

Investigation on the prevalence of thyroid cancer in Graves' patients in northeastern part of Turkey: Is surgery a better option for patients with Graves' disease who develop antithyroid drug-related major adverse events?

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Abstract. – OBJECTIVE: To determine the prevalence of thyroid cancer in Graves' patients who underwent surgical intervention with and without a history of anti-thyroid drug related major adverse events.

PATIENTS AND METHODS: The data of 530 patients with Graves' disease between 2015 and 2020 were retrospectively reviewed. Preoperative ultrasonography reports and thyroid-stimulating hormone receptor antibody values and postoperative histopathological findings were available for 94 patients that had undergone total thyroidectomy procedure. We compared the prevalence of thyroid cancer between patients with and without a history of anti-thyroid drug related major adverse events.

RESULTS: Thyroid cancer was detected in 31 of 94 patients that had undergone total thyroidectomy. Of these patients, 18 had at least one nodule; however, thyroid cancer was incidentally detected in 13 patients without nodule. The 31 patients had the following cancer subtypes: 22 had papillary microcarcinoma, 8 papillary carcinoma and 1 noninvasive follicular thyroid neoplasm with papillary-like nuclear features. While thyroid cancer was present in half of the patients operated owing to anti-thyroid drug-related major adverse event, it was detected in 30% of the patients operated due to other reasons.

CONCLUSIONS: In the present study, the prevalence of thyroid cancer among patients with Graves' disease was found to be much higher than those of other studies in the literature, suggesting that surgery can be considered primarily for the treatment of Graves' disease. Considering the surgical option in the first plan instead of radioactive iodine therapy appears to be reasonable in patients who develop anti-thyroid drug-related major adverse events.

Key Words:

Graves' disease, Prevalence, Surgical treatment, Anti-thyroid drug, Thyroid cancer.

Introduction

Graves' disease is an autoimmune disease that may consist of hyperthyroidism, goitre, eye disease (orbitopathy) and occasionally a dermatopathy referred to as pretibial or localized myxedema. Hyperthyroidism is the most common feature of Graves' disease, affecting nearly all patients and is caused by thyroid-stimulating hormone (TSH, thyrotropin)-receptor antibodies (TRAb) that activate the receptor, thereby stimulating thyroid hormone synthesis and secretion as well as thyroid growth (causing a diffuse goitre). The therapeutic approach to Graves' hyperthyroidism consists of both rapid amelioration of symptoms with a beta blocker and measures aimed at decreasing thyroid hormone synthesis, such as the administration of a thionamide, radioiodine ablation, or surgery¹. All three options are effective; however, all three options have significant side effects. Because there is no consensus as to the 'best' treatment option, the American Thyroid Association (ATA) guidelines emphasize the significance of fully discussing the options with patients and considering their values and preferences before deciding on a treatment plan^{1,2}. Additionally, the three options are not mutually exclusive. Antithyroid drugs may be initially used to control hyperthyroidism prior to a definitive

therapy with radioiodine or surgery. These drugs may be prescribed for 1–2 years or even longer to attempt and attain remission, or they may be used in long term. Radioiodine may be administered as an initial therapy or after pretreatment with antithyroid drugs and surgery is frequently preceded by antithyroid drugs to attain a euthyroid state preoperatively. In the future, immunotherapy may be a therapeutic option. In a phase I study utilizing antigen-specific immunotherapy with thyrotropin receptor peptides, hyperthyroidism improved in 70% of patients³.

The incidence of thyroid cancer continues to rise worldwide, mostly as a result of the increased use of diagnostic imaging and surveillance. Although the incidence is steadily rising, mortality from thyroid cancer has minimally changed over the past five decades. The challenge faced by physicians who treat thyroid cancers is to balance the therapeutic approach so that patients with lower-risk disease or benign thyroid nodules are not over treated. At the same time, they need to recognize those patients with more advanced or high-risk disease, who need a more aggressive treatment approach⁴. Thyroid follicular epithelial-derived cancers are divided into three categories: the most common papillary cancer (85%), the second follicular cancer (12%) and the least anaplastic (undifferentiated) cancer (<3%). Papillary and follicular cancers are considered differentiated cancers and patients with these tumours are often treated similarly, despite numerous biologic differences. Most anaplastic (undifferentiated) cancers appear to arise from differentiated cancers. Other malignant diseases of the thyroid include medullary thyroid cancer, which can be familial, either as part of the multiple endocrine neoplasia type 2 syndrome or isolated familial medullary thyroid cancer and primary thyroid lymphoma. Cancers that metastasize to the thyroid include breast cancer, colon cancer, renal cancer, and melanoma.

