THE MEDICAL BULLETIN OF
SISLI ETFAL HOSPITAL

DOI: 10.14744/SEMB.2023.09216
Med Bull Sisli Etfal Hosp 2023;57(2):224–231

Original Research

Differentiated Thyroid Cancer in Children and Adolescents: Clinicopathological Characteristics of 32 Patients Followed up in our Pediatric Endocrinology Unit

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ABSTRACT

Objectives: This study aims to investigate the clinical and pathological features of patients with differentiated thyroid cancer (DTC) treated at our tertiary care institution.

Methods: Thirty-two children and adolescents followed up with the diagnosis of DTC between 2001 and 2017 were enrolled. We classified patients with DTC into two groups as below and above 10 years of age, and compared their clinical and pathological features.

Results: The mean age at presentation was 11.2±4 years. The female/male ratio was 7 (28:4). The diagnosis was papillary thyroid cancer (PTC) in 90.6% (n=29). The frequencies of lymph node and pulmonary metastases were 53.1% and 21.8%, respectively. The groups were comparable in terms of gender, initial clinical signs and tumor histopathology. The mean tumor size was greater in the younger age group (p=0.008). However, there was no difference between the two groups in terms of lymph node and pulmonary metastases. The pathological parameters associated with tumor aggressiveness were also similar between the groups, except lymphovascular invasion. Lymphovascular invasion was more frequent in the younger age group (p=0.01). Patients with lymph node and pulmonary metastases were more likely to have extrathyroidal extension and lymphovascular invasion.

Conclusion: PTC was the most common type of DTC and presented with considerable rates of lymph node and pulmonary metastases. Tumor size was greater and lymphovascular invasion was more common in younger patients. Overall prognosis was favorable despite high rates of lymph node and pulmonary metastases.

Keywords: Children, differentiated thyroid cancer, papillary thyroid cancer

Please cite this article as "Dagdeviren Cakir A, Tahmiscioglu Bucak F, Tarcin G, Turan H, Ozcan R, Evliyaoglu O, Kabasakal L, Ercan O. Differentiated Thyroid Cancer in Children and Adolescents: Clinicopathological Characteristics of 32 Patients Followed up in our Pediatric Endocrinology Unit. Med Bull Sisli Etfal Hosp 2023;57(2):224–231".

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Submitted Date: December 21, 2022 **Revised Date:** March 07, 2023 **Accepted Date:** March 15, 2023 **Available Online Date:** June 20, 2023

Differentiated thyroid cancers (DTCs), which include papillary, follicular and Hurthle cell cancers, are the most frequent pediatric endocrine neoplasia, although they are rare in children and adolescents.[1-3] Pediatric DTCs have a different clinical presentation and course than those of adults. Compared to adults, lymph node metastasis, extrathyroidal extension (ETE) and distant metastasis at presentation are more frequent in the pediatric age group.[4-6] However, the prognosis of thyroid cancer in children is usually more favorable compared to adults. The stepwise combination of surgery and radioactive iodine (RAI) therapy is curative with a 10 year survival of >98%.[7] Until recent years, children with thyroid cancers were managed according to the recommendations in adult guidelines. However, a more comprehensive diagnostic approach is essential in the pediatric age group, realizing that pediatric thyroid cancers have different clinical outcomes. In 2015, the American Thyroid Association (ATA) published a guideline regarding the management of pediatric thyroid cancer. Since then, diagnosis and treatment modalities recommended in the ATA guideline have been used for pediatric thyroid cancers.[8]

Papillary thyroid cancer (PTC) is the most common thyroid cancer, accounting for more than 90% of all cases, while follicular thyroid cancer (FTC) is rare in children.[9,10] The clinical features of PTC are quite different than FTC. In the great majority of pediatric patients, PTC tends to be multicentric, and metastases to cervical lymph nodes are common.[9-12] Distant metastases to lungs are observed in up to 25% of cases.[6,13,14] Therefore, total or near-total thyroidectomy is recommended as initial surgical treatment modality.[15] In the case of extensive ETE and/or regional lymph node metastasis, central neck dissection (CND) is recommended. If there is cytological evidence of metastases to the lateral lymph nodes, a lateral neck dissection (LND) should be performed.[8] On the other hand, pediatric FTC is less aggressive than PTC, and distant metastasis and recurrence are less likely in FTC. The tumor is typically unifocal in FTC, and metastasis to cervical lymph nodes are rare.[6,8] Lobectomy alone is a sufficient treatment modality for minimally invasive FTC.[16,17] However, if there are more than three vascular invasions or the tumor size is larger than 4 cm, thyroidectomy is recommended due to high risk of distant metastasis in childhood FTC.[18]

In this study, our aim was to review the clinical course of children and adolescents treated for DTC and to present our clinical experience.

