A few of these investigations revealed no statistically significant difference in THS beliefs between smokers and nonsmokers.[23,28] As shown in our results, the healthy smokers recorded the highest scores in BATHS health scale.

This study had several limitations. It was an exploratory observational study conducted in a single center using patient self-reports, therefore the findings should be interpreted with cautiously.

On the other hand, our strength was that the questionnaires were administered face-to-face not online, so, during the interviews, health professionals' advice on quitting was also reaffirmed as part of the counseling process.

Conclusion

Even though it is commonly recognized that smoking impairs lung function and the course of COPD disease, our respondents with COPD tend to underestimate the harmful effects of THS.

The respondents with asthma expressed a lack of knowledge regarding the health implications of THS. Further-

more, exposure to secondhand smoking was higher than expected among the examined subjects, which was a very intriguing finding. Involuntary exposure to secondhand or thirdhand smoke produces harmful environmental conditions that persist over time and for protecting non-smokers, this research might shed light on the duty of physicians.

The questionnaire administered during the outpatient visit included statements such as "the residue of the smoke stays at home even after several months," which made sense to patients with smoking-related diseases and may have convinced them to change their opinions toward tobacco usage. Spreading the awareness of people about tobacco smoke exposure and changes in social skills might result in feedback that motivates people creating smoke-free homes and vehicles. Therefore, even stating a simple message to the smokers that THS cannot be completely removed from the furniture or walls by regular cleanup might help implement a smoke-free home policy and improve the health of children by limiting smoke exposure, which are essential components of tobacco control programs.

In this way, we may better understand how social influences and risk perceptions make people continue smoking and so by developing new educational strategies and paying attention to these challenges, we will ultimately achieve our more significant objective of preventative action against tobacco use and its adverse health effects.

Disclosures

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Original Research

Gastrointestinal Kaposi Sarcoma: Histopathological Features and Diagnostic Challenges – Insights from a Single Center

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Abstract

Objectives: Gastrointestinal Kaposi sarcoma (GI-KS) is a rare vascular neoplasm associated with human herpesvirus 8 (HHV 8), most often emerging in immunosuppressed individuals. Its endoscopic appearance—ranging from nodular and polypoid lesions to ulcerations—can be subtle. In addition, histopathological features of KS may mimic benign inflammatory conditions or other mesenchymal tumors, delaying accurate diagnosis. This study aimed to evaluate the histopathological features of GI-KS and to clarify the neoplastic and non-neoplastic diagnostic challenges in a single-center cohort.

Methods: We retrospectively reviewed 13 GI-KS cases diagnosed between 2005 and 2025. Clinical data and endoscopic findings were retrieved from the hospital's electronic medical records. Hematoxylin and eosin-stained sections, along with HHV-8 immunohistochemistry (IHC) slides, were retrospectively evaluated.

Results: Thirteen patients (11 male; mean age 47±18 years) were identified, of whom 84.6% were immunosuppressed (eight HIV-positive, two renal transplant recipients, and one receiving corticosteroids). Cutaneous or extraintestinal KS lesions were present in 11 cases. Endoscopic evaluation revealed nodular lesions (30.8%), polypoid lesions (23.1%), snake-skin–like hemorrhagic areas (7.7%), infiltrative lesions (7.7%), erythematous elevated lesions (7.7%), or nonspecific erythematous changes (7.7%). Suspicion of KS was documented in only three endoscopy reports. Lesions were most commonly located in the stomach (76.9%), followed by the rectum (15.4%) and colon (7.7%). Histologically, slit-like vascular channels and erythrocyte extravasation were observed in 84.6% of cases, hemosiderin deposits in 53.8%, chronic inflammatory infiltrates including plasma cells in 76.9%, and foveolar epithelial hyperplasia in 70% of gastric cases. The histologic spectrum included diagnostic pitfalls such as chronic gastritis–like features in three cases, reactive gastropathy–like changes in one case, granulation tissue–like appearance in one case, and GIST/leiomyoma–like spindle cell morphology in one case.

Conclusion: The histologic features of GI-KS can mimic both neoplastic and inflammatory conditions. Therefore, histopathological evaluation should be conducted alongside clinical information, as GI-KS may present with subtle or nonspecific findings. Given the potential for life-threatening complications such as obstruction, bleeding, or perforation, accurate diagnosis and timely treatment are critically important. Routine application of HHV-8 IHC -even in cases with minimal suspicion- is essential for ensuring diagnostic accuracy, guiding appropriate management, and preventing serious outcomes.

Keywords: Kaposi sarcoma, gastrointestinal tract, endoscopic biopsy, HHV-8 immunohistochemistry, differential diagnosis

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Kaposi sarcoma (KS) is a vascular neoplasm caused by human herpesvirus 8 (HHV-8) infection, predominantly affecting the skin of individuals infected with human immunodeficiency virus (HIV).[1] KS can occur not only in HIV-positive individuals but also in patients receiving immunosuppressive therapy for conditions such as autoimmune disorders or following solid organ transplantation.[2-4]

Visceral involvement can occur, with the gastrointestinal tract being the most common site.[5] Gastrointestinal KS (GI-KS) exhibits distinctive endoscopic appearances, including reddish nodules, polypoid masses, and ulcerated lesions.[3, 6] However, in the absence of a clearly visible endoscopic lesion or if the lesion is in the submucosa, it may easily be overlooked.[7] In addition to being endoscopically inconspicuous, GI-KS can also mimic other tumors histologically or be mistaken for a solely inflammatory process.[8-11]

In this study, we analyzed the histological features of GI-KS and discussed both neoplastic and non-neoplastic lesions that should be considered in the differential diagnosis.

Methods

Patients diagnosed with GI-KS between 2005 and 2025 were retrospectively identified from the pathology archives of our department. Clinical data and endoscopic findings were retrieved from the hospital's electronic medical records. Hematoxylin and eosin (H&E)-stained sections, along with human herpesvirus 8 (HHV-8) immunohistochemistry (IHC) slides, were retrospectively evaluated. The histologic characteristics of the tumors, as well as accompanying features such as inflammatory cell infiltration, hemosiderin deposition, ulceration, and epithelial cell changes were documented.

Retrospective HHV-8 immunohistochemical staining was applied to all paraffin blocks, even those lacking histologically suspicious lesions.

This study was approved by the Ethics Committee of Istanbul University Faculty of Medicine (Approval No: 2025/964, Date: 13.06.2025) in accordance with the Declaration of Helsinki.

Statistical Analysis

Descriptive statistics were used to analyze the data. Categorical variables were presented as frequencies and percentages, while continuous variables were expressed as means and standard deviations (mean±SD). All calculations, including percentage distributions and average values, were conducted in Excel (Microsoft Excel, Microsoft Corp., Redmond, WA, USA).

Results

Patient Characteristics

The study cohort consisted of 13 patients, including 11 males (84.6%) and 2 females (15.4%), with a mean age of 47 years (±18 SD; range: 27-81 years). In five patients, paraffin blocks were referred to our department from another center for consultation.

Of the 13 patients, 11 (84.6%) were immunosuppressed. However, in four cases (30.8%), clinical information regarding immunosuppression status was not provided at the time of biopsy submission. In these instances, the clinical data were retrieved either from the hospital's electronic medical records or by direct communication with the clinician. The underlying immunosuppressive conditions were as follows: eight patients (72.7%) were HIV-positive, two (18.2%) had a history of renal transplantation, and one patient (9.1%) was receiving corticosteroid therapy for IgA nephropathy. One patient had no documented immunosuppressive condition, and the immunosuppression status of another patient, referred to our department for consultation, remained unknown.

In 11 patients (84.6%), a histologically confirmed diagnosis of KS was present in organs /tissues outside the gastrointestinal tract. The distribution of KS involvement in other organs/tissues was as follows: the skin in five patients (45.5%), both the skin and oral mucosa in two patients (18.2%), the oral mucosa alone in one patient (9.1%), both the skin and lymph node in one patient (9.1%), and the lymph node alone in two patients (18.2%) one of which was associated with Castleman disease. Of the remaining two patients, one had suspicious cutaneous lesions, while the other presented with pleural effusion and multiple intra-abdominal, paraaortic, inguinal, and iliac lymphadenopathies, but no pathological sampling was performed from these sites.

Demographic and clinical characteristics of GI-KS cases are summarized in Table 1.

Three patients (23%) underwent ileocolonoscopy, while ten patients (77%) underwent esophagogastroduodenoscopy (EGD). Four patients (30.8%) were symptomatic. One patient presented with rectal bleeding, another demonstrated colonic FDG uptake on PET-CT accompanied by anemia, and two patients complained of dyspepsia. Endoscopic examination was performed for surveillance in nine patients (69.2%) with a prior diagnosis of KS in other organs/tissues, despite the absence of gastrointestinal symptoms; one of these also exhibited esophageal FDG uptake on PET-CT.

