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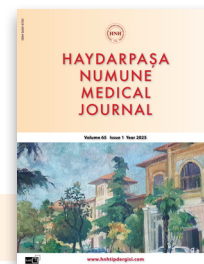
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Please refer to Table 1 below for word count specifications.

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Introduction: State the specific purpose and available data relevant to the study.

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Discussion: Data relevant to the study subject matter should be examined, evaluated, and substantiated with references from domestic and international sources. General information irrelevant or superfluous to the report should not be included.

Acknowledgement: The names of individuals who contributed to the study but who fail to meet the criteria of authorship should be mentioned in this section. The written consent of all individuals mentioned should be obtained.

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Haydarpaşa Numune Med J publishes the types of articles briefly described below.

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Units should be prepared in accordance with the International System of Units (SI).

Limitations, drawbacks, and the shortcomings of original articles should be mentioned in the Discussion section before the conclusion paragraph.

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Table 1. Limitations for each manuscript type

Type of manuscript	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
Original Article	3500	350 (Structured)	40	6	6
Review Article	5000	350	50	6	10
Case Report	1500	200	15	No tables	5

Tables should be included in the main document, presented after the reference list, and they should be numbered consecutively in the order they are referred to within the main text. A descriptive title must be placed above each table. Abbreviations used in the table should be defined below the table by footnotes (even if they are defined within the main text). Tables should be created using the word processing software "insert table" command and they should be arranged clearly to provide easy reading. Data presented in tables should not be a repetition of the data presented within the main text but should support the main text.

Figures and Figure Legends

Figures, graphics, and photographs should be submitted as separate files (in TIFF or JPEG format) through the submission system. The files should not be embedded in a Word document or the main document. When there are figure subunits, the subunits should not be merged to form a single image. Each subunit should be submitted separately through the submission system. Images should not be labeled (a, b, c, etc.) to indicate figure subunits. Thick and thin arrows, arrowheads, stars, asterisks, and similar marks may be used on the images to support the figure legends. Like the rest of the submission, the figures should also be blind. Any information within the images that may identify an individual or institution should be anonymized. The minimum resolution of each submitted figure should be 300 DPI. To prevent delays in the evaluation process, all submitted figures should be clear in resolution and large in size (minimum dimensions: 100 × 100 mm). Figure legends should be listed at the end of the main document.

References

References are numbered and listed by their order of appearance in text; the text citation is followed by the appropriate reference number in parentheses. References should be restricted to closely pertinent material. Accuracy of citation is the author's responsibility. References should conform exactly to the original spelling, accents, punctuation, etc. All references should be cited inside the text.

The reference styles for different types of publications are presented in the following examples.

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Marshall RD, Stein DJ, Liebowitz MR, Yehuda R.; A pharmacotherapy algorithm in the treatment of PTSD. *Psychiatric Annals* 1996;26:217–26.

Book Section:

Author. Title. In: Editor, `editor`. ^` editors`. Book Title. Edition ed. Place Published: Publisher; Year. p. Pages.

Philips SJ, Whisnant JP. Hypertension and Stroke. In: Laragh JH, Brenner BM (editors). *Hypertension pathophysiology, diagnosis, and management*. 2nd ed. New York: Raven Press, 1995: 465–78.

Books with a Single Author:

Author. Title. Edition ed. Place Published: Publisher; Year.

Sweetman SC. Martindale the Complete Drug Reference. 34th ed. London: Pharmaceutical Press; 2005.

Conference Proceedings:

Author. Title. In: Editor, 'editor', '^' editors'. Conference Name; Year of Conference Date; Conference Location: Publisher; Year of Conference]. p. Pages.

Bengissson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. pp.1561-5.

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Author. Title. Type. Place Published: Institution; Year Date. Report No.: Report Number.

Cusick M, Chew EY, Hoogwerf B, Agrón E, Wu L, Lindley A, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study Kidney Int: 2004. Report No: 26.

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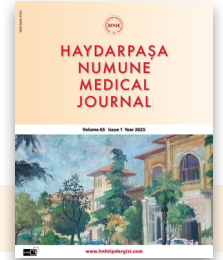
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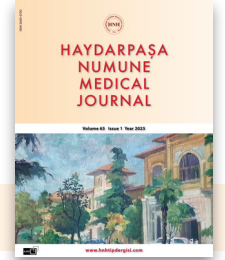
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Simultaneous Versus Staged Bilateral Total Hip Arthroplasty Via A Lateral Approach

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Abstract

Introduction: Studies comparing simultaneous bilateral total hip arthroplasty (simBTHA) and staged bilateral total hip arthroplasty (stgBTHA) using a lateral approach are rare. The aim of this study was to compare staged and simultaneous total hip arthroplasty surgeries performed with the lateral approach.

Methods: In this study, 53 BTHA patients (106 cases) treated in our clinic between 2015 and 2022 were included. Of these patients, 21 received simBTHA and 32 received stgBTHA. The patients were divided into two groups: simBTHA and stgBTHA. The groups were evaluated in terms of periprosthetic fracture, blood transfusion rate, gender, age, Body Mass Index (BMI), ASA scores, operation time, and hospital stay. Functional outcomes and major complication rates were compared between the groups. The Harris Hip Score was used to assess functional outcomes.

Results: Blood transfusion rates and hospital stay times were higher in the simBTHA group than in the stgBTHA group. Periprosthetic infection, pulmonary embolism, hematoma, mortality, and >10 mm leg length discrepancy were not found in either group. Harris scores of the simBTHA group and stgBTHA group were 94.3±6.5 and 92.3±5.9, respectively (p=0.203). The major complication observed was perioperative periprosthetic fracture (PPF) in 4 (7.6%) cases. The PPF rate was higher in the simBTHA group (14.2%) compared to the stgBTHA group (3.1%); however, this difference was not statistically significant (p=0.289). The blood transfusion rate was significantly higher in the simBTHA group than in the stgBTHA group (p=0.010).

Discussion and Conclusion: The main finding of this study is that simBTHA with a lateral approach is associated with increased blood transfusion requirements and periprosthetic fracture complications. Therefore, simultaneous BTHA via the lateral approach may not be preferable, especially in patients with increased perioperative risk.

Keywords: Bilateral; lateral approach; simultaneous; staged; total hip arthroplasty.

Approximately 15–25% of patients who have undergone total hip arthroplasty (THA) also require a second contralateral procedure within 5 years [1]. There are two THA surgery options for bilateral advanced hip osteoarthritis: simultaneous bilateral total hip arthroplasty (simBTHA) and staged bilateral total hip arthroplasty (stgBTHA). In the

literature, some opinions suggest that complications may increase due to the longer operation time in simultaneous surgeries [2].

simBTHA offers potential cost savings due to a single hospital admission and only one anesthesia exposure. However, periprosthetic fracture, perioperative bleeding,

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blood transfusion, pulmonary embolism, mortality, and complication rates may increase. In stgBTHA, the risk of deep venous thrombosis (DVT) and embolism may be higher as a result of later mobilization due to the continuation of pain in the contralateral hip [3]. To clarify this controversial situation in the literature, we compared the complication and functional results of simBTHA and stgBTHA.

Our experienced authors preferred the lateral approach for THAs over the anterior approach, which they were not accustomed to. Thus, all THA cases, including simBTHA, were performed using the lateral approach. In our study, we aimed to assess the reliability of the lateral approach in simultaneous surgeries by comparing simBTHA and stgBTHA via the lateral approach. Our hypothesis was that complications due to increased operative time in simBTHA with a lateral approach would be higher and that stgBTHA would be safer.

Materials and Methods

Patients and Groups

In our clinic, bilateral THA was administered to 68 patients out of 364 THA cases performed between 2015 and 2022. Ethics committee approval was obtained according to the Helsinki Declaration on 03.04.2023 (HNEAH-KAEK 2023/KK/55). Among them, 53 patients who met the inclusion criteria and were available during follow-up were included in the study. Of these patients, 21 received simBTHA and 32 received stgBTHA. The patients were evaluated retrospectively. Institutional Review Board (IRB) approval was obtained. Patients with bilateral primary or secondary osteoarthritis and patients who were recommended THA for both hips were included in the study. Patients with a previous hip surgery, bone ankylosis, high hip dysplasia (Crowe types 3 and 4), and insufficient follow-up time were excluded from the study (Fig. 1). The general indication for simultaneous bilateral hip replacement was determined to be cases where postoperative mobilization would be more difficult if only one hip was replaced. Both groups of patients were informed preoperatively about the advantages and disadvantages of bilateral and staged surgical techniques by the senior surgeons. The absolute indication for the surgical technique in both groups was determined according to patient preference. Staged BTHA cases with a stage interval >15 months were not included in the study. All patients underwent surgery with a cementless femoral stem and acetabular cup. Periprosthetic fracture, operation time, blood transfusion rate, hospital stay, American Society of Anaesthesiologists (ASA) score, and body mass index (BMI) were compared between the groups.

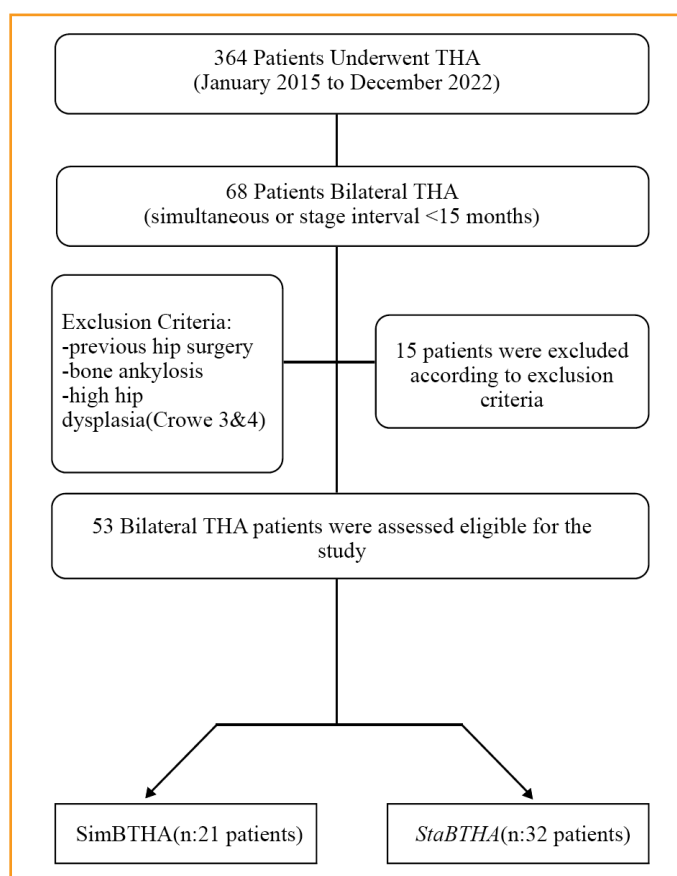


Figure 1. Flowchart of the study.

Outcome Measures

Major complications such as mortality, DVT, pulmonary embolism, periprosthetic fracture, prosthetic dislocation, acetabular cup malposition, and infection were recorded and compared between the groups. Leg length discrepancy (LLD) ≥ 10 mm was considered a major complication. Cases with LLD <10 mm were not considered to have a major complication because they were tolerable for patients and were not clinically significant. The rates of re-admission and revision surgery were compared. In the evaluation of acetabular cup malposition, cup inclination and anteversion were evaluated using the Lewinnek technique. For clinical outcomes, Harris Hip Scores were examined and compared.

Surgical Technique

All cases were prepared for the surgical procedure and operated on by two authors experienced in lateral THA surgery. A digital preoperative template was used to determine the hip rotation center, femoral offset, perioperative LLD, and optimal component length and position for all patients.

Patients were given low molecular weight heparin (enoxaparin 0.4 cc) 24 hours before surgery. One hour before surgery, prophylactic preoperative antibiotic cefuroxime axetil (i.v. 2 g) was administered. The cases were started primarily from the hip with the most common pain complaint. The procedure began by positioning the patient in the lateral decubitus position. A longitudinal incision was made extending 3–5 cm proximal and about 5–8 cm distal to the tip of the greater trochanter. The fascia was split at the interval between the tensor fascia latae and gluteus maximus in line with the skin incision. The tendon and muscle fibers of the gluteus medius were then visualized and split in a one-third anterior/two-thirds posterior fashion. The split was carried distally to the vastus ridge, leaving a cuff of the gluteus medius tendon for repair following the procedure. Anterior capsulectomy was performed, and the hip was dislocated anteriorly. The foot was placed anteriorly in the sterile bag. Then, the femoral neck osteotomy was performed approximately 15 mm proximal to the trochanter minor, and the femoral head was removed.

The acetabulum was prepared with the leg externally rotated and the knee extended on the table. Hohmann retractors were carefully placed anteriorly, posteriorly, and inferiorly around the acetabulum to provide adequate visualization. The acetabulum was deepened by medializing to the tabula interna. Soft tissue landmarks, such as the transverse acetabular ligament, reamer positioning relative to the floor, and cup positioning guides, were used to verify the acetabular version and inclination. The acetabulum was prepared at a 40° inclination and 15° anteversion angle. The acetabular cup was placed without cement as a press-fit. Then a 10° angled insert was placed as standard.

When preparing the proximal femur, the hip was flexed to

nearly 90° and externally rotated, and the foot was placed in the sterile bag anteriorly with the knee flexed. The femoral medulla was expanded to the bone cortex with a rasp. The optimal head/neck option was determined using the femoral rasp with trial implants. Hip movements were examined in all directions, stability was checked, and LLD was observed. The optimal size cementless femoral stem was placed, and the hip was reduced with the selected appropriate size femoral head. The amount of bleeding was recorded during the operation. Tranexamic acid was injected into the joint to control bleeding. A hemovac drain was placed. The gluteus medius fibers were repaired as much as possible. Then all subcutaneous soft tissues and skin were closed. The wound was dressed.

In simultaneous cases, surgical covers were removed, and lateral decubitus positioning was achieved on the operated side for the contralateral hip. The same procedures were applied to the other side.

Postoperative Rehabilitation

The postoperative rehabilitation protocols were similar in simultaneous and staged cases. Six hours after surgery, the patient was allowed to sit. All patients were allowed full weight bearing and to walk with a walker on the first operative day. Patients who were able to ambulate on their own after surgery were discharged. The first follow-up was performed during the third week after surgery, and physical therapy was started. Subsequent follow-up visits were performed at 6 weeks, 3 months, and 6 months.

Statistical Analysis

Mean, standard deviation, median, minimum, maximum, frequency, and percentage were used for descriptive statistics. The distribution of variables was checked using

Table 1. Preoperative diagnosis of the patients.

	Total BTHA		Simultaneous BTHA		Staged BTHA		p
	n	%	n	%	n	%	
Pre-Operative Diagnose							
Primer OA	29	54.7	13	61.9	16	50.0	0.394 ^{X²}
AVN	13	24.5	3	14.3	10	31.3	0.160 ^{X²}
DDH	7	13.2	2	9.5	5	15.6	0.521 ^{X²}
Achondroplasia	1	1.9	1	4.8	0	0.0	0.396 ^{X²}
Perthes Sequela	1	1.9	1	4.8	0	0.0	0.396 ^{X²}
Seconder OA(AS)	2	3.8	1	4.8	1	3.1	1.000 ^{X²}

X² Chi-square test; *Primer OA, primer osteoarthritis, *AVN, avascular necrosis, DDH, developmental dysplasia of hip, *Seconder OA(AS), seconder osteoarthritis(ankylosan spondylitis)

the Kolmogorov–Smirnov test. The Mann–Whitney U test was used for the comparison of quantitative data. The chi-square test was used for the comparison of qualitative data. SPSS 28.0 was used for statistical analyses.

Results

The mean follow-up period of our study was 27 (13–96) months. The mean age of the patients was 56.3 (24–74) years. There was no statistically significant difference ($p>0.05$) in patient age between the groups. In the study, 28 patients were women and 25 were men. The distribution of gender and ASA score was similar between the groups. The mean stage interval time of stgBTHA cases was 126.1 ± 118.6 days (range 4–455 days). BMI scores of simBTHA and

stgBTHA cases were 26.2 and 27.7, respectively. There was no statistically significant difference in BMI scores between the two groups. There was no significant difference ($p>0.05$) in the distribution of preoperative diagnosis between the stgBTHA and simBTHA groups (Table 1). The blood transfusion rate was significantly higher in the simBTHA group than in the stgBTHA group ($p=0.010$). The mean operation time was 184.0 minutes in the simBTHA group and 106.3 minutes in the stgBTHA group.

Hematoma, 90-day mortality, component malposition, pulmonary embolism, ≥ 10 mm LLD, and infection as major complications were not found in any cases. There was no significant difference ($p>0.05$) between the groups in the rate of LLD, component malposition, hematoma, DVT, dislocation, or revision surgery. The most common major complication (7.6%) was perioperative periprosthetic fracture. All cases were type A fractures in the Vancouver periprosthetic fracture classification. The PPF complication rate was higher in the simBTHA group (14.2%) compared to the stgBTHA group (3.1%); however, this difference was not statistically significant ($p=0.289$). Most of the periprosthetic fractures (75%) seen in the simBTHA group were specifically in the trochanteric region (only trochanteric tip). Placement of the acetabular cup in the safe zone using the Lewinnek technique was successful for both groups, and there was no statistically significant difference ($p>0.05$). There was no significant difference ($p>0.05$) between the revision and re-admission rates for simBTHA and stgBTHA. The Harris scores for the simBTHA cases were 94.3 ± 6.5 , and for the stgBTHA cases were 92.3 ± 5.9 . There was no significant difference ($p>0.05$) in Harris scores between the groups (Tables 2 and 3).

Table 2. The demographics and complications of the patients.

	Min-Max	Medyan	Mean $\pm$ SD/n-%
Age	24.0-74.0	55.0	56.3 $\pm$ 12.3
Gender			
Female			28-52.8%
Male			25-47.2%
BMI	22.0-37.6	27.0	28.4 $\pm$ 4.5
ASA			
I			14-26.4%
II			30-56.6%
III			9-17.0%
Staged BTHA			32-60.4%
Simultaneous BTHA			21-39.6%
Blood Transfusion			
(-)			20-37.7%
(+)			33-62.3%
I			26-49.1%
II			3-5.7%
III			4-7.5%
Stage Interval in stgBTHA	4.0-455.0	86.0	126.1 $\pm$ 118.6
Harris	77.0-100.0	92.0	93.1 $\pm$ 6.2
VAS	6.0-10.0	9.0	8.8 $\pm$ 1.3
Hospital Stay Time	2.0-7.0	3.0	3.3 $\pm$ 1.0
Operation Time	89.0-225.0	120.5	136.6 $\pm$ 39.9
Follow-Up Time	13.0-96.0	27.0	32.5 $\pm$ 17.0
Major complications			
Component malposition			1-1.9%
DVT			1-1.9%
Dislocation			1-1.9%
Periprosthetic fracture			4-7.6%
Revision surgery			2-3.8%
Re-admission			4-7.6%

*BMI, body mass index, *ASA, American society of anesthesiologist, *BTHA, bilateral total hip arthroplasty, *DVT, deep venous thrombosis.

Discussion

There are three main surgical approach options available for THA: the anterior, lateral, and posterior approaches. Each approach has its own advantages and disadvantages. In many studies in the literature, the anterior approach is often recommended because simBTHA surgery can be performed with a single surgical cover in the supine position and the operation time may be shorter. It is thought that the anterior approach has fewer complications due to the shorter operation time, and therefore this approach is recommended by many authors for simultaneous surgeries. However, studies in the literature have shown that complication rates increase when a surgeon uses an unfamiliar surgical approach [4–6].

Table 3. The demographics, functional score and complications of the patients.

	Simultaneous BTHA		Staged BTHA		p
	Mean±SD/n-%	Median	Mean±SD/n-%	Median	
Age	51.0±11.9	54.0	56.4±9.8	58.0	0.136m
Gender					
Female	9-42.9%		19-59.4%		0.239 X ²
Male	12-57.1%		13-40.6%		
BMI	26.2±2.8	26.0	27.7±3.1	27.0	0.098m
ASA					
I	7-33.3%		7-21.9%		0.145X ²
II	13-61.9%		17-53.1%		
III	1-4.8%		8-25.0%		
Pre-Operative Diagnose					
Primer OA	13-61.9%		16-50.0%		0.394X ²
AVN	3-14.3%		10-31.3%		0.160X ²
DDH	2-9.5%		5-15.6%		0.521X ²
Achondroplasia	1-4.8%		0-0.0%		0.396X ²
Perthes Sequela	1-4.8%		0-0.0%		0.396X ²
Seconder OA(AS)	1-4.8%		1-3.1%		1.000X ²
Blood Transfusion					
(-)	3-14.3%		17-53.1%		0.010X ²
(+)	18-85.7%		15-46.9%		
I	13-61.9%		13-40.6%		
II	2-9.5%		1-3.1%		
III	3-14.3%		1-3.1%		
Harris	94.3±6.5	96.0	92.3±5.9	92.0	0.208m
VAS	8.8±1.3	9.0	8.8±1.2	9.0	0.947m
LLD					
(-)	19-90.5%		31-96.9%		0.555X ²
(+)	2-9.5%		1-3.1%		
Lewinnek Ase. Cup Safe Zone					
(-)	0-0.0%		1-3.1%		1.000X ²
(+)	21-100%		31-96.9%		
Hematoma					
(-)	20-95.2%		31-96.9%		1.000X ²
(+)	1-4.8%		1-3.1%		
DVT					
(-)	21-100%		31-96.9%		1.000X ²
(+)	0-0.0%		1-3.1%		
Dislocation					
(-)	21-100%		31-96.9%		1.000X ²
(+)	0-0.0%		1-3.1%		
Revision Surgery					
(-)	20-95.2%		30-93.8%		1.000X ²
(+)	14.8%		2-6.3%		
Hospital Stay Time	4.0±1.1	4.0	2.8±0.7	2.5	0.000m
Operation Time	179.5±25.8	184.0	108.4±13.2	106.3	0.000m
Follow-Up Time	25.6±11.9	20.0	37.1±18.4	32.5	0.006m

X² Chi-square test / m Mann-Whitney u test; *BTHA, bilateral total hip arthroplasty, *BMI, body mass index, *ASA, American society of anesthesiologist, *LLD, leg length discrepancy, *DVT, deep venous thrombosis.

Similar to previous meta-analyses, there was no significant difference in the dislocation rate between the simBTHA and stgBTHA groups in the present study^[7–10]. Dislocation was detected in only one case in the stgBTHA group. We think that the reason for this low dislocation rate is that the lateral approach is very stable and safe.

The most common complication in our study was perioperative periprosthetic fracture (PPF). PPFs were seen in 4 (7.6%) cases: 3 (14.2%) in the simBTHA group and 1 (3.1%) in the stgBTHA group. Similar to the literature, the PPF complication rate in the simBTHA group was higher than in the stgBTHA group^[8]. In our study, although there was a noticeable percentage difference between the groups, it was not statistically significant. A high rate of trochanter-type fracture was observed in the simBTHA group as a specific complication. Three (75%) of the PPFs in the simultaneous group were trochanter-type fractures. This higher PPF rate compared to the literature may be attributed to the lateral approach and potentially accelerated surgical maneuvers during single-session simBTHA.

In this study, the average operation time of the simBTHA group was 76 minutes longer than that of the stgBTHA group. Berend et al.^[2] reported that infection rates may be higher due to the long operation time of simBTHA with the lateral approach. In addition, they reported that lying on the freshly operated wound side in the lateral decubitus position may also increase the infection rate by causing tissue irritation. Therefore, they did not recommend the lateral approach for simBTHA surgery^[2].

Gou et al.^[11] found cumulative blood transfusion rates significantly higher in the simultaneous group compared with the staged group. In our study, the cumulative blood transfusion rate was also significantly higher in the simultaneous group. At the same time, the cumulative amount of perioperative bleeding was high. Perioperative periprosthetic fracture may also have been a contributing factor. In conclusion, simultaneous surgery appears to be a disadvantage when complications related to blood transfusion are considered.

In this study, the Harris score was 94.3 ± 6.5 in the simultaneous group, similar to the literature, and 92.3 ± 5.9 in the staged group. There was no statistically significant difference between the two groups. Kim et al.^[3] found that the functional results and patient satisfaction of simBTHA cases were higher compared to the stgBTHA group in their study conducted with the posterior approach. In that study, they reported Harris scores

similar to ours, with 95.9 ± 4.8 in the simultaneous group and 90.7 ± 8.2 in the staged group. Kim et al.^[3] explained that the surgery was more accurate in the simultaneous group than in the staged group, rehabilitation of both hips was possible earlier, and patients had faster recovery and missed less work. However, due to the higher risk of periprosthetic fracture and increased blood transfusion rate in simultaneous surgery, it may be safer to perform bilateral hip arthroplasty in stages.

Limitations

The primary limitations of this study are its retrospective design and the relatively small sample size. The lack of preoperative gait analysis and hip scoring is also a limitation in terms of comparison with postoperative scores. Furthermore, the study was conducted in a single clinic, and all surgeries were performed by only two experienced authors. One of the strengths of the study is that it provides a detailed comparative analysis between simultaneous and staged BTHA via a lateral approach.

Conclusion

The main finding of this study is that simBTHA with a lateral approach is associated with increased perioperative bleeding and periprosthetic fracture complications. Therefore, we do not recommend simultaneous BTHA surgery via the lateral approach.

Ethics Committee Approval: The study was approved by Haydarpaşa Numune Training and Research Hospital Ethics Committee (No: HNEAH-KAEK 2023/KK/55, Date: 03.04.2023).

Conflict of Interest: The authors declare that there is no conflict of interest.

Informed Consent: Informed consent was waived because of the retrospective nature of the study and the analysis used anonymous clinical data.

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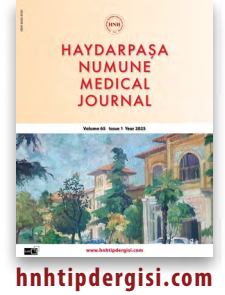
Authorship Contributions: Concept – E.K., İ.E.K.; Design – E.K., İ.E.K.; Supervision – E.K., A.G., N.A.A., A.P.; Data collection &/or processing – A.G., E.K., A.P.; Analysis and/or interpretation – H.S.Y., İ.E.K., E.K.; Literature search – E.K., N.A.A., A.G.; Writing – E.K., İ.E.K., H.S.Y.; Critical review – E.K., İ.E.K.

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Peer-review: Externally referees.

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Prognostic Value of Preoperative ALBI Score for Predicting Right Ventricular Dysfunction After Coronary Artery Bypass Surgery

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Abstract

Introduction: This study aimed to evaluate the prognostic utility of the albumin–bilirubin (ALBI) score in predicting right ventricular (RV) failure and postoperative outcomes in patients undergoing isolated coronary artery bypass grafting (CABG).

Methods: A total of 265 patients who underwent elective isolated CABG between 2020 and 2024 at a single tertiary center were retrospectively analyzed. Patients were divided into two groups based on a preoperative ALBI cut-off value of -2.44 . Preoperative, operative, and postoperative parameters were compared between groups. The primary outcome was postoperative RV failure. Secondary outcomes included in-hospital mortality, postoperative complications, and recovery metrics. Multivariate logistic regression was used to assess the independent association between ALBI and outcomes.

Results: Patients with high ALBI scores (>-2.44) were significantly older and had worse preoperative profiles, including lower ejection fraction ($p=0.003$), higher CRP ($p=0.017$), bilirubin ($p<0.001$), and BUN ($p=0.008$). No statistically significant differences were observed in postoperative atrial fibrillation, ICU stay, mechanical ventilation time, reoperation, or mortality between groups. However, high ALBI scores were consistently associated with markers of frailty and systemic inflammation.

Discussion and Conclusion: While the ALBI score did not predict short-term postoperative complications or mortality in isolated CABG patients, it demonstrated strong correlations with known risk factors such as advanced age, hypoalbuminemia, and inflammation. ALBI may serve as a useful adjunct in preoperative risk assessment. Further prospective studies are needed to confirm its role in long-term outcome prediction.

Keywords: Albumin; bilirubin; coronary artery bypass; mortality.

Coronary artery bypass grafting (CABG) outcomes are influenced not only by cardiac factors but also by the function of other organ systems, including the liver ^[1]. Impaired hepatic function in cardiac patients can worsen surgical prognosis; for example, chronic right-sided heart failure with elevated pulmonary pressures often leads to congestive hepatopathy and progressive liver dysfunction ^[2]. Yet conventional cardiac risk models (e.g., EuroSCORE

II, STS) largely omit quantitative liver function metrics. Emerging evidence suggests this is a critical oversight, as liver dysfunction scores such as the Model for End-Stage Liver Disease (MELD) correlate with worse outcomes after cardiac surgery ^[1]. Patients with significantly elevated MELD scores experience substantially higher postoperative mortality ^[1], underscoring the need to incorporate liver health into preoperative risk assessment for CABG.

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The albumin–bilirubin (ALBI) score is a recently established index of hepatic function that combines two readily available biomarkers (serum albumin and bilirubin) into a single prognostic score [3]. Initially developed in patients with hepatocellular carcinoma as an objective alternative to Child–Pugh class and MELD, the ALBI score provides a simple, evidence-based measure of liver reserve [3]. Recent studies have extended the application of ALBI beyond hepatology, noting that higher preoperative ALBI values are associated with worse outcomes in cardiovascular conditions such as acute and chronic heart failure [4]. In surgical populations, ALBI may capture subclinical liver impairment due to venous congestion or low cardiac output states. Notably, a study in cardiac valve surgery found that an elevated preoperative ALBI score was linked to higher pulmonary artery pressures and a greater incidence of acute kidney injury and in-hospital mortality [2]. This finding suggests that ALBI could serve as a useful preoperative marker for patients at risk of right ventricular (RV) failure and related complications following cardiac surgery.

The prognostic value of ALBI in the CABG patient population—particularly its ability to predict postoperative RV failure and mortality—remains poorly defined. Of note, even a single component of ALBI has been identified as an independent predictor of late mortality after CABG [5], suggesting that a composite score incorporating both albumin and bilirubin might further enhance risk stratification. Building on the known cardio-hepatic interactions, we hypothesized that the preoperative ALBI score could predict RV failure and adverse outcomes after CABG. This study was designed to investigate the relationship between preoperative ALBI scores and the incidence of postoperative RV failure, as well as short- and long-term mortality, in patients undergoing CABG surgery.

Materials and Methods

This retrospective observational study was conducted at Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital (Istanbul, Türkiye) between 2020 and 2024. The study protocol was approved by the institutional committee (date: 16/05/2025; no: E-28001928-604.01-276512887) with a waiver of informed consent due to the retrospective design, and the research was conducted in accordance with the principles of the Declaration of Helsinki.

All adult patients (aged ≥ 18 years) who underwent elective isolated coronary artery bypass grafting (CABG)

during the study period were eligible for inclusion, provided that complete preoperative biochemical (including albumin and total bilirubin) and transthoracic echocardiographic data were available in their records. Patients undergoing emergent or salvage CABG, those requiring concomitant cardiac procedures (e.g., valve or aortic surgery), and those with known liver failure or missing laboratory data necessary for ALBI calculation were excluded.

For each patient, the ALBI score was calculated using the preoperative serum albumin and total bilirubin values. Patients were then stratified into two groups based on an ALBI cut-off value of -2.44 , as previously reported by Duman and Timur in a valvular surgery cohort. Specifically, an ALBI score ≤ -2.44 was defined as low (indicating better hepatic reserve), and a score > -2.44 as high [2].

All relevant clinical and operative data, including patient demographics, comorbid conditions, and intraoperative details, were retrospectively extracted from the hospital's electronic health records. The primary outcome of interest was the development of postoperative RV failure, defined as hemodynamic instability due to RV dysfunction requiring high-dose inotropic support and/or mechanical circulatory or pulmonary vasodilator support. Secondary outcomes included in-hospital mortality, major postoperative complications (such as acute kidney injury requiring dialysis or reoperation for bleeding), and measures of postoperative recovery (duration of mechanical ventilation, length of intensive care unit stay, and total hospital length of stay).

Statistical Analysis

All statistical analyses were performed using R statistical software (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were expressed as mean $\pm$ standard deviation or median (interquartile range), as appropriate, and compared between the low-ALBI and high-ALBI groups using the Student's t-test or Mann-Whitney U test. Categorical variables were summarized as counts and percentages and compared using the chi-square test or Fisher's exact test.

To assess the independent association of preoperative ALBI status with postoperative RV failure and other outcomes, a multivariate logistic regression analysis was performed, including ALBI group and other potential confounding variables. Results were reported as odds ratios (OR) with 95% confidence intervals. A two-tailed $p < 0.05$ was considered statistically significant for all analyses.

Table 1. Preoperative demographical and laboratory values

	Group 1	Group 2	p
n	189	76	
Gender			
1	34 (18.0)	14 (18.4)	0.99
2	155 (82.0)	62 (81.6)	
DM			
-	85 (45.0)	40 (52.6)	0.278
+	104 (55.0)	36 (47.4)	
HTN			
-	78 (41.3)	34 (44.7)	0.680
+	111 (58.7)	42 (55.3)	
Carotid Stenosi			
-	154 (81.5)	65 (85.5)	0.478
+	35 (18.5)	11 (14.5)	
COPD			
-	167 (88.4)	60 (78.9)	0.054
+	22 (11.6)	16 (21.1)	
BMI	28.38 (4.46)	28.04 (4.68)	0.586
Height (cm)	168.88 (7.40)	167.14 (8.52)	0.099
BSA (m ²)	1.93 (0.17)	1.89 (0.20)	0.064
Weight (kg)	80.87 (13.01)	78.36 (14.33)	0.168
Age	59.37 (8.90)	63.22 (9.79)	0.002
Euroscore	2.00 (0.00, 4.00)	3.00 (1.00, 5.00)	0.003
Euroscore Mortality	1.33 (0.88, 2.40)	1.96 (1.33, 2.93)	<0.001
BUN	18.04 (6.98)	20.13 (11.51)	0.071
CRP	1.54 (2.00)	2.42 (3.32)	0.017
HB	13.59 (1.54)	13.25 (1.65)	0.105
CRE	0.93 (0.27)	0.96 (0.81)	0.558
Lymphocyte	2.33 (0.88)	2.21 (0.78)	0.330
MCV	89.01 (5.53)	89.51 (5.43)	0.506
Neutrophil	5.16 (1.94)	5.18 (1.81)	0.937
PLT	234365.08 (65676.02)	248828.95 (81526.99)	0.132
RDW	15.76 (1.34)	15.70 (1.84)	0.770
Uric Acid	6.32 (1.80)	6.13 (1.87)	0.538
WBC	8.40 (2.41)	8.43 (2.40)	0.925
Total Albumin	4.04 (0.26)	3.56 (0.23)	<0.001
Total Bilirubin	0.70 (0.40)	1.19 (1.36)	<0.001
Total Prot	6.85 (0.49)	6.36 (0.42)	<0.001

BMI: body mass index; BSA: body surface area; BUN: blood urea nitrogen; COPD: chronic obstructive pulmonary disease; CRE: creatinine; CRP: c-reactive protein; DM: diabetes mellitus; HB: hemoglobin; HTN: hypertension; MCV: mean corpuscular volume; PLT: platelet; RDW: red cell distribution width; WBC: white blood cell.

Results

A total of 265 patients who underwent elective isolated CABG between 2020 and 2024 were included in the final analysis. The cohort was divided into two groups based on

Table 2. perioperative data of the patients

	Group 1	Group 2	p
n	189	76	
X-clamp time	65.96 (28.60)	64.33 (27.49)	0.672
CPB time	105.68 (39.26)	102.08 (34.92)	0.487
Bypass number	3.00 (2.00, 3.00)	3.00 (2.00, 3.00)	0.037
CPB degree (Co)	30.00 (28.00, 32.00)	30.00 (28.00, 32.00)	0.876

CPB: cardiopulmonary bypass; x-clamp: cross clamp.

the preoperative ALBI score using a cut-off value of -2.44. Group 1 (n=189) comprised patients with an ALBI score $\leq$ -2.44, and Group 2 (n=76) included those with an ALBI score $>$ -2.44.