Methods

Thirty-two patients (28 girls, 4 boys) followed up with the diagnosis of DTC in our pediatric endocrinology clinic between 2001 and 2017 were enrolled in this retrospective cohort study. The patients with medullary thyroid cancer were excluded. The demographic data regarding age, gender, possible predisposing factors, family history of thyroid disorders or malignancies, and clinical data regarding histopathologic examinations, treatment modalities and follow-up were obtained from medical records. Signs of tumor aggressiveness such as multicentricity, lymphovascular invasion, capsule invasion, ETE, lymph node metastasis, and distant metastasis were recorded. Extra thyroidal extension (ETE) was classified as minimal and extensive ETE. Minimal ETE was defined as tumor invasion beyond the thyroid capsule detected on microscopy, and extensive ETE was defined as obvious extension of the primary tumor to adjacent structures detected during operation. The follow-up period was accepted as the length of time from the first presentation until the last documented contact. Data collection ended in October 2022. Approval for this retrospective study was obtained from the institutional review board. (Approval Number: 83045809–604.01.02), and the study was conducted according to the rules in the Declaration of Helsinki on Biomedical Research Involving Human Studies.

Initial treatment consisted of surgery, RAI, and L-thyroxine suppression therapy. The patients had been operated at different hospitals and 50% (n=16) of them were referred to our endocrine outpatient clinic after they were operated in other centers. The surgical treatment option was total thyroidectomy with or without neck dissection in all patients. However, lobectomy was performed primarily for a thyroid nodule in five patients, and then re-operation was performed when the patient was found to have thyroid cancer. In our center, preoperative assessment for lymph node involvement was made with neck ultrasonography (US). CND was performed in children with clinical evidence of gross ETE and/or locoregional metastasis on preoperative staging or intraoperative inspection. Compartment oriented LND, including levels III, IV, anterior V, and II, was performed in children with clinical evidence of metastasis to lymph nodes in lateral neck. Since it was noticed that locoregional and/or nodal disease persisted, reoperation was performed in our center for neck dissection in five patients who were initially operated in different centers.

The postoperative staging was made according to pathological tumor-node-metastasis classification recommended by the American Joint Committee on Cancer (AJCC).[19] We also made postoperative stratifications of PTC patients as low-, intermediate-, or high-risk categories to predict the patients at risk of persistent or recurrent cervical disease and/or distant metastases, according to definitions in ATA guideline.[8]

Tumors smaller than 1 cm in size and confined to thyroid gland were defined as microcarcinoma. Until 2015, RAI was given to all patients as a component of initial treatment except those with microcarcinoma. After 2015, however, postoperative RAI was performed only in ATA intermediate or high risk PTC patients. L-thyroxine suppressive therapy was given to all patients. Repeated RAI therapy was given to patients with evidence of recurrent or persistent locoregional or nodal disease that can not be resected as well as patients with distant metastases.

The follow-up strategy included the following: physical examination, thyroid function tests, serum thyroglobulin (Tg) levels when TSH was suppressed and elevated, neck US and diagnostic whole-body scintigraphy (DxWBS) with I^{131}. The serum level of Tg antibody (TgAb) was measured in all patients along with Tg, since the presence of TgAb might interfere with Tg measurement and render the Tg level uninterpretable. Negative results on DxWBS and neck US and undetectable or low serum Tg levels when TSH was elevated were accepted as remission signs in the absence of TgAb. An unstimulated serum Tg concentration of ≥1 ng/mL or a TSH-stimulated Tg concentration of ≥10 ng/mL in a patient who had undergone thyroidectomy and RAI was considered a possible indicator of persistent or recurrent disease. Patients with these findings underwent neck US and WBS to determine location and extension of disease. The trend in TgAb levels was evaluated to determine disease status in patients with positive TgAb. When the TgAb trend was clearly raised, further evaluation with neck US and DxWBS was made. Patients, who never entered remission, were accepted as having persistent disease. Recurrence was defined as the emergence of disease, with new RAI uptake or biopsy-proven disease, in any patient who had been free of disease.