Table 1. Demographic and clinical characteristics of gastrointestinal kaposi sarcoma cases

	Age	Gender	Clinic information	Clinic information given to pathologist at first	KS in other organ/tissues (biopsy-proven)	Sites of KS in other organ/tissues
Case 1 (year 2005)	45	E	Renal transplantation (6 months before)	Yes	Yes	Multiple skin lesions, oral mucosal lesions simultaneously
Case 2 (year 2007)	37	E	Renal transplantation	No	Yes	Skin
Case 3 (C) (year 2010)	77	K	No	No	Yes	Multiple skin lesions, prior to GI-KS
Case 4 (year 2011)	81	K	Steroid treatment for IgA nephropathy	Yes	Yes	Lower extremity skin, prior to GI-KS
Case 5 (C) (year 2011)	31	E	Unknown	No	Yes	Multiple skin lesions, prior to GI-KS
Case 6 (C) (year 2012)	65	E	HIV	Yes	Unknown	Suspicious skin lesions present
Case 7 (C) (year 2014)	27	E	HIV	No	Unknown	Pleural effusion, multiple intra-abdominal, paraaortic, inguinal, and iliac lymphadenopathies
Case 8 (year 2015)	34	E	HIV	Yes	Yes	Multiple skin lesions and lymph node involvement, simultaneously
Case 9 (year 2017)	63	E	HIV	Yes	Yes	HHV8 positive Castleman Disease in lymph node
Case 10 (C) (year 2018)	32	E	HIV	Yes	Yes	Multiple skin lesions, prior to GI-KS
Case 11 (year 2022)	40	E	HIV	Yes	Yes	Hard palate, prior to GI-KS
Case 12 (year 2023)	31	E	HIV	Yes	Yes	Axillary lymph node, prior to GI-KS
Case 13 (year 2017)	50	E	HIV	Yes	Yes	Skin and hard palate, prior to GI-KS

GI: Gastrointestinal; C: Consultation; KS: Kaposi sarcoma; HIV: Human immunodeficiency virus.

Endoscopic Findings

Endoscopically, a nodular appearance was observed in four patients (30.8%), a polypoid lesion in three patients (23.1%), and 'snake-skin-like' bleeding areas in one patient (7.7%). One patient (7.7%) had thickened gastric folds with an infiltrative appearance, another (7.7%) had an erythematous elevated lesion, and one (7.7%) showed nonspecific erythema and edema. Endoscopic findings were unavailable in two patients (15.4%).

A suspicion of KS was noted in the endoscopy report of three patients (23.1%). Notably, one patient with thickened gastric folds and an infiltrative appearance was initially suspected to have infiltrative gastric carcinoma or mucosa-associated lymphoid tissue (MALT) lymphoma. In two of the remaining nine patients, endoscopic findings were consistent with pangastritis. No preliminary diagnosis was provided for five patients, and in two cases, neither endoscopic details nor a preliminary diagnosis could be obtained.

Although complete treatment data for all patients were not available, two patients received chemotherapy. During follow-up, only two patients with gastric KS underwent control gastroscopy. Both demonstrated normal endoscopic and histopathological findings.

Endoscopic findings of the patients are shown in Figure 1 and Table 2.

Histologic Findings

GI-KS involvement was observed at the following sites: the stomach in 10 patients (76.9%), across 12 sites (two patients had lesion in the fundus, one in both the fundus and corpus, five in the corpus, one in both the corpus and antrum, and one in the antrum), the rectum in two patients (15.4%), and the colon in one patient (7.7%). During re-evaluation,

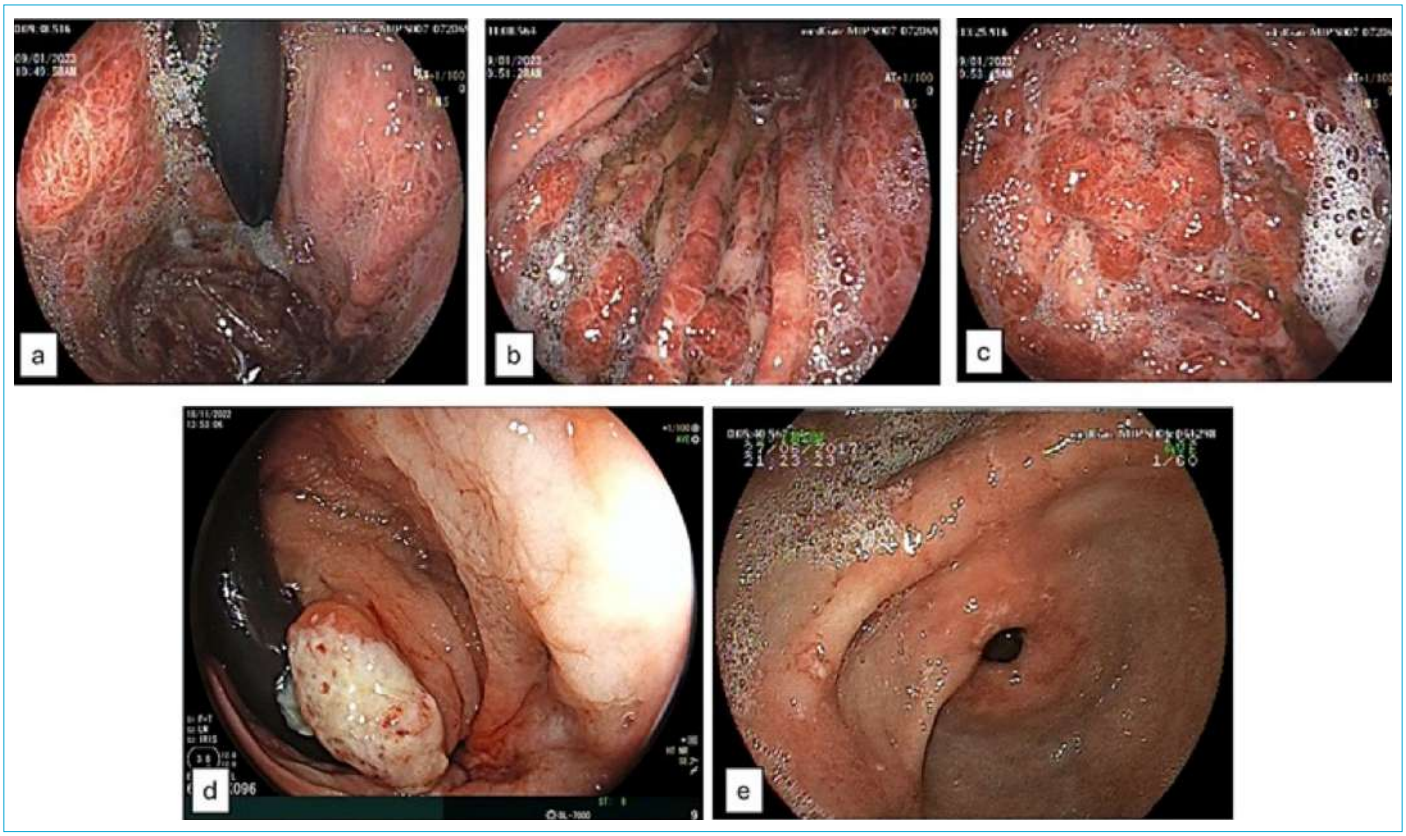

Figure 1. Endoscopic images from cases 12, 11, and 9. Erythematous elevated lesions are observed in the fundus and corpus of case 12 **(a-c)**. In case 11, a 2 cm ulcerated polyp surrounded by fibrinopurulent exudate is visible in the rectum **(d)**. Case 9 shows an erythematous area in the corpus **(e)**.

it was found that in one gastric KS case (Case 8), the lesions were located not only in the fundus but also in the corpus. This additional involvement was identified through HHV-8 IHC analysis, which had not been performed at that site during the initial evaluation.

The tumor was located in both the mucosa and submucosa in six cases (46.2%). In the remaining seven cases (53.8%), due to the absence of submucosal tissue in the biopsies, the proliferation was identified within the mucosa. Slit-like vascular spaces and erythrocyte extravasation were identified within the tumor in eleven cases (84.6%). Hemosiderin deposition was noted in seven cases (53.8%). Lymphoplasmacytic inflammation, with or without accompanying active inflammatory cells, was observed to varying degrees. Plasma cells were observed in ten (76.9%) cases. Ulceration was observed in three cases (23.1%). Among the gastric KS cases (n=10), foveolar epithelial hyperplasia was observed in seven cases (70%) as an accompanying histological feature.

Additionally, Helicobacter pylori was negative in all the gastric KS cases.

Histopathologic findings are presented in Table 3 and Figures 2-6.

