ISSN: 2619-9793 • E-ISSN: 2148-094X

istanbul MEDICAL JOURNAL

İSTANBUL TIP DERGİSİ

VOLUME 23 • ISSUE 4 • November 2022

Original Articles

istanbulmedicaljournal.org

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İstanbul MEDICAL JOURNAL

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Publisher Certificate Number: 14521

Publication Date: November 2022
ISSN: 2619-9793 **E-ISSN:** 2148-094X
International periodical journal published three times in a year.

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

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İstanbul Med J 2022; 23(4): 237-40
DOI: 10.4274/imj.galenos.2022.78137

The Prevalence of Hypertension in Children and Adolescents and Affecting Factors

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ABSTRACT

Introduction: The incidence of hypertension (HT) has recently increased among children, and factors affecting the development of HT vary between regions; therefore, we determined the prevalence of high blood pressure (BP) and HT in children and adolescents in our region and risk factors affecting HT.

Methods: BP measurements were properly conducted in 3170 children and adolescents aged between seven and 17 years in our province. Children's BP measurements evaluated anthropometrically were also classified under the nomograms of the American Academy of Pediatrics-2017. Statistical analysis were evaluated regarding gender, age, and anthropometric values.

Results: HT was detected in 4.83% of 1592 children aged between seven and 12 years, and 7.6% of 1,578 children aged between 13 and 17 years, with a total rate of 6.21% (n=197). The risks of high BP and HT increased 1.231 times with a one-year increase in age ($p<0.001$). Likewise, the male gender also increases those risks 2,071 times, compared with the female gender ($p<0.001$). Compared to underweight participants, the risk of HT was observed to increase approximately six times among overweight individuals. Finally, obesity was also found to increase the risk of HT by approximately 26 times, compared with underweight individuals ($p<0.001$).

Conclusion: As a result, such effects as malnutrition, increase in age, and male gender were detected as the factors increasing the risk of HT development in children aged between seven and 17 years. The measurement of BP should be a part of routine physical examination in children and adolescents.

Keywords: Blood pressure, children, hypertension, obesity

Introduction

The fact that the prevalence of hypertension (HT) in childhood period is lower than that in adults may cause the physicians to pay less attention to childhood HT. It is now known precisely that HT detected in adulthood starts in childhood (1). Additionally, it has also been proven in many studies that having high blood pressure (BP) in childhood is a significant risk factor for developing chronic renal failure and cerebrovascular diseases, primarily atherosclerosis and cardiovascular diseases in adulthood (1).

In previous studies conducted to determine the prevalence of childhood HT, so different results have been obtained. The increase in BP is affected by various contributors, such as nutritional habits, socioeconomic status of families, and genetic and environmental factors (2). It is seen that there are differences between countries and even between regions of the same country, and so those differences in the prevalence of HT lead each region to determine its prevalence of childhood HT (3). However, different classification methods can be used in these studies. To prevent differences arising from the use of different classification criteria, current guidelines can be used to determine a common approach to the diagnosis and treatment of HT (1).

This study determined the prevalence of HT and the risk factors affecting BP in children and adolescents aged between seven and 17 years in our province, based on up-to-date guideline.

Methods

Study Population

After obtaining approval from the Konya University, Meram Faculty of Medicine Local Ethics Committee (approval number: 2012/29, date: 13.03.2012) and written informed parents' consent, 3,170 children between seven and 17 years of age were included in the study through the random sampling method from primary and high-school schools with similar socio-economic and cultural features. Both parents and the participants were informed about the voluntary participation and the design of the study. Those refusing to participate were excluded from the study.

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Cite this article as: Kılıçaslan C, Arslan Ş. The Prevalence of Hypertension in Children and Adolescents and Affecting Factors. İstanbul Med J 2022; 23(4): 237-40.

Received: 21.04.2022
Accepted: 24.08.2022

Assessments

The measurements of BP were performed at least thrice on the right arm of each child in the study in a calm and comfortable environment, and the average of three measurements was calculated for each child. In performing the measurements, the arm circumference of each child was measured from the middle of the arm, and the appropriate cuff was selected for the cuff length to be 80-100% of the arm circumference and for the cuff width to be 45-55% of the arm circumference. A benchtop mercury sphygmomanometer ERKA 3000 (ERKA, Kallmeyer Medizintechnik, Bad Tölz, Germany) was used to perform the measurements.

After choosing the appropriate cuff, the stethoscope was placed on the brachial artery as proximal and medial to the cubital fossa and at the lower end of the cuff while the child was in the sitting position. Attention was paid to ensure that the cubital fossa was at the level of the heart. The cuff was inflated to approximately 20 mmHg above the point of loss of pulse and deflated at a rate of 2-3 mmHg per second. During the measurements, the first stage of Korotkoff sounds (K1) heard as the cuff pressure was released was accepted as systolic BP. The point (K5) at which Korotkoff sounds disappeared and when the cuff pressure was sufficiently released to allow normal blood flow was accepted as diastolic BP.

The findings after the measurements were analyzed under the staging criteria standards released by the American Academy of Pediatrics in 2017 (AAP-2017) (4). Percentile curves were evaluated in terms of age and gender differences. While those in the 90-95th percentile or those having a value of BP above 120-80 mmHg despite <90th percentile were assessed to have high BP, that <95th percentile was accepted to be hypertensive. Additionally, those having a value of ≥95 P +12 mmHg or ≥140/90 mmHg were considered stage-2 HT. For the children evaluated to have HT and high BP, the measurements of BP were carried out three times more (six times), and the average measurements were recalculated. Those having the value of 90th percentile for both systolic and diastolic BP readings were considered normotensive.

The body mass index (BMI) values of the children who appropriately underwent the anthropometric evaluation concerning the height and weight measurements were calculated by the formula defined as a child's weight in kilograms divided by the square of the child's height in meters (kg/m^2). Based on the charts constituted for Turkish children by the age and gender differences, while the children below the 5th percentile and those between the 5th and 85th percentiles were defined as underweight and normal weight recently, those between the 85th and 95th percentiles and above the 95th percentile were evaluated as overweight and obese, respectively (4).

Statistical Analysis

Based on the statistics of the census database, it has been accepted that there are approximately 450,000 individuals between the seven and 17 age group, meeting the study inclusion criteria throughout the province of Konya. The information related to the prevalence of HT based on the literature was taken as approximately 6%, and the sample size to be reached such a rate with a 2% difference and 95% confidence interval (CI) was calculated as at least 2808 for the bilateral hypothesis at 0.80 power and 0.05 error level.

In evaluating the data obtained in the study, the Statistical Package for Social Sciences (SPSS) for Windows 21.0 software package was used to perform the statistical analyses (SPSS Inc., Chicago, IL, USA) (5). The calculation of the sample size, however, was performed using GPower (3.1.9.6, Franz Faul, Universintäl Kiel, Germany). In our study planned as a prevalence study, the descriptive statistics were summarized as the frequency distributions and percentages for categorical variables, and the mean ± standard deviation and the median (minimum-maximum) for continuous quantitative variables. The variables questioned and found significant as the risk factors affecting HT in our study were analyzed by the multiple logistic regression analysis, and the findings were stated with the odds ratios of 95% CI and the relevant p-values. The type-1 error rate was accepted as 0.05 for all statistical analyses.

Results

The demographic data and study findings of 3,170 children included in the study are presented in Table 1.

The mean age of 3,170 children was found as 12.68±3.26, and HT was detected in 77 (4.83%) of 1,592 children aged between seven and 12 years included in the study. Even so, in those aged between 13 and 17 years, HT was determined in 120 (7.6%) of 1,578 children.

In this study, the normotensive children and those diagnosed with high BP and HT were evaluated in terms of gender and weight status, and the statistical differences evaluated in the study are presented in Table 2.

High BP and risk factors affecting the status of HT were examined by the multiple logistic regression analysis, and the findings are shown in Table 3. Accordingly, when the age included in the model increases by one

Table 1. Data from the study

		n	%
Gender	Male	1624	51.23
	Female	1546	48.77
Percentile of BMI	Obese	339	10.69
	Overweight	370	11.67
	Normal weight	2255	71.14
	Underweight	206	6.50
Systolic HT	HT	190	5.99
	High BP	136	4.29
	Normal	2844	89.72
Diastolic HT	HT	65	2.05
	High BP	147	4.64
	Normal	2958	93.31
AAP 2017	HT	**197**	**6.21**
	Stage 1 HT	94	2.97
	Stage 2 HT	103	3.25
	High BP	141	4.45
	Normotensive	2832	89.34

AAP: American Academy of Pediatrics, BP: Blood pressure, BMI: Body mass index, HT: Hypertension

unit, the risks of high BP and contracting HT also increase 1,231 times, and the finding is statistically significant (p<0.001).

Similarly, when compared to the female gender, the male gender was seen to increase the risks of high BP and HT 2,071 times (p<0.001). It was also observed that compared to underweight status, overweight status was detected to increase the risk of HT approximately six times (p<0.001). Finally, obesity was determined as a factor increasing the risk of HT approximately 26 times, compared to the underweight (p<0.001).

Discussion

In this study, the rates of HT were detected as 4.83% in children aged between seven and 12 years, 7.6% in those aged 13 and 17 years, and 6.21% in those aged between seven and 17 years. In previous studies conducted in different countries and centers worldwide, the prevalence of HT varied between 1 and 11%. In a study by Kamath et al. (6) on 2,067 school children in South India in 2010, the prevalence of HT was emphasized to be 2.2%. Again, in another study conducted by Vivek and Singh (7) in the province of Gujarati in India in 2012, the prevalence of HT was found to be 9.2% in 1087 school children between five and 18 years of age. Under the report of AAP-2017, the prevalence of HT was announced as 9.4% (11.1% for boys and 7.5% for girls) (1). Many epidemiological studies have so far been conducted to determine the prevalence of HT in the different provinces of Turkey over the years. Although the prevalence of HT in children and adolescents varies between 0.6 and 14.4% in the studies conducted in Turkey, the study by Duzova et al. (8) found the frequency of HT as 6.1% in children aged between five and 18 years. However compatible our study results are with the findings detected both in Turkey and in the world, differences can be observed among the findings of those studies, and such differences can be attributed to the diversity of ethnic and genetic structures, the changes in socioeconomic status, the evaluation of different age groups, the changes seen in BP rates of age groups, and the different techniques used to measure BP (9).

In the study conducted in Western India by Buch et al. (10), it was reported that the prevalence of HT increases with age. In the same study, although the prevalence of BP was observed to increase after 10 years of age in girls (0.62% for <10 years, 8.67% for 10-13 years, and 8.48% for >13 years), BP prevalence elevated in boys following 13 years of age (5.88% for <10 years, 6.04% for 10-13 years, and 9.19% for >13 years). In our study, there was also a significant difference between the values of BP among the different age groups, and as the age increases by one unit, the risks of high BP and HT increase 1,231 times; in other words, the prevalence of HT was determined to increase with age.

Unfortunately, different studies investigating the association between BP and gender have found and reported different findings. While some studies found the mean BP values to be different, others detected BP values to be higher in boys or *vice versa*. However, the prominent view reported in previous studies is that the male gender has a higher rate of BP (1-11). In the study by Kamath et al. (6) with 2,067 school children in South India, the prevalence of HT was determined to be 2.1% in boys and 2.4% in girls, and no significant difference was reported between the genders. In a study conducted in Russia, however, it was found that the prevalence of HT was higher in children living in cold regions (12.7%), than those in the general population (12.7%), and it was also revealed that the rate of HT was higher in boys than that in girls (12). Based on the AAP-2017 criteria, statistically significant differences were

Table 2. The presentation of the data obtained from the study

n		HT		High BP		Normal		p
		%	n	%	n	%		
Gender	Male	116	58.88	91	64.54	1417	50.04	**<0.001**
	Female	81	41.12	50	35.46	1415	49,96	
Percentile of BMI	Obesity	102	51.78	34	24.11	203	7.17	**<0.001**
	Overweight	35	17.77	27	19.15	308	10.88	
	Normal weight	58	29.44	73	51.77	2124	75.00	
	Underweight	2	1.02	7	4.96	197	6.96	

BP: Blood pressure, BMI: Body mass index, HT: Hypertension

Table 3. The results were obtained through the multiple logistic regression analysis

	B	S.E.	Six.	Exp (B)	95% CI for exp (B)	
					Lower	Upper
Constant	-6.671	0.505	-	-	-	-
Age (years)	0.207	0.022	**<0.001**	1.231	1.178	1.285
Male	0.728	0.133	**<0.001**	2.071	1.597	2.685
Underweight	-	-	-	-	-	-
Obesity	3.260	0.370	**<0.001**	26.062	12.626	53.795
Overweight	1.912	0.376	**<0.001**	6.767	3.241	14.129
Normal weight	0.648	0.357	**<0.001**	1.911	0.949	3.849

CI: Confidence interval

found in high BP in terms of gender differences (11.8% for boys and 5.8% for girls) (1). In studies conducted at various centers, different findings were obtained about the effects of male and female genders on BP in children. In our study, the male gender has increased the risk of HT 2,071 times, compared with the female gender.

Although the underlying etiology is complex, obesity-related HT is a serious problem during the childhood period (13). Obesity and high sodium intake have been strongly reported to affect the prevalence of HT (14). The prevalence of obesity-associated HT in childhood is increasing rapidly worldwide as a crucial health problem (15). The frequency of HT increases 2.5-3.7 times among the children with BMI ≥90th percentile (16). Additionally, studies have shown that the rates of both systolic BP and diastolic BP are higher in obese children with insulin resistance (17). In our study, it was also observed that obese individuals face approximately 26 times higher risk of HT, compared to underweight individuals, and the overweight status increases the risk of HT approximately six times, compared to underweight individuals.

Study Limitations

Although the prevalence of HT was found to be 6.21% in our study, several studies have revealed that the frequency of HT decreases in repeated measurements performed due to the high measurements of BP, and therefore, the true prevalence is considered lower (18). To evaluate BP more appropriately, Ambulatory blood pressure monitoring is gaining vital importance in the diagnosis, treatment, and management of HT in childhood and adolescence (19). We consider that long-term studies are needed to elucidate the prevalence of HT and related factors.

Conclusion

In conclusion, while each one-year increase in age causes the risk of HT to increase approximately 1.2 times in children aged between seven and 17 years, such factors as male gender, being overweight, and obesity also elevate the risk of HT twice, six times and 26 times increases, respectively. As in adults, the measurement of BP should also be a part of routine physical examination in children.

Ethics Committee Approval: The study was approved by the Ethics Committee of Konya University, Meram Faculty of Medicine Clinical Research Ethics Committee (approval number: 2012/29, date: 13.03.2012).

Informed Consent: It was obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions: Concept - C.K., Ş.A.; Design - C.K., Ş.A.; Data Collection or Processing - C.K.; Analysis or Interpretation - C.K., Ş.A.; Literature Search - C.K., Ş.A.; Writing - C.K.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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İstanbul Med J 2022; 23(4): 241-6
DOI: 10.4274/imj.galenos.2022.69741

The Effect of Intratumoral Budding and Other Histological Features in Predicting Treatment Response in Breast Cancer Patients Receiving Neoadjuvant Therapy

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ABSTRACT

Introduction: Neoadjuvant chemotherapy (NAC) is used with increasing frequency in breast cancers. Various clinicopathological parameters predict treatment response (TR). Tumor budding (TB), which is a prognostic parameter in many cancers, can be considered the first stage of the metastatic process. In our study, the relationship between TR and clinicopathological parameters and TB in core biopsy samples of patients before NAC was investigated.

Methods: Seventy-four patients were included in our study. The association between the patients' TR and clinicopathological parameters such as estrogen (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), Ki67, molecular subtype, axilla metastasis was examined. All core biopsy specimens of the cases were evaluated, subsequently the area with the highest intratumoral budding (ITB) was determined, and finally ITB was counted in one area in a 20x objective. Cut-off was determined according to receiver operating characteristic analysis and cases were grouped as <4: low budding; ≥4: high ITB.

Results: High nuclear grade, ER and PR negativity, HER2 positivity, molecular groups, and absence of angiolymphatic invasion or axillary lymph node metastasis were statistically correlated with a complete response to treatment ($p<0.05$). ITB was not associated with TR ($p>0.05$). ITB correlated significantly with ER, PR positivity and luminal group molecular subtype ($p<0.05$).

Conclusion: ER, PR negativity, HER2 positivity, high Ki67, and high nuclear grade, invasive ductal carcinoma histological subtype were associated with complete TR, whereas ITB was not associated with TR. Further studies are required to elucidate the prognostic significance of ITB in core biopsy specimens.

Keywords: Intratumoral budding, neoadjuvant chemotherapy, treatment response, breast cancer, core biopsy

Introduction

Tumor budding (TB) can be considered as the initial stage of the metastatic process. In the metastatic process, cells lose their epithelial properties and gain mesenchymal properties, later invade and metastasize, ultimately in the tissue they metastasize, they gain epithelial properties again through the cancer stem cell properties in the tissue. It has been supported by many studies that TB, which can be easily evaluated in hematoxylin-eosin (H&E) sections, is a prognostic parameter, especially in colon cancers (1-3). In rectal tumors, tumors for which neoadjuvant chemotherapy (NAC) is commonly used, pre-NAC TB has been proven to be a predictive factor for poor response to NAC (4). Similarly, TB in esophageal squamous cell carcinoma has been reported to be associated with poor prognosis after neoadjuvant chemo-radiotherapy (5).

Although many studies have shown that TB in pre-NAC materials is a predictive parameter for treatment response in many cancers; there are a limited number of studies investigating the relationship of pre-NAC TB with treatment response in breast cancers. (4,5). Parameters associated with treatment response in pre-NAC core biopsy materials provide invaluable information to predict patients' NAC response and guide subsequent treatment selection in BCs.

Methods

Patient Selection and Clinicopathologic Evaluation

The study was approved by the Recep Tayyip Erdoğan University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (approval number: 2021/210, date: 27.12.2021). Written informed consent was obtained from each patient.

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Cite this article as: Öztürk Ç, Duman Öztürk S, Okcu O, Şen B, Yasin Aİ, Bedir R. The Effect of Intratumoral Budding and Other Histological Features in Predicting Treatment Response in Breast Cancer Patients Receiving Neoadjuvant Therapy. İstanbul Med J 2022; 23(4): 241-6.

Received: 15.04.2022
Accepted: 29.08.2022

By using the hospital database, patients who received NAC after core biopsy between January 2010 and December 2021 were identified. Among these patients, 74 patients who were operated on in our hospital after NAC were included in our study. The exclusion criteria were as follows: cases for which H&E sections of core biopsy and resection materials could not be found in the pathology archive, and cases whose clinical information and follow-up data could not be reached.

The age, gender, development of metastasis and recurrence, and survival information of the cases were obtained from the hospital database, and tumor size and axillary lymph node status were acquired from the pathology reports. Tumor grade, presence of angiolymphatic invasion, and perineural invasion were determined by re-evaluating H&E sections.

Our cases were divided into molecular subtypes as luminal A (LA), luminal B (LB), human epidermal growth factor receptor 2 (HER2), and triple negative (TN). Over 1% staining for estrogen (ER) and progesterone receptor (PR) in immunohistochemical staining and more than 10% complete and membranous staining for HER2 in tumor cells were considered positive. The cut-off for the Ki67 proliferation index was taken as 14% and below this value was accepted as low and above it as high (6). In our study, there were cases diagnosed with invasive ductal carcinoma (IDC) and invasive lobular carcinoma (ILC) according to the World Health Organization breast cancer classification (7).

Cases were graded according to the Nottingham histological-grade scoring system (7). The response to treatment in the resection materials of the cases was classified into three categories, according to the American Joint Committee on Cancer. Accordingly, the cases were classified as having no residual tumor, partial response, and no response to treatment in resection material (8). Since the number of cases was low, cases with no response and cases with partial pathological responses to treatment were included in the same category. The relationship between the patient's response to treatment and clinicopathological parameters such as ER, PR, HER2, Ki67, molecular subtype, and axilla metastasis was investigated.

Assessment of Tumor Budding

Although TB has been defined differently in diverse studies, it is generally defined as up to 5 tumor cell groups separated from the main tumor mass (9,10). If TB is evaluated at the invasive edge of the main tumor, it can be named peritumoral budding. If it is evaluated within the main mass of the tumor, it can be named intratumoral budding (ITB). In the literature, TB was studied solely in IDC cases in studies based on tumor morphology. In our study, ITB was evaluated only in cases of IDC, since only morphology was evaluated without additional immunohistochemical studies. Due to its easy application in routine pathology practice, ITB counting was performed as recommended by the International Tumor Budding Consensus Conference 2016. All core biopsy specimens of the cases were evaluated by two pathologists (Ç.Ö., S.D.Ö.), the area with the highest ITB in these samples was determined in a 10x objective, and ITB was counted in one area in a 20x objective (Olympus, BX-51, ocular 22 mm, field size 0.950 mm^2) (11). The cases with different scores were re-evaluated under the double-headed microscope, and a third pathologist opinion (O.O.) was obtained where no consensus could be reached. Examples of cases with low and high budding are seen in Figure 1a, b. The ITB cut-off value was determined by performing a receiver operating characteristic (ROC) analysis based on the response to treatment. Cases were divided into low and high ITB groups according to the determined cut-off (Figure 1c).

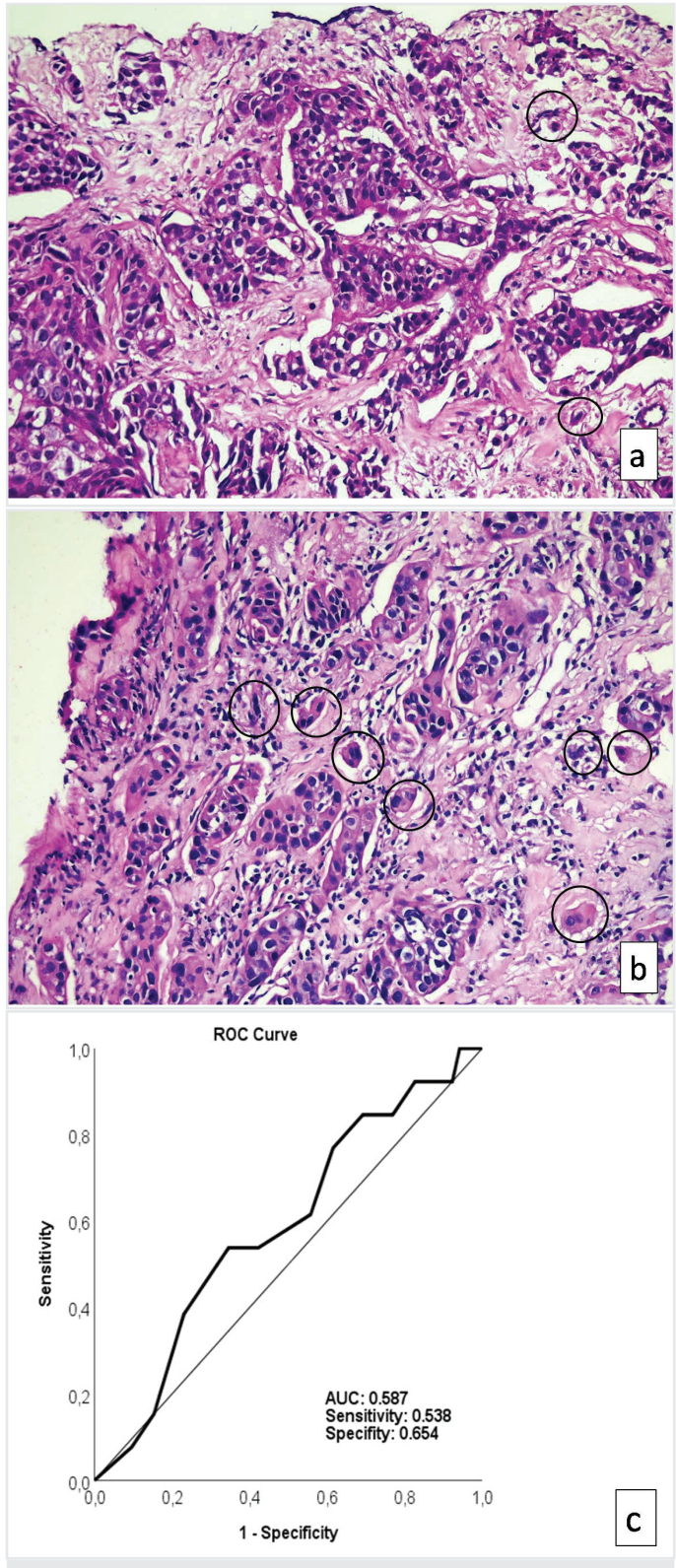

Figure 1. Low (a), high (b) intratumoral budding samples of patients (H&E, x200) (tumor budding shown in circle) and ROC analysis (c) with tumor budding values and treatment response status
H&E: Hematoxylin-eosin, ROC: Receiver operating characteristic, AUC: Area under the curve

Statistical Analysis

Statistical analyses were performed using the SPSS program (IBM, SPSS Inc., Version 23.0, Chicago, USA). The optimum cut-off value was established by ROC analysis for the number of tumor buds of the patients, considering treatment response status. Based on the defined cut-off value, the patients were split into two categories as low and high TB groups. Descriptive statistics of categorical variables were reported as frequency and percentage (n, %). The relationship between categorical variables was evaluated with the chi-square test (Pearson chi-square and Fisher's exact test) considering the size of the patient groups in the categories.

Kaplan-Meier method and Log-rank test were carried out to analyze the correlation between tumor buds and survival in patients with breast cancer. A p-value of <0.05 was considered for statistical significance.

Results

General Characteristics

All 74 patients were female and their ages ranged from 33 to 84, with a mean age of 57. Among the core biopsy samples examined, 67 patients (90.5%) were diagnosed with IDC, whereas 7 patients (9.5%) were diagnosed with ILC. While 20 cases (27.0%) were LA, 35 cases (47.3%) were LB. 8 cases (10.8%) were HER2+, 11 cases (14.9%) were TN. When the response to treatment was evaluated, no response was observed in 8 cases (10.8%), a partial response was observed in 37 cases (50.0%), and complete response was observed in 29 cases (39.2%).

Treatment Response and Clinicopathological Parameters

When the relationship between the response and treatment and clinicopathological parameters was examined, the ratio of complete response to treatment was statistically low in ILCs ($p<0.05$). Additionally, high nuclear grade, ER, PR negativity, HER2 positivity, molecular groups, absence of angiolymphatic invasion, and axillary lymph node metastasis were statistically associated with a complete response to treatment ($p<0.05$). ITB and treatment responses were not correlated ($p>0.05$). The relationship between the response to treatment and clinicopathological parameters is shown in Table 1.

ITB and Prognostic Associations with Outcome

In the ROC analysis performed with ITB and treatment response, the low and high ITB cut-off were found to be 3.5/0.950 mm^2 (area under the curve: 0.587; 0.538 and 0.654 for sensitivity and specificity) (Figure 1c). Accordingly, 42 (≥4; 62.7%) of the cases contain high ITB, 25 (<4; 37.3%) low ITB.

Thirty-eight (56.7%) patients had partial or no response to treatment; 29 (43.3%) had a complete response to treatment. There was partial or no response in 26 patients (61.9%) with high ITB, whereas 16 patients (38.1%) had a complete response. No statistically significant correlation was found between ITB and response to treatment ($p=0.267$) (Table 1).

When the relationship between ITB and clinicopathological parameters was examined, it was found that high ITB was associated with ER, PR positivity, and the luminal group ($p<0.05$). The relationship between ITB and clinicopathological parameters is shown in Table 2.

Even when performing Kaplan-Meier curve for DFS and OS; trend was seen toward a worse DFS and OS for patients with low ITB compared to patients with high ITB ($p=0.118$, $p=0.309$); however, there was no statistically significant difference.

Discussion

NAC is used with increasing frequency in locally advanced breast cancers (10). While the survival of patients with a complete pathological response to NAC is excellent, the recurrence and death rates of patients without a complete response are higher (13). For this reason, it is critical to examine all pathological features in the core biopsy materials of patients before NAC to determine the parameters that predict treatment response.

The most common histological subtype of all breast cancers is IDC, and NAC regimens are well established in IDCs. However, in other histological subtypes, which are less frequent, the information on the relationship between NAC and treatment response is unclear yet (14-16). Nagao et al. (14) evaluated 562 patients in their study and found that IDCs responded better to NAC than other special types. Similarly, most patients in our study were IDC, s and IDCs had a better response to NAC than ILC. These results may lead to the development of new treatment options according to the histological subtype in the selection of NAC.

Nottingham histological scoring system is used for grading breast carcinomas, and the interobserver agreement is low in this system (17). Therefore, most of the cases in our study were in grade 2. However, when the relationship between treatment response and grade was investigated, the rate of complete response to treatment in grade 1 cases was low. There was a complete response to treatment in approximately 77% of grade 3 cases. In a study of 353 patients, Jarzab et al. (17) found that high nuclear grade, mitosis, Ki67, ER, PR positivity, and TN status were associated with a complete response to treatment. The nuclear grade was an independent prognostic factor in their study (17). These results contribute to the predictive value of nuclear grade in the NAC response.

Ki67, which is a marker that indicates cell proliferation, reflects the G1, S, G2, and M phases of cells and is not expressed in resting-phase G0 cells. NAC's target cells. Therefore, it is an expected result that patients with a high Ki67 will benefit more from NAC (18). Many studies with contradictory results have investigated the relationship between the Ki67 level and NAC response. While some studies have argued that high Ki67 is not associated with a complete response; many other studies found the Ki67 as an independent prognostic factor for NAC response (18-20). As expected, the rate of complete response to treatment was high in patients with high Ki67 in our study.

The predictivity of many parameters in predicting the NAC response is still controversial. However, the predictive value of molecular subtypes has been proven. Accordingly, HER2 and TN subtypes respond better to NAC than ER+ luminal types. In our study, the ratio of a complete response to NAC was significantly lower in ER, PR positivity, and HER2 negativity. Based on these results, the distribution according to molecular subtypes was evaluated, the complete response ratio was significantly lower in the ER+ luminal group, whereas the complete

Table 1. Correlation between treatment response and clinicopathological parameters

		Treatment response				
		No response/partial response		Complete response		p-value
		Count	Column, (n %)	Count	Column, (n %)	
Histological types	IDC	38	84.4	29	100.0	0.038
	ILC	7	15.6	0	0.0	-
Intratumoral budding	Low budding	12	48.0	13	52.0	0.267
	High budding	26	61.9	16	38.1	-
Nuclear grade	Grade 1	15	33.3	2	6.9	0.005
	Grade 2	27	60.0	19	65.5	-
	Grade 3	3	6.7	8	27.6	-
ER expression	ER negative	8	17.8	13	44.8	0.012
	ER positive	37	82.2	16	55.2	-
PR expression	PR negative	10	22.2	16	55.2	0.004
	PR positive	35	77.8	13	44.8	-
HER2 expression	HER2 negative	30	66.7	15	51.7	0.023
	HER2 positive	10	22.2	14	48.3	-
	HER2 unknown	5	11.1	0	0.0	-
Ki67	Low	13	30.2	1	4.3	0.024
	High	30	69.8	22	95.7	-
Molecular subtype groups	LA + LB	38	84.4	17	58.6	0.013
	HER2 + TN	7	15.6	12	41.4	-
Anjiolymphatic invasion	Negative	24	53.3	24	82.8	0.01
	Positive	21	46.7	5	17.2	-
Perineural Invasion	Negative	36	80.0	28	96.6	0.078
	Positive	9	20.0	1	3.4	-
Lymph node metastasis	Negative	17	37.8	20	69.0	0.017
	Positive	28	62.2	9	31.0	-
Metastasis	Negative	27	65.9	28	96.6	0.002
	Positive	14	34.1	1	3.4	-
Death status	Alive with/no disease	35	85.4	28	96.6	0.226
	Death of disease	6	14.6	1	3.4	-

IDC: Invasive ductal carcinoma, ILC: Invasive lobular carcinoma, ER: Estrogen, PR: Progesterone receptor, HER2: Human epidermal growth factor receptor 2, LA: Luminal A, LB: Luminal B, TN: Triple negative

response ratio was significantly higher in the HER2 and TN groups in line with the literature (21,22).

TB in breast cancers, especially in TN breast cancers, was associated with a worse prognosis compared to the ER+ subtype (23). Similarly, although studies in which high TB presence was associated with poor prognosis in breast cancers are available in the literature, limited studies have investigated the relationship between treatment response and prognosis in pre-NAC TB. Mozarowski et al. (1), in their study comprising 75 patients with different molecular subtypes, argued that ITB did not predict the effectiveness of NAC. Although the rate of complete response to treatment decreased in the presence of high ITB in our study, this was not statistically significant. However, in survival analyses, it was noted that patients with a high ITB in both OS and DFS tended to have better survival. When the relationship between ITB and clinicopathological parameters was evaluated, ER, PR positivity, and accordingly, luminal group status was associated with high ITB. Similar to our results, Gujam et al. (9) found that ER, PR positivity, and HER2 negativity were associated with high TB in their study consisting of 471 patients. Additionally, in a study by Salhia et al. (23) ER, PR positivity and HER2 negativity were associated with high budding (24).