Statistical Analysis

Statistical analyses were performed using SPSS 22.0 (SPSS Inc., Chicago, IL, USA). The results were presented as mean±standard deviation or as percentage. Mann–Whitney U test were used for the comparison of quantitative data. Chi-square test and Fisher's exact test were used for the comparison of qualitative data. The statistical significance was defined as a two-tailed $p \leq 0.05$.

Results

Demographic Characteristics of the Patients

We evaluated 32 patients diagnosed with DTC between 2001 and 2017, and about 40% (n=13) of these patients were diagnosed in the last 3 years of the study period. The tumor size was smaller than 10 mm in four patients diagnosed in the last 3 years and all had PTC. In one of these patients, minimal ETE and lymph node metastasis were detected, although the tumor size was <10 mm. The mean age of the patients at the time of diagnosis was 11.2±4 years (range 2.5–17) and thyroid cancer was diagnosed before the age of 5 in 12.5% (n=4) of them. Of the 32 patients, four were male. The demographic, clinical and histopathological features of the whole cohort are shown in Table 1.

Table 1. Demographic, clinical, histopathological features of the differentiated thyroid cancer patients

	Number (%)
Gender	
Female	28 (87.5)
Male	4 (12.5)
Age, years	
<5	4 (12.5)
5–10	7 (21.9)
10–18	21 (65.6)
Status at the time of diagnosis	
Disease limited to thyroid gland	15 (46.8)
Cervical lymph node involvement	17 (53.1)
Distant metastasis to lung*	7 (21.9)
Tumor hystopatology	
Papillary	14 (43.8)
Follicular variant papillary	14 (43.8)
Diffuse sclerosing variant	1 (3.1)
Follicular	3 (9.3)
Tumor focality	
Unifocal	23 (71.8)
Multifocal	9 (28.1)
Type of operation	
Total/near-total thyroidectomy	10 (31.2)
Complementary thyrodectomy after lobectomy	5 (15.6)
Total thyroidectomy+lymph node dissection	17 (53.1)
RAI treatment	
RAI for ablation	28 (87.5)
RAI for recurrence/persistence	15 (46.8)
None	4 (12.5)

*All patients with distant metastasis also had lymph node involvement.

Clinical Characteristics of the Patients

Swelling in the neck was the presenting sign in the majority of the patients (%94). Three patients had dysphonia, 1 patient had dyspnea, and thyroid cancer was detected during the follow-up of congenital hypothyroidism in one patient. History of radiotherapy for the treatment of Hodgkin's lymphoma was present in one patient. Nine patients had

thyroidal disease at presentation (autoimmune thyroiditis [AT] in 7 [21.8%], multinodular goiter in 1 and congenital hypothyroidism in 1). In the patient with congenital hypothyroidism, the etiology was dyshormonogenesis due to Tg synthesis defect. During the follow-up of this patient, progressive goiter with a thyroid nodule up to 18.5 mm in size was observed and classical variant PTC was confirmed after thyroidectomy. Twelve patients had a family history of thyroid disease. Only one patient had a family history of thyroid cancer.

Surgical Treatment

Total thyroidectomy with or without neck dissection was the surgical procedure of choice for all patients. In five patients, however, lobectomy was performed for a thyroid nodule initially and then re-operation for completion thyroidectomy was performed when the patient was found to have thyroid cancer. Three of these patients had FTC. CND was performed in 9.3% (n=3) patients, unilateral neck dissection was performed in 18.7% (n=6) and bi LND was performed in 25.0% (n=8). Reoperation for neck dissection was performed in our center in 5 patients, who were operated initially in different centers, due to persistence of locoregional or nodal disease.

Surgical Complications

The most common surgical complication was hypocalcemia. Hypoparathyroidism developed in 31.2% (n=10) of the patients and persisted in 5 of them. All patients who developed hypoparathyroidism had extensive locoregional involvement that required extensive surgery. Two patients had unilateral recurrent laryngeal nerve injury. Tracheostomy due to bilateral recurrent laryngeal nerve injury was performed in two patients. These two patients also had extensive locoregional involvement. In one patient, cyclous leakage developed after surgery. With respect to surgical complications, there were no differences between the groups.