First Histological Impressions of the Cases

In three cases (Cases 2, 6, and Case 8 at corpus site), the initial histological impression resembled chronic gastritis (Figs. 2, 3), with case 2 also showing ulceration. In case 12, the histological features closely mimicked reactive gastropathy at low-power magnification (Fig. 4). One of the rectal KS cases (Case 11) resembled inflammatory granulation tissue and was also positive for cytomegalovirus (CMV) on IHC (Fig. 5). In the other rectal KS case (Case 10), ulceration was accompanied by spindle cells and vascular structures, with the spindle cells surrounding the crypts (Fig. 5). This pattern could easily be misinterpreted as granulation tissue or a perineurioma. In one gastric KS case (Case 4), a dense spindle cell proliferation involving the mucosa and submucosa raised a diagnostic suspicion of gastrointestinal stromal tumor (GIST) or leiomyoma (Fig. 6). In the remaining six cases, more usual morphology, spindle cell proliferation, slit-like vascular structures, and varying degrees of inflammation were observed. In some of these cases, thickening of the muscularis mucosae with intermingled vascular spaces initially appeared as a nonspecific finding (Fig. 6).

The histological spectrum and initial diagnostic impressions of all cases are summarized in Table 4.

Table 2. Endoscopic findings of the patients

	Upper or lower GI endoscopy	Endoscopy indication	Endoscopic appearance	Endoscopic diagnosis	Biopsy site	KS site	Control endoscopy or treatment
Case 1 (year 2005)	Upper	Control	Nodular lesion in fundus	Absent	Fundus	Fundus	Normal endoscopy (4 years later),unknown treatment
Case 2 (year 2007)	Upper	Control	Nodular lesions in corpus and antrum	KS?	Antrum and corpus	Antrum and corpus	No endoscopy, unknown treatment
Case 3 (C) (year 2010)	Lower	Colonic FDG accumulation, anemia	Diffuse multiple segmental reddish polypoid lesions involving the ascendant and transverse regions of the large bowel	KS?	Colon	Colon	No endoscopy, unknown treatment
Case 4 (year 2011)	Upper	Control	Sub-centimetric polypoid lesion in corpus	Absent	Corpus	Corpus	No endoscopy, unknown treatment
Case 5 (C) (year 2011)	Upper	Control	Unknown	-	Corpus	Corpus	None
Case 6 (C) (year 2012)	Upper	Dyspepsia	Unknown	-	Corpus	Corpus	No endoscopy, unknown treatment
Case 7 (C) (year 2014)	Upper	Dyspepsia	'Snake-skin-like' bleeding areas throughout the fundus to the antrum	Absent	Duodenum and antrum	Antrum	No endoscopy, unknown treatment
Case 8 (year 2015)	Upper	Control	Thick gastric folds, Lack of gastric motility in fundus	Infiltrative gastric tumor? MALToma?	Duodenum, antrum, corpus, fundus	Fundus, corpus*	No endoscopy, unknown treatment
Case 9 (year 2017)	Upper	Control	Erythema, edema in corpus and antrum	Pangastritis	Antrum, corpus	Corpus	Yes, Normal (1 month later), received chemotherapy
Case 10 (C) (year 2018)	Lower	Rectal bleeding and rectal pain	Ulcerated nodular appearance	KS?	Rectum	Rectum	No endoscopy, received chemotherapy
Case 11 (year 2022)	Lower	Control	Rectal 2 cm in diameter polypoid lesion	Absent	Rectum	Rectum	No endoscopy, unknown treatment
Case 12 (year 2023)	Upper	Control (Esophageal involvement in PET-CT)	Erythematous elevated areas in fundus and corpus	Absent	Duodenum, antrum, corpus, fundus	Fundus	No endoscopy, unknown treatment
Case 13 (year 2017)	Upper	Control	Nodular appearance	Pangastritis	Antrum and corpus	Corpus	No endoscopy, unknown treatment

GI: Gastrointestinal; KS: Kaposi sarcoma; *: Detected during re-evaluation.

Table 3. Histologic findings of the cases

	Site	Layer	Marked atypia/ mitosis	Slit like areas	EE	Hemosiderin	P	L	N	Ulcer	FCH	HHV-8 IHC	*H. Pylori*
Case 1 (y, 2005)	Fundus	Mucosa, submucosa	No	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Positive	Negative
Case 2 (y, 2007)	Corpus, antrum	Mucosa, submucosa	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Positive	Negative
Case 3 (C) (y, 2010)	Colon	Mucosa	No	Yes	Yes	No	Yes	Yes	No	No	-	Positive	-
Case 4 (y, 2011)	Corpus	Mucosa, submucosa	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Positive	Negative
Case 5 (C) (y, 2011)	Corpus	Mucosa	No	No	Yes	No	Yes	No	No	No	No	Positive	Negative
Case 6 (C) (y, 2012)	Corpus	Mucosa	No	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Positive	Negative
Case 7 (C) (y, 2014)	Antrum	Mucosa	No	No	Yes	No	Yes	No	No	No	No	Positive	Negative
Case 8 (y, 2015)	Fundus, corpus*	Mucosa, submucosa	No	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Positive	Negative
Case 9 (y, 2017)	Corpus	Mucosa, submucosa	No	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Positive	Negative
Case 10 (C) (y, 2018)	Rectum	Mucosa	No	Yes	Yes	Yes	No	No	Yes	Yes	-	Positive	-
Case 11 (y, 2022)	Rectum	Mucosa	No	Yes	Yes	Yes	No	No	Yes	Yes	-	Positive	-
Case 12 (y, 2023)	Fundus	Mucosa	No	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Positive	Negative
Case 13 (y, 2017)	Corpus	Mucosa, submucosa	No	Yes	No	No	Yes	Yes	No	No	No	Positive	Negative

Y: year; EE: Eritrocyte extravasation; FCH: Foveolar cell hyperplasia; L: Lymphocyte; N: Neutrophile; P: Plasma cell; IHC: Immunohistochemistry.

As demonstrated in this series, a broad spectrum of neoplastic and non-neoplastic inflammatory conditions may be considered in the differential diagnosis of GI-KS, as summarized in Table 5.

Discussion

We conducted a histopathological analysis of GI-KS cases (ten gastric and three colorectal KS cases). In addition, we discussed neoplastic and inflammatory processes that may mimic or lead to challenges in the differential diagnosis.

Most reported cases of GI-KS, including those from our study, occur in male HIV positive patients.[12] However, iatrogenic cases have also been documented. The first iatrogenic case of KS (disseminated visceral KS) in the setting of immunosuppression was reported in 1969 in a patient who had undergone renal transplantation.[4] Subsequent studies have reported an association between immunosuppressive therapy and GI-KS, as also noticed in our study.[3, 13] In our study, three patients were receiving corticosteroid therapy -one for IgA nephropathy and two following renal transplantation.

Other organ/tissue involvement, most commonly cutaneous, frequently accompanies GI-KS.[12] In the majority of our cases (11 out of 13), extra-gastrointestinal involvement was present, predominantly as cutaneous lesions. Additionally, two cases exhibited suspicious skin lesions and lymphadenopathy; however, histological confirmation was not possible due to the absence of tissue sampling from these sites.

GI-KS patients are generally reported to be asymptomatic, as in our cohort.[6, 12] Most patients (10 out of 13) detected during endoscopic surveillance for known a diagnosis of KS at other organs/tissues. However, gastrointestinal complications such as bleeding, perforation, and obstruction can occasionally occur, where one of our patients presented with rectal bleeding caused by a polypoid KS lesion in the rectum.[2, 6, 12, 14]

Although GI-KS has characteristic endoscopic features-such as reddish nodules, polypoid masses, or ulcerated lesions-the tumor may be overlooked if it is submucosal or not visibly apparent.[7, 15, 16] The most common endoscopic finding in our series was a nodular appearance. Other findings included a polypoid lesion, 'snake-skin-like' hemorrhagic areas, thickened gastric folds with an infiltrative appearance, and an erythematous elevated lesion. In addition to being endoscopically nonspecific or inconspicuous, the histomorphologic features of GI-KS may mimic other tumors or be mistaken for a solely inflammatory