In the preoperative evaluation, patients in Group 2 were significantly older than those in Group 1 (63.22 ± 9.79 vs 59.37 ± 8.90 years, $p=0.002$). EuroSCORE and predicted mortality values were also higher in the high-ALBI group (EuroSCORE: 3.00 [1.00–5.00] vs 2.00 [0.00–4.00], $p=0.003$; EuroSCORE mortality: 1.96 [1.33–2.93] vs 1.33 [0.88–2.40], $p<0.001$). Among laboratory parameters, C-reactive protein (CRP) levels were elevated in Group 2 (2.42 ± 3.32 vs 1.54 ± 2.00 mg/L, $p=0.017$), while serum albumin, total protein, and total bilirubin levels differed significantly between groups (albumin: 3.56 ± 0.23 vs 4.04 ± 0.26 g/dL, $p<0.001$; bilirubin: 1.19 ± 1.36 vs 0.70 ± 0.40 mg/dL, $p<0.001$; protein: 6.36 ± 0.42 vs 6.85 ± 0.49 g/dL, $p<0.001$). Left ventricular ejection fraction (EF) was lower in patients with high ALBI scores ($49.21 \pm 10.39\%$ vs $52.96 \pm 8.53\%$, $p=0.003$), though all patients included had preserved left ventricular systolic function preoperatively (Table 1).

Operative characteristics were largely comparable between groups, except for the number of distal anastomoses performed, which was marginally higher in the high-ALBI group (3.00 [2.00–3.00] in both groups, $p=0.037$). There were no statistically significant differences in cardiopulmonary bypass or cross-clamp durations (Table 2).

Postoperative laboratory results showed that blood urea nitrogen (BUN) levels at 24 hours were significantly higher in Group 2 (23.59 ± 10.65 vs 20.67 ± 6.83 mg/dL, $p=0.008$), while postoperative lymphocyte counts were lower (1.03 ± 0.51 vs $1.22 \pm 0.69 \times 10^3/\mu\text{L}$, $p=0.036$). However, CRP values at 24 hours were similar between the two groups ($p=0.663$). There were no significant differences in mechanical ventilation duration, intensive care unit (ICU) stay, or total hospitalization time. Similarly, the incidence of postoperative atrial fibrillation, renal dysfunction requiring dialysis, or

Table 3. Postoperative data and laboratory findings of the patients

Factor	Group 1	Group 2	p
n	189	76	
infection			
-	132 (69.8)	50 (65.8)	0.559
+	57 (30.2)	26 (34.2)	
IABP			
-	183 (96.8)	71 (93.4)	0.304
+	6 (3.2)	5 (6.6)	
Inotropic need			
-	132 (69.8)	54 (71.1)	0.883
+	57 (30.2)	22 (28.9)	
Atrial fibrillation			
-	150 (79.4)	59 (77.6)	0.742
+	39 (20.6)	17 (22.4)	
Postoperative CRF			
-	187 (99.5)	76 (100.0)	1.000
+	1 (0.5)	0 (0.0)	
Postoperative dialysis need			
-	184 (97.4)	74 (97.4)	1.000
+	5 (2.6)	2 (2.6)	
Revision			
-	167 (88.4)	63 (82.9)	0.235
+	22 (11.6)	13 (17.1)	
Time of Entubation (days)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.063
Hospital stay (days)	7.00 (6.00, 8.00)	7.00 (6.00, 8.00)	0.197
ES use	2.00 (1.00, 4.00)	2.00 (1.00, 3.25)	0.968
X3TAM.KAN	0.00 (0.00, 1.00)	0.00 (0.00, 1.00)	0.462
FFP use	3.00 (1.00, 4.00)	3.00 (3.00, 3.00)	0.234
Plt use	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.631
ICU stay (days)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	0.707
1 year mortality (%)			
-	180 (95.2)	71 (93.4)	0.552
+	9 (4.8)	5 (6.6)	
2 years mortality (%)			
-	175 (92.6)	69 (90.8)	0.621
+	14 (7.4)	7 (9.2)	
3 years mortality (%)			
-	173 (91.5)	68 (89.5)	0.638
+	16 (8.5)	8 (10.5)	
30 day mortality (%)			
-	184 (97.4)	73 (96.1)	0.693
+	5 (2.6)	3 (3.9)	
In hospital mortality			
-	129 (81.6)	51 (73.9)	0.213
+	29 (18.4)	18 (26.1)	
Postop 1 CRP	11.70 (5.07)	11.36 (4.64)	0.663
Postop 1 Lymphocyte	1.22 (0.69)	1.03 (0.51)	0.036
Postop 1 Neutrophil	10.27 (2.95)	10.38 (3.79)	0.806
Postop1 PLT	178699.47 (54126.47)	180450.00 (58212.76)	0.816
Postop 2 BUN	23.45 (9.41)	26.05 (13.72)	0.079
Postop 1 BUN	20.67 (6.83)	23.59 (10.65)	0.008
Postop 1 CRE	1.05 (0.34)	1.10 (0.58)	0.343
Postop 1 Uric Acid	5.90 (1.91)	5.34 (1.48)	0.273
Postop 1 WBC	12.52 (3.33)	12.50 (4.15)	0.970
Postop 2 CRE	1.00 (0.39)	1.06 (0.72)	0.377
Postop 2 Uric Acid	6.50 (6.29)	5.55 (1.74)	0.574

BUN: blood urea nitrogen; CRE: creatinine; CRF: chronic renal failure; CRP: c-reactive protein; ES: erythrocyte suspension; FFP: fresh frozen plasma; IABP: intraaortic balloon pump; ICU: intensive care unit; PLT: platelet; WBC: white blood cell.

surgical revision for bleeding did not differ significantly between groups. Mortality outcomes at 30 days and up to three years showed a trend toward higher event rates in the high-ALBI group, though these differences did not reach statistical significance (Table 3).

Discussion

In this retrospective study, we investigated the prognostic value of the preoperative ALBI score in patients undergoing isolated CABG. Our findings revealed that patients with higher ALBI scores were significantly older and had worse preoperative profiles, including lower ejection fraction, higher CRP, elevated total bilirubin, and increased BUN. These associations support the hypothesis that the ALBI score reflects not only hepatic dysfunction but also a systemic inflammatory and metabolic burden, aligning with previous studies demonstrating the score's correlation with cardiovascular risk profiles [6–9].

The inverse relationship observed between ALBI and ejection fraction in our cohort is consistent with findings from Bedir et al., [10] who demonstrated that ALBI correlates with echocardiographic indices of pressure overload in patients with valvular disease. This suggests that ALBI may indirectly reflect chronic right-sided congestion and myocardial dysfunction. Similarly, elevated CRP levels in patients with poor ALBI scores reinforce the inflammatory dimension of this marker, as highlighted in prior heart failure and cardiac surgery cohorts [2,8]. Elevated BUN values in this subgroup also mirror systemic hypoperfusion and renal congestion, conditions previously shown to cluster with elevated ALBI and worse cardiac outcomes [9,11].

Despite the associations with several high-risk preoperative markers, we found no statistically significant differences between ALBI groups regarding key postoperative endpoints such as atrial fibrillation, mechanical ventilation duration, ICU stay, reoperation for bleeding, or early mortality. These findings merit discussion. First, the low overall event rate in our study population, composed of elective and hemodynamically stable CABG patients, may have limited statistical power. Additionally, robust perioperative care protocols may have mitigated differences in short-term outcomes. This phenomenon has been previously reported in similar low-risk surgical series, where biomarkers failed to predict outcomes under optimized conditions [12,13].

In particular, the absence of an association between ALBI and postoperative AF deserves mention. Given the complex, multifactorial pathogenesis of post-CABG AF—including

autonomic imbalance, atrial stretch, inflammation, and surgical trauma—hepatic biomarkers alone may be insufficient predictors. Indeed, Apaydin et al. [14] showed that even thoracic tube positioning independently altered AF incidence by modulating pericardial irritation. Similarly, our results may reflect the overriding influence of intraoperative and procedural factors in arrhythmogenesis, diminishing the discriminative value of preoperative ALBI in this context.

Furthermore, although ALBI was not significantly associated with mortality in our cohort, its strong correlation with frailty markers such as hypoalbuminemia, inflammation, and reduced cardiac function suggests a latent prognostic role. Prior studies have shown that ALBI may stratify long-term risk rather than early postoperative events. For instance, Jurkiewicz et al. [7] reported that ALBI predicted long-term survival in elderly heart failure patients, while Qiao et al. [12] demonstrated its prognostic validity in hypertrophic cardiomyopathy. These findings imply that the prognostic window of ALBI may extend beyond the immediate postoperative period, and long-term follow-up could reveal more robust associations.

This study has several limitations that must be acknowledged. First, the retrospective design inherently introduces the possibility of selection and information bias, as data were extracted from electronic records and not originally intended for research. Second, although the sample size was adequate for detecting differences in biochemical and demographic parameters, it may have been underpowered to reveal statistically significant differences in low-frequency clinical outcomes such as mortality or reoperation. Third, the study was conducted in a single high-volume tertiary center with standardized perioperative protocols, which may limit the generalizability of our findings to other institutions with different practice patterns. Furthermore, we did not include long-term follow-up beyond the early postoperative period and thus cannot fully evaluate the predictive value of the ALBI score on long-term mortality or morbidity after CABG. Finally, hepatic imaging or elastography data were not available, and subclinical liver disease could not be excluded with certainty.

Conclusion

In conclusion, our findings suggest that the preoperative ALBI score is a valuable surrogate marker of systemic risk in patients undergoing elective isolated CABG. Although it did not independently predict short-term clinical outcomes such as mortality or postoperative complications, the ALBI

score demonstrated strong associations with age, cardiac function, inflammation, and renal parameters—factors known to contribute to perioperative vulnerability. Its simplicity, availability, and multidimensional nature make it an appealing adjunct to traditional risk assessment tools. We believe that incorporation of ALBI into preoperative evaluation may enhance patient stratification and guide individualized care in cardiac surgery. Future prospective and multicenter studies are warranted to validate its role and define its utility in long-term prognostication.

Ethics Committee Approval: The study was approved by Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital Ethics Committee (No: E-28001928-604.01-276512887, Date: 16.05.2025).

Conflict of Interest: The authors declare that there is no conflict of interest.

Informed Consent: The study's participants gave their written informed consent.

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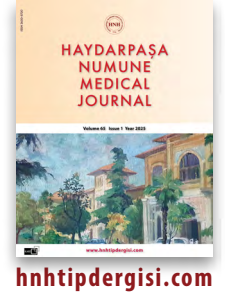
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Cardiac Rhythm in Inpatient Physical Therapy and Rehabilitation Patients

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Abstract

Introduction: This study aimed to document the presence of cardiac arrhythmia in inpatient physical therapy and rehabilitation patients and to evaluate whether physical therapy and exercises cause an increase in cardiac arrhythmias.

Methods: The study was conducted with patients hospitalized in the physical therapy and rehabilitation clinic due to any neuromusculoskeletal system disease between January 2022 and June 2022. Twenty-four-hour Holter recordings were performed before any treatment was initiated and again on the 21st day of hospitalization during treatment. Arrhythmias were then evaluated.

Results: A total of 63 patients (mean age: 58±14.5 years; range, 22–86 years) were included. The frequency of supraventricular and ventricular premature beats was 65.1% and 50.8%, respectively, in the initial 24-hour Holter recordings. Ventricular bigeminy was detected in 11.1%, ventricular trigeminy in 11.1%, ventricular couplets in 15.9%, nonsustained ventricular tachycardia in 9.5%, >1000 ventricular premature beats in 9.5%, and sinus pauses over 1.8 seconds in 11% of patients. No statistically significant difference was observed between the first and second 24-hour Holter recordings regarding supraventricular and ventricular arrhythmias.

Discussion and Conclusion: The incidence of arrhythmia in inpatient physical therapy and rehabilitation patients is higher than in the general healthy population. Although the frequency of arrhythmia did not increase during the treatments in our study population, meticulous follow-up for cardiac symptoms and signs is recommended, considering the high risk of cardiovascular disease in this patient group.

Keywords: Adverse events; Cardiac arrhythmia; Rehabilitation.

Physical therapy and rehabilitation departments are generally considered to be at lower risk of adverse events than other departments because the treatments applied are generally conservative. However, there is a possibility of encountering unfavorable events, especially during inpatient rehabilitation, since the population served is mostly composed of elderly patients in the post-acute period

with low functional levels and various health problems. Unfortunately, due to the lack of reporting of unfavorable situations observed during inpatient rehabilitation, few data are available on this subject. In addition, it is observed that different terms such as adverse event, adverse outcome, and complication are used in these studies, and the terminological standardization is poor^[1-7].

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Adverse events are defined as any unfavorable sign, symptom, or disease that occurs during or after the use of a drug or intervention, whether or not considered drug- or intervention-related. Additionally, the severity of adverse events can range from asymptomatic to fatal [8-10]. Siegler et al. [3] classified the adverse events that developed during inpatient treatment according to their severity and stated that serious surgical, infectious, cardiac, and thromboembolic complications were observed, and complications were generally observed in patients with deconditioning or spinal cord injury. The rate of development of cardiac complications was 9.5%, and 4 out of 5 deaths observed during the study were due to cardiac causes.

Detailed examination of cardiac signs and symptoms in inpatient rehabilitation patients is important for the prevention and control of these adverse cardiac events. Arrhythmias are well-known indicators of cardiovascular disease-related morbidity and mortality, with or without cardiovascular risk factors [11]. In this study, we aimed to document the presence of cardiac arrhythmia in inpatient physical therapy and rehabilitation patients and to evaluate whether physical therapy and exercises cause an increase in cardiac arrhythmias.

Materials and Methods

Design

The study was carried out as a cross-sectional study at the Physical Medicine and Rehabilitation Clinic of Trakya University Faculty of Medicine between January 2022 and June 2022. Participants volunteered for the study in accordance with the Declaration of Helsinki and signed the informed consent form. Approval of the local ethics committee (TUTF-BAEK 2021/423) was obtained for the study. Financial support for this study was provided by the Trakya University Scientific Research Project Unit with decision no 2021/161.

Participants

Patients over the age of 18 who were scheduled to receive inpatient physical medicine and rehabilitation treatment due to any neuromusculoskeletal system disease were included in the study. Exclusion criteria were initiation or change in dose of medication affecting heart rhythm in the last two weeks and failure to complete both 24-hour Holter recordings.

Clinical Evaluations

At study initiation, all patients were clinically evaluated, and exercise and physical agents required by their clinical condition were prescribed. In addition to recording the patients' age, gender, body mass index, smoking and alcohol use status, comorbidities, and drugs used, 10-year atherosclerotic cardiovascular disease (ASCVD) risk categories were determined by examining their medical records. Patients were grouped as low risk (<5%), borderline risk (5%–7.4%), high risk (7.5%–19.9%), and very high risk ($\geq 20\%$) in terms of 10-year ASCVD risk [12].

24-hour Holter Electrocardiogram (ECG) Evaluations

Twenty-four-hour Holter ECG recordings were performed before any treatment was started (first 24-hour Holter recording) and during treatment (second 24-hour Holter recording) on the 21st day of hospitalization using a 24-hour Holter ECG recorder (BORSAM Biomedical Instrument Co., Ltd. Shenzhen). On the day of the first 24-hour Holter recording, patients were instructed to rest except for eating and toilet needs, and no treatment (medical, physical agents, or exercise) was initiated. During the second 24-hour Holter recording, the medical treatments, exercises, and physical agent applications the patients were receiving were continued. On 24-hour Holter recording days, patients were instructed to record all activities throughout the day with corresponding times.

Arrhythmias were evaluated using the 24-hour Holter recordings by the principal investigator, who specializes in both cardiology and physical medicine and rehabilitation. In addition, the types and durations of exercises applied to the patients were recorded, and the maximum heart rates observed during these periods were compared with patients' resting heart rates.

Statistical Analysis

The obtained data were analyzed using the SPSS program. The distribution normality of the data was evaluated with the Shapiro-Wilk test. McNemar test was used to compare categorical dependent variables, and Wilcoxon signed rank test was used for repeated measurement comparisons of dependent groups. A p-value of <0.05 was considered statistically significant.

Table 1. Clinical characteristics of the patients

Variables	n	%	Mean±SD (min-max)
Age (year)			58±14.5 (22-86)
BMI (kg/m ²)			28.7±5.7 (15.2-46.7)
Smokers	25	39.7	
Alcohol users	8	12.7	
Comorbidities			
Hypertension	30	47.6	
Hyperlipidemia	24	38.1	
Diabetes mellitus	11	17.5	
Coronary artery disease	11	17.5	
Cerebrovascular disease	16	25.4	
Pulmonary disease	9	14.3	
Thyroid disease	9	14.3	
Drugs used			
Analgesics	46	73	
Antihypertensives	30	47.6	
Negative Chronotropic Drugs	14	22.2	
Levothyroxine	9	14.3	
Beta agonists	8	12.7	
10-year risk for ASCVD			
Low risk	24	41.4	
Borderline risk	8	13.8	
Moderate risk	14	24.1	
High risk	12	20.7	

ASCVD: atherosclerotic cardiovascular disease. Chronotropic Drugs: Beta blockers, digoxin, non-dihydropyridine calcium channel blocker, amiodarone.

Results

A total of 203 patients were screened to determine eligibility, and 78 met the criteria to participate. The second 24-hour Holter recordings could not be performed and were excluded from the study, as 12 patients had

a hospital stay shorter than 3 weeks, 1 patient had tuberculosis, 1 patient had coronavirus disease 2019 (COVID-19), and 1 patient was referred to another clinic because of acute myocardial infarction. Data of 63 patients, 41 (65.1%) women and 22 (34.9%) men, were analyzed. Table 1 presents patients' age, body mass index, smoking and alcohol use, comorbidities, medications that may affect heart rate and blood pressure, and 10-year atherosclerotic cardiovascular risk levels.

The frequency of patients with arrhythmia according to the first and second 24-hour Holter recordings is shown in Table 2. None of these arrhythmias were symptomatic. Multifocal atrial tachycardia, atrial flutter, atrial fibrillation, atrioventricular nodal tachycardia, atrioventricular nodal reentrant tachycardia, sustained ventricular tachycardia, Torsades de Pointes, and ventricular fibrillation were not detected in any of the patients in the first and second 24-hour Holter recordings.

No statistically significant difference was observed between the first and second 24-hour Holter recordings in terms of heart rate (resting, maximum, and minimum) and the number of supraventricular premature beats, ventricular premature beats, ventricular bigeminy, ventricular trigeminy, ventricular couplets, and nonsustained ventricular tachycardia (Table 3) ($p>0.05$).

When the maximum heart rate values during different exercise types and the differences compared to resting heart rate were evaluated, it was observed that the highest heart rate (116.5 ± 24.45 bpm) occurred during isotonic exercises, with an average increase of 38.87 ± 21.49 beats compared to resting heart rate. This was followed by aerobic, balance, range of motion, isometric, stretching, and breathing exercises, respectively (Table 4).

Table 2. Comparison of the frequency of patients with arrhythmia in the first and second 24-hour Holter recordings

Variables	First 24-hour Holter recording n (%)	Second 24-hour Holter recording n (%)	*p
Supraventricular premature beats	41 (65.1)	45 (71.4)	0.424
Ventricular premature beats	32 (50.8)	31 (49.2)	1.00
Ventricular bigeminy	7 (11.1)	8 (12.7)	1.00
Ventricular trigeminy	7 (11.1)	9 (14.3)	0.687
Ventricular couplet	10 (15.9)	9 (14.3)	1.00
Nonsustained ventricular tachycardia	6 (9.5)	6 (9.5)	1.00
Frequent (>1000) ventricular premature beats	6 (9.5)	6 (9.5)	1.00
Sinus pause (>1.8 seconds)	7 (11.1)	8 (12.7)	1.00

*p value by McNemar test. Statistically significant p-value < 0.05.

Table 3. Analysis of the number of the arrhythmias and the heart rates detected in the first and second 24-hour Holter recordings

Variables	First 24-hour Holter recording	Second 24-hour Holter recording	p*
	Mean±SD Median (min-max)	Mean±SD Median (min-max)	
Number of supraventricular premature beats/24 h	899.46±2359.77 14 (0-13165)	706.84±2362.68 37 (0-13300)	0.389
Number of ventricular premature beats/24 h	456.06±1449.96 2 (0-8159)	457.92±1667.09 0 (0-9919)	0.572
Number of ventricular bigeminy/24 h	5.54±35.26 0 (0-276)	4.87±30.65 0 (0-241)	0.918
Number of ventricular trigemini/24 h	12.92±81.32 0 (0-629)	17.92±112.47 0 (0-884)	0.385
Number of ventricular couplets/24 h	4.73±24.79 0 (0-189)	3.62±15.33 0 (0-107)	0.559
Number of nonsustained ventricular tachycardia/24h	2.11±14.55 0 (0-115)	0.48±2.21 0 (0-15)	0.876
Resting heart rate (bpm)	77.69±9.84 78 (50-100)	78.17±9.62 79 (56-105)	0.886
Maximum heart rate (bpm)	119.28±20.30 118 (78-170)	119.49±21.08 120 (75-184)	0.997
Minimum heart rate (bpm)	55.04±9.06 56 (35-72)	53.80±9.02 54 (35-76)	0.107

*p value by Wilcoxon signed rank test. Statistically significant p-value < 0.05.

Table 4. Maximum heart rates detected during exercises and their differences compared to resting heart rates

Type of exercises	n (%)	Maximum heart rate during exercise (bpm) Mean±SD (min-max)	Difference with resting heart rate (bpm) Mean±SD (min-max)
Range of motion exercise	50 (79.4)	95.48±13.04 (73-123)	19.62±10.81 (0-45)
Isometric strengthening exercise	46 (73)	98.84±13.77 (72-142)	22.73±11.82 (1-64)
Isotonic strengthening exercise	8 (12.7)	116.5±24.45 (86-150)	38.87±21.49 (16-72)
Balance exercise	35 (55.6)	103.51±20.09 (73-165)	27.74±17.16 [(-2)-87]
Stretching exercise	24 (38.1)	93.87±12.63 (72-123)	16.04±12.12 [(-3)-49]
Aerobic exercise	4 (6.3)	106±11.22 (91-118)	27.75±4.99 (23-33)
Breathing exercises	13 (20.6)	86.07±16.14 (60-111)	13.30±13.51 [(-4)-36]

Discussion

In the current study, heart rhythms were observed with 24-hour Holter recordings at admission and after 3 weeks of treatment in inpatient physical therapy and rehabilitation patients. While the frequency of supraventricular and ventricular premature beats was 65.1% and 50.8%, respectively, in the first 24-hour Holter recordings, arrhythmias with greater clinical importance—such as

ventricular bigeminy, ventricular trigeminy, ventricular couplets, nonsustained ventricular tachycardia, >1000 ventricular premature beats, and sinus pause (>1.8 seconds)—were observed in approximately 1 out of every 10 patients, and these rates were higher than those in the general healthy population [13].

In their study of 24-hour Holter ECG recordings in healthy adults, Hingorani et al. [13] observed supraventricular

premature beats in 60.8% of volunteers, ventricular premature beats in 43.4%, multifocal premature ventricular beats in 5.3%, >200 ventricular premature beats in 3.3%, supraventricular tachycardia in 2.2%, nonsustained ventricular tachycardia in 0.7%, and sinus pause for >3 seconds in 0.3%. This indicates that inpatient physical therapy and rehabilitation patients constitute a high-risk group in terms of complex arrhythmias.

However, when the first and second Holter recordings were compared, it was observed that physical agents and exercises did not increase cardiac arrhythmias. In addition, nearly half of the patients were at moderate or high risk for atherosclerotic cardiovascular disease. Moreover, one patient (excluded) experienced a heart attack while the study was in progress. For these reasons, meticulous monitoring of inpatient physical therapy and rehabilitation patients for cardiac signs and symptoms is essential.

The main purpose of patient rehabilitation is to improve the functional status of patients, and the main options used are therapeutic exercise and physical agents, in addition to medical treatment. Although the treatments applied in physical therapy and rehabilitation clinics usually do not involve a high risk of adverse events, this should not mean that there is no risk at all. Studies have shown that the most common adverse event in patients receiving inpatient rehabilitation is falling [5-7]. However, the risk of life-threatening complications is <1%, which is quite low, and deaths occur mainly due to cardiac and pulmonary causes [3,14]. It is important to determine the cardiovascular risk factors of patients as well as to assess known cardiovascular diseases at the time of admission to prevent these cardiovascular adverse events. When defining pre-exercise screening procedures in the Australian Sports Medicine system, 43–73% of men and 44–61% of women stated that they would need medical screening [15]. Typically, hyperlipidemia, hypertension, smoking, diabetes mellitus, and obesity are risk factors for cardiovascular disease [16]. Kirkness et al. [17] found the prevalence of hypertension and diabetes in patients referred for outpatient physical therapy to be 70.4% and 13.2%, respectively. In the current study, the prevalence of hypertension, hyperlipidemia, diabetes, and coronary artery disease was 47.6%, 38.1%, 17.5%, and 17.5%, respectively. In addition, 44.8% of patients had a moderate or high 10-year ASCVD risk. On the other hand, studies have shown that the rate of routine evaluation of vital signs in physical therapy and rehabilitation practice is as low as 14.8–50% [18-20].

Increased exercise and physical activity levels are associated with a reduced risk of cardiovascular disease, including myocardial infarction, cardiovascular disease-related death, and all-cause death, although the potential adverse effects of vigorous exercise levels and the ideal intensities of exercises continue to be explored [21]. Vigorous exercise may pose various cardiovascular risks, especially in individuals with cardiovascular or structural heart diseases, and in physically inactive individuals when exercise is not graded or when the exercise prescription is not individually adapted [22]. One of the most important pieces of evidence regarding the safety of rehabilitation programs is whether cardiac arrhythmia is observed during and after treatment. Benninghoven et al. [23] evaluated cardiac arrhythmias such as atrial fibrillation, ventricular tachycardia, and cardiac syncope in patients with Marfan syndrome by monitoring them during personalized exercises in a 3-week inpatient rehabilitation program and reported that no side effects disrupting the heart rhythm of the patients were observed.

In recent years, the use of 24-hour Holter ECG recordings has become increasingly common due to their ability to detect transient and infrequent arrhythmias in cardiac safety studies for both drugs and interventions. We also preferred to perform 24-hour Holter ECG follow-up before and during the 3rd week of inpatient rehabilitation in order to document whether there were cardiac rhythm abnormalities, symptomatic or otherwise. According to the first 24-hour Holter recordings, the arrhythmia rates observed in the patients were higher than in the normal healthy population. While the percentages of supraventricular premature beats, ventricular premature beats, ventricular bigeminy, ventricular trigeminy, nonsustained ventricular tachycardia, and sinus pause were 60.8, 43.4, 0.6, 0.5, 0.7, and 4, respectively, in a 24-hour Holter examination by Hingorani et al. [13] in healthy volunteers aged 18–65 years, these percentages were 65.1, 50.8, 11.1, 11.1, 9.5, and 11.1, respectively, in the current study.

Although it is accepted that supraventricular and ventricular extra beats in healthy individuals are not prognostic, recent studies show that high-frequency ventricular premature beats are associated with an increased risk of heart failure and death in individuals with normal ejection fraction [24,25]. In particular, more is known about the prognostic value of ventricular beats in relation to subsequent arrhythmic events and sudden death in people with myocardial pathologies. The Lown classification is valuable for understanding the prognostic

value of ventricular premature beats. In this system, in which ventricular premature beats are classified according to their frequency and origin, Lown class 3 and above—that is, multiform ventricular premature beats, ventricular couplets, ventricular tachycardia of ≥ 3 beats, and early-cycle ventricular premature beats—are predictors for all-cause deaths after acute myocardial infarction [26,27].

In the current study, the incidence of ventricular tachycardia with a frequency of 15.9%, ventricular couplets with a frequency of 9.5%, and frequent ventricular premature beats with a frequency of 9.5% in inpatient physical therapy and rehabilitation patients is important for demonstrating the risk level of this patient group in terms of cardiac arrhythmias. Therefore, the holistic evaluation of patients by physicians is very important for proper management.

Irsay et al. [28] stated that in patients with degenerative knee osteoarthritis with or without heart disease, no significant increase was observed in heart rate, supraventricular premature beats, or ventricular premature beats during and immediately after electrotherapy with 24-hour Holter recording. Similarly, in this study, it was observed that there was no significant increase in the number and incidence of arrhythmias during physical therapy and rehabilitation in inpatients.

Changes in heart rate and blood pressure during exercise types differ due to the varying autonomic responses to dynamic and static exercises. In our study, the increase in heart rate compared to rest during different exercise types was evaluated, and it was seen that the exercise that caused the highest increase in heart rate was isotonic strengthening exercise. Iellamo et al. [29] also stated that isotonic exercise increased heart rate 50% more than isometric exercise. In our study, aerobic and balance exercises were observed to be the other exercise types that caused the highest increase in heart rate following isotonic exercise. In fact, it is expected that more cardiovascular load would develop during aerobic exercises, since only one extremity muscle is used during isotonic exercises, whereas all body muscles are engaged during aerobic exercises. However, in our study, aerobic exercises were applied with monitoring within the predetermined heart rate limits; therefore, it is not appropriate to evaluate them as the exercise type with the highest heart rate increase. On the other hand, it is noteworthy that the heart rate increase observed in isotonic and balance exercises was comparable to the target heart rate level in aerobic exercises. This finding raises the question of whether monitoring may also be required during some exercises

other than aerobic exercises, especially in patients with high cardiovascular risk.

The study had a prospective design that provided objective and comparable data with Holter recordings before and during treatment. Twenty-four-hour Holter recording is an effective method to analyze arrhythmias in detail and to increase the reliability of the results [30]. The standardization of the time interval between Holter recordings for all patients enhanced the homogeneity of the results. In addition to these advantages, our study also had some limitations. The sample size was not calculated, as all eligible patients within the given time period were included. The 21-day study focused on short-term effects and did not provide information on long-term outcomes. The study was limited to a single clinic; therefore, the generalizability of the results to other centers is restricted. Furthermore, the types and specific indications of the physical agents used, as well as the body parts to which they were applied, were not recorded, limiting the ability to examine treatment-related changes in detail. Future studies with larger sample sizes and subgroup analyses may provide more comprehensive information about the cardiac safety of physical medicine and rehabilitation treatments, taking into account different indications, types of physical agents, and application sites.

Conclusion

A significant portion of the population served in inpatient physical therapy and rehabilitation consists of patients of advanced age with various comorbidities and drug use that can affect heart rhythm. The incidence of arrhythmia in these patients is higher than in the general healthy population. No increase in cardiac arrhythmias was observed during and after the application of physical agents and exercises in our study population. However, considering the high risk of cardiovascular disease, it is recommended that this patient group be followed meticulously for cardiac symptoms and signs.

Ethics Committee Approval: The study was approved by Trakya University Clinical Research Ethics Committee (No: TUTF-BAEK 2021/423, Date: 15.11.2021).

Conflict of Interest: The authors declare that there is no conflict of interest.

Informed Consent: The study's participants gave their written informed consent.

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Incidence and Size of the Fossa Navicularis in Chiari Type I Malformation

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Abstract

Introduction: This study aimed to compare the morphology of the fossa navicularis (FN) in patients with Chiari type I malformation (CIM) and healthy subjects.

Methods: Radiologic views of 50 CIM patients (21 men/29 women) with a mean age of 26.93 ± 16.03 years and 50 healthy subjects (29 men/21 women) with a mean age of 33.13 ± 21.40 years were included in this computed tomography study. The presence or absence of FN was noted, and the depth (FN-D), width (FN-W), and length (FN-L) of FN, as well as the clivus length (CL), were measured.

Results: FN was observed in 14 CIM patients (28%) and in eight controls (16%). In CIM patients, FN-L, FN-W, FN-D, and CL were measured as 3.62 ± 1.64 mm, 4.91 ± 1.31 mm, 2.71 ± 1.06 mm, and 43.45 ± 5.62 mm, respectively. In controls, FN-L, FN-W, FN-D, and CL were measured as 4.95 ± 1.18 mm, 3.42 ± 0.97 mm, 1.98 ± 1.22 mm, and 48.01 ± 3.51 mm, respectively. CIM subjects had greater FN-W ($p=0.008$) but smaller CL ($p=0.042$). FN-L ($p=0.059$) and FN-D ($p=0.070$) were similar between the groups. In CIM patients, all parameters were similar between sexes. In controls, men had greater FN-L compared to women ($p=0.029$).

Discussion and Conclusion: CIM patients had greater FN-W compared to controls. FN incidence was not affected by CIM. These findings may help clinicians better understand clivus anatomy in CIM patients.

Keywords: Chiari type I malformation; clivus; fossa navicularis.

The fossa navicularis (FN) — also referred to as the large pharyngeal fossa, fossa pharyngea, medial basal fossa, keyhole defect, and fossa navicularis magna — is a small pit situated on the lower surface of the clivus, anterior to the pharyngeal tubercle [1–6]. Clinicians may encounter FN incidentally on radiologic views, as its incidence has been reported between 3.04–27.50% [1,3,7]. Although rare,

FN has clinical implications [3,8]. FN-related pathologic entities include sphenoidal sinus mucocoele, Thornwaldt's cyst, Rathke pouch cyst, adenoid hypertrophy, adenoid retention cyst, and local or metastatic tumors [3]. Due to its close relationship with the nasopharynx, this small pit may facilitate the spread of infection from the pharyngeal region to the intracranial area [8]. Therefore, clinicians

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should be well aware of FN morphology to understand its possible role in various diseases.

Chiari type I malformation (CIM) is defined as the downward herniation of the cerebellar tonsils through the foramen magnum [9]. This malformation has a prevalence of 0.24–3.6% [10]. The primary cause of this anomaly is believed to be deviations in the development of the occipital somite, which originates from the paraxial mesoderm [11]. This malformation primarily affects the bony structures of the posterior cranial base and causes approximately a ¼ reduction in its volume [11,12]. This volumetric reduction may lead to overcrowding of the hindbrain and diverse symptoms [9,11,12]. One of the bony structures most affected by CIM is the clivus [13,14]. Despite the obvious changes in clivus morphology, no study systematically focusing on clivus variations (including FN or canalis basilaris medianus) in patients with CIM has been encountered in the literature. In this regard, our main aim is to evaluate the incidence and dimensions of FN in CIM to improve current knowledge regarding the morphometric features of the cranial base.

Previous research has established an association between CIM and morphometric alterations in skull base bony structures [11,12]. Numerous studies have specifically demonstrated structural deviations in the cranio-cervical junction and clivus compared with the normal population [11,14]. Therefore, the present study was designed to investigate the morphological impact of CIM on the fossa navicularis, a component of the cranial base and cranio-cervical junction [11,12,14].

Materials and Methods

Study Population

The Clinical Research Ethics Committee approved our retrospective examination (confirmation no: I10-711-23, date: 21.11.2023). All participants provided informed consent, and the study was conducted in accordance with the principles outlined in the Helsinki Declaration, ensuring ethical standards throughout the research process. Subject folders were reviewed according to the study criteria (Table 1). Patient files included the following information: cranial computed tomography (CT) and magnetic resonance imaging (MRI) views, sex, age, treatment and diagnostic procedures, hospital admission/discharge dates, and complaints. Cases without a history of meningocele but exhibiting tonsillar herniation >5 mm downward from the foramen magnum were accepted as CIM. The study population was divided into two groups: CIM and controls.

CT Protocol

A 64-row multidetector scanner (Aquillion 64, Toshiba Medical Systems, Tokyo, Japan; 0.3-mm interval, 120 kV, 230 mA, 0.5-mm slice thickness, pixel size 0.46 mm, field of view 240 mm, and matrix 512×512) was used to acquire radiologic data. The raw data were processed to obtain coronal, axial, and sagittal images, which were then reformatted to acquire three-dimensional (3D) images. Study parameters were measured using the RadiAnt DICOM Viewer.