In the literature, the prevalence of thyroid cancer among patients with Graves' disease ranges from 0.4% to 10%⁵⁻⁷. Current hypotheses of the carcinogenesis mechanism center around pathways activated by binding of thyroid-stimulating antibodies, where it can promote growth as well as promote invasion and angiogenesis⁸ and activate insulin-like growth factor pathways⁹.

Thyroid ultrasonography is considered to be the most sensitive method in detecting thyroid nodules¹⁰. Using ultrasonography to evaluate the thyroid gland in patients with Graves' disease al-

lows the detection of thyroid nodules that cannot be detected with routine physical examination¹¹.

The development of antithyroid drug-related major adverse event is an indication for radioactive iodine therapy or surgery; nevertheless, there is no study in the literature evaluating whether there is a relationship between developing antithyroid drug-related major adverse event and the prevalence of cancer.

The present study aimed to determine whether the prevalence of thyroid cancer among patients with Graves' disease that underwent surgical intervention at our centre is consistent with the literature, detect whether there is a difference between thyroid nodule (solitary and multiple) and diffuse goitre in terms of the prevalence of thyroid cancer and identify whether the prevalence of cancer is increased among patients that had undergone surgical intervention owing to developing antithyroid drug-related major adverse event.

Patients and Methods

The data of 530 patients that were diagnosed with Graves' disease between 2015 and 2020 at Erzurum Ataturk University Research Hospital were retrospectively reviewed. Of these patients, 94 had undergone total thyroidectomy. The diagnosis of Graves' disease had been confirmed by the presence of a history of Graves' disease together with the clinical symptoms of hyperthyroidism, the presence of orbitopathy and dermopathy in some patients, a thyroid scintigraphy result that is consistent with hyperthyroidism, elevated free thyroxine, and free triiodothyronine and suppressed TSH levels and TRAb positivity in all patients. Indications for surgery included disease recurrence, unresponsiveness to medical therapy, the presence of symptoms of suppression, the development of antithyroid drug (propylthiouracil or methimazole)-related major adverse event (hepatotoxicity or agranulocytosis) and patient's preference of surgery. In the preoperative period, the structure of the thyroid gland and presence of nodule had been evaluated by ultrasonography in all patients. Preoperative thyroid scintigraphy (Tc-99 m pertechnetate) was available in 46 of 94 patients that had undergone total thyroidectomy. All the study participants had detailed postoperative histopathological findings and the presence of thyroid cancer and subtypes were identified based on these

findings. Patients with negative or unavailable TRAb result or those that have not been diagnosed with Graves' disease before surgery were not included in the study. This study was approved by the Research Ethics Committee of Medical Faculty, Erzurum Ataturk University (Number: B.30.2.ATA.0.01.00/37 Decision: 40/04.03.2021).

Statistical Analysis

Data analysis was performed using SPSS-22 for Windows (Statistical Package for Social Science, SPSS IBM, Armonk, NY, USA). Variables were investigated using visual (histograms, probability plot) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk test) to determine whether or not they are normally distributed. We performed analyses to describe and summarize variable distributions. Differences between qualitative/categorical variables, such as gender distribution between groups, were compared using the chi-square test since the values observed in the cells provided assumptions. Student's *t*-test was used to compare the variables with normal distribution. One-way ANOVA test was used to compare multiple groups. Levene test was used to assess the homogeneity of the variances. The

statistically significant two tailed *p*-value was considered as <0.05 . When an overall significance was observed, pairwise post hoc tests were performed using Tukey test.

Results

Of the 94 participants that had undergone surgery for Graves' disease, 24 (25.5%) and 70 (74.5%) were male and female patients, respectively and the mean age was 41.3 ± 12.6 years. Forty-six (48.9%) of the cases had at least one thyroid nodule, whereas the remaining 48 (51.1%) had diffuse goitre without nodule. While 13 of the 46 patients with nodule had a solitary nodule, 33 had two or more (multiple) nodules. In addition, the largest diameter of the nodule was 1 cm or higher in 31 patients (67.4%). Based on the post-operative pathology reports, thyroid cancer was detected in 33.0% ($n = 31$) of the overall cases. The cancer subtype was papillary microcarcinoma in 71.0% ($n = 22$), papillary thyroid carcinoma in 25.8% ($n = 8$) and noninvasive follicular thyroid neoplasm with papillary-like nuclear features in 3.2% ($n = 1$) of the 31 thyroid cancer patients (Figures 1 and 2).