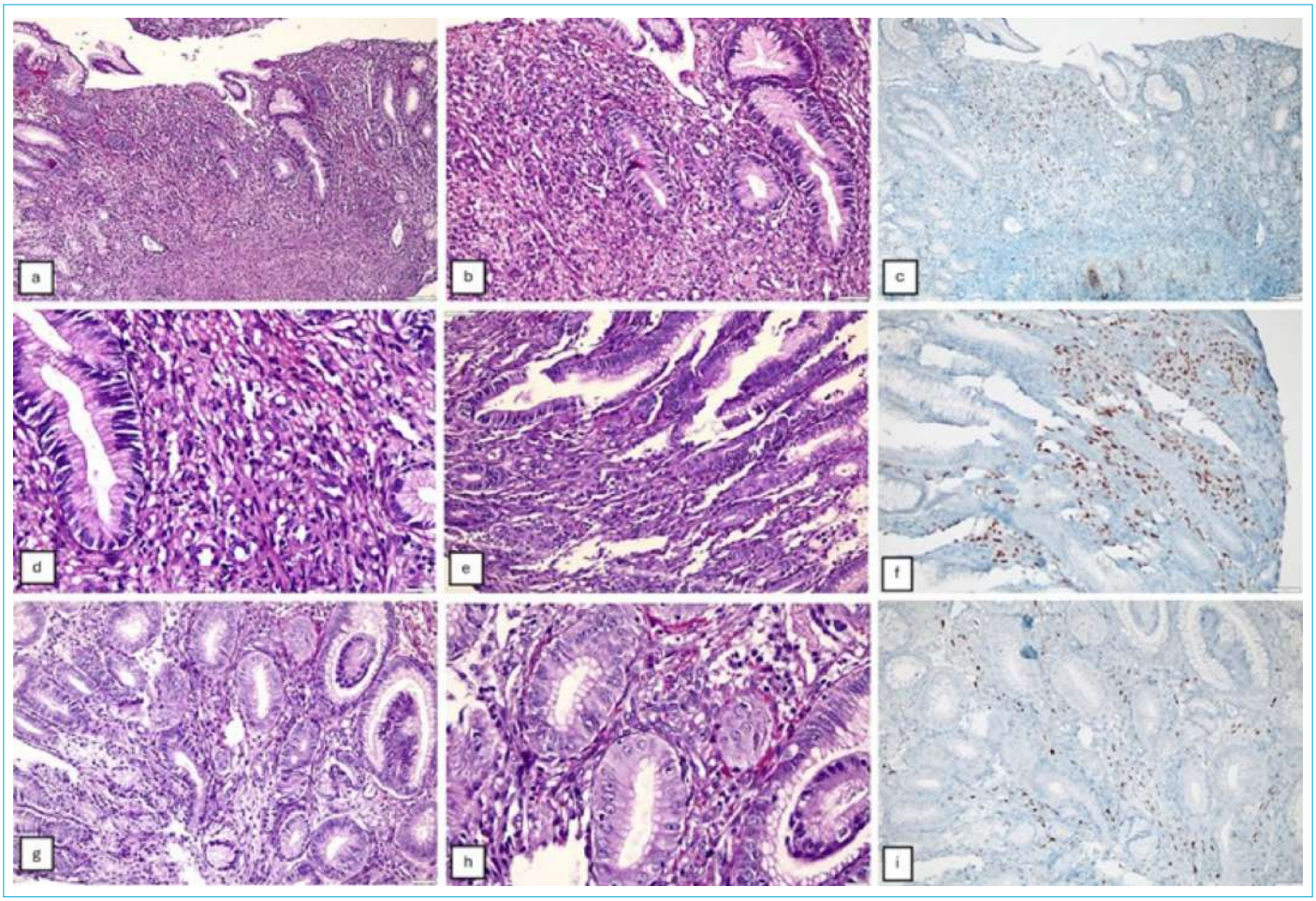

Figure 2. Histopathologic and HHV-8 IHC findings in case 2: **(a)** The initial histological impression resembling chronic gastritis at low-power field; **(b, d, e, g, h)** Subtle bland-appearing spindle cell proliferation intermixed with chronic inflammatory cells at high-power field; **(c, f, i)** Anti-HHV-8 positivity in the spindle cells. (a-f: antrum, g-i: corpus)

process. Given this potential for misinterpretation and the necessity of selecting appropriate treatment to prevent complications, histomorphological findings should be carefully evaluated to avoid misdiagnosis or underdiagnosis.

Histomorphologic variants of GI-KS have not been extensively studied. In a multicenter study involving 46 patients, seven distinct histomorphologic variants were identified in addition to the conventional histology. These included lymphangioma/lymphangiectatic-like, mucosal hemorrhage/telangiectatic-like, mucosal inflammation-like, granulation tissue-like, mucosal prolapse-like, gastrointestinal stromal tumor (GIST)-like, and inflammatory myofibroblastic tumor-like variants.[10] In our study, three gastric KS cases exhibited histologic features resembling chronic gastritis -so called mucosal inflammation-like variant KS. In one of these cases (Case 2), the bland-appearing spindle cell proliferation was subtle and accompanied by foveolar epithelial hyperplasia, which contributed to an initial impression of chronic gastritis with ulceration. Furthermore, the patient's immunosuppression status was not provided to the pathologist, increasing the risk of misdiagnosis.

In another case (Case 8), classic morphology characterized by spindle cell proliferation with slit-like vascular spaces was observed in the fundus. Upon re-evaluation of this case, lesions were found not only in the fundus but also in the corpus. The histological findings in the corpus resembled chronic gastritis and were initially overlooked. The focal atypical vascular proliferation was located at the base of the gastric glands. This additional involvement was detected through HHV-8 IHC staining, which had not been performed on the corpus biopsy during the initial assessment. Either clinical information

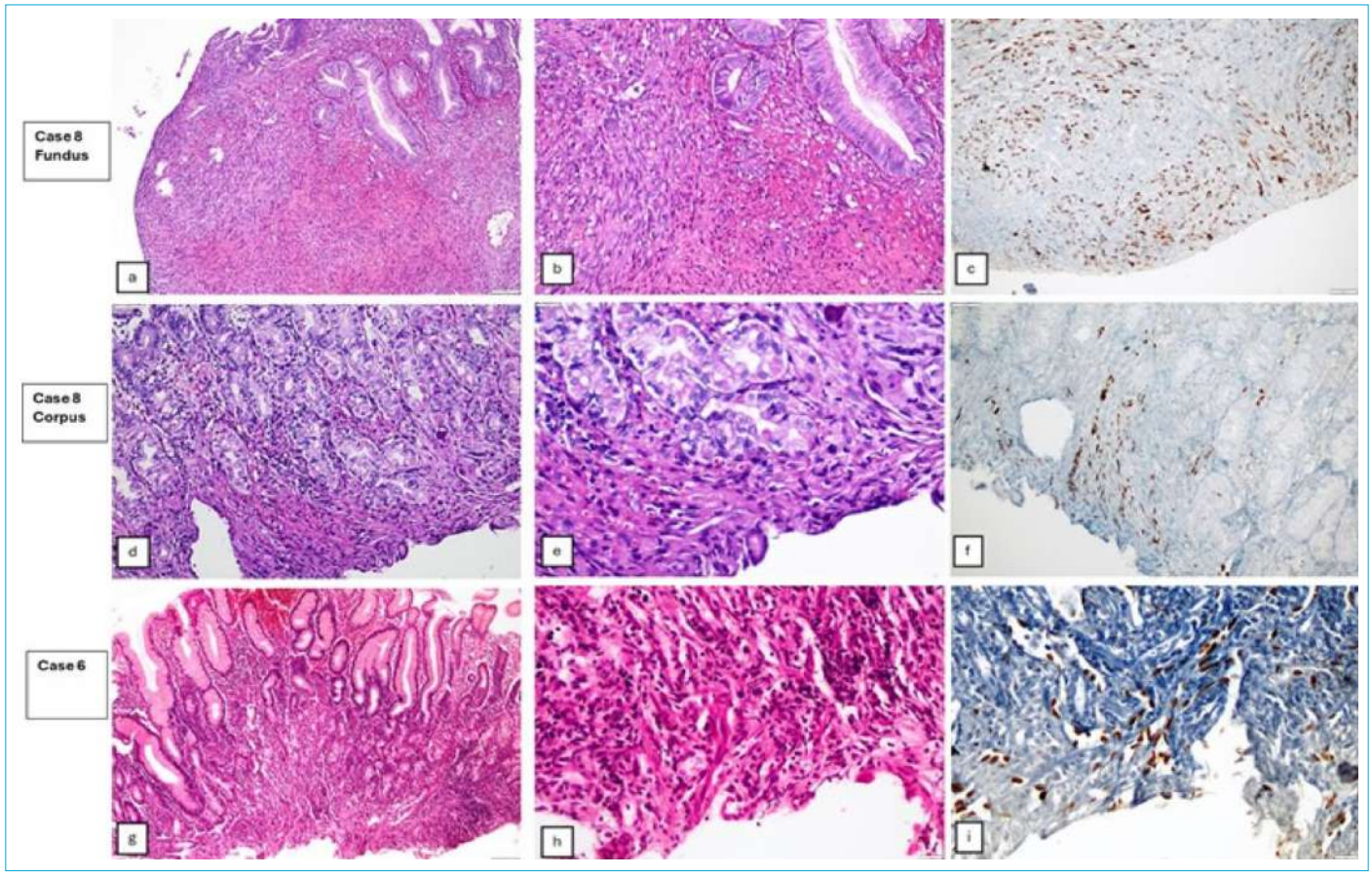

Figure 3. Histopathologic and HHV-8 IHC findings in cases 8 and 6: **(a-b)** Classic morphology characterized by spindle cell proliferation with slit-like vascular spaces in the fundus; **(c)** Anti-HHV-8 positivity in spindle cells in the fundus of case 8; **(d-f)** The focal atypical vascular proliferation located at the base of the gastric glands which was detected through HHV-8 IHC staining **(f)**; **(g)** The initial histological impression resembling chronic gastritis with foveolar epithelial hyperplasia at low-power field in case 6; **(h)** Spindle cell proliferation with slit-like vascular spaces at the base of the glands at high-power field; **(i)** Anti-HHV-8 positive endothelial cells that form slit-like vascular spaces.

or a preliminary diagnosis of KS was provided in all three cases; otherwise, the mucosal inflammation-like variant of KS may be easily overlooked.[10] This highlights the importance of providing clinical information, as it may prompt the pathologist to perform HHV-8 IHC, thereby facilitating an accurate diagnosis. In such cases, performing HHV-8 IHC on all gastric biopsies may improve the detection of KS foci.