Postsurgical Histopathologic Findings

The mean tumor diameter was 3.0±1.7 cm (range: 0.7–7.5 cm). Three patients (12.5%), had microcarcinoma and 6 (18.7%) patients had tumors exceeding 4 cm in diameter. As described above, minimal ETE and lymph node metastasis were detected in one patient, although the tumor size was <10 mm. Fourteen (43.8%) patients had classical variant of PTC, 14 (43.8%) patients had follicular variant of PTC, and one patient (3.1%) had diffuse sclerosing variant. At presentation, the frequencies of lymph node and pulmonary metastases were found to be 53.1% (n=17) and 21.8% (n=7), respectively. All patients with pulmonary metastases also had lymph node metastases. There were 3 patients with FTC and one of them had minimally invasive FTC. The mean age of these 3 patients with FTC was 11.8±2.3 years. Two of them were female. The mean tumor diameter was 3.1±1.1 cm. One had lymph node metastasis and none of them had distal metastasis. Multicentricity was not observed in any of the FTC patients. One had lymphovascular invasion and one had minimal ETE.

All patients were classified according to the AJCC staging system postoperatively. Seventy eight % (n=25) of the patients were in clinical stage I and 21.9% (n=7) of the patients were in stage II. According to the ATA initial pediatric risk stratification, 40.6% (n=13), 21.8% (n=7), and 37.5% (n=12) of the patients were classified as low-, intermediate-, and high-risk, respectively.

Comparison of Clinical and Pathological Features between Children and Adolescents with DTC

The patients were categorized in two groups as below and above 10 years of age. The clinical features of patients were compared between the two groups (Table 2). The mean tumor size was greater in the younger age group (p=0.008). Three patients with microcarcinoma were all aged above 10 years. The groups were comparable in terms of gender, clinical features, tumor histopathology and tumor aggressiveness parameters (multicentricity, lymphovascular invasion, ETE, lymph node and lung metastasis) except for lymphovascular invasion (p=0.01). The tumor sizes were similar in patients with and without lymph node metastases and also in patients with and without pulmonary metastases. The mean tumor diameters of the patients with and without lymph node metastases were 3.06±1.5 cm, 2.8±1.8, respectively (p=0.6), and the mean tumor diameters of the patients with and without pulmonary metastases were 3.4±1.6 cm, 2.8±1.6, respectively (p=0.4). Patients with lymph node metastases were more likely to have ETE (76% vs. 20%, p=0.005) and lymphovascular invasion (58.8% vs. 6.7%, p=0.006) compared to those who did not have lymph node metastases.

Radioiodine Treatment

Initially, all patients except those with microcarcinoma and the patients with minimally invasive FTC were treated with RAI. So RAI was given to 87.5% (n=28) of the patients initially. Multiple doses (ranging between 2 times and 6 times) were given to 46.8% (n=15) of the patients for recurrent and persistent disease.

Follow-Up

During the follow-up period, RAI-related secondary malignancies were not observed in any of the patients. However,

Table 2. Comparison of clinical and pathological features between children and adolescents with differentiated thyroid cancer

	Children (n=11)	Adolescents (n=21)	p
Age (years)	6.8±2.7	13.5±2.1	<0.001
Gender, Female (n,%)	8 (72.7)	20 (95.2)	0.10
Initial signs (n,%)			
Solitary nodule	3 (27.3)	9 (42.9)	0.76
Multinodular guatr	2 (18.2)	6 (28.6)	0.94
Nodular guatr/lymphadenopathy	6 (54.5)	4 (19)	0.06
Multinodular guatr/lymphadenopathy	0 (0)	2 (9.5)	-
Tumor diameter (cm)	4.1±1.8	2.4±1.2	0.008
Tumor histopathology (n,%)			
Papillary thyroid cancer	10 (90.9)	19 (90.4)	
Classical variant	5 (45.5)	9 (42.8)	0.99
Follicular variant	4 (36.4)	10 (47.6)	0.99
Diffuse sclerosing variant	1 (9.1)	0 (0)	0.81
Folicular thyroid cancer	1 (9.1)	2 (9.5)	0.11
Pathological evidence of tumor aggresiveness (n,%)			
Multicentricity	4 (36.4)	5 (23.8)	0.45
Lympho vascular invasion	7 (63.6)	4 (19)	**0.01**
Capsule invasion	7 (63.6)	9 (42.8)	0.26
Extrathyroidal invasion (minimal)	5 (45.5)	9 (42.8)	0.81
Extrathyroidal invasion (extensive)	2 (18.2)	0 (0)	0.11
Lymph node metastasis	7 (63.6)	10 (47.6)	0.43
Central	0 (0)	3 (14.2)	
Ipsilateral	2 (18.2)	4 (19.0)	
Bilateral	5 (45.5)	3 (14.2)	
Lung metastasis	2 (18.2)	5 (23.8)	0.71