While a significant relationship was found in resection materials between TB and prognostic parameters, the reason why no relationship was found in our study may be the difficulty of distinguishing ITB in core biopsy materials. Because TB defines cells that lose their epithelial properties and gain mesenchymal properties, these cells are evaluated in the intratumoral area since the invasive margin cannot be selected in the core biopsy materials. In the intratumoral area, it is almost impossible to distinguish cells that acquire mesenchymal features from small tumor nests. It has been reported in the literature that antigens such as ZEB1, ZEB2, SNAIL, TWIST can be used to indicate epithelial-

Table 2. Intratumoral budding and clinicopathological parameters

		Intratumoral budding				
		Low budding (<4)		High budding (≥4)		p-value
		Count	Column (n, %)	Count	Column (n, %)	
Nuclear grade	Grade 1	3	12.0	11	26.2	0.09
	Grade 2	15	60.0	27	64.3	-
	Grade 3	7	28.0	4	9.5	-
ER expression	ER negative	14	56.0	7	16.7	0.001
	ER positive	11	44.0	35	83.3	-
PR expression	PR negative	15	60.0	9	21.4	0.001
	PR positive	10	40.0	33	78.6	-
HER2 expression	HER2 negative	18	72.0	20	47.6	0.071
	HER2 positive	7	28.0	17	40.5	-
	HER2 unknown	0	0.0	5	11.9	-
Ki67	Low	2	8.7	9	25.0	0.174
	High	21	91.3	27	75.0	-
Molecular subtype groups	LA + LB	11	44.0	37	88.1	<0.001
	HER2 + TN	14	56.0	5	11.9	-
Anjiolymphatic invasion	Negative	16	64.0	27	64.3	0.981
	Positive	9	36.0	15	35.7	-
Perineural invasion	Negative	20	80.0	38	90.5	0.277
	Positive	5	20.0	4	9.5	-
Lymph node metastasis	Negative	17	68.0	18	42.9	0.046
	Positive	8	32.0	24	57.1	-
Metastasis	Negative	18	72.0	34	85.0	0.202
	Positive	7	28.0	6	15.0	-
Death status	Alive with/no disease	21	84.0	37	92.5	0.415
	Death of disease	4	16.0	3	7.5	-

ER: Estrogen, PR: Progesterone receptor, HER2: Human epidermal growth factor receptor 2, LA: Luminal A, LB: luminal B, TN: Triple negative

mesenchymal transition (25). However, since immunohistochemistry is not cost-effective, our study was based only on the light microscopic examination to obtain an opinion.

Study Limitations

Our study included various limitations. The cases were not homogeneously distributed and we may not have been able to obtain significant results because of the small number of different molecular subtypes, particularly HER2 and TN breast cancer cases.

Conclusion

Core biopsy materials are the only material reflecting the morphological features of pre-NAC cases, therefore all features in these samples are precious. ER, PR negativity, HER2 positivity, high Ki67, and high nuclear grade, IDC histological subtype was associated with a complete response to treatment, whereas ITB was not associated with treatment. More reliable results may be obtained if additional immunohistochemical studies are conducted to differentiate ITB from small tumor cell nests.

Ethics Committee Approval: The study was approved by the Recep Tayyip Erdoğan University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (approval number: 2021/210, date: 27.12.2021).

Informed Consent: Written informed consent was obtained from each patient.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions: Concept - Ç.Ö., O.O., A.İ.Y., R.B.; Design - Ç.Ö., S.D.Ö., O.O., B.Ş., R.B.; Data Collection or Processing - Ç.Ö., S.D.Ö., O.O., B.Ş., R.B.; Analysis or Interpretation - Ç.Ö., S.D.Ö., B.Ş., A.İ.Y., R.B.; Literature Search - Ç.Ö., A.İ.Y.; Writing - Ç.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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İstanbul Med J 2022; 23(4): 247-53
DOI: 10.4274/imj.galenos.2022.03342

Unusual Histopathological Findings in Cases with a Preliminary Clinical Diagnosis of Acute Appendicitis: What was Expected, What Did We Discover?

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ABSTRACT

Introduction: The most common cause of acute abdomen is appendicitis. Besides lymphoid hyperplasia and fecalith, less common lesions such as diverticulum, endometriosis, infectious agents, preneoplastic and neoplastic lesions are also in the etiology of acute appendicitis. Our aim is to document the findings after histopathological examination of appendectomy materials and to detect the lesions, which we call other diagnoses.

Methods: The findings were divided into four groups as acute appendicitis, perforated appendicitis, lymphoid hyperplasia and "other diagnosis" in the appendectomy materials. Other diagnoses were also divided into two subgroups: Group 1 consisted of cases of acquired and anatomical abnormalities, chronic appendicitis, infectious agents and miscellaneous lesions. Group 2 consisted of serrated lesions, carcinomas, neuroendocrine neoplasia, mesenchymal tumor and secondary neoplasia.

Results: Our study was conducted in 4,335 appendectomy materials and there were 562 (12.96%) cases in the "other diagnosis" group. Group 1 consisted of cases with diverticula (5.74%), fibrous obliteration (2.84%), skip lesion of ulcerative colitis (0.02), granulomatous inflammation (0.07%), enterobius vermicularis (0.55%), endometriosis externa (0.16%), and amyloid deposition (0.05%), while group 2 comprised cases with hyperplastic polyp (0.53%), sessile serrated adenoma (0.83%), low-grade mucinous neoplasia (0.28%), neuroendocrine cell proliferation (0.28%), neuroendocrine tumor (NET) (1.2%), gastrointestinal stromal tumor (0.02%), and secondary neoplasia (0.39%).

Conclusion: In our study, most commonly, we detected diverticula and the most frequently found neoplastic lesion was NETs. Recently, due to the increased awareness of the presence of serrated lesions, the rate of diagnosis of these cases has also increased. In addition to neoplastic lesions detected because of histopathological examination of appendiceal materials, lesions characterized by parasitosis, endometriosis externa and granulomatous inflammation, as well as cases that require sustained treatment and follow-up will not be skipped.

Keywords: Acute appendicitis, amyloid, endometriosis externa, neuroendocrine tumor, serrated lesion, low-grade mucinous neoplasia

Introduction

The most important factor causing appendicitis is luminal obstruction. The factors responsible for its formation include lymphoid hyperplasia in those under 20 years of age and fecaloid plug in the elderly, although rare lesions such as parasites and neoplasia are also seen, albeit rarely (1-4).

Despite the advances in imaging methods, histopathological examination maintains its importance in guiding diagnosis and treatment in appendectomy materials (5). In addition to confirming the diagnosis of appendicitis, a histopathological examination can also enable the recognition of less common lesions (1-4,6). Rare lesions detected in appendectomy materials are diverticulum, fibrous obliteration, infectious agents, endometriosis externa, and preneoplastic and neoplastic lesions such as serrated lesions, low-grade mucinous neoplasia (LGMN), neuroendocrine neoplasia, mesenchymal tumor, and secondary neoplasms. The reported incidence rates for such lesions range from 0.9% to 8.3% in the literature (1,2,5). While some studies reported that the most common among these lesions were enterobius vermicularis, it was fibrous obliteration in some others (1,2,5). The most common neoplasm was neuroendocrine tumor (NET), followed by LGMN (2,4-6).

We described rare lesions that were diagnosed during routine histopathological examinations of appendectomy materials and play a role in the etiology of appendicitis and present them with clinical and epidemiological findings.

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Cite this article as: Erhan SŞ, Dobral A, Kulduk G, Alemdar A. Unusual Histopathological Findings in Cases with a Preliminary Clinical Diagnosis of Acute Appendicitis: What was Expected, What Did We Discover? İstanbul Med J 2022; 23(4): 247-53.

Received: 18.02.2022
Accepted: 01.09.2022

Methods

The study involved patients who were operated on with a diagnosis of acute appendicitis between January 2011 and June 2021. Incidental appendectomy materials performed during other surgical procedures were also included (such as colorectal and gynecological cancer surgery). The cases' demographic characteristics (age and gender) were retrieved from the hospital's electronic record system. All sections of biopsy materials (hematoxylin-eosin (H&E) and histochemical and immunohistochemical markers) were reviewed.

Based on the histopathologic findings, the appendectomy specimens were classified into four groups; acute appendicitis, perforated appendicitis, lymphoid hyperplasia and "other diagnosis". The other diagnoses category was also classified into two subgroups (3,4).

The first group includes acquired and anatomical abnormalities, chronic appendicitis, infectious agents, and miscellaneous lesions. The second group, which includes preneoplastic and neoplastic lesions, includes serrated lesions, carcinoma, neuroendocrine neoplasia, mesenchymal tumors, and secondary neoplasia.

On microscopic examination, fibrous obliteration in the first group was divided into subtypes as central obliterative neuroma, intramucosal appendiceal neuroma and submucosal obliterative neuroma. Additional studies on the etiology of granulomatous appendicitis in the group defined as chronic appendicitis included endoscopic examination as well as microbiologic examinations for infectious agents (tuberculosis, etc.). In the second group, the positivity of the surgical margin and the mucosal depth of the lesion (lamina propria or muscularis mucosa location) were evaluated in LGMN, which is among the neoplastic lesions. In NET cases, tumor size of 2 cm or more, mesoapendiceal or vascular invasion and positive surgical margin, which are among the risk parameters for recurrence, were evaluated. In addition to location, size and mitotic activity, which are prognostic factors defined for GIST, were evaluated.

Finally, the cases included in both groups were grouped as pediatric (0-17 years) and adult (18 years and older) according to age. Informed consent was obtained from the patients for the publication of this study. The ethics committee approval was granted by the Ethics Committee of University of Health Sciences Turkey, Okmeydanı Training and Research Hospital (approval number: 810, date: 23.01.2018).

Statistical Analysis

The data were presented with frequency distribution (number, percentage) for categorical variables, and descriptive statistics (mean, standard deviation) for numerical variables. An Independent sample t-test was used to determine whether there was a difference between the two groups. The level of significance was $p<0.05$ in the statistical evaluation.

Results

General Characteristics of Appendectomy Materials

The study included appendectomy materials from 4,335 cases. Of the cases, 2,379 (54.9%) were male and 1,956 (45.1%) were female. Their age ranged from 2 to 90 years.

Histopathological examination revealed that 3,256 patients (75.11%) were in the acute appendicitis group (acute + suppurative), 418 (9.64%) were in the perforated appendicitis group, 99 (2.29%) were in the lymphoid hyperplasia group, and 562 (12.96%) were in the "other diagnoses" group.

The general distribution of diagnoses based on histopathological examination of appendectomy materials is given in Table 1.

The Group of "Other Diagnoses"

Thirty of 562 cases were in the pediatric age group in this group. Of the cases, 372 (66.2%) were male and 190 (33.8%) were female. The age ranged from 4 to 90 years.

In the first group, diverticulosis (n=249, 5.74%) (Figure 1) and fibrous obliteration (n=123, 2.84%) in the subgroup of acquired and anatomical anomalies, skipped lesion of ulcerative colitis (n=1, 0.02%) and granulomatous inflammation (n=3, 0.07%) in the subgroup of chronic appendicitis, enterobius vermicularis (n=24, 0.55%) in the subgroup of infectious agents, endometriosis externa (n=7, 0.16%) (Figure 2) and amyloid deposition (n=2, 0.05%) (Figure 3) in the subgroup of miscellaneous lesions were included.

In the second group including the preneoplastic lesions and tumors, hyperplastic polyp (n=23, 0.53%) and sessile serrated adenoma (SSA)

Table 1. The distribution of patients according to diagnosis

	n	%
Acute appendicitis (acute + suppurative)	3,256	75.11
Perforated appendicitis	418	9.64
Lymphoid hyperplasia	99	2.29
Other (unusual) diagnoses	562	12.96
Total	4,335	100

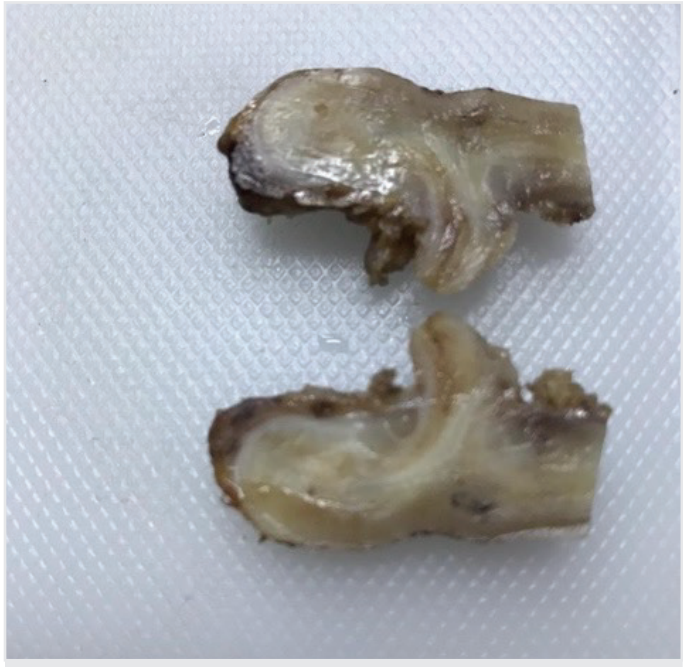

Figure 1. Diverticulosis found incidentally in the sections of the appendix

(n=36, 0.83%) in the subgroup serrated lesions (Figure 4), LGMN (n=12, 0.28%) in the subgroup carcinoma (Figure 5), neuroendocrine cell proliferation (NCP) (n=12, 0.28%) and NET (n=52, 1.2%) in the subgroup neuroendocrine neoplasia, gastrointestinal stromal tumor (GIST) (n=1, 0.02%) in the subgroup of mesenchymal tumors (Figure 6) and secondary neoplasm (n=17, 0.39%) subgroups were involved.

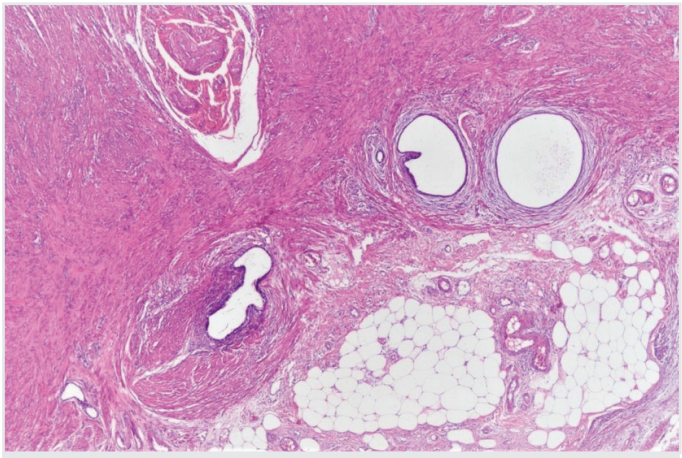

Figure 2. Endometriosis externa. The presence of endometrial glands and stroma in the appendiceal wall (H&E, x40)
H&E: Hematoxylin and eosin

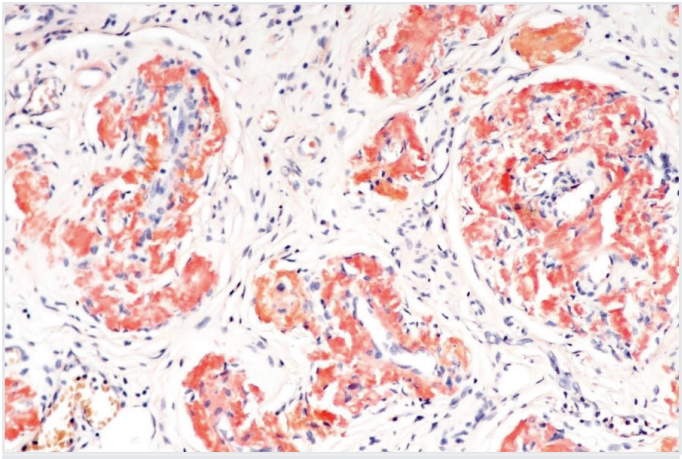

Figure 3. Amyloidosis. Amyloid deposits found in vascular walls (Congo red, x200)

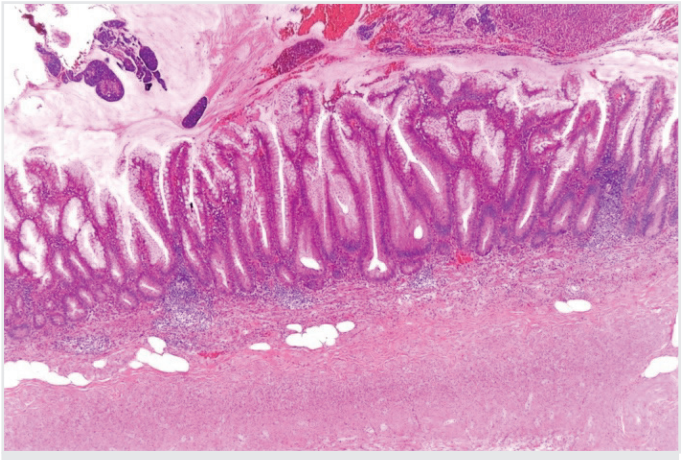

Figure 4. Sessile serrated adenoma. Showing abnormal crypt proliferation, elongation and basal crypt dilatation (H&E, x40)
H&E: Hematoxylin and eosin

Clinicopathological Features of the Other Diagnoses Group

While endometriosis externa, amyloid deposition, LGMN and secondary neoplasia were observed more frequently in women, diverticula, fibrous obliteration, skip lesion of ulcerative colitis, granulomatous inflammation, enterobius vermicularis, hyperplastic polyp, SSA, NHP, NET and GIST were more often observed in men.

Histopathological examination revealed that diverticulum, which was in the subgroup of acquired and anatomical abnormalities in the first group, was the most common rare lesion with a rate of 5.74%. Fifty-six (22.5%) of the cases had perforation and 39 (15.7%) had inflammation. NET, SSA, NCP, and endometriosis externa were secondary lesions accompanying the diverticulum. In the fibrous obliteration group, there was central obliteration, one of its subtypes, in 114 (92.7%) cases, whereas nine (7.3%) had intramucosal obliteration with nodular proliferation.

In the second group, a case with a diagnosis of hyperplastic polyp in the serrated lesion group was accompanied by NCP, while other lesions accompanying the SSA were diverticulum, NCP and GIST. Cases with a diagnosis of hyperplastic polyp were mostly in their 50s, and cases with a diagnosis of SSA were in their 59s. There was no significant difference in terms of mean age (p=0.089) and gender (p=0.155).

In LGMN cases, the lesion is limited to the muscularis propria. No positive surgical margin, appendiceal rupture, mucin, or atypical cells outside the appendix were detected. Two of the cases with LGMN in the carcinoma subgroup were accompanied by NET as secondary neoplasia.

Hyperplastic polyps and diverticula were other accompanying lesions in two of the cases diagnosed with NCP in the subgroup of neuroendocrine neoplasia. The number of cases diagnosed with NET was 52, and 45 of the cases were grade 1 (G1) and seven were G2. The mean tumor diameter was 0.68 cm (0.1-2.5 cm). Tumor size was 2 cm and in two cases. The tumor was located in the apex of 37 cases, in the body part of ten, and the apex + body part of five. The tumor spread to the mucosa

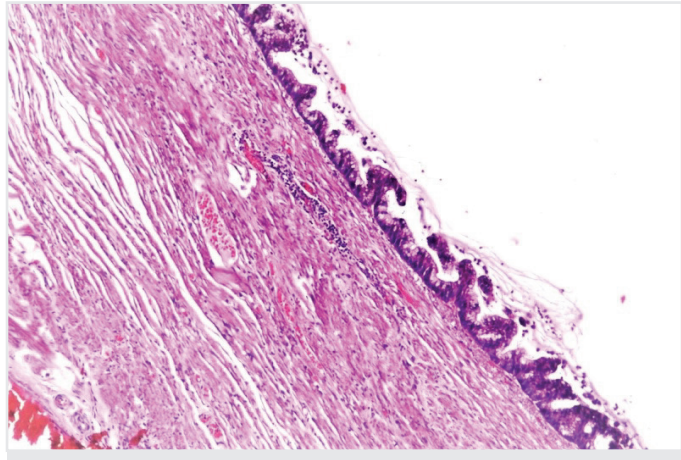

Figure 5. Low-grade mucinous neoplasm. Showing fibrous stroma covered by dysplastic epithelial cells (H&E, x20)
H&E: Hematoxylin and eosin

in nine, submucosa in five, muscle in 18, and subserosa/mesoappendix in 20. There was no vascular invasion and the surgical margins were free. Accompanying lesions were the diverticulum, LGMN, and SSA. We did not find a significant difference between the cases diagnosed with NET and NCP in terms of mean age (p=0.333) and gender (p=0.739). Similarly, there was no significant difference between the cases diagnosed with NET G1 and G2 in terms of mean age (p=0.382) and gender (p=0.397).

GIST, which is in the mesenchymal tumor subgroup, was centered within the muscularis propria reaching up to the subserosa. The tumor at the apex was 0.3 cm in diameter and was accompanied by SSA as a secondary lesion. Mitosis was not observed.

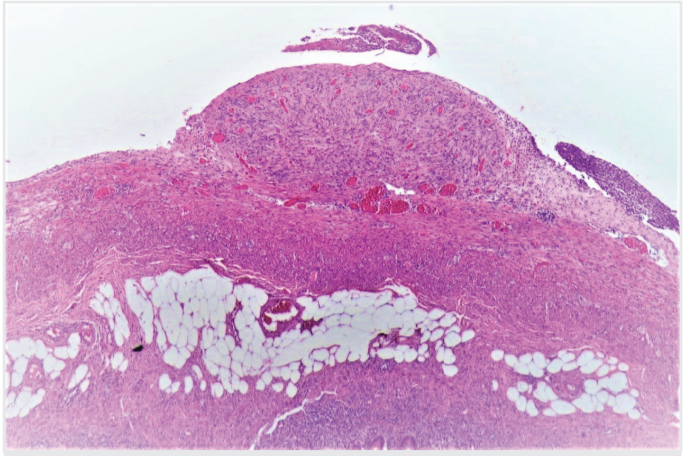

Figure 6. Gastrointestinal stromal tumor. The tumor was located in the subserosal layer of the appendix (H&E, x100)
H&E: Hematoxylin and eosin

Cases in the secondary neoplasia subgroup were detected in incidental appendectomy materials, and primary neoplasia foci originated from the upper and lower gastrointestinal tract (GIT) and female genital tract.

In the pediatric age group, cases with diverticulum (n=13), enterobius vermicularis (n=8), NET (n=5), SSA (n=2), endometriosis externa (n=1), and NCP (n=1) were detected.

The classification and clinicopathologic characteristics of patients with "other diagnosis" in Table 2, 3 and the data on accompanying secondary lesions are in Table 4.

Discussion

Histopathological examinations of appendectomy materials also allow the detection of rarely seen additional pathological conditions that are not grossly noticed (5). In our study, microscopic examination revealed acute and perforated appendicitis as well as lymphoid hyperplasia and other (miscellaneous) lesions. In a histopathological examination, appendicitis can be classified as acute focal, acute suppurative, and perforated appendicitis, according to its stage and frequency (7). According to the stages of appendicitis, acute appendicitis took the first place and our incidence rates were similar to the literature.

Lymphoid hyperplasia stands out among the factors in the etiology of appendicitis and is observed as a physiological response rather than inflammation. It has been described to be particularly associated with viral gastroenteritis and mesenteric adenitis (3,8). The frequency has been reported to be 6% (8). Lymphoid hyperplasia, which was found in the lowest group (2.3%) in our study, was also lower than the literature. Lesions such as diverticulum, fibrous obliteration, infectious

Table 2. Demographic and clinicopathologic characteristics of patients classified as group 1

		Age	M (n)	F (n)	Total (n, %)
	Diverticulum	40.33±16.49	179	70	249 (5.74)
Acquired and anatomical anomalies	Fibrous obliteration	42.90±19.17	81	42	123 (2.84)
Chronic appendicitis	Ulcerative colitis (skipped lesion)	79	1	0	1 (0.02)
	Granulomatous inflammation	35.00±14.11	2	1	3 (0.07)
Infectious agents	Enterobius vermicularis	24.67±13.89	17	7	24 (0.55)
Miscellaneous disorders	Endometriosis externa	38.57±19.07	0	7	7 (0.16)
	Amyloid deposition	77.00±18.38	0	2	2 (0.05)

M: Male, F: Female

Table 3. Demographic and clinicopathologic characteristics of patients classified as group 2

		Age	M (n)	F (n)	Total (n, %)
Serrated lesion	Hyperplastic polyp	50.22±16.31	17	6	23 (0.53)
	Sessile serrated adenoma	59.14±20.97	20	16	36 (0.83)
Carcinoma	LGMN	51.17±17.06	4	8	12 (0.28)
	NCP	31.58±12.57	8	4	12 (0.28)
Neuroendocrine neoplasms	NET GI	37.60±17.98	33	12	45 (1.04)
	NET GII	31.29±14.63	4	3	7 (0.16)
Mesenchymal tumor	GIST	77.00	1	0	1 (0.02)
Secondary neoplasms	Upper and lower GIT and female genital system	55.65±12.81	5	12	17 (0.39)

M: Male, F: Female, LGMN: Low-grade mucinous neoplasm, NCP: Neuroendocrine cell proliferation, NET: Neuroendocrine tumor, G: Grade, GIST: Gastrointestinal stromal tumor, GIT: Gastrointestinal tract

Table 4. Data on accompanying secondary lesions

	Endometriosis externa	NCP	NET	GIST	SSA
Diverticulum	1	1	5	-	4
Hyperplastic polyp	-	1	-	-	-
SSA	-	-	1	1	-
LGMN	-	-	2	-	-

NCP: Neuroendocrine cell proliferation, NET: Neuroendocrine tumor, GIST: Gastrointestinal stromal tumor, SSA: Sessile serrated adenoma, LGMN: Low-grade mucinous neoplasm

agents, endometriosis externa, serrated lesions, LGMN, neuroendocrine neoplasia, mesenchymal tumor, and secondary neoplasms that mimic the clinical manifestations of appendicitis observed less frequently and the incidence of these lesions has ranged from 0.9% and 8.3% in the literature (1-6). We classified this group as other (unusual) diagnoses. The incidence rate was 12.96%, above the literature data.

Diverticulum, a lesion in the subgroup of acquired and anatomical abnormalities, is rare and its frequency varies between 0.014% and 2% (9,10). It was the most common rare lesion we detected in our study and its rate was higher than the literature data. Two types are defined: Congenital and acquired (9). The congenital type is a true diverticulum and is very rare. Our study included cases diagnosed with an acquired type of diverticulum, there were no cases with a diagnosis of congenital type. Increased intraluminal pressure is thought to play a role in the etiology of the acquired diverticulum. In addition to fecaloid material, lesions such as adenoma LGMN, and NET (10,11) can cause increased intraluminal pressure. Our study also supports these data, and the accompanying lesions in some cases were NET, NCP, SSA, and endometriosis externa. It is usually seen after the third decade and was found in a similar age group in our study. Although usually asymptomatic, complications of the diverticulum include inflammation and, to a lesser extent, perforation. The mortality risk due to perforation is higher than in cases of acute appendicitis without diverticulum. Our results included perforation as well as inflammation. Serous mucin deposits that may occur because of perforation may lead to a misdiagnosis as LGMN. Therefore, diverticulum should always be considered in the differential diagnosis (11). While hyperplastic changes in the epithelium, mucosal neuroma-like proliferation, and fibrosis are observed in the diverticulum, the dysplastic epithelium observed in LGMN is important in this distinction. We did not have a diverticulum case misdiagnosed as LGMN in our study. Fibrous obliteration is observed more frequently than diverticulum and has an incidence rate of up to 10% in the literature (1,3,7). The incidence of fibrous obliteration was quite low in our study compared with the literature (2.84%). Fibrous obliteration, also called appendiceal neuroma, is a lesion whose frequency increases with age. Accordingly, it was detected more frequently in the fourth decade and in our study. Three structural patterns are observed in the histopathological examination of fibrous obliteration, which is thought to develop because of neurogenic proliferation (7). The most common pattern is the central obliterative neuroma, which is followed by the intramucosal appendiceal neuroma. Intramucosal ones are well-circumscribed and have a nodular growth pattern between the crypts. The third pattern is the submucosal obliterative process, which is localized but with indistinct borders. Among these structural patterns, the central obliterative neuroma constituted most our cases. An intramucosal neuroma was observed at a lower rate and submucosal neuroma was not detected.

The chronic appendicitis subgroup involved skip lesions of ulcerative colitis and granulomatous inflammation. Appendiceal involvement of ulcerative colitis can be observed in cases with pancolitis or cases with left side or rectum involvement as skip lesion (12). Histopathological examination reveals active inflammation with crypt abscess, panmucosal plasmacytosis, and crypt distortion (3). In addition to these findings in appendiceal sections, crypt atrophy and one focus of pyloric gland metaplasia were noted in our single case with a diagnosis of ulcerative colitis. Granulomatous inflammation is also observed in appendectomy materials at rates varying between 0.1-2%. Infectious agents (such as Mycobacterium tuberculosis and Schistosoma) and non-infectious factors (such as Crohn's disease, sarcoidosis, and foreign body reaction) are involved in the etiology (1,3,13). Geographic distribution can be decisive in terms of factors (13). Definitive diagnosis requires long-term follow-up and sometimes additional investigation (5). The rate we found in our study was 0.07%, which was below the literature data. And additional examinations for the definitive diagnosis in these cases did not lead to a conclusion regarding the etiology.

Enterobius vermicularis, which is in the infectious agent subgroup, is the most common helminthic agent of GIT. It is the most common infectious agent among rare lesions detected in appendectomy specimens. Its incidence varies between 0.2-3.8% (3,14). Our rate of enterobius vermicularis found to be consistent with the literature data. The literature data also report different parasitic agents such as Schistosoma, Ascaris lumbricoides, and taenia; however, we only found one agent (1,3).

In our study, the subgroup of miscellaneous diseases included endometriosis externa and amyloid deposition. Localized endometrial tissue outside the uterine cavity, which is called endometriosis externa, is rare in the GIT and is observed in 10% of women with endometriosis (3,15,16). Endometriosis externa, mostly observed in the rectum and sigmoid colon, is very rare in the appendix and included in the literature as case reports (16). The number of cases in this group was very low in our study. Systemic amyloidosis is characterized by the extracellular deposition of the insoluble fibrillar protein aggregates (17). GIT involvement is common. It can cause upper and lower gastrointestinal bleeding, motility disorders, severe malabsorption, infarction, and perforation (18). One of our cases was operated on for ischemia and the other for a colon tumor. There was an eosinophilic hyalinized deposit compatible with amyloid, which also showed positive staining with Congo red on the vessel walls of their appendectomy materials. Because of additional examinations, the findings observed in both cases were interpreted as secondary amyloidosis.

Serrated lesions, previously defined as mucosal hyperplasia or metaplasia, are now divided into three groups as hyperplastic polyps, SSA, and traditional serrated adenoma (TSA) (19). These lesions are rare in the appendix and their true incidence remains unknown. However, there has been an increase in these lesions recently because of increased

awareness (20) and a study reported that these lesions were detected in approximately 7% (20). The frequency of serrated lesions was less in our study compared to that in the literature. However, the number of cases diagnosed was higher recently than in previous years. Our study included cases diagnosed with hyperplastic polyp and SSA and there was no case with a TSA diagnosis. Among serrated lesions, SSA and TSA are considered precancerous and it has been suggested that these appendiceal lesions shows more aggressive behavior (20). It has been reported in the literature that polyps can be observed along the colon and appendix and that may be a part of serrated polyposis syndrome (21). Polyps are mostly in SSA morphology and colon adenocarcinoma development is common in these cases. Therefore, a total colonoscopic examination is recommended especially in cases diagnosed with SSA and TSA accompanied by dysplasia (19). We detected no dysplasia or malignancy with SSA in our cases.

LGMN is among mucinous epithelial tumors with a frequency of less than 1%. It is detected incidentally during surgery for other reasons in 15-20% of cases (4,22). The rate of LGMN in our study was consistent with the literature. As long as dysplastic epithelium is not observed at the surgical margin, appendectomy is considered sufficient in the treatment. In these cases, positive surgical margins, appendiceal rupture, presence of mucin outside the appendix, or atypical cells and pseudomyxoma peritonei may increase the development of potential malignancy (22). The cases diagnosed in our study were limited to the muscularis propria and the surgical margins were negative. Some studies have reported very rare appendiceal collision tumors, which consist of histologically different tumor types and are included in the LGMN tumor group (23,24). In these studies, reported as case reports, LGMN is mostly accompanied by NET. NET was the accompanying secondary tumor in both of our cases in the category of collision tumors.

NCPs, which are included in the neuroendocrine neoplasia group and detected incidentally in the appendix wall, are defined as a proliferative phenomenon similar to early NCP seen in other organs of the GIT (4). There is no clear information about the underlying medical or genetic structure that may predispose to this proliferation. It is observed as patchy groups smaller than one millimeter and is called incidental NCP. Our study included ten cases in this category.

NET, which is in the neuroendocrine neoplasia group, is the most common primary tumor of the appendix (1,4). Its incidence in appendectomy materials varies between 0.3-2.3%. The frequency of our cases diagnosed with NET in our study was consistent with the literature data. It is usually observed between the ages of 30-40. The NET cases in our study were in a similar age range. NETs with a tumor size of less than 1 cm are also usually detected incidentally in approximately 70% of cases (4). As in our study, they were mostly localized at the apex. In these tumors, where metastasis is very rare, appendectomy is considered sufficient for the treatment (1). A tumor size of 2 cm or more, mesoappendix or vascular invasion, and positive surgical margins are risky parameters for recurrence (4). We did not find any other risk factors predicted for recurrence, except for the presence of mesoappendix invasion and a tumor size of 2 cm and observed above in a few of our patients with NET.

GIST is the most common primary mesenchymal tumor of the GIT. While it is frequently observed in the stomach and small intestine, it is very rare in the appendix (25-27). The number of reported cases is less than 100 in the literature. Besides location, size and mitotic activity are factors that play a role in determining the behavior of GIST (25). However, since it is rarely observed in the appendix, there are no definite data on its behavior. As in our case, it is more common in men and has a size of less than 3 cm.

Secondary neoplasms are rare in the appendix and may originate from the GIT, urogenital tract, ovary, lung, and gallbladder. Metastatic tumors can most commonly be seen as serosa involvement due to transcoelomic spread (28). In our study, secondary neoplasms originated from the GIT and female genital tract and were detected in incidental appendectomy materials accompanying primary tumor resections.

