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RESEARCH ARTICLES

RESEARCH ARTICLE
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Prognostic Importance of Ki-67 Expression in Early-Stage Glottic Larynx Cancer Treated with Radiotherapy

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ABSTRACT

Objective: The prognostic importance of Ki-67 expression in early-stage glottic larynx cancer is controversial. In this study, we aimed to evaluate the prognostic importance of Ki-67 expression in early-stage glottic cancer treated with curative radiotherapy at a single centre.
Material and Method: Between 2010 and 2021, patients with T1a/bN0 stage glottic larynx cancer treated with curative radiotherapy were identified. The cases included in this study were re-evaluated by a single pathologist retrospectively. According to the ROC curve, the optimal cut-off value was 35% for Ki-67. Above these cut-off points were accepted as high expression levels (Ki-67-high), while below these points were accepted as low expression levels (Ki-67-low).
Results: A total of 49 patients with early-stage glottic larynx cancer treated with definitive radiotherapy were included. The median follow-up time was 35.74 (range; 7.03-161.65) months. The median OS was 95.4 (range; 62.1-128.8) months. According to univariate analysis, tumour grade (p=0.006) and Ki-67 expression level (low vs high; p=0.039) were the prognostic factors that predict OS. The median DFS was 42.1 (range; 32.8-51.3) months. According to univariate analyses, tumour grade (p=0.008) and Ki-67 expression level (low vs high; p=0.007) were the prognostic factors that predict DFS.
Conclusion: Higher Ki-67 expression was associated with lower OS and DFS. Ki-67 expression level can be used as a biomarker to determine treatment choice in these patients. Additional prospective studies with more patients are needed to confirm our results.
Keywords: Larynx Cancer, Ki-67, survival outcomes, radiotherapy

INTRODUCTION

Larynx cancer is one of the most common cancer types in head and neck malignancies (HNCs), and about 60% of cases originate from the glottis (1,2). The patients are often detected at an early stage, due to the tumour-associated hoarseness. Early detection provides an opportunity for organ preservation and cure (3). Radiotherapy, open partial laryngectomy, and transoral laser microsurgery are the current treatment options for early-stage glottic larynx cancer (3,4). Although the number of large, randomised studies is limited, the oncologic and quality-of-life outcomes of studies comparing both treatment modalities are similar (4). Institutional experience and the patient's preference often determine the treatment type. The 5-year local control rate varies between 80-95% for radiotherapy (3). Despite high control rates, salvage surgery in radioresistant tumours is usually performed as a total laryngectomy (1). Knowing the proliferation pattern of tumour cells before deciding on the treatment modality may guide the prediction of radio resistance and the choice of treatment.

In clinical practice, immunohistochemical determination of the Ki-67 proliferation index is usually used to evaluate the proliferation pattern of tumours (5). The prognostic importance of the Ki-67 proliferation index has been investigated in many types of cancer and also in HNCs (6). The studies showed that patients with a higher expression of Ki-67 had poorer outcomes. Additionally, a high Ki-67 expression is associated with a higher rate of lymph node metastasis (6) But, the prognostic importance of Ki-67 expression in early-stage glottic

Corresponding Author: Gül Kanyılmaz **E-mail:** drgulgun@yahoo.com
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larynx cancer is controversial because of the heterogenous design of the studies that included patients with different stages of disease.

In the current study, we aimed to evaluate the prognostic importance of Ki-67 expression in early-stage glottic cancer treated with curative radiotherapy at a single centre.

MATERIALS AND METHODS

Patient population

Ethical approval of the study was obtained from the ethics committee of our university. The stage of disease was clinically determined according to the 8th edition of the TNM classification established by the American Joint Committee on Cancer (AJCC). The tumour is limited to the one vocal cord with normal mobility staged as T1a (may involve anterior or posterior commissure) and the tumour involves both vocal cords with normal mobility staged as T1b (may involve anterior or posterior commissure) (7). Between 2010 and 2021, the data of patients with T1a/bN0 stage glottic larynx cancer treated with curative radiotherapy were collected. Among them, whose histopathological identification was carried out at our university were included in this study. 49 patients' data from the hospital records, consisting of age, sex, Karnosky Performance Status, TNM status, sites of disease, grade of tumour, and treatment details, were evaluated retrospectively. All patients were newly diagnosed, biopsy-proven T1a/b stage squamous cell carcinoma of the glottis. The exclusion criteria were age < 18 years, Karnofsky Performance Status (KPS) < 70, history of another type of cancer within the last 5 years, previous head and neck radiotherapy, and follow-up time < 6 months.

Table 1: Patients, disease and treatment characteristics

Variables	No. of patients (Total:49)	%
Age (years)		
Median (range)	68 (45-83)	
≥68	27	55
<68	22	45
Sex		
Male	46	94
Female	3	6
Clinical stage*		
Stage T1a	38	78
Stage T1b	11	22
Anterior commissure involvement		
No		
Yes	34	70
Tumour Grade	15	30
Grade I		
Grade II	20	41
Grade III	17	35
Ki-67 expression level	12	24
Low-Ki-67		
High Ki-67	18	37
RT dose	31	63
6600 cGy		
6800 cGy	24	49
7000 cGy	8	16
	17	35

RT: Radiotherapy. * According to version of the American Joint Committee on Cancer (AJCC) 8th edition, 2017.

Treatment

All patients were examined by a multidisciplinary head and neck tumour board. The treatment decisions were routinely decided by board members based on functional and individual patient-related factors.

Radiotherapy

Radiotherapy was performed using a three-dimensional conformal technique with a linear accelerator. Typically, radiotherapy was applied with a pair of wedged lateral opposed fields using 6MV photon energy. The whole larynx was included in the target volume. Eclipse Treatment Planning System version 8.9.08 (Varian, Palo, Alto, CA) was used in treatment planning. The total radiation dose was 66-70 Gy/5 fraction per week according to clinician preference.

Follow-up

All patients were evaluated throughout the radiotherapy at least once a week. After the completion of radiotherapy, the patients were examined every 3 months for the first two years, every six months for the third year, and once a year thereafter. A historical, physical, and endoscopic examination was done at each follow-up visit. Additional imaging studies were done as needed to assess locoregional or distant failure.

Immunohistochemical determination

The cases diagnosed with early-stage glottic larynx cancer and included in this study were re-evaluated by a single pathologist (F.S.) retrospectively, according to the guideline recommendations of the American Society of Clinical Oncology/ College of American Pathologists (ASCO/CAP protocols) (8) Histological type and grading were redone from H&E-stained slides. The cases were histologically classified as keratinized and non-keratinized squamous cell carcinoma. The cases were graded as well differentiated (Grade-1), moderately differentiated (Grade-2), and poorly differentiated (Grade-3). 4 micron thick sections were taken from paraffin blocks of the cases on positively charged slides for immunohistochemical Ki-67 staining. Slides cut for the immunohistochemical study were incubated for 30 minutes in EDTA buffer at 97 degrees. Then, the immunohistochemical Ki-67 (DAKO-Clone-MIB-1) staining protocol was applied in the DAKO OMNIS machine. The stained slides were evaluated under the light microscope (Olympus BX 46) by the same pathologist. Ki-67; nuclearly positively stained cells were given a percentage as a hot spot.

Statistical analysis

Statistical Package for Social Sciences for Windows version 20 (SPSS. Inc. Chicago. IL) was used for all statistical analyses. Descriptive statistics were performed to evaluate the patient, disease, and treatment characteristics. The overall survival (OS)

Table 2: Univariate and multivariate Cox proportional hazard regression analysis related to OS

	Univariate analysis		Multivariate analysis	
Variables	**HR**	**95% CI p-value**	**HR**	**95% CI p-value**
Tumour Grade				
Grade I	1	**0.05***	1	
Grade II	1.96	0.43-8.82 0.37	1.01	0.20-5.16 0.98
Grade III	23.26	1.78-302.78 **0.01***	10.98	0.81-147.56 0.07
Ki-67 expression level				
Low Ki-67	1		1	
High Ki-67	7.49	1.85-65.75 **0.02***	6.79	0.64-71.25 0.1

*Statistically significant

was calculated as the time from the pathological diagnosis to the date of death or last follow-up. The disease-free survival (DFS) was calculated as the time from the pathological diagnosis to the date of documented locoregional or distant recurrence/progression or the date of death or last follow-up. The local recurrence-free survival (LRFS) was calculated as the time from the date of pathological diagnosis and the first event of local recurrence. Kaplan–Meier analysis was carried out to measure the OS, DFS, and LRFS. The two-sided long-rank test was performed to make a comparison between the survival curves of subgroups. ROC (Receiver Operating Characteristics) curve analysis was performed to measure the ability of the ki-67 value to predict locoregional or distal recurrence/progression or death. The possible associations between Ki-67 and survival outcomes were measured by Cox regression analysis. If the two-sided p-value < 0.05, the outcome was mentioned as statistically significant.

RESULTS

Patients, disease, and treatment characteristics

A total of 49 patients with early-stage glottic larynx cancer treated with definitive radiotherapy between 2011 and 2021 were included in the current study. The median follow-up time was 35.74 (range; 7.03-161.65) months. The patient, disease, and treatment characteristics are summarized in Table 1.

Ki-67 evaluation

The median Ki-67 level was 40% (range: 10 to 90%; mean: 44.5%). According to the ROC curve, the optimal cut-off value was 35% for Ki-67. Above these cut-off points were accepted as high expression levels (Ki-67-high), while below these points were accepted as low expression levels (Ki-67-low).

Ki-67 expression and survival outcomes

During the follow up, local failure was observed in 9 of 49 patients (18%). Salvage surgery with total laryngectomy was performed in 8 out of 9 patients with local failure (%89). 37 patients were alive at the time of statistical analysis, and there was no disease either clinically or radiologically. Distant metastases were not seen in any of the patients.

The median OS was 95.4 (range; 62.1-128.8) months. The 2- and 5-year OS were 91% and 76%, respectively. Tumour grade (p=0.006) and Ki-67 expression level (high vs low; p=0.039) were the prognostic factors that predict OS, according to Kaplan Meier analysis (Figure 1a, 1b). The 2- and 5-year OS were 93% and 93% in the low expression group whereas 85% and 48% in the high expression group. To further evaluate these survival differences, we used a multivariate Cox regression analysis that controlled for other known prognostic factors. However, we did not show any association between prognostic factors

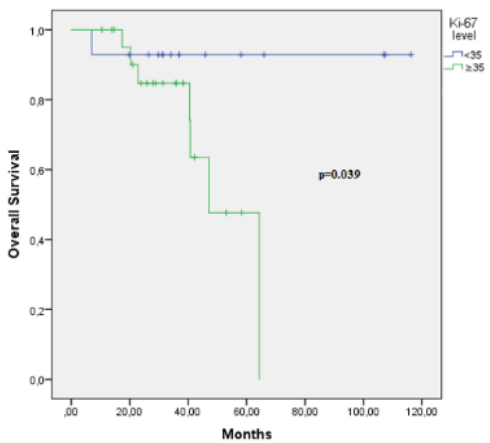

Figure 1a: Overall survival difference between Ki-67 level < 35% vs ≥ 35%.

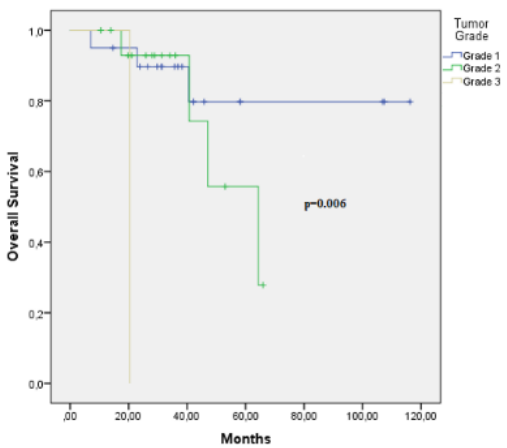

Figure 1b: Overall survival difference between grade1 vs grade2 vs grade3 tumours.

Table 3: Univariate and multivariate Cox proportional hazard regression analysis related to DFS

Univariate analysis Multivariate analysis Variables HR 95% CI p-value HR 95% CI p-value		
Tumour Grade		
Grade I	1 0.57	1 0.83
Grade II	0.91 0.28- 2.88 0.87	1.38 0.28-6.84 0.68
Grade III	3.24 1.06- 9.84 **0.038***	1.49 0.39-5.67 0.55
Ki-67 expression level		
Low-Ki-67	1	1
High Ki-67	6.60 1.41-30.86 **0.016***	6.69 1.04-32.36 **0.050***

*Statistically significant

according to multivariate Cox regression analysis. The median DFS was 64.3 (range; 44.8-83.8) months. The 2- and 5-year DFS were 89% and 56%, respectively. Ki-67 expression level (high vs low; p=0.007) and tumour grade (p=0.04) were the prognostic factors that predict DFS, according to Kaplan Meier analyses (Figure 2a, 2b). The 2- and 5-year DFS was 93% and 74% in the low expression group whereas 81% and 21% in the high expression group. According to multivariate Cox regression analysis, only the Ki-67 expression level was the prognostic factor that predicted DFS (p=0.05). The details of univariate and multivariate Cox proportional hazard regression analysis were summarized in Table 2 and Table 3.

According to Kaplan Meier analysis, both OS and DFS outcomes were shorter in patients with anterior commissure involvement when compared with no anterior commissure involvement, but the results did not reach statistical significance. The fact remains that local recurrence was found to be significantly higher in patients with anterior commissure extension after curative radiotherapy (p=0.01). The median LRFS was 116.2 (range; 62.1-190.3) months. The 2- and 5-year LRFS were 93% and 64%, respectively. Tumour grade (p=0.006) and Ki-67 expression level (high vs low; p=0.015) and anterior commissure involvement (no vs yes; p=0.019, Figure 3) were the prognostic factors that predict LRFS, according to Kaplan Meier analysis. To further evaluate these survival differences, we used a multivariate Cox regression analysis that also controlled for other known prognostic factors. We did not show any association between prognostic factors according to multivariate Cox regression analysis.

DISCUSSION

While investigating the prognostic effect of the Ki-67 proliferation index in HNCs, differences in tumour location, tumour stages, and treatment types make it difficult to clearly understand the prognostic impact of Ki-67 on survival (9,10). Even patients with the same stages and clinical features have differences in survival times. We aimed to overcome this problem by evaluating the prognostic significance of Ki-67 expression in only T1N0 stage glottic laryngeal cancer treated with radiotherapy. Despite very conflicted results that have been presented in the literature with the prognostic impact of Ki-67 expression in laryngeal cancer patients, overexpression of Ki-67 was found as an indicator of poor prognostic factors that related to survival outcomes according to our study results.

Some of the studies investigating the effect of Ki-67 expression in laryngeal cancer showed that Ki-67 expression is higher in poorly differentiated tumours and associated with more advanced TNM stage, higher lymph node metastases, and tumour recurrence. Additionally, overexpression of Ki-67 correlated with shorter DFS and treatment failure (9-11).

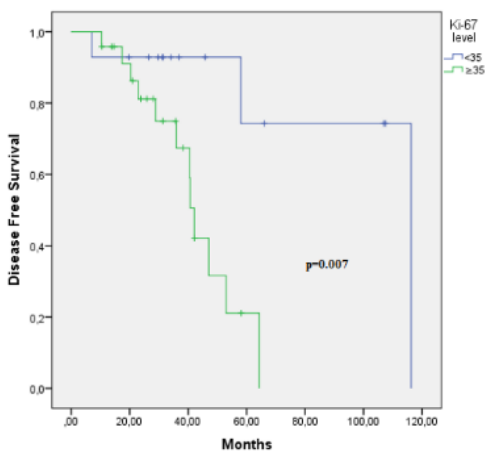

Figure 2a: Disease free survival difference between Ki-67 level < 35% vs ≥ 35%.

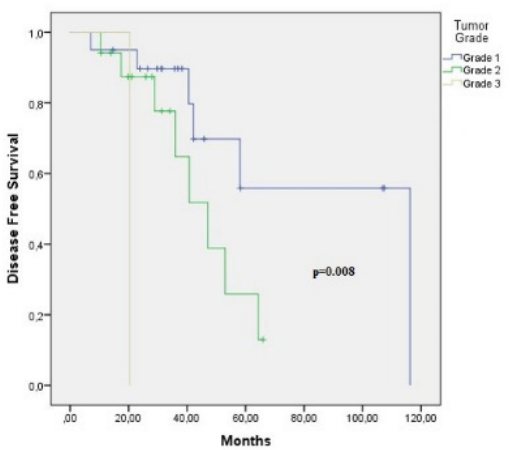

Figure 2b: Disease-free survival difference between grade1 vs grade2 vs grade3 tumours.

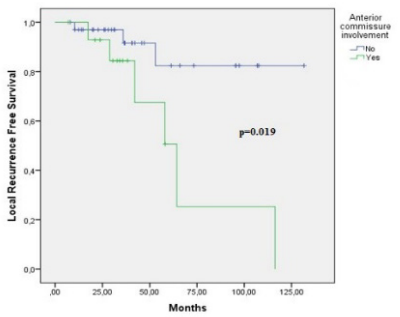

Figure 3: Local recurrence-free survival difference between with or without anterior commissure involvement.