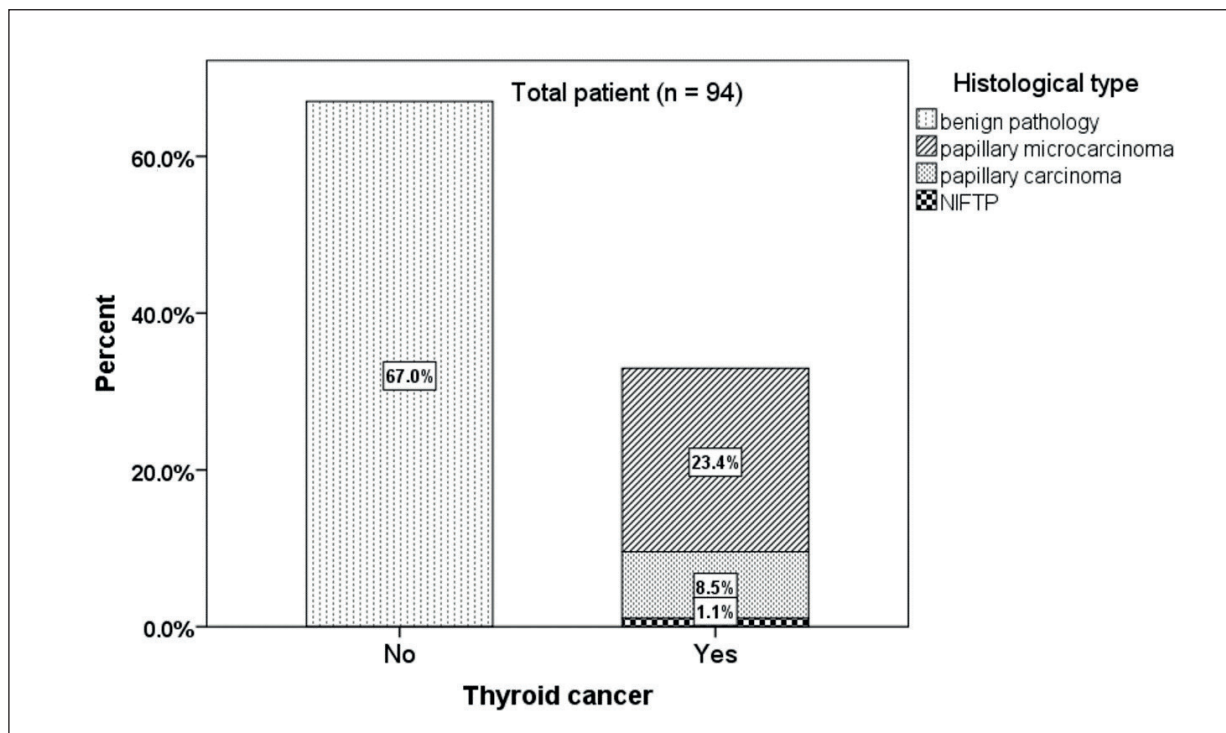


Figure 1. Presence of thyroid cancer and histological type distribution according to the postoperative pathology result.