Acute appendicitis is one of the most common diseases requiring surgical treatment in the pediatric age group as well (29). Enterobius vermicularis is detected more frequently among rare lesions in this age group (29). The most common lesion was the diverticulum in our study, followed by enterobius vermicularis, NET, SSA, endometriosis externa, and NCP, in order of frequency. Among these lesions, SSA is very rare in this age group. It is recommended to examine the entire appendix and follow up the case closely, particularly in those with dysplasia findings (30). In our study, the appendiceal materials diagnosed SSA were completely examined. There was no sign of dysplasia.

Study Limitations

The limitations of this retrospective study include the inaccessibility of macroscopy materials and the fact that sampling was performed by different pathologists.

Conclusion

Lesions classified as “other diagnostic” are usually detected incidentally during histopathological examination of appendectomy materials. Among the “other diagnostic” group, the most common lesion was the diverticulum, and the most common neoplastic lesion was NET in our study. These lesions may also coexist together, and mentioning such concomitant lesions in pathology reports will provide more accurate frequency rates. Thus, besides neoplastic lesions; in cases such as parasites, endometriosis externa and granulomatous inflammation, the treatment and follow-up of the patients will continue as recommended by the clinician. As in our study, due to the raising awareness of serrated lesions, the rate of diagnosis of these cases will increase.

Ethics Committee Approval: The ethics committee approval was granted by the Ethics Committee of University of Health Sciences Turkey, Okmeydanı Training and Research Hospital (approval number: 810, date: 23.01.2018).

Informed Consent: Informed consent was obtained from the patients for the publication of this study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - S.Ş.E., A.D., G.K., A.A.; Concept - S.Ş.E., A.D.; Design - S.Ş.E., A.D., G.K., A.A.; Data

Collection or Processing - S.Ş.E., A.D., A.A.; Analysis or Interpretation - S.Ş.E., A.D., G.K., A.A.; Literature Search - S.Ş.E., A.D., G.K.; Writing - S.Ş.E., A.D., G.K.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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İstanbul Med J 2022; 23(4): 254-9
DOI: 10.4274/imj.galenos.2022.22804

Serum Adiponectin Related to Neovascularization Process in Diabetic Retinopathy

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ABSTRACT

Introduction: There's are similar mechanisms in the development of diabetic retinopathy (DR) and diabetic nephropathy (DN) in terms of inflammation and oxidative stress. We wanted to measure serum adiponectin (ADPN) levels in DR, considering the other clinical/laboratory findings in subgroups with or without DN.

Methods: A total of 122 patients were included; group 1 (non-diabetic, healthy subjects), group 2 (diabetic without DR, with/without albuminuria/proteinuria), group 3 (mild to moderate DR, without albuminuria/proteinuria) and group 4 (severe non-proliferative or proliferative DR, with albuminuria/proteinuria). DR grades were defined by the same ophthalmologist based on the clinical examination and angiographic findings.

Results: In diabetics, mean hemoglobin A1c was over 8.0%. Estimated glomerular filtration rate values and serum albumin levels were significantly lower in group 4 compared to group 1. Not ADPN/C-reactive protein (CRP) levels, but ADPN, ADPN/waist circumference, ADPN/body mass index and ADPN/fibrinogen were all significantly higher in group 4 compared to group 2. ADPN/CRP was positively correlated with high-density cholesterol in group 1, 2, 4, negatively correlated with triglyceride in group 3, 4, and positively correlated with hypertension in group 4.

Conclusion: We had increased serum ADPN and indices in the DR neovascularization process among diabetics. But, further loss of kidney function itself prevented the increase in serum ADPN/CRP levels. To estimate progression in the advanced stages of DR, serum ADPN/CRP was a valuable follow-up marker in DR, if there was no urinary loss of ADPN.

Keywords: Adiponectin, inflammation, diabetic complications, neovascularization, diabetic retinopathy

Introduction

Diabetic retinopathy (DR), seen in approximately 80% of patients with 10 or more years of type 2 diabetes mellitus (T2DM), is a major microvascular complication. Possibly, it is responsible for a large proportion of vision problems and blindness in the population (1). In addition to the duration of diabetes, DR development is strongly linked with chronic hyperglycemia; dyslipidemia, diabetic nephropathy (DN), hypertension and mitochondrial dysfunction accompanied by induced oxidative stress and is associated with abnormal adiponectin (ADPN) levels (1,2). Mitochondrial dysfunction is also associated with renal tubular epithelial cell injury and the occurrence of DN, and ADPN is involved in promoting mitochondrial biogenesis and functional renal tubular epithelial cells (3). The mechanisms in the development of DR and DN seem very similar in terms of inflammation and oxidative stress.

ADPN secreted by adipocytes exists as a trimer and three multimer forms: low molecular weight, medium molecular weight, high molecular weight (HMW). It has effects such as antidiabetic, anti-inflammatory, regulating endothelial functions, antioxidant, antiapoptotic, antiatherogenic, antithrombotic, inhibiting smooth muscle proliferation and facilitating vasodilation (4). In studies conducted in different ethnic groups, plasma ADPN levels were found to be low in patients with obesity and T2DM. In contrast, the degree of hypoadiponectinemia was closely related to the degree of insulin resistance and hyperinsulinemia rather than the degree of adiposity (5). There was a relation between CRP, ADPN and quantitative insulin resistance check index to detect microvascular

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Cite this article as: Margunato MG, Aral H, Ayrancı Osmanbaşoğlu Ö, Güngel H, Altunoğlu E, Usta M, Köse Ş, Serin E, Karataş S. Serum Adiponectin Related to Neovascularization Process in Diabetic Retinopathy. İstanbul Med J 2022; 23(4): 254-9.

Received: 20.04.2022
Accepted: 18.09.2022

measurements [capillary density, urine albumin creatinine ratio (UACR) and endothelial measurements] in non-diabetic and normotensive healthy subjects (6).

The development of DR or albuminuria/proteinuria is accepted as findings in favor of endothelial dysfunction in the organism. The impact of UACR and estimated glomerular filtration rate (eGFR) on serum ADPN is clearly observed. As is known, the risk of cardiovascular disease (CVD) increases with endothelial dysfunction. As a result, ADPN has a positive effect on cardiovascular health. Its protective role against atherosclerosis is mediated by inhibiting vascular smooth muscle and endothelial cell proliferation. ADPN has been shown to be a good marker for metabolic control and atherosclerotic risk (7).

In this study, we investigated the relationship between serum ADPN or related indices and DR degree with or without albuminuria/proteinuria. Demographic/clinical/anthropometric findings, smoking status, blood pressure values, inflammatory blood markers and other routine laboratory findings were also considered.

Methods

A total of 122 patients, followed up in out-patient clinics of ophthalmology and internal medicine, were included our study. Patients with known thyroid dysfunction, urinary infection, nephropathy (of the non-diabetic causes), malignancy, diabetic neuropathy or eGFR <30 mL/min were all excluded. An approval of the research protocol was received by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethics Committee (approval number: 117, date: 08.04.2022) in accordance with international agreements (World Medical Association Declaration of Helsinki) was received.

All the cases were divided into four different groups; group 1 (non-diabetics, n=27), group 2 (T2DM without retinopathy, with/without albuminuria and/or proteinuria n=45), group 3 (mild to moderate DR, without any albuminuria or proteinuria, n=26) and group 4 (severe non-proliferative or proliferative retinopathy, with albuminuria and/or proteinuria n=24). DR grades were defined by the same ophthalmologist based on clinical examination and angiographic findings.

Serum ADPN was run via immunoturbidimetric method (catalog no: AO 2999, Randox Laboratories Limited, Crumlin, UK) using AU2700 (Beckman Coulter Inc, Brea, Ca, USA). We found a coefficient of variation (within-run precision) of 1.45% at a serum level of 5.85 µg/mL (n=17), and 1.00% at a serum level of 12.05 µg/mL (n=19).

Anthropometric measurements of waist circumference (WC), height, weight and blood pressure were recorded. Data from the patient records were retrieved, the measurements were performed as follows; chemistry/immunochemistry assays using AU 2700 and Image 800 (Beckman Coulter Inc.), fibrinogen levels using BCS XP coagulometer (Siemens Healthcare Diagnostics Inc.), hemoglobin A1c (HbA1c) using (ADAMS HA-8180V (Arkray Inc.) and complete blood counts using BC 6800 (Mindray Medical International Ltd.). Spot urinalysis and some definitions were used as albuminuria (albumin/creatinine: ≥30 mg/g) and proteinuria (protein/creatinine >0.2 g/g).

Low-density-lipoprotein cholesterol (LDL-C) levels were calculated using the Friedewald equation. In eGFR values were estimated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation by Levey et al. (8); as follows, $eGFR_{CKD-EPI}$=141 x minimum (Scr/k,1)$^{\alpha}$ x maximum (Scr/k, 1)$^{-1.209}$ x0.993Age x 1.018 [if female].

Indices of ADPN were estimated as ADPN/BMI, ADPN/WC, ADPN/fibrinogen, ADPN/CRP.

Statistical Analysis

We used MedCalc (MedCalc Software, Broekstraat, Mariakerke, Belgium). The Kolmogorov-Smirnov tests investigated Gaussian distribution. Non-gaussian variables were given as median (25th percentile-75th percentile), or else mean ± standard deviation. In comparison, One-Way ANOVA or Kruskal-Wallis H test was used in multiple group comparisons. Tukey HSD and Tamhane's T^2 test for One-Way ANOVA, or Mann-Whitney U test for Kruskal-Wallis H test were used in post hoc comparisons. Pearson's chi-square test, Pearson's correlation coefficient (r) or Spearman's rank correlation coefficient (rs) was used. All statistical tests were two-sided, and p-values less than 0.05 were considered to indicate significance, except p values less than 0.008 when the Mann-Whitney U test was used for post-hoc test.

Results

No significant difference in the male-to-female ratio was found among all the groups (groups 1-4), as shown in Table 1. Also, no statistically significant difference was found among the age, body mass index (BMI), and WC among the diabetics (groups 2-4).

Each diabetic-subgroup presented a mean of HbA1c over 8.0% and dyslipidemia with high triglyceride levels, as shown in Table 2. Also, diabetics had significantly decreased iron, hemoglobin levels and increased white blood cell values. CRP was higher in group 2, 3 than the controls. Serum urea and creatinine were higher in group 4 compared to group 1. However, eGFR values and serum albumin levels decreased in group 4 compared with group 1.

Table 1. Demographic data, anthropometric measurements and smoking status of controls and diabetic sub-groups

	Group 1 (n=27)	Group 2 (n=45)	Group 3 (n=26)	Group 4 (n=24)	p
Age (years)	49.7±10.1	58.0±11.1[a]	62.2±6.5[b]	62.2±8.9[b]	**<0.0001**
Male/female (N/N)	11/16	19/26	15/11	10/14	=0.5440
Body mass index (kg/m^2)	25.5±4.3	31.9±6.1[b]	31.9±4.4[b]	32.2±5.5[b]	**<0.0001**
Waist circumference (cm)	89.8±15.5	105.4±11.1[b]	103.6±23.5[a]	108.3±10.6[b]	**<0.0001**
Smoking (%)	22.2%	42.2%	50.0%	29.2%	=0.2990

[a]Tukey test, p<0.01 vs. group 1, [b]Tukey test, p<0.0001 vs. group 1

In healthy subjects (group 1), we had higher ADPN/CRP median values compared to group 2 and group 3 (Table 3). However, ADPN, ADPN/WC, ADPN/BMI and ADPN/fibrinogen were higher in group 4, compared with group 2, except ADPN/CRP.

ADPN/CRP was correlated with high-density cholesterol (HDL-C) in group 1, 2, 4 (Table 4). There was a negative correlation between ADPN/CRP and triglycerides in group 3, 4. In group 4, ADPN/CRP was also correlated with hypertension.

Discussion

The results demonstrated in this work provide a new perspective on understanding ADPN pathophysiology in different grades of DR. ADPN/CRP was significantly decreased in group 2, 3 (in diabetics), according to the healthy subjects. Theoretically, the terminal stage of various chronic diseases can occur in different ways in humans and experimental models; the ADPN paradox is alive among them. One possibility is that the persistence of the terminal stage of chronic diseases for which medical care is sought in humans contributes to the loss of ADPN function and may be related to metabolic syndrome (9). Although a significant negative correlation was shown between serum ADPN levels and smoking in women by Persson et al. (10), we had no difference in smoking percentage among all the groups in our study.

ADPN and indices of ADPN/BMI, ADPN/WC, ADPN/fibrinogen values significantly increased in group 4, in which microvascular complications increased mostly (both DR ad DN), compared with group 2. We also showed that UACR and eGFR values had a significant effect on serum ADPN levels. ADPN levels increasing with DR degree may be associated with its anti-inflammatory protective effect. ADPN/CRP indices did not differ significantly, although there was no any increase in CRP levels decreasing ADPN/CRP ratio in group 4, compared with group 2. There was a negative correlation between ADPN/CRP and triglycerides in patients with DR, group 3, 4. Also, ADPN/CRP was correlated with hypertension as a macrovascular complication in group 4. The prominence of the ADPN/CRP index highlights the importance of both inflammation and neovascularization. ADPN influences endothelial adhesion and transmigration of leukocytes and macrophages (11).

Both positive and inverse associations between ADPN and DR progression have been reported in meta-analysis studies that combined various ethnic groups (1). ADPN plays a critical role in retinal oedema and neovascularization, and it's a potential therapeutic target for treating diabetic macular oedema, proliferative DR, and retinal vein occlusion (12) or DN (13); in an observational study, Kuo et al. (14) showed that ADPN levels increased with DR, and ADPN was seen positively correlated with DR progression.

Table 2. Routine laboratory data of controls and diabetic sub-groups

	Group 1 (n=27)	Group 2 (n=45)	Group 3 (n=26)	Group 4 (n=24)	p
Glucose (mg/dL)	94±9	175±64[d]	181±77[d]	161±58[d]	**<0.0001**
Hemoglobin A1c (%)	5.4±0.3	8.4±2.2[d]	8.9±2.1[d]	8.3±1.7[d]	**<0.0001**
Urea (mg/dL)	31±7	41±19[c]	39±16	49±17[d]	**<0.0010**
Creatinine (mg/dL)	0.77±0.22	0.99±0.41	0.94±0.49	1.10±0.49[a]	**=0.0330**
$eGFR_{CKD-EPI}$ (mL/min/1.73m^2)	95.1±16.8	78.7±27.6[a]	83.9±23.2	67.9±21.2[c]	**<0.0010**
Total cholesterol (mg/dL)	212±58	199±65	207±42	209±72	=0.8220
Triglyceride (mg/dL)	93 (64–108)	161 (121-198)[ε]	160 (93-204)[ε]	140 (106-219)[ε]	**<0.0001**
High-density lipoprotein cholesterol (mg/dL)	56±12	44±9[d]	45±7[c]	46±12[c]	**<0.0001**
Low-density lipoprotein cholesterol (mg/dL)	145±43	118±41	132±36	135±48	=0.0740
Total protein (g/dL)	7.3±0.5	7.4±0.5	7.5±0.4	7.2±0.4	=0.3010
Albumin (g/dL)	4.4±0.3	4.3±0.3	4.3±0.3	4.1±0.3[b]	**=0.0040**
Alanine aminotransferase (U/L)	18 (14-33)	20 (16-27)	21 (17-26)	19 (12-24)	=0.3550
Gamma-glutamyl transferase (U/L)	17 (14-23)	26 (19-37)[β]	20 (17-29)	21 (14-30)	**=0.0200**
Iron (µg/dL)	101 (74-132)	70 (46-97)[δ]	66 (50-83)[ε]	65 (53-99)[γ]	**<0.0010**
Total iron binding cap. (µg/dL)	326 (311-365)	369 (307-398)	364 (328-381)	349 (315-384)	=0.2470
Ferritin (ng/mL)	60 (27-96)	34 (11-82)	30 (10-56)	30 (15-52)	=0.0670
C-reactive protein (mg/dL)	0.24 (0.17-0.43)	0.48 (0.32-0.81)[ε]	0.47 (0.31-0.67)[α]	0.34 (0.15-0.88)	=0.0030
Fibrinogen (mg/dL)	342±70	379±91	364±63	396±91	=0.1170
Hemoglobin (g/dL)	14.4±1.1	13.5±2.0	13.1±2.3[e]	11.6±2.6[d,f]	**<0.0001**
Hematocrit (%)	44±3	42±6	42±5	39±5[c]	**=0.0060**
Thrombocyte (x10^3/µL)	220±43	277±75[c]	261±56[a]	249±91	**=0.0090**
White blood cell (x10^3/µL)	5.9±1.0	7.6±2.0[d]	7.7±2.2[d]	7.3±1.7[a]	**<0.0010**

[a]Tamhane's T^2 or Tukey test, p<0.05 vs. group 1, [b]Tamhane's T^2 or Tukey test, p<0.01 vs. group 1, [c]Tamhane's T^2 or Tukey test, p<0.001 vs. group 1, [d]Tamhane's T^2 or Tukey test, p<0.0001 vs. group 1, [e]Tamhane's T^2 or Tukey test, p<0.01 vs. group 2, [f]Tamhane's T^2 or Tukey test, p<0.05 vs. group 3, [α]Mann-Whitney U test, p=0.002 vs. group 1, [β]Mann-Whitney U test, p=0.003 vs. group 1, [γ]Mann-Whitney U test, p=0.006 vs. group 1, [δ]Mann-Whitney U test, p<0.001 vs. group 1, [ε]Mann-Whitney U test, p<0.0001 vs. group 1, eGFR: Estimated glomerular filtration rate

In diabetic animal models, ADPN was upregulated in damaged muscle tissue (15), and it was shown that after myocardial injury ADPN levels increase to be a part of the revascularization process (16). Therefore, it is possible in the DR neovascularization process to have increased ADPN levels.

In a cross-sectional study, there was an association between plasma ADNP level and the variance of ADPN related genes on the DR status, individually and in combination (17). Moreover, genes associated with CVD are the *ADPN* gene and apolipoprotein E polymorphism gene with the x2 allele (18).

In another study, serum ADPN levels decreased in DN, but higher levels were found in DR or diabetic neuropathy (19), these findings support our results. In a meta-analysis, ADPN levels were higher in T2DM patients with microvascular complications (20). Plasma ADPN levels increased significantly with the severity of DN; they were associated with eGFR and UACR. The relative risk of impaired renal function requiring dialysis was found to be independent of ADPN levels (21). Additionally, a cohort study showed that ADPN levels were significantly increased in patients with chronic kidney disease (22), however when we consider that clearance of ADPN is mainly processed in the liver, renal function loss itself doesn't contribute to ADPN elevation (23).

According to some studies, no correlation was found between ADPN and serum lipids in the form of triglycerides, LDL-C or total cholesterol (24,25). In another study, ADPN correlated positively with total cholesterol and HDL-C (21). In our study, ADPN/CRP was negatively correlated with triglycerides in group 3 and group 4. Additionally, there were varying degrees of positive correlations between ADPN/CRP and HDL-C levels in group 1, group 2, and group 4. Still a stronger correlation was found in non-diabetics, group 1. Patients with DR were included in groups 3 and 4; also, there was DR progression, especially in the proliferative phase in group 4. In group 4, a weak negative correlation was found between ADPN/CRP and hypertension. The fact that the parameters of eGFR or albumin in group 4 did not differ from the diabetic control group (group 2) strengthened our study to see the pure effect of the severity of DR progression, especially in the proliferative phase.

Blood levels of irisin, another adipokine, decreased with increasing stage of chronic kidney disease (UACR ≥300 mg/g, eGFR <60 mL/min 1.73 m^2) and insulin resistance. It was also significantly associated with sarcopenia and carotid atherosclerosis in patients receiving peritoneal dialysis (26).

Recently, increased HMW level or HMW/total ratio has been associated with visceral fat type obesity, diabetes, glucose tolerance and insulin resistance, CVD, metabolic syndrome. Urinary ADPN was shown to be useful as a surrogate marker for DN risk performed with ultra-sensitivity by employing a two-site immune complex transfer enzyme immunoassay fluorescently after gel filtration of immunoreactivity; urinary concentrations of HMW- ADPN (size, >250 kD) increased as the disorder progresses in the glomerular molecular barrier (27). Urinary ADPN levels were much better than that of UACR, as a reliable indicator of proteinuria (28). Also, it was suggested that the increase in urinary ADPN was associated with the decreased renal function (UACR ≥30 mg/g or eGFR <60 mL/min/1.73 m^2) (29). Total and HMW-ADPN levels correlated moderate to highly with UACR and eGFR within a fully automated immunoassay system (30).

Study Limitations

The most important limitation was the number of patients and having no sub-groups at variable stages of diabetes. Moreover, it should be better to include diabetic neuropathy. For technical reasons, we could not reach the patient group with isolated or accompanying diabetic

Table 3. Comparison of uric acid and adiponectin findings of all the groups

	Group 1 (n=27)	Group 2 (n=45)	Group 3 (n=26)	Group 4 (n=24)	p
Uric acid (mg/dL)	5.0±1.2	6.0±1.4	5.6±1.5	5.6±1.2	**=0.0160**
Adiponectin (µg/mL)	8.4 (5.3-10.3)	6.5 (4.3-11.0)	6.6 (4.7-9.9)	11.6 (6.0-14.9)[d]	**=0.0280**
Adiponectin/body mass index (µg.m^2/kg.mL)	0.36 (0.21-0.49)	0.21 (0.13-0.34)	0.21 (0.15-0.30)	0.36 (0.21-0.43)[e]	**=0.0070**
Adiponectin/waist circumference (µg/cm.mL)	0.093 (0.058-0.138)	0.064 (0.039-0.099)	0.06 (0.05-0.102)	0.106 (0.056-0.134)[e]	**=0.0150**
Adiponectin/C-reactive protein (µg.dL/mg.mL)	34.2 (16.3-50.6)	15.4 (8.1-23.0)[a]	13.0 (8.3-23.7)[b]	21.3 (10.3-92.2)	**<0.0010**
Adiponectin/fibrinogen (µg.dL/mg.mL)	0.022 (0.016-0.032)	0.019 (0.011-0.025)	0.019 (0.015-0.024)	0.030 (0.018-0.042)[c]	**=0.0180**

[a]Mann-Whitney U test, p<0.0001 vs. group 1, [b]Mann-Whitney U test, p=0.003 vs. group 1, [c]Mann-Whitney U test, p=0.004 vs. group 2, [d]Mann-Whitney U test, p=0.005 vs. group 2, [e]Mann-Whitney U test, p=0.008 vs. group 2

Table 4. Lipid panel, and inflammatory parameters significantly correlated with ADPN/CRP, in the groups

Parameters	Group 1 (n=27)	Group 2 (n=45)	Group 3 (n=26)	Group 4 (n=24)
Total cholesterol	N.S.	rs=0.381 (p=0.012)	r_s=-0.457 (p=0.019)	N.S.
Triglyceride	N.S.	N.S.	r_s=-0.540 (p=0.004)	r_s=-0.450 (p=0.027)
High-density lipoprotein cholesterol	r_s=0.520 (p=0.005)	r_s=0.387 (p=0.010)	N.S.	r_s=0.398 (p=0.054)
Low-density lipoprotein cholesterol	N.S.	r_s=0.365 (p=0.016)	r_s=-0.409 (p=0.038)	N.S.
White blood cell	N.S.	N.S.	r_s=-0.378 (p=0.057)	N.S.
Fibrinogen	N.S.	N.S.	N.S.	N.S.
Hypertension	N.S.	N.S.	N.S.	rrb=-0.362 (p=0.082)

ADPN: Adiponectin, CRP: C-reactive protein

neuropathy, another microvascular complication. The second limitation was that the control group was younger. And data including diabetic age was confidential.

Conclusion

We had increased serum ADPN and indices of ADPN/BMI, ADPN/WC, ADPN/fibrinogen values in the DR neovascularization process among diabetics, so clinicians can be encouraged to benefit from this immunoturbidimetric assay for diabetics via personalized medicine approach. But, further loss of kidney function itself prevented the increase in serum ADPN/CRP levels. To estimate progression in the advanced stages of DR, serum ADPN/CRP was a valuable marker, if there was no urinary loss of ADPN.

Meanwhile, more expanded studies should be performed where ADPN isoforms (molecular weight and immunoreactivity) or indices evaluated together with hepatic steatosis determined sonographically, and endothelial dysfunction or heart status determined radiologically for monitoring other vascular complications of diabetes. Besides biomarkers and imaging findings, life-style conditions, including exercise and dietary options/habits, should be recorded.

Ethics Committee Approval: An approval of the research protocol by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethics Committee (approval number: 117, date: 08.04.2022) in accordance with international agreements (World Medical Association Declaration of Helsinki) was received.

Informed Consent: It wasn't obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - Ö.A.O., H.G., E.A., Ş.K.; Concept - M.G.M., H.A., S.K.; Design - M.G.M., H.A., M.U., E.S., S.K.; Data Collection or Processing - M.G.M., M.U., E.S.; Analysis or Interpretation - M.G.M., H.A., Ö.A.O., H.G., E.A., M.U., Ş.K., E.S., S.K.; Literature Search - M.G.M., H.A., S.K.; Writing - M.G.M., H.A., M.U., S.K.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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İstanbul Med J 2022; 23(4): 260-3
DOI: 10.4274/imj.galenos.2022.99248

The Effect of Transulnar Pinning in Preventing Postoperative Radial Collapse and Wrist Motions in Distal Radius Fracture

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ABSTRACT

Introduction: It is thought that transulnar (a Kirschner wire from radius to ulna) pinning provided less collapse at the fracture site in the percutaneous pinning of distal radius fracture. In this study, we compared the radiological and clinical results of the patient groups with and without transulnar pinning for percutaneous pinning of distal radius fracture.

Methods: Patients who underwent 16 isolated radius pinning and 11 radius pinning and additional transulnar pin between 2016 and 2021 were included in the study. Disabilities of the arm, shoulder, and hand (DASH) score, range of motion of the injured wrist at final examination and radiological parameters in terms of ulnar variance, radial height, and volar tilt of the operated wrist were evaluated. The results were compared between the two groups.

Results: There was no statistical difference in terms of DASH score, radial height, volar tilt, radial inclination, pronation, supination, and flexion degrees between the two groups. The final extension degrees were found to be statistically higher in the transulnar pinning group.

Conclusion: It was observed in our study that radius collapse and radial shortening were less in patients who underwent transulnar pinning in addition to radius pinning; but the difference was not statistically significant.

Keywords: Distal radius fracture, percutaneous pinning, colles fracture treatment

Introduction

Distal radius fractures (DRFs) are among the most common fractures seen in the emergency department and account for nearly one-sixth of all fractures (1,2). Conservative management with closed reduction and casting is considered the first-line treatment (3). However, radial shortening is the most common complication of conservative treatment (4). Shortening of the distal radius could lead to poorer clinical outcomes such as pain, restricted wrist movements, and arthrosis (5,6). Surgical treatment of DRF restores the anatomy of the distal radius and includes closed reduction and percutaneous pinning (CRPP) or external fixation and open reduction-plate osteosynthesis (7,8).

CRPP is a minimally invasive surgical treatment (7,9); however, the distal radius may collapse even after pin removal (5). Transulnar pinning with CRPP of the DRF was previously reported to be the most biomechanically stable method and prevents radial shortening (10-12).

In this study, we assessed the functional and radiological outcomes of adding transulnar pinning and compare its outcomes with those of CRPP without transulnar pinning. Our hypothesis is that additional transulnar pinning prevents fracture collapse and results better radiologic and clinical outcomes.

Methods

This retrospective study was approved by the Acıbadem University Institutional Review Board with (approval number: 2021-08/42, date: 21.04.2021) and informed consent was obtained from the patients included in the study. Data of patients who were treated with CRPP for DRF between January 2016 and July 2021 were reviewed. Patients with dorsally displaced DRF without articular involvement or with minimally displaced articular involvement, had failed initial closed reduction attempt at the emergency department, and who were treated with CRPP were included in the study. Patients with a history of surgery at the same upper extremity had a distal ulnar shaft fracture, aged <18 years, and did not want to participate in the study were excluded. Finally, 27 patients were included in the analysis. Patient registration data consisting of radiological and physical examination findings (postoperative day 1, 3 weeks, 6 weeks, and 12 weeks) were retrospectively evaluated. The patients were divided into two groups. Group 1 consisted of patients who received isolated radial pinning with K-wires, whereas group 2 had additional transulnar K-wires.

All patients underwent surgery under general or regional anesthesia. Closed reduction was performed manually or with finger straps under

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Cite this article as: Ekinci M, Karaytuğ K. The Effect of Transulnar Pinning in Preventing Postoperative Radial Collapse and Wrist Motions in Distal Radius Fracture. İstanbul Med J 2022; 23(4): 260-3.

Received: 28.06.2022
Accepted: 02.10.2022

fluoroscopy. The reduction was confirmed. After achieving optimal reduction, two (1.6-2 mm) K-wires were inserted percutaneously from the styloid process of the radius to engage with the opposite cortex. Thereafter, one (1.6-2 mm) K-wire was percutaneously inserted to strengthen the stability at a different angle (from the dorsal cortex of the radius (medial to Lister's tubercle) to the volar and lateral opposite cortex of the radius or from the opposite direction). However, patients in group 2 were introduced with an additional transulnar K-wire to prevent the collapse of the fracture. This K-wire was inserted from the radius to the ulna parallel to the joint line and controlled under fluoroscopy. K-wires were bent and cut. Following the K-wire fixation, a short arm cast was applied to the patients to allow elbow movements. Finger range of motion (ROM) exercises were started on the day of surgery.

Patients underwent clinical and radiographic assessments (bone healing, wire positions, collapse of the fracture, wound checks) at 3, 6, and 12 weeks postoperatively. The union was defined as spotting at the fracture gap or callus tissue between the fractured proximal and distal cortices or trabeculae on standard X-ray images. The K-wires and casts were removed at week 6 of follow-up, and physiotherapy was initiated (Figure 1, 2).

Radiographic measurements were performed using the Picture Archiving and Communication System of the institution. Radiographic measurements were performed on postoperative day 1 and postoperative weeks 3rd, 6th and 12th. Ulnar variance (mm), radial inclination angle (degrees) and volar tilt angle (degrees) were measured the preoperative X-rays and compared with values measured at 12th weeks postoperative radiographs. Radial shortening was calculated as the difference in ulnar variance measurements obtained immediately after surgery and at 12 weeks after surgery. Radiographic ROM of the wrist joint (flexion-extension and forearm supination pronation) was assessed using a goniometer at the final follow-up. At the final follow-up, the disabilities of the arm, shoulder, and hand (DASH) questionnaire was used to assess functional outcome scores.

Statistical Analysis

Statistical analyzes were performed using SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0., Armonk, NY: IBM Corp.) program. The radial height, ulnar variance, and functional outcomes of the two groups were compared and analyzed using Mann-Whitney U test. P-value <0.05 was considered significant.

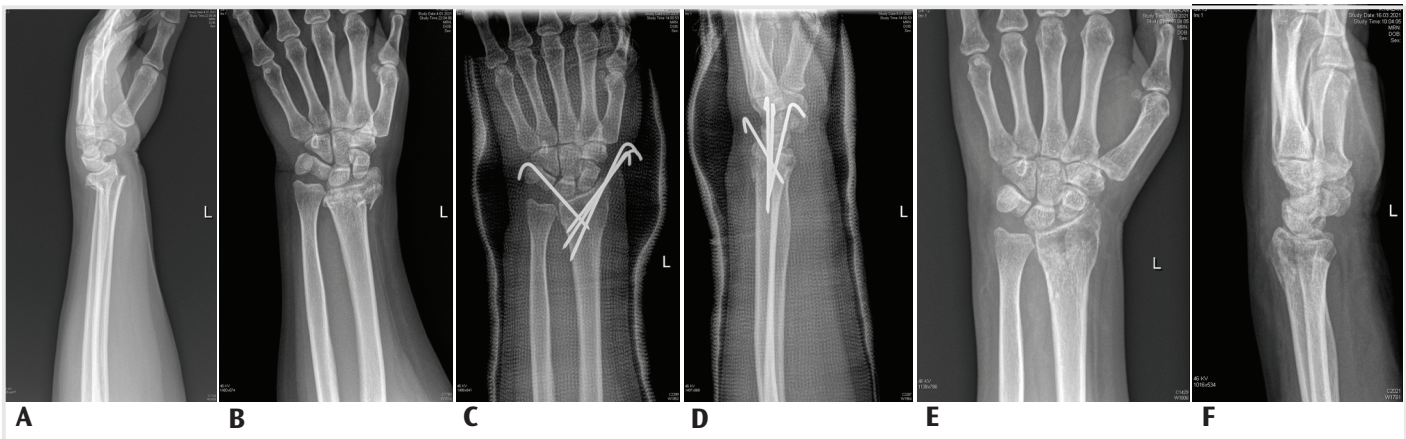

Figure 1. Displaced distal radius fracture operated with isolated radial pinning technique. (A) Preoperative anteroposterior X-ray. (B) Preoperative lateral X-ray. (C) Early postoperative anteroposterior X-ray, (D) Early postoperative lateral X-ray. (E) Postoperative 12th week anteroposterior X-ray, (F) postoperative 12th week lateral X-ray

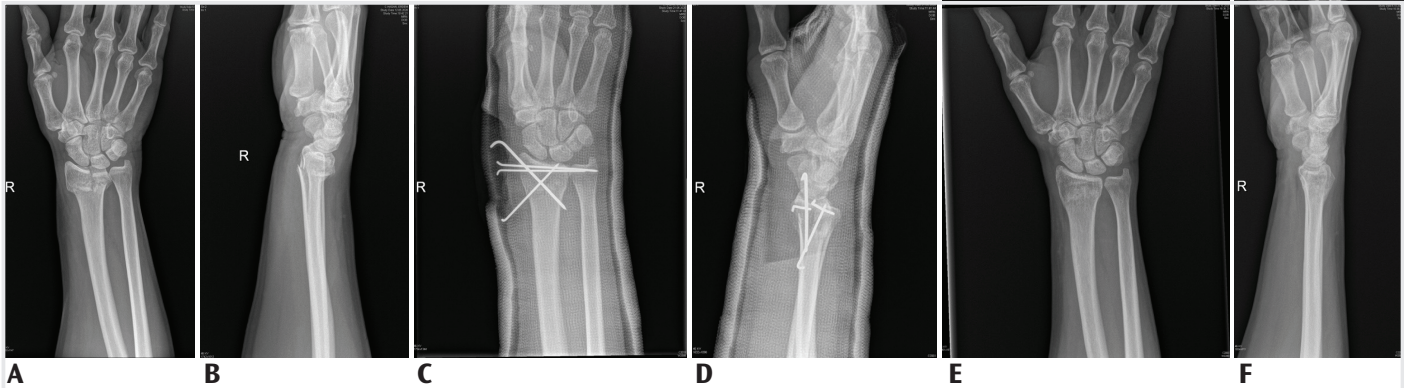

Figure 2. Displaced distal radius fracture was operated with the transulnar radial pinning technique. (A) Preoperative anteroposterior X-ray. (B) Preoperative lateral X-ray. (C) Early postoperative anteroposterior X-ray, (D) early postoperative lateral X-ray. (E) Postoperative 12th week anteroposterior X-ray, (F) postoperative 12th week lateral X-ray

Results

In group 1, 16 patients received isolated radius pinning, while in group 2, 11 patients were treated with additional transulnar pinning. There were seven men and nine women in group 1 and four men and seven women in group 2. The average age of the patients was 55.2 years in group 1 and 58.5 years in group 2. Fracture occurred in 57.1% of the patients in group 1 and in 56.2% in group 2. The mean follow-up duration was 22.4 and 20.2 months in groups 1 and 2, respectively. The mechanism of injury was a simple fall in 9 patients, motor vehicle accidents in 7 patients, falling from a height in 5 patients, and sports injury in 6 patients (Table 1).