Nevertheless, contradictory results have overall been published regarding radiotherapy. Kropveld et al. investigated the effect of Ki-67 expression on response to therapy in T2 glottic laryngeal cancer patients treated with radiotherapy and they found that tumours with higher Ki-67 expression respond significantly better to radiotherapy (12). Similarly, Ahmed et al. analysed the prognostic significance of Ki-67 expression in 24 glottic cancer involving the anterior commissure treated with radiotherapy and the authors reported that Ki-67 overexpression is a predictive marker for radiosensitivity (13).

Similar to our study results, Sakata et al. demonstrated that patients with T1 glottic cancer have a better local control rate when the Ki-67 index is less than 50% (14). In accordance with this study's results, Nichols et al. evaluated the predictive role of Ki-67 index in early-stage laryngeal cancer treated with radiotherapy and they found that overexpression of Ki-67 was significantly associated with tumour recurrence and predictor for lower DFS. They also concluded that Ki-67 expression may be a guide in identifying a group with an increased risk of local recurrence after radiotherapy and can potentially guide more effective personalized treatments in patients with early-stage glottic laryngeal cancers (15). Lavertu et al. evaluated the prognostic effect of Ki-67 expression in advanced-stage laryngeal cancer patients treated with concomitant chemo-radiotherapy. According to multivariate analysis, Ki-67 positivity was significantly associated with poor OS, and Ki-67 negativity was significantly associated with higher OS and organ preservation. Although the authors concluded that it was not appropriate to modify the treatment based on their results, they recommended closer follow-up in patients with Ki-67 positivity to detect possible recurrence earlier (16).

The other prognostic factor that predicts survival outcomes is anterior commissure involvement. Despite the suggestions that anterior commissure involvement predict a worse prognosis, it is not included in the staging system (17). We also evaluated the prognostic impact of anterior commissure invasion and we found that patients with anterior commissure involvement had a statistically significant shorter LRFS when compared with no anterior commissure involvement. The mean LRFS was 66 months for patients with anterior commissure involvement whereas 115 months for patients without anterior commissure involvement. Additionally, local recurrence was found to be significantly higher in patients with anterior commissure extension after curative radiotherapy (p=0.01). Anterior commissure invasion was detected in 15 of 49 patients (%30) in the current study. Compared to the literature, our relatively high rates of local recurrence may also be associated with anterior commissure involvement in one-third of our patients.

The limitations of our research were its retrospective design and relatively limited number of patients. Due to the retrospective design, analysis of parameters that will affect local recurrence and survival, such as the continuation of smoking and alcohol usage after treatment, could not be performed. We think that it will contribute to the literature in terms of the fact that it was performed on a homogeneous patient group treated in a single centre with a similar treatment protocol and that Ki-67 expression analysis was re-evaluated by a single pathologist. Additionally, our study is important in terms of guiding prospective studies on this subject.

CONCLUSION

In conclusion, according to our study, higher Ki-67 expression was related to lower OS and DFS in early-stage glottic larynx cancer treated with radiotherapy. Ki-67 expression level can be a guide for determining treatment selection in these patients. Additional prospective research with more patients is needed to validate our results.

Ethics Committee Approval: This study was approved by the Ethics Committee of Necmettin Erbakan University (Date: 27.10.2022, No: 161).

Informed Consent: Written informed consent was obtained.

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RESEARCH ARTICLE
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The Association of Antibody Levels with Body Mass Index, Stress Management Ability and Lipid Peroxidation in Patients with Hashimoto's Thyroiditis

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ABSTRACT

Objective: The potential predictive value of body mass index, stress management ability, and thiobarbituric acid reactive substances (TBARS) levels for antibody levels in Hashimoto's thyroiditis (HT) were evaluated.
Materials and Methods: Two hundred patients with HT were included in the study. The patients were allocated into four groups as Group 1, patients with a body mass index (BMI) of 30 or higher (n=54); Group 2, patients with stress management difficulties (n=59); Group 3, patients with a BMI higher than 30 and stress management difficulties (n=11), and Group 4 (control, n=76), those without obesity or stress management issues. The mean age of patients, BMI, stress management abilities, anti-thyroid peroxidase (anti-TPO) antibodies levels, weekly T4 drug dosages, duration of levothyroxine usage, quality of life scores, as well as thiobarbituric acid reactive substances (TBARS) were evaluated.
Results: The antibody levels were significantly associated with body mass index and stress management. The antibody level increased 533 times ($p<0.0001$) in the group without stress management difficulties, and was affected 525 times ($p<0.0001$) in the obesity group.
Conclusion: The findings of our investigation revealed that stress management ability and obesity are the important factors influencing antibody levels.

Keywords: Hashimoto's thyroiditis, thyroid peroxidase antibodies, stress management ability, quality of life scores, TBARS

INTRODUCTION

Hashimoto's thyroiditis (HT), is alternatively referred to as chronic lymphocytic thyroiditis and is classified as an autoimmune disorder characterized by the progressive deterioration of the thyroid gland (1,2). The prevalence of Hashimoto's thyroiditis is significantly higher in females than in males. Typically, the onset of symptoms occurs between ages 30 and 50 (1-4).

HT is considered to arise from a blend of genetic and environmental factors. The risk factors for the development of the syndrome encompass a familial predisposition and the co-occurrence of another autoimmune disorder (3,4). The confirmation of diagnosis typically involves conducting blood tests to measure levels of thyroid-stimulating hormone (TSH), thyroxin (T4), and anti-thyroid autoantibodies, as well as performing a thyroid ultrasound (5-8).

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The symptoms and signs of hypothyroidism are nonspecific. The most common ones are skin dryness, cold intolerance, fatigue, voice alterations, and constipation. Others include bradycardia, slow speech, eye and facial swelling, weight gain, decreased sweating, hair loss, forgetfulness, decreased concentration, depression, menstrual irregularities, and muscle pains and cramps (7-10).

Currently, there is a lack of clinical studies investigating the relationship between antibody increase and the specific characteristics of individuals who have HT. The present study aimed to examine the associations between antibody levels and several factors including age, body mass index (BMI), quality of life, stress management abilities, and length of thyroid hormone drug usage as well as thiobarbituric acid reactive substances (TBARS) levels.

MATERIALS AND METHODS

This study was conducted at the Istanbul University, Istanbul Faculty of Medicine, Department of General Surgery, after obtaining ethical approval from the Bezmialem Vakif University Non-Interventional Research Ethics Committee (Date: 05.03.2019, No:3427) and written informed consent was obtained from each participant prior to the process.

The research comprised 280 individuals who were diagnosed with HT with the presence of thyroid auto-antibodies and/or ultrasound findings of thyroiditis between 2019 and 2022. Male patients (n=12) were omitted from the study due to the small sample size. The study also excluded individuals who were being treated for diabetes, cardiovascular diseases, other autoimmune diseases, previous thyroid surgery, or other diseases interfering with thyroid metabolism.

All patients underwent hormone replacement therapy with Levothyroxine (LT4) due to hypothyroidism. The drug dosage was adjusted by measuring patients' weekly T4 levels. The duration of the disease was determined by calculating the number of months between the date of diagnosis and the date of study enrollment.

In the study, two hundred participants were organized into four separate groups. *Group 1* consisted of patients with a BMI of 30 or higher (n=54), *Group 2* comprised those who experienced stress management difficulties (n=59), *Group 3* included patients with a BMI above 30 and stress management difficulties (n: 11), and *Group 4* (control) included 76 patients who did not have obesity or stress management issues.

Peripheral blood samples from patients with HT were taken into dry tubes. Subsequently, they were centrifuged at 3500 rpm, and sera were separated and preserved at -80 ^{o}C until analyses.

The BMI was determined by measuring the patients' weight and height and calculated by using the kg/height^2 formula.

The SF-36 is a multi-cultural assessment comprising 36 questions and organized into eight domain profiles of scores: physical functioning, general health, role limitation due to physical health, bodily pain, general social functioning, vitality, and role limitations due to emotional and mental health (11). The quality of life was assessed according to patients' answers for SF-36. All questions are rated on a 5-point Likert scale, and the item is scored between 1 and 5.

The ability of patients to control their stress was evaluated using the perceived stress scale, which is frequently used to measure stress sensitivity (12). Two questions from the scale were translated into Turkish and utilized: "How often have you felt that you were unable to control the important things in your life?" and "How often have you found that you could not manage all the things that you had to do?". The answer options were: "never" (score=1), "almost never" (score=2), "sometimes" (score=3), "fairly often" (score=4), and "very often" (score=5).

Anti-thyroid peroxidase (anti-TPO) antibody levels were determined by chemiluminescent assay using DPP Modular System manufactured by Roche Diagnostics (Mannheim, Germany). Lipid peroxidation was carried out by determination of thiobarbituric acid reactive substances (TBARS) levels (13). The Buege-Aust reagent was combined with the homogenates, and the mixture was subjected to incubation in a boiling water bath for 15 minutes, followed by cooling and subsequent centrifugation at 1000xg. The absorbances of supernatants were then recorded at 532 nm and the results were calculated using the extinction coefficient ($1.56x10^{-5}M^{-1}cm^{-1}$) and expressed as nmol/mL

Statistical analyses

Statistical analysis was conducted using the SPSS software (version 21.0; SPSS Inc., Chicago, IL, USA) program. The data for all variables were presented as mean ± standard deviation (SD). Comparisons of data were done by student's t, Spearman correlation, the chi-squared test, and logistic regression analysis. Results were considered statistically significant when p value of the two-tailed was less than 0.05.

RESULTS

The mean age was 38.6±8 years (20-60 years), quality of life score was 4.2±1 (1-5), duration of drug usage was 52±46 months (2-240 months), and drug dosage was 470±324 µg/week (87.5-1200 µg/week) for all patients in the study.

The demographic characteristics of patients in each group are demonstrated in Table 1. Statistical significant variation was not found among groups in terms of age, BMI, quality of life score, duration of drug usage, and LT4 dose.

Significant increases were detected in anti-TPO antibody (4.4, 14, 11 fold; p<0.001) and TBARS (1.76, 1.6, 2.3 fold; p<0.001) levels in Group 1, 2 and 3, respectively, as compared to patients without obesity or stress management issues in group 4 (Table 2).

No correlation was found between antibody levels and the patients' age, duration of drug usage, and weekly drug doses. However, body mass index (r=0.215; p= 0.002), stress control (r=0.700; p= 0.0001), and TBARS levels (r=0.543; p= 0.0001)

Table 1: Demographic data of the patients with Hashimoto's thyroiditis

	Group 1 BMI >30 (n=54)	Group 2 Stress management difficulty (n=59)	Group 3 BMI >30 and stress management difficulty (n=11)	Group 4 Control (n=76)
Mean age (years)	36±8	38±8	35.7±9	40±9
BMI (kg/height^2)	36.4±11	26.2±0.8	35.7±9	35.7±9
Quality of life score	4.1±0.9	4±1	4.6±0.8	4.1±1.1
Duration of drug usage (months)	62±59	53±50	47±48	50±42
LT4 dose (mcg/week)	455±327	495±392	602±266	483±338

*p< 0.001 as compared to the control group

Table 2: Anti-thyroid peroxidase antibodies (anti-TPOAb) and thiobarbituric acid reactive substances (TBARS) levels of the patients with Hashimoto's thyroiditis

	Group 1 BMI >30 (n=54)	Group 2 Stress management difficulty (n=59)	Group 3 BMI >30 and stress management difficulty (n=11)	Group 4 Control (n=76)
Anti-TPOab (IU/mL)	**563±505***	1782±1290*	1443±792*	127±74
TBARS (nmol/mL)	9.7±2.9*	9±2.8*	12.7±3.6*	5.5±1.4

*p<0.001 compared with control group

were found to be positively correlated with antibody levels (Figure 1).

Considering the parameters affecting the antibody level, the antibody level increases 533 times (p<0.0001) in the group struggling with stress management, and it is affected 525 times (p<0.0001) in the obesity group.

DISCUSSION

HT is characterized by the immune system's T-cells directly attacking the thyroid gland. This is demonstrated through histological observations, which reveal the infiltration of lymphocytes and plasma cells, the development of fibrosis, the formation of lymphatic follicles, and the atrophy of the thyroid tissue (9,10,14,15).

The autoimmune manifestation of Hashimoto's thyroiditis (HT) is influenced by the interaction of environmental factors and genetic predisposition, including variations in human leukocyte antigen, T lymphocyte-associated 4, protein tyrosine phosphatase, non-receptor type 22 genes, and patterns of X chromosome inactivation. This interplay results in an impaired balance between self-tolerance mechanisms mediated by regulatory T and B lymphocytes (3-7).

The prevalence of HT is estimated to range from 0.3 to 1.5 cases per 1000 individuals, with a higher occurrence in females compared to males, with a ratio of 7 to 10 females for every male. The prevalence of the condition tends to rise with advancing age, particularly among those who have been diagnosed with additional autoimmune disorders, such as myasthenia gravis, systemic sclerosis, and other connective tissue diseases. Other ailments that are associated with an increased prevalence include Sjögren's syndrome, pernicious anemia, autoimmune liver disease, and celiac disease (2-8).

The diagnosis of HT relies on the evaluation of clinical manifestations associated with hypothyroidism and the detection of TPO antibodies (6-9).

The utilization of ultrasonic imaging in assessing the morphology of the thyroid gland can be beneficial in distinguishing between various medical conditions. Approximately 95% of patients exhibit the presence of serum anti-TPO antibodies, while positive anti-thyroglobulin antibodies are observed in 60% to 80% of cases (1-5). TPO antibodies are acknowledged as potential risk factors for the development of overt hypothyroidism in the general population as time progresses (3,4).

The relationship between anti-TPO antibodies and quality of life score has been investigated in two recent studies. The first study unveiled a negative correlation between quality of life scores in HT patients and the levels of thyroglobulin and anti-TPO antibodies. However, no evidence of correlation emerged between autoantibody levels and thyroid function tests within this study (16). In the latter one, these autoantibodies have demonstrated a positive correlation with hypothyroidism symptoms. However, no correlation was present between thyroid hormones and thyroglobulin antibodies (17).

Although there are studies investigating the relation between the symptoms of thyroid antibodies in patients, there is no study examining the factors affecting the height of antibodies. In our study, no correlation was found between antibody levels and age, hormonal status, quality of life, and complaints, which was in accordance with the literature. TBARS, which is by product of lipid peroxidation, serves as a biochemical indicator that can effectively signify the presence of cellular stress. The study

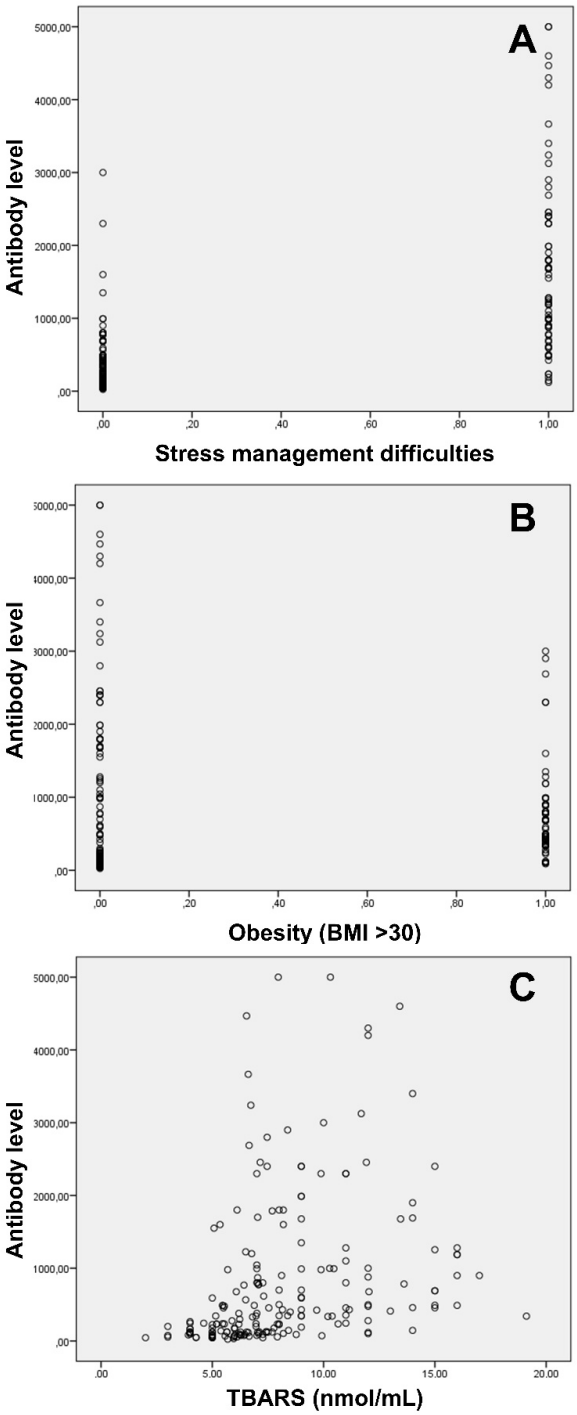

Figure 1: Relationship between antibody levels and stress management difficulties (A); and body mass index (BMI), (B); and thiobarbituric acid reactive substances (TBARS) levels (C) in Hashimoto disease.

revealed an important positive correlation between elevated levels of antibodies and indicators of stress. Similarly, TBARS levels were found to be high in obesity group patients. A significant positive link was seen between obesity and elevated levels of antibodies. The present study indicated that both stress and obesity have an impact on high antibody levels. However, our findings revealed that stress exerted a more significant influence on antibody elevation compared to obesity.