Table 1. The inclusion and exclusion criteria for the study populations.

Criteria	CIM	Controls
Inclusion criteria	Patients with CIM Patients without a history of surgical intervention around the clivus Patients with good quality CT images	Patients without malformations (syndromic or genetic) Patients without fractures, infections, tumors Patients without a history of surgical intervention around the clivus Patients without a history of medical treatment related to the clivus Patients with good quality CT images
Exclusion criteria	Patients with the other types of Chiari malformation Patients with a history of surgical intervention around the clivus Patients with low quality CT images	Patients with malformations (syndromic or genetic) Patients with fractures, infections, tumors patients with a history of surgical intervention around the clivus Patients with a history of medical treatment related to the clivus Patients with low quality CT images

CT: Computed tomography; CIM: Chiari type I malformation.

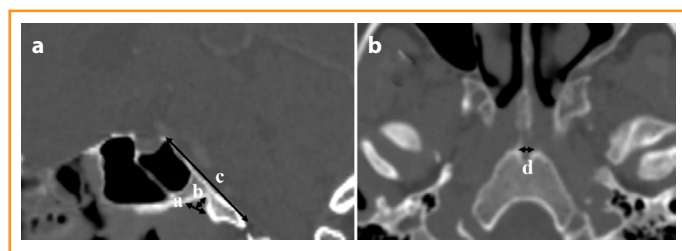


Figure 1. The measurements. **(a)** FN-L, (Length of the fossa navicularis) **(b)** FN-D, (Depth of the fossa navicularis), **(c)** CL (Length of Clivus), and **(d)** FN-W (Width of the fossa navicularis).

Study Parameters

The presence or absence of FN was noted, and the depth (FN-D), width (FN-W), and length (FN-L) of FN, as well as the clivus length (CL), were measured. Descriptions of the measured parameters were as follows (Fig. 1):

- FN-L: FN's sagittal diameter (i.e., the farthest distance in the anteroposterior direction on sagittal CT views)
- FN-W: FN's transverse diameter (i.e., the farthest distance in the mediolateral direction on axial CT views)
- FN-D: FN's depth (i.e., the distance at the deepest part of FN on sagittal CT views)
- CL: Clivus length (i.e., the furthest diagonal distance between the basion and dorsum sellae on sagittal CT views)

Statistical Analysis

Correlations between FN-D, FN-W, FN-L, and CL were analyzed using the Pearson correlation coefficient test. Sex and group comparisons were carried out using the independent student's t-test. The relationship of FN incidence with the study groups was evaluated using the Chi-square test. The normality of data was assessed using the Shapiro-Wilk test. Statistical evaluations were performed using SPSS version 22.0 (IBM, Armonk, NY). A $p < 0.05$ was considered significant.

Table 2. Comparisons of CIM and controls

Parameters	CIM (N=14)	Controls (N=8)	p
FN-L (mm)	3.62±1.64	4.95±1.18	0.0591
FN-W (mm)	4.91±1.31	3.42±0.97	0.0081
FN-D (mm)	2.71±1.06	1.98±1.22	0.0701
CL (mm)	43.45±5.62	48.01±3.51	0.0421

N: numbers of subjects, CIM: Chiari type I malformation, FN-L: fossa navicularis length, FN-W: fossa navicularis width, FN-D: fossa navicularis depth, CL: clivus length

Results

The CIM group consisted of 50 patients (21 men/29 women) with a mean age of 26.93 ± 16.03 years. The control group consisted of 50 healthy subjects (29 men/21 women) with a mean age of 33.13 ± 21.40 years. Our findings are as follows:

- In CIM, FN was observed in 14 patients (28%), while in controls, FN was found in eight subjects (16%).
- Compared with controls, CIM subjects had greater FN-W ($p=0.008$) but smaller CL ($p=0.042$). FN-L ($p=0.059$) and FN-D ($p=0.070$) were similar between the groups (Table 2).
- In CIM, all parameters were similar between sexes ($p > 0.05$). In controls, all parameters except FN-L were similar between sexes ($p > 0.05$). Men had greater FN-L compared with women ($p=0.029$) (Table 3).
- In CIM, a positive correlation was found between FN-W and FN-D ($p=0.048$, $r=0.537$). In controls, a positive correlation was found between FN-L and FN-D ($p=0.045$, $r=0.719$) (Table 4).
- The distribution of FN presence and absence according to study groups is presented in Table 5, which showed that FN incidence was not affected by CIM ($p=0.227$).

Table 3. Sex comparison for CIM and controls.

Parameters	CIM			Controls		
	Females (N=9)	Males (N=5)	p	Females (N=4)	Males (N=4)	p
FN-L (mm)	3.58±1.47	3.70±2.11	0.898	4.07±0.75	5.83±0.80	0.0291
FN-W (mm)	4.76±1.22	5.20±1.59	0.438	2.92±0.62	3.93±1.07	0.2001
FN-D (mm)	2.38±1.01	3.32±0.96	0.147	1.47±0.30	2.49±1.65	0.1141
CL (mm)	42.73±6.14	44.74±4.89	0.606	46.82±2.71	49.20±4.20	0.4861

N: numbers of subjects; CIM: Chiari type I malformation; FN-L: fossa navicularis length; FN-W: fossa navicularis width; FN-D: fossa navicularis depth; CL: clivus length.

Table 4. Correlations between the parameters for CIM and controls

Groups	Parameters	FN-W (mm)	FN-D (mm)	CL (mm)
CIM	FN-L (mm)	0.392	0.090	0.138
		0.166	0.759	0.637
	FN-W (mm)		0.537*	-0.240
			0.048	0.409
	FN-D (mm)			-0.262
Controls	Parameters	FN-W (mm)	FN-D (mm)	CL (mm)
	FN-L (mm)	0.333	0.719*	-0.071
		0.420	0.045	0.867
	FN-W (mm)		0.539	0.571
			0.168	0.139
	FN-D (mm)			0.168
				0.691

CIM: Chiari type I malformation, FN-L: fossa navicularis lenght, FN-W: fossa navicularis width, FN- D: fossa navicularis depth, CL: clivus lenght.

Table 5. Distribution of FN incidence in CIM and controls.

	CIM	Control	Total	p
Presence	14 (28%)	8 (16%)	22	0.227
Absence	36 (72%)	42 (84%)	78	
Total	50	50	100	

FN: fossa navicularis; CIM: Chiari type I malformation.

Discussion

Recent publications focusing on skull base morphology in CIM suggest that, presumably due to a mesodermal defect, CIM substantially affects the bony components of the entire cranial base [14,15]. For instance, subjects with CIM have been shown to possess a smaller sella volume and area, a greater angle of the optic canal in the axial plane, a shorter and wide-angled anterior clinoid process, a longer optic strut, a longer anterior fossa, and a more pneumatized posterior clinoid process compared with healthy controls [14–18]. Some studies have investigated morphometric features of the cranium in an effort to determine additional signs specific to CIM [14].

In the present study, we observed that CIM subjects (43.45 ± 5.62 mm) had a smaller CL ($p=0.042$) compared with controls (48.01 ± 3.51 mm). Nwotchouang et al. [14] reported a smaller CL in CIM (43.6 ± 3.9 mm) compared to controls (47.3 ± 3.1 mm) ($p<0.001$). Similarly, Milhorat et al. [13] found reduced CL in this malformation (CIM: 36.6 ± 4.2 mm; control: 40.4 ± 5.1 mm). Our results are consistent with the findings in the literature. Nwotchouang et al. [14] also noted that CIM subjects had significantly smaller clivus thickness, surface area, volume, width, and height compared with controls. Shah and Goel [19] described clival dysgenesis in an 11-year-old boy with CIM, emphasizing that this anomaly should not be confused with FN, since the lateral parts of FN are ossified.

Therefore, we believe that novel studies focusing on FN morphology in patients with different malformations such

Table 6. Data related to FN in the literature

Study	Samples	Methods	Numbers	Incidence of FN	FN-L (mm)	FN-D (mm)	FN-W (mm)
Magat [6]	Patients	CBCT	168	46 (27.50%)	8.55 ± 3.19	2.22 ± 0.98	5.37 ± 2.06
Bayrak et al. [1]	Patients	CBCT	649	59 (9.08%)	7.15 ± 1.80	2.76 ± 1.09	5.23 ± 1.57
	CT	410	23 (5.60%)	4.12 ± 0.52	4.17 ± 0.54	4.08 ± 0.47	
Ersan [28]	Patients	CBCT	723	48 (6.60%)	5.80 ± 2.20	2.20 ± 1.00	4.70 ± 1.40
Aktan-İkiz et al. [30]	Dry skull	Dry skull	95	6 (6.30%)	6.50 ± 1.73	1.58 ± 0.84	4.66 ± 1.43
Cankal et al. [3]	Patients	CT	525	16 (3.04%)	-	-	-
	Dry skull	Dry skull	492	26 (5.28%)	-	-	-
	All	All	1017	42 (8.32%)	$5.12 (1.79-9.33)$	$2.24 (1.10-4.11)$	$2.85 (1.50-3.90)$
Adanır et al. [7]	Patients	CBCT	900	122 (13.55%)	4.04 ± 1.71	1.79 ± 0.68	4.28 ± 1.34
Serindere et al. [29]	Patients	CT	500	27 (5.40%)	3.77 ± 2.15	4.96 ± 2.73	3.48 ± 1.11
Akbulut et al. [27]	Patients	CBCT	500	130 (26%)	4.65 ± 1.93	1.87 ± 0.66	4.47 ± 1.61
This study	CIM	CT	50	14 (28%)	3.62 ± 1.64	2.71 ± 1.06	4.91 ± 1.31
	Controls	CT	50	8 (16%)	4.95 ± 1.18	1.98 ± 1.22	3.42 ± 0.97

CIM: Chiari type I malformation, FN-L: fossa navicularis lenght, FN-W: fossa navicularis width, FN- D: fossa navicularis depth, CT: computed tomography, CBCT: cone beam computed tomography.

as CIM are necessary to determine whether the anatomical properties of FN are altered in CIM compared with healthy individuals.

In the literature, FN formation is explained by two different theories: first, the fossa is considered to be the remnant of an emissary vein's opening, and second, the remnant of the notochord canal [1,8,10]. In utero, the notochord moves downward and connects with the primitive pharynx endoderm before reaching the precordial plate. At this stage, Seessel's pocket is formed by the spread of the pharyngeal mucosa toward the brain. During the notochord's ascension, central adhesions may develop between the endoderm and notochord, causing part of the pharyngeal mucosa to be carried along with the notochord toward the developing cranial base. Thus, a diverticulum (also known as Tornwaldt's bursa or pharyngeal bursa) covered by pharyngeal mucosa is seen in the midline. Obstruction of the opening of this diverticulum for any reason may result in a Tornwaldt's cyst [3,20,21]. This pathology is usually asymptomatic, but infection or enlargement may cause eustachian tube dysfunction, neck stiffness, headache, halitosis, postnasal drip, or nasal obstruction [20,22,23]. The pharyngeal bursa and tubercle lie posterior to FN.[3] Therefore, certain clinicians suggest that there may be a connection between clivus anomalies or variations (including FN) and Tornwaldt's cyst [3,8,24,25].

On the other hand, FN may be a route for the spread of infection from the pharyngeal region to the intracranial area [3,8]. For example, Segal et al. [26] presented a 12-year-old girl with bacterial meningitis and stated that the patent FN caused the spread of infection from the pharynx to the intracranial region. Prabhu et al. [10] reported a 5-year-old girl with clival osteomyelitis and a retropharyngeal abscess situated in FN. Thus, clinicians recommend examining the presence of FN in cases of clival osteomyelitis, meningitis, or skull-base infection [7,26].

In this study, a significant increase in the width of the fossa navicularis (FN-W) was observed in patients with Chiari type 1 malformation (CIM). Embryological anomalies affecting the development of the skull base, particularly involving the posterior cranial fossa and the clivus, have been well documented in CIM, highlighting disruptions in normal ossification processes and cranio-cervical morphogenesis [13,14]. There are two primary embryological theories explaining FN formation: one proposing that the FN represents a remnant of the notochordal canal, and another suggesting that it originates from persistent openings

associated with emissary veins during embryological development. The mesodermal defects inherent to CIM might disrupt normal ossification and developmental dynamics of the skull base, potentially leading to altered dimensions or exaggerated anatomical variations, such as the enlarged FN observed in our CIM cohort. However, due to the cross-sectional and retrospective design of our study, the findings do not conclusively determine whether these observed differences in FN morphology are a direct consequence of CIM or whether both conditions stem from a common embryological anomaly. To definitively establish a causal relationship between FN characteristics and CIM, future prospective longitudinal studies, as well as experimental embryological investigations, are warranted [1,8,10,13,14].

FN was observed in 14 patients (28%) with CIM, whereas FN was found in eight subjects (16%) in controls. The distribution of FN presence and absence according to study groups showed that its incidence was not affected by CIM ($p=0.227$). Our incidence rates for both groups were compatible with previous studies (Table 6) [1,3,6,7,27–30]. In those studies, FN incidence was reported between 3.04–27.50%.

In CIM, FN-L, FN-W, and FN-D were measured as 3.62 ± 1.64 mm, 4.91 ± 1.31 mm, and 2.71 ± 1.06 mm, respectively. In controls, FN-L, FN-W, and FN-D were measured as 4.95 ± 1.18 mm, 3.42 ± 0.97 mm, and 1.98 ± 1.22 mm, respectively. CIM subjects had greater FN-W ($p=0.008$), while FN-L ($p=0.059$) and FN-D ($p=0.070$) were similar between the groups. Our mean values for both groups were consistent with previous studies (Table 6) [1,3,6,7,27–29]. In those reports, the average range was presented as 3.77–8.88 mm for FN-L, 1.58–4.96 mm for FN-D, and 3.48–5.37 mm for FN-W.

In CIM, all parameters were similar between sexes. In controls, men had greater FN-L compared with women ($p=0.029$). Similarly, Bayrak et al. [1] observed greater FN-L in men (7.86 ± 1.88 mm) compared with women (6.76 ± 1.65 mm). FN incidence and size have been reported within a wide range in the literature, probably due to differences in study methods (radiologic vs direct anatomic examinations), demographic features (race, sex, etc.), and sample selections (patients vs dry skulls) [1,3,6,28]. For example, FN incidence determined on CT or cone-beam CT images may be lower than that detected on dry skulls, since it can sometimes be difficult to identify FNs with a depth <2 mm radiologically [3]. Ersan [28] observed a higher incidence in males (29 subjects) compared with females (19 subjects) ($p<0.05$).

Conclusion

CIM subjects had greater FN-W ($p=0.008$) but smaller CL ($p=0.042$). FN incidence was not affected by CIM ($p=0.227$). Our results may help clinicians better understand clivus anatomy in CIM patients.

Ethics Committee Approval: The study was approved by Ankara University Ethics Committee (No: I10-711-23, Date: 21.11.2023).

Conflict of Interest: The authors declare that there is no conflict of interest.

Informed Consent: Approval from the Institutional Review Board was obtained and in keeping with the policies for a retrospective review, informed consent was not required.

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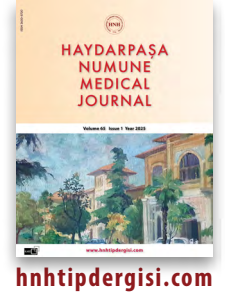
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Does Advanced Obesity Affect CABG Surgery Outcomes?

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Abstract

Introduction: Obesity has been identified as a key risk factor for coronary artery bypass grafting (CABG) surgery. This study examines the short-term effects of obesity on clinical outcomes and mortality following CABG.

Methods: A total of 216 CABG patients were recruited and categorized into two groups according to body mass index (BMI): ≥ 35 kg/m² and < 35 kg/m². Preoperative data included age, sex, height, weight, EuroSCORE II, diabetes mellitus (DM), hyperlipidemia (HL), chronic obstructive pulmonary disease (COPD), ejection fraction (EF), and smoking status. Postoperative outcomes included intubation time, intensive care unit (ICU) stay, wound complications, sternal separation, atrial fibrillation (AF), cerebrovascular disease (CVD), pleural effusion (PE), mortality, and reoperation.

Results: Patients with BMI ≥ 35 kg/m² had higher rates of DM, hypertension, HL, COPD, smoking, and EuroSCORE II scores, while EF scores were lower. In this group, the durations of intubation, ICU stay, and hospital stay were longer; wound complications, sternal separation, atrial fibrillation, and pulmonary embolism were more frequent. Obesity was identified as an independent risk factor for prolonged ICU stay (OR: 5.16; 95% CI: 1.39–19.17; p=0.014). No significant difference in mortality rates was observed between the two groups.

Discussion and Conclusion: Although early mortality is not affected in obese patients with BMI ≥ 35 kg/m², the durations of intubation, ICU stay, and hospital stay are prolonged; wound healing problems, sternal separation, AF, and PE incidence are increased.

Keywords: Atrial fibrillation; body mass index; coronary artery bypass grafting; mortality; obesity; pulmonary embolism.

Obesity is a chronic disease whose prevalence is on the rise and is now a global epidemic ^[1]. This increase has been attributed primarily to sedentary lifestyles, unhealthy dietary habits, and changing socioeconomic structures ^[2]. Obesity is a multifaceted condition that has been demonstrated to be a risk factor for the development of cardiometabolic diseases. These diseases include, but

are not limited to, hypertension, heart failure, peripheral arterial disease, atrial fibrillation, and coronary disease ^[3]. As a result, the need for coronary artery bypass grafting (CABG) is increasing in obese individuals. The importance of revascularization in patients with severe comorbidities has been clearly emphasized in the literature ^[4]. In clinical practice, obesity is often considered a surgical risk factor.

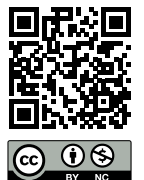
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Recent studies have suggested that overweight or class I obese patients ($\text{BMI}=30\text{--}34.9\text{ kg/m}^2$) may have better outcomes after CABG compared to non-obese individuals, which could be explained by the "obesity paradox". However, results in patients with class II and III obesity ($\text{BMI}\geq 35\text{ kg/m}^2$) are inconsistent [5,6]. The widespread prevalence of obesity in the general population necessitates an examination of its effects on clinical outcomes of CABG procedures, with particular emphasis on high-risk patient demographics. This research aimed to evaluate the initial clinical outcomes after CABG in obese individuals with a $\text{BMI}\geq 35\text{ kg/m}^2$.

Materials and Methods

In this study, patients who underwent CABG surgery at Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Hospital between 2020 and 2023 and had a body mass index ($\text{BMI}\geq 35\text{ kg/m}^2$) were retrospectively evaluated. The study included patients who underwent isolated CABG surgery. Patients with a history of previous cardiac surgery, emergency surgery, minimally invasive surgery, or chronic renal failure were excluded from the study.

The study comprised 122 patients who underwent surgery from November to December 2023 and fulfilled the established criteria. A total of 100 patients who underwent CABG surgery were randomly selected from the hospital database using the RAND function in Excel. A grand total of 100 patients were initially considered, from which individuals with a $\text{BMI}<35\text{ kg/m}^2$ were excluded, resulting in a control cohort of 94 patients. The study examined data from 216 patients.

Patients were categorized into two groups based on the World Health Organization's classification system for obesity to maintain a standardized approach. A $\text{BMI}\geq 35\text{ kg/m}^2$ indicates Class II obesity ($35\text{--}39.9\text{ kg/m}^2$) or Class III obesity ($\geq 40\text{ kg/m}^2$). The classification of body mass index (BMI) is as follows: Class I obesity is defined as a $\text{BMI}=30\text{--}34.9\text{ kg/m}^2$; overweight is categorized as a $\text{BMI}=25\text{--}29.9\text{ kg/m}^2$; normal weight ranges from $\text{BMI}=18.5\text{--}24.9\text{ kg/m}^2$; and underweight is indicated by a $\text{BMI}<18.5\text{ kg/m}^2$. Acute kidney injury (AKI) is characterized by an elevation in serum creatinine levels of $\geq 0.5\text{ mg/dL}$ from baseline or a reduction in creatinine clearance of $\geq 50\%$.

Hyperlipidemia (HL), hypertension (HT), and diabetes mellitus (DM) diagnoses were made according to the 2021 Dyslipidemia Guidelines, 2022 Hypertension Guidelines, and 2024 Diabetes Guidelines of the Türkiye Endocrine

and Metabolism Association, respectively [7–9]. Sternal separation was defined as disruption of sternal integrity on physical examination.

Wound healing failure was defined as the absence of a healthy scar at the surgical site (leg or sternum) within 1 month. Atrial fibrillation (AF) was diagnosed by electrocardiography (ECG). Cerebrovascular disease (CVD) diagnoses were confirmed by neurological consultation. Pleural effusion (PE) was diagnosed on the basis of costodiaphragmatic sinus occlusion on chest radiographs. An intensive care unit (ICU) stay of ≥ 4 days was considered a "prolonged ICU stay". Deaths occurring before discharge after surgery were defined as "in-hospital mortality," and deaths occurring within 1 month after discharge were defined as "1-month mortality".

Ethical Approval

This research received approval from institutional and national ethical boards and complied with the principles of the Declaration of Helsinki and its supplementary protocols. Prior to data collection, approval was obtained from the Clinical Research Ethics Committee of Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Hospital (approval number: 2024.05-49, date: 10.09.2024). To protect patient confidentiality throughout the study, identifying information was removed and only anonymous data were used. The entire process was completed in accordance with established ethical guidelines.

Statistical Analysis

Statistical analyses were performed utilizing IBM SPSS Statistics 23.0 software (SPSS Inc., Chicago, IL, USA). Continuous data were presented as mean $\pm$ standard deviation (SD), whereas categorical variables were reported as counts and percentages (%). The Kolmogorov-Smirnov test was employed to assess the normality of data distribution. The independent sample t-test was used to compare variables exhibiting a normal distribution, whereas the Mann-Whitney U test was applied to variables lacking a normal distribution. Chi-square and Fisher's exact tests were employed to assess differences among categorical variables. A logistic regression analysis was conducted to identify preoperative factors influencing the length of stay in the ICU. Variables of significance revealed through univariate testing were further evaluated in multivariate analysis. Statistical significance was established at $p<0.05$.

Results

A total of 216 patients participated in the study, categorized into two groups based on BMI: BMI $\geq$ 35 kg/m² (122 patients, 56.5%) and BMI<35 kg/m² (94 patients, 43.5%). The percentage of female patients was greater in the BMI $\geq$ 35 kg/m² cohort. Moreover, the prevalence of DM, HT, HL, chronic obstructive pulmonary disease (COPD), and smoking was significantly higher in this group ($p<0.05$). In this group, EuroSCORE 2 scores were elevated, while ejection fraction (EF) was diminished ($p<0.05$). Table 1 delineates the demographic and preoperative characteristics of the study cohort.

Postoperative outcomes are presented in Table 2. Patients with BMI $\geq$ 35 kg/m² experienced significantly longer intubation times (17.6 ± 14.2 vs. 10.2 ± 4.3 hours, $p<0.001$),

ICU stays (2.6 ± 2.3 vs. 1.4 ± 0.7 days, $p<0.001$), and total hospital stays (10.7 ± 6.7 vs. 5.8 ± 1.6 days, $p<0.001$). Moreover, the incidence of postoperative complications, including wound healing defects (17% vs. 1.6%, $p<0.001$), sternal dehiscence (8.5% vs. 1.6%, $p=0.022$), pulmonary embolism (25.5% vs. 4.9%, $p<0.001$), and AF (18.1% vs. 7.4%, $p=0.016$), was significantly higher in the BMI $\geq$ 35 kg/m² group. However, no statistically significant differences were observed between the groups in terms of AKI, CVD, need for surgical revision, in-hospital mortality, or early mortality (all $p>0.05$), suggesting that obesity mainly affects morbidity rather than early mortality.

The univariate analysis results indicate that a high EuroSCORE 2, elevated BMI, hyperlipidemia, and the

Table 1. Demographic and Preoperative Characteristics

	Total (216, 100%)	BMI <35 kg/m ² (122, 56.5%)	BMI $\geq$ 35 kg/m ² (94, 43.5%)	p
Age / years	59.1 $\pm$ 8.8	60.1 $\pm$ 8.2	57.9 $\pm$ 9.4	0.078
Gender / female %	53 (24.5%)	17 (13.9%)	36 (38.3%)	<0.001*
Height / m	1.67 $\pm$ 0.07	1.71 $\pm$ 0.07	1.63 $\pm$ 0.05	<0.001*
Weight / kg	90 $\pm$ 16	78.2 $\pm$ 10.2	105.4 $\pm$ 8.8	<0.001*
EuroSCORE 2	1.37 $\pm$ 0.62	1.29 $\pm$ 0.60	1.48 $\pm$ 0.64	0.01*
DM %	149 (69%)	74 (60.7%)	75 (79.8%)	0.003*
HT %	138 (63.9%)	66 (54.1%)	72 (76.6%)	0.001*
HL %	109 (50.5%)	49 (40.2%)	61 (64.9%)	<0.001*
COPD %	48 (22.2%)	19 (15.6%)	29 (30.9%)	0.007*
Smoking %	129 (59.7%)	64 (52.5%)	65 (69.1%)	0.013*
EF %	55.06 $\pm$ 7.65	56.6 $\pm$ 6.1	53.0 $\pm$ 8.8	0.002*

DM: Diabetes Mellitus; HT: Hypertension; HL: Hyperlipidemia; COPD: Chronic Obstructive Pulmonary Disease; EF: Ejection Fraction.

Table 2. Postoperative Characteristics

	Total (216, 100%)	BMI <35 kg/m ² (122, 56.5%)	BMI $\geq$ 35 kg/m ² (94, 43.5%)	p
Intubation Duration / hours	13.4 $\pm$ 10.5	10.2 $\pm$ 4.3	17.6 $\pm$ 14.2	<0.001*
ICU Stay / days	1.93 $\pm$ 1.7	1.4 $\pm$ 0.7	2.6 $\pm$ 2.3	<0.001*
Ward Stay / days	5.9 $\pm$ 3.8	4.5 $\pm$ 1.3	7.7 $\pm$ 5.0	<0.001*
Wound Healing Defect %	18 (8.3)	2 (1.6)	16 (17)	<0.001*
Sternal Dehiscence %	10 (4.6)	2 (1.6)	8 (8.5)	0.022*
Postoperative AKI %	21 (9.7)	9 (7.4)	12 (12.8)	0.185
Postoperative AF %	26 (12)	9 (7.4)	17 (18.1)	0.016*
Postoperative CVD %	4 (1.9)	2 (1.6)	2 (2.1)	>0.99
Postoperative PE %	30 (13.9)	6 (4.9)	24 (25.5)	<0.001*
Postoperative Revision %	15 (6.9)	6 (4.9)	9 (9.6)	0.182
Hospital Mortality %	4 (1.9)	1 (0.8)	3 (3.2)	0.32
Early Mortality %	4 (1.9)	1 (0.8)	3 (3.2)	0.32
Discharge / days	7.8 $\pm$ 5.1	5.8 $\pm$ 1.6	10.7 $\pm$ 6.7	<0.001*

AKI: Acute Kidney Injury; AF: Atrial Fibrillation; CVD: Cerebrovascular disease; PE: Pleural Effusion.

Table 3. Univariate and Multivariate Analysis for Prolonged ICU Stay

Analysis	OR	CI	P
Univariate Analysis			
Age / years	1.05	0.99-1.11	0.065
Gender / female %	2.45	0.93-6.47	0.069
EuroSCORE 2	1.95	1.02-3.71	0.041*
BMI ≥ 35 kg/m ²	8.13	2.29-28.85	0.001*
EF %	0.98	0.92-1.03	0.505
DM %	0.97	0.35-2.67	0.956
HT %	2.25	0.72-7.05	0.162
HL %	4.02	1.29-12.5	0.016*
COPD %	3.64	1.38-9.58	0.009*
Smoking %	1.51	0.55-4.14	0.421
Multivariate Analysis			
EuroSCORE 2	1.93	0.92-4.04	0.082
BMI ≥ 35 kg/m ²	5.16	1.39-19.17	0.014*
HL %	2.71	0.8-9.17	0.109
COPD %	2.63	0.93-7.38	0.066

OR: Odds Ratio; CI: Confidence Interval; BMI: Body Mass Index; EF: Ejection Fraction; DM: Diabetes Mellitus; HT: Hypertension; HL: Hyperlipidemia; COPD: Chronic Obstructive Pulmonary Disease.

presence of COPD are associated with an extended ICU stay ($p < 0.05$). In multivariate analysis, a high BMI (≥ 35 kg/m²) emerged as an independent risk factor for extended ICU stay. The results are presented in Table 3.

Discussion

EuroSCORE 2 is one of the most commonly used risk assessment models in cardiovascular surgery practice [10]. In our study, we found that the prevalence of HT, HL, DM, and COPD was higher and the EF was lower in obese patients with a BMI ≥ 35 kg/m² before CABG. In line with these findings, the EuroSCORE 2 scores were also significantly higher in these patients.

Despite the expectation that early mortality would be higher in patients with a BMI ≥ 35 kg/m², no statistically significant difference in mortality was observed between the two groups after adjustment for demographic characteristics and risk scores. In the literature, several studies have reported lower early mortality rates in class I obese (BMI=30–34.9 kg/m²) and overweight patients compared to normal weight or underweight patients [6,11–13]. This phenomenon is explained by the concept of the "obesity paradox". The obesity paradox refers to the fact that although obesity is an important risk factor for the development of cardiovascular disease, it may confer a survival advantage for certain surgical procedures, such

as CABG surgery, in obese patients. Mechanisms such as increased metabolic reserves, increased secretion of amino acids and adipokines, lower levels of B-type natriuretic peptide, and reduced oxidative stress and inflammation have been proposed to explain this paradox [6]. However, there are conflicting findings in the literature regarding whether the protective effect of obesity—often referred to as the "obesity paradox"—applies to patients with class II and III obesity (BMI ≥ 35 kg/m²). Some studies have reported increased mortality in this subgroup, which contradicts the outcomes suggested by previous studies supporting the obesity paradox [5,6,14]. In our study as well, higher BMI was associated with adverse postoperative outcomes, although no significant difference in early or in-hospital mortality was observed. These inconsistencies highlight the need for further large-scale, prospective studies to clarify the impact of severe obesity on surgical outcomes in this patient population.

Our study also demonstrated that intubation duration, ICU stay, and ward stay were significantly prolonged in the BMI ≥ 35 kg/m² group. In multivariate analysis, high BMI was independently associated with prolonged ICU stay. These findings are consistent with the literature indicating that the recovery process is prolonged in obese patients [11,15]. Prolonged hospital stay increases both the workload of health care workers and hospital costs. In Türkiye, the number of ICU beds and the ratio of health care workers per patient are lower than those reported in the literature from other countries, while bed occupancy rates are higher [16]. This situation may lead to difficulties in meeting the demand for ICU beds, especially in emergency situations, and may place an additional burden on the health care system.

The negative effects of obesity on wound healing have been known for a long time. The risk of surgical site infection after open heart surgery is higher in obese patients, as several studies have shown [17–19]. In our investigation, the incidence of wound healing defects was significantly higher in patients with a BMI ≥ 35 kg/m². Although wound healing problems do not directly affect mortality, they prolong hospital stay, negatively affect patient psychology, and increase healthcare costs. Therefore, it is crucial to implement measures to support wound healing prior to CABG in patients with a BMI ≥ 35 kg/m².

This study's primary limitation is its single-center, retrospective design. This text aims to offer a thorough overview of the subject matter. Historically, obesity was solely characterized by an individual's BMI. However,

additional assessments, such as waist circumference measurement, which reflects body fat distribution and actual adiposity, were not routinely performed. In future studies, more detailed assessment of waist circumference measurements and body fat percentages in obese patients may contribute to more accurate results. In addition, there is a need for multicenter and prospective studies. Such studies may provide a clearer roadmap for clinical practice by more clearly demonstrating the effects of obesity on clinical outcomes after CABG.

Conclusion

Our study indicates that obesity, defined as a BMI ≥ 35 kg/m², does not directly contribute to increased early mortality following CABG. This patient cohort exhibited a significantly prolonged duration of intubation, ICU stay, and ward stay, as well as a significantly increased incidence of wound healing problems, sternal separation, AF, and PE. Based on these findings, we believe that reducing body mass index through appropriate preoperative nutrition programs in stable obese patients scheduled for CABG may help reduce the length of ICU and hospital stay, thereby reducing health care costs and improving the efficient use of hospital resources, even if it does not have a direct effect on mortality.

Ethics Committee Approval: The study was approved by Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Hospital Ethics Committee (No: 2024.05-49, Date: 10.09.2024).

Conflict of Interest: The authors declare that there is no conflict of interest.

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Prevalence of Bladder and Bowel Dysfunction in Children Scheduled for Outpatient Surgery: Evaluation of Functional Constipation and Lower Urinary Tract Symptoms

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Abstract

Introduction: To evaluate the frequency of bladder and bowel dysfunction (BBD), functional constipation, and lower urinary tract symptoms in pediatric patients undergoing outpatient surgical procedures.

Methods: This prospective study included 100 children aged 5–18 years who were scheduled for circumcision, inguinal or umbilical hernia repair, or orchiopexy between August and December 2024. Bowel dysfunction was assessed using the Rome IV criteria, and urinary symptoms were evaluated with the Voiding and Bowel Dysfunction Symptom Score (VBDS). Patients with chronic diseases or previous urological/anorectal surgery were excluded.

Results: The mean age was 7.22 ± 2.90 years, and 97% of patients were male. At least one lower urinary tract symptom was present in 47% of patients. VBDS scores ≥ 7 were detected in 18% of participants, but only 5% met the Rome IV criteria for functional constipation. The most common symptom was stool-holding behavior (44%), while only 2% had fecal incontinence. BBD was diagnosed in one patient (1%).

Discussion and Conclusion: Although the formal diagnosis of BBD was rare, urinary and bowel-related symptoms were common. Early identification and combined evaluation of urinary and bowel functions are essential for timely intervention and to prevent potential complications.

Keywords: Bladder and bowel dysfunction; functional constipation; lower urinary tract symptoms; pediatric surgery; Rome IV criteria.

Bladder and bowel dysfunction (BBD) refers to a group of lower urinary tract symptoms associated with bowel problems. Although its true incidence is not precisely known, it is estimated to account for approximately 40% of pediatric urology consultations [1].

Bowel dysfunctions include clinical conditions such as fecal incontinence (FI) and constipation. To establish a common language and standardize evaluation across the globe, the

Rome IV criteria are recommended for the assessment of bowel dysfunction [2].

Today, the importance of bowel health in bladder function is widely recognized, and constipation has been identified as the primary bowel disorder contributing to bladder symptoms [3]. Accordingly, the early identification and treatment of BBD is critically important in order to prevent secondary comorbidities that may adversely affect renal and bladder function [4].

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In this study, we aimed to determine the frequency of BBD in pediatric patients who were admitted for outpatient surgical procedures such as circumcision, inguinal or umbilical hernia repair, or orchiopexy in the pediatric surgery department.

Materials and Methods

Following approval from the Clinical Research Ethics Committee of Ümraniye Training and Research Hospital (Approval No: 215, Date: July 11, 2024), pediatric patients aged 5 to 18 years who were scheduled for outpatient surgical procedures (inguinal/umbilical hernia, undescended testis, or circumcision) between August 15 and December 15, 2024, were prospectively enrolled in the study. The study was conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from the parents of all participants. Demographic data and body mass index (BMI) values were recorded for all patients, and physical examinations were performed.

Bowel dysfunction was assessed according to the Rome IV criteria. These include the following six features: at least one episode of fecal incontinence per week, a history of retentive posturing or excessive voluntary stool retention, a history of painful or hard bowel movements, the presence of a large fecal mass in the rectum, and a history of large-diameter stools that may clog the toilet. Functional constipation was defined as the presence of at least two of these features occurring at least once per week for a minimum of one month.