Ulnar variance values were -1.46, -1.35, -1.32, and -1.32 mm in group 1 and -1.37, -1.32, -1.30, and -1.30 mm in group 2 on postoperative day 1 and weeks 3, 6, and 12, respectively. No significant difference was found between the two groups in terms of ulnar variance (Table 2). Radial collapse of 0.13±0.17 mm (0.03-0.78) was noted in group 1 and of 0.07±0.04 mm (0.02-0.14) in group 2. No significant difference was noted in radial shortening between the two groups (p=0.12). However, radial shortening was lower in the transulnar pinning group. There was no significant difference at 12th week radial inclination angle (p=0.73). No significant difference was found for 12th week volar tilt angle (p=0.34). The wrist flexion angle and pronation and supination ROM were significantly similar between the two groups. However, a significant difference was noted for the wrist extension ROM between the two groups at the final follow-up (p=0.039) (Table 3).

DASH scores were 13.6 and 14.2, respectively. The DASH scores were not significantly different by treatment types. No significant differences in functional scores were found except for wrist extensions.

Table 1. Demographic characteristics of the patients

	Group 1	Group 2
Number of the patients	16	11
Sex		
Male	7	4
Female	9	7
Age (years)	55.2	58.5
Follow-up (months)	22.4	20.2
Mechanism of injury		
Simple fall	5	4
Motor accident	4	3
Fall from height	3	2
Sports injury	4	2

Table 2. Measurement of ulnar variance in different time periods

	Ulnar variance in group 1 (mm)	Ulnar variance in group 2 (mm)	p-value
Preoperative	3.47±0.65	3.71±0.29	0.36
Postoperative 1st day	-1.46±0.27	-1.37±0.35	0.51
Postoperative 3rd week	-1.35±0.24	-1.32±0.37	0.68
Postoperative 6th week	-1.32±0.24	-1.30±0.36	0.9
Postoperative 12th weeks	-1.32±0.24	-1.30±0.37	0.89

No non-union was noted in our cohort, and no K-wires were broken during the postoperative period. One patient in the transulnar fixation group had superficial pin site infection, which was treated with debridement, pin removal, and antibiotherapy.

Discussion

The best fixation method for the surgical fixation of DRFs is controversial (13,14). CRPP is one of the surgical treatment options for DRFs (15-17). It is minimally invasive and leads to similar long-term outcomes compared with open reduction and plate osteosynthesis (18). However, stabilization with K-wires is considered unstable (19), and radial shortening may occur even after K-wire removal (5). Fracture collapse and radial shortening may result in lower functional outcomes and arthrosis of the wrist joint (5,6). Thus, we examined the effect of additional transulnar pinning to prevent radial shortening while performing CRPP of DRFs. This study showed that transulnar pinning prevented radial shortening more than isolated radial pinning; however, the results did not show any significant difference. Functional results were also comparable.

Onta et al. (20) examined the effects of transulnar fixation pinning to prevent postoperative radial shortening in their prospective and comparative study and reported that additional ulno-radial pinning significantly prevented radial shortening compared with the two simple K-wire technique. Kim and Tae (21) retrospectively evaluated the clinical and radiological outcomes of DRFs treated with closed reduction and percutaneous transulnar fixation using K-wires and assessed the effectiveness for preventing fracture settling. They revealed that the method effectively prevented the collapse of the fracture site and the functional outcome was favorable. Our study evaluated both the effects of transulnar pinning in preventing radial shortening and clinical outcomes because the distal radioulnar joint (DRUJ) is temporarily

Table 3. The table demonstrates the radial collapse, radial inclination angle, volar tilt angle and wrist range of motions of the patients

	Group 1 (isolated radial pinning group)	Group 2 (transulnar pinning group)	p-value
Radial collapse (mm)	0.13±0.17	0.07±0.04	0.12
Preoperative radial inclination angle at (degrees)	14.8±4.6	15.1±4.1	0.51
12th week radial inclination angle (degrees)	20.4±3.2	19.9±3.8	0.73
Operative volar tilt angle (degrees)	-21.64±8.18	-18.74±6.83	0.42
12th week volar tilt angle (degrees)	7.8±3	8.1±2.9	0.34
Wrist extension ROM at final follow-up (degrees)	62.8±2.1	64.7±2.0	**0.04**
Wrist flexion ROM at final follow-up (degrees)	72.7±2.1	72.7±2.0	0.64
Pronation ROM at final follow-up (degrees)	73.7±1.8	74.3±1.9	0.32
Supination ROM at final follow-up (degrees)	74.8±1.6	74.0±1.7	0.16

ROM: Range of motion

immobilized with a K-wire and the effect of DRUJ pinning on functional outcomes is not fully understood. We showed that transulnar pinning better prevented radial shortening compared with cross-pinning alone of the distal radius. However, our study showed no significant difference between the two groups in terms of radial shortening and functional outcomes. This is the study strength.

Study Limitations

However, this study has some limitations. First, this study followed a retrospective design and analyzed few patients. Second, comparing these fixation methods with plate and screw fixation groups could have strengthened the study. However, this study was designed to compare available techniques in patients who cannot be fixed with a plate and screw, such as patients with morbid diseases, advanced age, cardiac problems, and diabetes and had a preference. Third, although the aim was to prevent radial collapse with transulnar pinning, DRUJ arthrosis and pin breakage may occur. We did not experience any DRUJ arthritis at the last follow-up and any transulnar pin breakage, but further evidence can be obtained with long-term follow-up.

Conclusion

This study revealed that transulnar pinning did not significantly prevent radial collapse compared isolated radial pinning for DRFs. Radial collapse could not be completely prevented in both methods. In contrast to the radiological results, patient-reported results were similar in both groups. We predicted that similar functional results and more successful radiological results can be obtained with transulnar pinning in patients who planned to undergo closed reduction and pinning of DRFs.

Ethics Committee Approval: This retrospective study was approved by the Acıbadem University Institutional Review Board (approval number: 2021-08/42, date: 21.04.2021).

Informed Consent: Informed consent was obtained from the patients included in the study

Peer-review: Externally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - M.E., K.K.; Concept - M.E.; Design - K.K.; Data Collection or Processing - M.E.; Analysis or Interpretation - M.E., K.K.; Literature Search - M.E.; Writing - M.E., K.K.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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İstanbul Med J 2022; 23(4): 264-8
DOI: 10.4274/imj.galenos.2022.90757

Clinical Usage of Cardiovascular Magnetic Resonance Imaging: Single-Center Experience in the New Era of Cardiovascular Imaging

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ABSTRACT

Introduction: Utilization of cardiac magnetic resonance imaging (CMRI) has been increasing year by year for the most cardiovascular diseases. In this paper, we documented a real-life experience of our center as a high-volume CMRI performing center.

Methods: We have retrospectively analyzed the 100 patients who have undergone CMRI at our center during the last 1 year. All the preliminary diagnoses, specialty or subspecialty of referring physicians, patient characteristics and CMRI findings were analyzed.

Results: In 87 of 100 scans, a gadolinium-based contrast agent was used and in none of these procedures neither complications nor adverse events related to the contrast agent has occurred. Among these 100 consecutive CMRIs were referred to by a clinical cardiologist, invasive cardiologists, heart failure specialist, cardiovascular imaging specialists, electrophysiologists, and other specialists. On referral from a clinical cardiologist, the CMRI findings were high consistency. In these patients, the biggest number of preliminary diagnoses belongs to hypertrophic cardiomyopathy. The most common MRI finding was reduced left ventricular ejection fraction. In 25 patients we observed extracardiac findings.

Conclusion: CMRI is increasingly occurring in cardiovascular imaging and diagnosis of various cardiovascular diseases. CMRI not only produces high-resolution morphological images but also provides quantitative information on the severity of regurgitant or stenotic lesions in valvular diseases or cardiac shunts with the velocity and flow measurements.

Keywords: Cardiovascular imaging, cardiac magnetic resonance, cardiovascular diseases

Introduction

Imaging in human medicine is one of the fastest developing areas in the medical practice and cardiovascular imaging has also entered a period of rapid development by showing a parallel course to this general development with various novel methods. The utilization of cardiac magnetic resonance imaging (CMRI) has been increasing year by year, and it has emerged as the "gold standard" diagnostic test for most cardiovascular diseases. Despite numerous randomized controlled trials on CMRI, the use of this method in clinical practice is still disappointing. Some of the most important reasons for this are the insufficient number of trained physicians and technicians, high cost and lack of MR machines in several centers.

In this paper, we documented a real-life experience of our center as a high-volume CMRI performing center compared to with other centers in our country and serve a descriptive data about the clinical usage of CMRI.

Methods

Study Population

We have retrospectively analyzed the last 100 consecutive patients who have undergone CMRI in our center during the last 1 year. The study protocol was approved by the Local Ethics Committee of Memorial Bahçelievler Hospital (approval number: 19, date: 13.09.2021). Written consent was obtained from all patients. All the preliminary diagnoses, specialty or subspecialty of referring physicians, patient characteristics and CMRI findings were analyzed. All images were reviewed by an experienced and European Association of Cardiovascular Imaging (EACVI) CMR exam certified cardiovascular multimodality imaging specialist. Detailed patient characteristics are given in Table 1. Mean age of the patients was 42.9±15.3. In 87 of 100 scans, a gadolinium-based contrast agent was been used and in none of these procedures neither complications nor adverse events related to contrast agent occurred. Ninety-three patients were referred from an outpatient clinic, and 7 of

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Cite this article as: Özden Ö, Tokdil H, Ohtaroğlu Tokdil K, Sevgican Cİ, Bingöl G. Clinical Usage of Cardiovascular Magnetic Resonance Imaging: Single-Center Experience in the New Era of Cardiovascular Imaging. İstanbul Med J 2022; 23(4): 264-8.

Received: 03.08.2022
Accepted: 11.10.2022

them were the patients who were already hospitalized due to different etiologies (Table 1).

Statistical Analysis

Statistical Package for the Social Sciences (v.24., Chicago, Ill., USA) program was used in this study. As the statistical analyzes were based on categorical data, they were described as frequency and percentage.

CMR Setting

All CMR exams were performed on the same 1.5 T scanner (Magnetom Avanto, Siemens Healthcare, Erlangen, Germany). Our CMR services were provided for both outpatients and inpatients. The principal referring departments were our hospital's cardiology in- and outpatient departments, as well as other university and public hospitals outpatient departments from different cities of our country. CMR protocols were planned as follows: For CINE imaging steady-state free-precession, for myocardial edema triple-inversion T2-weighted spin-echo, for late enhancement T1-weighted inversion-recovery turbo fast low-angle shot sequence, for flow study two-dimensional (2D) phase contrast acquisition was used. Each exam and report was supervised by one cardiologist who trained at a level 3 certificated center and passed the EACVI board exam and an experienced radiologist.

A dedicated software was used for all qualitative and quantitative evaluations (CVI 42, Version 5.1, Circle Cardiovascular Imaging, Calgary, Canada).

Results

Among these 100 consecutive CMRIs, 27 were referred by a clinical cardiologist. Invasive cardiologists took the second place with 26 referrals. Other specialties in order are as follows, heart failure (HF) specialists (N:15), cardiovascular imaging specialists (N:12), electrophysiologists (N:10), sports cardiologists (N:4). After them; pulmonologist, oncologist, cardiovascular surgeon, pediatric cardiologist, neurologist, and rheumatologist came with 1 referral for each (Table 2).

As the most referral from a clinical cardiologist, 18 of 27 referrals, the CMRI findings were consistent with clinically suspected diagnosis (66.67%) with a high consistency. The second most referred specialty was invasive cardiologists by 26, and among these 26 patients, 20 patients' CMRI findings were consistent with clinically suspected diagnosis, which made the invasive cardiologists the highest consistency ratio (76.92%) except from the departments who have referred to 1 patient. Electrophysiologists referred 10 patients and 2 were consistent with clinical suspected diagnosis and 8 were not, which made them have the least consistency ratio by 20% (except from the departments who have referred single patient). Additional findings are below (Table 2).

Table 1. Patient characteristics

	Patients (n=100)
Year, age	42.9±15.3
Height, cm	172.28±11.23
BSA, kg/m^2	1.98±0.23
Hospitalized patients	7 (7%)
Contrast agent usage	87 (87%)

In these 100 patients, the biggest number of preliminary diagnoses belongs to hypertrophic cardiomyopathy (HCM) (26 referrals). After HCM, myocarditis, dilated cardiomyopathy (DCM) and etiology of ventricular tachycardia (VT) caused 10 referrals for each clinical situation. Five referrals have were made due to reduced ejection fraction (EF) and myocardial viability investigation. Other findings are below in Table 3.

Table 4 demonstrates the CMRI findings of these 100 patients. The most common MRI finding was reduced left ventricular EF [42], followed by mitral regurgitation [23]. In 25 patients we observed extracardiac findings. Nineteen patients were diagnosed with HCM and 15 with DCM. A total of 7 had pericardial effusion, and 11 had myocarditis. 10% of the patients (N:10) had completely normal CMRI findings. Additional findings are below Table 3.

The CMRI findings of patients are listed in Table 4, 5 shows the extracardiac findings that are detected in these scans. The most common extracardiac finding was pleural effusion [7] followed by renal and liver cysts (4 for each). Two patients had mediastinal lymphadenomegaly and two had pulmonary nodules.

Lastly, among the patients referred to CMRI, Table 6 demonstrates the consistency of preliminary diagnosis to final diagnosis. Twenty-six patients have been referred to CMRI with a preliminary diagnosis of HCM. Seventeen of them (65.38%) were diagnosed with HCM and showed the highest rate of consistency with the preliminary diagnosis. Ten patients were referred for DCM investigation and other 10 for myocarditis. For DCM, 8 patients have been diagnosed consistently (80%), and 7 for myocarditis (70%). Also, a notable point, among 10 patients who referred to CMRI to investigate the etiology of VT-such as arrhythmogenic substrate or scar tissue- none of them (0%) was diagnosed with preliminary diagnosis as arrhythmogenic right ventricular dysplasia and myocardial non-compaction, which were suspected in 3 patients for each and diagnosed in none of them with 0% consistency.

Table 2. Referred specialty and consistency of MRI findings with clinical diagnosis

	Patients (n=100)	Clinical diagnosis and MRI findings consistency	
Referred specialty		**Consistent**	**Inconsistent**
Clinical cardiologist	27 (27%)	18 (66.67%)	9 (33.33%)
Invasive cardiologist	26 (26%)	20 (76.92%)	6 (23.08%)
Heart failure specialist	15 (15%)	9 (60%)	6 (40%)
Cardiac imaging specialist	12 (12%)	9 (75%)	3 (25%)
Electrophysiologist	10 (10%)	2 (20%)	8 (80%)
Sports cardiologist	4 (4%)	2 (50%)	2 (50%)
Pulmonologist	1 (1%)	1 (100%)	0 (0%)
Oncologist	1 (1%)	1 (100%)	0 (0%)
Cardiovascular surgeon	1 (1%)	1 (100%)	0 (0%)
Pediatric cardiologist	1 (1%)	1 (100%)	0 (0%)
Neurologist	1 (1%)	0 (0%)	1 (100%)
Rheumatologist	1 (1%)	1 (100%)	0 (0%)

MRI: Magnetic resonance imaging

Table 3. Preliminary diagnosis

	Patients (n=100)
Hypertrophic cardiomyopathy	26 (26%)
Etiology of ventricular tachycardia	10 (10%)
Dilated cardiomyopathy	10 (10%)
Myocarditis	10 (10%)
Reduced ejection fraction	5 (5%)
Myocardial viability	5 (5%)
Mitral valve prolapsus	4 (4%)
Arrhythmogenic right ventricular dysplasia	3 (3%)
SLE myocarditis and pericarditis	3 (3%)
Aortic stenosis	3 (3%)
Myocardial non-compaction	3 (3%)
Sarcoidosis	2 (2%)
Amyloidosis	2 (2%)
Aort coarctation	2 (2%)
Mitral regurgitation	2 (2%)
Aortic regurgitation	2 (2%)
Operated tetralogy of fallot	2 (2%)
Left ventricular thrombus	1 (1%)
Aortic root dilatation	1 (1%)
Myocardial infarction with non-obstructive coronary arteries	1 (1%)
Tricuspid regurgitation	1 (1%)
Mitral annular disjunction	1 (1%)
Cardiac involvement in scleroderma	1 (1%)

SLE: Systemic lupus erythematosus

Table 4. Cardiac MRI findings

MRI finding	Patients (n=100)	MRI finding	Patients (n=100)
Reduced LVEF	42 (42%)	Tricuspid regurgitation	6 (6%)
Extracardiac findings	25 (25%)	Myocardial viability	5 (5%)
Mitral regurgitation	23 (23%)	Aortic stenosis	3 (3%)
HCM	19 (19%)	Pericarditis	3 (3%)
DCM	15 (15%)	LV non-compaction	3 (3%)
Pericardial effusion	14 (14%)	Amyloidosis	3 (3%)
Myocarditis	11 (11%)	Papillary muscle hypertrophy	2 (2%)
Normal findings	10 (10%)	Cardiac involvement in sarcoidosis	2 (2%)
Aortic regurgitation	8 (8%)	Operated tetralogy of Fallot	2 (2%)
Bicuspid aortic valve	7 (7%)	ARVD	1 (1%)
Mitral valve prolapsus	7 (7%)	Left ventricular thrombi	1 (1%)
Aortic root dilatation	7 (7%)	Subaortic aneurysm	1 (1%)
Ascending aort dilatation	7 (7%)	SLE Myocarditis	1 (1%)
History of MI	7 (7%)	SLE Pericarditis	1 (1%)
Reduced RVEF	6 (6%)	Scleroderma	1 (1%)
Mitral annular disjunction	6 (6%)	-	-

MRI: Magnetic resonance imaging, LVEF: Left ventricular ejection fraction, HCM: Hypertrophic cardiomyopathy, DCM: Dilated cardiomyopathy, LV: Left ventricular, MI: Myocardial infarction, RVEF: Right ventricular ejection fraction, ARVD: Arrhythmogenic right ventricular dysplasia, SLE: Systemic lupus erythematosus

Table 5. Extracardiac findings

	Extracardiac findings (n=25)		Extracardiac findings (n=25)
Pleural effusion	7 (7%)	Pectus excavatum	1 (1%)
Renal cysts	4 (4%)	Muscular atrophy	1 (1%)
Liver cysts	4 (4%)	Liver metastasis	1 (1%)
Mediastinal LAM	2 (2%)	Tumoral thickening of stomach	1 (1%)
Pulmonary nodule	2 (2%)	Splenic cyst	1 (1%)
Axillary LAM	1 (1%)	Eventration of diaphragm	1 (1%)
Splenomegaly	1 (1%)	-	-

LAM: Lymphadenomegaly

Discussion

Over the past few years, CMRI has been increasingly recognized as a valuable cardiovascular imaging modality in the evaluation of heart diseases. CMRI is generally evaluated and reported by radiologists, while in centers such as ours, cardiology and radiology collaborate with a multi-disciplinary approach from an anatomical, functional, and clinical perspective. There are many articles on CMRI physics and cardiovascular diseases prepared for clinicians (1) and the European Society of Cardiology has a practical pocket guide for cardiologists for CMR as well (2). In other words, CMRI is increasingly occurring in cardiovascular imaging and diagnosis of various cardiovascular diseases and the experience of cardiologists, who provide additional clinical information on this subject, is gradually increasing.

CMRI not only produces high-resolution morphological images compared with transthoracic echocardiography (TTE) but also provides quantitative information on the severity of regurgitant or stenotic lesions in valvular diseases or cardiac shunts with the velocity and flow measurements (3-5).

CMRI is widely used for the diagnosis and diagnosing of many cardiomyopathies. Particularly in HCM, the use of CMR is recommended to determine the sudden cardiac death (SCD) risk (6,7). In our study, the most common preliminary diagnosis was HCM, while in the articles sharing the experiences of other centers, it may be ischemic cardiomyopathy or myocarditis. It may vary according to the interests of the physicians in these centers or the interests of the centers to which they are referred (8,9). Patients with HCM may be asymptomatic and have a normal life expectancy, or they may present with more severe clinical manifestations and prognoses with ventricular arrhythmia, SCD, or HF (10-12).

CMRI is a very useful imaging method both in diagnosing HCM and in determining HCM phenotypes because it can clearly show cardiac

morphologies. The most accurate measurement of left ventricular wall thickness can also be measured by CMRI. CMRI helps risk stratification as it detects "high-risk" phenotypes and defines myocardial fibrosis as well. It is also highly valuable for differentiating HCM from other causes of left ventricular thickening (13,14).

Therefore, CMRI is of great importance in clinical practice in patients with or suspected of having HCM. In our clinic, CMRI was requested mostly with the pre-diagnosis of HCM (26%), and in 65.3% of these patients, the clinical pre-diagnosis and the CMRI result were compatible.

Having HCM as the most frequent referred pre-diagnosis, the most common finding was reduced EF in our study. In our daily clinical practice, 2D TTE is the most widely used method to determine systolic cardiac dysfunction. For this purpose, LV end-diastolic and end-systolic volumes and EF are commonly used. However, TTE is quite user-dependent and intra- and interobserver variability is high, especially in patients with poor image quality. The fact that EF is affected by many parameters creates limitations and reduces reliability as well (15). CMRI is a more reliable method to evaluate cardiac functions, chamber volumes compared with TTE, and it also allows to evaluate cardiac structure and provides tissue caharcterization such as inflammation, edema and fibrosis (16).

Table 6. Consistency of preliminary diagnoses and cardiac MRI findings

	Consistent	Inconsistent
HCM	17 (65.38%)	9 (34.62%)
DCM	8 (80%)	2 (20%)
Myocarditis	7 (70%)	3 (30%)
Myocardial viability	5 (100%)	0 (0%)
Mitral valve prolapsus	4 (100%)	0 (0%)
Reduced EF	4 (80%)	1 (20%)
Aortic stenosis	3 (100%)	0 (0%)
Amyloidosis	2 (100%)	0 (0%)
Mitral regurgitation	2 (100%)	0 (0%)
Aortic regurgitation	2 (100%)	0 (0%)
Operated tetralogy of fallot	2 (100%)	0 (0%)
Left ventricular thrombi	1 (100%)	0 (0%)
Sarcoidosis	1 (50%)	1 (50%)
Aort coarctation	1 (50%)	1 (50%)
Aortic root dilatation	1 (100%)	0 (0%)
MINOCA	1 (100%)	0 (0%)
Tricuspid regurgitation	1 (100%)	0 (0%)
SLE myocarditis or pericarditis	1 (33.33%)	2 (66.67%)
Mitral annular disjunction	1 (100%)	0 (0%)
Scleroderma	1 (100%)	0 (0%)
ARVD	0 (0%)	3 (100%)
Etiology of VT	0 (0%)	10 (100%)
Suboptimal echogenity	0 (0%)	0 (0%)
Pericarditis	0 (0%)	0 (0%)
Myocardial non-compaction	0 (0%)	3 (100%)

MRI: Magnetic resonance imaging, HCM: Hypertrophic cardiomyopathy, DCM: Dilated cardiomyopathy, EF: Ejection fraction, MINOCA: Myocardial infarction with non-obstructive coronary arteries, SLE: Systemic lupus erythematosus, ARVD: Arrhythmogenic right ventricular dysplasia, VT: Ventricular tachycardia

Another advantage of CMRI over TTE is the detection of extracardiac findings. Extracardiac findings such as pleural effusion, renal and hepatic cyst, lymphadenopathy, pulmonary nodule, etc. are the common ones. As CMRI cases assessed by both radiologist and cardiologist together in our center, it allows for an accurate evaluation of extracardiac findings in the image field, thus helping in early detection of conditions such as pulmonary nodules or malignant masses, where early diagnosis is vital.

Study Limitations

The main limitation of our study is its single-center nature, which would cause a bias regarding patient referral, selection of imaging procedures. Another limitation of the study is its retrospective nature, but it also overcomes the patient referral bias. It should also be noted as a limitation, that all images were reviewed by only two cardiovascular imaging specialists (one radiologist and one cardiologist), rather than multiple reviewers due of lack of CMRI specialists experienced in the field.

Conclusion

In the results of the study, despite the limited time and the small number of patients, it has been shown that the diagnoses that are not often considered in clinical practice, such as mitral annular dysjunction, papillary muscle hypertrophy, which haven't been noted to be associated with arrhythmia previously, can be clearly and easily detected by CMRI. In the era of multimodality cardiovascular imaging, where the use of CMR is the gold standard in some heart diseases and is increasingly widespread, we wanted to share our experience in the compatibility of the diagnosis of CMRI with the clinical prediagnosis, the extracardiac findings we determined, and the compatibility rate of the diagnoses according to the subspecialty in our clinic.

Ethics Committee Approval: The study protocol was approved by the Local Ethics Committee of Memorial Bahçelievler Hospital (approval number: 19, date: 13.09.2021).

Informed Consent: Written consent was obtained from all patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - Ö.Ö., G.B.; Concept - Ö.Ö., K.O.T.; Design - H.T., C.İ.S., G.B.; Data Collection or Processing - Ö.Ö., K.O.T., C.İ.S.; Analysis or Interpretation - Ö.Ö., H.T., C.İ.S., G.B.; Literature Search - H.T., K.O.T.; Writing - Ö.Ö., H.T., K.O.T., G.B.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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İstanbul Med J 2022; 23(4): 269-74
DOI: 10.4274/imj.galenos.2022.56804

Time to Castration Resistance as a Predictor of Response to Docetaxel in Metastatic Castration Resistance in Prostate Cancer

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ABSTRACT

Introduction: For metastatic prostate cancer (PC), androgen deprivation therapy (ADT) is the primary treatment option. Most patients develop resistance, after an initial response to treatment. This study aimed to evaluate real-life data of first-line docetaxel treatment for metastatic castration-resistant prostate cancer (mCRPC) and analyzed whether the response time to ADT could predict the response to docetaxel treatment.

Methods: The study included 111 patients with mCRPC who were treated with docetaxel. Time to castration resistance (TTCR) was defined as the time from initiation to the failure of primary ADT. Patients were divided into two groups based on TTCR. Patients with TTCR ≤12 months were assigned to group 1, while patients with TTCR >12 months were assigned to group 2.

Results: The median overall survival (OS) of the patients in group 1 was 16 months, whereas the median OS in group 2 was 38 months. Group 2 had a statistically significantly longer OS than group 1 ($p<0.001$). The median progression-free survival (PFS) of the patients in group 2 was 14 months while the median PFS in group 1 was 7 months. Group 2 had a statistically significantly longer PFS than group 1 ($p<0.001$). TTCR, Gleason score, and liver metastasis parameters were found to be predictive factors for OS.

Conclusion: In patients with mCRPC, TTCR was found to be a predictor of OS and PFS who were treated with docetaxel.

Keywords: Prostate cancer, androgen deprivation therapy, docetaxel, metastatic castration-resistant prostate cancer

Introduction

Prostate cancer (PC) is the second most common malignancy in men worldwide (1). The growth and proliferation of tumor cells are androgen-dependent. Therefore, for metastatic PC, androgen deprivation therapy (ADT) is the treatment of choice. Most patients develop resistance, after the initial response to ADT, and are termed castration-resistant prostate cancer (CRPC) at this stage. Previously, docetaxel was the primary treatment option at this stage (2). Recently, there have been many advancements in treatment options, and novel agents (radium-223, sipuleucel-T, abiraterone acetate, and enzalutamide) with various mechanisms of action prolong overall survival (OS) (3-6). Therefore, we should choose between taxane-based chemotherapy and new agents targeting the androgen receptor axis as first-line therapy for patients with metastatic CRPC (mCRPC). Cytotoxic chemotherapy still is central to patients with a visceral metastasis. There is a need for additional predictive markers to distinguish patients who may benefit from docetaxel treatment and to avoid unnecessary adverse effects and costs. Studies have shown that the time to castration resistance (TTCR) may be a predictive factor to use androgen receptor axis targeted agents for treatment choice (7,8). This study purposed to evaluate real-life data of docetaxel treatment and analyze whether TTCR could predict the response to docetaxel treatment in the mCRPC stage.

Methods

Patients with a diagnosis of mCRPC who were treated with docetaxel between August 2014 and 2021 were retrospectively analyzed. All patients had a pathologically confirmed diagnosis of PC and castrated testosterone level. CRPC was defined as radiological or biochemical progression of castrated testosterone levels with ADT. Biochemical progression was defined as a 50% increase in two of three sequential prostate-specific

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Cite this article as: Gültürk İ, Şahingöz Erdal G, Sönmezoz GB, Yılmaz M, Yıldız Tacar S, Özmen A, Tataroğlu Özyükseler D, Dulgar Ö, Çil İ, Tural D. Time to Castration Resistance as a Predictor of Response to Docetaxel in Metastatic Castration Resistance in Prostate Cancer. İstanbul Med J 2022; 23(4): 269-74.

Received: 21.07.2022
Accepted: 13.10.2022

antigen (PSA) measurements obtained at 1-week intervals, provided the PSA value was >2 ng/mL. The files of 126 patients in the mCRPC stage who received first-line docetaxel therapy were analyzed. Six patients were excluded from the study due to the use of abiraterone acetate or enzalutamide during the castration-sensitive period, and nine patients had missing data. One hundred and eleven patients were included in the study. Docetaxel treatment with 5 mg oral prednisolone twice a day was administered 75 mg/m² every 3 weeks for eight cycles in the form of an 1-hour infusion at a standard dose. Biochemical tests were performed and patients with PSA progression were evaluated for radiological response by thorax, abdomen, pelvis-computed tomography and 99mTc-methylenediphosphonate bone scintigraphy or prostate-specific membrane antigen positron emission tomography/computed tomography. Radiologic evaluation was performed after the third course of docetaxel in patients without biochemical progression. Follow-up data, including time to biochemical progression and date of exitus, were available for all patients. TTCR was calculated from the initiation of ADT to the confirmation of CRPC, regardless of the stage. Data of patients were collected by a retrospective review of medical records. Age, stage, Gleason score, previous treatments, metastatic sites, Eastern Cooperative Oncology Group (ECOG), PSA value, and TTCR data were obtained. Patients diagnosed with castration-sensitive metastatic PC, non-metastatic PC and received abiraterone acetate and enzalutamide before docetaxel treatment were excluded from the study.

The study was approved by the Institutional Ethical Committee of University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital (approval number: 2021-17-15, date: 06.09.2021).

Statistical Analysis

Progression-free survival (PFS) was defined as the length of time from initiating treatment with docetaxel in a castration-resistant setting to the date of disease progression or death. OS was defined as the length of time from the first diagnosis of mCRPC to the date of death. Exitus from PC and disease progression are acceptable events. Continuous variables were expressed as median and range (interquartile range: Quartile 1-Quartile 3). OS and PFS were calculated using the Kaplan-Meier method. To assess the difference in survival functions among subgroups, the two-sided log-rank test was used. When performing a multivariable analysis (Backward stepwise LR method), the Cox proportional hazards regression model was used, which only included factors that showed statistical significance in the univariable analysis. After calculating a variance inflation factor <5 for factors included in the multivariable analysis, the multicollinearity was also evaluated. PFS and OS were presented as median values with a 95% confidence interval (CI). The level of statistical significance was set at p=0.05. Clinical data were analyzed using IBM SPSS version 23.0 (SPSS Inc, Chicago, IL, USA).

Results

Patient Characteristics

The files of 111 patients who received docetaxel treatment for the diagnosis of mCRPC were analyzed. The median patient age was 60.7 (range: 40-88). Sixty-five (59%) patients had an ECOG performance score of 0 and forty-six (41%) patients had an ECOG score of 1-2. Forty-seven (42.3%) patients had a Gleason score of 6 or lower, twenty-two (19.8%) patients had a Gleason score of 7, forty-two (37.8%) patients had a Gleason score of 8 or higher. Fifty-two (47%) patients were admitted for locally advanced disease, while fifty-nine (53%) patients were admitted for metastatic disease. The median PSA at diagnosis and before docetaxel treatment were 16.5 ng/dL, 72.2 ng/dL, respectively. The clinicopathological and demographic characteristics of the patients are presented in Table 1.