In conclusion, these findings demonstrate that stress management ability and obesity are the important factors influencing antibody levels. Further functional investigations based on a larger sample size are required in order to clarify the relationship between additional biochemical parameters and high antibody levels in patients with HT.

Ethics Committee Approval: This study was approved by Bezmialem Vakif University Non-Interventional Research Ethics Committee (Date: 05.03.2019, No: 05/54).

Informed Consent: Written informed consent was obtained.

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RESEARCH ARTICLE
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Which Is the Best Inflammatory Index in Bell's Palsy?

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ABSTRACT

Objective: This study aims to analyze previously suggested hematological markers in addition to the systemic inflammation response index (SIRI) and the aggregate index of systemic inflammation (AISI) in patients with Bell's palsy (BP) and to identify the most important hematologic inflammatory marker among them.
Material and Methods: The study consisted of 87 patients with BP who were between the ages of 18 and 65. Sixty-three healthy controls with similar age and sex distribution were assembled. A retrospective examination was done on the patient and control group files. House Brackmann grading system stage at the admission of patients with BP was recorded. Routine complete blood count values obtained from the patients at the time of admission and before the start of treatment were recorded. The systemic immune-inflammatory index (SII), the neutrophil-to-lymphocyte ratio (NLR), the platelet-to-lymphocyte ratio (PLR), the monocyte-to-lymphocyte ratio (MLR), SIRI, and AISI were all generated from these values.
Results: There were 39 (44.8%) men, 48 (55.2%) women in the BP group, and 34 (54.0%) men and 29 (46.0%) women in the control group. The patient group had substantially increased neutrophil, white blood cell, NLR, PLR, SII, SIRI, and AISI levels (P values: 0.001, 0.001, 0.001, 0.033, 0.001, 0.001, and 0.001, respectively). NLR, PLR, SII, SIRI, and AISI values were lower in Receiver Operating Characteristics curves (ROC) analysis than neutrophil the areas under the curves (AUC) values.
Conclusion: Neutrophil count was found to be more valuable than other inflammatory indexes in the diagnosis of BP.
Keywords: Bell's palsy, hematologic parameters, inflammatory indexes

INTRODUCTION

Rapid and unilateral peripheral paresis or paralysis of the seventh cranial nerve is defined as Bell's palsy (BP) (1). The incidence of the disease has been reported as 11-40/100,000 (2). The etiology of BP is unclear therefore, it is also called idiopathic facial paralysis. Bell's palsy's genesis has been linked to inflammation, viral infections, anatomical structure, ischemia, and cold sensitivity (1).

One of the routine tests performed during hospitalization is the CBC, which does not require any extra cost. Data from CBC are frequently used to evaluate infection and inflammation. Important biomarkers of systemic inflammation and immune response are leukocytes consisting of neutrophils, lymphocytes, eosinophils, and basophils (3). The ratio of these cell counts to each other gives neutrophil/lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), Systemic immune-inflammatory index (SII), systemic inflammation response index (SIRI), and aggregate index of systemic inflammation (AISI). There are studies in which combined inflammation indexes are more valuable when compared to the evaluation of cell counts alone (4–6).

Complete blood count (CBC) values that demonstrate the importance of inflammatory events in the etiology of BP patients, as well as certain indicators generated from these data, have been extensively investigated in recent years (7,8). However, there are discrepancies between the data in these studies. In this study, we aimed to determine the most valuable hematological inflammatory index by analyzing hematological markers in patients with Bell's palsy.

MATERIAL AND METHODS

In a tertiary Konya City Hospital, this retrospective analysis was carried out between January 2015 and January 2020.

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The study consisted of 87 patients diagnosed with BP and 63 patients with age- and sex-matched healthy controls. Age, gender, comorbid disease, complete blood count values, and House Brackmann grading system (HB) stage at admission were recorded.

The study included individuals with BP diagnosed between the ages of 18 and 65. People with a history of infection, trauma, neurological or otological comorbidity, ototoxic drug use during the previous 10 days, and cerebral pathology on magnetic resonance imaging were eliminated from the research. In addition, those with inflammatory diseases such as autoimmune disease, diabetes mellitus, inflammatory bowel disease, dermatitis, and hepatitis were also excluded from the control group.

Blood samples were routinely taken from the patients at the time of admission and before starting the treatment. The samples were analyzed in the laboratory of our hospital. Complete blood count values from blood samples were recorded. From these values, NLR (neutrophil/lymphocyte), PLR (platelet/lymphocyte), MLR (monocyte/lymphocyte), SII (neutrophil×platelet/lymphocyte), SIRI (neutrophil×monocyte/lymphocyte) and AISI (neutrophil×platelet× monocyte/lymphocyte) were calculated.

The Ethics Committee of Necmettin Erbakan University has agreed to our study (Date: 04.02.2022, No: 2022/3630). Since this study was made from records, patient consent was not obtained. The study was carried out in conformity with the international ethical standards of the Declaration of Helsinki.

Statistical analysis

The statistical evaluations were carried out using SPSS edition 22 (IBM SPSS, Chicago, USA). The participants' ages and genders were compared using descriptive statistics. The Mann-Whitney U test and Student's t-test were used to compare numerical variables. The chi-square test was used to compare categorical variables. Through the use of Receiver Operating Characteristics curves (ROC) analysis, the areas under the curves (AUC) of hematological inflammatory markers were calculated. Youden Index was used for optimal cut-off values. By using Spearman correlation analysis, the association between the HB stage and hematological markers was examined. P values under 0.05 were accepted as significant.

RESULTS

In the BP group, 48 (55.2%) of the 87 patients were female, and 39 (44.8%) of them were male. In the control group, 34 (54.0%) of the 63 patients were male, and 29 (46.0%) were female. The patient group's median age was 53.0 (16) years, while the control group's was 55.0 (11.0). Age and gender did not significantly differ between the patient and control groups (P values of 0.269 and 0.935, respectively) (Table 1).

The patient group's values for neutrophils, WBC, SII, SIRI, AISI, NLR, and PLR were discovered to be significantly higher than those of the control group. It was observed that the patient group's lymphocyte levels were significantly lower than those of the control group (P value: 0.032). The patient group and the control group did not significantly differ in their platelet, monocyte, or MLR values (Table 1).

Table 1: The distribution of demographic data, hematologic parameters and inflammatory markers of both groups

	Bell's palsy (n=87)	Control group (n=63)	P value
Gender, n (%)			
Male	39 (44.8)	34 (54.0)	0.269
Female	48 (55.2)	29 (46.0)	
Age (year)	53.0 (16)	55.0 (11.0)	0.935
White blood cell ($10^3/mm^3$)	10.21 (4.92)	7.59 (2.62)	**<0.001**
Neutrophil ($10^3/mm^3$)	6.53 (4.06)	4.01 (1.65)	**<0.001**
Platelet ($10^3/mm^3$)	278.18±67.97	269.86±52.67	0.418
Lymphocyte ($10^3/mm^3$)	2.21 (1.46)	2.63 (1.30)	**0.032**
Monocyte	0.58±0.31	0.59±0.16	0.904
NLR	2.74 (2.91)	1.64 (0.78)	**<0.001**
PLR	116.08 (74.97)	105.20 (48.50)	**0.033**
MLR	0.23 (0.14)	0.21 (0.10)	0.720
SII	765.99 (819.41)	403.54 (240.32)	**<0.001**
SIRI	1.39 (1.48)	0.85 (0.51)	**<0.001**
AISI	411.36 (434.29)	222.51 (170.46)	**<0.001**

NLR: neutrophil-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio, MLR: monocyte-to-lymphocyte ratio, SII: Systemic Immune-Inflammation Index, SIRI: Systemic Inflammation Response Index, AISI: Aggregate Index of Systemic Inflammation. Parameters were expressed as n (%), median (Interquartile Range) and mean ±standard deviation.

In ROC analysis, the AUC of neutrophils was higher than that of the NLR, PLR, SII, SIRI, and AISI (Figure 1). For neutrophil, NLR, PLR, SII, SIRI, and AISI, the optimal cut-off values determined by the maximum Youden index were 5.17, 2.41, 144.14, 631.87, 1.10, and 340.18, respectively. The cut-off value of neutrophil was calculated as 5.17 x 10^3/mm^3 with rates of 77.0% sensitivity and 85.7% specificity in the diagnosis of BP (Table 2). WBC, lymphocyte, neutrophil, NLR, PLR, SII, SIRI, and AISI values were not found to significantly correlate with the HB stage (r = 0.460, 0.417, 0.990, 0.796, 0.761, 0.864, 0.845, and 0.761 respectively, and p > 0.05 for all).

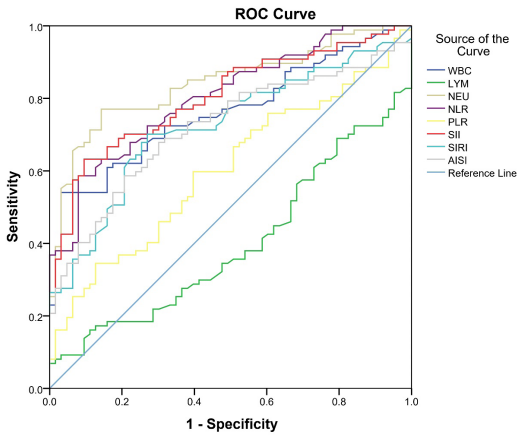

Figure 1: The graph of the ROC analysis

found between the HB stage and WBC, neutrophil, lymphocyte, NLR, SII, SIRI, and AISI. To our knowledge, this is the first study on SIRI and AISI in patients with BP.

PLR and NLR have reportedly been linked to poor prognosis in cardiovascular diseases, peripheral vascular diseases, head and neck cancers, and gynecological and gastrointestinal malignancies (9–11). In addition, it has been shown that there is a relationship between the prognosis of sudden sensorineural hearing loss and NLR. This suggests that the etiology of sudden sensorineural hearing loss is due to inflammatory events (12,13). In studies conducted on patients with BP, it was reported that neutrophils and NLR were significantly higher than controls (7,14–16). In addition, studies are reporting that there is no significant difference between lymphocyte counts, platelet counts, and PLR values of BP patients and controls (14,15). In our study, neutrophil, WBC, NLR, and PLR values were found to be significantly higher and lymphocyte levels were found to be significantly lower in the BP group. In addition, it was determined that there was no significant difference in platelet, monocytes, and MLR values between BP and control groups.

There are conflicting findings in the literature about the association between hematological inflammatory indices and the severity of BP. Atan et al. found no statistically significant relationship between the degree of facial paralysis and NLR and PLR (14). Bucak et al. showed that NLR levels were higher

Table 2: ROC analysis results of patients with Bell's Palsy

				95 % CI			
	Value	AUC	P	Lover	Upper	Sensitivity (%)	Specificity (%)
WBC (10^3/mm^3)	9.98	0.763	<0.001	.688	.838	54.0	96.8
Neutrophil (10^3/mm^3)	5.17	0.842	<0.001	.779	.905	77.0	85.7
Lymphocyte (10^3/mm^3)	2.49	0.397	0.032	.307	.487	37.9	41.3
NLR	2.41	0.805	<0.001	.737	.873	58.6	92.1
PLR	144.14	0.602	0.033	.512	.692	34.5	87.3
SII	631.87	0.802	<0.001	.733	.872	63.2	90.5
SIRI	1.10	0.723	<0.001	.642	.804	70.1	73.0
AISI	340.18	0.718	<0.001	.637	.800	58.6	79.4

NLR: neutrophil-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio, SII: Systemic Immune-Inflammation Index, SIRI: Systemic Inflammation Response Index, AISI: Aggregate Index of Systemic Inflammation, AUC: area under the curve, CI: confidence interval, ROC: receiver operator characteristic. Receiver operator curve evaluating NLR, PLR, SII, SIRI and AISI for BP. AUC > 0.600 and p < 0.05 were accepted as significant.

DISCUSSION

Bell's palsy is thought to be brought on by edema and inflammation of the facial nerves. In recent years, many publications have reported that inflammatory markers obtained from peripheral blood count are associated with prognosis and severity in patients with BP. In our study, patients with BP had significantly increased NLR, SII, SIRI, and AISI levels. We think that this is due to the number of neutrophils in the formulas of markers such as NLR, SII, SIRI, and AISI. Contrary to expectations, no correlation was

in patients with BP who did not fully recover than in those with complete recovery (15). In another study, it was reported that the NLR value increased with the severity of BP. This study demonstrated that the NLR values of patients with permanent facial motor impairment were considerably greater than those of the control group (16). Similarly, Ozler and Gunak. also found a positive correlation between NLR and HB stage (17). In this study, there was no difference in neutrophil, platelet, eosinophil, monocyte, and PLR values according to the BP stage. There was no significant correlation between the HB

stage and the WBC, lymphocyte, neutrophil, NLR, or PLR values discovered in our study. (r = 0.460, 0.417, 0.990, 0.796, and 0.761 respectively, and p > 0.05 for all). In ROC analysis, the AUC value of neutrophil count was higher than that of NLR and PLR values (AUC: 0.842, 0.805, and 0.602 respectively), and neutrophil count was found to be more valuable than NLR and PLR in the diagnosis of BP.

Another index that is considered to have prognostic value is SII. It has been reported that high SII can be used to predict the prognosis of the disease in breast cancers, gynecological cancers, gastrointestinal malignancies, lung cancer, and prostate cancer (18,19). Kinar et al. found that neutrophil count, SII, and NLR values were high in patients with BP (8). In the ROC analysis, they reported that the AUC value of SII was higher than that of the NLR (0.731 and 0.728, respectively), and SII was more valuable than NLR in the diagnosis of BP. In our study, patients with BP had higher SII values than the control group [765.99 (819.41) and 403.54 (240.32) respectively, and P<0.001]. The AUC value of NLR was found to be higher than that of SII in ROC analysis (0.805 and 0.802, respectively).

In acute diseases and malignancies, AISI and SIRI have been reported to be better prognostic indices than NLR (20,21). Wei et al. reported that SIRI is an indicator of poor prognosis in cancers (22). According to the authors, SIRI could be used as a useful marker in cancer therapy. A study of patients with idiopathic pulmonary fibrosis found that AISI was significantly associated with mortality (23). In contrast, Erre et al. reported that SIRI and AISI were not significantly associated with Rheumatoid Arthritis activity, but with systemic inflammation (24). According to this study, NLR was the index that outperformed SIRI and AISI. In our study, SIRI and AISI were found to be significantly higher in the patient group. However, in our study, the AUC of the neutrophil count, NLR, and SII were higher than SIRI and AISI according to ROC analysis (AUC: 0.842, 0.805, 0.802, 0.723, and 0.718, respectively).

The most important limitations of our study are its retrospective nature and lack of prognostic evaluation. The combined inflammation index calculated using multiple blood cell populations is expected to better reflect the inflammatory status and predict prognosis than a single hematological marker. Contrary to predictions, the neutrophil count's AUC was higher than that of the other hematological inflammatory indices. In our investigation, the data collected from BD patients before therapy showed no statistically significant difference in platelet or monocyte values between the patient and control groups. As a result, it was established that AISI and SIRI did not function properly (P values: 0.418 and 0.904, respectively). We think that prognostic studies with a large patient population, including post-treatment data on SIRI and AISI, should be performed.

CONCLUSION

The neutrophil count was found to be more valuable than other hematological indexes in the diagnosis of BP. Inflammatory indexes were not correlated with the BP stage.

Ethics Committee Approval: This study was approved by The Ethics Committee of Necmettin Erbakan University (Date: 04.02.2022, No: 2022/3630).

Informed Consent: Written informed consent was obtained.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- E.T., F.Y.; Data Acquisition- S.K.; Data Analysis/Interpretation- E.T., F.Y., M.E.K.; Drafting Manuscript- F.Y., E.T.; Critical Revision of Manuscript- M.E.K.; Final Approval and Accountability- E.T., F.Y., M.E.K.

Conflict of Interest: The authors have no conflict of interest to declare.

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Informed Consent: Patient consent was not obtained because this study was conducted from the records.