Lower urinary tract symptoms were evaluated using a 13-item Voiding and Bowel Dysfunction Symptom Score (VBDS) form. This form assessed the bladder filling and voiding phases, as well as bowel habits. It was completed by a trained nurse through interviews with the child and their parent. The age at which the child achieved daytime and

nighttime continence was also recorded. Each symptom in the form was scored on a scale from 0 to 3, where 0 indicated the absence of the symptom and 3 represented the daily presence of the symptom.

Children with a history of anorectal or urological surgery, or those with chronic systemic diseases, were excluded from the study.

Statistical Analysis

The data were analyzed using IBM SPSS Statistics Standard Concurrent User V29 (IBM Corp., Armonk, New York, USA). Descriptive statistics were presented as number of cases (n), percentage (%), mean±standard deviation, median, minimum, and maximum values.

Results

A total of 100 patients with a mean age of 7.22 ± 2.90 years were included in the study. Of these, 97 were boys and 3 were girls. The mean body mass index (BMI) was 17.65 ± 4.52 (range: 11.9–32.7). Based on BMI classification, 75 patients were underweight, 17 were of normal weight, 4 were overweight, and 4 were obese.

The distribution of surgical procedures was as follows: 11 patients underwent inguinal hernia repair, 8 underwent orchiopexy for undescended testis, 5 had hydrocele surgery, 1 patient underwent umbilical hernia repair, and 75 underwent circumcision alone. Additionally, 6 patients underwent circumcision in conjunction with their primary surgical procedure.

At least one lower urinary tract symptom was identified in 47 patients (47%), while 15 patients had more than one urinary symptom. The comparison of lower urinary tract symptoms among all patients and subgroups based on the Rome IV criteria is presented in Table 1. A history of febrile urinary tract infection was noted in 14 patients.

Table 1. Comparison of Lower Urinary Tract Symptoms Among All Patients and Subgroups Based on Rome IV Criteria

Symptom	All Patients (n=100)	Rome IV Positive (n=5)	Rome IV Criterion Only 1 (n=18)
History of urinary tract infection	14 (14.0)	1 (20.0)	4 (22.2)
Nocturnal enuresis	17 (17.0)	1 (20.0)	3 (16.7)
Daytime urinary incontinence	8 (8.0)	–	1 (5.6)
Intermittent voiding	9 (9.0)	–	4 (22.2)
Urgency	12 (12.0)	1 (20.0)	–
Dysuria	8 (8.0)	–	1 (5.6)
≥1 urinary symptom	47 (47.0)	2 (40.0)	8 (44.4)
>1 urinary symptom	15 (15.0)	1 (20.0)	4 (22.2)

Values are presented as number of patients (n) and percentage (%). “–” indicates that the symptom was not reported in the group.

According to the VBDS assessment, 18 patients (18%) had a score of 7 or higher. Of these, only one patient (5.5%) met two or more Rome IV criteria.

Five patients (5%) met at least two of the Rome IV criteria. Among the 95 patients (95%) who did not meet the Rome IV criteria, 81 reported daily defecation. In contrast, 19 patients had an average of three bowel movements per week, and 11 patients experienced painful and hard defecation. Of these 11, 7 were among the patients who defecated daily.

Fecal incontinence was reported in only 2 patients (2%). A total of 15 patients experienced defecation with stool large enough to clog the toilet. Delayed defecation or stool-holding behavior was observed in 44 patients. Eighteen patients (18%) met only one of the Rome IV criteria.

Discussion

Since 2013, the coexistence of voiding dysfunction symptoms and functional constipation and/or fecal incontinence (FI) in children has been referred to as bladder and bowel dysfunction (BBD), a condition that is considered quite common worldwide. Studies have shown that more than 17% of school-aged children experience long-term urinary tract symptoms, and the prevalence of constipation and/or FI ranges between 0.7% and 29.6% [5]. In our study, only one patient (1%) fully met the Rome IV criteria and was diagnosed with BBD, subsequently being referred to the relevant specialties.

The most common cause of functional constipation (FC) is stool-withholding behavior that begins after an episode of painful, hard, or frightening defecation [6]. Constipation is a frequent childhood condition with a global prevalence of up to 29.6% [7]. However, families do not always perceive it as a medical issue [8]. Additionally, children's understanding of constipation may vary; some define it as straining or passing hard stools, while others associate it with infrequent bowel movements or the inability to defecate when desired [9].

Although rates of painful defecation vary in the literature, one study reported this symptom in 92.3% of patients, large and hard stool in 93.7%, and fecal incontinence in 31% [10]. In our study, despite not fulfilling the full Rome IV criteria, the most frequent symptom was stool-holding behavior, present in 44% of patients. Stool retained in the rectum leads to water absorption by the rectal mucosa, making the stool harder and more difficult to evacuate. Consequently, rectal distension may exert pressure on the posterior

wall of the bladder [6]. Families were informed about the importance of recognizing these symptoms as early indicators of potential BBD, and behavioral interventions were recommended for the children.

Bowel dysfunction can be characterized by constipation alone, fecal incontinence alone, or a combination of both [11]. The Rome IV criteria are currently the most widely used diagnostic tool in pediatric practice for the evaluation of FC. However, these criteria are not suitable for assessing the severity of bowel dysfunction [12]. In our study, approximately half of the patients had only one of the Rome IV criteria.

Early diagnosis and treatment of BBD are essential to protect renal and bladder function and to support the psychosocial well-being of affected children [4]. There is now broad consensus that treating bowel dysfunction effectively plays a significant role in resolving urinary dysfunction [13].

Although our study was conducted over a short period and with a limited number of patients, findings indicate that nearly half of the patients experienced either lower urinary tract symptoms or defecation problems. However, the majority did not fully meet the Rome IV criteria, and their VBDS scores remained below the diagnostic threshold for BBD. Despite the low rate of confirmed BBD, this study provides valuable insights into raising awareness among families and children. Children identified with symptoms were referred to pediatric urology and gastroenterology clinics for further evaluation, aiming to prevent progression of potential complications.

Conclusion

Bladder and bowel dysfunction (BBD) is frequently associated with urinary and defecation symptoms in children. Although the confirmed diagnosis rate based on Rome IV criteria was low in our study, many patients exhibited related symptoms, particularly stool-holding behavior. These findings highlight the importance of early recognition and holistic evaluation of urinary and gastrointestinal functions. Raising family awareness and timely referrals are key to preventing complications and improving outcomes.

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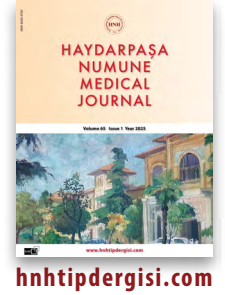
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Comparison of the Multidimensional Health Assessment Questionnaire (MDHAQ-RAPID3) with the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Bath Ankylosing Spondylitis Functional Index (BASFI) in Patients with Ankylosing Spondylitis

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Abstract

Introduction: To evaluate the correlation between the Routine Assessment of Patient Index Data 3 (RAPID3), derived from the Multidimensional Health Assessment Questionnaire (MDHAQ), and the commonly used indices Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI) in patients with Ankylosing Spondylitis (AS).

Methods: A total of 100 patients diagnosed with AS who attended our outpatient clinic between May 18 and September 30, 2009, were enrolled. All patients completed the BASDAI, BASFI, and MDHAQ questionnaires. RAPID3 was calculated using the pain, patient global assessment, and function subscales of MDHAQ. Spearman correlation analysis was used for statistical evaluation.

Results: The mean age was 30±10.9 years, and 69% of the participants were male. The mean disease duration was 5.0±6.7 years. Average BASDAI, BASFI, and RAPID3 scores were 4.93±2.5, 3.94±2.5, and 13.27±7.0, respectively. RAPID3 was strongly correlated with both BASDAI and BASFI ($r=0.77$ and $r=0.72$; $p<0.001$).

Discussion and Conclusion: RAPID3, based solely on patient-reported measures, shows strong correlation with established AS indices and can be considered a practical alternative for clinical monitoring in routine care.

Keywords: Ankylosing spondylitis; BASDAI; BASFI; disease activity; functional assessment; patient-reported outcome measures.

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Ankylosing spondylitis (AS) is a chronic, systemic inflammatory rheumatic disease that primarily affects the axial skeleton, especially the sacroiliac joints and spine [1,2]. It is considered the prototype of seronegative spondyloarthropathies, with a prevalence ranging between 0.5–1% in White populations, and it predominantly affects males in their second or third decade of life [3]. The pathogenesis of AS is strongly associated with genetic predisposition, particularly the presence of HLA-B27, which is positive in approximately 90–95% of patients with AS [4,5].

Clinically, AS leads to inflammation, pain, and progressive stiffness in the spine and peripheral joints, significantly impairing mobility and quality of life [6]. Over time, these symptoms contribute to physical disability, fatigue, sleep disturbances, and psychosocial burden, all of which can substantially reduce overall health status [7,8]. Therefore, regular assessment of disease activity and functional status is essential in the management of AS.

To address this clinical need, several validated instruments have been developed. The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Bath Ankylosing Spondylitis Functional Index (BASFI) are the most widely used tools for assessing disease activity and functional capacity, respectively [9,10]. These indices have demonstrated strong reliability, reproducibility, and sensitivity to change, making them valuable for both research and clinical use. However, they require time to complete and interpret, which may limit their feasibility in busy outpatient settings [11].

The Multidimensional Health Assessment Questionnaire (MDHAQ) was developed to provide a more efficient assessment of patient status, combining physical function, pain, fatigue, and patient global health evaluation [12]. From the MDHAQ, the Routine Assessment of Patient Index Data 3 (RAPID3) score was derived. RAPID3 includes only three patient-reported domains: physical function, pain, and global assessment, each scored from 0 to 10, yielding a total score from 0 to 30 [13]. Unlike BASDAI and BASFI, RAPID3 can be completed in less than one minute and scored without physician input, making it a promising tool for routine use. RAPID3 offers significant advantages in clinical settings due to its simplicity, rapid completion time (under one minute), and ease of scoring without physician input. These features make it particularly suitable for busy outpatient clinics, where time efficiency and practicality are essential.

Previous research has demonstrated that RAPID3 correlates well with disease activity indices in various rheumatologic conditions, including rheumatoid arthritis, osteoarthritis, fibromyalgia, and Behçet's disease [14–16]. However, its application and validity in AS patients have not been extensively studied, and current data are limited.

Given the need for practical, patient-centered outcome measures in rheumatology, the aim of this study was to evaluate the correlation between the MDHAQ-RAPID3 score and the more established BASDAI and BASFI indices in patients with ankylosing spondylitis. We hypothesize that RAPID3 may serve as a time-saving, feasible, and reliable alternative for assessing both disease activity and functional status in daily clinical practice.

Materials and Methods

This cross-sectional observational study was conducted between May 18 and September 30, 2009, in the Physical Medicine and Rehabilitation outpatient clinic of Haydarpaşa Numune Training and Research Hospital with 100 patients with AS diagnosed with the Modified New York Criteria (1984). Patients were between 18–65 years of age and had a confirmed diagnosis of AS. Exclusion criteria included the presence of other inflammatory rheumatic diseases, cognitive impairment preventing completion of the questionnaire, or missing clinical data.

All participants completed the following three validated questionnaires on the same day:

- Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [17],
- Bath Ankylosing Spondylitis Functional Index (BASFI) [18],
- Multidimensional Health Assessment Questionnaire (MDHAQ) [19].

The RAPID3 score from the MDHAQ was calculated by summing the scores of three components: physical function, pain, and global assessment of the patient. Each component is scored from 0 to 10, resulting in a total RAPID3 score ranging from 0 to 30.

Demographic data (age, gender, education level) and clinical characteristics (duration of disease, medication use, comorbidities) were obtained from patient records. Selected laboratory data, including C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), were also recorded. This study was conducted in accordance with the ethical principles of the 1964 Declaration of Helsinki

and its subsequent amendments and comparable ethical standards. All participants were informed about the study procedures before inclusion, and written informed consent was obtained.

Statistical Analysis

Statistical analyses were performed using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics are reported as mean±standard deviation (SD) for continuous variables and percentage for categorical variables. The primary analysis included the calculation of Spearman's rank correlation coefficients to assess the association between RAPID3 and the indices identified (BASDAI and BASFI). p -values<0.05 were considered statistically significant. Spearman's rank correlation was preferred due to the non-parametric distribution of the data, ensuring appropriate statistical assessment of associations.

Results

Demographic and Clinical Characteristics

A total of 100 patients with a confirmed diagnosis of AS were evaluated. The mean age was 30.0 ± 10.9 years, with an age range of 18 to 59 years. Among them, 69 were male (69%) and 31 were female (31%), yielding a male-to-female ratio of approximately 2.2:1.

The mean disease duration was 5.0 ± 6.7 years, ranging from less than 1 year to over 20 years. Education level analysis showed that 46% of patients had completed high school or higher education. Most patients (72%) were receiving non-steroidal anti-inflammatory drugs (NSAIDs), and 28% were on anti-TNF therapy at the time of the study.

Questionnaire Scores and Descriptive Data

Patients completed three self-reported instruments: BASDAI, BASFI, and MDHAQ (from which RAPID3 was derived). The results are summarized below (Table 1).

The distribution of RAPID3 scores was slightly right-skewed, indicating that a portion of patients reported moderate to high levels of disease impact, despite clinical stability in some.

Correlation Between RAPID3 and AS-Specific Indices

Spearman's rank correlation coefficients demonstrated strong and statistically significant correlations between the RAPID3 score and the established AS assessment tools:

- RAPID3 and BASDAI: $r=0.77$, $p<0.001$
- RAPID3 and BASFI: $r=0.72$, $p<0.001$

Table 1. Demographic and clinical characteristics of the study population and descriptive statistics of questionnaire scores

Variable	Mean±SD / n (%)	Range
Age (years)	30.0 ± 10.9	18–59
Gender (Male/Female)	69 (69%) / 31 (31%)	—
Disease duration (years)	5.0 ± 6.7	<1–>20
Education (High school or above)	46 (46%)	—
NSAID use	72 (72%)	—
Anti-TNF therapy	28 (28%)	—
BASDAI	4.93 ± 2.5	0.2–9.8
BASFI	3.94 ± 2.5	0.0–9.2
RAPID3	13.27 ± 7.0	1.0–29.0

SD: Standard Deviation; NSAID: Non-Steroidal Anti-Inflammatory Drug; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; RAPID3: Routine Assessment of Patient Index Data 3.

Table 2. Spearman correlation coefficients between MDHAQ components and BASDAI / BASFI

MDHAQ Component	r with BASDAI	r with BASFI	p
Pain	0.72	0.60	<0.01
Patient Global Assessment	0.70	0.76	<0.01
Fatigue	0.62	0.53	<0.01
Function (MDHAQ)	0.50	0.73	<0.01

Spearman correlation used; all correlations significant at $p<0.01$ level. BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; MDHAQ: Multidimensional Health Assessment Questionnaire.

This suggests that RAPID3 closely mirrors both disease activity (BASDAI) and functional limitations (BASFI) in AS patients.

Correlation with Individual MDHAQ Components

Further analysis showed that each RAPID3 component was independently associated with both BASDAI and BASFI. Detailed correlation coefficients between MDHAQ components and the AS indices are shown in Table 2.

Notably, the function subscale had a stronger correlation with BASFI, as expected, whereas pain and fatigue were more closely associated with disease activity as captured by BASDAI.

Discussion

This study demonstrated a strong and statistically significant correlation between the MDHAQ-RAPID3, a patient-reported outcome measure derived from the MDHAQ, and two widely used AS assessment tools: BASDAI

and BASFI. These findings suggest that RAPID3 can be a valid and practical alternative for assessing disease activity and functional impairment in patients with AS, especially in routine clinical settings.

The mean MDHAQ-RAPID3 score in our study (13.27 ± 7.0) showed strong positive correlations with both BASDAI ($r=0.77$) and BASFI ($r=0.72$), indicating that patient perceptions of pain, physical function, and global health status captured solely through MDHAQ-RAPID3 closely mirror more detailed disease-specific indices. These results align with previous studies in rheumatoid arthritis, osteoarthritis, fibromyalgia, and Behçet's disease, where MDHAQ-RAPID3 has also demonstrated high correlation with disease-specific activity indices [20-22].

A notable finding is the strong relationship between fatigue, patient global assessment, and disease indices. Fatigue, often underemphasized in traditional scoring systems, showed moderate-to-strong correlations with both BASDAI ($r=0.62$) and BASFI ($r=0.53$), reflecting its impact on both disease activity and functional capacity. This observation is consistent with prior studies highlighting fatigue as a significant symptom burden in patients with AS [23,24].

From a clinical standpoint, MDHAQ-RAPID3's brevity and ease of use make it particularly advantageous in high-volume settings, where time constraints often limit the use of multi-step assessment tools like BASDAI and BASFI [25]. RAPID3 can be completed by the patient in less than one minute and does not require physician scoring, unlike BASMI or ASDAS-CRP, further increasing its feasibility for routine use [26]. While RAPID3 demonstrates strong correlation with BASDAI and BASFI, it lacks components specific to axial spondyloarthritis, such as spinal mobility and enthesitis evaluations. Moreover, it does not capture morning stiffness duration or peripheral joint involvement, which are clinically relevant in AS. Therefore, RAPID3 should be viewed as a complementary tool rather than a replacement for comprehensive disease activity assessments. Its value lies in providing rapid patient-centered insight, especially in follow-up visits and high-volume clinical settings.

However, RAPID3 is not AS-specific, and unlike BASDAI, it does not include parameters such as morning stiffness duration or peripheral joint involvement, which are clinically relevant in AS [27]. Therefore, while it can complement other tools, RAPID3 may not fully replace comprehensive disease activity assessments in all clinical scenarios, especially in patients with complex presentations.

Strengths and Limitations

A key strength of this study is the inclusion of a well-characterized AS cohort in a real-world outpatient setting, increasing the generalizability of findings. The use of validated tools and standardized data collection adds further credibility.

However, some limitations must be acknowledged. First, this was a cross-sectional study, so causal inferences cannot be made. Second, data were collected from a single center, and the population was predominantly young and male, which may not represent the broader AS population. Lastly, the study did not include objective imaging markers or inflammatory biomarkers such as MRI findings or ASDAS-CRP, which could have added more depth to the disease activity evaluation.

Conclusion

This study demonstrates that RAPID3, a brief and fully patient-reported index derived from the MDHAQ, shows a strong correlation with established ankylosing spondylitis assessment tools BASDAI and BASFI. These findings suggest that MDHAQ-RAPID3 can be a valid, time-efficient, and practical alternative for evaluating disease activity and functional status in patients with AS, particularly in routine clinical settings where rapid assessment is essential.

While MDHAQ-RAPID3 is not disease-specific and may not capture all clinical dimensions of AS, its ease of use and strong association with core disease domains make it a valuable adjunct to traditional instruments. Further multicenter and longitudinal studies are recommended to explore its responsiveness to treatment and applicability in diverse AS populations.

***This study was produced from a specialization thesis.**

Ethics Committee Approval: The study was approved by Haydarpaşa Training and Research Hospital Ethics Committee (No: 771/06/2025, Date: 29.10.2010).

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Assessment of Artificial Intelligence Chatbots in Responding to Supraventricular Tachycardia Related Questions

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Abstract

Introduction: Supraventricular tachycardia (SVT) is the most prevalent arrhythmia among young adults. With the rapid advancement of artificial intelligence technologies, natural language processing models (NLPs) such as ChatGPT, Gemini, and Bing Chat are becoming increasingly widespread in the field of medicine. We aim to assess the precision and consistency of responses produced by ChatGPT-4o, Gemini, and Bing Chat to frequently asked questions regarding SVT.

Methods: A list of fifty commonly asked questions regarding SVT was inquired twice, with a one-week interval, to ChatGPT-4o, Gemini, and Bing Chat. Two cardiologists assessed the responses from each NLP without knowledge of each other's evaluations. The content was rated using the following scale: totally correct (1), incomplete (2), and incorrect (3).

Results: Most of the responses from all models were rated as either 'totally correct', 'incomplete', or 'incorrect'. Even though ChatGPT-4o did not generate any 'incorrect' answers, Bing Chat and Gemini produced some incorrect responses. Regarding the accuracy of responses, ChatGPT achieved a score of 92%, Gemini obtained 70%, and Bing Chat reached 58%. ChatGPT-4o also achieved the highest 'reproducibility' score at 90%, followed by Gemini at 86%, and Bing Chat at 72%.

Discussion and Conclusion: Our study highlighted that ChatGPT-4o is capable of generating valuable answers to patients' questions related to SVT. As NLPs—especially ChatGPT-4o—continue to improve, they hold great potential for the management of chronic conditions like SVT.

Keywords: Artificial intelligence; Bing Chat; ChatGPT; digital health; Gemini; natural language processing chatbots; supraventricular tachycardia.

Supraventricular tachycardia (SVT) is the most prevalent non-sinus tachyarrhythmia in young adults, with an incidence of approximately 3.5 per 1,000 person-years or 2.29 per 1,000 individuals^[1]. Clear communication is vital for assisting patients in understanding their conditions and ensuring accurate diagnosis, treatment, and follow-up care. Better patient awareness of SVT management has been associated with a decrease in symptoms^[2].

With the rapid advancement of artificial intelligence technologies, natural language processing models (NLPs) such as Chat Generative Pre-Trained Transformer (ChatGPT), Gemini, and Bing Chat are becoming increasingly widespread in the field of medicine^[3]. These models are being integrated into various healthcare applications, ranging from the analysis of patient records to clinical decision support systems, contributing significantly to

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critical processes such as diagnosis, treatment planning, and patient management. NLPs have the potential to process vast amounts of medical data, providing healthcare professionals with faster and more accurate information. In this context, the use of natural language processing techniques in medicine enhances the efficiency of healthcare services while also offering a significant opportunity to improve the quality of patient care. While this transition highlights the positive role AI can play in enhancing health literacy, it has also raised concerns about the potential for misuse and misinformation. The widespread utilization and growing dependence on AI applications by patients lead to important concerns about misinformation^[4,5].

Several studies have previously investigated ChatGPT's responses to common questions about heart failure, coronary artery disease, hypertension, hyperlipidemia, and atrial fibrillation^[6–10]. However, no comparative study has yet been conducted on chatbot responses specifically related to SVT. In our study, we seek to evaluate the precision and consistency of responses provided by ChatGPT-4o, Gemini, and Bing Chat regarding SVT.

Materials and Methods

Data Collection

In this study, we compiled a list of fifty frequently asked questions about SVT, sourced from the websites of the Mayo Clinic, Medline, Cleveland Clinic, and the National Health Service (NHS) UK. We compiled the most common questions asked by patients from independent and reliable sources, aiming to eliminate any potential bias that may arise from popular websites. In this way, we aimed to provide patients with accurate, scientific, and impartial information. These questions were categorized into five groups. Table 1 presents these questions related to basic content about the disease, diagnosis, treatment-procedure related risks/complications, follow-up, and lifestyle modification/dietary management recommendations.

Once the questions were finalized, they were entered into the online chat interface of three different NLPs: ChatGPT-4o (GPT-4, OpenAI, California, United States), Gemini (PaLM 2, Google, California, United States), and Bing Chat (Microsoft, Washington, United States). Each question was asked twice to ChatGPT-4o, Gemini, and Bing Chat on September 2, 2024, and again on September 9, 2024. All questions were asked in English within a separate new chat session.

Two cardiologists independently assessed the responses from each NLP, without knowledge of each other's evaluations. The responses were analyzed based on current

supraventricular tachycardia guidelines^[11]. The content was rated using the following scale: totally correct (1), incomplete (2), and incorrect (3). In cases where there were notable discrepancies between the two reviewers' assessments, a third reviewer was consulted to resolve inconsistencies.

Additionally, the responses were evaluated for consistency by classifying them as either reproducible or non-reproducible. If inconsistencies or variations were detected in the answers, the response was classified as non-reproducible, indicating a lack of reliability or stability.

The study strictly followed the ethical guidelines of the Declaration of Helsinki.

Statistical Analysis

Microsoft Excel (version 16.68; Microsoft Corporation, United States) was utilized for all statistical analyses. Data interpretation, which included proportions, was expressed in terms of frequencies and percentages.

Results

Most of the responses from all models were rated as either 'totally correct' or 'incomplete'. Even though ChatGPT-4o did not generate any 'incorrect' answers, Bing Chat and Gemini produced some incorrect responses.

For ChatGPT-4o, 46 out of the 50 answers (92%) were rated as 'totally correct', while 4 out of the 50 answers (8%) were deemed 'incomplete'. When evaluated by category, ChatGPT-4o achieved the highest performance in the areas of 'diagnosis', 'follow-up', and 'lifestyle modification/dietary management', delivering 'correct' responses at rates of 100%, 100%, and 100%, respectively. ChatGPT-4o also produced 'correct' answers for 91.7% of questions related to 'basic content about the disease' and 83.3% of those concerning 'treatment-procedure related risks/complications'. A summary of the evaluation of ChatGPT-4o's answers by category is presented in Table 2.

For Gemini, 35 out of 50 responses (70%) were assessed as 'totally correct', while 13 out of 50 responses (26%) were deemed 'incomplete', and 2 out of 50 responses (4%) were regarded as 'incorrect'. Gemini demonstrated the highest performance in the areas of 'lifestyle modification/dietary management', 'basic content about the disease', and 'diagnosis', providing correct responses in 83.3%, 75%, and 75% of cases, respectively. Additionally, Gemini produced 'correct' answers to 70% of 'follow-up' questions and 61.1% of 'treatment-procedure related risks/complications' questions. A summary of the evaluation of Gemini's answers by category is displayed in Table 3.

Table 1. Stratification of questions**Basic content about the disease:**

1. What is SVT (supraventricular tachycardia)?
2. What are the SVT (supraventricular tachycardia) types?
3. How common is SVT (supraventricular tachycardia)?
4. What are the symptoms of SVT (supraventricular tachycardia)?
5. What causes SVT (supraventricular tachycardia)?
6. Is SVT (supraventricular tachycardia) genetic?
7. What are the risk factors for SVT (supraventricular tachycardia)?
8. Can SVT (supraventricular tachycardia) be cured with lifestyle changes?
9. Can SVT impair heart function?
10. Who does SVT (supraventricular tachycardia) affect?
11. Can smart watches detect all SVTs?
12. Can SVT (supraventricular tachycardia) be reversed?

Diagnosis:

13. How is SVT (supraventricular tachycardia) diagnosed?
14. What tests will be done to diagnose SVT (supraventricular tachycardia)?
15. I have palpitation and they don't show up on the holter. What can I do?
16. What is implantable loop recorder?

Treatment- procedure related risks/complications:

17. How is SVT (supraventricular tachycardia) treated?
18. What medications are used to treat SVT (supraventricular tachycardia)?
19. How long does it take to recover from this treatment?
20. Are there complications or side effects to treatment for SVT (supraventricular tachycardia)?
21. How can I reduce my risk of experiencing symptoms from SVT (supraventricular tachycardia)?
22. I suffer from SVT which is the best: medical treatment or catheter ablation?
23. How do I take care of myself if I have SVT (supraventricular tachycardia)?
24. What is electrical cardioversion and how is done?
25. When to use electrical cardioversion in SVT (supraventricular tachycardia) patient?
26. What are the risks of cardioversion?
27. What is electrophysiology study (EPS) and how is it done?
28. When to electrophysiology study (EPS) use in SVT (supraventricular tachycardia) patient?
29. What is catheter ablation and how is done?
30. When to use catheter ablation SVT (supraventricular tachycardia) patient?
31. What are the risks of catheter ablation?
32. SVT (supraventricular tachycardia treatment): medical treatment or catheter ablation?
33. When to use implantable loop recorder SVT (supraventricular tachycardia) patient?
34. I suffer from SVT, which is better: cryoablation or radiofrequency ablation?

Follow-up:

35. What are the complications of SVT (supraventricular tachycardia)?
36. How long does it take to recover from SVT (supraventricular tachycardia) treatment?
37. What can I expect if I have SVT (supraventricular tachycardia)?
38. How do I take care of myself if I have SVT (supraventricular tachycardia)?
39. When should I see my healthcare provider? When to see a doctor/How long do I need to wait to see a cardiologist?
40. When should I go to the emergency room (ER)?
41. What questions should I ask my doctor about SVT (supraventricular tachycardia)?
42. I suffer from SVT, should I use anticoagulation?
43. What kind of exercises are better for a patient with a history of SVT (supraventricular tachycardia)?
44. I suffer from SVT how long should I continue antiarrhythmic treatment?

Lifestyle Modification/ Dietary Management:

45. I suffer from SVT (supraventricular tachycardia), Can I drink energy drink?
46. I suffer from SVT (supraventricular tachycardia). Should I avoid alcohol?
47. I suffer from SVT (supraventricular tachycardia). Should I avoid tobacco?
48. I suffer from SVT (supraventricular tachycardia). What should I eat?
49. I suffer from SVT (supraventricular tachycardia). What should I not eat?
50. I suffer from SVT (supraventricular tachycardia). Should I avoid coffee? Can I drink coffee and how much?

Table 2. Evaluation of ChatGPT 4o's answers on supraventricular tachycardia

	Totally correct		Incomplete	
	n	%	n	%
Basic content about the disease (n=12)	11	91.7	1	8.3
Diagnosis (n=4)	4	100	0	0
Treatment- procedure related risks/complications (n=18)	15	83.3	3	16.7
Follow-up (n=10)	10	100	0	0
Lifestyle modification/ dietary management (n=6)	6	100	0	0
Total (n=50)	46	92	4	8

For Bing Chat, 29 out of 50 responses (58%) were graded as 'totally correct', whereas 20 out of 50 responses (40%) were classified as 'incomplete', and 1 out of 50 responses (2%) as 'incorrect'. Bing Chat demonstrated the highest proficiency in the categories of 'follow-up', 'basic content about the disease', and 'lifestyle modification/dietary management', by delivering 'totally correct' responses in 80%, 66.6%, and 66.6% of questions, respectively. Furthermore, Bing Chat also produced 'totally correct' answers to 50% of 'diagnosis' questions and 38.9% of 'treatment-procedure related risks/complications' questions. A summary of the evaluation of Bing Chat's answers by category is displayed in Table 4.

Table 5 emphasizes the reproducibility of responses produced by ChatGPT-4o, Gemini, and Bing Chat to

Table 3. Evaluation of Gemini's answers on supraventricular tachycardia

	Totally correct		Incomplete		Incorrect	
	n	%	n	%	n	%
Basic content about the disease (n=12)	9	75	2	16.7	1	8.3
Diagnosis (n=4)	3	75	1	25	0	0
Treatment- procedure related risks/complications (n=18)	11	61.1	6	33.3	1	5.6
Follow-up(n=10)	7	70	3	30	0	0
Lifestyle modification/ dietary management (n=6)	5	83.3	1	16.7	0	0
Total (n=50)	35	70	13	26	2	4

Table 4. Evaluation of Bing Chat's answers on supraventricular tachycardia

	Totally correct		Incomplete		Incorrect	
	n	%	n	%	n	%
Basic content about the disease (n=12)	8	66.6	4	33.4	0	0
Diagnosis (n=4)	2	50	2	50	0	0
Treatment- procedure related risks/complications (n=18)	7	38.9	10	55.6	1	5.5
Follow-up (n=10)	8	80	2	20	0	0
Lifestyle modification/ dietary management (n=6)	4	66.6	2	33.4	0	0
Total (n=50)	29	58	20	40	1	2

Table 5. Comparative reproducibility of ChatGPT, Gemini, and bing responses to supraventricular tachycardia questions by subgroup

Question subgroup	Number of responses (%)					
	ChatGPT		Gemini		Bing	
	n	%	n	%	n	%
Basic content about the disease (n=12)	9	75	11	91.7	11	91.7
Diagnosis (n=4)	4	100	4	00	3	75
Treatment- procedure related risks/complications (n=18)	16	89	14	77.8	11	61.1
Follow-up (n=10)	10	100	8	80	6	60
Lifestyle modification/ dietary management (n=6)	6	100	6	100	6	100
Total (n=50)	45	90	43	86	37	74

Table 6. Analyzing Chatbots' answers and precision in responding to two example queries

Question: How do I take care of myself if I have SVT (supraventricular tachycardia)?	
ChatGPT's response	Totally correct
Taking care of yourself if you have supraventricular tachycardia (SVT) involves a combination of lifestyle adjustments, regular medical care, and self-awareness. Here are some detailed steps to help manage SVT:	
1. Follow Your Treatment Plan: - Medications: Take all prescribed medications exactly as directed by your healthcare provider. - Procedures: If you've undergone a procedure like catheter ablation, follow your post-procedure care instructions closely. 2. Lifestyle Changes: - Diet: Eat a heart-healthy diet rich in fruits, vegetables, whole grains, lean proteins, and healthy fats. Avoid excessive salt, sugar, and processed foods. - Exercise: Engage in regular physical activity. Choose moderate exercises such as walking, swimming, or yoga. Consult your healthcare provider before starting any new exercise regimen. - Hydration: Drink plenty of water throughout the day to stay hydrated. 3. Avoid Triggers: - Caffeine and Alcohol: Limit or avoid beverages that contain caffeine or alcohol. - Smoking: Quit smoking and avoid exposure to secondhand smoke. - Stress: Practice stress management techniques such as deep breathing exercises, meditation, or mindfulness. 4. Regular Monitoring: - Track Symptoms: Keep a diary of your symptoms, noting their frequency, duration, and any potential triggers. - Medical Appointments: Attend regular follow-up appointments with your cardiologist or healthcare provider to monitor your condition. 5. Learn Vagal Maneuvers: - Techniques like the Valsalva maneuver, coughing, or cold-water face immersion can sometimes stop an SVT episode. Learn and practice these under the guidance of your healthcare provider. 6. Weight Management: - Maintain a healthy weight through a balanced diet and regular exercise. 7. Avoid Stimulants: - Avoid over-the-counter medications containing stimulants, such as certain decongestants. - Avoid recreational drugs that can trigger SVT. 8. Sleep Hygiene: - Ensure you get adequate and restful sleep. Maintain a regular sleep schedule. 9. Manage Other Health Conditions: - Keep conditions like hypertension, diabetes, and thyroid disorders under control with appropriate treatment and lifestyle modifications. 10. Emergency Plan: - Know when to seek emergency medical attention. If you experience severe symptoms such as chest pain, fainting, or difficulty breathing, contact emergency services immediately. 11. Stay Informed: - Educate yourself about SVT and stay updated on new treatments and management strategies. By incorporating these practices into your daily routine, you can effectively manage SVT and maintain a good quality of life. Always consult your healthcare provider before making significant changes to your lifestyle or treatment plan.	
Gemini's response	Totally correct
Taking care of yourself when you have SVT involves a combination of lifestyle changes, medication adherence, and understanding your condition.	
Lifestyle modifications:	
• Manage stress: Practice relaxation techniques like meditation, deep breathing, or yoga. • Regular exercise: Aim for moderate-intensity workouts most days of the week, but avoid overexertion. • Healthy diet: Focus on fruits, vegetables, and whole grains. • Limit stimulants: Reduce or avoid caffeine, nicotine, and alcohol as they can trigger SVT episodes. • Adequate sleep: Ensure you get enough restful sleep.	

Table 6. Cont.

Understanding and managing your condition:

- **Learn about SVT:** Understand your specific type of SVT and its triggers.
- **Communicate with your doctor:** Keep your doctor informed about any changes in your symptoms or condition.
- **Carry identification:** Consider wearing a medical alert bracelet or necklace.
- **Identify triggers:** Keep a journal to track your activities, diet, and symptoms to identify potential triggers.
- **Avoid triggers:** Once you identify triggers, try to minimize exposure to them.

Medication adherence:

- **Take medications as prescribed:** Follow your doctor's instructions for any prescribed medication.
- **Regular check-ups:** Schedule regular appointments with your healthcare provider.