Survival Analysis

The median OS and PFS of the patients included in the study were 26.5 months [(95% CI; 19.6-33.4 months) and 11.5 months (95% CI, 9.5-13.5 months)], respectively. Patients treated with docetaxel were assigned to two groups based on TTCR. Patients with TTCR ≤12 months were assigned to group 1, while patients with TTCR >12 months were assigned to group 2.

In group 1, the median OS of the patients was 38 months, while in group 2 was 16 months, with a statistically significant difference (p<0.001). TTCR less than 12 months was found to be a predictive factor for a short survival time. The OS Kaplan-Meier plot for TTCR status is presented in Figure 1a. In group 2, the median PFS of the patients was 14 months (range, 11.1-16.9), while in group 1 was 7 months (range: 6.2-7.8). Group 2 had a statistically significantly longer PFS than group 1 (p<0.001). The PFS Kaplan-Meier plot for TTCR status is presented in Figure 1b. A TTCR value of less than 12 months was found to be a risk factor for short PFS in patients with mCRPC.

Clinical parameters considered having an effect on OS were analyzed using univariate Cox regression and the results of multivariate Cox regression analysis for the statistically significant variables are shown in Table 2.

TTCR, Gleason score, liver metastasis and high-volume parameters were found to have statistically significant effects (predictor of survival) on survival (p<0.05 in univariate analysis) (Figure 2a, b).

The results of the multivariate Cox regression analysis showed that TTCR, Gleason score and liver metastasis variables had a statistically significant effect on OS (p<0.05) (Table 2).

Clinical parameters considered having an effect on PFS were analyzed and the results of multivariate Cox regression analysis for the statistically significant variables are shown in Table 3. TTCR, visceral metastasis, and high volume were found to be significant predictors of survival independently of PFS (p<0.05 in univariate analysis). The results of the multivariate Cox regression analysis showed that visceral metastasis, TTCR and high-volume variables had statistically significant effects on PFS (p<0.05) (Table 3).

Twenty-three of the patients who progressed after docetaxel treatment were unable to continue treatment because of poor performance status or death. Fifty patients received abiraterone acetate, 29 patients received enzalutamide and 9 patients received cabazitaxel; in the second-line

Table 1. Clinical and pathological characteristics of patients with duration castration resistance

	TTCR <12 months		TTCR >12 months		p
	n	%	n	%	
Age median	66	-	66.5	-	-
<65	19	44.2	25	36.8	0.436
>65	24	55.8	43	63.2	-
Gleason score					
<6	16	37.2	31	45.6	**0.046**
7	5	11.6	17	25	-
>8	22	51.2	20	29.4	-
PSA on diagnosis					
Below the median PSA	24	55.8	32	47.1	0.369
Above the median PSA	19	44.2	36	52.9	-
PSA before docetaxel treatment					
Below the median PSA	13	30.2	42	61.8	**<0.001**
Above the median PSA	30	69.8	26	38.2	-
Metastasis at initial diagnosis					
No	18	41.9	34	50	0.402
Yes	25	58.1	34	50	-
Local treatment					
No treatment	23	53.5	29	42.6	0.329
Radiotherapy	11	25.6	16	23.5	-
Surgery	9	20.9	23	33.8	-
ECOG					
0	23	53.5	42	61.8	0.389
1-2	20	46.5	26	38.2	-
Visceral metastasis	28	65.1	15	22.1	**<0.001**
Liver metastasis	15	34.9	4	5.9	**<0.001**
High volume	36	83.7	21	30.9	**<0.001**
Lung metastasis	5	11.6	7	10.3	0.826
Bone metastasis	41	95.3	66	97.1	0.638

P-value was obtained from Exact or Pearson chi-square test. TTCR: Time to castration resistance, PSA: Prostate-specific antigen, ECOG: Eastern Cooperative Oncology Group

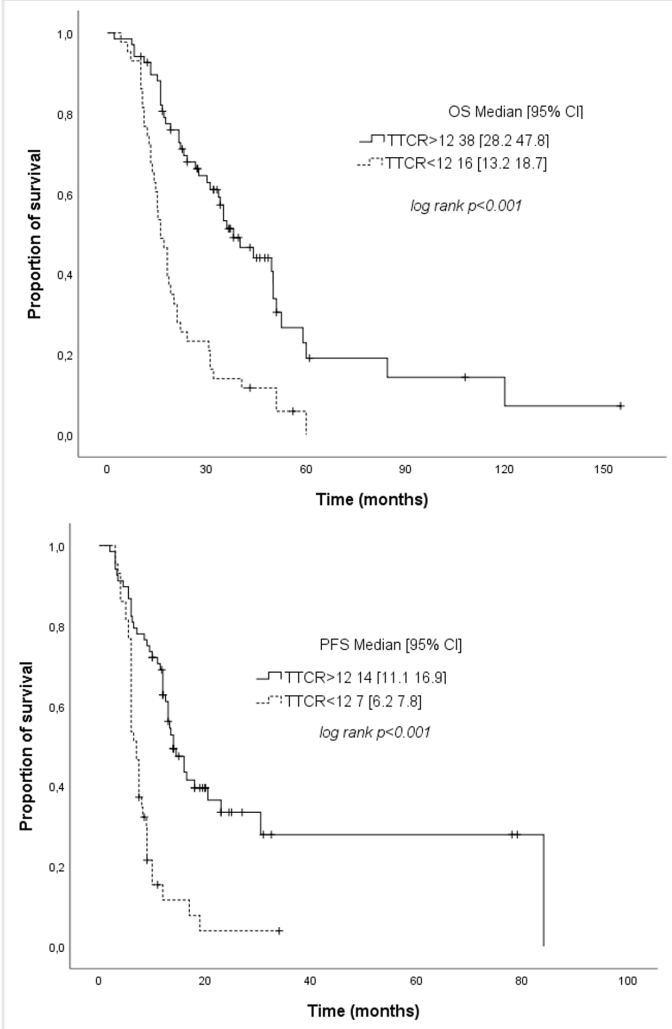

Figure 1. (**a**) Overall survival according to the time to castration resistance duration (over or under 12 months) (hazard ratio: 0.35). (**b**) Progression-free survival to the time to castration resistance duration (over or under 12 months) (hazard ratio: 0.30)
TTCR: Time to castration resistance, CI: Confidence interval, OS: Overall survival, PFS: Progression-free survival

treatment after docetaxel. The most common side effects related to docetaxel treatment; fatigue (n=24), diarrhea (n=13) and stomatitis (n=11) were observed. The incidence of grade 3 and 4 neutropenia was relatively low (n=8), and febrile neutropenia was rare (n=1). Side effects were managed with dose modification and no patients discontinued treatment.

Discussion

This study aimed to evaluate the relationship between survival and TTCR in patients who developed castration following ADT and were treated with first-line docetaxel in the mCRPC stage. The study results showed that patients with a response time shorter than 12 months to ADT before docetaxel had a poor response to chemotherapy. Moreover, this patient group had shorter OS and PFS compared to the other patient group. Furthermore, the multivariate analyses showed that it was a significant predictive factor of both OS and PFS. Prolonged TTCR can be considered a predictive factor to identify patients who may benefit from docetaxel in the castration resistance stage. A shorter TTCR is associated with shorter doubling time, a poor prognostic parameter, and a faster cell cycle. The cell cycle is fundamentally important in cancer treatment since many chemotherapy drugs only act on actively proliferating cells. Docetaxel stabilizes microtubules and prevents their depolymerization. This mechanism of action, is considered more effective in malignancies with a rapid cell cycle. There are a few studies in the literature evaluating the relationship between TTCR and the response to docetaxel treatment in PC. In this regard, the study of Bournakis et al. (7) including docetaxel and non-docetaxel regimens showed that TTCR <2 years for PFS and OS was an independent prognostic factor. Similar to that study, this study showed that shorter TTCR was linked with shorter OS and PFS. Especially, patients with TTCR <12 months showed a poorer prognosis in our study.

Docetaxel has been included for treating CRPC based on the results of two large, randomized studies (2,9). These studies showed that

Table 2. Prognostic factors for overall survival

	Univariate analysis		Multivariate analysis	
Variables	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**
Age				
<65 years old	1	0.089	-	-
≥65 years old	1.48 (0.94-2.33)			
TTCR				
<12 months	1	**<0.001**	1	**0.003**
>12 months	0.35 (0.22-0.55)		0.42 (0.24-0.73)	
Gleason score				
≤6	1	**0.023**	1	-
7	1.06 (1.00-1.93)	**0.014** **0.048**	1.59 (1.01-3.02)	-
≥8	1.91 (1.17-3.11)	**0.048** **0.009** **0.004**	2.13 (1.28-3.54)	-
PSA (diagnosis)				
PSA < median	1	0.360	-	-
PSA > median	0.81 (0.53-1.26)			
PSA (before docetaxel treat)				
PSA < median	1	0.277	-	-
PSA > median	1.27 (0.82-1.97)			
Metastatic on initial diagnosis				
Non-metastatic	1	0.479	-	-
Metastatic	0.86 (0.56-1.32)			
Local treatment				
(Ref: No treatment)	1	0.369	-	-
Radiotherapy	1.02 (0.60-1.74)			
Surgery	0.184 (0.85-2.37)			
ECOG				
(ref: 0)	1	0.647	-	-
1-2	1.11 (0.71-1.72)			
Visceral metastasis				
No	1	0.195	-	-
Yes	1.33 (0.86-2.06)			
Liver metastasis				
No	1	**0.004**	1	-
Yes	2.19 (1.29-3.72)	**0.037**	1.85 (1.04-3.31)	
High volume				
No	1	**0.002**	-	-
Yes	2.01 (1.29-3.14)			
Lung metastasis				
No	1	0.265	-	-
Yes	0.66 (0.32-1.37)			
Bone metastasis				
No	1	0.761	-	-
Yes	1.20 (0.38-3.81)			

HR: Hazard ratio, CI: Confidence interval, TTCR: Time to castration resistance, PSA: Prostate-specific antigen, ECOG: Eastern Cooperative Oncology Group

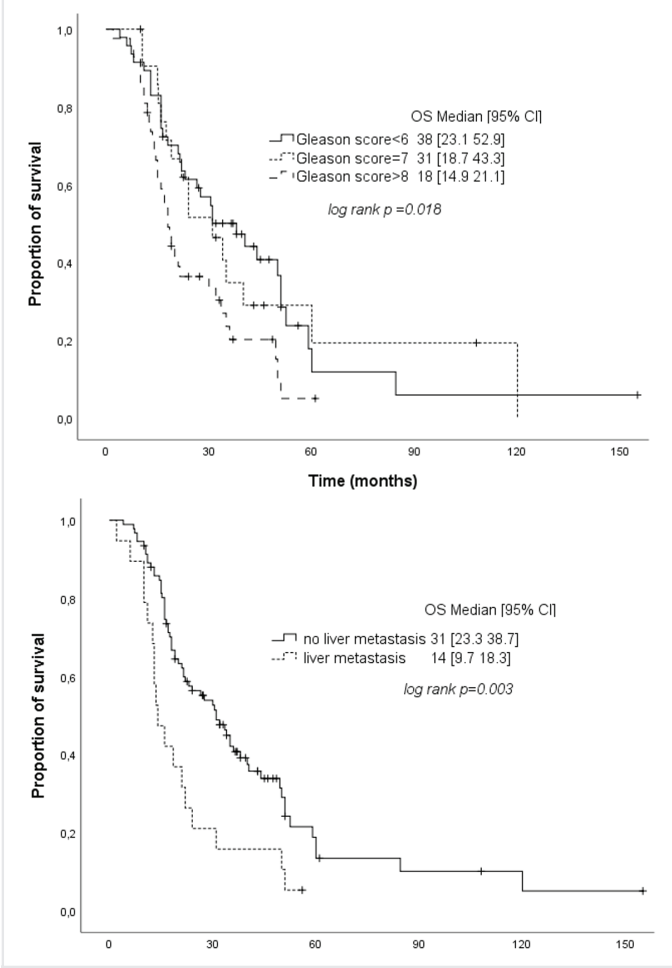

Figure 2. (**a**) Overall survival according to the Gleason score (hazard ratio: 1.59-2.13), (**b**) overall survival according to the liver metastasis (hazard ratio: 1.85)
CI: Confidence interval, OS: Overall survival, PFS: Progression-free survival

docetaxel treatment improved the quality of life of the patients as well as prolonged the OS time. It is important to initiate the right patient on the treatment at the right time since PC is seen in a relatively older population compared to other types of cancer and chemotherapy-related side effects cause more morbidity and mortality. To simplify these clinical decisions, a nomogram was created using independent prognostic factors in the TAX 327 studies. These prognostic factors include the Karnofsky performance status, pre-treatment PSA doubling time, baseline alkaline phosphatase, presence of liver metastases, number of metastatic sites, tumor grade baseline PSA, clinically significant pain, and baseline hemoglobin level (10). Additionally, the secondary analysis study of TAX 327 defined four independent risk factors to predict PSA decline and OS in patients with mCRPC and developed risk groups. These independent risk factors were defined as pain, visceral metastases, anemia, and progression of bone lesions (11). This study found that patients with liver metastases and patients with high-volume tumor burden had a faster disease progression and shorter OS. It was also observed that liver metastasis and high-volume tumor burden were significantly higher in the group with shorter TTCR (less than 12 months) compared to the group with longer TTCR.

Table 3. Prognostic factors for PFS

	Univariate analysis		Multivariate analysis	
Variables	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**
Age				
<65 years old	1	0.413	-	-
≥65 years old	1.21 (0.77-1.92)			
TTCR				
<12 months	1	**<0.001**	1	**0.007**
>12 months	0.30 (0.19-0.48)		0.44 (0.24-0.80)	
Gleason score				
≤6	1	0.062	-	-
7	0.78 (0.41-1.48)			
≥8	1.55 (0.95-2.52)			
PSA (diagnosis)				
<Median	1	0.504	-	-
>Median	0.86 (0.55-1.34)			
PSA (before docetaxel treatment)				
<Median	1	0.356	-	-
>Median	1.23 (0.78-1.92)			
Metastatic on initial diagnosis				
Non-metastatic	1	0.531	-	-
Metastatic	1.15 (0.74-1.80)			
Local treatment				
No treatment	1	0.680	-	-
Radiotherapy	0.79 (0.45-1.40)			
Surgery	1.02 (0.61-1.71)			
ECOG				
0	1	0.217	-	-
1-2	1.33 (0.85-2.08)			
Visceral metastasis				
No	1	**0.044**	1	**0.003**
Yes	1.58 (1.01-2.47)		2.71 (1.39 5.29)	
Liver metastasis				
No	1	0.061	-	-
Yes	1.73 (0.99-3.01)			
High volume				
No	1	**<0.001**	1	**0.001**
Yes	2.59 (1.64-4.11)		3.98 (1.77 8.95)	
Lung metastasis				
No	1	0.404	-	-
Yes	0.73 (0.35-1.53)			
Bone metastasis				
No	1	0.597	-	-
Yes	0.76 (0.28-2.09)			

PFS: Progression-free survival, CI: Confidence interval, TTCR: Time to castration resistance, PSA: Prostate-specific antigen, ECOG: Eastern Cooperative Oncology Group,

A retrospective study including 437 metastatic PC patients showed a relationship between the Gleason score and TTCR and OS (12). Our study also showed an inverse relationship between the Gleason score and TTCR and OS. It was found that patients' life expectancy and TTCR were shorter as their Gleason score increased. This result caused a statistically significant difference in patients who were assigned to two groups based on TTCR.

The approval of abiraterone and enzalutamide has increased the need to determine patients who may benefit more from chemotherapy for treating PC. The parameters that could predict the response to docetaxel treatment, which were analyzed in this study, were also investigated in some secondary hormone therapy studies. It has been shown that; short response time to previous ADT (<16 months) and patients with a high Gleason score at diagnosis, do not respond well to abiraterone and enzalutamide treatment (13,14). The study of Loriot et al. (14) evaluated the median response time to ADT in patients treated with ARATA. This study showed that patients with a longer initial ADT response responded better to secondary hormone therapies, and the ADT cut-off time was deemed 12 months (14). Bellmunt et al. (15) analyzed patients included in the COU-AA-301 and COU-AA-302 studies and demonstrated the positive effects of longer exposure to ADT on survival.

PC is more common in the geriatric population, which may have additional comorbidities. It is important to determine the appropriate treatment option to avoid undesired adverse effects in this patient group. For this reason, this study showed that TTCR could predict the response of mCRPC to docetaxel treatment.

Study Limitations

The limitations of this study are the small sample size, its retrospective design and the absence of patients receiving abiraterone, enzalutamide, and docetaxel treatments in the castration-sensitive stage.

Conclusion

This study demonstrated that TTCR could be a prognostic and predictive factor for the survival time of patients with mCRPC who were candidates for docetaxel therapy. For patients who show early progression in TTCR <12 months, close follow-up is needed. There is a need for prospective, randomized studies with longer follow-up periods and more patients to more effectively demonstrate the effect of TTCR on the survival of patients with mCRPC.

Ethics Committee Approval: The study was approved by the Institutional Ethical Committee of University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital (approval number: 2021-17-15, date: 06.09.2021).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Srugical and Medical Practices: İ.G., G.Ş.E., M.Y., S.Y.T., A.Ö., D.T.; Concept: İ.G., M.Y., D.T.; Design: İ.G., M.Y., A.Ö., D.T.; Data Collection or Processing: İ.G., G.Ş.E., G.B.S., S.Y.T., D.T.Ö., Ö.D., İ.Ç.; Analysis or Interpretation: İ.G., M.Y., D.T.; Literature Search: İ.G., S.Y.T., A.Ö.; Writing: İ.G., G.B.S.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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İstanbul Med J 2022; 23(4): 275-8
DOI: 10.4274/imj.galenos.2022.58822

Basic Life Support Training and Results for Non-Health Hospital Employees

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ABSTRACT

Introduction: Basic life support (BLS) is a non-medicated intervention to ensure that oxygen is delivered to the lungs and blood is pumped from the heart to save life in emergency situations where the heartbeat stops, respiratory functions become dysfunctional or both. The aim of this study was to evaluate the knowledge of non-healthcare staff on BLS and to investigate the contribution of BLS training to the development of their knowledge levels.

Methods: The current study was a retrospective, non-invasive descriptive study. It covers the BLS training given to hospital employees who are not health personnel and have not received BLS training before. Between June 1, 2021 and December 1, 2021, we performed pre-education knowledge measurement test and post-education evaluation test at Mardin State Hospital. The data were recorded on the spreadsheet program and their percentage changes were calculated using the tabulation program statistical formulas.

Results: A total of 594 subjects were included in the study plan, of which 290 did not complete the study. Of the 304 people who completed the study, 238 successfully passed the test at the end of the training process. Sixty-six people failed the test. The occupations of 304 people were examined and it was seen that these people consisted of 29 different occupational groups who had not received BLS training and were not health personnel.

Conclusion: As a result of the research, it has been seen that the BLS information of the personnel other than the healthcare workers is insufficient, but this problem can be overcome to a large extent with the regular training given and to be given. It was found that the knowledge levels of the employees who participated in the study and received BLS training were significantly higher than before they received BLS training.

Keywords: Basic life support, pretest, posttest

Introduction

Basic life support (BLS) is a non-medicated intervention to ensure that oxygen is delivered to the lungs and blood is pumped from the heart to save life in emergency situations where the heartbeat stops, respiratory functions become dysfunctional or both (1,2). The aim of BLS is to meet the oxygen needed by the tissues (1,2). BLS is the part of the resuscitation outside the hospital and is mostly applied by non-professional people. During the BLS, no additional tools, equipment and drugs are used except for basic training information and applied intervention information for cardiopulmonary resuscitation (CPR) (3).

CPR is defined as maintaining the airway and breathing and circulation of a patient whose breathing and circulation have stopped due to any reason (4). If CPR is not immediately applied to the patient with cardiopulmonary arrest, the brain will begin to be damaged within 4-6 minutes following the cessation of breathing and circulation. If the oxygen-free time of the brain tissue exceeds 10 min, irreversible brain damage will occur. For this reason, BLS to be carried until the professional health team arrives at the scene is critical (1-3).

CPR consists of two parts as BLS and Advanced Cardiac Life Support (ACLS). BLS includes simple treatment methods. It can be applied by all health personnel and people who have been trained in this subject. ACLS includes special treatment methods. It can be applied by doctors and specially trained health personnel (5). Extremely BLS practices are not limited to healthcare professionals, and that these life-saving interventions are well learned and applied by all individuals living in the country. For this purpose, it is necessary to provide compulsory BLS training in health institutions and to update this training at regular intervals (6). The aim of this study was to evaluate the knowledge of non-healthcare staff on BLS and to investigate the contribution of BLS training to the development of their knowledge levels.

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Cite this article as: Beştemir A, Tuncar A, Canbaz H. Basic Life Support Training and Results for Non-Health Hospital Employees. İstanbul Med J 2022; 23(4): 275-8.

Received: 20.07.2022
Accepted: 15.10.2022

Methods

The current study was a retrospective, non-invasive descriptive study. It covers the BLS training given to hospital employees who are not health personnel and have not received BLS training before and it also includes the knowledge measurement test before the training, and the evaluation test after the training in Mardin State Hospital between June 1, 2021 and December 1, 2021. With the BLS training, training was planned for 594 people and during this period, the participants consisted of 304 people who took part in the entire training and they were asked to answer the pre-test and end-test questions. Two hundred and ninety people who did not participate in the training, could incomplete their education, or did not participate in any pre-test and end-test were excluded from the study. In our training, the current BLS information was measured and the BLS information in the American Heart Association (AHA) Guide, which was published in 2015 and 2020, was included. The study consisted of 10 questions prepared from current sources and measuring the knowledge level of BLS. Each question was taken as 10 points, calculations were evaluated out of 100 points. Those who answered 7 questions or more correctly were considered successful in the exam. The test lasted for 20 min. Pre-test mean score and post-test mean score of 238 people who were successful with a score of 70 and above in the post-test and 66 people who failed with a score below 70 were examined. Persons from 29 different occupational groups, who are healthcare workers, were included in the study.

The study was approved by the Ethical Committee of Ankara City Hospital (approval number: E2-22-1658, date: 13.04.2022). The study was conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki and its subsequent amendments.

Statistical Analysis

The data were recorded on the spreadsheet program and their percentage changes were calculated using the tabulation program statistical formulas.

Results

In the study, the data of 304 people from 29 different occupational groups who were not healthcare professionals, who completed BLS training, pre-test and post-test after training, were analyzed. Seventy-nine cleaners, 41 security guards, 36 information processing officers workers, 32 maid, 16 patient receptionists, 16 data operators included 72% of the employees, and the remaining 28% consisted of 23 different occupational groups (Table 1). Of the 304 people who attended the training and completed the tests, 218 (71.7%) were male and 76 (29.3%) were female employees.

When the pre-test results were examined, it was seen that the average of the number of questions answered correctly was 4.5 questions, the average of the number of questions that were answered incorrectly was 5.5, there were no questions left blank, and the average of the pre-test score was 45. It was determined that there were 60 participants who passed the 70 points threshold in the pre-test, and 244 participants failed to pass the threshold (Table 2).

Table 1. Occupational groups participating in the study

Occupation	Number	Occupation	Number
Warehouse officer	3	Officer	14
Kitchen cook	1	Kitchen staff	6
Supply manager	2	Engineer	1
Information processing officer	36	Civil defense officer	1
Computer operator	6	Permanent worker	3
Environmental health technician	4	Chef	1
Ergotherapist	1	Driver	2
Dead washer	1	Technical personnel	10
Security staff	41	Technician	1
Patient admissions officer	14	Assistant technician	1
Patient reception officer	16	Cleaning staff	79
Maid	32	Tailor	1
Administrative support officer	2	Medical secretary	6
Employee	2	Data operator	16
Drugstore	1	Total	304

When the post-test results applied at the end of the training process were examined, it was seen that 238 people were successful by getting 70 points and above, and 66 people were unsuccessful with a score below 70 points. In the post-test results, it was determined that the average of the number of correct questions was 8, the average of the number of incorrectly answered was 1.93, and the average of the number of questions left blank was 0.063. It was determined that the mean score of 45 in the pre-test increased to 80 points in the post-test (Table 2). When the post-test and pre-test answers were examined, it was observed that 8 people got the same score in both tests and their average score was 80 points, and 5 people got higher scores in the pre-test, although they had 70 points in both pre-test and post-test mean scores.

The study revealed that the number of correct questions answered by 291 people in the post-test increased. Although there were 244 people who failed to pass the 70 points threshold in the pre-test before the training, the number of people who failed the 70 points threshold in the post-test after the BLS training was 66. While the pre-test mean score of the participants who could not pass the threshold in the pre-test was 38.5 points, the mean score of the participants who could not pass the threshold in the post-test was 53.5 (Table 2).

Discussion

The effects of BLS practices on human life, which were carried out in accordance with the published guidelines regarding BLS, were noticed by experts, and then the BLS Guidelines were updated and published at regular intervals. One of the most well-known among these guidelines is this guide published every 5 years by the AHA and was last updated in 2020. According to the AHA, BLSs are interventions applied by healthcare personnel and trained first responders for critically ill patients both before and within the hospital (7). In the European Resuscitation Council guideline, which is another widely known guide, having BLS

Table 2. Test evaluations of participants before and after training

Test	Average of correctly answered questions	Average of questions answered incorrectly	Number of successful participants (ratio)	The number of unsuccessful participants (ratio)	Unsuccessful participant average score	Average score of all participants
Pretest	4.5	5.5±1.35	60 (19.7)	244 (80.3%)	38.5	45
Post-test	8	1.93±0.32	238 (78.3)	66 (21.7%)	53.5	80

knowledge and skills is defined as a duty for doctors, nurses and other health personnel working in risky areas (8). Although health personnel and other health personnel are mentioned in these guidelines, there are also many occupational groups that are not health personnel in health institutions. In the health institution or in the garden, a non-healthcare professional can greet a patient first. For this reason, the importance of BLS training of non-health personnel, that are in the context of the study emerges. BLS is a link in the life-saving chain in CPR practices performed by professional healthcare professionals to establish life (6,7). These life-saving chains are early intervention, early BLS, early defibrillation, and early advanced life support. Each link in this chain increases survival (6,7). Studies have shown that the survival of a person who witnesses the arrest requires BLS two to three times more (6,7). For this reason, BLS is one of the critical links of the life-saving chain and it is recommended to offer BLS training to both healthcare and non-health personnel (6,7). Since there may not be health personnel in every living area of society, apart from the hospital, BLS training comes to the fore in saving lives. The fact that deaths resulting from cardiac arrest occur mostly outside the hospital has made it necessary to provide BLS training to non-health personnel as well as healthcare personnel (9,10). However, significant changes in patient habits have been reported during the Coronavirus disease-2019 (COVID-19) pandemic, such as a decrease in the hospital admissions in life-threatening situations or an increased rate of high-risk patients rejecting treatment despite medical advice (11-13). In particular, civilians who have received BLS training are as valuable as health professionals to respond quickly and effectively to many patients in disasters. BLS training is given regularly to people who are not health personnel, except those who receive BLS and advanced life support training (9,10).

In the study, the results of pre-test that was conducted before the BLS training showed us that 80.2% of the non-health personnel had no knowledge about BLS practices, and 19.8% had a lack of knowledge. Simultaneously, it reveals the importance of measuring the effectiveness of the training with pre-test and post-test while giving BLS training.

After the training, these deficiencies were largely eliminated, and the number of 244 (80.2%) people who failed the tests decreased to 66, that is, there was a 72.9% decrease in the rate of unsuccessful people. Achieving this success in a training period led us to suggest that if the training was given continuously or at frequent intervals, the success would be much higher. In the study, it was determined that the average score of 66 people (21.7%) who failed the pre-test, which was 38.5 points before the training, increased to 53.5 points in the post-test after the training. This result is another useful indicator of BLS training. The training materials and the language of the topics covered in BLS training have been prepared in a way that can be understood by non-health personnel from current sources. Another reason for the increase in the successful person and achievement score average between the pre-test and the post-test in our study may be the language of instruction used and the subjects. Similarly, it is recommended that rescuers who are not health personnel in the community attend more BLS training, with simplifications to be made in BLS guidelines. The number of rescuers can be increased thanks to simplified and memorable training. In a study on the prevalence of BLS training, it was reported that 19% of the population in Switzerland and 75% in Poland were trained on the BLS (14).

Study Limitations

The limitations of the study are the small number of pretest and posttest questions and the inability to examine the knowledge in more detail.

Conclusion

It was found that the knowledge levels of the employees who participated in the research and received BLS training increased significantly compared with their knowledge levels before they received BLS training. The results of the research suggested that the BLS knowledge of non-health personnel is insufficient, but it is possible to overcome this problem to a large extent with the regular training given and provided. In our country, it is recommended to create serious knowledge and awareness of BLS practices in society by providing repetitive training in many centers and to increase the number of life savers. Thus, it is expected that both the morbidity and mortality rates will decrease.

Ethics Committee Approval: The study was approved by the Ethical Committee of Ankara City Hospital (approval number: E2-22-1658, date: 13.04.2022).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept - A.B., A.T., H.C.; Design - A.B., H.C.; Data Collection or Processing - A.T., H.C.; Analysis or Interpretation - A.B., H.C.; Literature Search - A.B., A.T.; Writing - A.B., A.T.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support

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İstanbul Med J 2022; 23(4): 279-84
DOI: 10.4274/imj.galenos.2022.48264

Prevalence of Sensitive Skin Syndrome and Accompanied Diseases Among Women Doctors: A Nationwide Study

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ABSTRACT

Introduction: Sensitive skin is one of the small fiber neuropathies that significantly affects the quality of life with its accompanying comorbidities. Our aim in this study was to determine the frequency of irritable bowel syndrome (IBS) and/or fibromyalgia that may accompany sensitive skin.

Methods: Nine hundred and ninety-two female physicians participated in the study online with a questionnaire organized with the hybrid method. The study was conducted on female physicians with all three diseases (sensitive skin, fibromyalgia, and IBS) via a link using a Google form through WhatsApp, e-mail, and social media. The interviewed participants; for the diagnosis of IBS according to the Rome III criteria about chronic abdominal pain and altered bowel habits and for the diagnosis of FMS according to the criterion suggested by Wolfe et al. about generalized pain and its characteristics, were asked to answer questions.

Results: Participants with sensitive skin declared that they had fibromyalgia (15.0%) and IBS (14.6%). The prevalence of fibromyalgia and IBS was significantly higher in "moderately sensitive" and "very sensitive" patients than in others (p=0.017 and p=0.008).

Conclusion: In those with sensitive skin, care should be taken in terms of other disorders that may accompany sensitive skin and have a common pathogenesis with sensitive skin.

Keywords: Fibromyalgia, irritable bowel syndrome, sensitive skin, small fiber neuropathy

Introduction

Sensitive skin syndrome (SSS) is defined by tingling, prickling, heat, burning, pain, itching, and erythema on the skin due to multiple factors that do not trigger discomfort in healthy skin. SSS usually refers to the facial skin, but it may be seen in all areas of the body (1,2). It is a health problem that significantly affects the quality of life. SSS has recently been reported with increasing frequency. The European prevalence of sensitive skin in women was shown to be as high as 40%, but lower in men (3).

Cutaneous comorbidities of SSS include atopic dermatitis, psoriasis, rosacea, acne, vitiligo, and contact dermatitis (1,4,5). However, comorbidities of SSS other than skin diseases have been evaluated less frequently. Irritable bowel syndrome (IBS) is a disease accompanied by SSS, which has been conducted in a preliminary study (6). Patients with IBS suffer from abdominal pain and/or discomfort associated with bloating and/or defecation disorders and/or altered bowel habits (7). Although the pathophysiology of both diseases (SSS and IBS) is not clearly known, and multifactorial mechanisms are considered to play a role, peripheral and central neural mechanisms are thought to be major factors in the pathophysiology of these diseases (6,8-10). Fibromyalgia syndrome (FMS) is a chronic disease characterized by widespread and persistent non-inflammatory musculoskeletal pain. Its mechanisms are also unknown. Clearly, the presence of central sensitization to pain may be an important part of the pathophysiology of the disease (11,12). The relationship between SSS and FMS has not been previously evaluated.

In the cutaneous biopsy study of Buhé et al. (13), using immunohistochemical methods to detect neurosensory pathology, the intra-epidermal nerve fiber density was evaluated, and it showed that peptidergic C fibers are especially lower in the sensitive skin group. Small somatic sensory fibers and autonomic C fibers form small fibers. Therefore, if a decrease in peptidergic C fibers is detected, small fiber neuropathy (SFN) may develop (14). Therefore, studies evaluating the presence of SFN in sensitive skin have been conducted (15-17). Since it is thought that there is various organs and systems affected in SFN, FMS, and irritable bowel sensation have been investigated as SFN (18-20).

Our aim in this study was to investigate the comorbidities of participants with sensitive skin in a nationwide survey.

Methods

Study Participants

An online survey was performed among women doctors all around the country from August 2020 to October 2020. Nine hundred ninety-two

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Cite this article as: Manav V, Göre Karaali M. Prevalence of Sensitive Skin Syndrome and Accompanied Diseases Among Women Doctors: A Nationwide Study. İstanbul Med J 2022; 23(4): 279-84.

Received: 05.07.2022
Accepted: 19.10.2022

participants were interviewed via a link using a Google form through WhatsApp, e-mail, and social media. The study was conducted on female physicians as all three diseases (sensitive skin, fibromyalgia and IBS) are most common in women and because of their medical skills, the accuracy of their reports may be high for all three diseases. All participants completed the written consent form before the questionnaire, provided information and gave permission to use that information in the study regarding the online survey. Ethics committee approval was received from University of Health Sciences Turkey, İstanbul Training and Research Hospital Scientific Research and Publication Ethics Board (diary number: 2486, date: 24.07.2020).