Chi-square test or fisher's exact test/mann-whitney u test.

pulmonary fibrosis developed in a patient who was given RAI 6 times due to persistent pulmonary involvement. The mean follow-up period was 8.5±3.8 years (Median: 6.7 years, range:3.5–17.4) and no patient died due to thyroid cancer. Except five patients (15.6%), who had persistent disease, all patients were in remission at the last visit. The median follow-up period of these five patients was 5.4 years, ranging between 3.4 and 11.8 years. All patients with persistent disease had extensive locoregional tumors with lymph node metastases, and three of them also had pulmonary metastases.

Discussion

In our cohort, 90% of the patients had PTC, the frequency of lymph node metastasis was 53.1% and the frequency of pulmonary metastasis was 21.8% in accordance with the literature. Interestingly, approximately 40% of the patients with DTC were diagnosed in last 3 years of the study period. There were no differences in the referral patterns of these patients that could explain the increased rate. However, the tumor size was smaller than <10 mm in four of them. The increased rate might be related with increased incidence of DTC that was reported previously.[7]

Compared with adults, invasion rate in pediatric thyroid cancer is higher and lymph node and distal metastases are more frequent.[4-6] Multicentric disease is more common in children with DTC and lymph node metastases are present in more than 70% at the time of diagnosis.[2,20] The rate of pulmonary metastasis is reported to be 10–28%.[21] Despite its seemingly aggressive behavior, pediatric PTC is considered a cancer of favorable prognosis. Most patients have a long-term survival rate. The 30-year survival rate is over 90%.[3] Consistent with the literature, no deaths occurred in our cohort despite the high initial rates of lymph node and pulmonary metastasis.

In our cohort, there was no difference between the two age groups in terms of gender, clinical features, tumor histopathology, and tumor aggressiveness criteria other than lym-

phovascular invasion. However, the mean tumor diameter was significantly greater in the younger group, and microcarcinoma was observed only in the older group**.** Delayed diagnosis of thyroid cancer in younger children may be one reason for this situation. The parents might have become aware of the tumor only after its marked growth, despite its presence long before the diagnosis. There might be yet unknown facts. In contrast to our findings, increased prevalence of tumor aggressiveness criteria such as ETE, lymph node, and distant metastasis in younger children were reported in some studies.[22-24] Poyrazoğlu et al.[25] reported that pathological signs of tumor aggressiveness were similar between prepubertal and pubertal groups**,** but tumor sizes were larger in the prepubertal group as in our study. Handkiewicz-Junak et al.[26] also did not find any correlation between age and locoregional recurrence. Moreover, Machens et al.[27] reported that growth patterns and metastatic behavior were similar between children and adolescents.

Data obtained from our study confirm that ETE and lymphovascular invasion are tumor characteristics that have increased risk for lymph node metastasis. Previous studies had found that tumor size was a risk factor for nodal metastasis, as well as ETE and multicentric disease.[28-30] Caliskan et al.[31] found that tumor stage, presence of lymphovascular invasion, and multicentricity were independent risk factors for the development of central lymph node metastasis in adult populations. We did not find a difference in tumor sizes between the patients with and without nodal metastasis. In fact, one patient had lymph node metastasis and ETE, even though the tumor was <10 mm in size. However, our sample size was small to draw definite conclusions.