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RESEARCH ARTICLE
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Tinnitus, Equilibrium Disorders, and Anxiety in COVID-19

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ABSTRACT

Objective: Researchers have previously investigated the connection between COVID-19 and equilibrium disorders (ED) and tinnitus. The present study aims to investigate the prevalence of tinnitus and ED in people post-treatment after being positive for COVID-19 and the association of these symptoms with Anxiety and demographic features.
Material and methods: Patients from two tertiary hospitals with positive reverse transcription-polymerase chain reaction (RT-PCR) tests for SARS-COV-2 between August 2020 and May 2021 were contacted by phone. The recruited patients were asked to complete our questionnaire over the phone, a developed Turkish version of a previously applied '10-item close-ended questionnaire' by Viola et al.
Results: Sixty-two patients experienced ED before COVID-19 (8%). After COVID-19, the incidence of ED sufferers increased to 178 (22%), which was statistically significant (p=0.001).
110 (25.28%) of 435 female patients and 68 (18.37%) of 370 male patients had post-COVID ED. It was significantly more common in women among COVID-19 survivors (p=0.019).
The number of patients who experienced tinnitus before COVID-19 was 64 (7%) and 105 (13%) after COVID-19. It was found statistically significant that the tinnitus increased after COVID-19 (p=0.001)
Beck's Anxiety Inventory (BAI) scores were significantly higher in the post-COVID ED and post-COVID tinnitus sufferers (p=0.001, p=0.047).
Conclusions: COVID-19 survivors had significantly suffered tinnitus or ED. BAI scores were significantly higher in post-COVID ED and tinnitus sufferers. So, it can be said that the patients with high Anxiety experienced more tinnitus and ED post-COVID period.
Keywords: Tinnitus, balance, vertigo, COVID-19, Anxiety

INTRODUCTION

The clinical symptoms of COVID-19 include fever, sore throat, cough, myalgia, and gastrointestinal infection symptoms (1). Older people with comorbidity are more susceptible to infection and prone to severe outcomes (2).

Although symptoms seen in patients with COVID-19 are primarily related to the respiratory and cardiovascular systems, neurological symptoms, such as loss of consciousness, headache, smell, and taste changes, have also been reported (3, 4). In addition, Coronavirus-related otoneurological symptoms, such as tinnitus and balance disorders, have been described (5). Regarding balance disorders, vertigo or dizziness has been defined as a clinical manifestation of COVID-19 (6).

Dizziness is one of the most common neurological signs of COVID-19, which can be related to the neuroinvasive feature of SARS-Cov-2 (7).

Different researchers have previously investigated the connection between COVID-19 and equilibrium disorders (ED) and tinnitus, and a significant connection was found between COVID-19 and balance disorders tinnitus. It has also

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been demonstrated that COVID-19-related findings, such as vertigo, were more common in women over 60 (8). Tinnitus and vertigo can be related to vascular damage because the inner ear structures are more susceptible to ischemia due to their characteristics of terminal vasculature (5).

In light of the above information, the present study investigates the prevalence of tinnitus and equilibrium disorders in people after being positive for COVID-19 and evaluates the possible relationships of these symptoms with hospitalization, Anxiety, and demographic features.

MATERIAL AND METHODS

Başkent University Ethics Committee approved this study, and 805 patients from two different University Hospitals who had positive reverse transcription-polymerase chain reaction (RT-PCR) tests for SARS-COV-2 between August 2020 and May 2021 were contacted by phone. The questionnaire was applied to the patients after the COVID-19 diagnosis. Inclusion criteria were individuals aged 18 years or older without mental problems who had a positive RT-PCR test regardless of admission history after detecting COVID-19 and the severity of their presenting

Table 1: The Questionnaire

Part 1: Diagnosis and Treatment	
1)	What was your first complaint to apply hospital for COVID-19?
2)	Have you stayed in the hospital during your treatment?
3)	If the answer to the 2nd question is yes: How long did you stay in the hospital (days)?
4)	If the answer to the 2nd question is yes: Have you used anticoagulant or cortisone after you have been discharged from the hospital?
5)	If the answer to the 2nd question is no: Have you used aspirin or its derivative drugs during your outpatient treatment?
6)	Have you stayed in the intensive care Unit (ICU) during COVID-19?
7)	If the answer to the 4th question is yes, how long did you stay in ICU?
Part 2: Equilibrium disorders	
1)	Have you ever experienced vertigo before the COVID-19 diagnosis? (Yes/No)
2)	If the answer to the 1st question is yes, how would you describe the characteristics of your vertigo? A) Environment (world) was spinning B) I was spinning C) It was more like dizziness D) Feeling of unsteadiness
3)	Have you ever experienced vertigo after the COVID-19 diagnosis? (Yes/No)
4)	If the answer to the 3rd question is yes, how would you describe the character of your vertigo? A) Environment (world) was spinning B) I was spinning C) It was more like dizziness D) Feeling of unsteadiness
5)	Indicate the severity of your vertigo from 1 to 10.
6)	Have you experienced nausea or vomiting during vertigo attacks?
Part 3: Tinnitus	
1)	Have you ever experienced tinnitus before the COVID-19 diagnosis? (Yes/No)
2)	If the answer to the 1st question is yes, please select the following options that fit the characteristics of your tinnitus. A) Heartbeat B) High-frequency C1) Continuous C2) Discontinuous D1) Single ear D2) Both ears
3)	Have you ever experienced tinnitus after the COVID-19 diagnosis? (Yes/No)
4)	If the answer to the 3rd question is yes, please select the following options that fit the characteristics of your tinnitus. A) Heartbeat B) High-frequency C1) Continuous C2) Discontinuous D1) Single ear D2) Both ears
5)	Indicate the severity of your tinnitus from 1 to 10.
Part 4: Migraine and comorbidities	
1)	Do you suffer from migraines/Do you experience migraine headaches? (Yes/No)
2)	If the answer to the 1st question is yes, do you have vertigo during or after your migraine attack?
3)	Do you smoke?
4)	Do you have any known diseases?
5)	Do you have any regularly used medications?

symptoms. Exclusion criteria were previous ear, brain surgery, chronic ear infections, vestibular diseases, psychiatric comorbidity, and COVID-19 vaccination. Informed consent was obtained from all participants (Figure 1).

The recruited patients were asked to fill out our questionnaire over the phone, inspired by a previously applied '10-item close-ended questionnaire' by Viola et al. (5) and evolved by the senior author, a neurotologist working in a university hospital. The language of the questionnaire was Turkish.

The questionnaire consisted of four parts, each investigating a specific condition related to COVID-19, "initial symptoms and hospitalization history," "presence and characteristics of equilibrium disorder," "presence and characteristics of tinnitus," and "presence of migraine and comorbidities" was questioned (Table 1).

In the "presence and characteristics of equilibrium disorder" part, patients were asked to characterize the equilibrium disorder in detail, as if it was spinning (self/environment) or dizziness or unsteadiness. In the "presence and characteristics of tinnitus" part, patients were asked to characterize as pulsatile or high-frequency ringing, single or both sides and continuous or not. The severity of the symptoms was also noted in each part.

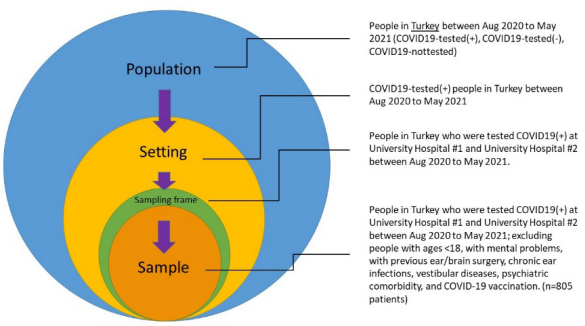

Figure 1: Target population and sampling frame

Statistical analysis

The severity of each condition was scaled from 1 (mild) to 10 (most severe). In addition to our questionnaire, the Beck anxiety scale was used to assess their anxiety levels (9). Beck anxiety inventory (BAI) is a self-reported scale that measures the level of Anxiety by scoring 21 items, which are mainly composed of somatic symptoms of Anxiety. The upper limit of the total score is 63 (10). The demographic data of the participants were recorded individually. The answers were recorded in the online Excel system, where access to the data was limited to the principal researchers.

At the end of the GPower 3.1.9.2 program analysis, when deciding the sample size, it was agreed to include 781 patients in the study for 81,0599 % statistical power (alpha: 0.05, beta: 0.20).

SPSS 25.0 package program was used for statistical analysis of the data. Categorical measurements were summarized as numbers and percentages, and continuous measurements as mean and standard deviation (in required parts median and minimum-maximum). Chi-square test or Fisher test statistics were used to compare categorical variables. In comparing continuous measurements between the groups, the distributions were controlled, and the dependent group t-test was used for the parameters that showed normal distribution according to the number of variables. The Mann-Whitney U test was used for the parameters that did not show normal distribution. In pre-and post-COVID-19 diagnoses, the Mc-Nemar test and intra-class correlation coefficient were used to analyze change. Binary logistic regression analysis was used to show the relationship between a dependent variable and independent variables. The statistical significance level was taken as 0.05 in all tests.

The reporting guideline that has been followed in this study was STROBE.

Table 2: Demographical Data

	n	$\bar{x}$± ±Std. Deviation	Median (IQR)	Min	Max
The interval between diagnosis and questionnaire presentation (days)	805	85.60±58.052	65 (96)	1	468
Age	805	40.77±14.441	39 (15)	18	95
ED Severity	193	5.52±2.494	5 (5)	1	10
Tinnitus Severity	122	4.93±1.976	5 (4)	1	10
Hospitalization (days)	81	9.31±9.68	6 (9)	1	67
ICU (days)	9	7.51±5.55	24 (21)	6	67
Beck's Anxiety Inventory Score	805	8.85±8.396	6 (9)	0	50

ED: Equilibrium Disorder, ICU: Intensive Care Unit, n: Number, Std: Standard deviation, IQR: Interquartile range, Min: Minimum, Max: Maximum

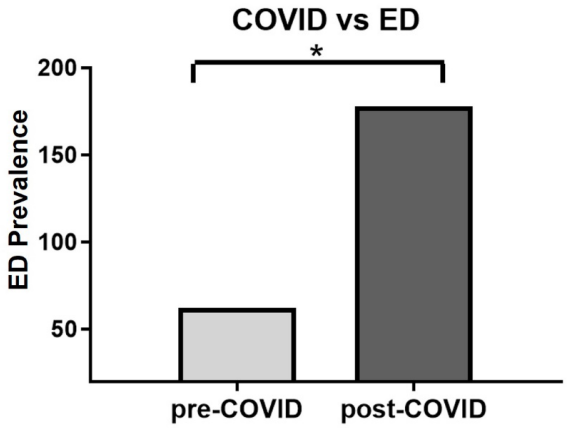

Figure 2: The Prevalence of Equilibrium Disorder pre- and post-COVID-19

RESULTS

There were 805 patients. Three hundred seventy were male (46%), and 435 were female (54%). The demographical data is shown in Table 2.

Sixty-two patients experienced ED before COVID-19 (8%). After COVID-19, ED sufferers increased to 178 (22%), which was statistically significant (p=0.001) (Figure 2). The characteristics of ED before and after COVID-19 are shown in Figure three.

The findings obtained in this study showed that 110 (25.28%) of 435 female patients and 68 (18.37%) of 370 male patients had post-COVID ED. ED was significantly more common in women among COVID-19 survivors (p=0.019).

It was found statistically significant that tinnitus increased after COVID-19 (p=0.001) (Figure 4). The number of patients who experienced tinnitus before COVID-19 was 64 (7%), and after COVID-19 was 105 (13%). The characteristics of tinnitus before and after COVID-19 are shown in Figure 5.

There was a statistically significant relationship between age and post-COVID ED (p=0.001) and post-COVID tinnitus (p=0.006).

There was a statistically significant relationship between age and BAI score with a positive correlation (13.3%) and between ED severity and BAI score with a positive correlation (21.3%) (p=0.001, p=0.003, respectively). BAI scores were significantly

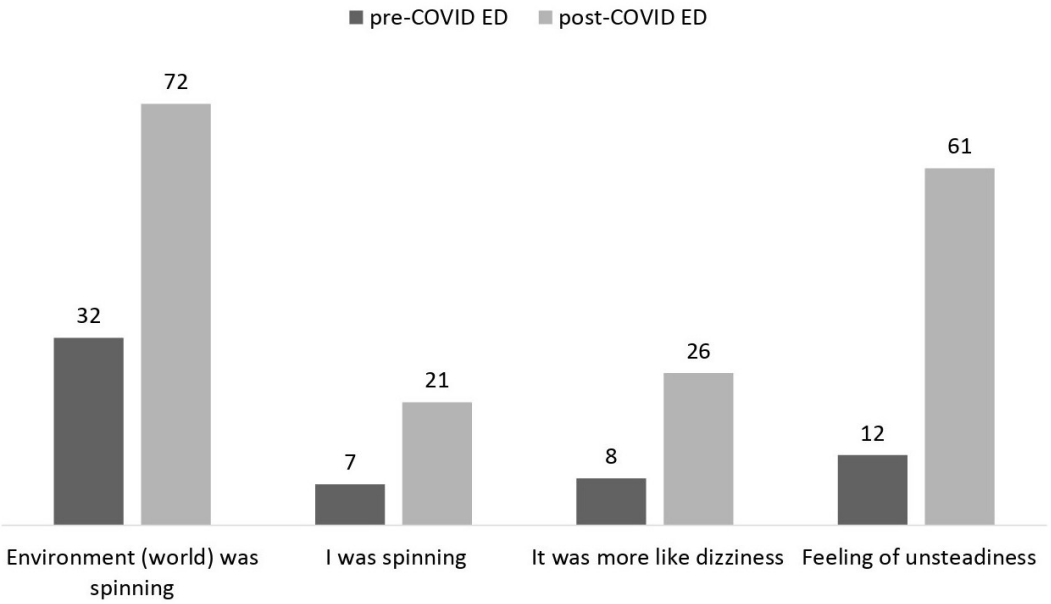

Figure 3: Characteristics of Equilibrium disorders before and after COVID-19

Table 3: Beck's Anxiety Inventory (BAI) Scores

Groups	BAI Score ±Std. Deviation	BAI Score Min-Max	BAI Score Median	*p*-value
Female	9.89±8.91	0-50	11	0.024
Male	7.64±7.58	0-48	7	
Pre-COVID ED (+)	12.02±9.01	0-33	11	0.001
Post-COVID ED (+)	13.84±9.96	0-50	14	
Pre-COVID Tinnitus (+)	12.16±7.98	2-41	11	0.047
Post-COVID Tinnitus (+)	13.44±10.06	0-50	13	
Migraine (+)	12.57±9.11	0-43	11	0.001
Migraine (-)	8.27±8.13	0-50	8	

ED: Equilibrium Disorder, STD: Standard deviation, Min: Minimum, Max: Maximum

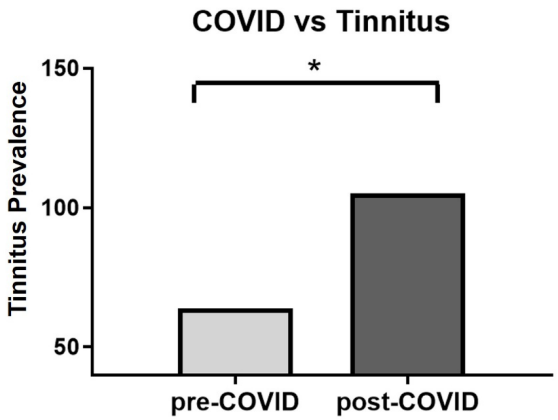

Figure 4: The Prevalence of Tinnitus pre- and post-COVID-19

higher in the post-COVID ED and post-COVID tinnitus sufferers; also, the scores were significantly higher in females and patients with migraine (Figure 6) (Table 3).

The number of patients with a migraine history was 110 (13.6%). There were statistically significant relationships between migraine and pre-COVID ED and post-COVID ED (p=0.012, p=0.002, respectively). In the non-migraine group, the number of patients with ED before COVID was 47, and it rose to 141 after COVID. Also, in the group with migraine, ED presented in 15 patients before COVID, which rose to 37 after COVID. There was no relationship between migraine status and tinnitus before and after COVID.

The number of hospitalized patients was 81 (10%), and intensive care unit patients were nine (1%). 342 (42.4%) of the patients who were not hospitalized had a history of aspirin in their treatment. Tinnitus was statistically more common in outpatients taking aspirin or its derivative drugs (p=0.004). Comorbid disease history was present in 115 (14%) patients, and 139 patients (17%) were smokers, and there was no statistically significant relationship between comorbidity or smoking history with post covid ED or tinnitus.