Questionnaire

The questionnaire was designed with a hybrid method (open-ended and multiple-choice questions), and it consisted of two sections.

In the first section, the demographic and clinical data of the participants were questioned. It included, in order: age, residential area, marital status, age of menarche (9-12 years, 13-15 years, and >15 years), women's life stages were self-declared by participants (periods: premenopausal = having regular menses, perimenopausal = irregular menses for 12 months, postmenopausal = no menses for 12 months), use of smoke, BMI (kg/m^2), presence of self and/or family atopy history (asthma, allergic rhinitis, atopic dermatitis, etc.), and presence of systemic, autoimmune and dermatological diseases.

The interviewed doctors were asked to answer questions for the diagnosis of IBS according to the Rome III criteria about chronic abdominal pain and altered bowel habits (21).

Additionally, the interviewed participants were asked to answer questions regarding FMS according to the criterion suggested by Wolfe et al. (22) about generalized pain and its characteristics.

For the second section, information about the sensitive skin was questioned, and evaluations were made with the Sensitive Skin scale-10 (23). Ten symptoms (skin irritability, stinging, burning, sensation of heat, tautness, itching, pain, general discomfort, flushing, redness) were evaluated. Additionally, the severity of sensitive skin (not sensitive, slightly sensitive, moderately sensitive, very sensitive), sensitivity localizations (face and body), and duration of sensitivity were recorded.

Statistical Analysis

SPSS 22.0 for Windows was used for statistical analyzes. Descriptive statistics were number and percentage for categorical and numerical variables as mean, standard deviation, minimum, maximum, and median. The rates in the independent groups were compared using the chi-square test. Since the numerical variable did not meet the normal distribution condition, comparisons of more than two groups were made using the Kruskal-Wallis test. Subgroup analyses were performed using the Mann-Whitney U test and interpreted with Bonferroni correction. The statistical alpha significance level was set as $p<0.05$.

Results

Demographic, Clinical, and Sensitive Skin Data

The mean age of the 992 female doctors in the study was 36.2±12.2 years (minimum-maximum: 23-68 years). Most of the participants were married (68.3%) and lived in a metropole (75.0%). 16.6% of the patients were smokers. Eight hundred eleven of the patients stated that their skin was sensitive (81.7%). Regarding skin sensitivity, 37.2% were slightly sensitive, 35.0% were moderately sensitive, 8.5% were very sensitive, and 19.2% were not sensitive (Figure 1). Duration of sensitivity in the patients was more than 10 years in 32.4% (264) of the patients, between 5 and 10 years in 27.2% (222), between 1 and 4 years in 25.8% (210), and less than one year in 14.6% (119). Four hundred and seventy-six (47.6%) participants had a dermatological disease affecting the face, and the distribution of dermatological disease is shown in Table 1. Rashes and scaling on the face with sensitivity were determined mostly in the "very sensitive skin" group ($p<0.001$). Therefore, the rate of applying to

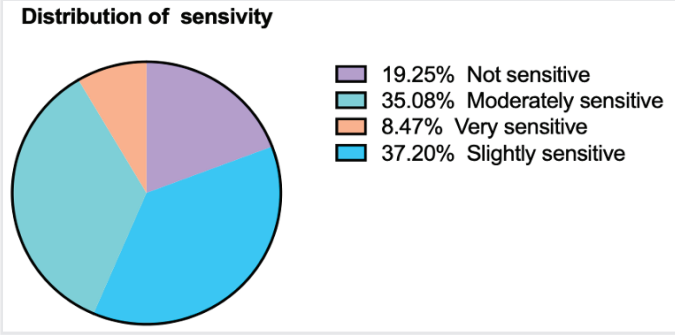

Figure 1. Distribution of sensivity

Table 1. Distribution of dermatological disease in sensitive skin

	Total, (n %)	Not sensitive, (n %)	Slightly sensitive, (n %)	Moderately sensitive, (n %)	Very sensitive, (n %)	p
Presence of any dermatologic disease affecting the face (n=999)	476 (47.6)	47 (28.3)	141 (39.8)	219 (61.5)	53 (64.6)	**<0.001**
Acne	264 (26.4)	34 (20.5)	96 (27.1)	98 (27.5)	23 (28.0)	0.330
Atopic dermatitis	42 (4.2)	-	6 (1.7)	23 (6.5)	13 (15.9)	**<0.001**
Seborrheic dermatitis	79 (7.9)	8 (4.8)	21 (5.9)	44 (12.4)	6 (7.3)	**0.004**
Rosacea	79 (7.9)	3 (1.8)	10 (2.8)	53 (14.9)	12 (14.6)	**<0.001**
Psoriasis	5 (0.5)	-	-	4 (1.1)	1 (1.2)	0.081
Allergic contact dermatitis	43 (4.3)	1 (0.6)	9 (2.5)	23 (6.5)	9 (11.0)	**<0.001**
Photocontact dermatitis	31 (3.1)	-	8 (2.3)	15 (4.2)	8 (9.8)	**<0.001**
Others	22 (2.2)	5 (3.0)	4 (1.1)	9 (2.5)	3 (3.7)	0.223

dermatology clinics was statistically significantly higher in those who were "very sensitive" (p<0.001). The body sensitivity of the participants is shown in Figure 2.

The rate of those who were "very sensitive" was higher for single participants than for married, and the rate of those who were "slightly sensitive" and "not sensitive" was higher in married participants than in singles (p=0.04). There was no significant difference in sensitive skin severity regarding BMI and smoking habit (p>0.05). There were no significant differences between the pre-, peri-, and postmenopausal groups (p=0.313), but those with an age of menarche significantly below 15 years had a higher occurrence of "very sensitive skin" (p=0.002). Discomfort (burning, itching, stinging, etc.) was statistically significant with episodic attacks (p <0.001).

Sensitive Skin Scale

When discomfort sensations felt on the face over the last three days were evaluated, there was a statistically significant difference in "very sensitive" (p<0.001; for all) (Table 2).

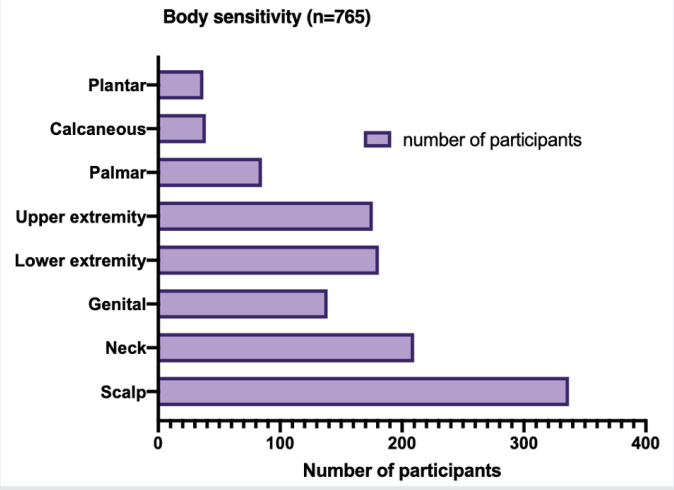

Figure 2. Body sensivity (n=765) in the body; neck (p<0.001), genital (p=0.019), upper extremity (p=0.001), and palmar region (p=0.002) were evaluated as "very sensitive"

Sensitive Skin Syndrome and Comorbidities

Two hundred sixty-two patients (26.4%) had a systemic disease, and 183 patients (18.8%) had an autoimmune disease (Table 3). The rates of self-atopy history, family atopy history, and systemic disease were high in the "moderately and very sensitive" groups (p<0.001, p<0.001, p=0.032).

Irritable Bowel Syndrome and Fibromyalgia Syndrome

Participants with sensitive skin had had FMS (15.0%) and IBS (14.6%). The prevalence of FMS and IBS was significantly higher in "moderately sensitive" and "very sensitive" patients than in others (p=0,017 and p=0,008) (Figure 3). Flushing occurred at a significantly higher rate on the very sensitive skin with FMS than in those with very sensitive skin with IBS (Table 4).

Discussion

SSS is an underestimated problem that significantly affects the quality of life. Frequently, environmental factors, including air pollution, heat, cold and wind, cosmetic usage, diet and alcohol consumption, and physiological factors, such as stress, or endogenous hormones, induce or worsen the symptoms of sensitive skin (24,25).

Although the pathophysiology of the disease is not clearly known, disruption of the epidermal barrier function, neurosensory dysfunction (alteration of nerve fiber density, functional hyperreactivity of cutaneous nerves, central sensitization, peripheral sensitization), the activation of transient receptor potential vanilloid 1 (TRPV1), and endothelin receptors are hypothesized to play a role in the induction of sensitive skin (1,24-26).

SSS has some known cutaneous comorbidities, including atopic dermatitis, psoriasis, rosacea, acne, vitiligo, and contact dermatitis (1,4,5). In a study from Korea, those in the sensitive skin group with cutaneous comorbidities were 2-4 times likelier to suffer from each skin disorder (atopic dermatitis, acne, seborrheic dermatitis, and facial blushing) than the nonsensitive skin group. Furthermore, a history of atopic dermatitis or eczema in childhood occurred more frequently in the sensitive skin group than in the non-sensitive skin group (27). In parallel with these studies, the cutaneous disorders most frequently stated in our study were acne, seborrheic dermatitis, and rosacea.

Table 2. The senstive scale 10 of patients according to severity of sensitive skin

	Not sensitive	Slightly sensitive	Moderately sensitive	Very sensitive	p
	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	
Skin irritability	1 (1-1)	1 (1-2)	2 (1-3)	3 (1-5)	<0.001
Stinging	1 (1-1)	1 (1-1)	1 (1-3)	2 (1-5)	<0.001
Burning	1 (1-1)	1 (1-2)	2 (1-4)	3 (1-5)	<0.001
Sensations of heat	1 (1-1)	1 (1-2)	2 (1-4)	3 (1-6)	<0.001
Tautness	1 (1-1.5)	2 (1-3)	2 (1-4)	3,5 (1-7)	<0.001
Itching	1 (1-1)	2 (1-3)	2 (1-4)	3 (1-6)	<0.001
Pain	1 (1-1)	1 (1-1)	1 (1-1)	1 (1-1.5)	<0,.01
General discomfort	1 (1-1)	1 (1-2)	2 (1-4)	3,5 (1-7)	<0.001
Flushes	1 (1-2)	1 (1-3)	2 (1-4)	3 (1-6)	<0.001
Redness	1 (1-2)	2 (1-3)	3 (2-5)	4 (2-8)	<0.001

IQR: Interquartile range

We observed a statistically significant difference in the rates of atopic dermatitis, seborrheic dermatitis, rosacea, allergic contact dermatitis, and photocontact dermatitis with respect to facial sensitivity. However, according to our study, sensitive skin can be considered a skin disease and a systemic disease because atopy and systemic diseases were significantly higher in the group with sensitive skin.

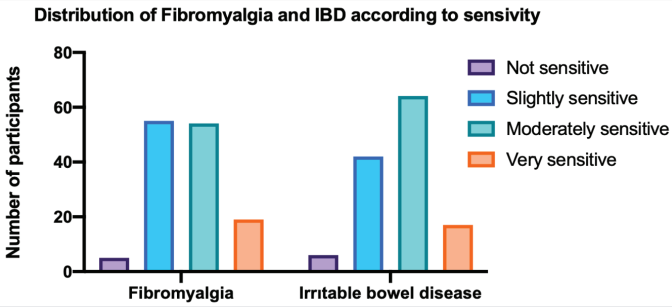

Figure 3. Distribution of fibromyalgia and irritable bowel disease according to sensivity
IBD: Irritable bowel disease

IBS is a disease accompanied by SSS that was conducted in a preliminary study. In this study, it was found that SSS was statistically significantly more common in patients with IBS, and the presence of SSS was highly associated with the presence of abdominal pain or discomfort (6). Similar findings were obtained in this study. Additionally, the SSS relationship with FMS was also evaluated, and flushing was significantly higher in participants with very sensitive skin who had FMS than in those with IBS.

The significant frequency of SSS with FMS and IBS and sensory symptoms' predominancy in these syndromes suggests that there is a common pathway in the pathogenesis of the diseases. As a matter of fact, from the perspective of IBS, hypersensitivity to physiological or experimental visceral stimuli is considered to play a major role (8). In Stabell et al.'s (28) study, patients with IBS showed increased visceral and somatic pain sensitivity. The sensitization of peripheral nociceptive afferents has been considered as one of the major mechanisms in the development of visceral hypersensitivity. SSS and IBS share similar mechanisms in terms of central sensitivity and peripheral sensitization-induced neural signaling in spinal and/or supraspinal structures, and which provokes

Table 3. Comorbidities according to severity of sensitive skin

		Not sensivite	Slightly sensitive	Moderately sensitive	Very sensitive	
		n (%)	n (%)	n (%)	n (%)	p
Atopy (self)		48 (28.1)	187 (51.2)	237 (63.7)	64 (73.6)	<0.001
Systemic disease		32 (20.0)	88 (24.9)	108 (30.3)	28 (34.1)	0.032
Diabetes Mellitus		1 (0.6)	6 (1.7)	9 (2.5)	5 (6.1)	0.051
Hypertension		5 (3.1)	14 (4.0)	21 (5.9)	4 (4.9)	0.483
Heart and vascular disorders		0 (0.0)	5 (1.4)	8 (2.2)	3 (3.7)	0.090
Thyroid disorders		18 (11.3)	57 (16.1)	60 (16.8)	9 (11.0)	0.257
Asthma		0 (0.0)	5 (1.4)	9 (2.5)	3 (3.7)	0.071
Renal disorders		2 (1.2)	0 (0.0)	3 (0.8)	1 (1.2)	0.107
Malignancy		2 (1.3)	3 (0.8)	5 (1.4)	0 (0.0)	0.752
Others		4 (2.5)	8 (2.3)	14 (3.9)	3 (3.7)	0.565
Autoimmune disease	Yes	19 (11.9)	68 (19.6)	74 (21.3)	17 (21.7)	0.081
Autoimmune disease	No	141 (88.1)	279 (80.4)	274 (78.7)	64 (79.0)	-

Table 4. IBS and FMS and SSS

	Very sensitive + FMS (n=19)		Very sensitive + IBS (n=17)	
	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)
Skin irritability	3.25±2.18	3 (1.25-5.5)	3.88±3.16	3 (1-6.25)
Stinging	2.56±2.25	2 (1-3)	3.33±2.66	3 (1-6)
Burning	3.69±2.77	3 (1-6)	3.80±3.55	2 (1-6)
Sensations of heat	3.44±2.96	2.5 (1-6.25)	4.07±3.63	2 (1-9)
Tautness	3.88±2.87	3.5 (1-6.75)	4.86±3.39	5.5 (1-7.25)
Itching	3.84±2.41	4 (1-6)	4.41±3.12	4 (1-7)
Pain	1.94±1.73	1 (1-2.75)	3.00±2.65	2 (1-4.5)
General discomfort	4.00±2.78	3 (1.5-6)	4.71±3.12	4.5 (1.75-7)
Flushes	4.18±3.63	3 (1-8.5)	3.87±3.68	2 (1-8)
Redness	4.28±3.01	3 (1.75-7.25)	4.88±3.56	3.5 (1.25-8.75)
p#	0.005		0.152	

#Friedman test *Wilcoxon test p=0.003 [Bonferroni correction (if not p<0,001)] minimum p-level. IBS: Irritable bowel syndrome, FMS: Fibromyalgia syndrome, SSS: Sensitive skin syndrome, SD: Standard deviation, IQR: Interquartile range

hyperexcitement in the central nervous system (9,10). Disruption of the balance of various neurotransmitters and neuromodulators has also been found to play a common role in the pathogenesis of IBS and SSS. Induction of visceral hypersensitivity by rectal tension in IBS has been demonstrated by rectal administration of capsaicin (29). TRPV1 hyperactivation is also one of the most widely known mechanisms of SSS, which induces neurogenic inflammation resulting in hyperalgesia. All these mechanisms can be explained by SFN (26,30).

From the perspective of FMS, the pathophysiology of FMS is also not precisely known. Central sensitization to pain, disruption in endogenous pain inhibition mechanisms, greater responses in areas of the neuromatrix that process pain during pain evocation, and SFN are among the hypotheses considered in the pathogenesis of the disease (12,31-33). In our study, the prevalence of FMS and IBS was significantly higher in the "moderately sensitive" and "very sensitive" groups of participants. Although there are many obscurities about these disorders, it is observed that there are common mechanisms. This is the first study to show a relationship between SSS and FMS. It also supports the relationship between SSS and IBS.

Study Limitations

Although the study was conducted on a population with a very high level of consciousness, such as women doctors, it was conducted by a questionnaire. A study in which dermatological and physical are examined will give much clearer results.

Conclusions

SSS may mean more than a skin disease. SSS, IBS, and FMS are diseases of unknown pathophysiology that are related to sensory perception. Determining the relationships among these disorders will shed light on the pathogenesis of the disease. The determination of common pathogenetic mechanisms will help us understand these diseases, and it may open up even new therapeutic pathways. It is important to be aware of the accompanying disorders in patients with SSS. Large epidemiological and pathophysiological studies are needed on this subject.

Ethics Committee Approval: Ethics committee approval was received from University of Health Sciences Turkey, İstanbul Training and Research Hospital Scientific Research and Publication Ethics Board (diary number: 2486, date: 24.07.2020).

Informed Consent: All participants completed the written consent form before the questionnaire, provided information and gave permission to use that information in the study regarding the online survey.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices: V.M., M.G.K.; Concept: V.M., M.G.K.; Design: V.M., M.G.K.; Data Collection or Processing: V.M., M.G.K.; Analysis or Interpretation: V.M., M.G.K.; Writing: V.M., M.G.K.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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İstanbul Med J 2022; 23(4): 285-9
DOI: 10.4274/imj.galenos.2022.83357

Contribution of Apparent Diffusion Coefficient Histogram Analysis Findings in Differential Diagnosis of Parotid Gland Masses

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ABSTRACT

Introduction: In this retrospective study, our purpose was to research the usefulness of apparent diffusion coefficient (ADC) histogram graphics for the preoperative diagnosis of parotis tumors with heterogeneous signal distribution.

Methods: Our patient group included 50 patients with total 52 parotid gland masses who had diffusion-weighted imaging and ADC maps before operation or biopsy, which were archived in our instutional Picture Archiving and Communications System. Free-hand region of interest-based ADC histogram parameters were minimum (ADC min), maximum (ADC max), mean (ADC mean) and standard deviation (SD) (ADC SD). Statistical analyses were performed with the SPSS 17.0 using Kruskal-Wallis, Mann-Whitney U tests, Spearmans' rho correlation and receiver operating characteristic (ROC) curve.

Results: ADC min, ADC max and especially the ADC mean were statistically significant in differentiating pleomorphic adenoma (PA) from Warthin tumor (WT). ADC min and ADC max values were also significant in differentiating PA from malignant tumor (MT) ($p<0.05$). In PA-WT differentiation ADC mean value with 1465.50 cut-off level, sensitivity was 94.1% and specificity was 88.6%. For PA-MT differentiation, ADC min value with 962.00 cut-off level, sensitivity was 82.4% and specificity was 94.3%. Whereas, ADC histogram values for WT-MT differentiation were statistically insignificant ($p>0.05$).

Conclusion: Our results support the assumption that ADC histogram parameters can help discriminate PA from WT and PA from MTs preoperatively. However, they are unhelpful in the differential diagnosis of malignant masses from WT.

Keywords: Diffusion weighted imaging, histogram analysis, apparent diffusion coefficient

Introduction

Parotid tumors comprise about 3% of head and neck neoplasia. Most of these are finally diagnosed as benign. They are frequently located in the parotid gland (1,2). Within parotid gland tumors there are various benign and malignant pathologic subtypes. Differentiation between not only malignant and benign subtypes but also within the benign tumor group is important to make the right choice of treatment strategy, as in the case of potentially malignant pleomorphic adenoma (3,4).

Ultrasound is a preliminary imaging tool for parotid tumor evaluation. It could also guide aspiration cytology. There are some drawbacks of ultrasound: it is only efficient when tumors are superficially located and applied by an expert sonographer (1,4).

Except few indications like sialolithiasis or bone invasion of deep-located tumors, computed tomography is not frequently used because of the relatively low soft tissue resolution (1,5).

Although contrast-enhanced magnetic resonance imaging (MRI) provides detailed structural information, it may accumulate in cerebral tissues even in patients without renal insufficiency (6,7).

Diffusion-weighted imaging (DWI) besides routine MRI series have been frequently used in parotid gland imaging. DWI is known to provide valuable quantitative information not only about components of tissues but also about the microscopic motion of water molecules (8). Apparent diffusion coefficient (ADC) derived parameters have been used for imaging in various organs to differentiate between benign and malignant lesions successfully. In contrast, there are also a few authors reporting that ADC data cannot be helpful in distinguishing between benign and malignant lesions (7,9-11).

In many studies mean ADC values, alone, have been reported not to be discriminative especially in Warthin and malignant groups. Many studies in the English literature also support current research that there is significant overlap between ADC measurements of these lesions (3,11,12).

Histogram analysis has been accepted as the first step texture analysis. In recent literature, there are many reports about histogram analysis of various tumors proven to be a diagnostic tool (13-19).

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Cite this article as: Karagöz Y, Bulut H, Mahmutoğlu Ö, Aksoy DÖ, Mahmutoğlu AS. Contribution of Apparent Diffusion Coefficient Histogram Analysis Findings in Differential Diagnosis of Parotid Gland Masses. İstanbul Med J 2022; 23(4): 285-9.

Received: 21.07.2022
Accepted: 19.10.2022

In this study, our aim was to evaluate the preoperative discriminative ability of ADC histogram values not only between malignant and benign parotid tumors but also within each group.

Methods

Study Population

We retrospectively searched the local Picture Archiving and Communications System archive between January 2015 and December 2018. MR DWI of 50 patients, 17 females and 33 males, with parotid masses were evaluated. In two patients ipsilateral multiple lesions were sampled separately. The age range of patients was between 17 and 90 years; the average age was 57.2 years.

All cases had cytological and/or histological diagnoses after MRI. Insufficient sequences or images with prominent artefacts were excluded from our study.

Ethical approval was obtained from the Local Ethics Committee of University of Health Sciences Turkey, İstanbul Training and Research Hospital (approval number: 2337, date: 22.05.2020).

MRI Protocols

MRI examinations were completed on a 1.5-T Signa Hdx MR unit (GE Medical Systems, Milwaukee, WI). Craniovascular or head coils with 8 channels were used to evaluate the upper head and the neck region. Axial and coronal TSE T1W (TR: 580 ms, TE: 13, NEX: 0.50; 5 mm slice thickness); axial, coronal and sagittal TSE T2W (TR: TSE 5400 ms TE: 99 ms; with 90 degrees flip angle: thickness: 4 mm), axial and coronal STIR (TR: 7260 TE: 65 ms; slice thickness: 4 mm) and postcontrast fat-sat T1W (TR: 880 ms TE: 16 ms; slice thickness: 4 mm) sequences were obtained.

Diffusion Weighted Imaging Protocol

At our institution, DW sequence is part of routine head and neck MR examination due to its contribution to differential diagnosis.

Single-shot spin-echo echo-planar imaging sequence (epiDWI) was performed. Imaging parameters were TR: 6250 ms, TE: 97 ms; flip angle: 90; thickness: 4.0 mm; spacing: 1.5 mm; field of view: 20X20 cm; matrix: 128x128; NEX: 1.00 and two sequences with B values 0 and 1000 s/mm^2 were obtained, respectively.

Image Processing and Interpretation

DWI data were transferred to Advantage Workstation (AW Volumeshare 7, GE Healthcare, Chicago, IL). ADC maps and histogram graphics were derived from epiDWI sequences by integrated software.

Only the solid components were included in the region of interest (ROIs) using data from the fusion of enhanced axial T1W and axial DW images. Gross unenhancing components (possible cystic or necrotic areas) and the surrounding glandular tissue were excluded while drawing free-hand ROIs (Figure 1-3). Slices with largest transverse dimensions of the solid parts were chosen.

Histogram graphics of these ROIs were evaluated to acquire parameters of min, mean, max and standard deviation (SD).

Statistical Analysis

Frequency analysis results were used to describe the distribution of pathological diagnoses within the groups. Mann-Whitney U test was used for differences between tumor groups.

The diagnostic significance of histogram parameters is shown in receiver operating characteristic (ROC) curve analysis. Spearmans' rho correlation was used for relational analysis for pathological diagnosis within groups. Statistical analysis was conducted using the IBM SPSS® Statistics 17 software within 95% confidence interval.

Results

The distribution of histopathological diagnoses of tumors is shown in Table 1.

In the benign group, 56.4% were diagnosed with Warthin tumor, and 43.6% as pleomorphic adenoma (PA). The distribution and statistical relations of mean histogram values of the study groups are shown in Table 2.

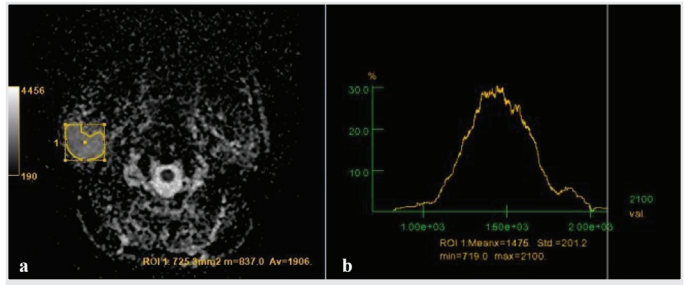

Figure 1. (a, b) Pleomorphic adenomas. Apparent diffusion coefficient maps. ROI with free-hand technique (a) and histogram graphic of the selected ROI (b)
ROI: Region of interest

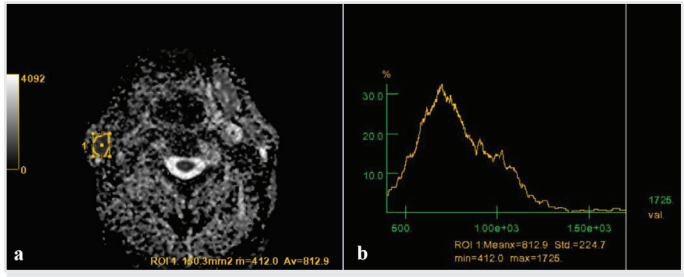

Figure 2. (a, b) Warthin tumor. Apparent diffusion coefficient maps. ROI with free-hand technique (a) and histogram graphic of the selected ROI (b)
ROI: Region of interest

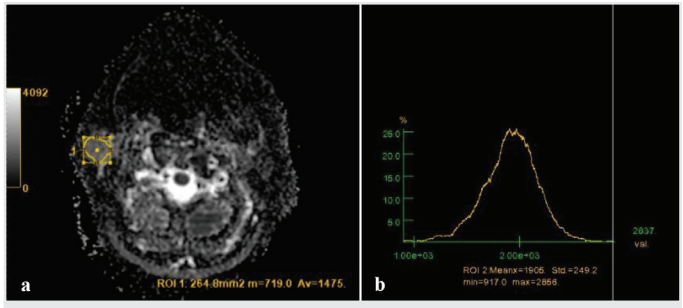

Figure 3. (a, b) Mucoepidermoid cancer. Apparent diffusion coefficient maps. Apparent diffusion coefficient maps. ROI with free-hand technique (a) and histogram graphic of the selected ROI (b)
ROI: Region of interest

All three parameters (ADC min, max and mean) were highest in PAs, while ADC min and mean were the lowest in WTs. The ADC SD parameter was higher in the WTs. Comparisons showed that min, max and mean values were significantly different between the tumor groups ($p<0.05$). To understand tumor intergroup differences, Mann-Whitney U analysis test was applied (Table 3).

Pair group analysis results showed that SD of ADC did not show a significant difference for any paired group ($p>0.05$). Additionally, Warthin tumor-malignant tumor differences were statistically insignificant ($p>0.05$). However, min, max and mean ADC levels were statistically significant for WT-PA and PA-MT pairs ($p<0.05$). Spearmans' rho correlations for malignancy are given in Table 4.

Correlation analysis for malignancy showed that ADC min ($r=-0.728$; $p<0.001$), max ($r=-0.547$; $p<0.001$) and mean ($p=-0.776$; $p<0.001$) values had significant correlations with tumor pairs.

Table 1. Distribution of tumors

	Benign (n=39)	Malignant (n=13)
Warthin tumor	22 (56.4)	-
Pleomorphic adenoma	17 (43.6)	-
Malignant		13 (100.0)

Table 2. Mean values of each histogram parameter (min, mean and max) for each group

	Warthin tumor (n=22)	Pleomorphic adenoma (n=17)	Malignant (n=13)	p
Minimum	430.32±249.98	1148.65±336.47	544.46±319.01	<0.05[a]
Maximum	1959.91±616.06	2754.94±598.68	1913.08±564.11	<0.05[a]
Mean	1076.28±342.88	2000.29±336.04	1125.44±377.77	<0.05[a]
SD	259.69±74.77	242.52±130.04	223.42±99.41	0.260[a]

[a]Kruskal-Wallis test, min: Minimum, max: Maximum, SD: Standard deviation

Table 3. Differences within tumor pairs (p-values)

Histogram parameters	Warthin tumor-pleomorphic adenoma	Warthin tumor-malignant	Pleomorphic adenoma-malignant
ADC min	<0.05	0.489	<0.05
ADC max	<0.05	0.960	0.001
ADC mean	<0.05	0.699	<0.05
ADC SD	0.172	0.180	0.967

ADC: Apparent diffusion coefficient, min: Minimum, max: Maximum, SD: Standard deviation

Table 4. Spearmans'rho correlation results

Histogram values*	r	p
ADC min	**-0.728**	<0.001
ADC max	**-0.547**	<0.001
ADC mean	**-0.776**	<0.001
ADC SD	-0.005	0.975

*Controlled for malignancy, ADC: Apparent diffusion coefficient, min: Minimum, max: Maximum, SD: Standard deviation

Results of the ROC analysis showed that both ADC min, max and mean levels have diagnostic value for pleomorphic tumor ($p<0.001$). area under the curve for ADC min was 0.931, for ADC max was 0.872, and for ADC, mean was 0.965. This shows that ADC min has 93.1%, ADC max has 87.2%, and ADC mean has 96.5% predictive values.

For ADC min with 663.50 cut-off value, sensitivity was 94.1% and specificity was 77.1%. For ADC min with 962.00 cut-off value, sensitivity was 82.4% and specificity was 94.3%.

For ADC max with 2156.50 cut-off value, sensitivity was 94.1% and specificity was 68.6%. For ADC max with 2349.00 cut-off value, sensitivity was 82.4% and specificity was 82.9%.

For ADC mean with 1465.50 cut-off value, sensitivity was 94.1%; specificity was 88.6%. For ADC mean with 1591.50 cut-off value, sensitivity was 88.2% and specificity was 91.4%.

Discussion

Salivary gland tumors are mostly benign involving 54-79% of all. Parotid is the most frequently involved gland. The majority (70-85%) of parotid lesions are also known to be benign (2,18). It is clinically crucial to differentiate between benign and malignant tumors preoperatively because the operator's choice of surgical procedure would change drastically with this information (20). While local excision would be sufficient to excise most benign tumors (with exception of PA), total parotidectomy with or without the sacrifice of the facial nerve would be performed in case of malignancy.

PAs have a high risk of recurrence and malignant transformation. Preoperative diagnosis would change the surgical approach, which will be different to other benign tumors (3,4,9).

Repeated aspiration cytology may be necessary because of insufficient sampling or successful access to deeply located tumor. Therefore, preoperative imaging plays an important role in surgical planning (7,20).

Although there are some clinical findings pointing to malignancy, most parotid tumors grow slowly and the findings such as facial nerve palsy occur late in the disease course (1).

Although sensitivities and specificities are not significant MRI findings of malignant salivary gland tumors include poorly defined borders, low T2W signal intensity, and heterogeneous structure (5,7,8,12,21). Advanced MRI techniques have also been studied for imaging salivary gland tumors. One of the most frequently used additional MRI sequences is DWI (9,19,20,22).

The Yuan et al. (23) also claimed that by adding DWI, MRI would be more powerful diagnostically. In contrast, Eida et al. (19) proposed a multiparametric method using DCE and DW MRI techniques and reported to differentiate benign and malignant tumors. There are other studies suggesting ADC histogram data and time intensity curve derived from gadolinium-enhanced dynamic MR data could be useful for differentiating benign and malignant salivary gland tumors (6,7,24). First-order histogram studies are simple and accessible to many investigators. ADC histogram analysis also appears be a real advantage for

patients with renal incapacity as it doesn't require intravenous contrast enhancement also considering many recent reports emphasizing intracranial gadolinium deposition (24-26).

Parotid gland tumors have different elements, including tumor cells, lymphoid tissues, myxomatous and necrotic components. Therefore, the analysis of all components of a tumor may cause unreliable results regarding tumor subtyping of tumors (18). Yabuuchi et al. (9) used dynamic enhanced T1W images to choose the tumor section with the lowest ADC value, which enhanced most vividly. Our results were similar to previous report of Habermann et al. (12), using mean ADC values Warthin tumors were found to be distinguishable from PAs and some other benign tumors. They have also failed to reveal any significant differences between WTs and most malignant tumors (12).

There are also some conflicting results in the literature, as in the study of Ma et al. (4), in their study including seventy-three parotid masses they reported that only ADC 10 value was the potential histogram parameter for discriminating malignant and benign tumors.

There are various studies demonstrating the potential of histogram analyses not only for diagnosis but also for grading, differentiating, assessing progression and tumor responses. Higher specificity, sensitivity and accuracy of histogram parameters have often been shown compared with conventional MRI methods or histopathological data (17,18).