Emergency preparedness:

- **Learn vagal maneuvers:** Practice techniques like the Valsalva maneuver (bearing down as if having a bowel movement) or splashing cold water on your face to potentially stop an episode.
- **Know when to seek medical attention:** Understand the signs of a serious SVT episode and when to call for emergency help.

Remember: Everyone's experience with SVT is different. What works for one person might not work for another. It's essential to work closely with your doctor to develop a personalized management plan.

Bing Chat's response**Totally correct**

If you've been diagnosed with **supraventricular tachycardia (SVT)**, here are some self-care tips to manage your condition:

1. **Avoid triggers:** Identify and avoid factors that can trigger SVT episodes. Common triggers include stress, caffeine, alcohol, and certain medications.
2. **Stay hydrated:** Dehydration can worsen SVT. Drink plenty of water throughout the day.
3. **Manage stress:** Practice relaxation techniques such as deep breathing, meditation, or yoga to reduce stress and anxiety.
4. **Quit smoking:** Smoking can exacerbate heart conditions. If you smoke, consider quitting.
5. **Follow your doctor's advice:** Take medications as prescribed and attend regular follow-up appointments.
6. **Learn vagal maneuvers:** These maneuvers can help slow down your heart rate during an SVT episode. Examples include the Valsalva maneuver (bearing down as if having a bowel movement) or splashing cold water on your face.
7. **Know when to seek help:** If you experience severe symptoms (such as chest pain, shortness of breath, or fainting), seek immediate medical attention.

Remember, always consult with your healthcare provider for personalized advice and to create a tailored management plan.

Question: What are the risks of catheter ablation?**ChatGPT's response****Incomplete**

1. ****Vascular Damage:****
- Damage to blood vessels during catheter insertion or removal.
2. ****Heart Damage:****
- Injury to the heart muscle, heart valves, or the heart's electrical system, possibly requiring a pacemaker.
3. ****Cardiac Tamponade:****
- Fluid accumulation around the heart, which can affect its function and requires immediate treatment.
4. ****Stroke or Heart Attack:****
- Blood clots can form, leading to a stroke or heart attack.
5. ****Pulmonary Vein Stenosis:****
- Narrowing of the veins that return blood from the lungs to the heart.
6. ****Infection:****
- Infection at the catheter insertion site or within the heart.
7. ****Bleeding:****
- Significant bleeding, especially if on blood thinners.
8. ****Death:****
- Very rare but serious complications can lead to death.

Please consult with your healthcare provider for detailed information and to address any concerns you may have. They can provide more personalized information based on your medical history and condition.

Table 6. Cont.

Gemini's response	Incomplete
Unfortunately, there is currently no cure for coronary artery disease (CAD) that completely reverses the existing plaque buildup in the arteries. Once plaque accumulates and hardens on the artery walls, it cannot be fully removed [Mayo Clinic, National Institutes of Health (.gov)]. However, this doesn't mean there's no hope! Here's the good news: • Management and improvement: Even though complete reversal isn't possible; CAD can be effectively managed and its progression slowed significantly. Through lifestyle changes, medications, and sometimes procedures, you can improve blood flow to the heart, prevent complications like heart attacks, and live a long and healthy life. • Lifestyle changes: Maintaining a heart-healthy diet, regular exercise, weight management, and stress management can significantly improve your heart health and slow the progression of CAD. • Medications: Medications like statins can help lower cholesterol levels and reduce the risk of further plaque buildup. • Procedures: In some cases, procedures like angioplasty and stenting can open blocked arteries and improve blood flow. Here are some studies showing progress in managing CAD: • High-dose statins: A 2006 study called ASTEROID found that high-dose statins might be able to reverse some plaque buildup in arteries, though it highlights the need for very low LDL cholesterol levels [WebMD]. • Research on plaque reversal: There's ongoing research into new methods to potentially reverse plaque buildup, but these are still under investigation [MedicalNewsToday]. If you have CAD, the focus should be on managing the condition to prevent complications and improve your heart health. Talk to your doctor about the best course of treatment for your individual situation.	
Bing Chat's response	Incomplete
Catheter ablation is a safe and effective treatment for various heart arrhythmias, including atrial fibrillation (AFib) and supraventricular tachycardia (SVT). However, like any medical procedure, it does carry some risks. Here are the potential complications: Bleeding and Bruising: Occur at the catheter insertion site. Infection: Although rare, there's a risk of infection where the catheter was placed. Blood Clots: Rarely, blood clots can form and potentially travel to the lungs or brain, causing a stroke. Damage to Blood Vessels: The catheter may inadvertently damage blood vessels during the procedure. Remember that these risks are infrequent, and your healthcare provider will carefully assess the benefits versus potential complications before recommending catheter ablation.	

inquiries. ChatGPT-4o achieved the highest 'reproducible' score at 90%, followed by Gemini at 86%, and Bing at 74%. The NLPs' answers and accuracy for two example questions are demonstrated in Table 6.

Discussion

In this study, we assessed the dependability, usefulness, and potential misapplication of information produced by ChatGPT-4o, Gemini, and Bing Chat in response to patient inquiries about SVT. ChatGPT-4o has the potential to provide important answers to frequently asked patient questions about SVT compared to Gemini and Bing Chat. Recent technological advancements have enabled the development of state-of-the-art AI systems, such as ChatGPT-4o, Bing Chat, and Gemini. Natural language processing models are proficient in executing a variety of linguistic tasks and generating responses that mimic human-like communication. Significant advancements in NLPs have enabled them to produce answers to numerous healthcare-related inquiries. The growing trust and dependence on these models by patients could contribute

to the widespread propagation of misinformation and detrimental guidance^[5]. ChatGPT-4o, among these NLPs, is extensively utilized and has been innovatively developed with a vast amount of information covering numerous topics. ChatGPT-4.0 was initially developed by OpenAI in 2018 and, through successive advancements, evolved over time, ultimately resulting in the launch of ChatGPT-4o in March 2023^[12]. Improvements in each new version of these models have expanded access to a more extensive dataset. While the adoption of NLPs by patients and healthcare professionals continues to grow, the likelihood of disseminating erroneous information must always be carefully appraised. This study emphasizes that ChatGPT-4o generated sufficient and precise responses to inquiries concerning fundamental aspects of the disease, diagnosis, treatment-related risks and complications, follow-up care, and lifestyle modifications, including dietary management of SVT. With ChatGPT-4o achieving the highest rate of 'totally correct' responses at 92%, followed by Gemini at 70% and Bing Chat at 58%, this suggests a greater degree of success in delivering precise

and thorough responses. While ChatGPT-4o delivered the most accurate and reproducible responses, Bing Chat exhibited the lowest performance in both categories. In terms of reproducibility, ChatGPT-4o attained the highest score at 90%, followed by Gemini at 86% and Bing Chat at 74%. Our findings suggest that ChatGPT-4o demonstrates competence in delivering precise and reliable responses to commonly asked questions about SVT. Furthermore, ChatGPT-4o has the potential to enhance patient education and facilitate improved communication between patients and healthcare professionals.

Natural language processing models such as ChatGPT, Gemini, and Bing Chat can assist in addressing questions that patients may hesitate to ask or require prompt answers to regarding their condition. The implementation of these technologies within healthcare services can substantially mitigate the workload of healthcare professionals and enhance overall time efficiency. Even though NLPs continue to evolve, a significant concern remains that excessive dependence on these tools by patients, without verifying the validity and consistency of their responses, may contribute to the dissemination of inaccurate medical information^[2–4]. It is crucial to demonstrate the precision and dependability of NLPs through more extensive research. Determining the trustworthiness of the responses generated by chatbot applications could assist in addressing this issue. Further research is necessary to substantiate the reliability and precision of these models.

In our study, we evaluated the trustworthiness and usefulness of responses to SVT-related inquiries produced by NLPs, including ChatGPT, Gemini, and Bing Chat. To the best of our knowledge, our study represents the first comprehensive investigation into the reliability, value, and potential risks associated with responses generated by NLPs to commonly asked questions concerning SVT.

Nevertheless, several limitations of this study should also be noted. Firstly, the reviewers are employed within the same facility, which may lead to common proficiency and viewpoints, potentially restricting the range of methodologies. While multiple reviewers were engaged in the study's assessment system, bias could still emerge due to the individual perspectives involved in the evaluation process. Although the questions included in our study were taken from the websites of esteemed organizations, they may not fully capture the concerns of all patients. In addition, in our study, the interpretation of the responses provided by NLPs was conducted from the perspective of physicians, which may have constrained the applicability of the evaluation from a patient's viewpoint.

In the future, multicenter studies that incorporate patient participation could facilitate the assessment of the utility and trustworthiness of information delivered by NLPs.

Conclusion

Consequently, our study highlighted that NLPs are capable of generating valuable answers to patient questions related to SVT. While ChatGPT-4o is a powerful tool, responses about SVT should be interpreted with caution due to the possibility of encountering misinformation. As NLPs—especially ChatGPT-4o—continue to improve, they hold great potential for the management of chronic conditions like SVT.

For patients, these models could assist with symptom tracking, medication reminders, or answering questions about their condition. For healthcare professionals, they could support the analysis of patient data, identification of trends, and even provide real-time decision support. The precision and reliability of information generated by NLPs are paramount in healthcare, and patients must be able to trust the accuracy of the information they receive.

In the future, as NLPs undergo further investigation and refinement, these models may offer substantial benefits for both patients and healthcare professionals in the management of chronic conditions such as SVT.

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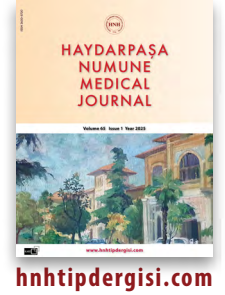
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The Importance of the Lesser Trochanter in Patients with Intertrochanteric Femur Fractures Treated Via Proximal Femoral Nailing

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Abstract

Introduction: The influence of factors believed to affect stability, such as an intact calcar (lesser trochanter), on surgical outcomes in intertrochanteric femur fractures remains debated. This retrospective study aims to clinically and radiologically assess how calcar intactness impacts treatment success and complication risk in patients aged 65–85 years treated with proximal femoral nailing (PFN).

Methods: We retrospectively evaluated 34 patients aged 65–85 years with intertrochanteric femur fractures treated by PFN at our institution who had complete documentation. Based on preoperative radiographs, patients were assigned to either the intact-calcar group (n=16) or the calcar-fractured group (n=18). We collected demographic, clinical, and radiological data, including age, sex, smoking status, preoperative delay, intensive care requirement, hemoglobin/hematocrit levels, varus alignment, tip-apex distance, lateral cortex integrity, lag screw migration and position, bone resorption, surgical failure (revision/nonunion), and time to union.

Results: The mean age was 77.8±7.5 years in the intact calcar group and 82.7±7.9 years in the calcar-fractured group (p=0.073). Preoperative delay was significantly longer in the calcar-fractured group, averaging 6.7±4.6 days compared to 3.8±1.6 days in the intact calcar group (p=0.02). Rates of varus alignment and tip–apex distance were similar across both groups (p>0.05), and lateral cortex integrity was preserved in approximately 94% of cases. Lag screw migration occurred in 25% of the intact calcar group and 55.6% of the calcar-fractured group (p=0.092), while bone resorption rates were 43.8% and 77.8%, respectively (p=0.076); neither reached statistical significance. Time to union was comparable—100.9±34.7 days for the intact calcar group and 103.4±26 days for the calcar-fractured group (p=0.812)—as were surgical failure rates (p>0.05).

Discussion and Conclusion: Despite a higher risk of mechanical complications from the loss of posteromedial support in calcar-fractured intertrochanteric fractures, precise anatomic reduction, preservation of lateral cortex integrity, and accurate lag-screw placement can achieve union and low failure rates similar to those of stable intertrochanteric fractures with an intact calcar.

Keywords: Intertrochanteric fractures; lesser trochanter; postoperative complications; prognosis.

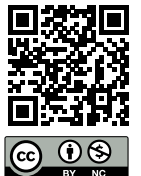
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The World Health Organization projects that by 2030, one in six people globally will be aged 60 or older^[1]. Additionally, by 2050, the population of individuals aged 80 and above is expected to grow to 426 million^[1].

Intertrochanteric fractures often occur in elderly, osteoporotic individuals, especially postmenopausal women^[2].

Older patients with hip fractures continue to face a high risk of various complications, including fixation failure, reoperation, surgical site infection, acute kidney injury, and more^[3].

One-year all-cause mortality following a hip fracture is 3.5 times higher in males and 2.4 times higher in females^[4].

The leading causes of death among hip fracture patients are pneumonia, circulatory system diseases, and dementia^[5].

Patients over 80 with multiple comorbidities, including low hemoglobin, heart, and lung issues, face a higher risk of death within a year following surgery^[6].

In the literature, some types of nails, like the proximal femur bionic nail for treating intertrochanteric femur fractures, offer better outcomes than the proximal femoral nail with antirotation^[7]. However, we prefer using the antirotation type due to our experience. To avoid mechanical failure, it is important to ensure proper reduction quality and correct center blade positioning on lateral hip X-ray^[8].

Patients with hip fractures who are mobilized early experience lower mortality and complication rates within the first 30 days compared to those who are not mobilized^[9].

This study aimed to examine how fractured versus unfractured lesser trochanters influence the clinical and radiological outcomes in patients with intertrochanteric femur fractures treated using proximal femoral nailing (PFN). Our objective was to support patient care and improve the accuracy of prognosis predictions.

Materials and Methods

This retrospective study collected data from patients with femoral intertrochanteric fractures who visited the emergency orthopedic clinic at Istanbul Kanuni Sultan Süleyman Training and Research Hospital between 2020 and 2025, using the hospital's electronic record system. Patients were divided into two groups: femoral intertrochanteric fractures with calcar fractures and femoral intertrochanteric fractures with calcar intact.

Patient Selection

The study included patients aged 65 to 85 with intertrochanteric femur fractures who underwent surgery at Istanbul Kanuni Sultan Süleyman Hospital from 2020 to 2025. Only those with complete records were eligible.

Exclusion criteria were: (1) pathological fractures (e.g., due to metastatic disease) and (2) metabolic or systemic conditions that could impair fracture healing (such as end-stage renal disease, coagulopathies, or severe cachexia).

Measurements

Demographic and clinical information for patients meeting the inclusion criteria was gathered from hospital records by the researchers. This data encompassed age, gender, radiological parameters, and other relevant variables. Radiographic parameters included the presence of varus alignment (postoperative fracture angulation), tip-apex distance (TAD) of the lag screw, and integrity of the lateral femoral cortex on postoperative X-rays.

We also noted whether patients required intensive care unit (ICU) admission and durations of hospitalization.

Surgical Approach Method

After anesthesia was administered, a urinary catheter was inserted. Each patient was positioned supine on a traction table. Fracture reduction was achieved under fluoroscopic guidance, and the patient's lower limb was positioned in traction on the fracture table. The surgical area was prepared aseptically and draped. A lateral incision (~5 cm) was made starting ~3 cm proximal to the tip of the greater trochanter to accommodate nail entry. Gluteal muscle fibers were separated with finger dissection until reaching the greater trochanter. Under fluoroscopy, an intramedullary guide wire was inserted across the fracture line, parallel to the femoral canal, passing from the proximal part of the greater trochanter. The femoral canal was then prepared, and an appropriately sized femoral nail was placed intramedullary. Using fluoroscopy, two screws were inserted and locked into the nail to fix the femoral neck from the proximal end, while two screws secured the distal end. The top screw of the nail was also locked. After verifying fracture stability with dynamic fluoroscopy, bleeding was controlled, irrigation was performed, and the incisions were sutured.

On the first post-op day, the patients were mobilized with partial weight-bearing and support, and in-bed rehabilitation was initiated.



Figure 1. A patient with an intact calcar.

Ethical Considerations

This study was approved by Istanbul University of Health Sciences Kanuni Sultan Süleyman Training and Research Hospital Ethics Committee (Ethics Approval Number: 2025.06.149) and conducted in accordance with the Helsinki Declaration and applicable ethical standards.

Statistical Analysis

The distribution of all continuous variables was initially assessed with the Shapiro–Wilk test. Data that are normally distributed are shown as mean±standard deviation (SD) and were compared between the “calcar-intact” and “calcar-fractured” groups using the independent-samples Student’s t-test. Variables that are not normally distributed are presented as median (range) and analyzed with the Mann–Whitney U test. Categorical variables are expressed as counts and percentages and compared using Pearson’s chi-square test or Fisher’s exact test, as appropriate. A two-tailed p -value<0.05 was considered statistically significant. All analyses were performed using NCSS (Number Cruncher Statistical System) version 2021.



Figure 2. A patient with a fractured calcar.

Results

The calcar-intact group (16 patients) had an average age of 77.8 ± 7.5 years (Fig. 1), while the calcar-fractured group (18 patients) averaged 82.7 ± 7.9 years (Fig. 2) (Table 1). This roughly 5-year age difference was not statistically significant ($p=0.073$). Women predominated in both groups. The calcar-intact group was about 81% female (13 of 16), compared to about 61% female (11 of 18) in the calcar-fractured group. This difference in sex distribution was not significant ($p=0.27$).

Only a few patients in each group were smokers (2 in the intact group versus 1 in the calcar-fractured group), with over 85% of patients being non-smokers. The prevalence of smoking did not differ significantly between groups ($p=0.59$). The calcar-fractured group experienced a notably longer average delay before surgery (6.7 ± 4.6 days, median 6) compared to the calcar-intact group (3.8 ± 1.6 days, median 3.5). This difference was statistically significant ($p=0.02$). Post-injury intensive care needs were similar: 25% of the calcar-intact group (4/16) and about 33% of the calcar-fractured group (6/18) required ICU care, a non-significant difference ($p=0.71$). At presentation, both groups had comparable blood measurements. The calcar-intact group’s mean initial Hgb was approximately



Figure 3. A patient with postoperative varus collapse.

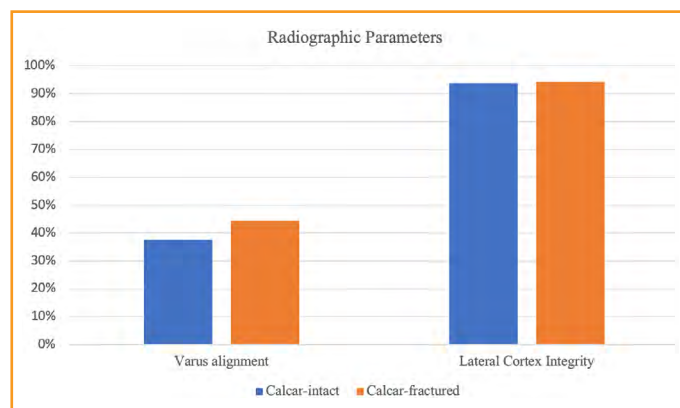


Figure 4. Distribution of varus alignment and lateral cortex integrity in calcar-intact and calcar-fractured groups.

11.65 g/dL versus about 11.38 g/dL for the calcar-fractured group ($p=0.60$), and mean Hct was about 35.8% versus about 35.4% ($p=0.74$). According to the AO/OTA classification, fracture types in the calcar-intact group were



Figure 5. A patient with screw migration after surgery.

classified as 6 patients with 31A-A1.1 and 10 patients with 31A1.2, and fracture types in the calcar-fractured group were classified as 8 patients with 31A2.1 and 10 patients with 31A2.2 (Table 1).

On radiographs, some patients from both groups showed varus collapse or alignment issues, with about 38% in the calcar-intact group and 44% in the calcar-fractured group (Fig. 3). This small difference was not statistically significant ($p=0.74$). Both groups achieved optimal lag screw placement, and the average tip-apex distance on the AP view was around 11.7 mm for calcar-intact patients compared to approximately 13.3 mm for calcar-fractured patients, with no significant difference ($p=0.59$). Nearly all

Table 1. Demographic and clinical features.

Variable	Calcar-intact (n=16)	Calcar-fractured (n=18)	Test	p
Age (years)	77.8±7.5; 79.5 (65–89)	82.7±7.9; 84 (67–96)	Independent sample t-test	0.073
Gender (Male/Female)	3/13	7/11	Fisher exact test	0.270
Smoker	2 (12.5%)	1 (5.6%)	Fisher exact test	0.591
Intensive care admission (yes)	4 (25.0%)	6 (33.3%)	Fisher exact test	0.715
Time until surgery (days)	3.8±1.6; 3.5 (2–7)	6.7±4.6; 6 (2–18)	Mann-Whitney U test	0.020
Preoperative Hgb (g/dL)	11.6±1.4; 11.9 (9.2–13.7)	11.4±1.6; 11.2 (8.9–14.1)	Independent sample t-test	0.600
Preoperative Hct (%)	35.8±4.0; 36.4 (28.8–41.8)	35.4±4.4; 35.2 (27.7–41.9)	Independent sample t-test	0.745
AO/OTA classification	31A1.1 (n=0.6) 31A1.2 (n=10)	31A2.1 (n=8) 31A2.2 (n=10)	Fisher exact test	<0.001

Continuous data are presented as mean±SD and median (min–max), while categorical data are presented as n (%). A p-value of less than 0.05 was considered statistically significant.

Table 2. Radiological measurements.

Variable	Calcar-intact (n=16)	Calcar-fractured (n=18)	Test	p
Varus alignment	6 (37.5%)	8 (44.4%)	Chi-square test	0.681
Tip-apex index (mm)	11.7±3.3; 12 (7–21)	13.3±4.8; 11.5 (8–22)	Mann-Whitney U test	0.589
Lateral cortex intact (yes)	15 (93.8%)	17 (94.4%)	Fisher exact test	1.000

Continuous data are presented as mean±SD and median (min–max); categorical data are presented as n (%). A p-value of less than 0.05 was considered significant.

Table 3. Clinical results.

Variable	Calcar-intact (n=16)	Calcar-fractured (n=18)	Test	p
Screw migration (yes)	4 (25.0%)	10 (55.6%)	Fisher exact test	0.092
Union time (days)	100.9±34.7; 92.5 (60–166)	103.4±26.0; 99.5 (65–150)	Independent sample t-test	0.812
Resorption (yes)	7 (43.8%)	14 (77.8%)	Fisher exact test	0.076
Proximal migration (yes)	4 (25.0%)	9 (50.0%)	Fisher exact test	0.172
Failure (yes)	4 (25.0%)	3 (16.7%)	Fisher exact test	0.681

Continuous data are presented as mean±SD and median (min–max); categorical data are shown as n (%). A p-value <0.05 was considered statistically significant.

fractures preserved an intact lateral cortex (15/16 in the calcar-intact group and 17/18 in the calcar-fractured group) (Fig. 4). Only one patient in each group had a compromised lateral wall, so there was no difference between the groups (Table 2).

Screw migration or removal of the lag screw was more frequently observed in the calcar-fractured group (10/18 patients, approximately 56%) compared to the calcar-intact group (4/16, 25%), although this difference was not statistically significant ($p=0.09$) (Fig. 5). Fracture healing times were similar across groups, with average union times around 101 days in the calcar-intact group and about 103 days in the calcar-fractured group (median roughly 90–100 days for

both), showing no significant difference ($p=0.82$). Signs of bone resorption at the fracture or lesser trochanter, seen on follow-up X-rays, were more common in the calcar-fractured group (14/18, approximately 78%) than in the calcar-intact group (7/16, approximately 44%), with this trend nearing significance ($p=0.08$). Proximal migration of the nail or screws occurred in about half of the calcar-fractured group (9/18, 50%) compared to 25% in the calcar-intact group (4/16), but this difference was not statistically significant ($p=0.17$). The overall failure rate, including cases requiring revision or nonunion, was similar: 4/16 patients (25%) in the calcar-intact group and 3/18 (16.7%) in the calcar-fractured group ($p=0.68$) (Table 3) (Fig. 6).

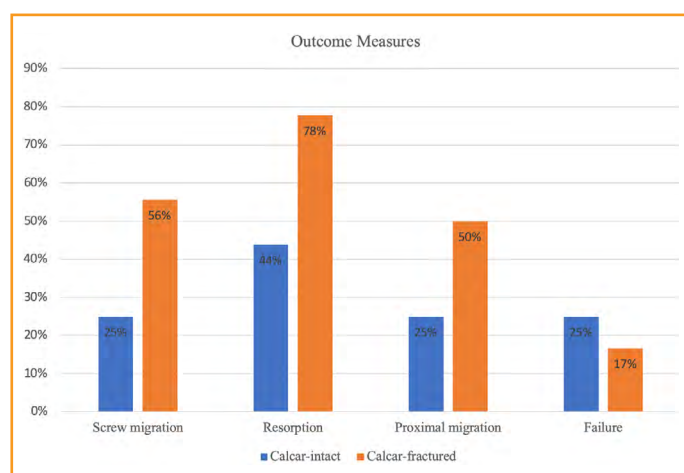


Figure 6. Distribution of screw migration, resorption, proximal migration, and failure percentages in calcar-intact and calcar-fractured groups.

Discussion

Male sex and age are significant factors affecting survival rates in patients over 65 with proximal femur fractures^[10]. In our study, the age and gender distributions were statistically similar between the calcar-intact and calcar-fractured groups.

The timing of surgery influences blood loss in proximal femoral nail fixation^[11]. In our study, the calcar-fractured group had a significantly longer average delay before surgery—about 6.7 days—compared to the calcar-intact group, which was around 3.8 days. This difference was statistically significant ($p=0.02$). Longer preoperative delays may result from more complex fracture management or the need for medical optimization; however, extended wait times did not appear to affect final union in this cohort.

Because there were few smokers, the effect of smoking on healing is likely to be minimal and similar across all groups.

Admissions to the intensive care unit were similar across both groups, indicating comparable severity of acute injury. The initial hemoglobin (Hgb) and hematocrit (Hct) levels were also alike, suggesting similar blood loss or anemia status at baseline. This reflects that the initial physiological conditions were equivalent.

Notably, preventing varus malreduction is recognized to reduce the risk of lag screw cut-out^[12]. In this series, both groups exhibited similar rates of varus angulation, suggesting comparable reduction quality. Consequently, differences in outcomes are unlikely due to initial varus malalignment.

All measured tip-apex distance values stayed comfortably below the standard threshold of 25 mm, which is linked to

lower failure rates^[13]. Accurate screw positioning—close to the femoral head apex on the AP view and centrally on the lateral view—is crucial to avoid cut-out^[14]. Both groups met this requirement.

This is significant because a fractured lateral cortex (lateral wall) is a recognized risk factor for excessive fracture collapse and fixation failure^[15]. In our study, lateral wall integrity was preserved in about 94% of cases, eliminating it as a confounding variable between the groups.

In our study, screw migration or cut-out of the lag screw was more frequently observed in the calcar-fractured group. Although this difference was not statistically significant, it suggests a trend: fractures without calcar support tend to have more screw migration. This is consistent with biomechanical research showing that loss of the calcar (posteromedial support) increases the load on the implant, raising stress on the lag screw^[15]. As a result, unstable fracture patterns are linked to higher cut-out rates in clinical studies^[14,15]. Our findings reflect this trend, though the limited sample size restricts definitive conclusions.

In our study, the fracture healing times were similar across groups. This indicates that, with successful fixation, unstable fractures can heal in approximately the same duration as stable fractures managed with intramedullary nailing. Both groups probably tolerated early weight-bearing, and the nails facilitated controlled collapse, resulting in comparable healing times when there was no failure.

We noted more cases of bone resorption at the fracture site or lesser trochanter in the calcar-fractured group compared to the calcar-intact group, with this difference nearly reaching statistical significance. This finding suggests that calcar deficiency may predispose to increased bone resorption, although it does not necessarily prolong the overall healing time when fixation is stable.

Proximal migration of the nail or screws was observed in roughly half of the fractured cases and 25% of the intact ones, indicating higher instability in calcar-fractured fractures. The absence of calcar support may cause the femoral head/neck fragment to telescope or the implant to slide further, leading to proximal migration. In unstable fractures, nail constructs tend to become more load-bearing, which can result in greater collapse or migration compared to fractures with support^[15].

Literature highlights that proper anatomical reduction and optimal screw placement are vital for preventing cut-out in unstable fractures^[14,16]. Both groups in our study achieved good reduction and screw positioning, which likely contributed to maintaining low failure rates

even in more difficult unstable fractures. Inadequate reduction was associated with failure after intramedullary nailing for trochanteric fractures^[17]. In the literature, a bionic triangular supporting intramedullary nail has shown advantages over proximal femoral nail antirotation in terms of stability and stress conduction when treating intertrochanteric fractures^[18]. In one study, for patients with low health status, PFN was advised^[19].

Failure rates for revision and nonunion were similar across both groups, indicating that a similar proportion faced major failure. This somewhat unexpected outcome might be attributed to the limited sample size and the fact that many unstable-fracture complications, such as screw migration and controlled collapse, were managed without resulting in complete failure. It is also possible that surgeons achieved adequate reduction and implant positioning in the calcar-fractured cases, thereby decreasing failure risk.

Conclusion

Apart from a longer preoperative delay in the calcar-fractured group, the two groups had similar baseline characteristics. Notably, both groups demonstrated comparable quality in surgical reduction and screw placement, evidenced by similar rates of varus alignment and tip-apex distances. The calcar-fractured (unstable) group showed higher rates of mechanical complications, including screw migration, fracture collapse or resorption, and implant migration. Nevertheless, careful surgical technique and possibly the small sample size contributed to only minor differences in final healing times and failure rates between groups. These results highlight the importance of restoring calcar support when possible and optimizing implant positioning to lower the risks associated with unstable intertrochanteric fractures.

Ethics Committee Approval: The study was approved by Istanbul University of Health Sciences Kanuni Sultan Süleyman Training and Research Hospital Ethics Committee (No: 2025.06.149, Date: 12.06.2025).

Conflict of Interest: The authors declare that there is no conflict of interest.

Informed Consent: Due to the retrospective design, informed consent form was not required, but all patient identifiers were kept confidential.

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Materials: S.S., B.K., F.Ş., S.P.; Data collection and/or processing: S.S., B.K., F.Ş., S.P.; Analysis and/or Interpretation: S.S., B.K., S.A., A.Ö.; Literature search: S.S., B.K., S.A.; Writing: S.S., B.K., A.Ö.; Critical review: S.S., B.K.

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Cytisine Use in a Smoking Cessation Clinic: The Case of Türkiye

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Abstract

Introduction: Smoking is a major public health concern worldwide. However, smoking cessation significantly reduces the negative outcomes associated with tobacco use. Therefore, smoking cessation treatments play a crucial role in public health. The two primary approaches to smoking cessation are psychotherapy and pharmacotherapy. In this study, we aim to share our experience with cytisine-based smoking cessation treatment in our outpatient clinic, which has recently been introduced in our country.

Methods: This is a retrospective cohort study conducted on individuals presenting to the Smoking Cessation Outpatient Clinic of Balıkesir Atatürk City Hospital between June 1, 2024, and December 31, 2024. Patients received cytisine treatment for one month, and their demographic data, smoking cessation status, and any reported side effects were recorded.

Results: A total of 754 patients presented to the Smoking Cessation Outpatient Clinic during the study period. After applying the exclusion criteria, the final study population included 557 patients. The smoking cessation rate among participants was 55.3% (n=308). Additionally, 124 out of 557 patients (22.3%) reported experiencing at least one side effect, with a total of 158 side effects recorded. Smoking cessation success was higher among patients who did not experience side effects.

Discussion and Conclusion: For a drug to be deemed appropriate for clinical use, it must be both effective and have minimal side effects. Previous studies have demonstrated the efficacy of cytisine, and its side-effect profile has been well documented in the literature. Our findings indicate that data from our country are generally consistent with existing literature. In our study, the most commonly reported side effects were nausea, dry mouth, and insomnia. We shared our experience with the use of cytisine, which has been recently introduced in our country. Our findings indicate that cytisine is effective in smoking cessation and is associated with mild, tolerable side effects.

Keywords: Cytisine; smoking addiction; smoking cessation.

Tobacco use is a significant public health concern and the leading preventable cause of morbidity and mortality worldwide. In the United States, an estimated 16 million adults currently live with a smoking-related disease [1]. Globally, smoking accounts for more than 7 million deaths annually. Long-term smokers have an average reduction in life expectancy of 10 to 11 years [2]. Furthermore, half of all smokers lose approximately 20 years of healthy life expectancy before succumbing to a smoking-related disease [3].

Smoking plays a significant role in the pathophysiology of various types of cancer, including lung, stomach, and colon cancers. It is also linked to numerous other diseases, such as chronic obstructive pulmonary disease (COPD), pulmonary infections, myocardial infarction, stroke, peripheral arterial disease, hypertension, and atherosclerosis [1]. Additionally, smoking imposes a substantial economic burden on societies. The economic costs associated with smoking include expenses related to the treatment of diseases

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in both active and passive smokers, loss of workforce productivity, premature mortality, and the environmental damage caused by smoking [4].

Fortunately, quitting smoking reverses much of the damage caused by smoking. Quitting before age 35 can prevent almost all premature deaths. Quitting smoking by age 60 increases life expectancy by three years. Quitting smoking after age 60 reduces mortality, cardiovascular disease, and cancer risk [2]. For these reasons, smoking cessation is crucial for reducing the associated health risks. Both psychotherapy and pharmacological treatments are employed in smoking cessation. Psychotherapy may involve individual therapy, group therapy, or behavioral interventions. Individual therapy can be delivered through brief physician consultations or telephone counseling. Pharmacological treatments include nicotine replacement therapies, varenicline, bupropion, and cytosine. Nicotine replacement therapies are available in various forms, such as patches, gum, inhalers, oral sprays, and lozenges [1,5].

Smokers often struggle to quit without assistance, primarily due to the development of addiction. The mechanism underlying this addiction and the subsequent chronic and repeated use of tobacco is rooted in the pharmacodynamics of nicotine. Nicotine binds to specific acetylcholine receptors in the central nervous system, predominantly subtypes of neuronal nicotinic acetylcholine receptors, and stimulates the release of neuromodulators, primarily dopamine. This release promotes pleasure, which reinforces the desire for continued consumption, ultimately leading to addiction [6].

To address nicotine addiction, nicotine replacement therapies have been developed, offering various forms of treatment. Varenicline, a partial agonist selective to $\alpha 4\beta 2$ nicotinic acetylcholine receptors (nAChR)—receptors involved in dopamine release following nicotine binding—helps alleviate cravings and withdrawal symptoms. Consequently, varenicline supports smoking cessation by maintaining moderate dopamine levels in the brain, thereby preventing withdrawal symptoms [7].

Bupropion is believed to exert its pharmacological effects by weakly inhibiting the reuptake of both dopamine and norepinephrine, thereby prolonging the duration of dopamine activity in the synapse. When used for smoking cessation, bupropion inhibits the dopamine reuptake associated with nicotine use. It offers both anti-craving and anti-withdrawal effects by antagonizing the nicotinic acetylcholine receptors [8].

Cytisine, a natural alkaloid found in plant genera such as *Cytisus laburnum* and *Sophora tetraptera*, acts similarly to varenicline. It is a selective partial agonist of the $\alpha 4\beta 2$ nicotinic acetylcholine receptors, which mediate nicotine's effects. Cytisine prevents nicotine binding, thereby reducing rewarding effects, withdrawal symptoms, and cravings [9].

In this study, we aimed to investigate the effectiveness of cytosine, which has recently been introduced as a smoking cessation treatment in our country. Our article is the first study reporting the results of cytosine use in smoking cessation in our country.

Materials and Methods

Study Design and Participants

This retrospective cohort study was conducted on individuals who presented to the Smoking Cessation Outpatient Clinic of Balıkesir Atatürk City Hospital. Patients who visited the clinic between June 1, 2024, and December 31, 2024, were included in the study. Demographic data included age, gender, and comorbidities such as cardiovascular disease (ischemic heart disease, heart failure, arrhythmia), pulmonary disease (COPD, asthma, pulmonary fibrosis, bronchiectasis, atelectasis), hypertension, diabetes, thyroid disease, and peripheral arterial disease.