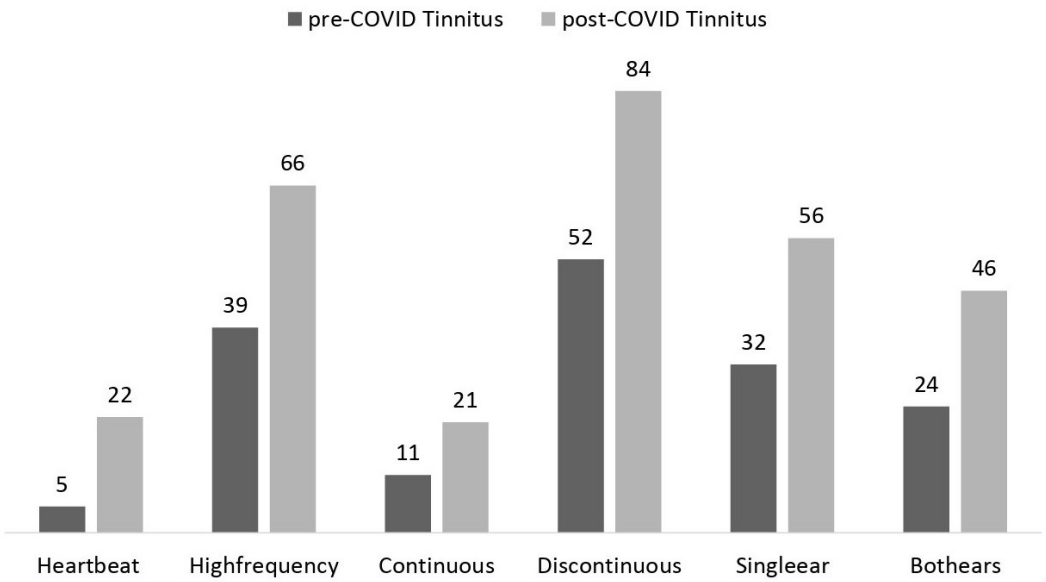

Figure 5: Characteristics of Tinnitus before and after COVID-19

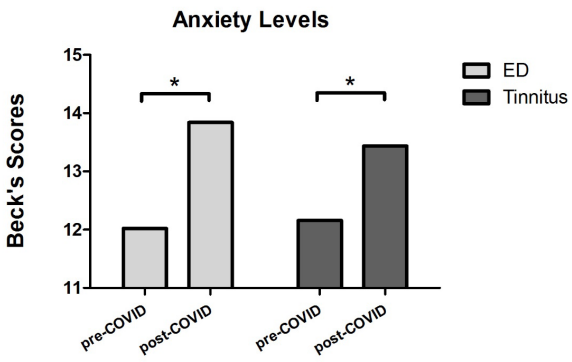

Figure 6: Beck's Anxiety Inventory Scores in Pre- and Post-COVID-19 Equilibrium Disorder and Tinnitus Sufferers

When we investigated the relationship between hospitalization and ED, post-COVID ED was observed in 26 (32%) hospitalized patients. The ED rates of hospitalized patients were significantly higher than non-hospitalized patients (p=0.014). When we looked at the post-COVID ED severity correlation, there was no statistically significant relationship with hospitalization. On the other hand, post-COVID tinnitus was observed in 16 (19.7%) hospitalized patients, and there was no statistically significant relationship between hospitalization and post-COVID tinnitus (p=0.42). However, there was a statistically significant relationship between hospitalization and tinnitus severity (p=0.001).

When we look at the logistic regression analysis, the equation was statistically significant (-2 LL=69.803; Cox & Snell R2=0.185; Nagelkerke R^2=0.249; *X*2=12.305 p=0.041).

Binary logistic regression analysis revealed that males were 3.514 times more affected than females from ED before COVID. In addition, the patients with lower BAI scores were unaffected by ED before COVID ($p< 0.05$). The other parameters did not have a significant effect.

DISCUSSION

Our survey study presented that; COVID-19 increases the prevalence of tinnitus and ED, negatively affecting the quality of life and increasing anxiety levels with advanced age. Hospitalization significantly increases the prevalence of ED. Migraine has a clear relationship with ED regardless of COVID. Some of our findings, the prevalence of ED in females with advanced age with COVID-19, were consistent with the literature (8, 11). The new findings were that; hospitalization significantly increased the prevalence of ED in COVID-19 survivors; the presence of migraine was significantly related to ED regardless of COVID, and BAI scores were significantly higher in females, patients with migraine, and the post-COVID ED and tinnitus sufferers.

Hospitalization could increase stress and Anxiety not only in COVID-19 patients but also in patients with severe illnesses that require hospitalization. Coping support interventions can alleviate psychological distress during hospitalization. These interventions could prevent severe and bothersome symptoms like tinnitus and ED in COVID-19 survivors. More evidence is needed to determine if such interventions benefit patients with COVID-19 during their hospitalization. Migraine is a multifactorial disorder, with genetic, hormonal, environmental, dietary, sleep, and psychological aspects playing different roles in each individual. Studies reported that mood and anxiety disorders are two to ten times more common in migraineurs than in the general population(12). Our study also showed a positive correlation between migraine and BAI scores.

Many studies have been conducted on clinical findings resulting from COVID-19, and dizziness has been accepted as a significant symptom (13-16). Mao et al.(7) have found neurological findings in 76 of 214 hospitalized patients with COVID-19. The most common symptoms in patients with CNS findings have been dizziness (16.8%) and headache (13.1%). In another study, dizziness has been more common in intensive care unit patients than in non-ICU patients (17). None of the survivors had dizziness as a presenting symptom in our study. On the contrary, most of the patients had presented with fever, sore throat, and headache simultaneously (75%), and 10% had presented with loss of smell and taste sensation. There was not any statistically significant relationship between presenting symptoms and post-COVID symptoms. Also, in the present study, true vertigo was more pronounced within ED disorders before and after COVID-19.

Waissbluth et al.(11) have observed an increase in the prevalence of benign paroxysmal positional vertigo after COVID-19. Compared to our study, their patients were generally younger and usually female. However, they have stated that the incidence by sex was not as striking as in the previous year.

In the study conducted by Özçelik et al., one hundred sixteen hospitalized patients with COVID-19 were questioned regarding otolaryngological symptoms associated with COVID-19. Additionally, clinical evaluations were conducted (8). The rate of otological/vestibular symptoms was dizziness (31.8%), tinnitus (11%), true vertigo (6%), and hearing impairment (5.1%), respectively. Unlike our study, these symptoms were observed more in patients under 60. Concerning gender distribution, dizziness was statistically higher in women in their study.

Freni et al.(18)used tinnitus handicap inventory (THI) on 50 patients with COVID-19. They applied the THI test to the patients twice after 15 days of RT-PCR SARS-COV-2 negativity. According to the results, tinnitus appeared or worsened in 10 patients (20%). In the second test, tinnitus persisted in five patients. They also evaluated hearing loss with Hearing Handicap Inventory for Adults. The current study showed that COVID-19 caused some deleterious effects on cochlear cell functions even if the disease process passed.

Li Xia et al.(19) have examined the relationship between Anxiety and tinnitus using a Self-Rating Scale system and have performed THI and test of loudness on the patients. During the COVID-19 Pandemic, they observed that tinnitus's severity increased in the presence of Anxiety, even if Sound Therapy and Educational Counselling treatment was performed. The first study confirmed Anxiety's causative/promotive role on tinnitus during COVID-19. Our study had a statistically significant relationship between tinnitus, ED, migraine, and BAI scores. Anxiety plays a critical role in these multifactorial symptoms in COVID-19 survivors.

Eldre Beukes et al. have conducted a systemic review of 33 studies published regarding tinnitus during COVID-19 (20). Twenty-eight studies have examined the effects of the Sars-Cov-2 virus; five studies have examined the impact of the Pandemic on tinnitus. COVID-19 impact studies have failed to find a consistent pattern of presentation of tinnitus or additional factors that may contribute to the development of tinnitus. For pandemic impact studies, it has been suggested that stress and Anxiety associated with the Pandemic consistently contribute to tinnitus experiences. Consistent with our study, they have underlined that stress affects the development of tinnitus.

Viola et al.'s study applied the online questionnaire to 185 patients with COVID-19 (5). Thirty-four (18.4%) stated they had an equilibrium disorder after COVID-19. Of these, 32 patients had dizziness, and two had acute vertigo attacks. Forty-two patients (23.2%) stated that they experienced tinnitus after COVID-19, and 14 (7.6%) experienced tinnitus and equilibrium disorders. This study was a survey study like ours.

Ototoxic drugs, such as azithromycin and hydroxychloroquine, frequently used in pandemics, may also be associated with equilibrium disorders. Post-COVID ED and tinnitus have been lately observed besides the COVID-19 findings. Considering the progression of the Pandemic, the number of these cases

will gradually increase; thus, the differential diagnosis of post-COVID ED from diseases, such as acute neuritis, should be made in the future. Since much data, including the pattern of balance disorder and the sound heard in tinnitus, may be helpful in further studies, the characteristics of ED and tinnitus and the effects on the individual should be examined in further studies.

Our study was a cross-sectional questionnaire study and had some potential limitations. Since we could not contact the patients face to face due to the Pandemic, we reached the patients through phone calls. Thus, clinical evaluation could not be performed. In addition, this was a survey study, and the data consisted of subjective patient-reported symptoms. Therefore, unpredictable factors, such as the patient's psychological state, could affect the data and the result of the study. Nevertheless, our survey consisted of a significant number of patients and the subjective symptoms like tinnitus and ED could be evaluated through questionnaires at some level. The number of patients evaluated in this study is the principal strength that helps us conclude.

CONCLUSIONS

COVID-19 survivors had significantly suffered tinnitus or ED with a positive correlation with age. Also, post-COVID ED was seen more in women than men. Hospitalization has significantly increased the prevalence of ED, and the presence of migraine before and after COVID-19 has a significant relationship with ED. Beck's Anxiety Inventory scores were significantly higher in female patients with migraine and post-COVID ED and tinnitus sufferers. It can be said that the patients with high Anxiety experienced more tinnitus and ED in the post-COVID period.

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Informed Consent: Written informed consent was obtained.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- S.E., D.T., S.N.B., D.T.D., P.D., P.K.; Data Acquisition- S.E., D.T., S.N.B., D.T.D., P.D.; Data Analysis/Interpretation- S.E., D.T., S.N.B., D.T.D., P.D., P.K.; Drafting Manuscript- S.E., D.T., S.N.B., D.T.D., P.D., P.K.; Critical Revision of Manuscript- P.K.; Final Approval and Accountability- S.E., D.T., S.N.B., D.T.D., P.D., P.K.

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RESEARCH ARTICLE
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Evaluation of the Readability of Online Turkish-Language Patient Education Materials on Congenital Hearing Loss

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ABSTRACT

Objective: The aim of this study was to assess the readability of online patient education resources on congenital hearing loss written in Turkish.
Materials and Methods: We used Google Search to identify Patient Education Materials (PEM) for "congenital hearing loss". A total of 50 websites were included initially, but after applying the inclusion and exclusion criteria, a total of 20 websites were analyzed. We divided these into two categories: Health Professionals and General Websites. The readability of the materials was calculated using the Ateşman readability formula.
Results: The mean Ateşman readability score was 61.78±13.03. Health professional websites had a mean score of 68.69±9.8, while general websites had a mean score of 53.33±11.74. Health professionals websites were found to be easier to read than the General websites (P=0.009). There were 6 easy-level articles, all of which were from health professional websites. Four articles were of a hard level and all were general websites. The remaining 10 articles were of intermediate level.
Conclusion: Although many online resources are available to provide information about congenital hearing loss, the readability level of these sources is above the easy-to-read level. To better serve parents and affected individuals, these resources should be revised to enhance their readability. Health professionals, in particular, have an opportunity to contribute more comprehensible materials.

Keywords: Congenital hearing loss, patient education materials, readability score, ateşman readability formula

INTRODUCTION

Hearing loss is an impairment of auditory function that can have lasting effects on social and linguistic development. It can develop before or after language development (1). Social development can be significantly impacted by congenital hearing loss. To avoid the condition's long-term effects, it must be promptly diagnosed and treated.

The United States initially implemented the Newborn National Screening program to facilitate the prompt identification and intervention of congenital hearing loss in patients (2,3). Otoacoustic emission, ABR, was used for scanning. Later in 1998, the Neonatal Hearing Screening (NHS) program was recommended by the European Consensus Statement (4). Over the subsequent years, the program expanded its reach globally. The program was started on a hospital-based basis in Turkey, first at Marmara University (Istanbul 1996) and then at Hacettepe University (Ankara 1998). The NHS program, which started as a pilot in 2011, was transformed into a national NHS program and started to be carried out in a total of 584 centers and spread all over the country (5).

The Internet has recently been seen as an important source for accessing health-related information. According to the most recent data in Turkey, internet use over the age of 16 has reached 85% (6). Parents whose children have been diagnosed with hearing loss are very likely to turn to online resources to gather information regarding the health status of their child. Initiation of treatment in children with congenital hearing loss

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as soon as possible will positively affect the child's cognitive and language development. Considering that it is a treatable disease, the importance of patient education materials about congenital hearing loss emerges.

Given the high prevalence of Internet usage among people nowadays, the Internet can be a good tool to raise awareness about congenital hearing loss and to reach a large segment of society. Online patient information resources can serve as valuable tools to aid patients in the informed consent process by providing an explanation of the indicators, benefits, and potential risks of medical practice. Due to the fact that the value of the information is contingent on the patients' ability to understand it, the legibility of this information on the Internet is crucial. Based on the guidelines provided by the American Medical Association (AMA) and the National Institutes of Health (NIH), it is recommended that patient education materials available on the internet should be composed in a manner that is accessible to individuals at or below a sixth-grade reading level (7). If the legibility of online content on a website exceeds this value, it can be considered as difficult to read and understand for an average reader. For this reason, it is important that health-related information on internet sites is suitable for the reader and carefully evaluated before use.

Readability means objectively measuring how easy or difficult a text is for the reader, based on mathematical formulas. The specific grammatical structure of each language is taken into account in the creation of these formulas. The Ateşman readability formula was constructed using data about Turkish syllables and words, and this formula aims to determine the ease of reading of Turkish texts (8). The texts are divided into five distinct levels according to the Ateşman formula: very easy, easy, medium, difficult and very difficult (Table 1). Generally, it is advisable to ensure that the texts are written in a manner that are easy or very easy to read. Texts at this level offer greater accessibility and intelligibility to the reader.

The objective of this research is to examine the comprehensibility of online patient educational resources that are written in the Turkish language about congenital hearing loss.

Table 1: Ateşman Readability Formula

Scores	Levels
90-100	very easy
70-89	easy
50-69	medium difficulty
30-49	difficult
1-29	very difficult

MATERIAL AND METHODS

Patient Education Materials (PEM) for "congenital hearing loss" were identified through use of Google Search. When searching, the term 'congenital hearing loss' was used. In the advanced search, the selection is limited to only "full sentence" and "Turkish language". The initial 50 websites that are included in our study as a consequence of the search query. Websites that were excluded are the ones solely consist of graphics or tables, scholarly journals, videos, and websites that undergo iterative updates. Since our investigation utilized public records, it is not necessary to form an ethical commission.

The articles were divided into two categories; (1) Health Professionals and (2) General websites. Health Professionals were defined as websites belonging to institutionally operating private, public, and foundation hospitals as well as physician-owned websites. On the contrary, the term "general websites" encompassed online platforms such as newspapers and websites that provide general health information, excluding the first two categories.

Each meaningful congenital hearing loss-related text was transferred into a distinct Microsoft Word (version 2010; Microsoft, Redmond, WA) document. In order to prevent any impact on readability scores, extraneous non-academic content has been excluded from the text. This includes elements such as web page navigations, copyright notices, disclaimers, author information, feedback surveys, links, website URLs, references, figures, tables, appendices, addresses, and phone numbers.

Statistical Analyses

Using the Ateşman readability formula (198,825-40,175x (total syllables/total words)-2,610x (total words/total sentences), the determination of the readability levels of the texts was conducted. The mean, standard deviation, median, minimum, maximum value, frequency, and percentage were utilized for summarize and describe the data. The examination of variable distribution was conducted utilizing the Kolmogorov-Smirnov test. Using Kruskal-Wallis to conduct a comparative analysis of quantitative data. For statistical analysis, SPSS 28.0 was utilized.

RESULTS

After the application of inclusion and exclusion criteria, a total of 20 websites were subjected to review. Health professionals met the inclusion criteria for 11 PEM articles on their website. A comprehensive compilation of 14 articles pertaining to PEM was incorporated from various general websites.

The mean Ateşman readability score of the articles was 61.78±13.03. The minimum score observed was 38, while the maximum score recorded was determined to be 82.60 (Table 2).

Table 2: Analysis of all data (without group discrimination)

	N	Minimum	Maximum	Mean	Std. Deviation	Mean±S.D (Min-Max)
Ateşman Score	20	38.00	82.60	61,7750	13,03485	61.78±13.03 (38-82.6)

While the mean score of health professionals websites was 68.69±9.8, the minimum score was 54.1 and the maximum score was 82.6. General websites mean score was 53.33±11.74, the lowest score was 38, and the highest score was 72.4 (Table 3). Health professionals websites were found to be easier to read than the General websites (P=0.009) (Table 4).

Although there was not a very easy level article, there were 6 easy level articles. Five of the six easy-level articles were health professional websites. There were no very difficult articles. There were four articles on the hard level. The hard level articles were all general websites. The remaining 10 articles were of intermediate level.

Table 3: The analysis obtained when both groups were examined separately

		N	Minimum	Maximum	Mean	Std. Deviation	Mean±S.D (Min-Max)
Health Professionals Websites	Ateşman score	11	54.10	82.60	68,6818	9,79641	68.69±9.80 (54.10-82.60)
General websites	Ateşman score	9	38.00	72.40	53,3333	11,73904	53.33±11.74 (38-72.4)

Table 4: Comparison of two groups with Mann Whitney U test

	Ateşman score
Mann-Whitney U	15.000
Wilcoxon W	60.000
Z	-2.621
Asymp. Sig. (2-tailed)	**.009**

DISCUSSION

This research aimed to measure the readability levels of online resources on congenital hearing loss in Turkish. Resources were evaluated in two main categories: Health professionals and General websites. The readability level of the majority of these sources was found to be above the easy-to-read level.