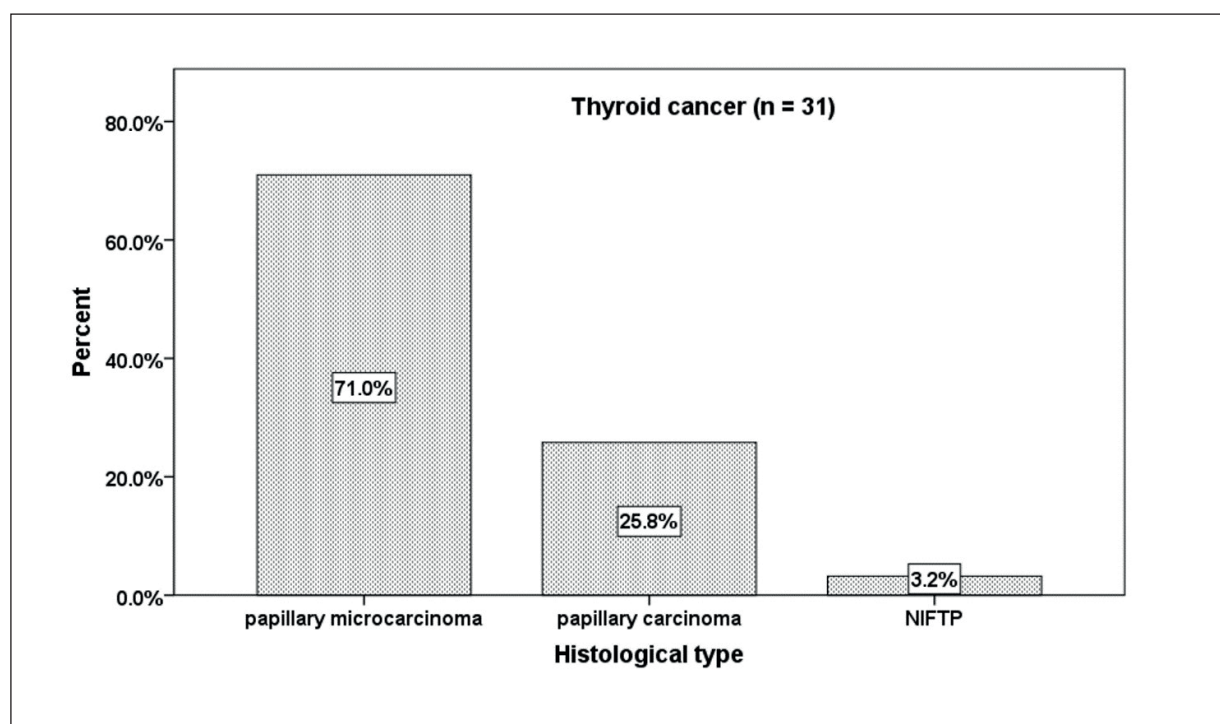


Figure 2. Histological type distribution in thyroid carcinoma cases.

The female/male distribution among thyroid cancer patients was found to be 24/7 (77.4%/22.6%), whereas it was found to be 46/17 (73%/27%) among those with benign pathology ($p = 0.645$). The presence of thyroid cancer showed no correlation with gender. Although the difference between the groups with and without thyroid cancer was not statistically significant in terms of the development of antithyroid drug-related major adverse event ($p = 0.179$), the group with thyroid cancer (19.4%, $n = 6$) had a higher proportion of patients that developed major adverse event than the group without thyroid cancer (9.5%, $n = 6$). These findings are summarised in Table I.

While 50% (6/12) of the patients that developed antithyroid drug-related major adverse event had thyroid cancer, thyroid cancer was detected in

30% (25/82) of the patients that did not develop the adverse event.

When grouped according to the presence of nodules in the thyroid, a significant difference in terms of age was found between the groups (diffuse goitre, 35.6 ± 11.1 ; solitary nodule, 40.9 ± 7.3 ; multiple nodules, 49.8 ± 11.8 ; $p < 0.001$). While no difference was noted between the 'diffuse goitre' and 'solitary nodule' groups ($p = 0.269$), differences were observed between the 'diffuse goitre' and 'multiple nodules' groups ($p < 0.001$) and between the 'solitary nodule' and 'multiple nodules' groups ($p = 0.039$). However, no difference was noted between the groups in terms of thyroid cancer rates ($p = 0.161$; Table II).

Analyzing the cases with thyroid cancer according to the presence of nodule, the mean age

Table I. The analysis of some clinical features according to the presence of thyroid cancer.

	Thyroid cancer		p-value
	Yes (n = 31) n (%)	No (n = 63) n (%)	
Sex (F/M)	24/7 (77.4/22.6)	46/17 (73.0/27.0)	0.645
Antithyroid drug major side effect, positive	6 (19.4)	6 (9.5)	0.179

Abbreviations: F: female; M: male.