Smoking history was categorized based on daily cigarette consumption (0–10, 11–20, 21–30, and >30 units/day) and smoking duration (0–10, 11–20, 21–30, and >30 years). Vital signs recorded at the time of presentation included blood pressure, pulse rate, body temperature, respiratory rate, and oxygen saturation. Educational status was classified as high school or lower, associate degree, undergraduate, or graduate. Additionally, smoking cessation status and reported side effects following cytosine use were documented. Our study is a descriptive study.

All data were obtained from patient files, which were created separately for each individual during their initial visit to the Smoking Cessation Outpatient Clinic, as well as from patient follow-up forms and the hospital automation system.

Inclusion Criteria:

- Age between 18 and 65 years
- Presentation to the Smoking Cessation Outpatient Clinic and initiation of cytosine treatment

Exclusion Criteria:

- Patients for whom cytosine was deemed inappropriate by the physician

- Patients who refused medication
- Patients who did not adhere to the prescribed smoking cessation treatment or discontinued the medication
- Patients who did not attend follow-up visits
- Patients with incomplete or inaccurate data in their records
- Pregnant or breastfeeding individuals
- Patients with a known allergic reaction to cytisine

Procedure

The study data were obtained from patient files, which were completed separately for each individual, and from the hospital automation system. Patient files are documented by physicians for every patient who presents to the Smoking Cessation Outpatient Clinic. The clinic is staffed by physicians authorized by the Ministry of Health of the Republic of Türkiye, and all treatments are administered by certified physicians.

During the study, all patients received cytisine (Nikitabs® 1.5 mg, 100 tablets; Nobel Pharmaceuticals) following a standardized medical treatment protocol (Table 1). The duration and dosage of treatment were identical for all patients. Smoking cessation status was recorded at the end of the treatment period. After completing the pharmacological intervention, patients were scheduled for follow-up visits, during which they were assessed for any side effects associated with cytisine use. These follow-ups were conducted through face-to-face interviews by the physician, and all reported side effects were documented.

All reported side effects were evaluated by the coordinator physician of the study. The classification of side effects was conducted using the method described by Courtney et al.^[10] For an adverse event to be considered a side effect, the patient must have received at least one dose of cytisine. All side effects were categorized according to the Medical Dictionary for Regulatory Activities (MedDRA) terminology, and causalities were evaluated using the criteria defined by the World Health Organization. Patients were permitted to report more than one side effect. Side events were

Table 1. Cytisine treatment regimen

Days	Cytisinea
1 to 3	One capsule every 2 hours. Maximum of 6 capsules a day
4 to 12	One capsule every 2.5 hours. Maximum of 5 capsules a day
13 to 16	One capsule every 3 hours. Maximum of 4 capsules a day
17 to 20	One capsule every 5 hours. Maximum of 3 capsules a day
21 to 28	1-2 capsules a day

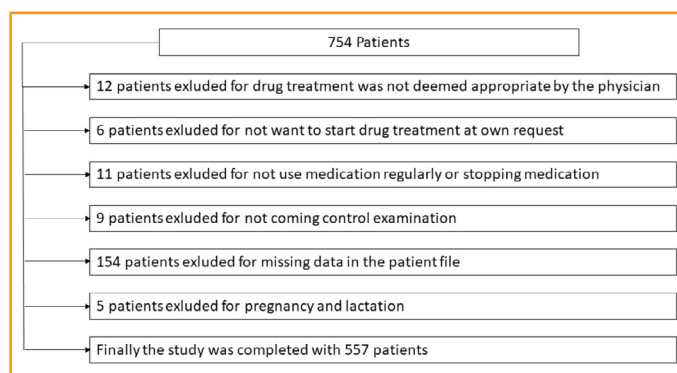


Figure 1. Flow Chart.

documented one month after the initiation of treatment.

The study was approved by the local ethics committee and conducted in accordance with the principles of the Declaration of Helsinki (Balıkesir Atatürk City Hospital Ethics Committee, Date: 26.12.2024, Decision No: 2024/12/85).

Statistical Analysis

Statistical analyses were conducted using SPSS version 23 (IBM). Data were presented as number and percentage. Categorical variables were analyzed using the chi-square test. A p-value of <0.05 was considered statistically significant.

Results

This study was conducted on patients who presented to the Smoking Cessation Outpatient Clinic. During the study period, 754 patients visited the clinic; however, after applying the exclusion criteria, the final analysis included 557 patients. The study flowchart is presented in Figure 1.

Table 2. Distributions of Side Effects in Our Study

	n	%	Total (n)
Nausea	34	6,1	557
Dry Mouth	18	3,2	557
Insomnia	17	3,1	557
Headache	16	2,9	557
Weakness	15	2,7	557
Dizziness	15	2,7	557
Stomach Ache	10	1,8	557
Skin Rash	8	1,4	557
Chest Pain	6	1,1	557
Diarrhea	5	0,9	557
Constipation	5	0,9	557
Palpitation	4	0,7	557
Anorexia	4	0,7	557
Sweating	1	0,2	557

The patients included in the study were between 18 and 65 years of age, with a mean age of 48.94 ± 12.23 years. Of the participants, 370 (66.4%) were male.

The distribution of comorbidities among the study population was as follows: 129 patients (23.2%) had cardiovascular disease, 115 (20.6%) had pulmonary disease, 140 (25.1%) had hypertension, 62 (11.1%) had diabetes, 40 (7.2%) had thyroid disease, and 18 (3.2%) had peripheral vascular disease.

The number of cigarettes smoked per day was categorized as follows: 1–10 cigarettes/day in 23 patients (4.1%), 11–20 cigarettes/day in 147 patients (26.4%), 21–30 cigarettes/day in 295 patients (53%), and >30 cigarettes/day in 92 patients (16.5%). Smoking duration was classified as follows: 0–10 years in 124 patients (22.3%), 11–20 years in 149 patients (26.7%), 21–30 years in 183 patients (32.9%), and >30 years in 101 patients (18.1%).

Regarding educational status, 378 patients (67.9%) had a high school education or lower, while 179 patients (32.1%) had an associate, undergraduate, or graduate degree. The smoking cessation rate at the end of the one-month treatment period was 55.3% ($n=308$).

Among the 557 patients included in the study, at least one side effect was reported by 124 patients (22.3%). A total of 158 side effects were reported by these 124 patients. The reported side effects are presented in Table 2.

In our study, among the 308 patients who successfully quit smoking, 223 did not report any side effects, while 85 experienced at least one side effect. This difference was statistically significant ($p<0.05$).

Discussion

This is the first study on cytisine use for smoking cessation in our country. The use of cytisine for smoking cessation treatment was introduced in our country for the first time in April 2024. In this article, we present the initial national data on cytisine.

Cytisine was first developed in Bulgaria in the 1960s for the treatment of tobacco addiction and was marketed under the trade name Tabex. It was derived from the plant *Cytisus laburnum* L. (Golden Rain) [11]. Similar to varenicline, cytisine acts as a partial agonist of nicotinic acetylcholine receptors [12]. Notably, cytisine is approximately ten times more affordable than both nicotine replacement therapies and varenicline [13].

Clinical studies have demonstrated that cytisine more than doubles the likelihood of smoking cessation success

compared to placebo. Additionally, it has been reported to be more effective than nicotine replacement therapy. When compared with varenicline, another pharmacological smoking cessation agent, cytisine was found to be at least equally effective. Furthermore, in terms of side effect profile, cytisine has been shown to cause fewer side effects than varenicline [12,14].

In July 2021, varenicline was withdrawn from the market due to the detection of high levels of N-nitroso-varenicline, a potentially harmful compound [15]. Given these factors, cytisine has emerged as a promising alternative for smoking cessation treatment. However, for a pharmacological agent to be widely adopted in smoking cessation therapy, it must demonstrate both high efficacy and a favorable safety profile with minimal side effects.

In a study evaluating the efficacy of cytisine, the experimental group received both cytisine and smoking cessation counseling, while the control group received only smoking cessation counseling. The smoking cessation rate was 32.1% in the cytisine group and 7.3% in the control group [15]. A 2014 study on cytisine's effectiveness for smoking cessation found a 40% cessation rate at the end of one month [12]. Tinghino et al. [16] reported a smoking cessation success rate of 50.5% with cytisine in their study. In our study, the smoking cessation success rate with cytisine treatment was 55.3%. These results highlight cytisine as a viable treatment option for smoking cessation.

Regarding its side effect profile, cytisine has generally been reported to have no serious side effects. In a study by Pastorino et al., [15] cytisine was administered to 470 patients, with 41.7% ($n=196$) reporting a total of 399 side effects. The most commonly reported side effects included sleep disturbances (12.1%), nausea and vomiting (8.5%), and increased appetite and weight gain (4.0%). In another study, 71.4% ($n=482$) of 675 patients receiving cytisine reported at least one side effect. A total of 997 side effects were reported, with the most common being abnormal dreams (16.6%, $n=120$), nausea (10.9%, $n=79$), sleep disturbances (18.6%, $n=135$), and headaches (9.2%, $n=67$) [10].

Rigotti et al. [17] conducted a study with 269 patients, where 64% ($n=172$) reported side effects after using cytisine for six weeks. In total, 459 side effects were reported, with the most common being insomnia (9%, $n=23$), abnormal dreams (8%, $n=22$), headaches (7%, $n=18$), nausea (6%, $n=16$), constipation (6%, $n=16$), anxiety (3%, $n=7$), and diarrhea (4%, $n=10$).

In a study by Walker et al. [12] comparing cytisine and nicotine replacement therapy (NRT), 31% ($n=204$) of the total 655

patients in the cytisine group experienced side effects. The most common side effects included nausea and vomiting (4.6%, n=30), sleep disorders (4.3%, n=28), circulatory and respiratory symptoms (1.4%, n=9), depressive disorder (2%, n=8), colitis and diarrhea (1.2%, n=8), headache (1.2%, n=8), dizziness (1.2%, n=8), weakness and fatigue (0.9%, n=6), and somnolence (0.8%, n=5).

In the efficacy and safety study conducted by Phusahat et al. [18] in Thailand, 67 patients received cytisine, and side effects were reported in 37 of these patients (55.22%). The reported side effects included insomnia (11.94%, n=8), drowsiness (7.46%, n=5), dizziness (5.97%, n=4), abdominal distension (4.48%, n=3), headache (4.48%, n=3), dry mouth (4.48%, n=3), and sore throat (4.48%, n=3).

A study conducted in New Zealand on 313 participants receiving cytisine for smoking cessation found that 111 patients (35.46%) reported a total of 297 side effects. The most common side effects were headache (18.5%, n=55), nausea (10.1%, n=30), insomnia (6.4%, n=19), fatigue (3.4%, n=10), stomach pain (3.4%, n=10), vivid dreams (3%, n=9), and dry mouth (3%, n=9) [19].

In our study, the incidence of side effects was 22.3%. It is important to consider that genetic, environmental, and cultural factors may influence the occurrence of drug side effects. The most commonly reported side effects in our study were nausea, dry mouth, and insomnia, which were consistent with the findings in the literature.

In our study, a high success rate in quitting smoking was achieved with the use of cytisine, in line with the literature. Four systematic reviews reported that cytisine was superior to placebo in short- and long-term smoking cessation [20]. Studies in the literature show that cytisine is a proven drug for smoking cessation. Therefore, in our country, the Ministry of Health recommends that patients who want to quit smoking start cytisine within the indication.

Although cytisine is used almost exclusively as a smoking cessation drug, it has been tried in a few other cases. In these trials, it has been reported to increase appetite and to be a potential chemotherapeutic because it induces apoptosis [21,22].

Cytisine is generally regarded as a safe drug, which may be attributed to its relatively short half-life (4.8 hours) compared to other smoking cessation medications [12]. Furthermore, cytisine is excreted unchanged through the kidneys without undergoing hepatic metabolism, thereby reducing the risk of drug interactions [23]. This characteristic contributes to its safety profile. It is well established that smoking cessation success is negatively

impacted by the occurrence of side effects, as these can lead to discontinuation of the treatment. In our study, we observed that fewer side effects were associated with higher rates of smoking cessation.

Among the patients who successfully quit smoking, 89% (with 2 missing cases) of those who experienced side effects after 1 week recommended cytisine to other individuals attempting to quit smoking [12]. Additionally, it has been reported that the use of cytisine does not negatively impact quality of life. In a study comparing cytisine with a placebo, no significant differences in quality of life were observed [18]. These findings suggest that cytisine does not cause severe side effects and that any side effects experienced are generally mild and tolerable.

Conclusion

Cytisine is a recently introduced smoking cessation medication in Türkiye, demonstrating significant potential in this domain. This article shares our experiences regarding its efficacy and side effect profile. Our findings indicate that cytisine is effective in promoting smoking cessation in our country. The side effect profile was also evaluated, revealing that the most common side effects include nausea, dry mouth, and insomnia. Consequently, cytisine has proven to be an affordable and effective smoking cessation option in Türkiye, with mild, tolerable side effects.

Ethics Committee Approval: The study was approved by Balıkesir Atatürk City Hospital Ethics Committee (No: 2024/12/85, Date: 26.12.2024).

Conflict of Interest: The authors declare that there is no conflict of interest.

Informed Consent: The study's participants gave their written informed consent.

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Adolescent Pregnancy Neonatal Birth Outcomes: A Single-Center Retrospective Cohort Study

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Abstract

Introduction: Adolescent pregnancies, which directly influence adolescent health, are considered high-risk pregnancies due to poor maternal and fetal outcomes. In this study, we aimed to investigate the effects of adolescent pregnancies, which are a global problem, on early newborn health and to raise awareness about adolescent pregnancies.

Methods: This study was designed as a retrospective, cross-sectional, single-center study. Newborns of 94 adolescent mothers aged 10–19 who gave birth between January 2021 and January 2022 were included in the study. Newborns of 106 non-adolescent (young adult) mothers aged 20–24 who gave birth during the same period were included in the control group. Anthropometric measurements, demographic data, early morbidity and mortality rates, diagnostic information, and hospitalization data of the babies in both groups were obtained retrospectively from electronic file records.

Results: During the study period, 6.62% (n=94) of 1419 women who gave birth in our hospital were in the adolescent age group, and 7.47% (n=106) were in the young adult age group. Gestational weeks at birth, rates of hospitalization in the neonatal unit, Apgar scores, and mortality and morbidity rates of infants of adolescent mothers were similar to those of young adult mothers ($p>0.05$). The median birth weight of infants of adolescent mothers was 3060 g (645–4085), which was significantly lower than the 3210 g (688–4410) median birth weight of infants of non-adolescent mothers ($p=0.003$). The frequency of small for gestational age (SGA) infants born below the 10th percentile for gestational age was 14.9% in adolescent mothers, while only 3% of infants of young adult mothers were born SGA ($p=0.003$).

Discussion and Conclusion: Adolescent pregnancies are considered high-risk pregnancies. In terms of maternal and neonatal health, close follow-up of adolescent pregnancies in both the early and late periods can help prevent possible complications.

Keywords: Adolescent pregnancy; newborn health; small for gestational age.

The adolescent period is defined as the transition period from childhood to adulthood in the process of psychological and social change between the ages of 10–19 [1]. Even though the somatic and psychological development of adolescent individuals is not yet mature, they become fertile with menarche, and pregnancy-related risks may occur with increasing frequency. When assessed from a multidisciplinary perspective including education,

health, economy, sociology, and law, adolescent pregnancies are classified as high-risk pregnancies [2]. Since the growth and maturation of pregnant adolescents are still ongoing, their reserves are low. The nutritional needs of adolescents increase with the growth of the fetus, puerperium, and breastfeeding in the postnatal period [3]. The risks of both adolescence and pregnancy are reflected onto the mother and the newborn. Adolescent

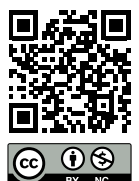
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pregnancies are associated with maternal risks including maternal anemia, eclampsia, and maternal death, as well as neonatal risks including preterm birth, low birth weight, and perinatal mortality [2–6]. The ability of the adolescent mother to cope with the problems she will encounter in the early neonatal period is not yet adequate. In addition, lack of support from a partner and family poses a significant threat to the health of the newborn. The anticipated risks can be reduced if these adverse conditions are improved with close antenatal monitoring and support of the adolescent mother [7,8].

In this study, we aimed to investigate the effects of adolescent pregnancies, which are a global problem, on early newborn health and to raise awareness about adolescent pregnancies.

Materials and Methods

Study Design and Setting

This study was designed as a retrospective, cross-sectional, single-center study. It was conducted in a tertiary city hospital in Istanbul, Türkiye, where approximately 2000 babies are born per year, between January 2021 and January 2022. The study was approved by the Clinical Research Ethics Committee of Istanbul Medeniyet University Goztepe Education and Research Hospital (Registration No: 2023/0959, date: 20.12.2023). It complied with the principles of the Declaration of Helsinki and Good Clinical Practice.

Participants

The study group included infants of adolescent mothers aged 10–19 who gave birth during the study period, and the control group included infants of young adult mothers aged 20–24. Anthropometric measurements, demographic data, early morbidities, diagnostic information, and hospitalization data of infants in both groups were obtained retrospectively from electronic file records. Newborns were categorized into subgroups according to gestational week. Those born at ≥ 37 weeks of gestation were classified as term, 34–36 weeks as late preterm, 32–33 weeks as moderate preterm, 28–<32 weeks as very preterm, and <28 weeks as extremely preterm [9]. A newborn whose weight was <10th percentile for gestational age was defined as small for gestational age (SGA) [10].

Statistical Analysis

SPSS software version 20.0 (Statistical Packages for Social Sciences: SPSS Inc., Chicago, IL, USA) was used

for all statistical analyses in the study. Demographic data and distribution of diagnoses were analyzed with descriptive methods. Continuous variables with a normal distribution were presented as mean $\pm$ standard deviation, while those without a normal distribution were expressed as median and interquartile range (IQR). The Kolmogorov–Smirnov test was used to assess the normality of distribution. In comparisons between adolescent and non-adolescent mothers, an independent samples t-test was used for continuous variables with a normal distribution, while the Mann–Whitney U test was applied for those without a normal distribution. For categorical variables, if the frequency in the cells was <5, Fisher’s exact test was applied instead of the chi-square test. A p-value of <0.05 was considered statistically significant.

Results

During the study period, 6.62% (94/1419) of the 1419 women who gave birth in our hospital were in the adolescent age group, and 7.47% (106/1419) were in the young adult age group. Study findings revealed that young adult mothers gave birth more frequently than adolescent mothers ($p=0.001$). There was no significant difference in gestational age between the babies of adult and adolescent mothers ($p=0.750$). The rate of spontaneous vaginal delivery was found to be 63.8% (60/94) among adolescent mothers, whereas it was 48.1% (51/106) among adult mothers ($p=0.071$). Demographic data of mothers, including age, number of pregnancies, and nationality, are presented in Table 1.

When the infants of adolescent mothers were compared with those of young adult mothers in terms of neonatal unit admission frequency and mortality rates, no significant difference was found between the groups ($p=0.860$). In both groups, the cause of mortality was extreme prematurity, as the infants were born at <24 weeks of gestational age. The most common reasons for neonatal hospitalization were similar across groups and included indirect hyperbilirubinemia, inadequate feeding, and abnormal weight loss. Apgar scores of infants of adolescent mothers were similar to those of young adult mothers ($p=0.240$).

The median birth weight of infants of adolescent mothers was 3060 g (645–4085), which was significantly lower than the 3210 g (688–4410) median birth weight of infants of non-adolescent mothers ($p=0.003$). The frequency of

Table 1. Obstetric and perinatal characteristics of adolescent and adult pregnant women

Characteristics	Study group n=94	Control group n=106	p
Maternal age year	18 (14-19)	20 (22-24)	0.001**
Gestation	1 (1-4)	2 (1-5)	0.001*
Gestational age at birth weeks	39.4 (25.1-42.1)	39.5 (25-42.1)	0.75**
Ethnic group n (%)			0.88***
Turkish	86 (91.5)	93 (93)	
Syrian	7 (7.4)	5 (5)	
Other	1 (1.1)	2 (2)	
Mode of delivery vaginal n (%)	60 (63.8)	51 (48.1)	0.071

The values are given as medians (25th to 75th percentiles); Pearson's chi-squared test, *p<0.05 systatistically significant, ***Fisher exact test; **Mann-Whitney U test; Numbers in bold indicate statistically significant values.

Table 2. Early neonatal period outcomes of infants of adolescent and adult mothers

Newborn outcomes	Study group n=94	Control group n=106	p
Apgar score $\geq$ 7n (%)	84 (89.4)	94 (94)	0.240
Birth weight [†] gr	3060 (645-4085)	3210 (688-4410)	0.003**
Sex female n (%)	45 (47.87)	48 (45.28)	0.980
SGA (%)	14 (14.89)	3 (2.83)	0.003***
Admission to NICU n (%)	14 (14.89)	14 (13.2)	0.860
Mortality rate n (%)	1 (1.06)	1 (0.94)	0.960***

NICU: Neonatal intensive care unit, SGA: Small gestational age; [†]The values are given as medians (25th to 75th percentiles); Pearson's chi-squared test, *p<0.05 systatistically significant **Mann-Whitney U test; ***Fisher exact test; Numbers in bold indicate statistically significant values.

small for gestational age (SGA) infants born below the 10th percentile for gestational age was 14.9% (14/94) in adolescent mothers, while only 2.8% (3/106) of infants of young adult mothers were born SGA (p=0.003) (Table 2).

Discussion

The largest adolescent population in world history is living today. The vast majority of this population consists of 1.2 billion girls and boys between the ages of 10–19 living in low- or middle-income countries [11,12]. Therefore, the economic, social, and political development of countries is closely related to the physical and mental health of adolescents [13]. Adolescent pregnancies, which directly influence adolescent health, are associated with poor maternal and fetal outcomes. In this cross-sectional study, we compared infants of adolescent mothers aged $\leq$ 19 and infants of young adult mothers in terms of early neonatal outcomes. We showed that infants in adolescent pregnancies were born with lower birth weights, and the incidence of SGA was higher.

Adolescent pregnancies are a major health problem in both developing and developed countries [14,15]. The

World Health Organization (WHO) prioritizes issues related to the management of adolescent pregnancies within the scope of the Millennium Development Goals [16]. Although the incidence has decreased due to the impact of comprehensive evidence-based projects and practices for prevention, adolescent pregnancies maintain their importance [7,16,17]. The prevalence of these pregnancies has been reported as 11% of all births worldwide [4]. Adolescent pregnancies are 3–4 times more common in low- and middle-income countries (LMIC) than in high-income countries. Poverty, difficulty in accessing healthcare services, lack of educational opportunities, gender inequality, and cultural practices regarding sexual health and marriage may explain the high incidence of adolescent pregnancies in LMIC [17–20].

Our country is among LMIC. According to the Türkiye Demographic and Health Survey, 12.1% of women have their first child before the age of 18. The adolescent fertility rate varies between regions, ranging from 3% in the Eastern Black Sea Region to 10% in Central Eastern Anatolia [21]. In this cross-sectional study conducted in a tertiary city hospital in Istanbul, the adolescent fertility rate was found

to be approximately 7%. Accordingly, it can be estimated that the incidence of adolescent pregnancy is even higher in real life. Istanbul is the most populous megacity in Türkiye and receives the most internal and external migration [22]. Therefore, we believe that the adolescent fertility rate we found reflects the national average.

In this study, we did not observe a correlation between the nationality of the pregnant women and the adolescent birth rate. An analysis assessing 65 studies from 12 countries in the literature reported that the pregnancy outcomes of immigrant women were poorer than those of native mothers [23]. The adolescent birth rate was found to be higher in Turkish immigrant women residing in the Netherlands than in the native-born population [24]. However, in the current study, most of the foreign mothers were Syrian. Even though the western part of our country is more similar to European countries, the eastern and southern regions share a similar cultural geography with Syria. Therefore, we interpreted that the birth rates of Syrian adolescent mothers could be similar to those of Turkish adolescent mothers. In addition, significant differences may not have been detected due to the limited sample size. Only 6% of the mothers in the cohort of this study were Syrian.

Adolescents' tendency to engage in risky behaviors negatively affects the newborn [2,4,6,25–28]. The health risk behaviors of adolescents are grouped into six categories: behaviors that contribute to unintentional injuries and violence; sexual behaviors that contribute to unintended pregnancies and sexually transmitted infections; alcohol and substance use; tobacco use; unhealthy dietary behaviors; and physical inactivity [29]. Adolescent pregnancy is largely a result of these behaviors. While the adolescent continues to grow and mature, she also has to experience the changes related to pregnancy. The adolescent's reserve for pregnancy is very low.

In concordance with the literature, the birth weight of infants of adolescent mothers was lower than that of infants of young adult mothers in the current study. The incidence of SGA was significantly increased in infants of adolescent mothers. However, early neonatal outcomes of adolescent mothers, including low Apgar scores, incidence of prematurity, frequency of admission to the neonatal intensive care unit, and mortality and morbidity rates, did not exhibit significant differences compared with infants of young adult mothers. The mortality rate of infants of adolescent and young adult mothers was also similar, and the deaths were associated with extreme prematurity. Adverse effects other than the low

birth weight and high incidence of SGA attributed to infants of adolescent mothers not demonstrated in our study may be due to the very limited number of early adolescents. In addition, the median ages of adolescent and young adult mothers were not far apart in our study. The median age of the adolescent group was 18 years. The youngest adolescent mother was 14 years old, and there was only one case at this age. The younger age of the early adolescent mother (10–14 years), who has just finished childhood, imposes more obvious risks for both the mother and the baby. Akseer et al. [25] compared adolescent and older mothers and their babies and observed that early adolescent mothers (10–14 years) had the highest rates of prematurity, SGA, low birth weight (LBW), and neonatal mortality.

They showed that these risks gradually decreased with increasing age and increased again in older mothers (over 40 years), forming a U-shaped trend. Other studies also reported parallel results [5,6].

This study has certain limitations. First, it is a single-center study; therefore, the number of early adolescents in the 10–14 age group, which is at higher risk for adolescent pregnancies, is very small. Secondly, the age range of the control group is narrow and close to that of the adolescent group.

Conclusion

Adolescent pregnancies constitute a global problem that negatively influences the lives of both the mother and the infant. Adolescent mothers, whose growth and maturation have not yet been completed, and their babies require special care. Awareness of the consequences of adolescent pregnancies should be increased, and adolescent pregnancies should be prevented for the health of the world's population in the future.

Ethics Committee Approval: The study was approved by Istanbul Medeniyet University Goztepe Education and Research Hospital Ethics Committee (No: 2023/0959, Date: 20.12.2023).

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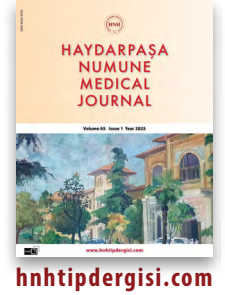
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Acute Right-sided Colonic Diverticulitis is an Unusual Cause of Right Lower Quadrant Pain: A Retrospective Single-center Cohort Study

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Abstract

Introduction: Acute right lower quadrant pain is a common symptom in emergency departments. The most common etiology is acute appendicitis, while other causes may be overlooked. Acute right-sided colonic diverticulitis is one of them. It is usually seen in young male patients. Ultrasonography (USG) and computed tomography (CT) are used for radiologic diagnosis. The aim of this study was to investigate the diagnosis, treatment, and surgical management of right-sided colonic diverticulitis.

Methods: Patients hospitalized in our clinic between 2018 and 2022 with a diagnosis of right-sided colonic diverticulitis were retrospectively analyzed. Age, gender, WSES grade, surgical status, laboratory values, intravenous antibiotic therapies, length of hospitalization, and mortality were evaluated.

Results: Between 2018 and 2022, a total of 20 patients were followed with acute right-sided colonic diverticulitis. Twelve patients were diagnosed by imaging and clinical examination, while 4 patients (20%) were operated on with a prediagnosis of acute appendicitis, and right-sided colonic diverticulitis was detected perioperatively. All patients diagnosed with acute right-sided colonic diverticulitis in the emergency department and hospitalized were managed conservatively and did not require surgery.

Discussion and Conclusion: In the differential diagnosis of right-sided colonic diverticulitis and acute appendicitis, physical examination and laboratory values are insufficient. Radiologic imaging, especially USG and CT, is essential. Following diagnosis, right-sided colonic diverticulitis can be effectively managed with conservative treatment. In our study, all patients with a radiologic diagnosis were followed conservatively and did not require percutaneous drainage or surgery.

Keywords: Acute; conservative treatment; right lower quadrant pain; right-sided diverticulitis.

Acute diverticulitis (AD) affects approximately 50% of the population over the age of 60 in Western societies [1]. In Asian societies, however, this rate has been increasing in

recent years, with the incidence rising to around 0.5% [2]. The prognosis of acute diverticulitis varies, with uncomplicated diverticulitis being the most frequently observed form [3].

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Complicated diverticulitis, on the other hand, can present with an abscess, obstruction, or perforation [4]. In Western societies, left-sided diverticulitis is more common, whereas in Asian societies, right-sided diverticulitis is more frequently observed [5,6]. Ultrasonography (USG) is highly sensitive in the diagnosis of uncomplicated diverticulitis [7]. Computed tomography (CT) has become the gold standard imaging method for the diagnosis of diverticulitis and assessment of its severity, offering high sensitivity and specificity [8]. In uncomplicated acute diverticulitis, outpatient treatment is more common [9].

Intravenous (IV) hydration, along with oral or IV antibiotherapy, is considered part of inpatient treatment for diverticulitis [10]. As our understanding of the disease improves, the need for imaging techniques to differentiate uncomplicated acute diverticulitis from the presence of diverticula has become increasingly important [11]. The World Society of Emergency Surgery (WSES) recommends intravenous (IV) antibiotics up to grade 2a, and percutaneous drainage is suggested if an abscess larger than 4 cm is present and the procedure is feasible. For WSES grade 2b and higher grades, source control with surgery is advised [12]. In a study in the literature, the surgical procedures described included appendectomy with diverticulectomy, ileocecal resection, right hemicolectomy, and prophylactic appendectomy [13].

Right lower quadrant pain is an important cause of emergency admission that requires experience and extreme caution in management, as it can lead to increased morbidity when rare conditions are missed. The most common cause of right lower quadrant pain is acute appendicitis (AA) [14]. Other causes include gynecologic diseases, urinary system pathologies, terminal ileitis, inflammatory bowel disease, typhlitis, isolated cecal ischemia, and right colon diverticulitis [15].

Diverticulitis is the active inflammation of diverticula, and diverticula are herniations of the colonic mucosa and submucosa through defects in the circular muscle layers within the colonic wall. In Western countries, diverticula are more common in the sigmoid and descending colon, whereas right colonic diverticula and right colonic diverticulitis are more common in Asian populations [16]. In Western countries, right-sided diverticulosis affects approximately 5% of the population and accounts for 1.5% of patients presenting with diverticulitis. Disease prevalence is significantly higher in Asian countries, where right-sided diverticulosis accounts for 20% of patients with diverticular disease and 75% of cases of diverticulitis.

Right colonic diverticulitis is usually single and represents a true diverticulum [17]. It is a rare diagnosis in Western countries [18]. For this reason, it may be confused with more common conditions such as acute appendicitis, which requires emergency surgery. Typically, it presents with right lower quadrant abdominal pain, tenderness, nausea, and vomiting.

Right colonic diverticulitis is mostly seen in young and male patients [1]. It has been reported that hospitalization, restriction of oral intake, intravenous fluids, and antibiotic treatment may be sufficient for the conservative management of uncomplicated right colonic diverticulitis [19]. In the diagnosis of acute right colonic diverticulitis, ultrasonography (USG) and computed tomography (CT) are useful radiologic examinations [20]. One study reported high accuracy and specificity for US performed by an experienced radiologist, but this finding was not supported by other studies [21]. Although CT offers high specificity and sensitivity, it can be confused with other diseases in some cases [1].

There are several classification systems for diverticulitis severity grading, most of which are for left colonic diverticulitis. The grading system we used was the WSES classification, introduced in 2015, for left colonic diverticulitis. There is no specific classification system for acute right colonic diverticulitis (ARCD). The WSES classification is a simple system based on CT findings, dividing acute diverticulitis into two groups: uncomplicated (Stage 0) and complicated (Stage 1–4) (Table 1) [22].

In recent years, there has been a rise in studies on the differential diagnosis of right colonic diverticulitis. However, the presence of appendiceal pathologies and the lack of studies by radiologists focusing on differentiating ARCD from acute appendicitis (AA) continue to challenge surgeons in managing this condition.

In our study, we aimed to analyze the management of ARCD in our clinic in light of the literature. The management of ARCD is less extensively covered compared to left-sided diverticulitis, which has been more widely studied and understood. Since the guidelines for colonic diverticulitis are usually based on left colonic diverticulosis, it remains unclear whether the recommendations for left-sided diverticulitis are applicable to right-sided diverticulitis. We aimed to share our experience with the diagnosis, treatment, and management of this disease.

Materials and Methods

Study approval was obtained from the local ethics committee with registration number 2023/126. Our study was registered and approved as Clinical Trials number NCT06153030. The study was conducted in accordance with the Declaration of Helsinki. Patients with right colonic diverticulitis who were followed up in our clinic were screened using our hospital's health information system. There is no specific 10th revision of the International Classification of Diseases (ICD-10) code for ARCD. The K57 code represents diverticular disease of the intestine.

We reviewed 121 patients diagnosed with ICD-10 code K57 and its subgroups between 2018 and 2022. Patients over 18 years of age who were diagnosed with ARCD radiologically, pathologically, or intraoperatively were included in the study. Patients under 18 years of age and those whose diagnosis could not be confirmed were excluded. A total of 20 of these 121 patients were diagnosed with ARCD and were eligible for our study. Among them, 19 patients had CT at the time of initial diagnosis, while 1 patient had only USG.

Age, gender, World Society of Emergency Surgery (WSES) grade, surgical status, laboratory values, intravenous antibiotherapies administered, length of hospitalization, and mortality were analyzed.

Statistical Analysis

SPSS version 28.0 was used for the analysis. Mean, standard deviation, median, minimum, maximum, frequency, and ratio values were used in the descriptive statistics of the data.

Table 1. WSES Driven Classification of Diverticulitis^[22]

Stage	Description
Uncomplicated diverticulitis	
Stage 0	Diverticula, thickening of the colonic wall or increased density of the pericolic fat
Complicated diverticulitis	
Stage 1	Pericolic air bubbles or little pericolic fluid without abscess (within 5 cm from inflamed bowel segment)
Stage 2	Abscess ≤ 4 cm
Stage 3	Abscess > 4 cm
Stage 4	Distant air (>5 cm from inflamed bowel segment)

Table 2. Demographic and clinic characteristics of the groups

	Min-Max	Mean (SD)	n (%)
Age	19.0-65.0	40.1 (12.9)	
Length of Stay	1.00-14.00	4.9 (2.9)	
Sex			
Male			8 (40)
Female			12 (60)
WSES CD classification			
Uncomplicated			17 (85)
Complicated			3(15)
Ia			1 (5)
Ib			1 (5)
IIa			1 (5)
Antibiotherapy			
Ciprofloxacin+ Metronidazole			5 (25.0)
Ceftriaxon + metronidazole			15 (75.0)
Surgical Intervention			4 (20.0)
Relapse			0 (0.0)
Mortality			0 (0.0)

WSES: World Society of Emergency Surgery, CD: Complicated Diverticulitis, Min: Minimum, Max: Maximum, SD: Standard Deviation.

Table 3. Laboratory Results

	Min – Max	Median	Mean (SD)
CRP(mg/L)	0.20–213	13.9	45.3 (62.8)
WBC (/μl)	7110–17520	13990	12906 (3061)
Neutrophil(/μl)	4110–12950	10925	9797(2620)
Eosinophil (/μl)	0–370	145	156.5 (120)
Lymphocyte/μl)	810–3170	2330	2110.5 (722.3)
Monocyte(/μl)	350–1930	795	849.5 (340.7)
Platelet(/μl) (x10 ³)	138–390	254.5	258.8 (53.3)

WBC: White Blood Cell, MIN: Minimum, MAX: Maximum, SD: Standard Deviation, mg/L: miligram/litre, μl: microlitre.