In one of our cases (Case 12), the initial impression at low-power magnification was reactive gastropathy[17] due to the presence of polypoid foveolar epithelial hyperplasia, smooth muscle proliferation oriented perpendicularly to the surface, and small vascular structures. Although this case might resemble the proposed mucosal prolapse variant of GI-KS, the absence of characteristic features—such as cystic dilatation of the pit region, thick-walled vessels, and organized thick bundles of arborizing smooth muscle—was not consistent with the histomorphologic criteria described for that variant.[10, 18] It can be suggested that GI-KS may present with a pattern mimicking reactive gastropathy and can therefore be easily overlooked.

One of the cases (Case 11), presenting as a polypoid rectal lesion, histologically mimicked inflammatory granulation tissue. Ulceration was observed on the surface, accompanied by a subtle proliferation of spindle cells. CMV immunoreactivity was notably identified within the granulation tissue. Given that immunosuppression is a common risk factor for both CMV infection and GI- KS, their coexistence is possible.[19] As a result, the granulation tissue-like appearance may be misinterpreted as solely due to CMV infection, potentially leading to the underlying spindle cell proliferation at the base of the ulcer being overlooked.[10]

Several mesenchymal tumors may arise in the gastroin-

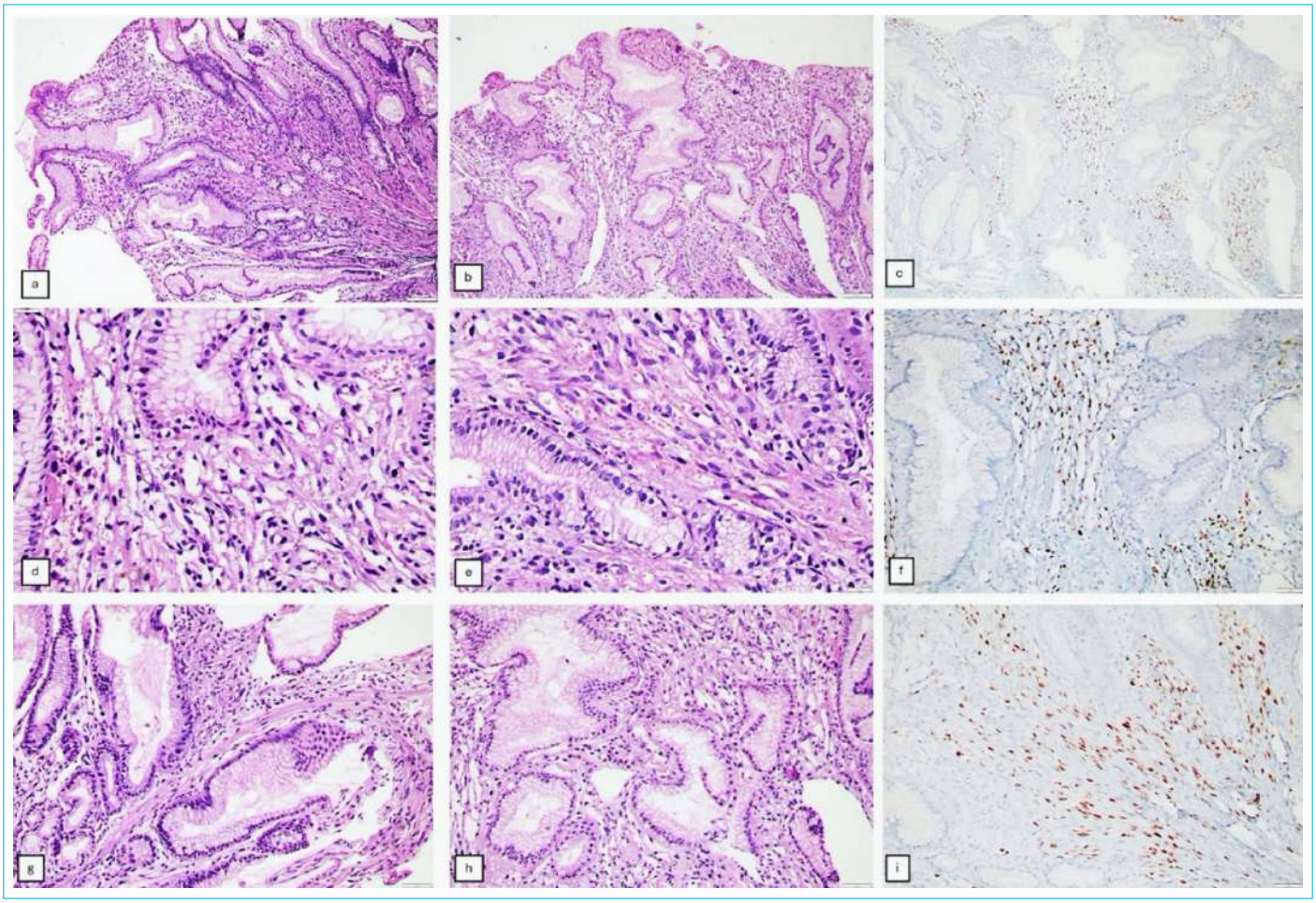

Figure 4. Histopathologic and HHV-8 IHC findings in case 12: **(a-b)** Reactive gastropathy-like appearance with polypoid foveolar epithelial hyperplasia and vascular structures admixed with sparce inflammatory cells in the lamina propria at low-power field; **(d-e)** Small vascular structures in the lamina propria at high-power field; **(g-h)** Smooth muscle proliferation oriented perpendicularly to the surface and small vascular structures in the lamina propria mimicking reactive gastropathy; **(c, f, i)** Anti-HHV-8 positivity in the bland-appearing spindle cells forming vascular spaces.

testinal tract[9] and GI-KS can mimic low-grade mesenchymal neoplasms. In one of our cases (Case 4), dense spindle cell proliferation involving the mucosa and submucosa raised suspicion for GIST or leiomyoma. GIST, the most common mesenchymal tumor in this region, represents a significant diagnostic challenge. Notably, CD117 immunoreactivity-characteristic of GIST-can occasionally be observed in KS as well, potentially leading to diagnostic confusion and misinterpretation.[8, 11] Other tumors to consider in the differential diagnosis include leiomyoma, schwannoma, hemangioma, inflammatory myofibroblastic tumor, perineurioma, and inflammatory fibroid polyp.[20] In case 10, ulceration was associated with spindle cells and vascular structures, with spindle cells surrounding the crypts-an appearance that may resemble, although less likely, perineurioma. Despite overlapping morphological features, each of these entities exhibits distinct histopathological characteristics, and immunohistochemistry remains essential for accurate diagnosis.[9, 16]

Conclusion

The histological features of GI-KS may mimic other neoplastic tumors as well as inflammatory processes. Given that complications such as obstruction, bleeding, or perforation can be life-threatening, accurate diagnosis and appropriate treatment are of critical importance. Histopathological evaluation should be performed in conjunction with clinical information, keeping in mind that GI-KS may present with subtle or nonspecific histological findings. In cases of even minimal suspicion, HHV-8 immunohistochemistry should be performed to ensure an accurate diagnosis.