Table II. Descriptive statistics showing clinical characteristics based on the presence or absence of nodule

	Diffuse goitre (n = 48)	Solitary nodule (n = 13)	Multiple nodules (n = 33)	p-value
Percentages, %	51.1	13.8	35.1	-
Age (years), mean ± SD	35.6 ± 11.1	40.9 ± 7.3	49.8 ± 11.8	<0.001
Sex (M/F), n/n	13/35	5/8	6/27	0.343
Thyroid cancer, n (%)	13 (27.1)	3 (23.1)	15 (45.5)	0.161

Abbreviations: F: female; M: male; SD: standard deviation.

was 50.0 ± 12.4 years in those with multiple nodules, which was significantly higher than both the diffuse goitre group ($p < 0.001$) and the solitary nodule group ($p = 0.039$). Similarly, the postoperative histological findings were compared between the three groups and no difference was detected in terms of the distribution of pathological diagnosis ($p = 0.296$). In the groups with nodule, the analysis according to the largest nodule diameter, with 1 cm taken as the reference, revealed no significant difference between the groups ($p = 0.442$). The results are summarized in Table III.

Discussion

In this retrospective study, the prevalence of thyroid cancer among patients with Graves' disease that had been surgically treated was determined for our centre. In our study, the prevalence of thyroid cancer among patients with Graves' disease was much higher than that of all studies in the literature, which suggests that surgery for the treatment of Graves' disease can be considered in the first plan in suitable patients. Furthermore, it raised the assumption that considering the surgical option in the first plan instead of radioactive

iodine therapy would be reasonable in suitable patients that develop antithyroid drug-related major adverse event. The prevalence of palpable thyroid nodules in patients with Graves' disease ranges from 25% to 45%^{5,12,13}. In some cases, Graves' disease itself may cause thyroid nodules¹⁴. In recent years, the coexistence of thyroid cancer and Graves' disease has been of great concern. Occasionally, an unsuspected thyroid cancer was incidentally discovered on pathologic examination in a patient with Graves' disease¹⁵. In the present study, thyroid nodule was detected in 48.9% of the patients that were diagnosed with Graves' disease and evaluated by ultrasonography at the preoperative period; this ratio was higher than that of other studies in the literature. Ren et al¹⁶ detected thyroid cancer in 58 (13.7%) of 423 patients with Graves' disease that were surgically treated. In the same study, the prevalence of thyroid cancer in the patients with Graves' disease was 56% and 45% for those with solitary nodule and multiple nodules, respectively; the incidence of nodule in Graves' disease with malignancy was reported to be 47.9%. Patients with nodular Graves' disease were found to have a higher risk of developing thyroid cancer than those with diffuse goitre (47.9% vs. 3.6%). Moreover, this study indicat-

Table III. Statistical details according to the presence of nodules in cases with thyroid cancer.

	Thyroid carcinoma			p-value
	Diffuse goitre (n = 13)	Solitary nodule (n = 3)	Multiple nodules (n = 15)	
Age (years), mean ± SD	40.1 ± 8.15	38.3 ± 8.0	50.0 ± 12.4	<0.001
[p-value]	[p < 0.001]*	[p = 0.039]*		
Sex (M/F), n/n	3/10	1/2	3/12	0.879
Nodule size, n (%)	<1 cm	1 (33.3)	2 (13.3)	0.442
	≥1 cm	2 (66.7)	13 (86.7)	
Histopathological type, n (%)	Microcarcinoma (papillary)	11 (84.6)	3 (100)	0.296
	Papillary carcinoma	2 (15.4)	0 (0)	
	NIFTP	0 (0)	0 (0)	

*It was obtained by the post hoc analysis of one-way ANOVA test. No significant difference was observed between the diffuse goitre and solitary nodule groups and both groups are different from multinodular goitre (p-value was shown in square brackets).

ed that the male gender is not associated with a higher risk of cancer, which is not consistent with some other studies¹⁷⁻¹⁹.