Results

Among the patients diagnosed with ARCD, 8 were female (40%) (Table 2). The mean age of the participants was 40.1 years. The mean CRP level among the patients was 45.3 mg/L, and the mean WBC count was 12,906/μL (Table 3). The initial radiological examination included CT for 19 patients, while 1 patient had USG only, and this patient was among those diagnosed perioperatively.

Seventeen patients had noncomplicated diverticulitis. The WSES classification included 3 patients in the Grade 1A–1B and 2A categories, with one patient in each category. For treatment, 5 patients received ciprofloxacin

and metronidazole, while 15 patients were treated with ceftriaxone and metronidazole. The average length of hospital stay was 4.9 days (Table 2). Thirteen patients were diagnosed with CT; 10 of these patients were given intravenous (IV) contrast only, while 3 of them were given oral and IV contrast. Four patients initially diagnosed with acute appendicitis were found to have ARCD during surgery. Thirteen patients were managed conservatively and discharged without complications.

Colonoscopy was performed on 9 patients starting 6 weeks after discharge according to American Gastrointestinal Association (AGA) guidelines, with no malignancies detected. Right hemicolectomy was performed on 1 patient, and the pathology result was reported as complicated diverticulitis. Other patients were followed for a median of 26 months (range, 5–70 months), and no recurrence was observed during this period.

The recurrence status of the patients was obtained from the records in the hospital information system. Additionally, there were no deaths among the patients.

Discussion

It is very difficult to differentiate right colonic diverticulitis from acute appendicitis by physical examination and laboratory investigations. CT and USG are effective methods in differentiating acute right colonic diverticulitis from acute appendicitis and other causes of right lower quadrant pain [23]. In our study, CT was the first radiologic choice for diagnosis. Computed tomography (CT) is widely recognized as the preferred imaging method for diagnosing colonic diverticulitis. However, ultrasonography (US) is a more cost-effective option and does not involve radiation, which is especially significant given that patients with right-sided diverticulitis are generally younger and more vulnerable to radiation-induced malignancies [24].

While CT has a sensitivity of 79% to 99%, US for right-sided diverticulitis, when performed by an experienced operator, has reported 91.3% sensitivity and 99.8% specificity for correct diagnosis [25,26]. In our study, CT diagnosis of 19 patients was confirmed in retrospective analysis, while USG was performed in 1 patient.

In order to make more effective and accurate decisions in the management of ARCD, care should be taken to distinguish it from AA, which is much more common. In a retrospective study of 450 patients, 92 patients were evaluated as ARCD and 358 patients as AA, and it was reported that it was difficult to distinguish these two diseases based on clinical findings [27].

In our literature review, we could not find a prevalence study on patients who underwent surgery for AA and were diagnosed with ARCD. We believe that the prevalence of laparoscopy is a protective factor against increased morbidity and mortality in this diagnostic complexity. However, we still believe that information sharing should be encouraged in multidisciplinary meetings so that this patient group can be recognized in emergency services, just like acute left colonic diverticulitis (ALCD).

In Türkiye, CT reporting in emergency services often lacks clinical information, which is one of the obstacles preventing radiologists from focusing on the distinction between ARCD and AA. If we want to manage ARCD well, we must first eliminate the deficiencies in differential diagnosis and correctly determine the incidence of this disease. The presence of the retroperitoneal part of the right colon may be an advantage over the sigmoid colon in terms of self-limiting the disease and reducing the incidence of peritonitis [28].

The lifetime risk of diverticulitis in a patient with diverticulosis is between 10–25% [14]. Therefore, right colonic diverticulitis should be considered in right lower quadrant pain, especially in patients with known diverticulosis. One study reported that the pain duration of right colonic diverticulitis was longer than that of acute appendicitis [27]. Right colonic diverticulitis is a disease in which conservative treatment is effective [17,19,29]. In our study, all patients who could be diagnosed radiologically were treated conservatively. Although some cases of right colonic diverticulitis are congenital, there are increasing medical opinions that some are acquired [14].

Diverticulitis of the cecum is usually single and located on the anterior Wall [30]. In a meta-analysis investigating risk factors for recurrence in diverticulitis, no risk factors were reported [31]. However, multiple diverticula and intraperitoneal diverticulitis were reported as risk factors for recurrence in one study [32,33]. In another study, smoking and prolonged hospitalization were reported as risk factors for recurrence [34]. Kim et al. [35] reported a high rate of recurrence of right colonic diverticulitis in patients over the age of 40. Since right colonic diverticulitis is usually single, recurrence rates are low. In a meta-analysis, the recurrence rate was reported to range from 0% to 26.9% [31]. Another study reported that the recurrence rate of right-sided diverticulitis after conservative treatment was approximately 3% to 15% [36].

Colonoscopy was recommended after an attack in a study that found a 0.3% probability of cancer following

colonoscopy performed in patients with uncomplicated right colonic diverticulitis [37]. In our study, colonoscopy was performed in 9 patients during follow-up, and no malignancy was found.

We think that prospective multicenter studies with long follow-up periods and evaluating all causes of right lower quadrant pain will provide a better understanding of right colonic diverticulitis and may help create a more effective management algorithm. To summarize the results we have drawn from our literature review, although treatment strategies have been determined for uncomplicated ARCD, patient-based evaluations regarding antibiotic therapy and IV hydration would be useful. There is not enough literature on the use of percutaneous treatments in the management of complicated ARCD. We believe that the literature on this subject will expand with the widespread use of CT in the differential diagnosis of right lower quadrant pain.

The first main issue we want to emphasize in complicated ARCD surgery is that CT should definitely be evaluated together with the radiologist working in the clinic, and an aggressive decision for surgery should not be made. If possible, we think that performing a colonoscopy before surgery will prevent poor oncological outcomes that may arise from incorrect diagnoses. Additionally, if surgery is to be performed, initiating the procedure laparoscopically, if feasible, will contribute to determining the right strategy.

Study Limitations

The most important limitations of our study are that it was designed as a retrospective, single-center study and included a small number of patients. Another limitation is that colonoscopy was not performed on all patients. This restriction limited our data in determining the presence of diverticula in other colonic segments in patients who did not undergo colonoscopy.

In a prospectively designed study, the inclusion of emergency physicians and radiologists will allow for a more accurate estimate of the ARCD rate in emergency department presentations and will help determine whether outpatient cases present with more complicated features. In addition, evaluating patients together with the surgeon and radiologist before deciding on surgery will contribute to understanding the effectiveness of conservative treatment and guide future research on how to better manage this patient group. Furthermore, initiating surgery laparoscopically in patients initially planned for appendectomy may help prevent morbidity in overlooked cases despite clinical and radiologic efforts.

Conclusions

Right colonic diverticulitis is an important cause of right lower quadrant pain that should be managed in general surgery clinics when recognized, and conservative treatment should be attempted. However, morbidities may occur when the diagnosis is delayed or missed. Therefore, in this article, we aimed to emphasize that right colonic diverticulitis should be considered in the differential diagnosis of right lower quadrant pain. Patient history and radiologic imaging are essential for accurate diagnosis. Especially in cases where ultrasonography cannot distinguish the condition from acute appendicitis, cross-sectional imaging should be performed, and the patient should be evaluated for right colonic diverticulitis before surgical intervention.

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Comprehensive Analysis of Novel Inflammatory Biomarkers (dNLR, NHR, MHR, SIRI): Reference Intervals in Healthy Adults and Diagnostic Value in AMI and HF

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Abstract

Introduction: Inflammatory indices derived from routine blood tests, such as the systemic inflammatory response index (SIRI), the derived neutrophil-to-lymphocyte ratio (dNLR), the neutrophil-to-HDL ratio (NHR), and the monocyte-to-HDL ratio (MHR), have gained interest as potential cardiovascular biomarkers. This study aimed to establish reference intervals for these indices in healthy adults and assess their clinical relevance in acute myocardial infarction (AMI), heart failure (HF), and heart failure following AMI.

Methods: This retrospective study included adult patients from the Istanbul Faculty of Medicine Central Laboratory. Reference intervals were established using the Bhattacharya method, and odds ratios (ORs) were calculated to assess the association between elevated inflammatory indices and cardiovascular conditions.

Results: The upper reference limits (URLs) for the inflammatory indices were as follows: dNLR $\leq$ 2.57, MHR $\leq$ 0.49, NHR $\leq$ 3.62, and SIRI $\leq$ 1.24. Elevated levels of SIRI, MHR, and NHR were significantly associated with increased odds of AMI (ORs of 3.43, 3.44, and 2.93, respectively). In HF patients, all four indices were significantly elevated, with MHR (OR=7.82) and SIRI (OR=5.52) showing the strongest associations. In the AMI+HF group, SIRI (OR=2.38) and dNLR (OR=2.63) were significantly elevated.

Discussion and Conclusion: This study demonstrates the clinical relevance of CBC-derived inflammatory indices, particularly SIRI and MHR, in distinguishing patients with coexisting myocardial infarction and heart failure. Our robust approach, including healthy controls and precise determination of reference intervals, highlights the potential utility of these markers for enhanced risk stratification and management in cardiovascular disease.

Keywords: Acute Myocardial Infarction; Derived Neutrophil-to-Lymphocyte Ratio (dNLR); Heart Failure; Monocyte-to-HDL Ratio (MHR); Neutrophil-to-HDL Ratio (NHR); Systemic Inflammatory Response Index (SIRI).

Cardiovascular diseases (CVDs) remain a major public health concern across Europe, accounting for more than four million deaths annually. Acute myocardial infarction (AMI) and heart failure (HF) are common clinical manifestations of CVDs, frequently leading to serious health complications and increased risk of mortality^[1–3]. Cardiac-specific biomarkers such as hs-cTnI and hs-cTnT are widely used for the diagnosis

of myocardial infarction, while BNP and NT-proBNP are considered essential indicators for heart failure evaluation^[4,5]. Systemic inflammation plays a central role in both conditions, contributing to atherosclerosis, plaque rupture, myocardial injury, and ventricular dysfunction. It is also a shared underlying mechanism in various pathological states, including infections, autoimmune diseases, cancers,

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and cardiovascular disorders. Several inflammation-based indices, including the systemic inflammatory response index (SIRI), neutrophil-to-lymphocyte ratio (dNLR), neutrophil-to-HDL ratio (NHR), and monocyte-to-HDL ratio (MHR), have recently been investigated for their potential to support diagnosis and follow-up in various conditions, particularly cardiovascular diseases^[6–9]. The examination of the distribution of laboratory values in healthy individuals is of significant importance in the context of reference interval studies, as it contributes to the enhancement of the precision of diagnostic evaluations and clinical judgments^[10]. According to the EP28-A3C guideline, population-based reference intervals can be determined either by directly recruiting healthy individuals or by applying indirect statistical techniques such as data mining^[11].

Studies suggest that indirect methods often produce results comparable to those derived from direct sampling^[12]. Bhattacharya analysis is a data mining technique that facilitates the evaluation of extensive laboratory databases. It enables the stratification of subjects according to age and sex without compromising statistical power, even after the application of stringent exclusion criteria^[13,14]. The primary objective of this study was to establish reference intervals for four complete blood count (CBC)-derived inflammatory indices (dNLR, MHR, SIRI, and NHR) in a healthy adult population using indirect statistical methods (Bhattacharya analysis) and to evaluate their distribution in patients with AMI and HF, both separately and combined. Despite the investigation of these indices in various cardiovascular conditions, there is an absence of comprehensive reference interval data from healthy populations. The present study also examines their diagnostic performance in AMI and HF using high-sensitivity biomarkers (hs-Troponin, NT-proBNP), providing insight into their potential clinical utility.

Materials and Methods

Subjects

This study utilized retrospective data collected between 2019 and 2023 from the Central Laboratory of Istanbul University, Faculty of Medicine. To isolate a healthy population, we extracted records of individuals who had a complete blood count (CBC) test performed in conjunction with concurrent measurements of HDL, LDL, triglycerides (TG), total cholesterol, HbA1c, and CRP (n=155,901). We applied a comprehensive set of exclusion criteria to ensure the selection of a metabolically and hematologically healthy population. Patients with conditions that affect inflammatory or hematologic indices, such as hospitalization, intensive care unit (ICU) admission, hematologic or oncologic diseases, dialysis, active infections, rheumatologic conditions, and incomplete or repeated laboratory records, were excluded. Additionally, individuals under 18 and over 60 were excluded from the study. Only those whose results for these parameters fell within the reference ranges were included in the study, ensuring a more reliable dataset for calculating reference ranges (n=14,290). A visual representation of the data filtering and selection process, including all inclusion and exclusion steps, is provided in the Sankey diagram (Fig. 1). After this thorough data cleaning process, we applied the Bhattacharya method to determine the distribution of dNLR, MHR, SIRI, and NHR in the healthy population, ensuring the highest standards of accuracy and reliability in our results. This study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Istanbul University Faculty of Medicine Ethics Committee (Approval No. 3330770, Date: May 23, 2025). Since the study used anonymized retrospective data, the requirement for informed consent was waived.

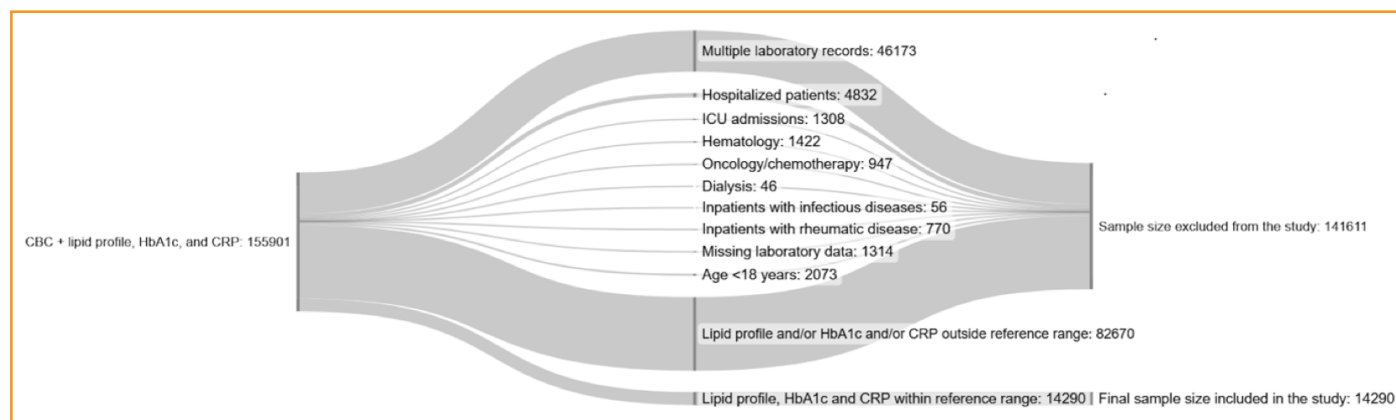


Figure 1. Sankey diagram illustrating the inclusion and exclusion criteria of the study population.

Methods

From 2019 to 2023, plasma levels of NT-proBNP and high-sensitivity troponin T (hs-TnT) were measured using the Roche Elecsys immunoassay platform. Complete blood count (CBC) analyses were conducted using the LH-780 hematology analyzer (Beckman Coulter), while biochemical parameters including total cholesterol, HDL, LDL, triglycerides, and CRP were assessed on the Roche C8000 automated platform. Measurement of HbA1c levels was performed using the Lifotronic H100 hemoglobin analyzer.

Patients with troponin T levels exceeding 14 ng/L were classified as having MI, based on the manufacturer's cut-off value, while those below this threshold were considered non-MI. Similarly, in accordance with the National Institute for Health and Care Excellence (NICE) guidelines, an NT-proBNP level ≥ 300 pg/mL was considered indicative of heart failure (HF) [15]. Patients were stratified into MI, HF, and combined MI+HF groups according to whether their SIRI, MHR, NHR, and dNLR values fell within or above the reference intervals established from the healthy population. Risk associations (ORs) were calculated by comparing individuals with values above the reference range to those

within it. This approach enabled evaluation of the clinical relevance of these indices not only for isolated MI or HF but also for their coexistence.

Statistical Analysis

1. Reference Interval Analysis

Data analysis was performed using SPSS version 26 (SPSS Inc., Chicago, IL), with a significance threshold set at $p < 0.05$. The normality of continuous variables was assessed using the Kolmogorov-Smirnov test, which revealed that none of the variables followed a normal distribution. Consequently, continuous data were reported as medians with interquartile ranges (IQRs) and compared using the Mann-Whitney U test. Categorical variables were analyzed using the Chi-square test. To assess whether reference interval partitioning by age or sex was required, the Lahti algorithm was applied (Tables 1 and 2) [16,17]. Reference ranges for dNLR, MHR, NHR, and SIRI were then calculated using the Bhattacharya statistical method [12]. In this approach, data were grouped into equal intervals and smoothed to minimize random variation. A weighting factor was applied to improve precision, facilitating the identification of the

Table 1. Partitioning of inflammatory indices by age was assessed using the Lahti criteria

Index	Age Group	LL	UL	Mean $\pm$ SD	D(s) LL	Decision for LL	D(s) UL	Decision for UL	Final Decision
dNLR	20–29	0.79	4.25	1.92 $\pm$ 1.25	0.02	NP	0.07	NP	NP
dNLR	30–39	0.87	4.33	2.0 $\pm$ 1.0	0.02	NP	0.37	M	NP
dNLR	40–49	0.89	4.7	2.1 $\pm$ 1.17	0.01	NP	0.4	NP	NP
dNLR	50–59	0.88	4.32	1.94 $\pm$ 0.95	-	-	-	-	-
MHR	20–29	0.16	0.71	0.37 $\pm$ 0.17	0.08	NP	0.13	NP	NP
MHR	30–39	0.15	0.69	0.36 $\pm$ 0.14	0.08	NP	0.13	NP	NP
MHR	40–49	0.16	0.71	0.37 $\pm$ 0.17	0.0	NP	0.2	NP	NP
MHR	50–59	0.16	0.74	0.37 $\pm$ 0.15	-	-	-	-	-
NHR	20–29	1.16	5.8	2.9 $\pm$ 1.16	0.05	NP	0.14	NP	NP
NHR	30–39	1.1	5.65	2.8 $\pm$ 1.2	0.03	NP	0.14	NP	NP
NHR	40–49	1.1	5.4	2.72 $\pm$ 1.12	0.03	NP	0.36	M	NP
NHR	50–59	1.1	5.4	2.72 $\pm$ 1.12	-	-	-	-	-
SIRI	20–29	0.32	2.7	1.04 $\pm$ 0.98	0.015	NP	0.23	NP	NP
SIRI	30–39	0.33	2.56	1.0 $\pm$ 0.65	0.015	NP	0.37	M	NP
SIRI	40–49	0.34	2.8	1.1 $\pm$ 1.0	0.14	NP	0.28	M	NP
SIRI	50–59	0.33	2.6	1.1 $\pm$ 1.0	-	-	-	-	-

LL: Lower limit; UL: Upper limit; Mean $\pm$ SD: Mean (average) and standard deviation of the inflammatory index within the subgroup; D(s): Distance between subgroup reference limits (LL or UL), expressed in units of the smaller subgroup's standard deviation; P: Partitioning; M: Marginal; NP: Non-partitioning.

For partitioning decisions, the distance between subgroup reference limits (D(s) LL and D(s) UL) was calculated using the Lahti method, where the distance between the limits is measured in terms of the narrower subgroup's standard deviation. Partitioning was recommended if either D(s) LL or D(s) UL > 0.75 , not recommended if both < 0.25 , and considered marginal if either value was between 0.25 and 0.75. The limits were based on the 2.5th and 97.5th percentiles within each subgroup.

Table 2. The partitioning of inflammatory indices by sex was assessed using the Lahti criteria

Index	Age group	Sex	LL	UL	Mean±SD	D(s) LL	D(s) UL	Final Decision
dNLR	20–29	Male	0.77	4.0	1.8±1.62	0.03	0.21	NP
		Female	0.81	4.3	1.98±1.37			
dNLR	30–39	Male	0.84	4.1	1.9±0.83	0.05	0.36	NP
		Female	0.88	4.4	2.0±1.0			
dNLR	40–49	Male	0.87	5.0	1.8±1.3	0.02	0.35	NP
		Female	0.89	4.6	2.1±1.12			
dNLR	50–59	Male	0.89	4.5	2.0±1.0	0.01	0.40	NP
		Female	0.88	4.1	1.9±0.9			
MHR	20–29	Male	0.19	0.77	0.43±0.15	0.30	0.08	NP
		Female	0.15	0.66	0.35±0.15			
MHR	30–39	Male	0.19	0.76	0.43±0.15	0.33	0.66	NP
		Female	0.15	0.68	0.33±0.12			
MHR	40–49	Male	0.20	0.80	0.43±0.16	0.25	0.62	NP
		Female	0.16	0.70	0.35±0.17			
MHR	50–59	Male	0.20	0.78	0.44±0.16	0.38	0.46	NP
		Female	0.15	0.72	0.35±0.13			
NHR	20–29	Male	1.30	5.65	3.0±1.13	0.18	0.13	NP
		Female	1.10	5.50	2.7±1.17			
NHR	30–39	Male	1.36	5.90	3.16±1.29	0.30	0.43	NP
		Female	1.02	5.40	2.7±1.17			
NHR	40–49	Male	1.40	5.90	3.2±1.29	0.26	0.52	NP
		Female	1.10	5.30	2.76±1.15			
NHR	50–59	Male	1.40	5.80	3.17±1.14	0.40	0.70	NP
		Female	1.00	5.10	2.5±1.0			
SIRI	20–29	Male	0.33	2.5	1.0±0.65	0.05	0.30	NP
		Female	0.30	2.7	1.1±1.1			
SIRI	30–39	Male	0.34	2.7	1.1±0.67	0.015	0.30	NP
		Female	0.33	2.5	1.0±0.65			
SIRI	40–49	Male	0.36	3.0	1.1±1.0	0.05	0.24	NP
		Female	0.34	2.76	1.1±1.03			
SIRI	50–59	Male	0.37	2.78	1.15±0.7	0.10	0.54	NP
		Female	0.30	2.4	0.95±0.72			

LL: Lower limit; UL: Upper limit; Mean±SD: Mean (average) and standard deviation within each subgroup; D(s): Distance between subgroup-specific limits, expressed in units of the smaller subgroup's standard deviation; NP: Non-partitioning. Partitioning decisions were made using the Lahti method described in Table 1.

Gaussian portion of the distribution. The relationship between frequency and concentration was examined with particular attention to the linear segment of the frequency curve, characterized by a high coefficient of determination ($R^2 > 0.99$). Where appropriate, a Box-Cox transformation was applied to enhance data normality, with the transformation parameter (λ) selected for optimal model fit (Fig. 2), following procedures outlined at <https://www.statology.org/box-cox-transformation-excel/>. Lower and upper reference limits (LRL and URL) were calculated as $\text{mean} \pm 1.96 \times \text{SD}$ from the Gaussian portion of the data. While the Bhattacharya method served as the primary tool

for reference interval estimation, non-parametric methods were also employed due to the overall non-normality of the dataset, allowing for estimation of 95% confidence intervals (CI). Final graphical analyses and calculations were conducted using Microsoft Excel.

2. Odds Ratio Analysis Using Reference Interval Cut-offs

To evaluate the association between inflammatory indices and cardiovascular conditions, binary logistic regression was performed using upper reference limits (URLs) as cut-off values derived from the healthy population. The

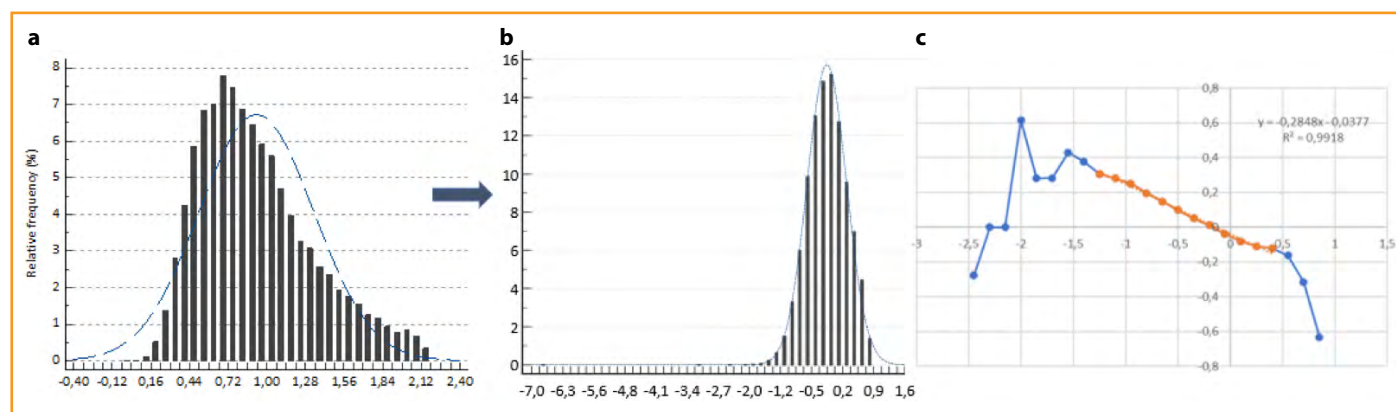


Figure 2. Reference range determination for SIRI using the Bhattacharyya method.

(a) Distribution of raw SIRI data. **(b)** SIRI data after Box-Cox transformation ($\lambda=0.15$). **(c)** Linear segment of the frequency–concentration plot with a high coefficient of determination ($R^2=0.99$), used to calculate reference intervals.

independent predictive values of dNLR, MHR, SIRI, and NHR were assessed for AMI, HF, and the overlapping AMI+HF group. Odds ratios (ORs) with corresponding 95% confidence intervals were calculated, and a two-tailed p -value <0.05 was considered statistically significant. This analysis enabled the evaluation of both individual and combined diagnostic utility of these inflammatory markers based on elevated index levels.

Results

Inflammatory indices showed no requirement for age- or sex-based partitioning, and reference intervals were established for the 18–60-year age group (Table 3). As shown in Table 4, systemic inflammatory indices demonstrated significant associations with cardiovascular conditions when compared to healthy controls. Specifically, SIRI, MHR, and NHR were significantly elevated in patients with myocardial infarction (MI), with ORs of 3.43, 3.44, and 2.93, respectively ($p<0.001$). In contrast, dNLR did not show a significant association with MI (OR=1.04; 95% CI: 0.92–1.33; $p=0.58$).

When comparing patients with HF to healthy controls, all four indices were significantly elevated. Notably, MHR

(OR=7.82) and SIRI (OR=5.52) showed the strongest associations, followed by dNLR (OR=4.84) and NHR (OR=2.79) ($p<0.001$ for all comparisons).

In subgroup analyses comparing patients with MI only versus those with both MI and HF, significant differences were observed for SIRI (OR=2.38; 95% CI: 1.84–3.08; $p<0.001$) and dNLR (OR=2.63; 95% CI: 2.00–3.48; $p<0.001$), suggesting their potential utility in identifying the presence of HF among MI patients. However, MHR and NHR did not differ significantly between these two groups ($p>0.05$).

These findings highlight SIRI and MHR as robust inflammatory markers across distinct cardiovascular conditions, with SIRI and dNLR also showing discriminatory potential in identifying combined disease states.

Table 4. Odds Ratios of Inflammatory Indices

Index	Comparison	OR	95% CI	p
SIRI	HC vs. MI	3.43	3.03–3.68	$<0.001^*$
MHR	HC vs. MI	3.44	3.11–3.81	$<0.001^*$
dNLR	HC vs. MI	1.04	0.92–1.33	0.58
NHR	HC vs. MI	2.93	2.60–3.30	$<0.001^*$
SIRI	HC vs. HF	5.52	5.30–5.80	$<0.001^*$
MHR	HC vs. HF	7.82	7.30–8.40	$<0.001^*$
dNLR	HC vs. HF	4.84	4.54–5.00	$<0.001^*$
NHR	HC vs. HF	2.79	2.55–3.05	$<0.001^*$
SIRI	MI vs. MI+HF	2.38	1.84–3.08	$<0.001^*$
MHR	MI vs. MI+HF	1.06	0.81–1.39	0.68
dNLR	MI vs. MI+HF	2.63	2.00–3.48	$<0.001^*$
NHR	MI vs. MI+HF	1.13	0.65–1.96	0.67

HC: Healthy Controls; MI: Myocardial Infarction Patients; HF: Heart Failure Patients; OR: Odds Ratio; CI: 95% Confidence Interval; * $p<0.05$ indicates statistical significance.

Table 3. Reference intervals of inflammatory indices

Indices	LL	LL (%95 CI)	UL	UL (%95 CI)
dNLR	1.02	1.0 – 1.02	2.57	2.56 – 2.58
MHR	0.17	0.17 – 0.18	0.49	0.49 – 0.49
NHR	1.47	1.47 – 1.48	3.62	3.60 – 3.63
SIRI	0.39	0.38 – 0.40	1.24	1.24 – 1.25

Reference intervals for inflammatory indices (dNLR, MHR, NHR, and SIRI) in adults aged 18–60 were calculated using the Bhattacharyya method. The 2.5th and 97.5th percentiles were used to define the reference limits. LL: Lower limit; UL: Upper limit; CI: 95% confidence interval.

Discussion

This study examined systemic inflammatory indices—SIRI, MHR, dNLR, and NHR—across healthy individuals and patients with MI, HF, or both conditions. These indices, derived from CBC and lipid parameters, have emerged as cost-effective and easily accessible markers reflecting systemic immune and inflammatory responses. They integrate the relative proportions of leukocyte subtypes and lipid levels, offering insight into the balance between pro-inflammatory and anti-inflammatory mechanisms [18]. There has been growing interest in evaluating these markers across diverse pathological conditions, such as cardiovascular disorders [19,20], malignancies [21–23], infectious diseases [24], and autoimmune disorders [25–27]. Given the role of chronic low-grade inflammation in the development and progression of atherosclerosis, MI, and HF, these indices may offer additional clinical value in cardiovascular risk evaluation and patient monitoring [28,29]. All four inflammatory markers were significantly increased among patients compared to controls, indicating their possible involvement in cardiovascular pathophysiology. Among all groups, patients with coexisting MI and HF demonstrated the most pronounced elevations in inflammatory indices, implying a synergistic increase in systemic inflammation. Another central objective of the present work was to estimate normal reference limits for these markers among healthy adults, utilizing the Bhattacharya technique to ensure robust statistical validity. The analysis of our reference cohort revealed that the upper limits for these indices were 2.57 for dNLR, 0.49 for MHR, 3.62 for NHR, and 1.24 for SIRI.

Notably, several studies have reported that values exceeding these thresholds may already be associated with increased cardiovascular risk in specific patient populations. For instance, Jiang et al. [30] reported that MHR levels associated with elevated mortality in cardiovascular disease patients were higher than our upper reference limit of 0.49. Conversely, significantly elevated MHR and SIRI levels were observed in high-risk polycythaemia vera patients, with both indices demonstrating independent association with thrombotic progression [31]. Elevated dNLR-PNI scores have also been found to predict adverse outcomes in acute coronary syndrome (ACS) patients following percutaneous coronary intervention (PCI) [32]. Furthermore, elevated NHR levels have been identified as independent predictors of in-hospital major adverse cardiovascular events (MACE), severe coronary artery stenosis, and thrombosis in patients with ST-segment elevation myocardial infarction (STEMI), all of which were above our upper reference values [33].

The study demonstrates that not only are these novel indices clinically informative, but elevations beyond the reference ranges derived from healthy individuals may indicate a higher risk profile.

However, these studies do not define specific reference intervals for healthy individuals, limiting the possibility of direct comparison. These discrepancies likely reflect differences in study populations, disease states, or methodological approaches. Thus, our findings may provide valuable reference data for using these biomarkers in healthy populations. Among the indices, SIRI, a marker of systemic inflammation, has been widely studied in cardiovascular diseases. Due to its reflection of systemic inflammatory burden, SIRI has become a focus of many studies examining its importance in cardiovascular disease. For example, Qu et al. [34] reported that higher SIRI levels were linked to poorer outcomes in myocardial infarction. At the same time, Gao et al. [35] found similar links with hospitalization and death among heart failure patients.

Consistent with these findings, our study showed significantly higher SIRI values in all patient groups compared to healthy controls, with the highest values observed in patients with both MI and HF. This may reflect a greater inflammatory burden in patients with overlapping cardiac conditions. Previous research has primarily examined MI or HF separately, but our results indicate that SIRI might be helpful in detecting high-risk patients with both conditions. Similarly, MHR has been linked to adverse cardiovascular outcomes [6,36,37]. In our study, MHR was significantly higher in MI and HF groups than in healthy individuals, with the highest values observed in patients with both conditions. The results demonstrate that inflammation levels are elevated in individuals suffering from both heart attack and heart failure. Although the prognostic value of MHR has been addressed in cardiovascular research, its capacity to distinguish overlapping disease states like MI+HF has not been thoroughly investigated. Our findings suggest that both MHR and SIRI may have the potential to identify patients with compounded disease burden.

In contrast, dNLR showed a more limited association with MI in our analysis, yet demonstrated stronger associations in HF and the MI+HF group. This pattern may indicate that dNLR is more relevant in chronic or advanced disease states. Supporting this, Li et al. [38] demonstrated that dNLR is associated with all-cause and cardiovascular mortality in patients with cardiovascular disease, emphasizing its potential as a prognostic tool, particularly in later stages of disease progression.

Our findings for NHR were also consistent with previous reports. NHR levels were notably higher in patients with MI and HF compared to healthy individuals, supporting its function as a reliable marker of cardiovascular inflammation^[39]. However, among the studied indices, NHR was the only marker that did not show a significant increase in patients who developed HF after MI. This may be attributed to the complex, multifactorial nature of post-infarction HF. As emphasized by Jenča et al.,^[40] factors such as infarct size, residual ventricular function, and comorbidities play critical roles in post-MI HF progression. These mechanisms may limit the sensitivity of specific inflammation-based markers such as NHR in this subgroup.

Conclusion

In summary, using a single dataset, this study evaluated multiple CBC-derived inflammatory indices (SIRI, MHR, dNLR, and NHR) across various cardiovascular conditions. Our study offers novel insights that may support clinical practice, achieved through the inclusion of healthy controls and the application of a robust method for determining reference ranges. Our findings suggest that SIRI and MHR may be particularly useful in identifying patients with concomitant MI and HF. This subgroup may otherwise be underrecognized despite their elevated inflammatory burden.

Ethics Committee Approval: The study was approved by Istanbul University Faculty of Medicine Ethics Committee (No: 3330770, Date: 23.05.2025).

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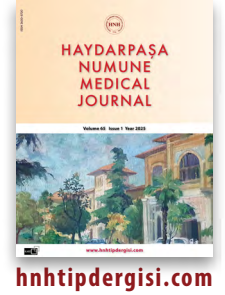
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Evaluation of *Neisseria gonorrhoeae* Culture Results and Antibiotic Usage in Patients Presenting with Urethral Discharge: Four-Year Retrospective Study

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Abstract

Introduction: The aim of this study was to evaluate the microbiological diagnostic results of *Neisseria gonorrhoeae* (*N. gonorrhoeae*) infections, assess the frequency of empirical antibiotic usage, and determine compliance with current treatment guidelines among patients presenting with urethral discharge.

Methods: A retrospective analysis was conducted among 387 patients admitted with suspected gonococcal infection between June 2014 and February 2018 to the Departments of Infectious Diseases, Urology, and Gynecology at Ankara Numune Training and Research Hospital. Demographic characteristics, microscopy and culture results, treatment protocols, and antibiotic prescriptions were obtained from hospital information systems. The chi-square test was applied for statistical analysis, and $p < 0.05$ was considered statistically significant.