The era of digitalization in the field of health has begun and not only has the internet emerged as a resource for patients, but also for doctors and other medical professionals. There has been a notable rise in the participation of doctors and healthcare professionals in generating and disseminating health-related content on the internet. Consequently, patients are able to conveniently access these resources through the utilization of search engines. Approximately 50% of parents with children experiencing ear-nose-throat issues resort to online platforms to seek medical information for their children (9).

According to research, the estimated incidence rate of sensorineural hearing loss in children ranges from one to three cases per one thousand individuals (10). If sensorineural hearing loss (SNHL) with a severity of ≥90 dB HL is left untreated, the aforementioned phenomenon is expected to exert an adverse influence on the timely progression of speech and language abilities. The early identification and treatment of a condition are crucial, and the provision of accurate information to families is highly significant (11). Online patient education materials can be helpful for parents to be informed correctly. It is important that the content of the educational materials is at a level that can be understood by the parents, no matter how accurate the information is.

Upon examination of the prevailing conditions in Turkey, it is evident that a significant proportion of the nation's populace, specifically 97%, possesses the ability to read and write (12). Furthermore, the utilization of the internet among individuals aged 16 and above surpasses the threshold of 85% (6). The National Newborn Screening Program was initiated in Turkey during the 2000s, mirroring the global trend. On average, the prevalence of hearing loss among children in Turkey is 2.2 per 1000 births (13). Given the annual occurrence of more than one million live births, the significance of this matter is further underscored (14).

During the course of the study that was carried out on instructional materials written in Turkish, a variety of topics were investigated. In the study, in which 54 educational materials on Substance Addiction were examined, The study revealed that the materials predominantly exhibited a high level of readability difficulty (15). In the study, in which 87 online training materials related to anaesthesiology were examined, the observation indicated that the materials consistently demonstrated a high level of difficulty in terms of readability (16). In the study in which 100 patient education materials on low back pain were examined, the materials were generally found at a moderate readability level (17). In another study examining skin cancers and online patient education materials, the materials were generally at a moderate readability level (18). Online educational materials on colorectal cancer also appear to be of medium readability (19). Duymaz et al. also reviewed online patient education materials about laryngeal cancer. The researchers reached the conclusion that the materials exhibited predominantly moderate levels of readability (20). On the other hand, in the study conducted on the online education materials related to vertigo, the materials were generally found at the level of easy readability (21). Although different results have been obtained according to the subject studied in the literature, in general, the materials are at medium and more difficult readability levels. In the present study, akin to the existing body of literature, the materials were determined to possess a moderate level of readability.

Congenital hearing loss is an important issue that should not be underestimated. Considering that parents will review the online materials with their children's conditions, the importance of the readability level of online materials with

congenital hearing loss emerges. Duymaz et al. reviewed online materials in English for hereditary hearing loss. A total of 29 articles were subjected to review and subsequently categorized into three distinct groups: professional organizations, clinical practices, and general information sources. The readability level of a text was assessed using various tools, including the Flesch Reading Ease, Flesch-Kincaid grade level, Gunning-Fog Index, Simple Measure of Gobbledygook, Coleman-Liau Index, and Automated Readability Index. They reported that the majority of the articles were fairly difficult and above difficulty level. They also reported that there was no difference in the degree of difficulty between the three categories (22). Similarly, in our study, we examined online patient education materials with congenital hearing loss in Turkish. In our study, we used the Ateşman readability formula, which is suitable for the Turkish language. We divided the websites into Health Professional and General websites. In our study, too, there was no easy-to-read material. It was mostly found at a moderate readability level. In our study, the materials prepared by the health professionals were more easily readable than the materials on the general websites. Although this is a positive thing, the Turkish language materials still often seem far from easy and very easy to read. We think that health professionals have more duties to prepare more understandable materials.

Studies on the National Screening Program in Turkey show that the age at which patients are diagnosed is getting younger . However, it is seen that the age at which patients start treatment is not yet at the desired level (23,24). It has been argued that qualified personnel who can work with parents should be trained in order to decrease the starting age for treatment (25,26). It is an undeniable fact that training qualified personnel is important. However, online materials that will be prepared at the recommended levels of readability to inform parents will also serve this purpose. In terms of parents, there will be materials that they can access whenever and as often as they want, and it will be more effective.

The present study is subject to certain limitations. Firstly, it should be noted that relying solely on the Google search engine may not provide a comprehensive representation of all users' experiences. This study does not encompass search engines other than Google. Second, the top 50 websites that meet our inclusion criteria, regardless of quality, are included. Furthermore, it is important to note that the readability score does not assess the scientific validity or accuracy of websites. In the calculation of readability scores, it is important to note that only written materials are taken into consideration. In contrast, the utilization of an online resource containing visual elements such as graphics or videos may significantly enhance comprehensibility.

CONCLUSION

The management of congenital hearing loss is contingent upon early identification and intervention. Hence, it is of utmost significance to furnish parent education materials that are both comprehensible and accessible. In light of our analysis, it is evident that the current web-based sources would benefit from enhancing their readability in order to effectively fulfill their intended purpose.

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Functional and Olfactory Outcomes of Inferior Turbinate Hypertrophy Reduction with Laser, Radiofrequency, and Bipolar

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ABSTRACT

Objective: This study aims to compare the effects of bipolar cauterization, radiofrequency ablation, and laser reduction methods, which are frequently used for turbinate reduction, on recovery times and olfactory functions in the early postoperative period.
Materials and Methods: The olfactory functions of all patients were preoperatively evaluated with the Sniffin' Sticks test. To assess the effects on olfactory functions, olfactory tests were repeated in the third month after the operation. The patients were examined weekly, and the resolving time of the crusts was recorded.
Results: The endoscopic turbinate reduction was performed with bipolar cautery in 50 patients, with radiofrequency ablation in 50 patients, and with laser ablation in 50 patients. There was no statistically significant difference between the techniques used regarding the severity of the olfactory function loss in the third month (p=0.546). It was observed that the resolving time of the crusts was the shortest in the group treated with the Holmium-YAG laser and the longest in the patients who underwent bipolar cautery (p<0.001). Parosmia persisted in only 9 patients in the postoperative third month (BP:7, RF:2, L:0) (p=0.049). In addition, it was determined that nasal dryness and pain (as assessed by visual analog score) were the most in the bipolar group (p=0.001 and p=0.005, respectively), and there was no significant difference between the laser and radiofrequency groups in terms of these symptoms (p=0.53 and P=0.96, respectively).
Conclusion: Patients who underwent Holmium laser turbinate ablation had less crusting and less olfactory function loss in the early period compared to those who underwent radiofrequency and bipolar turbinate reduction.

Keywords: Smell disorder, inferior turbinate surgery, sniffin sticks, turbinate

INTRODUCTION

The nose is the first organ of the respiratory system and provides humidification and heating of the inhaled air to the lungs (1). In addition, the olfactory function, one of our five senses, is the most important function of the nose (2). Olfactory cells are located on the roof of the nose at the level of the middle turbinate, where odor molecules reach here by diffusion (2). Intranasal pathologies such as septum deviation, turbinate hypertrophy, and sinus polyps are the most important causes of nasal congestion (1). Allergic rhinitis and non-allergic rhinitis-related mucosal hypertrophy play an important role in the etiology of turbinate hypertrophy, which we frequently encounter in otolaryngology practice (3). Although non-surgical methods such as topical nasal sprays and saline irrigation are used in the treatment, their effectiveness is more limited (4,5). For this reason, surgical turbinate reduction continues to be performed increasingly today. Various surgical techniques have been described for the reduction of the hypertrophic inferior turbinate. However, there is no clear consensus in the literature about the most appropriate surgical method and the effectiveness of surgical treatment (5). The primary purpose of surgical treatment is to provide optimum volumetric shrinkage of the turbinate to reduce nasal congestion while not harming the functions of the nose and minimizing possible complications. The crusting that occurs during the healing period after turbinate reduction causes temporary congestion,

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decreased olfactory functions, a bad smell in the nose, and adversely affects the quality of life (3). However, in the long term, it is known that the improvement in nasal congestion and the increase in air circulation within the nose positively affect the patients' olfactory functions (3).

This study aims to compare the effects of bipolar cauterization, radiofrequency ablation, and laser reduction methods, which are currently frequently used in the treatment of turbinate reduction, on early crusting times and olfactory functions.

MATERIAL AND METHODS

This study included patients who were admitted to the otorhinolaryngology outpatient clinics of Ulus Liv Hospital between June 2020 and June 2022 for nasal obstruction and had inferior turbinate reduction for turbinate hypertrophy. The study was approved by the Medical Ethics Committee of Istinye University (Date: 17.11.2021, No: 2/2021.K-84). Informed consent forms were signed by the patients beforehand, and those who voluntarily agreed to participate in the study were included. The study was conducted in accordance with the Declaration of Helsinki. Each patient was first evaluated with nasal endoscopy by an otolaryngologist. Patients who had previous turbinate reduction due to nasal obstruction, known olfactory disorders, allergic rhinitis, chronic sinusitis, or septum deviation were not included in the study. In addition, patients with any known systemic and chronic diseases (diabetes, MS, Alzheimer's, etc.) were excluded.

Methods were explained to the patients, and turbinate reduction was planned according to patient selection. Skin prick test was performed on all patients, and negative test results patients were included in the study. The patients in the first group underwent turbinate reduction with bipolar cautery, the second group underwent ablation with radiofrequency, and the third group underwent laser. The baseline olfactory functions of all patients were evaluated with Sniffin' Sticks before surgery. The same surgeon performed all operations. After the surgery, a nasal humidifier and rinsing with physiological saline were recommended for all patients. Controls were performed by another doctor who did not know which method was used. The patients were examined weekly for nasal crusting. The olfactory functions of the patients were assessed on the 1st week, 1st month, and 3rd month postoperatively.

A visual analog scale was performed once preoperatively and weekly after the operation to measure nasal dryness and postoperative pain sensation.

Olfactory Tests

Psychophysical testing of olfactory function was performed with the validated Sniffin' Sticks (Burghart, Wedel) test, in which odorants were adsorbed into commercially available felt-tip pens. First, the cap of the pen was opened by the experimenter before starting the test, then the experimenter waited for 3 seconds so that the scent was exposed, and then the tip of the pen was placed approximately 1-2 cm in front of the nostrils. The test consisted of one threshold and two suprathreshold subtests. That is, it consisted of a test for PEA thresholds, a test for odor discrimination (16 triplets with two different odors), and a test for odor identification (16 common odors presented in four) (alternative, forced selection procedure). The maximum score for each subtest is 16, and the maximum composite score is 48 (TDI - threshold, discrimination, and identification score). TDI composite scores higher than 30.3 were considered normosmia, scores lower than 16.5 were considered functional anosmia, and scores between 16.5 and 30.3 were considered hyposmia.

Parosmia Assessment Scale

Parosmia was quantified in 4 degrees (0 to 3) with these factors: frequency of occurrence: daily=1 point, otherwise=0 points, intensity: very strong=1 point, otherwise=0 points, social effects (e.g., weight loss, significant change of habits): yes=1 point, no=0 points. The total score represents the degree of the disorder.

Turbinate Reduction Methods

Bipolar cauterization: After the patient was anesthetized with the help of LMA, cauterization was performed submucosally into the concha using a 0-degree endoscope. Ellman Surgitron® Dual EMC 90 Energy Source Bipolar mode (1.7 MHz and 15 Watt) and Ellman Surgitron® Bipolar Forceps Cushing were used during the procedure.

Radiofrequency Ablation: After the patient was anesthetized with the help of LMA, the radiofrequency ablation probe was applied submucosally using a 0-degree endoscope. Olympus Celon® Elite instrument (15 Watts, Fine RFITT mode) and Celon® ProBreath probe were used during the procedure.

Laser Ablation: After the patient was placed under anesthesia with the help of LMA, the submucosal application was performed with a 0-degree endoscope. During the procedure, Medilas® H Solvo Holmium: Yag Laser was applied at 400 nm wavelength, 0.8 watts, and 6 Hz.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 21.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean and standard deviation (SD), median (min-max), or number and frequency. The Kruskal-Wallis test was used to compare continuous variables. A p-value of <0.05 was considered statistically significant.

RESULTS

150 people were included in the study, of which 82 were female, and 68 were male. The mean age of the patients included in the study was 34.1 years (18-47). The patients were divided into three groups, and endoscopic turbinate reduction was performed in 50 patients using bipolar cautery, 50 patients using RF, and 50 patients using a laser. The mean preoperative TDI score of the patients in the bipolar cautery

ablation group was calculated as 26.775. This value was found to be 20.425 in the postoperative 1st week, 22.575 in the postoperative 1st month (T=13 D=11 I=12), and 31.075 in the postoperative 3rd month. The nasal crusting duration was 35.3 days. The mean preoperative TDI score of the patients in the radiofrequency ablation group was 26.425. The mean TDI of the patients in this group was 20.025 in the postoperative 1st week, 24.675 in the postoperative 1st month, and 31.925 in the postoperative 3rd month. The mean duration of nasal crusting in this group was 22.3 days. The mean preoperative TDI score in the holmium-YAG laser ablation group was 26.3. The postoperative 1st-week, 1st-month, and 3rd-month values were recorded as 19.575, 26.425, and 31.975, respectively. In this group, the duration of nasal crusting was 12.6 days. All three techniques used in turbinate reduction caused a decrease in olfactory functions in the 1st postoperative week. There was no statistically significant difference between the groups regarding the severity of the decrease in olfactory functions (p=0.546). When olfactory functions were assessed at the end of the first month, it was observed that the deterioration was most common in patients who underwent bipolar cautery and the least in patients who underwent Holmium-YAG laser, and the difference between these two groups was statistically significant (p=0.003). On the other hand, there was no statistically significant difference between the groups in terms of olfactory functions after three months (p=0.045). The crusting durations were the shortest in the Holmium-YAG laser group and the longest in the bipolar cautery group. The difference between these two groups regarding crusting durations was significant (p<0.001). Preoperatively, none of the patients had a complaint of parosmia. In the first postoperative week, 46 patients had parosmia (BP:23, RF:18, L:5) (p=0.005). While parosmia persisted in 22 patients at postoperative 1 month (BP:15, RF:7, L:0) (p=0.005), only 9 patients had parosmia after 3 months (BP:7, RF:2, L:0) (p=0.049) (Table 1). The preoperative VAS scores for nasal dryness were 1.4 +/- 0.69 in the laser group, 1.6 +/- 1.07 in the radiofrequency group, and 1.3 +/- 1.05 in the bipolar cautery group. No significant difference was observed between these three groups regarding preoperative nasal dryness VAS scores. In the postoperative 3rd month follow-up, these scores were 2.6 +/- 0.51 in the laser-treated group, 3.1 +/- 1.19 in the radiofrequency group, and 5.4 +/- 0.84 in the bipolar cautery group. In the postoperative 3rd month, nasal dryness was found to be significantly more severe in the bipolar cautery group (p=0.001), while no statistically significant difference was observed between the radiofrequency and laser groups (p=0.53).

It was determined that the VAS scores for postoperative pain were highest in the bipolar group and lowest in the laser-applied group, but the difference between these two groups was not significant (P=0.96).

DISCUSSION

Nasal obstruction due to turbinate hypertrophy is an important health problem that otolaryngologists frequently encounter in their daily practice and significantly affects patients' quality of life. Surgical reduction of the turbinates is an easy and effective treatment modality (3,5,6). Crusting, which occurs due to the deterioration of mucosal ciliary activity on the turbinates in the early postoperative period, both affects the psycho-social lives of the patients due to bad odor and causes nasal congestion to continue for a while (6). Today, with the Covid-19 infection, which continues as a pandemic, elective surgical interventions continue in a controlled manner, similar to all activities worldwide. Olfactory dysfunction is one of the typical findings of COVID-19 infection (7), and the occurrence of anosmia/hyposmia and malodor during the crusting process after turbinate reduction leads to COVID-19 concerns in patients. In addition, the resulting bad odor affects the daily social life of the patients. For these reasons, turbinate reduction operations are aimed at the improvement of nasal congestion (5), improvement in olfactory functions as a result of increased nasal airflow (8), and early resolution of crusting and thus of bad odor (9,10).

In the study of Harju et al., it was reported that the crusting duration after concha reduction with radiofrequency was longer than the patients in the diode laser group, and in some cases, crust formation continued for up to three months (11).