Although the present study is methodologically similar to that conducted by Ren et al¹⁶, the results were strikingly different, excluding that the risk of cancer is not increased by gender. In the present study, the prevalence of cancer among patients with Graves' disease that had been surgically treated was as high as 33.0% and the prevalence of cancer was similar between the group with nodular goitre and the group with diffuse goitre without thyroid nodule. In their meta-analysis, Staniforth et al²⁰ reviewed 33 studies and reported that thyroid cancer is present in 498 (4.7%) of 10,594 patients with Graves' disease. It was stated that histological diagnosis was available in 325 of 498 cases of thyroid cancer reported in 28 studies in this meta-analysis; cancer subtypes were papillary, follicular, mixed papillary-follicular, medullary and anaplastic in 88%, 10%, 0.6%, 0.6% and 0.3% of the cases, respectively. Furthermore, they stated that not only the histological subtype, but also the size of lesion was available in 254 of the reported cases. It was reported that 29% of overall papillary carcinomas were microcarcinomas with a diameter of ≤ 1 cm and that the papillary microcarcinomas accounted for 23% of overall thyroid carcinomas; no lymphoma cases were recorded. In this meta-analysis, 20 studies had some data about the presence of concurrent thyroid nodules in relevant patients; in general, 51% of the reported cancers existed in patients with nodular Graves' disease²⁰. A recent review²¹ noted that the thyroid carcinoma incidence is increasing worldwide, representing both an apparent increase due to more sensitive diagnostic procedures and a true increase.

In the present study, thyroid cancer was detected in 33.0% of the cases. Histological subtyping revealed papillary microcarcinoma, papillary carcinoma and noninvasive follicular thyroid neoplasm with papillary-like nuclear features in 23.4%, 8.5% and 1.1% of the cases, respectively; other types of cancer were not present. No statistically significant difference was determined between diffuse goitre, solitary nodule and multiple nodule groups in terms of the prevalence of cancer. Rago et al¹⁹ investigated the prevalence of papillary thyroid carcinoma in 286 patients with Graves' disease (55 males, 231 females) and reported positive correlation between male gender and cancer in Graves' disease, whereas the present study found that the presence of thyroid can-

cer in patients with Graves' disease is not associated with gender.

The outcome of the present study that the prevalence of cancer is not increased in patients with nodular Graves' disease was not consistent with the literature. This can be attributed to the fact that nodules might have been unnoticed because, given the retrospective design of the present study, the patients' preoperative ultrasonographic examinations had been performed by different radiologists.

Comparing the groups in terms of the development of antithyroid drug-related major adverse event, it was found that the group with thyroid cancer had a more than two-fold higher percentage of patients that developed major adverse event than the group without thyroid cancer; although, the difference was not statistically significant. Cancer was positive in 50% of the patients that developed antithyroid drug-related major adverse event and in 30% of the patients that did not develop drug side effect. We believe that the limited patient number is the reason for this difference not reaching a statistical significance. This raises the question whether developing antithyroid drug-related major adverse event can be used as a marker for the presence of cancer. Should surgery be considered in the first plan in such situations instead of radioactive drug therapy? We believe that this needs to be investigated in further studies performed with a larger patient population.

In the present study, the prevalence of thyroid cancer among patients with Graves' disease was much higher than that of other studies in the literature, suggesting that surgery can be considered primarily for the treatment of Graves' disease wherein the patients are unsure to undergo radioactive iodine therapy or surgery.

The strengths of the present study include all patients being histopathologically evaluated, TRAb positivity had been considered in all patients, patients without Graves' disease were not included in the present study and it is the first study in the literature investigating the prevalence of cancer among patients that underwent surgery owing to antithyroid drug-related major adverse event. The limitations of the present study include the limited patient number, the presence of nodule might have been overlooked because thyroid ultrasonography had been performed by different radiologists due to the retrospective study design and not having data about follow-up period, presence of metastasis and patients' prognosis. In addition, since the time between the diagnosis of Graves' disease and surgical intervention is un-

known, perhaps longer time would be responsible for the increase in the prevalence of cancer.

Conclusions

We conclude that determining the prevalence of thyroid cancer in the patients that develop anti-thyroid drug-related major adverse event in multi-centre, larger retrospective studies and identifying the percentage of patients that develop thyroid cancer during follow-up among those treated with radioactive iodine therapy can be a guide in deciding whether to choose radioactive iodine therapy or surgery as the first-line therapy.

Conflict of Interest

The authors declare that they have no conflict of interest.

Authors' Contributions

R.D researched the data, contributed to discussion, and wrote the manuscript. A.B, S.C, E.C, F.M, E.O conducted the research and contributed to discussion. İ.C and H.B drafted the manuscript and made critical revisions to the manuscript. T.D contributed to data analysis. All authors read and approved the final manuscript.

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Ethical Approval

This study was approved by the Research Ethics Committee of Medical Faculty, Erzurum Ataturk University (Number: B.30.2.ATA.0.01.00/37 Decision: 40/04.03.2021).

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