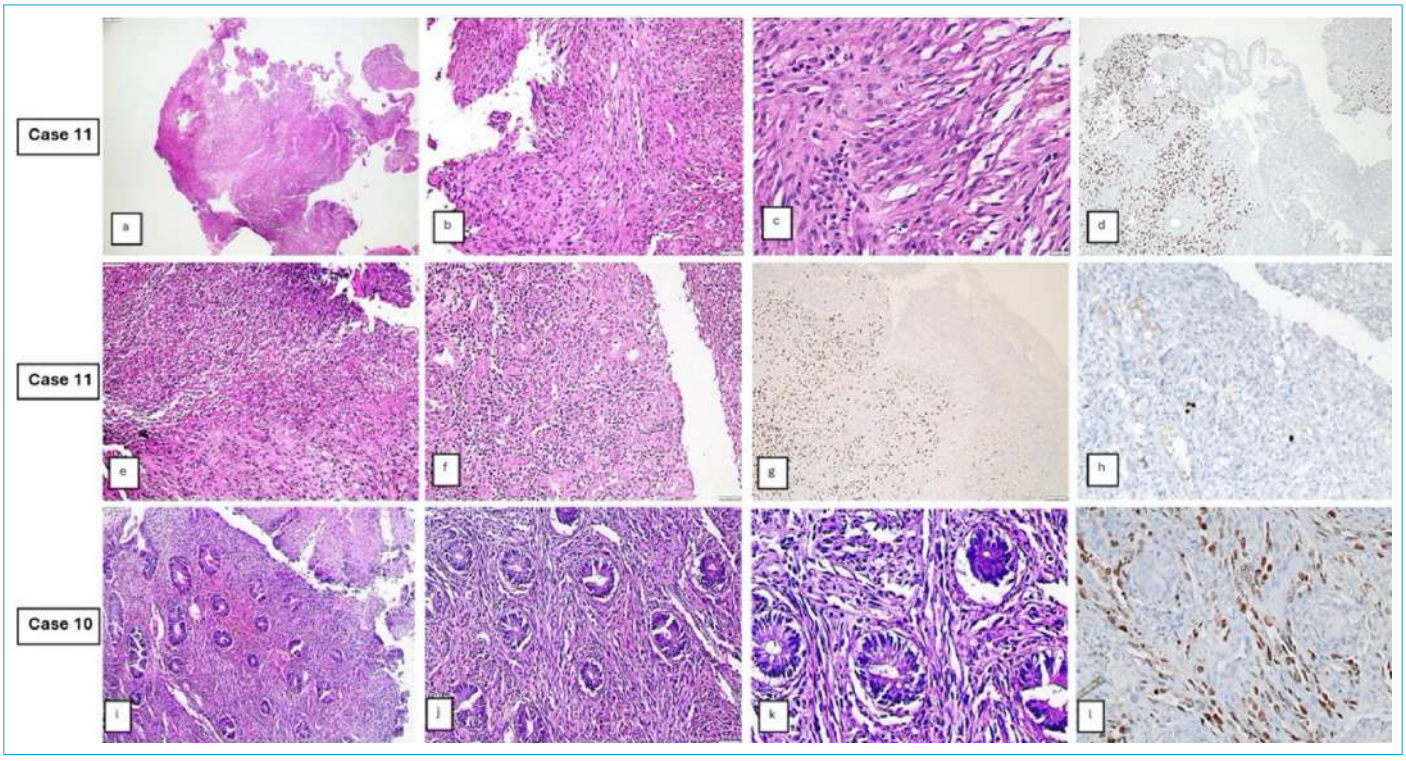

Figure 5. Histopathologic and HHV-8 IHC findings in cases 11 and 10: **(a)** Inflammatory granulation tissue in ulcerated rectal mucosa at low-power field; **(b–c)** Spindle cell proliferation, some forming vascular structures at high-power field; **(d)** Anti-HHV-8 positivity in spindle cells; **(e–h)** Inflammatory granulation tissue with underlying spindle cell proliferation, showing anti-HHV-8 positivity in tumor cells **(g)** and anti-CMV positivity in granulation tissue covering the tumor **(h)**; **(i)** Ulcerated rectal mucosa at low-power field; **(j–l)** Spindle cells and vascular structures surrounding the crypts, showing anti-HHV-8 positivity **(l)**.

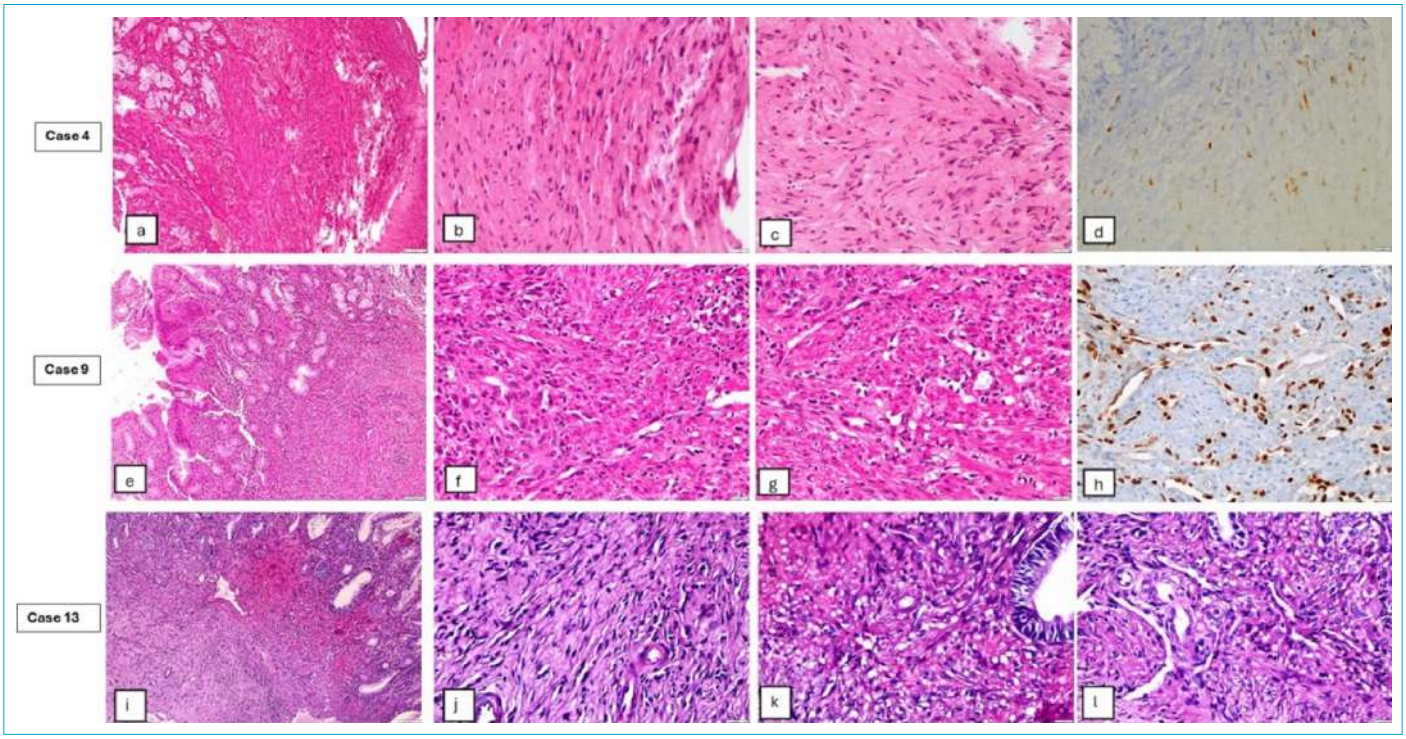

Figure 6. Histopathologic and HHV-8 IHC findings in cases 4, 9 and 13: **(a)** Dense spindle cell proliferation involving the mucosa and submucosa, suspicious for gastrointestinal stromal tumor or leiomyoma, at low-power field; **(b-d)** Spindle cells at high-power field, demonstrating anti-HHV-8 positivity **(d)**; **(e-l)** Slit-like vascular proliferation infiltrating the muscularis mucosa and submucosa, showing anti-HHV-8 positivity **(h)**.

Table 4. The first histopathologic impressions of the tumors

	Site	Included clinic information in endoscopy report	Endoscopic diagnosis	First histopathologic impression	Diagnosis
Case 1	Fundus	Yes	No	Spindle cell proliferation	KS
Case 2	Corpus, antrum	No	KS?	Antrum and corpus: Ulcerative chronic gastritis	KS
Case 3	Colon	No	KS?	Spindle cell proliferation	KS
Case 4	Corpus	Yes	No	Mesenchymal tumor	KS
Case 5	Corpus	No (KS in skin biopsy simultaneously)	No	Spindle cell proliferation	KS
Case 6	Corpus	Yes	No	Chronic gastritis	KS
Case 7	Antrum	No	No	Vascular proliferation at base of biopsy	KS
Case 8	Fundus, corpus*	Yes	Infiltrative gastric tumor? MALToma?	Fundus: Spindle cell proliferation Corpus: Chronic gastritis	KS
Case 9	Corpus	Yes	Pangastritis	Mild chronic inflammation and vascular proliferation	KS
Case 10	Rectum	Yes	KS?	Ulceration with spindle cell proliferation surrounding crypts	KS
Case 11	Rectum	Yes	No	Granulation tissue	KS and CMV immunoreactivity
Case 12	Fundus	Yes	No	Reactive gastropathy	KS
Case 13	Corpus	Yes	No	Spindle cell proliferation	KS

*: Detected during re-evaluation.

Table 5. Differential diagnosis of GI-KS

Tumors	IHC						
	HHV-8	SMA	CD117	CD34	S100	ALK	Others
Kaposi sarcoma	(+)	(-)	(-)	(+)	(-)	(-)	
GIST	(-/+)	(-/+)	(+)	(+)	(-)	(-)	DOG1
Leiomyoma	(-)	(+)	(-)	(-)	(-)	(-)	Caldesmon
Schwannoma	(-)	(-)	(-)	(-)	(+)	(-)	
Hemangioma	(-)	(-)	(-)	(+)	(-)	(-)	ERG
Inflammatory myofibroblastic tumor	(-)	(-/+)	(-)	(-)	(-)	(+)	
Inflammatory fibroid polyp (stomach)	(-)	(-/+)	(-)	(+)	(-)	(-)	Fascin
Perineurioma	(-)	(-)	(-)	(-)	(-)	(-)	EMA, GLUT-1

Infectious/inflammatory conditions; H. Pylori gastritis; Ulcerative gastritis; Reactive gastropathy; Granulation tissue; Inflammatory pseudopolyp; CMV infection.