Results: A total of 387 patients with a mean age of 32.6 ± 10.8 years were included; 99.9% ($n=386$) were male and 0.1% ($n=1$) were female. Among these patients, 73.9% ($n=286$) were referred from the Urology outpatient clinic, whereas 26.1% ($n=101$) were from Infectious Diseases. The overall isolation rate of *N. gonorrhoeae* was 13.7% ($n=53$). Among patients who received empirical antibiotic therapy ($n=79$), gonococcal culture positivity was 11.4% ($n=9$), whereas positivity was 14.3% ($n=44$) among those who did not receive empirical treatment ($n=308$) ($p > 0.05$). Antibiotics were prescribed based on culture results to 88.1% ($n=341$) of patients. The most frequently prescribed antibiotic regimen was a combination of cephalosporin+doxycycline+azithromycin (19.1%). Among the 53 patients with gonococcal growth, antibiotics were prescribed to 96.2% ($n=51$), yet the recommended standard regimen of cephalosporin+azithromycin was administered to only 7.5% ($n=4$).

Discussion and Conclusion: This study revealed that culture and antimicrobial susceptibility testing were inadequately utilized in the diagnosis and management of gonococcal infections, and empirical antibiotic therapy demonstrated poor compliance with current guidelines. Increased clinical awareness and strict adherence to updated guidelines are required for the accurate diagnosis and effective treatment of gonococcal infections.

Keywords: Antibiotic therapy; antimicrobial resistance; *Neisseria gonorrhoeae*; urethritis.

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Neisseria gonorrhoeae (*N. gonorrhoeae*) infection is a sexually transmitted infection that is increasingly prevalent worldwide and causes significant morbidity [1–3]. Infection of mucosal surfaces such as the urethra, endocervix, rectum, oropharynx, and conjunctiva with *N. gonorrhoeae* results in urethritis, cervicitis, and pelvic inflammatory disease [4,5]. Each year, approximately 82 million new cases of gonorrhea are reported worldwide according to the World Health Organization (WHO) [3,5,6].

Recently, the increasing antibiotic resistance has created significant challenges in the control and treatment of gonorrhoeae infection [7,8]. Treatment options are currently quite limited due to the rapid development of resistance to penicillin, tetracyclines, and fluoroquinolones [9]. Due to the widespread use of cephalosporins, decreased susceptibility of gonococci to third-generation cephalosporins such as ceftriaxone and cefixime is considered a major threat to global health [9,10]. This situation highlights the importance of reviewing current treatment protocols and performing antimicrobial susceptibility testing regularly [6,10].

Studies on the frequency of gonococcal infection in Türkiye have reported significantly high prevalences, particularly in at-risk groups [11–13]. In a study conducted by Pelit and colleagues, *N. gonorrhoeae* was detected in 4.5% of men with urethritis symptoms [10], while in a study conducted by Aksu among sex workers, this rate was reported as 12.4% [12]. Other studies conducted across Türkiye also show that gonococcal infections are not adequately controlled due to barriers in accessing diagnosis and treatment and the lack of awareness [11–14].

The aim of this study was to evaluate patients presenting with complaints of urethral discharge in terms of *N. gonorrhoeae*, to emphasize the importance of culture and antibiogram instead of treating patients based only on symptoms, and to assess the compliance of drugs used in standard treatment with the recommendations of current guidelines.

Materials and Methods

Study Design and Patient Population

In this retrospective study, a total of 387 patients who applied to the Infectious Diseases, Urology, and Gynecology and Obstetrics outpatient clinics of Ankara Numune Training and Research Hospital with complaints of urethral discharge between June 2014 and February

2018 and who underwent urethral discharge microscopy and culture with a preliminary diagnosis of gonococcal infection were evaluated. The clinical and laboratory data of 387 patients were evaluated retrospectively using the hospital information management system (FONET) and the Medulla doctor system.

Data on the demographic characteristics of the patients (age and gender), the number of tests requested from clinical departments, microscopic examination and culture results, recommended treatment protocols, and post-treatment follow-up of the patients were collected. For microbiological examination of urethral discharge samples, smears were stained with Gram stain and cultured in Modified Thayer-Martin medium. The media were incubated for 24–48 hours at 35–37°C in an environment of 5% CO₂. Standard biochemical methods were used for the identification of bacteria grown in culture. Antibiotic susceptibility testing of patients with positive culture results was performed by the disk diffusion method as recommended by the Clinical Laboratory Standards Institute (CLSI).

Ethical Approval

The study was approved by the Ethics Committee of Ankara Numune Training and Research Hospital (dated 08/05/2018, decision no: E-18-1971 and 1971). Since the study was retrospective, informed consent was not obtained by its nature. The study was conducted in accordance with the Declaration of Helsinki.

Statistical Analysis

Statistical analyses were conducted using IBM SPSS Statistics version 18.0. For continuous variables, the mean±standard deviation, minimum, and maximum values were calculated. Categorical variables were presented as counts and percentages. Differences between groups were evaluated using the chi-square test, and $p<0.05$ was considered statistically significant.

Results

In total, 387 patients were included in the study. The mean age of the patients was 32.6 ± 10.8 years, and 99.9% ($n=386$) of the patients were male. Among the 387 patients, 73.9% ($n=286$) were admitted to Urology, and 26.1% ($n=101$) were admitted to Infectious Diseases outpatient clinics. It is noteworthy that the number of tests requested from Urology clinics increased over the years. The distribution of 368 patients by year and clinic is shown in Table 1.

Table 1. Number of patients who requested urethral discharge microscopy by clinic and year

Years	Department of Infectious Diseases 101 (26.1) n (%)	Urology Department 286 (73.9) n (%)
2014 (n=48)	21 (43.8)	27 (56.3)
2015 (n=79)	16 (20.3)	63 (79.7)
2016 (n=100)	23 (25)	69 (75)
2017 (n=144)	37 (25.7)	107 (74.3)
2018 (January-February) (n=24)	4 (16.7)	20 (83.3)

Table 2. Distribution of urethral discharge culture results in patients receiving and not receiving empirical treatment

	Percentage receiving empirical treatment (%) 79 (20.4)	Not receiving empirical treatment (%) 308 (79.6)
<i>N. gonorrhoeae</i> has grown	9 (11.4)	44 (14.3)
Other microorganisms	49 (62.0)	183 (59.4)
No growth in culture	21 (26.6)	81 (26.3)

Table 3. Post-culture antibiotic administration status and distribution of administered antibiotics

Antibiotic	n	%
Not given	46	11.9
Given	341	88.1
Doxycycline	20	5.4
Cephalosporin	13	3.4
Quinolone+Doxycycline	61	15.8
Cephalosporin+Doxycycline	60	15.5
Cephalosporin+Azithromycin	36	9.3
Cephalosporin+Doxycycline+Azithromycin	74	19.1
Azithromycin+Doxycycline	28	7.2
Other	28	7.2

Table 4. Distribution of antibiotics given to patients with positive gonococcal cultures

Antibiotic	n	%
Not given	2	3.8
Given	51	96.2
Quinolone	1	1.9
Doxycycline	3	5.7
Cephalosporin	5	9.4
Quinolone+Doxycycline	6	11.3
Cephalosporin+Doxycycline	10	18.9
Cephalosporin+Azithromycin	4	7.5
Cephalosporin+Doxycycline	1	1.9
Azithromycin+Doxycycline	14	26.4
Other	7	13.2

Of the 387 patients included in the study, 79 (20.4%) received empirical treatment, while 308 (79.6%) did not receive treatment. *N. gonorrhoeae* was grown in culture in 9 of 79 patients (11.4%) who received empirical treatment and in 44 of 308 patients (14.3%) who did not receive treatment, as shown in Table 2. No statistically significant difference was found between the two groups in terms of gonococcal growth rates ($p>0.05$). Antibiotic treatment was recommended to a total of 341 (88.1%) patients based on culture results. The most frequently prescribed antibiotic combination, with a rate of 19.1% ($n=130$), was cephalosporin+doxycycline+azithromycin. Other frequently recommended antibiotic combinations were quinolone+doxycycline 15.8% ($n=61$) and cephalosporin+doxycycline 15.5% ($n=60$). Table 3 shows the distribution of antibiotics prescribed according to culture results.

Fifty-one of the 53 patients whose cultures yielded *N. gonorrhoeae* were given antibiotic treatment. The most frequently prescribed treatment for these patients was the azithromycin+doxycycline combination (26.4%, $n=14$), followed by cephalosporin+doxycycline (18.9%, $n=10$). Only 4 patients (7.5%) were prescribed cephalosporin+azithromycin treatment, which is recommended as the standard regimen by the guidelines. Table 4 shows the distribution of antibiotic treatments given to patients with positive *N. gonorrhoeae* cultures.

Discussion

In our study, a total of 387 patients presenting with urethral discharge complaints were evaluated, and the vast majority of the cases (99.9%) consisted of male patients. This finding is consistent with data in the literature indicating that men generally constitute the vast majority of symptomatic gonorrhea cases. According to WHO data, approximately 82 million new cases of gonorrhea are reported worldwide each year, and men tend to seek medical attention more frequently because they are often symptomatic^[1].

In our study, the rate of *N. gonorrhoeae* growth in culture was found to be 13.7%. This rate is higher than the 4.5% reported by Pelit et al.^[13] in Türkiye but similar to the 12.4% reported by Aksu among sex workers^[11]. Similar high prevalences have been reported in other studies conducted in our country^[12,14].

Although the rate of gonococcal growth in culture (11.4%) in patients given empirical treatment was lower than in those who did not receive empirical treatment (14.3%), it was not found to be statistically significant. This supports

the idea that empirical treatment has limited effectiveness in *N. gonorrhoeae* eradication and that treatment should be planned according to culture and antibiogram results. The literature also notes that high resistance rates increasingly limit empirical treatment approaches [8,10,15,16].

In our study, it was observed that the majority of the prescribed antibiotics (88.1%) were given according to culture results. The most frequently used antibiotic combination in these patients was cephalosporin+doxycycline+azithromycin (19.1%). However, the combination of cephalosporin+azithromycin, recommended as the standard treatment in the guidelines, was preferred by only 7.5%. This rate is parallel to other studies published in Türkiye, showing that full compliance with treatment protocols is generally low [17,18].

Today, the antibiotic resistance of *N. gonorrhoeae* has become a significant global health issue. According to Quillin and Seifert's research, treatment options have become very limited as bacteria become increasingly resistant to antibiotics such as penicillin, tetracycline, and fluoroquinolones [9]. In addition, the decreased susceptibility of gonococci to third-generation cephalosporins such as ceftriaxone and cefixime following widespread use of these drugs is considered a serious health threat [7,9].

Studies investigating the epidemiology of gonorrhea infections in Türkiye show that the prevalence of *N. gonorrhoeae* infections is high, especially in at-risk populations [11,19]. However, studies conducted in the general population indicate that awareness of gonorrhea infections is low among large segments of society and that access to healthcare services is insufficient [18,20].

It is noteworthy that there was only one female patient in our study. Gonococcal infections in women are often asymptomatic, leading to limited access to diagnosis and treatment, which causes the infection to spread silently and increases complications [21]. In this context, it is important to promote more active screening and diagnostic methods among female patients.

One of the significant limitations of our study is the risk of incomplete records and the inability to fully verify information due to the retrospective design. Additionally, methodological differences may limit the use of the disk diffusion method for conducting antibiotic susceptibility tests. The literature emphasizes that ensuring standardization in antibiotic susceptibility tests is critically important for the accurate evaluation of resistance rates [10,22].

Limitations of the Study

The main limitations of this study are its retrospective design and the fact that the data were obtained retrospectively from hospital information management systems. Additionally, antimicrobial susceptibility testing was not routinely and systematically performed in patients with positive gonococcal culture results. This means that the data obtained do not fully reflect the antimicrobial resistance profile and limits our ability to evaluate antibiotic susceptibility. Although the sample size of the study was sufficient, the extremely low number of female patients made it impossible to conduct a clinical and epidemiological evaluation of gonorrhea infections in women. Therefore, the generalizability of our findings to the female population is extremely limited.

Conclusion

In this retrospective study, it was determined that microscopy and culture methods were used at a low rate in the diagnosis of gonococcal infection in patients presenting with urethral discharge complaints and that empirical antibiotic treatment practices were widespread but insufficient in terms of adherence to guidelines. It was noteworthy that compliance with standard treatment protocols when prescribing antibiotics was low and that, despite culture results, appropriate treatment regimens were rarely applied. This indicates that the guidelines for gonorrhea treatment are not adequately reflected in clinical practice and that clinicians need to improve their adherence to current treatment protocols.

Our study highlights the need to increase clinical awareness for the effective treatment of gonococcal infections through rapid diagnosis, culture, and antibiotic susceptibility testing. Additionally, the very low number of female patients presenting with urethral discharge complaints indicates that diagnostic and screening programs for women need to be strengthened. In today's world, where antimicrobial resistance rates are rising globally, routinely conducting antibiotic susceptibility tests for *N. gonorrhoeae* and adopting a targeted treatment approach instead of empirical treatment is of critical importance. Finally, multidisciplinary approaches and continuous education for healthcare workers are of great importance in the fight against gonococcal infections.

Ethics Committee Approval: The study was approved by the Ethics Committee of Ankara Numune Training and Research Hospital (No: E-18-1971 and 1971, Date: 08/05/2018).

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Peer-review: Externally referees.

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CASE REPORT



Lipoid Proteinosis: A Case Report

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Abstract

Lipoid proteinosis (LP), also referred to as Urbach-Wiethe disease or hyalinosis cutis et mucosae, is a rare autosomal recessive storage disorder. It is characterized by the deposition of amorphous hyaline material in the mucous membranes, skin, brain, and internal organs. The symptoms of lipoid proteinosis are variable but typically begin with hoarseness in the newborn period. Skin-related symptoms usually appear during childhood and include acneiform scars, wart-like papules, and plaques. The clinical presentation of this condition varies between individuals, which can make diagnosis difficult and often requires a detailed dermatological examination.

Keywords: Acneiform scars; hoarseness of voice; hyaline material; temporal calcifications; yellowish papules.

Lipoid proteinosis (LP), also known as Urbach-Wiethe disease or Hyalinosis cutis et mucosae, is a rare autosomal recessive disorder. It is characterized by hoarseness from early infancy, along with various skin manifestations such as acneiform scarring, waxy papules, eyelid papules (moniliform blepharosis), and more. Additionally, non-cutaneous manifestations occur due to the infiltration of hyaline-like material in the skin, larynx, and multiple internal organs [1]. In various parts of the body, there is extracellular and perivascular deposition of hyaline material that stains positive with periodic acid-Schiff (PAS) [2]. LP is a genetic disease, and diagnosis can be established on the basis of characteristic clinical symptoms, confirmed by histopathology.

Case Report

A 28-year-old male patient presented to us with complaints of stiffening on the palms and soles, along with rashes on the oral mucosa and the body. The patient had experienced skin symptoms for a long time. In the following years, he developed oral and cutaneous lesions.

On dermatological examination, the patient had edema and infiltration on the lower lip, macroglossia, and nodular infiltration on the tongue (Fig. 1a–1b). Bilateral yellowish papules, measuring 2–3 mm in diameter, were observed in a linear distribution along the eyelid margin (Fig. 2b). On the face and scalp, acneiform scars were concentrated in the frontal and temporal regions (Fig. 2a–2c). Bilateral hyperpigmented verrucous plaques

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Figure 1. (a-b) Fissures at the oral commissures, macrostomia, ankyloglossia, and flattening of the tongue papillae.

and hyperkeratosis were present on the elbows (Fig. 3a–3b). On the lower extremities, xerotic-looking skin was observed bilaterally in the pretibial area, along with hyperpigmented papules and atrophic scars in the gluteal region (Fig. 3c).

The patient's medical history revealed that he had been diagnosed with epilepsy for two years, but he had discontinued his medication on his own. He had hoarseness of voice since infancy. The examination of other systems was normal. The patient's cousin on his mother's side also had similar complaints. Routine laboratory tests were within normal limits, and his ophthalmological, psychiatric, and neurological examinations were normal. No pathological findings were observed in the imaging studies.

Biopsies were taken with differential diagnoses of lipoid proteinosis, papular mucinosis, hydroa vacciniforme, systemic amyloidosis, and pseudoxanthoma elasticum.

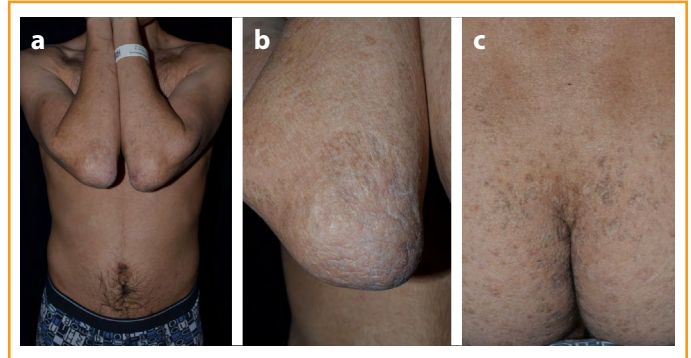


Figure 3. Bilateral hyperpigmented hyperkeratotic areas on the elbows (a, b). Hyperpigmented atrophic lesions in the gluteal region (c).

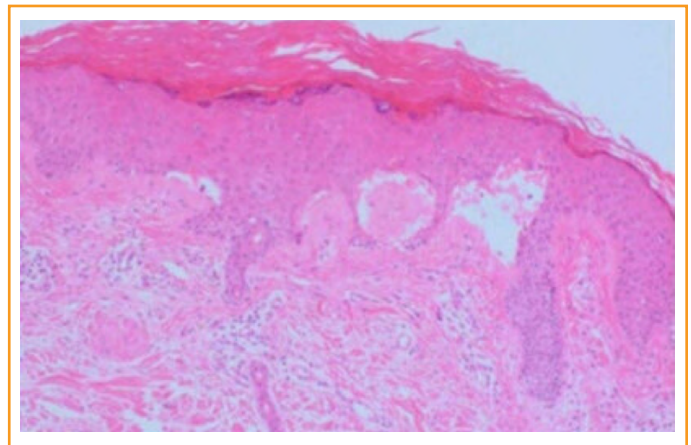


Figure 4. Histopathological examination showing amorphous eosinophilic material in the papillary dermis, staining positive for PAS. Image from Gambichler et al. [16], licensed under CC BY 4.0.

Histopathological examination of the skin biopsy showed hyperkeratosis and acanthosis in the epidermis, with the deposition of amorphous eosinophilic hyaline material in the upper dermis. Based on the clinical findings and histopathological examinations, the patient was diagnosed with lipoid proteinosis.

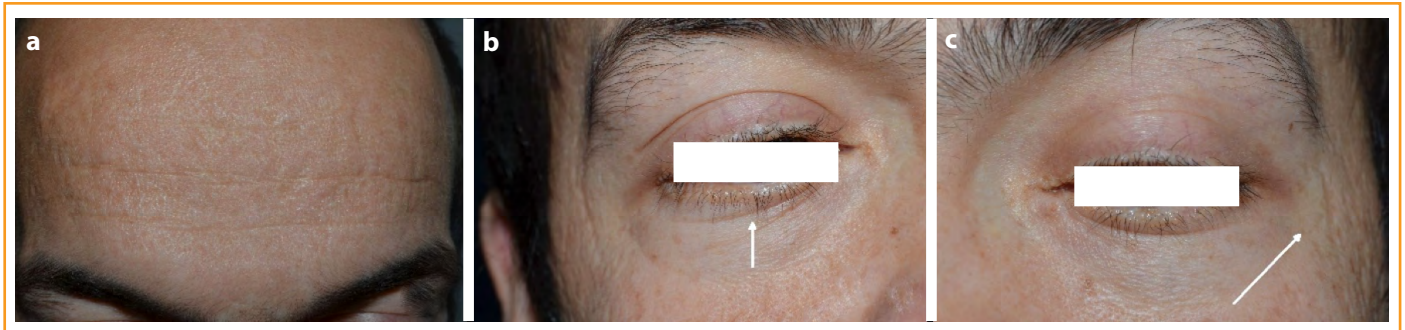


Figure 2. Acneiform scars concentrated in the frontal and temporal regions (a) Yellowish, translucent papules measuring 1-2 mm, showing a linear distribution along the eyelash line. (b) Acneiform scars concentrated in the frontal and temporal regions (c).

Discussion

Lipoid proteinosis was described in 1929 by the dermatologist Urbach and the otolaryngologist Wiethe, who referred to it as "lipoidosis cutis et mucosae."^[3] LP is a very rare autosomal recessive disorder, characterized by infiltration of hyaline material into the skin, oral cavity, larynx, and internal organs. LP affects males and females equally. As per the literature, it is more commonly observed in regions such as Sweden, South Africa, and Asia^[4]. The pathogenesis of this disease is unknown. Recent molecular genetic studies have revealed that the disease's pathogenesis is associated with mutations that result in the loss of function of the extracellular matrix protein (ECM1) gene^[5]. This gene encodes a glycoprotein that acts as a negative regulator in endochondral bone formation and affects angiogenesis^[6]. Mutations in the ECM1 gene lead to disruptions in the glycolipid or sphingolipid degradation pathway, reduced synthesis of fibrous collagens, and excessive production of basal membrane collagens, resulting in the deposition of PAS-positive hyaline materials in the dermis and submucosa^[7].

The first clinical manifestation is usually a weak, cry-like, or hoarse voice caused by diffuse deposition of hyaline material in the mucous membranes of the vocal cords. This condition generally persists throughout life and may progress to dysphonia or even aphonia^[8].

Cutaneous lesions typically present in two successive stages. In the initial stage, trauma-related vesicles and hemorrhagic crusts are commonly seen on the skin of the face, extremities, and oral mucosa. These skin lesions may develop into "ice-pick"-shaped acneiform scars. In the second stage, skin changes are observed, which are thought to be related to an increase in the deposition of hyaline material. The skin becomes thickened, with a waxy appearance and yellowish discoloration. Papules, plaques, and nodules also appear in the axilla, scrotum, and face^[9]. Yellowish papules arranged in a linear pattern along the eyelid margins, known as moniliform blepharosis, are a characteristic feature of lipoid proteinosis^[9]. Verrucous lesions may appear on extensor surfaces, particularly the elbows, knees, and hands. Other skin manifestations include alopecia and palmoplantar hyperkeratosis. Additionally, dental abnormalities and parotitis may be observed^[10].

Neurological findings are common. Epilepsy, mental retardation, and other neuropsychiatric illnesses may occur. The pathognomonic radiographic finding is the presence of bilateral intracranial temporal lobe horn-shaped calcifications^[11,12]. Multiple yellowish nodules can be

found throughout the esophagus, stomach, duodenum, and colon, and are usually asymptomatic^[13].

In histopathological studies, there is hyperkeratosis and acanthosis in the epidermis, along with the deposition of amorphous eosinophilic hyaline material in the upper dermis, particularly around blood vessels and eccrine glands. Histochemical staining reveals that the material deposited in the dermis is PAS(+) (Fig. 4).

Lipoid proteinosis (LP) is a chronic disease that generally has a benign prognosis and does not impact the patient's lifespan. However, complications such as laryngeal obstruction or respiratory failure during infancy or adulthood, along with neurological complications, can present life-threatening risks. There is no effective treatment for the lesions; management is available for complications like secondary infections and epilepsy^[14]. The management of patients with LP should be individualized based on the characteristics of the individual affected. A multidisciplinary approach is often necessary, involving specialists such as dermatologists, otolaryngologists, neurologists, psychiatrists, ophthalmologists, dentists, and genetic counselors^[15].

In summary, lipoid proteinosis is a rare disease involving multiple systems. A history of hoarseness and weak crying since infancy, typical skin findings such as acneiform scars on the face and body, yellowish papules arranged in a linear pattern along the eyelid margins, a family history of lipoid proteinosis or consanguinity between the parents, a history of seizures, and the presence of typical calcifications in the temporal region on imaging should raise suspicion for lipoid proteinosis. Life expectancy is usually normal, and treatment is symptomatic. A multidisciplinary approach is recommended.

Ethics Committee Approval: This is a single case report, and therefore ethics committee approval was not required in accordance with institutional policies.

Informed Consent: The patient gives consent to the use of information about him in relation to the above topic for the purpose of display in a journal article or mature presentation or for the presentation of a thesis.

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Authorship Contributions: Concept – D.I.Ç., Ş.Y.; Design – D.I.Ç.; Supervision – D.I.Ç., Ş.Y.; Fundings – Ş.Y., S.B.; Materials – Ş.Y., S.B.; Data collection &/or processing – Ş.Y., S.B.; Analysis and/or interpretation – D.I.Ç.; Literature search – D.I.Ç.; Writing – D.I.Ç.; Critical review – Ş.Y., S.B.

Peer-review: Externally referees.

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Outcome of Aortocoronary Bypass in a Patient with a History of Hemophilia

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Abstract

Hemophilia is a congenital disorder of the blood coagulation system linked to the X chromosome and manifested by a deficiency of blood coagulation factor VIII (hemophilia type A) or factor IX (hemophilia type B). We present our clinical case involving the combination of myocardial infarction (MI) and hemophilia type A. A 42-year-old man with a known history of hemophilia A was admitted to the emergency department of an external center with complaints of pressing chest pain radiating to the left arm. He was treated with 300 mg of ecopryine and 300 mg of Plavix, and a significant increase in troponin level was detected. The patient was then transferred to the emergency department of our hospital.

In the emergency department, he was evaluated by cardiology. The control troponin level was 72, and the patient was admitted to the coronary intensive care unit with a preliminary diagnosis of non-ST elevation myocardial infarction (NSTEMI). Coronary angiography was planned. Internal medicine and hematology clinics were consulted to adjust anticoagulant therapy for the procedure, and dual antiplatelet therapy (ecopryine + Plavix) was administered.

After coronary angiography, the patient was evaluated by a joint council of cardiovascular surgery and cardiology, and coronary bypass surgery was recommended. He was transferred to the cardiovascular surgery unit for preoperative preparation. During this period, he was also evaluated by the hematology clinic due to his hemophilia A history. Based on the clinic's recommendation, specific factor VIII (FVIII) therapy was administered pre- and postoperatively, along with daily aPTT monitoring.

No complications occurred during surgery. Cardiopulmonary bypass was initiated once the activated clotting time (ACT) exceeded 450. No bleeding complications were observed in the postoperative period. The patient was successfully discharged.

Keywords: Bypass; coronary angiography; FVIII, hemophilia A.

Hemophilia is a congenital disease of the blood coagulation system, linked to the X chromosome, and develops with a deficiency of blood clotting factor VIII (hemophilia type A) or factor IX (hemophilia type B). The number of people with hemophilia in the world is about 400,000 people [1]. In Russia, there are about 7,500 people with hemophilia [2]. It was previously believed that the presence of hemophilia protects against the occurrence

of coronary heart disease [3]. However, subsequently published studies have shown that with improved treatment of hemophilia, the life expectancy of these patients increases, and the number of risk factors and concomitant diseases, including coronary artery disease, also increases [4]. Indeed, in a study conducted in Canada on 294 hemophilia patients, arterial hypertension was found in 30.3%, diabetes in 10.5%, and dyslipidaemia in 22.4%.

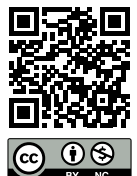
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There were 14 cases of ischaemic heart disease; 3 patients underwent coronary artery bypass surgery, and 9 patients underwent percutaneous coronary intervention. The combination of myocardial infarction (MI) and hemophilia type A is very rare. As of 2006, only 36 cases of MI due to hemophilia were described in the world literature [5]. We present our own clinical case involving the combination of myocardial infarction and hemophilia type A.

Case Report

A 42-year-old male patient, diagnosed with hemophilia A about 3 years ago and who had not received any treatment for hemophilia A, was admitted to the emergency department of an external centre with complaints of pressing chest pain radiating to the left arm. A significant increase in troponin value was observed, and the patient was treated with 300 mg ecopirin and 300 mg plavix. The patient was then transferred to the emergency department of our hospital.

In the emergency department, he was evaluated by cardiology. Echocardiography showed an ejection fraction of 65%, and rheumatic mitral valve disease was suspected. The control troponin level was 72, and the patient was admitted to the coronary intensive care unit with a prediagnosis of non-ST myocardial infarction. Coronary angiography was planned (Figs. 1–3). The patient was consulted to the internal medicine and haematology clinics for adjustment of anticoagulant treatment for angiography, and dual antiplatelet therapy (ecopirin +

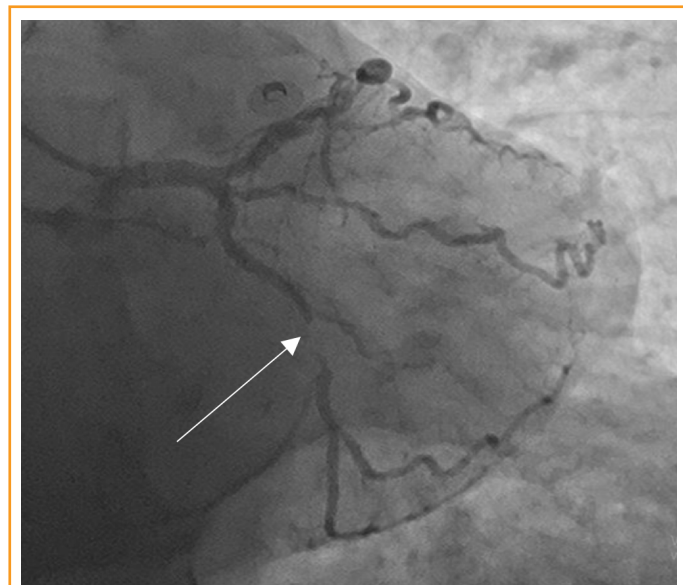


Figure 1. Coronary angiography image. CX (circumflex artery) middle segment, total occluded.

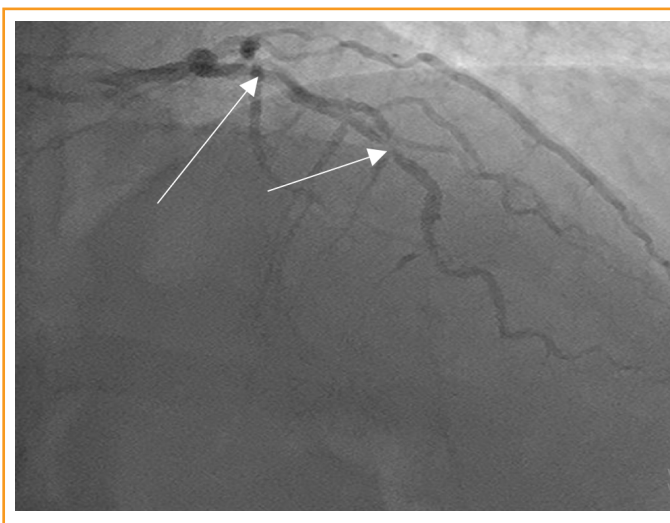


Figure 2. Coronary angiography image. LAD (left descending artery) proximal and middle segments, severe stenosis is present.

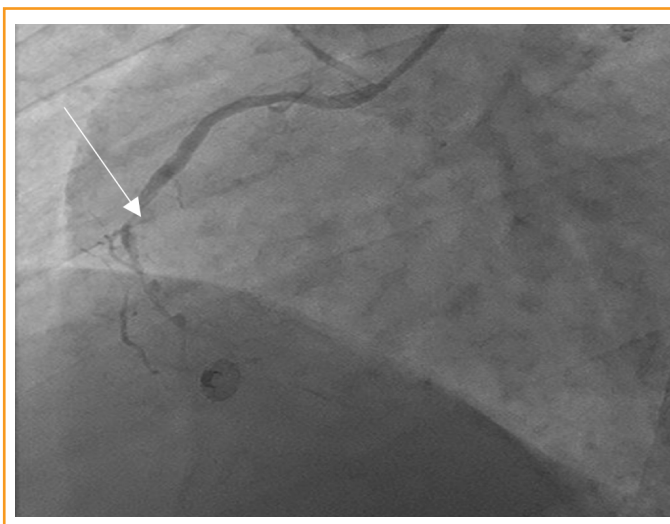


Figure 3. Coronary angiography image. RCA (right coronary artery) middle segment, subtotally occluded.

plavix) was administered due to acute coronary syndrome. The patient underwent coronary angiography performed by cardiology. Coronary main vessels were visualised, and a coronary stent procedure was attempted. However, since the stent procedure could not be performed, the patient was evaluated by the cardiology and cardiovascular surgery (CVS) council for aortocoronary bypass surgery. Coronary bypass surgery was recommended, and the patient was transferred to the cardiovascular surgery ward for preoperative preparation.

The patient was evaluated by the haematology clinic due to his history of hemophilia A and the surgical indication. HEMOFIL-M treatment was initiated with

the recommendation of the hemophilia clinic and administered as 4,500 units on the day of surgery and 2,000 units daily for the first 3 postoperative days. The patient underwent elective surgery 6 days after coronary angiography, following the completion of preoperative preparations. During the operation, heparinisation was applied, and cardiopulmonary bypass was performed while maintaining the ACT value >450. Saphenous vein grafts were routinely used for the coronary arteries. The procedure was completed without complications. At the final stage, heparin was neutralised with protamine.

After the operation, the patient was transferred to the intensive care unit and extubated after 4 hours. In the postoperative period, no significant complaints from the drains were noted. The patient's blood tests and vital signs showed no serious abnormalities, and there was no decrease in hemogram values. Daily activated partial thromboplastin time (aPTT) and factor VIII monitoring were performed upon the recommendation of the haematology clinic. The patient was transferred to the ward after 3 days of intensive care monitoring and was successfully discharged a few days later.

Discussion

There are very few published studies on the combination of hemophilia and MI. Girolami et al. [5] analyzed 36 cases of MI in patients with hemophilia. The mean age of patients with hemophilia was 44 years. Twenty-two cases of MI occurred during or immediately after infusion of factor VIII concentrate. The authors emphasized that the high incidence of MI occurring after infusion of factor VIII or prothrombin complex concentrate suggests that a thorough clinical evaluation of each patient is necessary to develop an adequate therapeutic approach. Replacement therapy with blood clotting factors was performed in all cases.

Mannucci et al. [6] presented recommendations for the management of hemophilia patients with acute coronary syndrome. Radial access is recommended because it is safer in terms of bleeding. It is advised to administer 40 U/kg factor VIII bolus during diagnostic coronary angiography and stenting, 20 U/kg bolus 12 hours later, and to maintain the blood level at 80 U/dL during heparin administration. When dual antiplatelet therapy is used, it is recommended to administer factor VIII at a dose of 50 U/kg every other day. If treatment with two antiplatelet agents lasts up to 1 month, it is recommended to maintain the blood concentration of factor VIII at 30 U/dL. The use of bare metal stents is preferred.

Regarding the presented clinical observation, this is the first case of a combination of MI and hemophilia among more than 7,000 cases of MI in our clinic over 10 years. The lack of practical experience in the treatment of MI with such a rare and dangerous pathology as hemophilia did not allow us to decide to perform coronary angiography. In addition, invasive intervention, as mentioned above, should be accompanied by the administration of factor VIII, which is not available in routine emergency cardiology practice. An additional obstacle in the treatment of MI in a patient with hemophilia is the need for continuous monitoring of the level of factor VIII in the blood when using anticoagulants and antiplatelet agents, which is also not a routine practice. The mild course of myocardial infarction, without ST segment elevation on ECG, without hemodynamic disturbances, and without any complications, led us to opt for conservative treatment during the patient's first MI. However, recurrent MI developed more aggressively due to occlusion of the trunk of the left coronary artery (the electrocardiographic sign of this localization of thrombosis is ST segment elevation in aVR and ST segment depression in leads V3–V6, which was confirmed by autopsy), pulmonary edema, and cardiogenic shock, leading to death.

Ethics Committee Approval: This is a single case report, and therefore ethics committee approval was not required in accordance with institutional policies.

Conflict of Interest: The authors declare that there is no conflict of interest.

Informed Consent: The patient agrees to the use of information about himself/herself in a journal article or mature presentation, or for use in a thesis presentation.

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