In the future, the standardization of histogram data in larger patient populations may be reliable additional tool for MRI to characterize salivary tumors non-invasively.

Study Limitations

The current study was a retrospective study including a small sample size, particularly the number of malignant tumor subtypes. We have included only macroscopically enhancing parts of mass so discarding some parts, which would have added diagnostic value. Studies with larger numbers of both malignant and benign subtypes and with comparisons to whole tumor ROIs would yield more objective results.

Conclusion

Histogram analysis of ADC maps as first line texture analysis appears to provide valuable information about tumor heterogenity. Although Warthin tumors and malignant lesions could not be differentiated from each other, solely on the basis of histogram values, minimum, mean and maximum ADC histogram parameters are found to be significant to diffentiate Warthin tumors from pleomorphic adenomas and pleomorfic adenomas from malignant tumors.

Ethics Committee Approval: Ethical approval was obtained from the Local Ethics Committee of University of Health Sciences Turkey, İstanbul Training and Research Hospital (approval number: 2337, date: 22.05.2020).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept: Y.K., Ö.M., A.S.M.; Design: Y.K., Ö.M., A.S.M.; Data Collection or Processing: Y.K., H.B., D.Ö.A.; Analysis or Interpretation: Y.K., A.S.M.; Literature Search: Y.K., H.B., D.Ö.A.; Writing: Y.K.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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İstanbul Med J 2022; 23(4): 290-5
DOI: 10.4274/imj.galenos.2022.90359

Silicone Breast Implant/Tissue Expander Applications and Complication Management: Retrospective Patient Analysis of 172 Patients

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ABSTRACT

Introduction: This study aimed to investigate the complications and their management following breast implant surgeries for patients undergoing breast augmentation, augmentation mastopexy and breast reconstruction.

Methods: One hundred and seventy-two patients were included in this study. The implants were used to increase the breast volume, treat ptosis and for breast reconstruction in patients who had breast tissue removed completely or partially.

Results: Overall complication rate was 76%. The complication rate in the breast augmentation group (n=60) was 76%. The complication rate in two session mastopexy augmentation groups (n=9) was 55%. The complication rate in the single session mastopexy augmentation group (n=27) was 66%. The complication rate in the breast reconstruction group (n=71) was 84.5%.

Conclusion: Despite high complication rates, successful results can be obtained using correct patient selection, correct planning, correct implant selection, correct surgical technique and appropriate management of complications during the postoperative follow-up. The compliance of the patients to recommendations given by the surgeon during the follow-up and treatment process also is central to increasing the success rates.

Keywords: Silicone breast implant, tissue expander, breast augmentation

Introduction

At the end of the 20th century, with the changing trends of the modern world, plastic surgery started to turn to aesthetic applications (1-3). silicone breast implants have been increasingly used in plastic surgical operations since the 1980s. Silicone breast implants have gained their place in plastic surgical operations for both aesthetic and reconstructive purposes. Today, silicone breast implants are preferred for immediate or late reconstruction purposes in breast cancer patients and for breast augmentation.

There are various types of silicone breast implant with different features and sizes according to their surface structures, anatomical shape, and internal structure. According to their anatomical shapes, silicone gel implants are available in anatomical and round shapes. They are produced in smooth and textured forms according to their surface structure. Depending on their internal properties, there are saline-inflatable, gel-filled, and semi-filled implant options such as "Becker" implants (4-6).

Considering the wishes of the patients, implant selections are made on the appropriate size and shape. Tissue expanders are implant materials inflated with saline, which are often used to create a suitable bed and to provide the width of the pouch before the permanent implant to be placed on the breast in patients who are planned for reconstruction and have a high probability of receiving radiotherapy.

The breast is a critical organ pair for women. It is one of the most important parts of a woman's body, both in breastfeeding and in terms of body image and psychological self-confidence development. As plastic surgeons, we encounter breast structures of various sizes, symmetry and shapes, with the effect of racial differences.

Patients who present with a complaint of developmental delay of the breast at a young age can request a breast augmentation with a breast implant. In older ages, patients who apply with the complaints of breast sagging and shrinkage along with factors such as breastfeeding, childbirth, weight changes, usually require the breast to be lifted and augmented at the same time.

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Cite this article as: Altınel D, Serin M, Toplu G. Silicone Breast Implant/Tissue Expander Applications and Complication Management: Retrospective Patient Analysis of 172 Patients. İstanbul Med J 2022; 23(4): 290-5.

Received: 25.07.2022
Accepted: 27.10.2022

In another group of patients, reconstructive operation planning is performed in patients who have had all or part of their breasts removed due to breast cancer or for different reasons. In suitable patients, a silicone implant placement or a tissue expander placement before a permanent breast implant can be performed.

Although patient demands and cases are different, the main goal in aesthetic and reconstructive breast surgery should be to obtain the breast shape and symmetry suitable for the age and body structure of the woman. Before surgery, patients should be discussed in detail and detailed explanations should be given to the patient about the planned process. Patients should be informed beforehand about undesirable early and late complications that may be encountered in the perioperative and postoperative period. These explanations should be communicated to the patients not only verbally but also in writing. Photographs of the patients during the entire process, namely, preoperative, peroperative and postoperative, should be taken and archived.

Methods

The 172 patients included in the retrospective study who were operated by the same surgical team between the years 2010 and 2020. Written informed consent was received from the patients. This study was approved by the Ethics Committee of Universtiy of Health Sciences Turkey, İstanbul Training and Research Hospital (approval number: 223, date: 01.07.2022). The patient age ranged from 18 to 53. All patients were fitted with Food and Drug Administration and Conformite Europeenne approved breast implants from the same manufacturer (Table 1). The patients were evaluated in three groups: breast augmentation (n=60), augmentation mastopexy (n=36) and breast reconstruction (n=76) Complications and complication management were noted according to the groups.

Statistical Analysis

Descriptive analysis was performed using GraphPad Prism version 8.00 for Windows (GraphPad Software, La Jolla California USA).

Results

Bilateral breast augmentation with silicone breast implant was applied to 60 of these patients. The same size and shape implant was placed on both breasts in 35 patients, and silicone breast implants of the same shape but different sized implants were placed in 25 patients. An anatomical implant pair was applied to 10 patients, and a round-shaped implant pair was applied to 50 patients. Of the round-shaped implants, 13 pairs had smooth surfaces and 30 pairs had textured surfaces. We placed gel-filled implants between 200 cc and 375 cc in breast augmentation surgery. The implants were placed in the submuscular dual plane through the inframammary fold incision. The drain was placed in 32 of the patients, and no drain was placed in 21 of them. Elastic bandages and sports bras were fitted to all patients at the end of the surgery (Table 2) (Figure 1).

Table 1. List of patients included in the study

	Number	Percentage
Breast augmentation with silicone implants	60	34.88%
Augmentation mastopexy	36	20.93%
Breast reconstruction with silicone	76	44.19%
Implants/tissue expanders	-	-
Total	172	-

One-session breast augmentation and mastopexy surgery was performed in 27 patients. Bilateral implants were applied to 24 patients and unilateral implants applied to 3 patients who underwent a single-session procedure. In unilateral implant patients, the implant was not applied to the other breast due to the size of the breast. The reduction is done. Among the patients who had bilateral breast implant in one session, 13 different size implants were placed and 11 the same size implants were placed. All implants placed in a single-session surgery were round in shape and textured surfaced. Two-session breast augmentation and lift surgery were performed on both breasts in 9 patients. In the two-session procedure, the same size, textured surface and round-shaped implants were used for both breasts. In the first session, the implants were placed in the submuscular dual plane by entering through the incision made in the inframammary fold. The final skin scars of single-session and two-session patients at the end of the second session were inverted-t and short inverted-t scars. The implant sizes used in our patient group with augmentation combined with mastopexy were in the range of 225-325 cc. Drain was placed and a sports bra was fitted in all the patients who underwent combined augmentation with mastopexy in one and two sessions (Table 3) (Figure 2, 3).

Table 2. Breast augmentation with silicone implants (n=60)

	Number	Percentage
The same size implants	35	58.33%
Different size implants	25	41.67%
Anatomic implants	10	16.67%
Round implants	50	83.33%
Smooth	13	21.67%
Textured	47	78.33%
Total	60	-

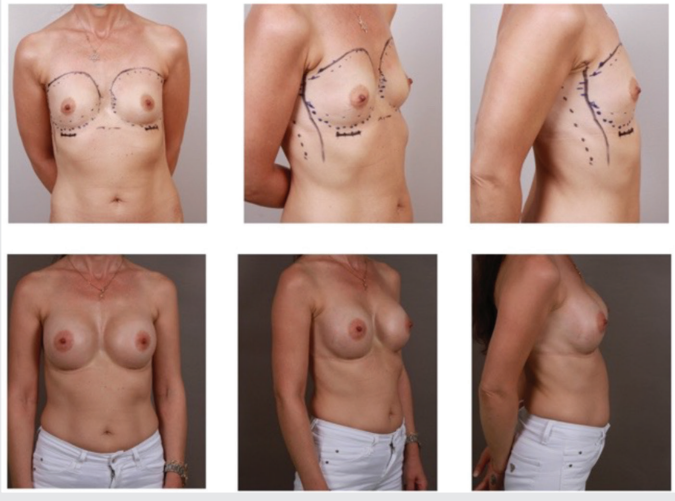

Figure 1. Preoperative (upper) and postoperative (lower) photographs of a patient undergoing breast augmentation with a silicone.
Written informed consent is obtained from the patient for demonstration

Of the 76 patients who were operated for reconstructive purposes. A bilateral breast implant was applied to 5 of these patients due to congenital tubular breast deformity. Bilateral the same sized textured surface round-shaped implants were used in 3 patients, and different size textured surface round-shaped implants were used in 2 patients (Table 4) (Figure 4, 5).

Of the 76 patients, 71 had a diagnosis of breast cancer or a history of previous mastectomy. Late reconstruction planning was performed in 25 of 76 patients after mastectomy. A tissue expander was placed in all the patients who underwent late repair, and after at least 6 months of inflation and waiting period, they were replaced with a permanent implant. Immediate reconstruction with skin-sparing mastectomy was planned in 46 patients. A direct permanent implant was placed in 19 of the patients who were planned for immediate reconstruction, and a tissue expander was placed in 27 of them, which would later be replaced with a permanent implant. Round-shaped textured surface implant was used for all reconstruction patients. Implant sizes were in the range of 300-375 cc (Table 4).

The overall complication rate was 76%. The complication rate in the breast augmentation group (n=60) was 76%. The complication rate in two session mastopexy augmentation groups (n=9) was 55%. The complication rate in the single session mastopexy augmentation group (n=27) was 66%. The complication rate in the breast reconstruction group (n=71) was 84.5%.

Superficial cellulitis (incision site infection) which were treated with antibiotics occurred in 8 patients in the early postoperative period in 60 of the operated augmentation patients. No implant exposure was observed in these patients. Mild capsular contracture was encountered in the late period in 6 patients. Unilateral hematoma occurred in 7 patients. Unilateral self-limiting and resorbing hematomas were observed in 5 patients. In 2 patients, a case of hematoma requiring surgical evacuation was encountered in the unilateral breast. The drain was not used in only 2 of the hematoma cases. Five cases were the cases in which drains were used. Two surgically evacuated hematoma cases were also cases in which we used drains. A total of 8 stated that they noticed asymmetry but were not bothered enough to request surgery again. Self-limiting and resorbing seroma was seen in 5 patients in the early period. A case of late seroma was encountered in 2 patients. In these, thinning of the skin and implant exposure occurred because of the ongoing flow at the incision site. First, the implant was tried to be saved with antibiotic irrigation, but it was unsuccessful. Ultimately, total capsulectomy and implant replacement were performed in these 2 patients. Keloid occurred in the incision scar unilaterally in 6 patients

Table 3. Augmentation mastopexy (n=36)

	Number	Percentage
Single session	27	75.00%
Two session	9	25.00%
Bilateral	24	66.67%
The same size implants	13*	-
Different size implants	11*	-
Unilateral	3	8.33%
Total	36	-

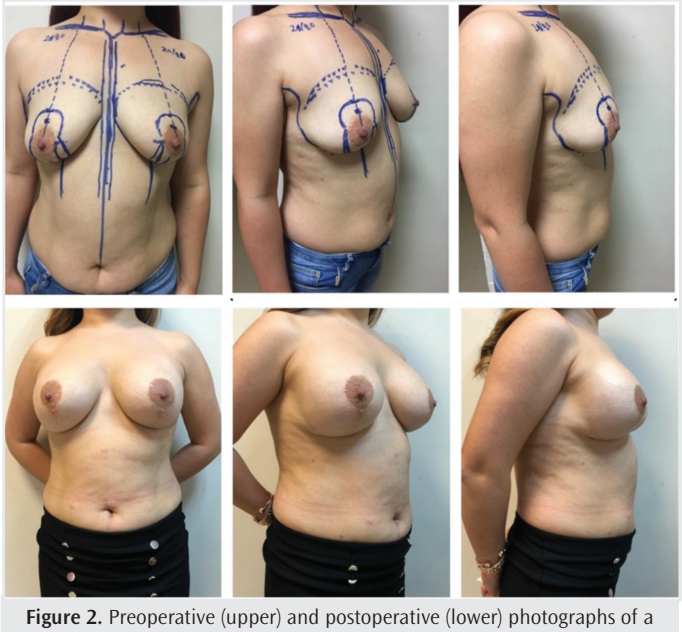

Figure 2. Preoperative (upper) and postoperative (lower) photographs of a patient undergoing single stage mastopexy and augmentation with silicone implant.
Written informed consent is obtained from the patient for demonstration

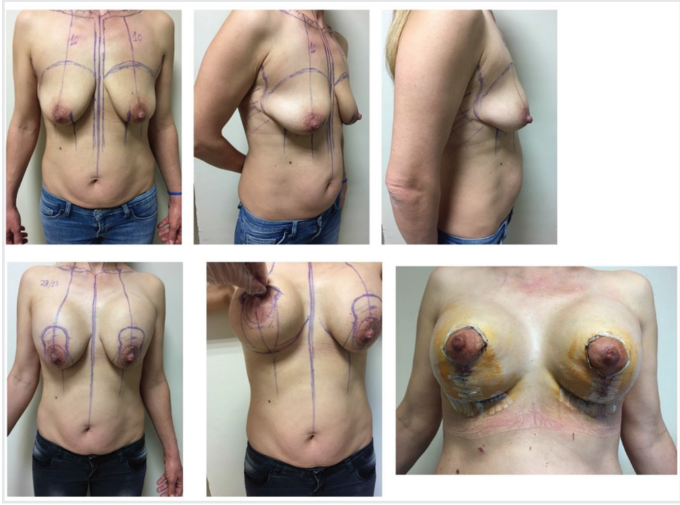

Figure 3. Photographs of a patient undergoing two stage mastopexy and augmentation with a silicone implant. [Preoperative (upper), postoperative following the first stage augmentation with impact (lower left, lower middle) and postoperative following the second stage mastopexy surgery (lower right)].
Written informed consent is obtained from the patient for demonstration

Table 4. Breast reconstruction silicone implants (n=76)

	Number	Percentage
Congenital	5	6.58%
Immediate reconstruction	46	60.53%
Only implant	19*	-
Implant following expansion	27*	-
Late reconstruction	25	32.89%
Total	76	-

and bilaterally in 3 patients. The scar revision was performed in 2 patients. Others responded favorably to the local steroid injection. One patient was reoperated because of the suspicion of a unilateral capsule tumor. Capsulectomy and implant replacement were performed (Table 5) (Figure 4).

No major complications were observed in 9 patients who were planned for two sessions among the patients in whom mastopexy and augmentation were planned together. Three patients had hypertrophic scars and 2 patients had slight asymmetry. Of the 27 patients who underwent a single session mastopexy augmentation, 5 had unilateral seroma, 4 had unilateral hematoma, and 3 had unilateral limited superficial skin necrosis at the t-scar junction. Seroma in 1 patient and hematoma in 1 patient were surgically evacuated, and new drains were placed in the patients. Necrotic areas healed secondarily. Six patients were re-operated due to asymmetry and double bubble appearance (Table 6).

There were no complications and no reoperation planning in the patients who were operated due to tubular breast deformity among the patients who underwent implant for reconstruction purposes.

Reoperation was performed for repositioning the implant in 6 of the 71 patients who underwent breast reconstruction due to breast cancer, which were immediate reconstruction cases in which the implant was placed without expansion. Skin necrosis developed in 7 patients who underwent immediate reconstruction with implant, which were replaced with a smaller size implant and asymmetry correction was performed on the contralateral breast. Skin necrosis developed in 18 patients, who received radiotherapy during the postoperative period. The tissue expander was salvaged in 8 of these, but had to be removed in 10 of them. Capsular contracture of varying severity was observed in all patients who received postoperative therapy (Table 7) (Figure 5, 6).

Table 5. Complications of patients with breast augmentation with silicone implants (n=60)

	Number	Percentage
Superficial cellulitis	8	13.3%
Implant exposure	0	0.0%
Mild capsular contracture	6	10.0%
Unilateral hematoma requiring surgery	2	3.3%
Unilateral self-limiting and resorbing hematoma	5	8.3%
Minimal asymmetry	8	13.3%
Self-limiting and resorbing seroma	5	8.3%
Late seroma requiring implant replacement	2	3.3%
Hypertrophic scars in response to steroids	7	11.7%
The hypertrophic scar that required surgical revision	2	3.3%
Capsule tumor which required surgery	1	1.7%
Total	**46**	**76%**

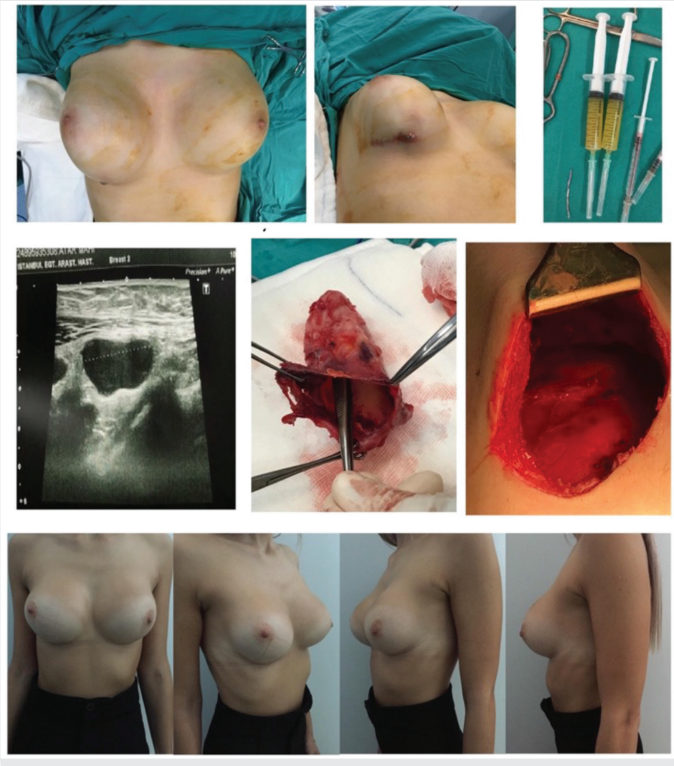

Figure 4. Photographs of a patient with complication following breast augmentation of the right breast. Photographs of the patient before revision surgery (upper). Seroma was drained. Capsulectomy was performed (middle). Photographs of the patients following the revision surgery (lower). Written informed consent is obtained from the patient for demonstration

Table 6. Complications of patients with single session augmentation mastopexy (n=27)

	Number	Percentage
Unilateral seroma, which was self-limited	4	14.8%
Unilateral seroma which required surgery	3	11.1%
Unilateral hematoma, which was self-limited	1	3.7%
Unilateral hematoma which required surgery	1	3.7%
Limited superficial skin necrosis	3	11.1%
Asymmetry	6	22.2%
Hypertrophic scar	2	7%
Mild capsular contracture	1	3.7%
Total	**21**	**77%**

Table 7. Complications of patients with breast reconstruction due to breast cancer (n=71)

	Number	Percentage
Implant malposition that required re-operation	6	8.4%
Skin necrosis on silicone implant that required implant replacement	7	9.8%
Skin necrosis on expander, which requires implant removal	10	14%
Skin necrosis on an expander in which implant was salvaged	8	11%
Mild capsular contracture	15	21 %
Hypertrophic scar	5	7%
Seroma	4	5.6%
Hematoma	5	7%
Total	**60**	**84.5%**

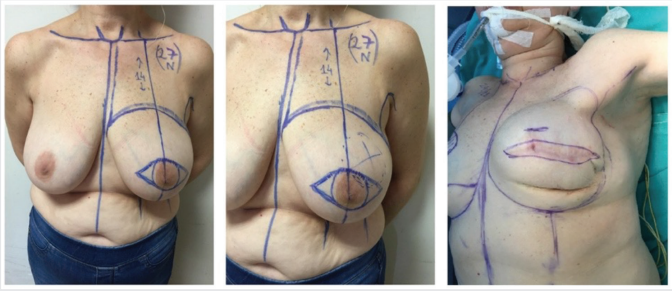

Figure 5. Photographs of a patient with breast reconstruction with expander placement before surgery (left, middle) and following the surgery with hypertrophic scar formation (right).
Written informed consent is obtained from the patient for demonstration

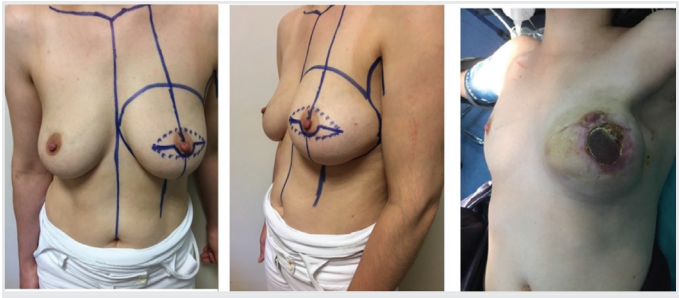

Figure 6. Photographs of a patient with breast reconstruction with silicone implant before surgery (left, middle) and following the surgery with exposed implant (right).
Written informed consent is obtained from the patient for demonstration

Discussion

Silicone breast implant applications have now become a routine of plastic surgery. Although the ranking varies from country to country, it is among the top five most frequently performed surgical applications (7-9). It is the most commonly used for breast augmentation. The implants were inserted through different incisions. Although inframammary, areolar, axillary and umbilical incisions are available according to the content structure of the implant, gel-filled implants are preferably placed through inframammary and areolar incisions. Preferred incisions have advantages and disadvantages compared to each other (10-12). We preferred inframammary incision in all of our cases. Our main reason for choosing this mode was the advantage of easier intervention in cases of complications and problem solving.

Augmentation cases combined with mastopexy is one of the most difficult and challenging procedures in plastic surgery. Especially the difficulty level of the single-session procedure is quite high. Although two-session applications require a longer process, they are less difficult and less likely to be revised. One-session mastopexy augmentation applications were the aesthetic procedures that we had the most difficulty with and we were the least satisfied with the results. Combined augmentation with mastopexy is similar to reduction surgery. A nipple-areolar complex carrier pedicle is designed. If a wise pattern drawing is made on the final closure scar, inverted t-scar results in short inverted t-scar, particularly in more drooping breasts. In cases with a lower degree of ptosis, it results in a periareolar scar or vertical scar, j scar, l scar suitable for vertical planning. In various literature studies of the procedure, the patient satisfaction rate and surgical success results are the most variable in the surgical group (13-15).

The use of silicone breast implants in oncoplastic surgery for reconstruction purposes is perhaps the most psychologically beneficial practice for the patient. Systemic and regional treatments such as chemotherapy and radiotherapy, which patients receive because of their existing oncological diseases, cause us to encounter serious postoperative recovery problems and complication processes. However, even the hope that the image of the breast will be maintained in place of the organ lost by the woman who has gone through a traumatic process such as cancer gives the patient a positive power and endurance to fight the process. In these cases, the event is actually the psychological beneficial gains of surgery. The absence of a breast causes the woman to collapse not physically, but mainly spiritually. Of course, it also has the obvious benefit of eliminating the asymmetrical appearance order to prevent postural disorders (16-18).

Study Limitations

This study has several limitations. This was a retrospective study and the patient data were collected from a single-center. Patient standardization is unideal and prospective randomized studies must overcome these limitations.

Conclusion

Breast implant surgery is an operation where the complication rate can be minimized and the existing complications can be managed in the most accurate way, owing to the surgical teams kneaded with experience that requires care and attention at all stages.

First all, these procedures should not be seen as simple. Including aesthetic cases, it is necessary to look at the cases from a reconstructive perspective. We accept that complications are in this job, but to minimize these rates, we should experience choosing the right patient and applying the right procedure.

There are critical studies in which the complication rates are minimized in the case series conducted around the world and presented in the literature. By openly sharing our current complications in our own studies, we will have taken the most important step toward a successful surgical process management and we will have the opportunity to lower our complication rates over time. Surgery and plastic surgery, which is a part of it, is a world where learning never ends and we should constantly gain new experiences and gains. A successful plastic surgeon is not a person who feels that he or she is the best and is experienced enough to perform every case, but is someone who can apply the right procedure in the right patient, has developed the ability to analyze and transfer the case to a more experienced physician when necessary not to harm the patient.

Ethics Committee Approval: This study was approved by the Ethics Committee of Universtiy of Health Sciences Turkey, İstanbul Training and Research Hospital (approval number: 223, date: 01.07.2022).

Informed Consent: Written informed consent was received from the patients.

Peer-review: Internally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices: D.A., M.S., G.T.; Concept: D.A., M.S., G.T.; Design: D.A., M.S., G.T.; Data Collection or Processing: D.A., M.S., G.T.; Analysis or Interpretation: D.A., M.S., G.T.; Writing: D.A., M.S., G.T.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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İstanbul Med J 2022; 23(4): 296-300
DOI: 10.4274/imj.galenos.2022.29794

A Comparison of BUN/Albumin Ratio with PSI and CURB-65 for Predicting Mortality in COVID-19 Pneumonia in the Emergency Department

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ABSTRACT

Introduction: The coronavirus disease-2019 (COVID-19) pandemic was the leading cause of high mortality and morbidity in the previous two years. Rapid determination of the severity of the disease is important in terms of reducing the intensity and initiating effective treatment. Although the pneumonia severity index (PSI) and CURB-65 classifications are widely employed to predict mortality and morbidity in patients diagnosed with pneumonia, biomarkers predicting the mortality and severity of COVID-19 in the emergency department (ED) are also needed. This study investigated the relationship between the blood urea nitrogen (BUN)/albumin ratio (BAR) and mortality and disease severity.

Methods: Five hundred eighty-one patients presenting to the ED between March 2020 and January 2022 and diagnosed with COVID pneumonia were included in this observational study. Patients' BUN and albumin levels, and PSI and CURB-65 scores were calculated, and in-hospital mortality was recorded. The power of BAR in predicting mortality was compared with that of PSI and CURB-65 by using statistical analysis.

Results: A significant association was determined between increased BAR and mortality. The area under the curve (AUC) value of BAR was 0.684, with 76.6% selectivity and 53.4% sensitivity at a cut-off point of 6.85. The CURB-65 score AUC value was 0.571, with 56% selectivity and 55.9% sensitivity at a cut-off point of 1.5. The AUC value for the PSI score was 0.609, with 63.3% selectivity and 50.3% sensitivity at a cut-off point of 107.5.

Conclusion: BAR is a simple but independent marker of mortality and severity in COVID-19 viral pneumonia.

Keywords: BUN/albumin ratio, emergency department, COVID-19, mortality

Introduction

The coronavirus disease-2019 (COVID-19) has caused very considerable numbers of cases and deaths since it was first observed in December 2019. According to the World Health Organization, more than 500 million cases and 6 million deaths have been reported in the intervening period (1,2) Considering the disease's ability to mutate, insufficient availability of vaccines, especially in developing countries, and the constant threat of novel variants, it is still impossible to conclude that COVID-19 is no longer a part of daily life.

Hospital presentations due to COVID-19 reached extraordinary levels in all countries, and a large part of these involved emergency departments (EDs). Serious difficulties were encountered in patient management because of the resulting intensity and uncertainties concerning the prognosis of the disease. Although new guidelines aimed at treatment have been continuously published, studies regarding the management of EDs are still insufficient.

Easily calculated follow-up parameters and biomarkers for predicting mortality and mortality are required for the successful emergency management of patients with COVID-19. Predicting the severity of the disease will both facilitate the ED management of patients and enable accurate and effective treatment to be initiated without loss of time. Several biomarkers have been studied for this purpose, including D-dimer, troponin, and ferritin (3). The principal biomarkers in recent studies are albumin and blood urea nitrogen (BUN) levels. BUN is a component of CURB-65 used in pneumonia and exhibits a powerful correlation with disease severity. As a regulator of osmotic pressure and an acute phase reactant, albumin is a marker of mortality. These two critical markers have also been tested in conditions other than pneumonia and have been proved to be successful indicators of mortality in such different conditions as chronic obstructive pulmonary disease (4), pancreatitis (5, 6), and acute myocardial infarction.

Recent studies have reported that the BUN/albumin ratio (BAR) is a more successful indicator of mortality than BUN and albumin in pneumonia,

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Cite this article as: Efgan MG, Payza U, Çınaroğlu OS, Acar H, Kayalı A. A Comparison of BUN/Albumin Ratio with PSI and CURB-65 for Predicting Mortality in COVID-19 Pneumonia in the Emergency Department. İstanbul Med J 2022; 23(4): 296-300.

Received: 14.09.2022
Accepted: 27.10.2022

the elderly, and non-chronic kidney failure patients (7). The present study investigated the role of the BAR in predicting mortality in patients presenting to the ED and diagnosed with COVID-19. To determine its success in predicting mortality, we also compared it with CURB-65 and the pneumonia severity index (PSI), contemporary, and reliable follow-up parameters used in calculating early period mortality in pneumonia (8).

Methods

Study Design

This observational retrospective study was conducted in the ED of an affiliated tertiary university hospital in the province of İzmir, Turkey, between March 2020 and January 2022. The laboratory parameters of patients diagnosed with COVID-19 in the ED were analyzed. Data were calculated for predicting mortality and morbidity, and were compared with PSI and CURB-65 data.

Patients and Setting

Patients aged over 18, presenting with symptoms suggestive of COVID-19 pneumonia, and with positive polymerase chain reaction (PCR) test results were included in the study. Patients with additional diseases other than COVID-19 pneumonia, or with medical history of kidney failure or chronic liver diseases were excluded. Patients' whose data were inaccessible or with deficient laboratory data were also excluded.

Patients with findings in favor of COVID pneumonia on thoracic computed tomography (CT) and positive PCR tests for the confirmation of pneumonia were subjected to analysis.

Data Collection

Data for patients presenting to the ED were collected from the hospital information system. The vital parameters, demographic data, and laboratory test results of the patients included in the study were recorded for statistical analysis. Exitus and discharge information for patients admitted to COVID treatment and intensive care units from the ED was also noted. BAR and PSI and CURB-65 scores were calculated from the data obtained and were compared to analyze their value in predicting mortality.

Statistical Analysis

Number and percentage were calculated for categorical variables, and mean, standard deviation and interquartile range (IQR) for numerical variables. Histogram curves, kurtosis, skewness, and the Shapiro-Wilk test were employed to determine whether continuous variables were normally distributed. Receiver operating characteristic (ROC) analysis was performed to evaluate the power of the test to predict mortality. Since the data did not show a normal distribution, the Mann-Whitney U test was used when comparing the mean of the 2 independent groups. Logistic regression analysis was performed to evaluate the success of the BAR, PSI, CURB65 tests in predicting mortality. All statistical calculations were carried out on SPSS 22.0 software and at a 95% confidence interval.

Results

Examination revealed that 1086 patients presented to our ED between March 2020 and January 2022, and 581 patients who met the inclusion criteria were enrolled. The exclusion criteria are shown in the consult diagram (Figure 1).

Men constituted 281 (37.5%) patients included in the study and women 363 (62.5%). The patients' mean age was 65 (19-97) years.

One hundred seventy-nine (30.8%) of these patients were admitted to intensive care units and 207 (35.6%) to COVID treatment units. One hundred ninety-five patients (33.6%) were discharged after treatment planning in the ED. Worsening was observed during follow-up in 108 (52.1%) of the 207 patients admitted to COVID treatment units, and these were transferred to the intensive care unit. In-hospital mortality occurred in 175 (30.1%) patients treated in the intensive care units.

Laboratory results, BAR, PSI, and CURB-65 scores were compared between the in-hospital non-survivor and survivor patient groups. BAR, PSI, CURB-65, BUN, creatinine, albumin, sodium, hematocrit, white blood cell, neutrophil, lymphocyte and C-reactive protein, were statistically significant in predicting mortality (Table 1).

ROC analysis was performed to determine the predictive power of BAR, PSI, and CURB-65 in terms of in-hospital COVID-19 mortality (Figure 2). Cut-off values were determined for BAR, CURB-65, and PSI parameters. The area under the curve (AUC) value for BAR was 0.684, exhibiting 76.6% specificity and 53.4% sensitivity, with a cut-off value of 6.85. The AUC value for CURB-65 was 0.571, with specificity of 56%, sensitivity of 55.9%, and a cut-off value of 1.5. The equivalent values for PSI were AUC 0.609, specificity 63.3%, sensitivity 53%, and a cut-off value of 107.5 (Table 2).

Regression analysis was performed to determine the value of BAR and PSI and CURB-65 scores in predicting mortality. BAR and PSI emerged as significant indicators of in-hospital mortality. However, regression analysis also showed that the BAR variable was a more relevant predictor of mortality compared with the other markers for each standard deviation change (Table 3).