Table 1: TDI, Parosmia, Nasal Dryness scores at beginning,1 week, 1 Month, 3 Months after Treatment; Nasal Crusting Time (NCT) (days)

Technique	Beginning		1st Week		1st Month		3rd Month		
	TDI	Parosmia Nasal Dryness	TDI	Parosmia	TDI	Parosmia	TDI	Parosmia Nasal Dryness	NCT(days)
BP	26.775	0 1.34/-1.05	20.425	23	22.575	15	31.075	7 5.4+/0.84	35.3
RF	26.425	0 1.6+/-1.07	20.025	18	24.675	7	31.925	2 3.1+/1.19	22.3
L	26.3	0 1.4+/-0.69	19.575	5	26.425	0	31.975	0 2.6+/0.51	12.6
Total (Patients)		0		46		22		9	
p	0.54	1	0.69	0.005	0.003	0.005	0.045	0.049	<0.001

(BP: Bipolar, RF: Radiofrequency, L: Laser)

In a study by Janda et al., moderate-to-severe nasal congestion, crusting, and nasal discharge were observed in patients during the first four weeks following diode laser treatment (12). In this current study, we found that patients who underwent the radiofrequency method had a shorter crusting time compared to bipolar cauterization; however, the shortest crusting time was observed in patients who underwent Holmium laser.

There is no study in the literature evaluating the effects on olfactory functions in the early postoperative period. However, Garzaro et al. (8) showed improvement in olfactory functions after radiofrequency, and Back et al. (13) after submucosal bipolar cauterization. According to our observations in this study, a decrease in olfactory functions was observed in the 1st week after turbinate reduction, regardless of the technique used. Olfactory functions tended to improve earlier in patients who underwent laser reduction. In the 3rd month after the operation, olfactory functions improved in all groups, and no difference was found between the olfactory scores. Similarly, the mean TDI scores increased in all three groups.

Nasal dryness occurs due to thermal damage after turbinate reduction. It has also been shown that nasal dryness affects the quality of the nasal microbiome in patients, thus causing a decrease in olfactory functions (14). Especially during the application of bipolar cautery, submucosal damage caused by the temperature reaching 400 °C causes scar development. The resulting mucous gland damage eventually leads to reduced mucus and nasal dryness (15). In our study, the group in which nasal dryness was mildest was the laser group.

The highest mean VAS score for intraoperative pain was in the bipolar cautery group and was significantly different from those in the other groups. In this group, an uptrend was observed in the mean VAS scores for postoperative pain over ten days. The most likely cause of this is direct tissue trauma caused by the procedure. Pain scores showed similar trends during the first two days in the Ho-YAG laser group and the first four days in the radiofrequency treatment group. Still, there was no significant difference between these two groups.

Another important issue examined in our study is the characteristics of parosmia caused by the techniques used for turbinate reduction and its recovery times. In the study, the highest rate and most prolonged duration of parosmia occurred in the bipolar cauterization group. The group in which parosmia was seen at the lowest rate was the laser group, and it completely recovered by the end of the 1st month. The exact mechanism of parosmia after turbinate reduction is not known. The correlation between nasal crusting durations and parosmia suggests that malodor may be due to crusting. Rather than the smell of burnt rubber and rotten vegetables described in classical parosmia, our patients often told what they sensed resembled the smell of pus.

CONCLUSION

This research is important because it gives information about the crusting times and the effects of different surgical modalities on olfactory functions in the early recovery period. In addition, there is no study showing the effect of Ho-YAG laser application on olfactory functions. Although we demonstrated the positive effects of the Ho-YAG laser on early olfactory functions in this study, we believe that further studies with longer-term results will contribute more to the literature.

Ethics Committee Approval: This study was approved by Istinye University Clinical Research Ethics Committee (Date: 10.11.2021, No: 2/2021.K-84).

Informed Consent: Written informed consent was obtained.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- A.A.; Data Acquisition- M.C.K.; Data Analysis/Interpretation- E.Y.; Drafting Manuscript- M.C.K., E.Y.; Critical Revision of Manuscript- A.A.; Final Approval and Accountability- M.C.K.; Material or Technical Support- A.A., M.C.K., E.Y.; Supervision- A.A.

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RESEARCH ARTICLE
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Survival Analysis of Surgical Tracheotomy in Pediatric Patients With Chronic Diseases in a Tertiary Health Center

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ABSTRACT

Objective: To investigate the effect of age group (infants and non-infants) and demographics on survival in pediatrics with tracheotomy.
Materials and Methods: Sex, age at the time of the tracheotomy, nationality, parental consanguinity, primary disease, date of discharge from the intensive care unit, and date of death were obtained from the medical records. The study population was categorized by nationality, parental consanguinity, and age group for survival analysis.
Results: The study included 140 pediatric patients who underwent a tracheotomy. The median age of the patients at the time of the tracheotomy was 1.23 years. The median follow-up after tracheotomy was 5.4 months. Consanguinity was present in 70.4% of the parents. Primary diseases were grouped as neurologic (37.1%), neuromuscular (29.3%), metabolic (12.1%), cardiopulmonary (8.6%), traumatic (6.4%), and syndromic (6.4%). Neuromuscular diseases were more common in infants, while neurologic and metabolic diseases were more common in non-infants. Eighteen patients were weaned and four patients were decannulated. The overall mortality rate was 70%. The median overall survival was 214 days. Infants (147 days) had a shorter survival than non-infants (286 days). Parental consanguinity and nationality did not affect survival.
Conclusion: In this study, among pediatric patients, infants are associated with a poor prognosis in survival. Neurologic and neuromuscular diseases may be thought to increase mortality among primary diseases. According to our study, it can be suggested that infants who cannot be decannulated due to neuromuscular diseases and are discharged with a tracheostomy are the group that should receive most attention regarding mortality among pediatrics with a tracheostomy.

Keywords: Infants, nationality, neurologic, parental consanguinity, pediatric tracheotomy, survival

INTRODUCTION

Tracheostomy is the surgical procedure used to open a window on the trachea. A tube is inserted into the window to create a new airway through which the patient is ventilated (1). This airway allows ventilation in the event of upper airway obstruction, more convenient removal of pulmonary secretions, and better management of ventilation in patients who required prolonged mechanical ventilation (2). An additional benefit is an increase in tissue oxygenation (3). Tracheotomy, previously indicated mainly for trauma and upper respiratory tract infections, is now often indicated for chronic diseases requiring prolonged mechanical ventilation (2).

Children with complex chronic diseases are more likely to be admitted to the intensive care unit (ICU) than children without those diseases. Length of stay and mortality in the ICU are higher in patients with complex chronic diseases (4). While the frequency of emergency tracheotomy has reduced in pediatrics, the rate of tracheotomy has increased due to better survival rates in the pediatrics and neonatal ICU (5). As the survival rate of children with congenital defects has improved, 41-63% of pediatric tracheotomies are performed on infants, and this rate has been increasing during the last few years (1,6).

This increasing number of tracheotomies prompted us to further investigate the demographics, chronic diseases, and survival of tracheostomized infants. The present study

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compared the demographics, chronic diseases and, survival of pediatric patients, both infants and non-infants, at a tertiary healthcare center. The study is specific because the target population of our hospital is patients with low income.

MATERIAL AND METHODS

Study population

Ethics committee approval was obtained. All parents of the patients gave informed consent. The study comprised 140 pediatric patients who underwent tracheotomy in the pediatric ICU from August 2017 to December 2022. The inclusion criteria were age under 18 years at the time of tracheotomy and tracheotomy for prolonged intubation. Patients who underwent emergency tracheotomy for acute airway obstruction and patients with a history of previous tracheotomy were excluded from the study. The medical records of the patients were reviewed to determine gender, age at the time of tracheotomy, nationality, parental consanguinity, primary diseases, date of discharge from the ICU, and date of death. Data up to the last observation date, 31 December 2022, were used for survival analysis. All tracheotomies were performed by otolaryngologists at our hospital.

For statistical analysis, 63 patients up to 1 year of age were classified as infant group and 77 patients between 1 year and 18 years of age were classified as non-infant group. One hundred and eight patients were divided into two groups based on parental consanguineous status: consanguineous or nonconsanguineous. Patients were divided based on their nationality as either Syrian or Turkish.

Statistical analysis

Data analysis was performed using SPSS version 26.0 software (IBM Corp.; Armonk, NY, USA) statistical program. The distribution of the data was evaluated with the Shapiro-Wilk Test. For the analysis of non-parametric continuous variables, the Mann-Whitney U Test was used to compare independent groups. Pearson chi-squared test and Fisher exact test were used to compare categorical variables. The survival rate was calculated using the Kaplan-Meier method. The survival difference between the groups was evaluated by the log-rank test. The level of statistical significance was accepted as <0.05.

RESULTS

The median age of 140 patients at the time of tracheotomy was 1.23 years (interquartile range 0.50- 4.04 years, age range 1 month to 17.5 years). The analysis of the age distribution indicated a peak in infants, comprising of 45% of the patients (Figure 1). The male/female ratio was 1:1.26. The median follow-up period post-tracheotomy was 5.4 months (interquartile range 1.9 - 10.6 months) with the longest follow-up period being 59.5 months.

In the study, 109 patients were Turkish and 31 patients were Syrian. Of the patients, 76 had parental consanguinity, 32 did not, and for 32 of the patients, there was no information on consanguinity in the medical records. The most common chronic disease among patients was neurologic disease (37.1%), followed by neuromuscular disease (29.3%), metabolic disease (12.1%), cardiopulmonary disease (8.6%), trauma (6.4%), and syndromic disease (6.4%), as shown in Table 1.

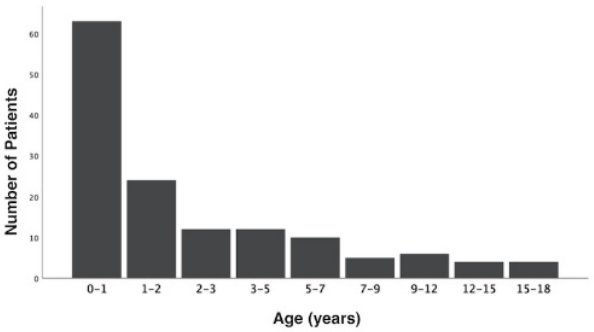

Figure 1: Age distributions of pediatrics at the time of tracheotomy

Table 1: Chronic diseases of the patients

Neurological disease (n, %)		**52 (37.1%)**
	Cerebral palsy	24
	Myelomeningocele	8
	Hypoxic ischemic encephalopathy	6
	Brain tumor	2
	West syndrome	2
	Hydrocephalus	2
	Herpes simplex virus encephalitis	1
	Encephalocele	1
	Metachromatic leukodystrophy	1
	Krabbe disease	1
	Holoprosencephaly	1
	Leigh syndrome	1
	Corpus callosum agenesis	1
	Canavan disease	1
Neuromuscular disease (n, %)		**41 (29.3%)**
	Spinal muscular atrophy	31
	Hypotonic infant	5
	Muscular dystrophy	3
	Mitochondrial myopathy	1
	Myasthenia gravis	1
Metabolic disease (n, %)		**17 (12.1%)**
	Neurometabolic Disease	11
	Mucopolysaccharidosis	1
	Congenital lactic acidosis	1
	Glutaric aciduria type 1	1

Table 1: Continue

Metabolic disease (n, %)		**17 (12.1%)**
	Tay-Sachs disease	1
	I-cell disease	1
	Sandhoff disease	1
Cardiopulmonary disease (n, %)		**12 (8.6%)**
	Asphyxia	7
	Bronchiolitis	2
	Laryngomalacia	2
	Foreign body aspiration	1
Syndromic disease (n, %)		**9 (6.4%)**
	Down syndrome	3
	Pierre Robin sequence	2
	DiGeorge syndrome	1
	Miscellaneous	3
Trauma (n, %)		**9 (6.4%)**
	Head trauma	5
	Traffic accident	4
Total (n, %)		**140 (100%)**

During the follow-up period, 18 patients were successfully weaned from mechanical ventilation. The median duration for successful weaning was 21 days (12-30.5 IQR). The median time to decannulation was 54 days (20.25-84 IQR) in four patients. None of the patients with neurologic and neuromuscular diseases were able to be decannulated. Fifty patients (35.7%) were discharged from the hospital. The median duration from tracheostomy to discharge was 73 days (30.25-132 IQR).

The overall mortality rate during follow-up was 70%, with 78% observed in infants and 64% in non-infants. No deaths were attributed to tracheotomy. When comparing patients who died to those who were alive during the last observation, there was no difference between the groups regarding their sex, nationality, chronic diseases, and tracheotomy timing (Table 2).

The analysis of infants and non-infants showed a tendency for more females in the infant group and more males in the non-infant group (p=0.037). No difference was found between the groups in terms of nationality, parental consanguinity, discharge rates, discharge times, and tracheotomy timing. The primary diagnosis showed a statistically significant difference between groups (Table 3). Post-hoc tests indicated a greater occurrence of neuromuscular disease in the infant group and a greater occurrence of neurological and metabolic disease in the non-infant group (Figure 2).

The survival analysis revealed a median survival of 214 (166-262 95% CI) days for all patients. The 1-year and 3-year survival rates for these patients were 0.319 and 0.158, respectively (Figure 3).

The median survival time for infant and non-infant groups was 147 days (119-175 95% CI) and 286 days (190-382 95% CI), respectively (Figure 4). Non-infants had a higher overall survival rate than infants (p=0.005). The survival rates at one year were 0.192 for the infants and 0.415 for the non-infants. Survival rates at three years were 0.076 and 0.217 in infants and non-infants, respectively.

Survival analysis based on parental consanguinity showed that the median survival was 214 (158-270 95% CI) days in patients with consanguineous parents and 285 (0-652 95% CI) days in patients without consanguineous parents (Figure 5). There was no statistically significant difference between these groups (p=0.084).

Table 2: Chronic diseases and demographics of the pediatric patients who were alive at last observation and died

	Alive at last observation (n=42)	Died (n=98)	p
Sex (n, %)			**0.373**
Female	21 (33.9)	41 (66.1)	
Male	21 (26.9)	57 (73.1)	
Nationality (n, %)			**0.564**
Turkish	34 (31.2)	75 (68.8)	
Syrian	8 (25.8)	23 (74.2)	
Primary diagnosis (n, %)			**0.108**
Neurological disease	17 (32.7)	35 (67.3)	
Neuromuscular disease	8 (19.5)	33 (80.5)	
Neurometabolic disease	8 (47.1)	9 (52.9)	
Cardiopulmonary disease	3 (25)	9 (75)	
Syndromic disease	1 (11.1)	8 (88.9)	
Trauma	5 (55.6)	4 (44.4)	
Tracheotomy timing, day (median, IQR)	319 (152 - 672)	146 (40 - 261)	0.752

IQR: interquartile range

Table 3: Chronic diseases and demographics of the infants and non-infants

	Infants (n=63)	Non-infants (n=77)	p
Sex (n, %)			**0.037**
Female	34 (54%)	28 (36%)	
Male	29 (46%)	49 (64%)	
Nationality (n, %)			**0.402**
Turkish	47 (75%)	62 (81%)	
Syrian	16 (25%)	15 (19%)	
Parental consanguinity (n, %)			**0.711**
Yes	28 (44%)	48 (62%)	
No	13 (21%)	19 (25%)	
Unknown	22 (35%)	10 (13%)	
Primary diagnosis (n, %)			**<0.001**
Neurologic disease	15 (23.8%)	37 (48.1%)	
Neuromuscular disease	30 (47.6%)	11 (14.3%)	
Trauma	2 (3.2%)	7 (9.1%)	
Metabolic disease	5 (7.9%)	12 (15.6%)	
Syndromic disease	7 (11.1%)	2 (2.6%)	
Cardiopulmonary disease	4 (6.3%)	8 (10.4%)	
Tracheotomy timing, day (median, IQR)	39 (27.0-76.0)	38 (24.5-73.5)	0.744
Discharged patients	22 (34.9%)	28 (36.4%)	0.859
Discharge timing, day (median, IQR)	73 (34-132)	65 (28.75-48.25)	0.953

IQR: interquartile range

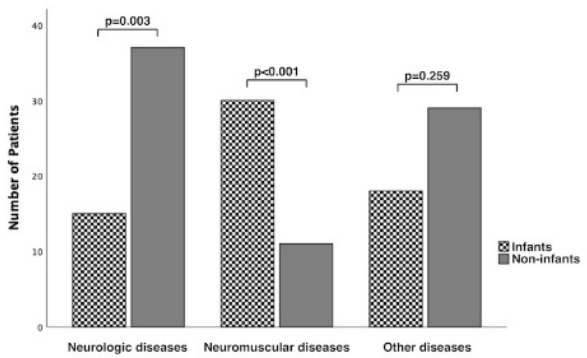

Figure 2: The bar graph represents the relationship between age groups (infants and non-infants) and primary diseases. Note that the p values obtained from post-hoc tests after the chi-square test

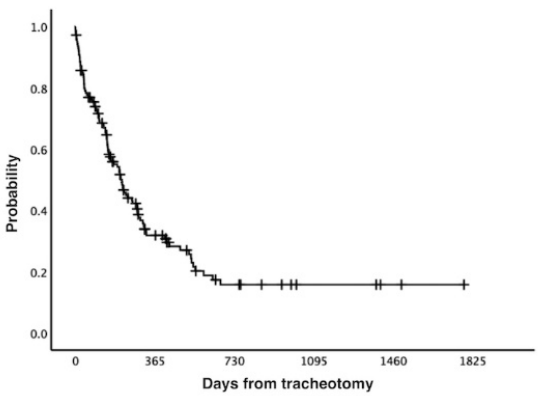

Figure 3: Kaplan-Meier survival curve of all patients after the time of tracheotomy

Survival analysis based on nationality showed that the median survival was 215 (172-258 95% CI) days in Turkish patients and 163 (69-257 95% CI) days in Syrian patients. Statistically significant differences in survival were not found between nationalities (p=0.693).