Disclosures

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Case Report

A Case of Button Battery Ingestion Mimicking Inferior Myocardial Ischemia and Atypical Chest Pain

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Abstract

With the increasing use of electronic toys, the number of cases involving battery ingestion has risen significantly in recent years. This case report presents a child who attended the emergency department with sudden chest pain and crying episodes. The electrocardiogram (ECG) revealed signs of myocardial ischemia in inferior leads, despite completely normal cardiac function. A chest X-ray detected a button battery lodged in the esophagus.

A 4-year-old boy presented to the emergency department with sudden, intense chest pain and crying while playing with his toys. An electrocardiogram showed prolonged corrected QT interval (cQT 0.56), marked ST depression, and negative T waves in leads DII, DIII and aVF. Echocardiography (ECHO) revealed normal cardiac function. Cardiac enzyme and biochemical tests returned normal results (troponin-I ≤ 3.2 ng/L, CK-MB 29.8 U/L). A disc-shaped battery was detected on chest radiography, and electrocardiographic findings completely normalized after the battery was removed endoscopically.

In the literature, rare adult cases of multiple cylindrical battery ingestion have been reported with ECG findings that mimic myocardial ischemia or infarction. Our case is notable as it presents a single disc battery lodged in the esophagus of a pediatric patient that mimicked an inferior myocardial infarction.

Keywords: Arrhythmias, cardiac, chest pain, foreign bodies, myocardial ischemia

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Chest pain is a common symptom in pediatric practice, although it is usually attributed to non-cardiac causes. Foreign body aspiration is a rare cause of chest pain. With the increased use of electronic toys, the number of batteries has also risen among ingested foreign bodies.[1] The esophagus is the most frequently affected organ; however, vascular injuries are the most dangerous and often fatal.[2] In a comprehensive meta-analysis by Varga and colleagues, the complication rate for battery ingestion was found to be 0.2%, and the mortality rate 0.04%.[2] The most common complications include esophageal injury, perforation, tracheoesophageal fistula formation, stricture with obstruction, vascular injury, necrosis, bilateral vocal cord paralysis, bronchopneumonia, and spondylitis.[2] Ingestion of small cylindrical batteries (such as AA and AAA batteries) is rare and generally considered less risky than disc battery ingestion.[1,3] Among children under six, ingestion of disc batteries with a diameter of ≥2 cm poses a high risk of complication 12%. These 2 cm batteries have a shelf life of up to 10 years and retain about half of their charge even when not in use.[4,5] One of the rare

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complications following battery ingestion is cardiac arrhythmia. In the literature, four case reports involving adults documented this complication, and the ingested batteries were cylindrical.[6-9] Our case represents the first report of a pediatric patient with disc battery ingestion mimicking an inferior myocardial infarction.

Case Report

A 4-year-old male patient, followed by a child psychiatrist for atypical autism, presented to the pediatric emergency clinic with severe chest pain. The chest pain was intense and persistent, and the patient pointed to the anterior chest wall and epigastric area. He had no prior history of cardiac medication use, nor was there any family history of heart disease. He exhibited no shortness of breath, nausea, or vomiting. The patient's history revealed that he had undergone bronchoscopy at age 2 in our clinic for foreign body aspiration, during which a peanut fragment was removed. Physical examination revealed no pathological findings, and a detailed cardiac examination due to chest pain was unremarkable, with no murmur detected. After establishing intravenous access and administering oxygen, cardiac enzyme and biochemical tests were ordered.

On the electrocardiogram (ECG), prolonged corrected QT interval (cQT), ST depression, and negative T waves were observed in leads DII, DIII and aVF, findings consistent with inferior cardiac ischemia (Fig. 1). The pediatric cardiology department was consulted, and cardiac enzyme levels were assessed showing troponin-I at ≤3.2 ng/L (normal range: 0-34.2) and CK-MB at 29.8 U/L (normal range <24.0), which was mildly elevated. Echocardiography (ECHO) was also normal. A chest X-ray revealed a foreign object, identified as a disc battery, in the distal esophagus, leading to a consultation with our department (Fig. 2). The abnormal ECG findings were thought to be related to the active battery. Emergency endoscopy was performed, and the disc battery was removed from the lower esophagus with forceps. A stage 2b burn was observed at the site where the battery had lodged.

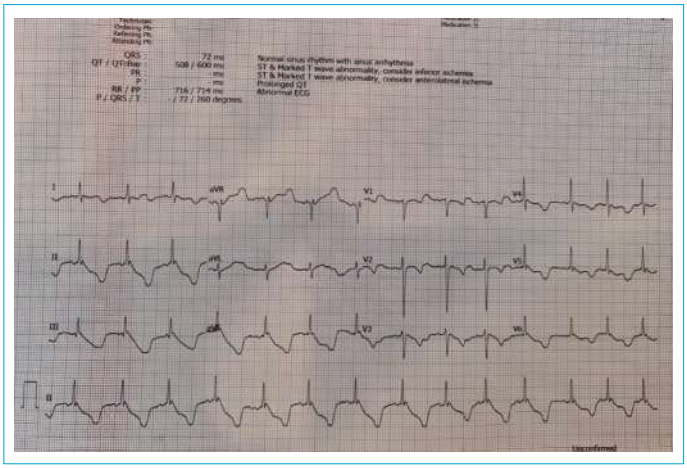

Figure 1. Electrocardiogram (ECG) obtained in the pediatric emergency department.

Prolonged corrected QT interval (cQT), ST-segment depression, and negative T waves were observed in leads DII, DIII and aVF findings consistent with inferior myocardial ischemia.

During surgery, the abnormal T-wave patterns on cardiac monitoring resolved immediately after battery removal. A follow-up ECG taken in the ward showed no ST depression in leads DII, DIII, and aVF, and the cQT interval had normalized (Fig. 3). The patient was fed through a nasogastric tube postoperatively, and a follow-up endoscopy on postoperative day 5 showed the mucosal injury had regressed to stage 2a. An esophagogram performed after discharge showed no esophageal stricture. The patient, weighing 19 kg (75th-90th percentile), displayed no swallowing difficulties or weight loss.

Discussion

In the literature, battery ingestion has been associated with numerous complications; however, this is the first reported case in pediatric patients where ECG findings mimicking myocardial infarction accompanied chest pain. This case contributes uniquely to the literature due to the patient's young age, prior history of foreign body aspiration, the presence of a disc battery lodged in the esophagus, and

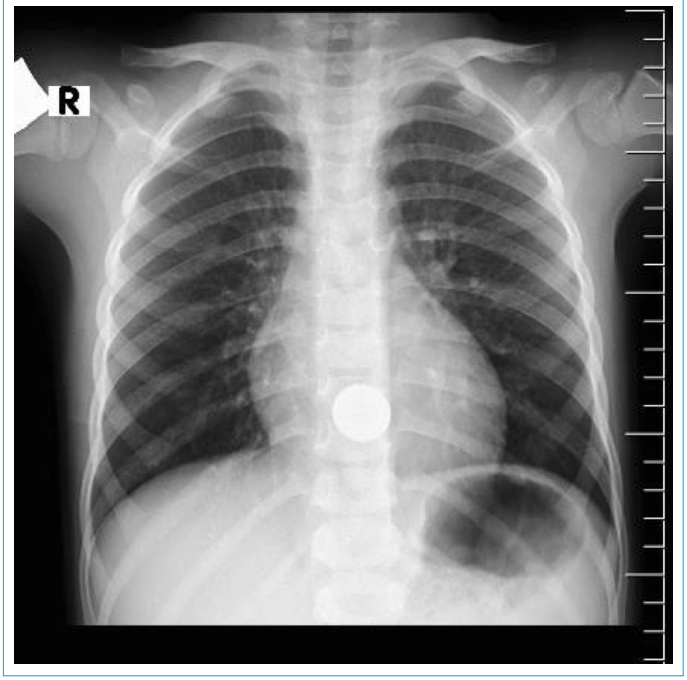

Figure 2. Chest X-ray.

The chest X-ray revealed a disc battery lodged in the distal esophagus.

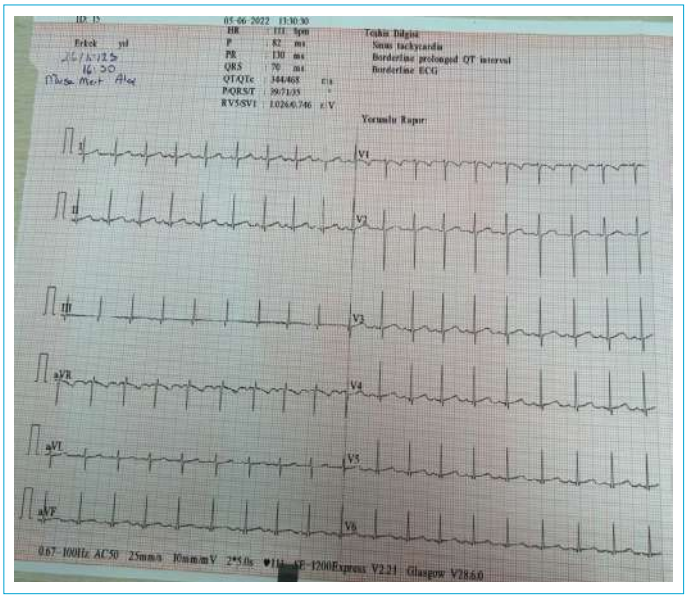

Figure 3. Postoperative electrocardiogram (ECG).