In our cohort, the rate of AT was found to be 21%. AT could play a role in the development of DTC secondary to chronic inflammation. This association has been observed in other studies, yet the causal relationship of HT as a premalignant state still needs to be further investigated.[32,33] The rates of other known risk factors like radiotherapy (3%) or family history of thyroid cancer (3%) were low in our cohort. One of the patients had congenital hypothyroidism due to Tg synthesis defect. Hishinuma et al.[34] reported a high prevalence of thyroid malignancy (63.6%) in patients with long-standing goiter due to Tg mutations. The pathophysiologic changes underlying the development of thyroid cancer in dyshormonogenetic tissues are unknown. It has been suggested that prolonged stimulation by TSH may result in the malign transformation of thyroid follicular cells.[35,36] Poor compliance to treatment causing TSH elevation and goiter was also present in our patient.

In the pediatric population, the lower incidence of thyroid cancer together with a higher incidence of cervical lymph node metastasis, may be a possible reason for the increased risk of surgical complications. Therefore, it is recommended that thyroid surgery in children should be performed by high-volume thyroid surgeons.[8] The rate of surgical complications, especially hypoparathyroidism, was high in our cohort. However, our patient group was very heterogeneous and involved patients operated in many different centers. Hence, it is difficult to draw conclusions about surgical complications. Nevertheless, the high complication rate shows that pediatric thyroid surgery should be performed by high volume surgeons. In all patients who had surgical complications, extensive locoregional tumor was present. CND was reported as an independent risk factor for the development of hypoparathyroidism and vocal cord paralysis by Unlu et al.[37] All children with newly diagnosed PTC should be comprehensively evaluated prior to surgery by a multidisciplinary team consisting of pediatric endocrinologists, radiologists, and surgeons to optimize surgical outcomes. However, this was not the case in 50% of our cohort, who were referred to our clinic after surgery. In all patiens, a comprehensive neck US should be performed by an experienced radiologist to define lymph node involvement and to determine whether neck dissection is necessary. In our cohort, reoperation for neck dissection was performed in 5 patients due to inappropriate radiologic evaluation before surgery.

In previous years, RAI was given reflexively to eliminate post-operative residual thyroid tissue with a view to increase sensitivity to the use of serum Tg as a marker of recurrence and to decrease the risk of recurrence. However, recent ATA guidelines do not support routine RAI treatment after surgery due to a possible increase in the risk for secondary malignancies. RAI was recommended only for the patients with ATA intermediate and high risk groups that hold risks for persistent cervical disease and/or distant metastasis. In our cohort, multiple doses (ranging from 2 times to 6 times) were given in 46.8% (n=15) of the patients for recurrent and persistent disease. Repeated RAI treatment can result in remission in many, but not all children with pulmonary metastases, the great majority of whom will have stable, persistent disease with low disease-specific mortality.[8] In our cohort, 3 of the 7 patients with pulmonary metastases demonstrated stable metastatic disease despite multiple doses of RAI. Since children with pulmonary metastases have previously been treated aggressively with repeated RAI, multiple doses of RAI was also given to our patients with pulmonary metastases. Unfortunately, pulmonary fibrosis developed in one of these patients during follow-up. It has been reported that there is a significant risk for RAI-related pulmonary fibrosis when the retained I activity exceeds 80 mCi.[15] Currently, the ATA

guidelines recommend repeated RAI therapy for pulmonary metastases only in children with demonstrated disease progression and who have previously responded to RAI therapy.[8] In our cohort, secondary malignancy related with RAI treatment was not observed during our follow-up period. However, our follow-up period is not enough to draw definitive conclusions. A long-term study reported deaths from second primary malignancies after 30 and 50 years of follow-up.[38]

Conclusion

In conclusion, our findings suggest once again that DTC in children is more disseminated with increased lymph node and pulmonary metastasis compared to adults, but the overall prognosis is favorable.

Disclosures

Ethics Committee Approval: The study was approved by the Ethics Committee of Cerrahpasa Medical Faculty (No: 83045809-604.01.02, dated 02.07.2020).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – A.D.C., OY.E.; Design – A.D.C., OY.E.; Supervision –OY.E., L.K., R.O.; Materials – F.T.B., G.T., R.O.; Data collection &/or processing – A.D.C., F.T.B., G.T.; Analysis and/ or interpretation – A.D.C., OY.E., OL.E.; Literature search – A.D.C., G.T., H.T.; Writing – A.D.C., OY.E., OL.E.; Critical review –OY.E., OL.E., L.K., R.O.

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