DISCUSSION

In this study, infants with tracheotomy had a lower survival than non-infants with tracheotomy. Non-infants were more likely to have neurologic and metabolic diseases, whereas infants were more likely to have neuromuscular diseases, thus primary diseases may be one of the factors that could cause the difference in survival.

Our study population had a high prevalence of neurological and neuromuscular diseases. Consanguineous marriage and low income status are risk factors for neurologic diseases (e.g., SMA and cerebral palsy) (7–9). Our hospital has patients from low-income populations and is located in the province with

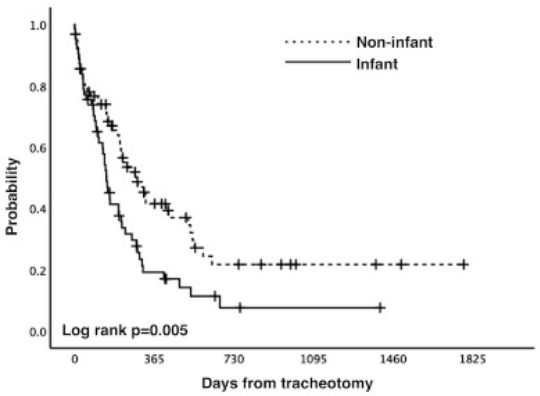

Figure 4: Kaplan-Meier survival curve of infants and non-infants after the time of tracheotomy

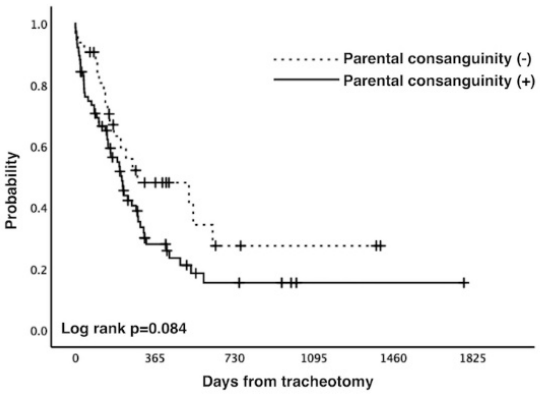

Figure 5: Kaplan-Meier survival curve of parental consanguinity status after the time of tracheotomy

the highest rate of consanguineous marriages (18.4%) in the country. A significantly elevated incidence of neurologic and neuromuscular conditions in our study was probably due to a very high rate of parental consanguinity (70%). Patients with parental consanguinity demonstrated a lower survival rate, although not statistically significant (p=0.084).

The indications for tracheotomy have changed in recent years from air-way compromises to neurologic diseases requiring prolonged ventilation (10). Additionally, patients who underwent tracheostomy due to neurological reasons have lower decannulation rates and a higher risk of mortality after being discharged (11). Therefore, analyzing the survival of tracheotomized pediatrics after discharge from the ICU and determining the prevalence of neurologic disease may provide a different perspective on the interpretation of mortality reported in the literature. Hebbar et al. revealed that the occurrence of neurological diseases was 24%, and the mortality rate was 27% (12). A 10-year study by McPherson et al. of pediatric tracheostomies found neurologic conditions were associated with higher mortality and lower decannulation rates than airway conditions (13). The study reported a neurological disease rate of 52% and a mortality rate of 23%. According to Funamura et al., bronchopulmonary dysplasia and congenital heart diseases were found to be predictors of mortality (14). Despite the rate of neurologic disease being 31.6%, their overall mortality rate (16.6%) was lower in comparison to the above studies. Salley et al. reported 16% mortality in patients under 3 years of age in their survival analysis, most of whom had respiratory failure (15). Akangire et al. conducted a study that found an overall mortality rate of 21%. The study also revealed that 70.6% of the reasons for tracheotomies were respiratory, and 6.86% were neurological (16). According to Cristea et al., the study revealed an 18.6% mortality rate in patients with severe bronchopulmonary dysplasia (17).

In our study, the mortality rate was 70%. The most common chronic disease group was neurological/neuromuscular disease (66%). In this context, it seems reasonable to assume that the mortality rate may increase as the primary diseases of patients shift from respiratory diseases to neurologic and neuromuscular diseases. Possible reasons for the high mortality found in this study are: (1) A high number of pediatric patients with complicated diseases were referred to our hospital from nearby hospitals, (2) Neurologic and neuromuscular diseases are prevalent in our ICU, (3) The low income status affecting home care, and (4) High rate of consanguineous marriages.

Evaluating the Kaplan-Meier overall survival curve in our study, most deaths occurred between 6-12 months after tracheotomy (Figure 2). Similar to our study, Hebbar et al. reported that although most of the primary diseases were cardiopulmonary diseases, the greatest decrease in survival occurred between 6-12 months in the survival analysis (12). They proposed that progression of the underlying disease, comorbidities, cannula dislocation, cannula plugging, tracheotomy-related accidents (e.g., bleeding), and inadequate post-discharge care are the factors leading to this situation. Despite the low discharge rate in our study, progressive neurologic, neuromuscular, and metabolic disease and increased pulmonary problems due to the low decannulation rate may have resulted in the greatest decrease in survival between 6 and 12 months.

Neonatal survival has increased over the years owing to the improvement in ICUs. These improvements led to an increase in congenital anomalies, followed by a rise in the rate of tracheotomy in infants from 41% to 63% in pediatrics (1,6). Therefore, infants deserve special consideration regarding tracheotomy outcomes in pediatrics. Berry et al. found higher in-hospital mortality in infants compared to patients aged 1-4 years in each year from 1997 to 2006 in their retrospective study of 18806 tracheotomized patients (18). Similarly, Sakai et al. reported increased overall mortality in the infant group in pediatrics (19). Our study also reveals that infants exhibited lower survival rates than non-infants.

This study has some limitations. In infants, mortality rates are higher when there is low birth weight and preterm birth (18,20). Since our hospital received a large number of referred patients from other hospitals and refugee patients from cross-border, factors such as preterm birth and low birth weight could not be analyzed in the study because the birth information of

most patients could not be reached. Furthermore, concerning the timing of tracheotomy, the delay in parental informal consent may have influenced the survival outcome of this study. The high mortality rate of our research, as opposed to the literature, demonstrates the strength of our study. Hence, this has highlighted that different socio-demographic characteristics may lead to different survival outcomes. Based on the limitations of this study, it is recommended that future studies on the survival of pediatrics with tracheotomy should examine sociodemographic characteristics in a thorough and comprehensive way.

CONCLUSION

The result of the present study showing that tracheotomized infants have a lower survival compared to tracheotomized non-infants is valuable because infants have become a peak group of pediatrics requiring tracheotomy in recent years. Nowadays, tracheotomy-related mortality has decreased in infants, whereas the risk of mortality after discharge increases due to the primary disease or the progression of primary disease, especially in neurologic and neuromuscular diseases. Therefore, family education on home care is critical for the caregivers of infants. In addition, if needed due to sociodemographic characteristics, the organization of educational programs on issues such as consanguineous marriage and prenatal diagnosis is important to reduce the frequency of diseases that predispose to tracheotomy in infants.

Ethics Committee Approval: This study was approved by Harran University Clinical Research Ethics Committee (Date: 21.03.2022, No: 06).

Informed Consent: Written informed consent was obtained.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- O.E., H.F.A., B.A.K., S.İ., A.Y.; Data Acquisition- O.E., H.F.A., B.A.K., S.İ., A.Y.; Data Analysis/Interpretation- O.E., H.F.A.; Drafting Manuscript- O.E., H.F.A.; Critical Revision of Manuscript- O.E., H.F.A., B.A.K., S.İ., A.Y.; Final Approval and Accountability- O.E., H.F.A., B.A.K., S.İ., A.Y.; Material or Technical Support- O.E., H.F.A.; Supervision- O.E., H.F.A., B.A.K., S.İ., A.Y.

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AIM AND SCOPE

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INSTRUCTION TO AUTHORS

The Turkish Journal of Ear Nose and Throat (Tr-ENT) is an international, scientific, open acces and peer-reviewed publication of Istanbul University. It is published quarterly in March, June, September and December. The publication language of the journal is English. The journal started off in 1990 under the editorship of Professor Behbut Cevanşir. Since then it has been a significant source of knowledge in the field of otorhinolaryngology for researchers, residents and specialists. As of year 2018 Volume 28 Issue 1, the title of the journal was changed from “Kulak Burun Boğaz İhtisas Dergisi” (ISSN: 1300-7475, E-ISNN: 2147-67569) to “The Turkish Journal of Ear Nose and Throat” and the journal decided to publish articles only in English with a frequency of four issues per year. The Turkish Journal of Ear Nose and Throat aims to contribute to the literature by publishing high quality original articles, case reports, surgical techniques and invited reviews focusing on key subjects and contemporary developments in the field. The scope of the journal includes otology, neurootology, rhinology, head and neck, general ORL, facial plastic surgery and laryngology. The journal welcomes articles from other disciplines as well, provided that these are related to the major subject area. The target audience of the journal consists of academicians, researchers, professionals, students, related professional and academic bodies and institutions. Former title of the journal: Kulak Burun Boğaz İhtisas Dergisi (P-ISNN: 1300-7475 / E-ISNN: 2147-6756)

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The subjects covered in the manuscripts submitted to the Journal for publication must be in accordance with the aim and scope of the Journal. Only those manuscripts approved by every individual author and that were not published before in or sent to another journal, are accepted for evaluation.

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All parties involved in the publishing process (Editors, Reviewers, Authors and Publishers) are expected to agree on the following ethical principles.

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Each manuscript is reviewed by at least two referees under double-blind peer review process. Plagiarism, duplication, fraud authorship/denied authorship, research/data fabrication, salami slicing/salami publication, breaching of copyrights, prevailing conflict of interest are unethical behaviors.

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- The research team and participants should be fully informed about the aim, methods, possible uses and requirements of the research and risks of participation in research.
- The confidentiality of the information provided by the research participants and the confidentiality of the respondents should be ensured. The research should be designed to protect the autonomy and dignity of the participants.
- Research participants should participate in the research voluntarily, not under any coercion.
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- The independence of research must be clear; and any conflict of interest or must be disclosed.
- In experimental studies with human subjects, written informed consent of the participants who decide to participate in the research must be obtained. In the case of children and those under wardship or with confirmed insanity, legal custodian's assent must be obtained.
- If the study is to be carried out in any institution or organization, approval must be obtained from this institution or organization.
- In studies with human subject, it must be noted in the method's section of the manuscript that the informed consent of the participants and ethics committee approval from the institution where the study has been conducted have been obtained.

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The Turkish Journal of Ear Nose and Throat (Tr-ENT) takes as principle to comply with the ethical standards of World Medical Association (WMA) Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects revised in 2003 and WMA Statement on Animal Use in Biomedical Research revised in 2016.

An approval of research protocols by the Ethics Committee in accordance with international standards mentioned above is required for experimental, clinical, and drug studies and for some case reports. If required, ethics committee reports or an equivalent official document will be requested from the authors. For manuscripts concerning experimental research on humans, a statement should be included that shows that written informed consent of patients and volunteers was obtained following a detailed explanation of the procedures that they may undergo. For studies carried out on animals, the measures taken to prevent pain and suffering of the animals should be stated clearly. Information on patient consent, the name of the ethics committee, and the ethics committee approval number should also be stated in the Materials and Methods section of the manuscript. It is the authors' responsibility to carefully protect the patients' anonymity. For photographs that may reveal the identity of the patients, signed releases of the patient or of their legal representative should be enclosed.

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All the authors of a submitted manuscript must have direct scientific and academic contribution to the manuscript. The author(s) of the original research articles is defined as a person who is significantly involved in "conceptualization and design of the study", "collecting the data", "analyzing the data", "writing the manuscript", "reviewing the manuscript with a critical perspective" and "planning/conducting the study of the manuscript and/or revising it". Fund raising, data collection or supervision of the research group are not sufficient roles to be accepted as an author. The author(s) must meet all these criteria described above. The order of names in the author list of an article must be a co-decision and it must be indicated in the Copyright Agreement Form. The individuals who do not meet the authorship criteria but contributed to the study must take place in the acknowledgement section. Individuals providing technical support, assisting writing, providing a general support, providing material or financial support are examples to be indicated in acknowledgement section.

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A reviewer who feels unqualified to review the topic of a manuscript or knows that its prompt review will be impossible should notify the editor and excuse himself from the review process.

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PEER REVIEW

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Only those manuscripts approved by its every individual author and that were not published before in or sent to another journal, are accepted for evaluation.

Submitted manuscripts that pass preliminary control are scanned for plagiarism using iThenticate software. After plagiarism check, the eligible ones are evaluated by editor-in-chief for their originality, methodology, the importance of the subject covered and compliance with the journal scope.

The editor hands over the papers matching the formal rules to at least two national/international referees for double-blind peer review evaluation and gives green light for publication upon modification by the authors in accordance with the referees' claims.

Responsibility for the Editor and Reviewers
Editor-in-Chief evaluates manuscripts for their scientific content without regard to ethnic origin, gender, citizenship, religious belief or political philosophy of the authors. Editor-in-Chief provides a fair double-blind peer review of the submitted articles for publication and ensures that all the information related to submitted manuscripts is kept as confidential before publishing.

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- Does the abstract clearly and accurately describe the content of the manuscript?
- Is the problem significant and concisely stated?
- Are the methods described comprehensively?
- Are the interpretations and consclusions justified by the results?
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Reviewers must ensure that all the information related to submitted manuscripts is kept as confidential and must report to the editor if they are aware of copyright infringement and plagiarism on the author's side.

A reviewer who feels unqualified to review the topic of a manuscript or knows that its prompt review will be impossible should notify the editor and excuse himself from the review process.

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Author(s) are required to submit the following documents together with the manuscript and must ensure that the abstract and keywords are in line with the standards explained in below.

- **Copyright Agreement Form**
- **Author Form and ICMJE Potential Conflict of Interest Disclosure Form**
- **Ethics Committee Approval**
- **Cover Letter to the Editor**
- **Title Page**: A separate title page should be submitted with all submissions and this page should include:

- The full title of the manuscript as well as a short title (running head) of no more than 50 characters,
- Name(s), affiliations, academic degree(s) and ORCID ID(s) of the author(s),
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- Acknowledgment of the individuals who contributed to the preparation of the manuscript but who do not fulfil the authorship criteria.

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Statistical analysis to support conclusions is usually necessary. Statistical analyses must be conducted in accordance with international statistical reporting standards (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983: 7; 1489-93). Information on statistical analyses should be provided with a separate subheading under the Materials and Methods section and the statistical software that was used during the process must be specified.

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

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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 the tables. Abbreviations used in the tables should be defined below the tables by footnotes (even if they are defined within the main text). Tables should be created using the "insert table" command of the word processing software and they should be arranged clearly to provide easy reading. Data presented in the tables should not be a repetition of the data presented within the main text but should be supporting the main text.

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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 can be used on the images to support figure legends. Like the rest of the submission, the figures too should be blind. Any information within the images that may indicate an individual or institution should be blinded. 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.

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When a drug, product, hardware, or software program is mentioned within the main text, product information, including the name of the product, the producer of the product, and city and the country of the company (including the state if in USA), should be provided in parentheses in the following format: "Discovery St PET/CT scanner (General Electric, Milwaukee, WI, USA)"

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

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Periodicals: Author(s) Last Name initial(s) name of author(s) (if there are six or fewer authors, all authors should be written; if the number of authors are seven or more, only the first six of the authors should be written and the rest as "et al"). The title of the article, the abbreviated name of the journal according to the Index Medicus, Year; Volume (Issue): The first and last page numbers.

Example: Robson A, Greene J, Ansari N, Kim B. Eccrine porocarcinoma (malignant eccrine poroma): a clinicopathologic study of 69 cases. The American Journal of Surgical Pathology 2001;25:710-20. Books: Surname of the author(s) initial name(s) of author(s). The name of the book. The edition number. Place of publication: Publisher, Publication year.

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Example: AB Author, CD Author. Title of document. Retrieved from http://Web address (Accession date: aa/bb/2016).

Congress papers:

Thesis: Maden KL. Experimental investigation of the ..... Master Thesis, Health Science Institute of Ankara University, Ankara, 2005.

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- Cover letter to the editor
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  - Including disclosure of any commercial or financial involvement.
  - Confirming that the statistical design of the research article is reviewed.
  - Confirming that last control for fluent English was done.
  - Confirming that journal policies detailed in Information for Authors have been reviewed.
  - Confirming that the references cited in the text and listed in the references section are in line with NLM.
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- Acknowledgement of the study "in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration.
- Statement that informed consent was obtained after the procedure(s) had been fully explained. Indicating whether the institutional and national guide for the care and use of laboratory animals was followed as in "Guide for the Care and Use of Laboratory Animals".
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  - The title of the manuscript
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  - All authors' names and affiliations (institution, faculty/department, city, country), e-mail addresses
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  - Abstract 200-250 words
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