No ST-segment depression was observed in leads DII, DIII, and aVF, and the corrected QT interval (cQT) had normalized.

transient ECG findings suggestive of myocardial ischemia. Previous studies reporting cardiac-related complications primarily involved adult patients, with multiple cylindrical, rather than disc, batteries lodged in the stomach.[6-8] Alexander J. Ordoobadi et al.[6] and Chang H et al.[7] observed ST segment elevation in inferior leads on ECG, while Moritz Till Huttelmaier et al.[8] found ST elevation in leads I and aVR. In contrast, our case presented with ST depression. In each of the three studies,[6-8] the ingested cylindrical batteries were located in the stomach, with multiple batteries present. In our case however, the battery was positioned at the lower end of the esophagus. Previous adult studies suggested that such changes were observed only when the battery was located close to the heart's lower regions (specifically II, III and aVF leads reflecting inferior cardiac areas). We also believe that the proximity of the battery in the lower esophagus to the heart contributed to the ECG changes observed in our case.

While the mechanism behind ST segment changes caused by batteries has not been fully explained, it is believed to result from the electrical current generated by the batteries.[6] Moritz Till Huttelmaier et al.[8] proposed two hypotheses to explain the occurrence of ECG changes: Cardiac motion within the disturbance field generated by the battery causes electrical changes at a heart rate time scale above the high-pass filter threshold; and the electrotonic potential of the battery affects the membrane currents of cardiac myocytes, producing repolarization abnormalities without generating an action potential. According to Huttelmaier's hypothesis, gastric mucosa bridges the battery's anode and cathode, allowing current flow. Additionally, larger batteries (e.g., cylindrical) tend to produce higher frequencies of these effects than smaller designs, such as button batteries [8]. While detailed data on this topic are lacking, our case does not align with this hypothesis, as it involved a disc battery in the esophagus. While ST-segment depression is often observed in the context of cardiac ischemia, prolonged QT intervals are not commonly seen in battery ingestion cases, as they indicate an increased risk of sudden cardiac death due to ventricular arrhythmias. Aside from genetic long QT syndromes, prolonged QT intervals may also occur due to drugs that disrupt ventricular repolarization. Given that repolarization abnormalities, as seen in battery ingestion cases, resolve immediately after battery removal, a causal relationship between battery removal and ECG abnormalities was proposed.[8] In our case, the prolonged QT interval normalized immediately after battery removal. Additional pediatric cases are needed to better understand the relationship between battery ingestion and transient ECG abnormalities, particularly QT interval changes.

Conclusion

Prolonged cQT intervals and ST depression are rare but clinically significant complications of battery ingestion when the battery is lodged in the esophagus. In patients who are unable to communicate ingestion events (such as those with intellectual disabilities or under psychiatric follow-up), the possibility of battery ingestion should be considered if atypical chest pain is accompanied by abnormal ECG findings.

On such cases, both clinical symptoms and ECG abnormalities may resolve completely following timely battery removal.

Disclosures

Conflict of Interest: The authors declare no conflict of interest.

Informed Consent: Informed consent was obtained

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Use of AI for Writing Assistance: The authors declared that generative artificial intelligence tools such as ChatGPT (OpenAI) and AI-assisted translation software such as DeepL were used during the manuscript preparation.

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Letter to the Editor

Comment on "Performance of AI Models vs. Orthopedic Residents in Turkish Specialty Training Development Exams in Orthopedics"

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Dear Editor,

The publication on "Performance of AI Models vs. Orthopedic Residents in Turkish Specialty Training Development Exams in Orthopedics[1]" is hereby discussed. This study aims to be both modern and crucial in the era of AI's increasing role in medical education and clinical decision-making. It compares the performance of large language models (LLMs)—ChatGPT-4o, Gemini, Bing AI, and DeepSeek—with orthopaedic residents on the Specialty Training Development Exams (UEGS) from 2010 to 2021. While the results indicate that AI outperforms humans in terms of "accuracy," there are still some statistical and research design criticisms that need further consideration.

The first restriction is that the comparison is retroactive, with AI answering prior questions without taking into account environmental factors that may affect resident learning, such as curriculum changes, data access, or test stress levels. In contrast, AI responds to inquiries without regard for the environment. Furthermore, while one-way ANOVA is adequate for group comparisons, it does not offer critical markers such as effect size, standard deviation, or confidence interval, making it impossible to judge clinical, rather than statistical, significance.

A closer look suggests that "accuracy" may not be enough to evaluate AI's capabilities in a healthcare setting. Qualitative tools, such as specific rubrics or expert assessments, should be used to examine factors such as "depth of explanation" and "clinical consistency". Assuming that an AI is equivalent to a physician with 5 years of expertise is a subjective evaluation with no concrete benchmarks. Furthermore, ChatGPT-4o's lower-than-expected performance could be attributed to the model's emphasis on providing answers in general situations rather than highly specialized exams.

The appropriateness of utilizing AI in clinical skills testing or assessments is a hotly debated topic in academia. A correct answer does not imply that it can "think critically" or evaluate the circumstances of a genuine patient. Furthermore, it is worth considering if artificial intelligence should be created to "replace" or "support" physician decision-making. Clear ethical criteria should be provided for the use of these language models in teaching and evaluation situations, especially in disciplines that need extensive knowledge, experience, and judgment, such as orthopedic surgery.

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Use of AI for Writing Assistance: The authors declared that generative artificial intelligence tools such as ChatGPT (OpenAI) and AI-assisted translation software such as DeepL were used during the manuscript preparation.

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Author's Reply

Dear Editor,

We sincerely thank the readers for their thoughtful comments and constructive criticism on our recently published article. We are pleased to clarify several points raised.

First, by design, our comparison was retrospective. Residents' scores were drawn from UEGS examinations administered over multiple years, whereas the AI models' responses were generated on the same items within a short time window using a standardized, text-only protocol without personalization or web browsing. Consequently, environmental factors that may influence resident learning—such as curricular changes, access to archives/study materials, or exam-related stress—were not directly measured. In contrast, the AI systems were run under identical conditions (same model/version, prompt, and settings) and were therefore not exposed to such human environmental variability. Our findings should thus be interpreted as a comparison against a reference that is deliberately insulated from human contextual fluctuations.

Second, for multiple-group comparisons we used one-way ANOVA. We agree that reporting effect sizes and confidence intervals would strengthen clinical interpretation. We welcome this suggestion and, at the Editor's request, can provide effect sizes (e.g., η^2/Hedges' g) and 95% confidence intervals as a supplementary file. Moreover, we plan to report these metrics systematically in future work to enhance interpretability.

Third, we share the view that, in healthcare settings, simple "right/wrong" scoring does not fully capture the clinical value of AI. The scope of our study was a performance comparison on identical question sets; therefore, qualitative dimensions such as "explanatory depth" and "clinical coherence" were not systematically scored. Especially for open-ended or interpretive items, we believe future studies should incorporate blinded expert ratings based on a pre-specified rubric to evaluate the depth and coherence of AI-generated answers, accompanied by reliability reporting (e.g., ICC).

Fourth, our study does not claim general equivalence. Any phrasing suggesting "equivalence to a five-year physician" refers solely to relative performance on specific exam items. Clinical competence is multidimensional (e.g., EPAs, patient safety, team communication, decision-making under time pressure, and legal/ethical considerations) and cannot be inferred from item-level accuracy alone.

As acknowledged in our Limitations, although AI models may demonstrate high accuracy in certain contexts, they may not yet reflect the contextual understanding and nuanced clinical reasoning required in real-world practice. In future work, we intend to evaluate these qualitative dimensions using a standardized rubric, blinded expert grading, and reliability statistics (ICC).

We also agree that a correct answer alone does not demonstrate a model's capacity for critical thinking or for assessing the circumstances of a real patient. Our study presents a performance comparison on the same item sets; it does not assert high-stakes claims about clinical reasoning or bedside proficiency. Our stance is that AI should support—not replace—physician decision-making within appropriate boundaries. We likewise concur on the need for clear ethical principles governing the use of AI in teaching and assessment, particularly in specialties that demand extensive knowledge, experience, and judgment such as orthopedic surgery.

In summary, our findings illustrate AI's potential for item-level performance; however, in clinical practice AI should function as a decision-support tool under explicit ethical guidelines and institutional oversight. We are grateful for the opportunity to clarify these points and strongly support ongoing efforts to integrate AI into medical education responsibly.

Sincerely,

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