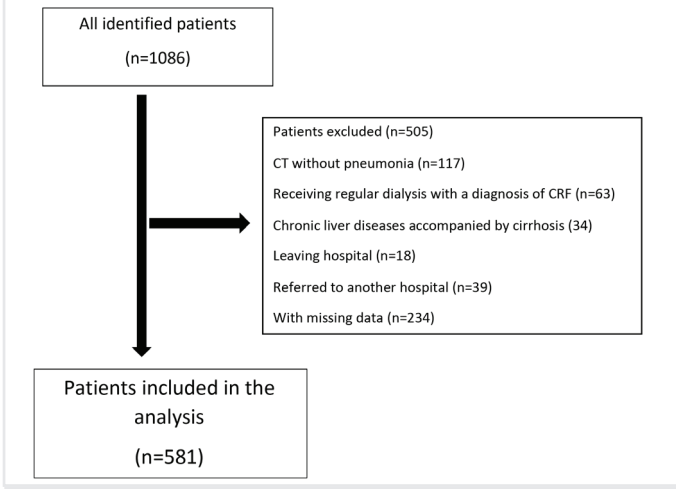

Figure 1. Consult diagram
CT: Computed tomography, CRF: Chronic renal failure

Table 1. Intragroup comparisons of variables in terms of in-hospital mortality

Parameters	Non-survivor, median (IQR)	Survivor, median (IQR)	p-value
BUN (mg/dL)	33 (40)	22 (17.25)	**0.001**
Albumin (g/dL)	3.2 (0.9)	3.4 (0.8)	**0.001**
Creatinine	1.32 (1.62)	1.07 (0.68)	**0.001**
Sodium	136 (7)	137 (6)	**0.036**
Glucose	136 (76)	132.50 (70.25)	0.882
Hematocrit	34.70 (9.30)	36.40 (8.80)	**0.004**
WBC	9.73 (7.15)	8.04 (6.24)	**0.001**
Neutrophil	7.71 (6.39)	5.76 (5.51)	**0.001**
Lymphocyte	1.15 (0.88)	1.30 (0.95)	**0.041**
Eosinophil	0.03 (0.11)	0.04 (0.11)	0.301
CRP	92.42 (124.50)	54.92 (113.55)	**0.006**
BAR (mg/g)	10.7 (13.7)	6.5 (5.5)	**0.001**
PSI	121 (46)	105 (45)	**0.001**
CURB-65	2 (1)	1 (1)	**0.005**

BUN: Blood urea nitrogen, IQR: Interquartile range, WBC: White blood cell, CRP: C-reactive protein, BAR: BUN/albumin ratio, PSI: Pneumonia severity index

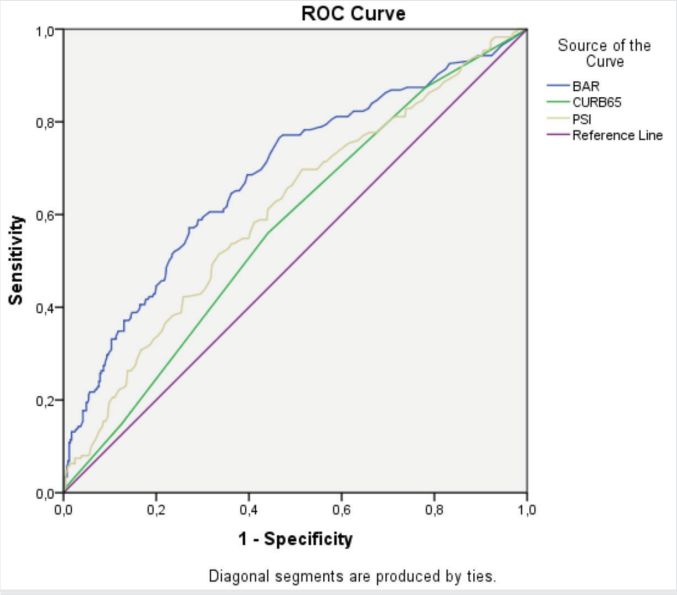

Figure 2. ROC curve for determining mortality prediction power
ROC: Receiver operating characteristic, BAR: BUN/albumin ratio, PSI: Pneumonia severity index

Discussion

The COVID-19 pandemic has resulted in significant research aimed at understanding viruses responsible for epidemics and at examining the characteristic findings of the disease. A significant study is also being performed on the development of powerful markers for determining the severity of existing viral pneumonia and predicting mortality. The objective is to be able to make predictions, not solely for the COVID pandemic, but also for subsequent epidemics.

This study analyzed many quantitative parameters potentially associated with the inflammatory response and potential markers associated with mortality. These novel biomarkers were then compared with classic scores such as CURB-65 and PSI.

Table 2. ROC analysis results by in-hospital mortality status

Test result variable(s)	AUC	Standard errora	Asymptotic Sig.b	Asymptotic 95% CI	
				Lower bound	Upper bound
BAR	0.684	0.025	0.001	0.635	0.732
CURB-65	0.571	0.025	0.007	0.521	0.620
PSI	0.609	0.026	0.001	0.559	0.659

ROC: Receiver operating characteristic, AUC: Area under the curve, Sig.: Significance, CI: Confidence interval, BAR: BUN/albumin ratio, PSI: Pneumonia severity index

Table 3. Regression analysis of BAR, PSI and CURB-65

	Beta	Six.	Exp (beta)	95% CI for EXP (B)	
				Lower	Upper
BAR	1.1	0.001	3.0	2.0	4.5
CURB-65	-0.1	0.601	0.891	0.6	1.4
PSI	0.5	0.035	1.6	1.1	2.4

BAR: BUN/albumin ratio, PSI: Pneumonia severity index, CI: Confidence interval

BUN is a valuable marker of mortality in several diseases, and particularly emerges in association with sepsis-related dehydration (9,10). It is also a component of the CURB-65 scoring system (11). Cheng et al. (12) reported that BUN values predicted mortality in a study investigating the validity of the infective parameters BUN and D-dimer in patients with COVID-19. In their meta-analysis, Shao et al. (13) suggested that acute kidney failure and increased BUN levels were useful in predicting mortality in patients with COVID-19. Liu et al. (14) calculated BUN-creatinine ratios and found that these were correlated with mortality. The mean BUN levels calculated in this study were significantly higher in the non-survivor patient group than in the surviving group, and the results were consistent with the current literature [median (IQR): exitus group: 33 (40); discharged group: 22 (17.25); p<0.001)].

Albumin is a negative acute phase reactant involved in the neutralization of endogenous and exogenous substances, antioxidation, immune system regulation, and anti-inflammatory processes (15,16). Albumin levels may decrease in cases of malnutrition, inflammation, and hepatocellular injury. Previous studies have reported that a decrease in albumin levels is associated with mortality in COPD, pancreatitis, acute coronary syndrome, and pneumonia (4,6,17,18). In their study of 319 patients, Violi et al. (19) reported a powerful negative correlation between mean albumin levels and mortality in patients with COVID-19. In another meta-analysis, Aziz et al. (20) reported a link between low albumin levels and mortality in COVID-19 patients. The results of this study were in agreement with the previous literature, with mean albumin levels significantly predicting non-survivor patients [median (IQR): exitus group: 3,2 (0.9); discharged group: 3.4 (0.8); p<0.001)].

BAR calculated using BUN and albumin is a powerful independent predictor of mortality and disease severity in current studies. Ugajin et al. (21) described BAR as significant in predicting in-hospital mortality

and determining the severity of community-acquired pneumonia. The odds ratio (OR) value calculated for BAR in that study was 1.10 (21). In a study of patients aged over 65 presenting to the ED, Dundar et al. (22) compared BUN, albumin, and epidermal growth factor receptor levels with BAR. Those authors concluded that the risk of hospitalization was higher in patients with increased BAR, and that BAR exhibited better correlation than other laboratory parameters studied in the ED in terms of determining disease severity. Dundar et al. (22) calculated an OR value of 2.82 for BAR. Küçükceran et al. (23) reported an OR value of 10.48 for BAR in the prediction of in-hospital mortality among patients with COVID-19 in the ED. The AUC value for BAR in that study was 0.809, with 87.5% sensitivity and 59.9% specificity and a cut-off point of 3.9 mg/g (23). The value for BAR in this study was 3 and was significantly higher in the non-survivor group than in the survivors [median (IQR): exitus group: 10.7 (13.7); discharged group: 6.5 (5.5); $p<0.001$)]. The AUC value for BAR in this study was 0.684, with selectivity of 76.6% and sensitivity of 53.4%. The threshold value for the cut-off point was 6.85.

BAR is a biomarker with results that provide a successful prediction recently. Ryu et al. (7) compared BAR and PSI and CURB-65 scores in patients with aspiration pneumonia and reported significant success. In an important study of patients receiving immunosuppressants, Xia et al. (24) reported that the use of classic biomarkers was not sufficient to show mortality and morbidity. The authors also concluded that BAR exhibited a powerful negative correlation with disease severity (24). The results in this study were similar to an AUC value of 0.684 for BAR, 0.571 for CURB-65, and 0.609 for PSI. BAR thus appears to exhibit a similar power to PSI scores in predicting in-hospital mortality in COVID-19 pneumonia. In the regression model established, the mortality risk increased three times for each one unit of standard deviation in the BAR value, and 1.6 times for each one unit of deviation in PSI values. However, CURB-65 was not statistically significant in the regression model. Additionally, PSI is an algorithm with many parameters, including patient characteristics, comorbidities, physical examination findings, radiographic findings, and laboratory results (25). In order for PSI to be use capable of as a predictor of mortality, it is therefore necessary to have a good knowledge of the patient's history, with parameters that can be calculated in routine clinical practice (26). CURB-65 is a simple and widely employed tool, particularly in EDs (11). However, the value of this scoring system decreases in young patient groups, and it is difficult to evaluate in patients with an uncertain mental state before infection (27) BAR represents an important biomarker for overcoming these difficulties in data acquisition.

Study Limitations

This study did not consider the possibility that patients with non-end-stage chronic kidney disease may have a high baseline BUN and that patients with liver disease without cirrhosis may have low baseline albumin levels.

The principal limitations of this study are its retrospective, single-center nature and the small patient numbers.

Conclusion

The results of this study showed that BAR can be used to predict mortality in patients with COVID-19 pneumonia since it can be calculated easily and quickly with simple laboratory parameters that can be obtained in all EDs. It also exhibited a strong predictive power compared with PSI and CURB-65 in predicting in-hospital mortality in patients with COVID-19 pneumonia.

Additionally, this is the first study to compare BAR with PSI and CURB-65 scores in terms of predicting in-hospital mortality in COVID-19 pneumonia.

Ethics Committee Approval: This study was approved by the Ethics Committee of İzmir Katip Çelebi University Non-Interventional Clinical Research Ethics Committee (approval number: 0596, date: 20.01.2022).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept: M.G.E., O.S.Ç., A.K.; Design: M.G.E., H.A.; Data Collection or Processing: M.G.E., U.P., A.K.; Analysis or Interpretation: M.G.E., H.A., A.K.; Literature Search: M.G.E., U.P., H.A.; Writing: M.G.E., U.P., H.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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İstanbul Med J 2022; 23(4): 301-5
DOI: 10.4274/imj.galenos.2022.49035

Does Previous Anti-thrombotic Use Affect the Course of Coronavirus Disease-2019?

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ABSTRACT

Introduction: Proinflammatory cytokines, produced as an immune response in severe acute respiratory syndrome-coronavirus 2 infection, activate the coagulation cascade as well. In this study, we investigated the difference in the clinical course of patients who had been already using anti-thrombotic therapy before coronavirus disease-2019 (COVID-19) for any reason compared to the group who had not.

Methods: In this retrospective, multicenter study; patients who were hospitalized between March 11 and July 1, 2020 were divided into two main groups as who had been on anti-thrombotic therapy for any indication use previously at the time of admission or who had not been on anti-thrombotic therapy at the time of admission, and their selected clinical parameters were compared.

Results: After analyzing the study population of 124 patients with a homogeneous distribution in terms of age and gender, the comparison of anti-thrombotic users and non-users showed no significant difference in hospitalization. There was a statistically significant decrease in mechanical ventilation apply rate, intensive care unit duration and mortality rate between the group using anti-thrombotic compared to the group not using it ($p<0.05$).

Conclusion: It has already been shown that COVID-19 patients are more prone to thromboembolic events as it activates the coagulation cascade with the cytokine storm it creates and thus the mortality of COVID-19 infection increases significantly. Parallel to this fact the results of our study demonstrated that using anti-thrombotic therapy for any reason may affect the bad prognosis of the disease positively.

Keywords: SARS-CoV-2, COVID-19, anti-trombotic treatments

Introduction

Coronavirus disease-2019 (COVID-19) spread rapidly worldwide and caused an inevitable pandemic. While most of the COVID-19 patients are in a mild clinical form, 6-19% of the patients develop a serious disease course (1,2). Although there has been a big obscurity about the disease, it has been getting enlightened over time and currently the pathophysiology of the disease is considered to be associated with the inflammatory cytokine storm (3-5).

Proinflammatory cytokines that are released as an immune response to infection are thought to activate the coagulation cascade as well (6). Thrombin is well known to be mainly responsible for the clot formation by activating the platelets. It provides protein kinase activator receptor accumulation with multiple cellular actions as well and primarily creates protease-activated receptor-1. The thrombin formation is under strict control of anti-thrombin 3 factors, tissue factor inhibition and protein C system and physiological and negative feedback mechanisms (6). With an increase in the inflammatory response, control mechanisms deteriorate and procoagulant-anti-coagulant balance gets impaired. As a result, microthrombus, diffuse intravascular coagulation, and thus D-dimer increase are observed. These markers indicate the poor prognostic course and severe organ failure in COVID-19 pneumonia (7,8). In the autopsy series of COVID-19 patients, deep vein, arterial, cardiac and pulmonary artery thrombosis were observed (9-12). In addition, alveolocapillary microthrombi are seen in patients with COVID-19 nine times more than that of influenza patients, suggesting that it leads to severe lung damage and hypoxemia (13).

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Cite this article as: Önur İ, Tural Önür S, Günlüoğlu G, Bingöl G, Sökücü SN, Özden Ö, Nasifov M, Bolat E, Toptaş M, Altın S. Does Previous Anti-thrombotic Use Affect the Course of Coronavirus Disease-2019? İstanbul Med J 2022; 23(4): 301-5.

Received: 20.03.2022
Accepted: 28.10.2022

Regrettably, neither anti-inflammatory drugs nor anti-coagulant drugs have sufficient studies on the course of COVID-19 disease. In our study, we investigated the prognosis of patients who had been using anti-thrombotic therapy for any reason in terms of hospital stay, intubation, and death by comparing it with the patients who had not been using that therapy.

Methods

In our study, 124 patients who were hospitalized between March and July 2020 for COVID-19 according to WHO interim guidance in 2 hospitals were retrospectively analyzed. One hospital was a training and research hospital and the other one was a private hospital, which were designated as pandemic hospitals. Forty-six patients who had been using anti-thrombotic therapy for any indication (such as a previous cerebro vascular event, cardiac arrhythmia, heart valve replacement) before hospitalization were included in the study. Acetylsalicylic acid, vitamin K antagonist, new generation oral anti-coagulant, clopidogrel and ticagrelol, which are used as anti-aggregant and anti-coagulantss, have been accepted as anti-thrombotic therapy (14). Since death was the primary endpoint of the population included in the study, the anti-thrombotic treatment group and the control group not using it were divided into those who died and those who did not. This study was approved by the Clinical Research Ethics Committee of University of Health Sciences Turkey, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital (approval number: 2020-03, date: 06.08.2020). Written informed consent was obtained from all patients.

The demographic data of the patients, medical histories and laboratory findings, radiological Images were retrospectively obtained through the hospital electronic information system. While taking the medical history of the patients, the drugs that they declared they used before were checked through the social security reporting and the prescription system. Hemogram data of the patients included in the study were studied with the Sysmex XT4000i device and biochemical examinations were performed with the Beckman Coulter AU2700 device in the hospital laboratory. Polymerase chain reaction were examined in the hospital laboratory where SARS-CoV-2 laboratory validation was performed. Swap samples were taken from the upper respiratory tract at the time of admission to the hospital and transported with viral transport medium to the laboratory. Whole RNA Extraction in the respiratory sample, which took 2 h, the Genmak RNA isolation kit was obtained using the Genome by the method previously described for SARS-CoV-2 (15).

Statistical Analysis

Descriptive and demographic statistics were applied for the investigated parameters and the chi-square test and Fisher's exact test were performed for categorical variables where appropriate. For group comparisons, Kolmogorov-Smirnov test was used to determine whether data were normally distributed. The Mann-Whitney U test was used due to the abnormal distribution of data. Logistic regression analysis was used to predict confounders and risk factors for COVID-19. All statistical tests were two-tailed and $p<0.05$ was considered statistically significant. The Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, Version 21.0) was used.

Results

Our study population consists of 124 patients, whose demographic data can be appreciated in Table 1, shows a homogeneous distribution in terms of age and gender. A statistically significant difference was found in favor of those using anti-thrombotic for death ($p<0.05$) (Table 1). The rate of anti-thrombotic use is higher in the control group. In other words, the mortality rate is higher in those who do not use anti-thrombotics. Anti-thrombotic use was found to be significantly different in patients with chronic obstructive lung disease and cardiovascular disease comorbidity depending on the current comorbidity (respectively $p=0.019$ and $p=0.001$). The use of statins, angiotensin-converting enzyme (ACE)

Table 1. Comparison of demographic and clinical characteristics of anti-thrombotic users and non-users before hospitalization

Variables	Total	Anti-thrombotic (+)	Anti-thrombotic (-)	p-value
		(n=46)	(n=78)	
Age groups-No. (%)				
<30 years	4 (3.2)	1 (2.2)	3 (3.8)	0.105
30-49 years	13 (10.5)	1 (2.2)	12 (15.4)	
50-69 years	69 (55.6)	27 (58.7)	42 (53.8)	
≥70 years	38 (30.6)	17 (37.0)	21 (26.9)	
Sex - No. (%)				
Male	77 (62.1)	32 (69.6)	45 (57.7)	0.188
Female	47 (37.9)	14 (30.4)	33 (41.3)	
Group - No. (%)				
Control	69 (55.6)	33 (71.7)	36 (46.2)	0.006
Death	55 (44.4)	13 (28.3)	42 (53.8)	
Intube group - No. (%)				
Intube	46 (37.1)	10 (21.7)	36 (46.2)	0.007
Non-intube	78 (62.9)	36 (78.3)	42 (53.8)	
RT-PCR - No. (%)				
Negative	73 (60.8)	31 (68.9)	42 (56.0)	0.161
Positive	47 (39.2)	14 (31.1)	33 (44.0)	
Comorbidity - No. (%)				
COPD	22 (17.7)	13 (28.3)	9 (11.5)	0.019
HT	24 (19.4)	10 (21.7)	14 (17.9)	0.606
DM	3 (2.4)	1 (2.2)	2 (2.6)	0.891
CVD	14 (11.3)	13 (28.3)	1 (1.3)	0.001
Pneumonia	31 (25.0)	10 (21.7)	21 (26.9)	0.520
Lung cancer	5 (4.0)	1 (2.2)	4 (5.1)	0.419
Medications - No. (%)				
Statin	24 (19.4)	17 (37.0)	7 (9.0)	0.001
ACE inhibitors	12 (9.7)	8 (17.4)	4 (5.1)	0.026
Beta blockers	32 (25.8)	25 (54.3)	7 (9.0)	0.001
Hospitalisation-median (IQR)/day	9.0 (8.0)	7.5 (7.0)	10.0 (9.0)	0.053
ICU-median (IQR)/day	1.0 (6.0)	0.0 (0.0)	1.0 (10.0)	0.001

RT-PCR: Real-time polymerase chain reaction, COPD: Chronic obstructive lung disease, HT: Hypertension, DM: Diabetes mellitus, CVD: Cardiovascular disease, ACE: Angiotensin-converting enzyme, IQR: Interquartile range

inhibitors and beta blockers in patients using anti-thrombotic therapy due to their existing comorbidities during hospitalization was also significant (respectively p=0.001, p=0.026, and p=0.001). No significant difference was found in patients using anti-thrombotic compared to those who did not use them during the total length of hospital stay. However, there was a tendency for a significant difference (p=0.053). It has also been shown that ICU stay duration was significantly shorter in the anti-thrombotic drug user group (p=0.007).

A comparison of the study groups with hemograms and biochemical laboratory results can be seen in Table 2. D-dimer, troponin, ferritin, and alanine aminotransferase values were found to be statistically significantly different between two groups ($p<0.05$). These values were higher in those who did not use anti-thrombotic. These results support our prediction of COVID-19 patients who do not use anti-thrombotic s have a worse prognosis.

When we examine the logistic regression analysis results of the independent variables in Table 3, the deaths of patients using anti-thrombotic and statin were found to be less than COVID-19, and no effect of ACE inhibitor and beta blocker use was detected.

Discussion

COVID-19 pandemic caused by SARS-CoV-2 has become a disease with its numerous unknown aspects of humanity. It is thought that the progression of the disease worsens with the formation of microthrombus and thrombosis, which causes disruption of the balance between the procoagulant and anti-coagulant systems with the widespread cytokine release. We determined that the anti-thrombotic therapy used in the patient group with comorbidity in which the disease progressed worse, depending on the existing comorbidity, may affect the duration of hospitalization, intubation and the course leading to death.

Anti-phospholipid syndrome of disseminated intravascular coagulation, activation of complement cascade and formation of endothelial dysfunction as a feature of the virus, constitutes the basis of the procoagulant pathophysiology (16,17). The tropism of the SARS-CoV-2 virus to angiotensin-converting enzyme 2 found in type 2 pneumocytes causes an inflammatory cascade causing generalized pulmonary hypercoagulability (18). In our study, we believe that our inability to determine the effect of ACE inhibitors on the mortality of the disease on intubation and length of stay was due to the small sample size.

In the literature, it has been shown that systemic anti-coagulant therapy reduces the mortality of COVID-19 patients on mechanical ventilation (19). Similar to our results, Chow et al. (20) compared the patient group using aspirin up to seven days before their hospital admission with non-users and found that hospitalized patients due to COVID-19 had lower mechanical ventilation, intensive care admission and hospital mortality (20). Additionally, the potential benefits of acetylsalicylic acid in lung damage reduce interleukin-6 production, platelet-neutrophil aggregation, inflammation and increase lipoxin formation, which improves pulmonary endothelial cell function (21,22).

In a multi-center observational study by Russo et al. (23) in Italy, it has been demonstrated that pre-admission anti-thrombotic treatment did not affect acute respiratory distress syndrome (ARDS) and death due to COVID-19.

In our study, we found that while the duration of hospitalization was not associated with the use of anti-thrombotic therapy before hospitalization, it had a positive effect on intubation and mortality. We think that a larger sample size is needed to the effect of patients using anti-thrombotic therapy before hospitalization on the length of hospital stay.

It is emphasized in the relevant guidelines that patients who use ACE inhibitors or angiotensin II receptor blocker (ARBs) due to their chronic diseases, continue their current treatment even if they have COVID-19 disease (24,25). Mehta et al. (26) investigated 18,472 COVID patients and found no relationship between the use of ACE inhibitors or ARBs during the pandemic process, and the positivity of COVID-19 tests, and findings supporting the recommendations of the guidelines were found. In the secondary analyses of the same study, no significant difference

Table 2. Comparison of laboratory parameters between anti-thrombotic users and non-users before hospitalization

Variables	Total (n=124) Median (IQR)	Anti-thrombotic (+) (n=46) Median (IQR)	Anti-thrombotic (-) (n=78) Median (IQR)	p-value
D-dimer	0.92 (1.05)	0.88 (0.64)	0.94 (1.3)	0.040
Troponin	6.6 (11.7)	5.7 (10.2)	8.6 (13.3)	0.033
Ferritin	298.2 (313.05)	283.1 (245)	304.0 (290.8)	0.048
Fibribojen	484.9 (217.2)	490.5 (231.8)	483.85 (206.5)	0.248
Procalcitonin	0.1 (0.23)	0.08 (0.21)	0.1 (0.27)	0.361
Albumine	37.35 (6.25)	36.65 (5.4)	37.4 (6.5)	0.934
CRP, (mg/L)	88.45 (97.6)	88.45 (87.9)	91.5 (109.6)	0.616
WBC, (×10e3/uL)	7.93 (8.05)	7.18 (3.64)	9.13 (11.72)	0.008
Hb, (g/dL)	13.1 (2.35)	12.9 (1.8)	13.3 (2.5)	0.677
Hct, (%)	38.35 (5.55)	37.85 (4)	38.75 (6.4)	0.629
LY, (×10e3/uL)	1.14 (0.67)	1.17 (0.93)	1.12 (0.61)	0.523
LY, (%)	16.5 (13.65)	17.15 (15.0)	16.35 (13.1)	0.687
LDH, (U/L)	381.0 (199.0)	363 (209.0)	397.0 (180.0)	0.291
AST, (U/L)	39.0 (28.0)	36.5 (23.0)	40.0 (38.0)	0.143
ALT, (U/L)	25.5 (21.0)	23.0 (15.0)	32.0 (23.0)	0.012

IQR: Interquartile range, CRP: C-reactive protein, WBC: White blood cell count, Hb: Hemoglobin, Hct: Hematocrit, LY: Lymphocyte count, LY: Lymphocyte count, LDH: Lactate dehydrogenase, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase

Table 3. Logistic regression analysis of factors affecting COVID-19 death

Independent variables	OR	95% CI	p-value
Anti-thrombotic	0.338	0.155-0.737	0.001
Statin	0.347	0.127-0.947	0.001
ACE	0.598	0.170-2.101	0.423
Beta	0.571	0.248-1.319	0.190

COVID-19: Coronavirus disease-2019, OR: Odds ratio, CI: Confidence interval, ACE: Angiotensin-converting enzyme

was found in the need for mechanical ventilation in patients using ACE inhibitors or ARB compared with those who did not (26). Reynolds et al. (27) showed that, in a large-scale observational study an increase in the probability of positive test result in patients who used 5 groups of anti-hypertensive (ACE inhibitor, ARB, beta blocker, Calcium channel blocker, or thiazide diuretic) but an increase in the severity of the disease was not detected in patients with positive test results (27). In our study; in accordance with the literature, ACE I and ARB and beta blockers used for comorbidity of the patients have been shown not to increase mechanical ventilation, ICU need and mortality.

In the meta-analysis of 4 large-scale studies involving 8,990 patients, in which the effects of statin use on the development of mortality and/or serious disease in patients with COVID-19 infection was evaluated and it was shown that the use of statin significantly reduced the rate of death and serious disease by 30%. Although more information is needed on statin regimens in COVID-19, evidence has shown that medium and high-dose statin therapy is effective (28). In our study, we found that patients using statin alone had decreased mechanical ventilation, ICU need and mortality.

Study Limitations

The main limitations of our study are its retrospective nature and small sample size. We believe that the use of pre-admission anti-thrombotic therapy should be investigated in a prospective controlled study group with a larger sample size, which will help prove with a stronger level of evidence that it may affect the course of the disease.

Conclusion

It has been shown that the use of anti-platelet therapy before hospital admission does not affect the duration of hospital stay in the clinical presentation of COVID-19, but significantly affects the intubation of the patient and the death. In the pathophysiology of COVID-19 pneumonia, we think that microvascular pulmonary thrombosis supports the existence of a complex relationship between the immune-mediated inflammatory response and the activation of the coagulation system during ARDS.

Ethics Committee Approval: This study was approved by the Clinical Research Ethics Committee of University of Health Sciences Turkey, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital (approval number: 2020-03, date: 06.08.2020).

Informed Consent: Written informed consent was obtained from all patients.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices: İ.Ö., S.T.Ö., G.G., G.B., S.N.S., Ö.Ö., M.N., E.B., M.T., S.A.; Concept: İ.Ö., S.A., M.T., M.N.; Design: İ.Ö., G.G., E.B., G.B.; Data Collection or Processing: M.N., G.G., S.A. M.T.; Analysis or Interpretation: S.T.Ö., E.B., S.N.S., S.A.; Writing: Ö.Ö., E.B., M.N., S.N.S.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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İstanbul Med J 2022; 23(4): 306-9
DOI: 10.4274/imj.galenos.2022.29895

Anatomic and Functional Effects of Systemic Corticosteroids for Treating Toxic Optic Neuropathy Due to Methanol Intoxication

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ABSTRACT

Introduction: The aim of this study was to examine the anatomical and functional effects of high-dose intravenous steroids for toxic optic neuropathy due to methanol intoxication.

Methods: In this retrospective study, we demonstrated six cases of toxic optic neuropathy due to acute methanol poisoning. Medical charts were evaluated for demographic characteristics of patients, best corrected visual acuity (BCVA), fundus examination, optical coherence tomography, visually evoked potential (VEP) before and after the high-dose intravenous steroid treatment in the first week and the first month.

Results: Ten eyes were involved. All patients were male and the mean age was 49.5±10.59 years. The duration of initiating the therapy was 4.5±1.3 days (3-6 days). BCVA values detected in the first week and the first month after the treatment were compared with those before the treatment, a statistically significant increase was found. In the total retinal nerve fiber layer (RNFL) and Ganglion cell complex (GCC) in the first week, an increased thickness, which was not detected statistically significant, but in the first month, a statistically significant thinning was found. No significant difference was found in the VEP values after the treatment.

Conclusion: For treating toxic optic neuropathy due to methanol, although an increase in visual acuity was observed at the end of the first month, optic nerve values such as RNFL and GCC continue to decrease.

Keywords: Methanol intoxication, retinal nerve fiber layer, toxic optic neuropathy

Introduction

The formaldehyde and formic acid that are formed when methyl alcohol is metabolized by the body have high toxicity to the central nervous system, gastrointestinal system and eyes. In patients who survive the acute phase of intoxication, permanent blindness and pathologies of the central nervous system may be observed (1-4).

Six-thirty hours after the ingestion of methyl alcohol (longer if ingested alongside ethyl alcohol), symptoms such as blurred vision, changes in color vision, diplopia are observed either alone or together with symptoms such as headache, dizziness, nausea, vomiting, abdominal pain. Papilledema, hyperemia, or atrophy can be detected in the fundus examination (1,5-9).

Treatment involves ethanol, gastric lavage, fomepizole, hemodialysis, alkalinization and folic acid (10,11). The aim of this study is to demonstrate six cases, who presented to our hospital during a period of sudden increase in the rate of methanol intoxication in Istanbul and were treated with hemodialysis, Folic Acid and high dose methylprednisolone. In this study, the cases were analyzed retrospectively in terms of the efficiency of systemic steroids on anatomic and functional symptoms together with the pre- and post-treatment.

Methods

Among the patients who presented to the Emergency Service of İstanbul Training and Research Hospital due to fake alcohol consumed at the same venue and diagnosed with methanol intoxication, those who had visual symptoms were referred to the Opthalmology Service of İstanbul Training and Research Hospital.

This retrospective study was conducted with the approval of the University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethics Committee (1183, date: 23.02.2018), in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients and/or relatives before the treatment. The files of the patients whose treatments were regulated and who met the inclusion criteria were analyzed.

The inclusion criteria were; administration of systemic steroid treatment, visual acuity on the seventh day and the first month before and after the treatment, and the completion of biomicroscopy fundus tests, spectral domain optical coherence tomography (OCT) and visual evoked potentials (VEP) measurements.

Patients who had accompanying factors that can cause optic neuropathy, patients who have chorio-retinopathy or amblyopia that can affect visual

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Cite this article as: Sultan P, Güngel H, Çiftci F. Anatomic and Functional Effects of Systemic Corticosteroids for Treating Toxic Optic Neuropathy Due to Methanol Intoxication. İstanbul Med J 2022; 23(4): 306-9.

Received: 01.06.2022
Accepted: 31.10.2022

acuity, patients who have uncontrolled systemic and ocular infection, patients who discontinued the steroid use were excluded from the study.

The diagnosis of methanol intoxication was diagnosed based on the fact that the subject attracted interest, all patients had a history of purchasing and ingesting fake alcohol at the same venue, clinical, systemic and ophthalmologic examination, increased anion and osmolar gap.

As treatment, all patients underwent hemodialysis with nephrology consultation. The nephrologists also helped in correcting the metabolic disturbance and sodium bicarbonate dosage. Three doses of folic acid (1 mg/kg) were administered intravenously every other day. The maintenance dose was administered at a dose of 10 mg/day for 2 weeks of oral intake. The patients received 1 g/day of intravenous methylprednisolone every other day for 5 days and continued oral prednisolone at 1 mg/kg for 10 days (12-18). The time of starting the treatment, and demographic characteristics of the patients were recorded.

Patients best corrected visual acuity (BCVA) testing with the logarithm of the minimum angle of resolution (logMAR) measurements were recorded. Anterior segment examination using biomicroscopy, and dilated fundus examination using an indirect ophthalmoscope were performed. VEP (The Neuro-MEP-Micro EMG system, Neurosoft Ltd., 5 Voronin Street, Ivanovo, Russia) and OCT [(Optovue OCT (V 5.1, RTVue 100-2, Optovue, Fremont, CA, USA)] measurements were performed. The patients' cranial magnetic resonance imaging (MRIs) were obtained.

In OCT measurements, the mean central macular thickness (CMT) of both eyes, macular ellipsoid zone integrity, choroidal thickness (CT), total retinal nerve fiber layer (RNFL) thickness, disk topography values (disc area, cup area, rim area, cup volume, rim volume) Ganglion cell complex (GCC) measurements (GCC-RNFL, GCC +, GCC ++) were recorded. BCVA (logMAR), CMT, RNFL, CT, and GCC measurements were compared statistically on the seventh day and the first month before and after the treatment.

Latency (N75, P100, N145) and amplitude (N75-P100, P100-N145) were measured in the pattern VEP measurements. The results were divided into three groups: unable to record data, low latency amplitude detected, and normal latency and amplitude detected.

In the fundus examination, the presence of optic nerve edema and atrophy of the optic disc 1 month before and after the treatment were examined.

Statistical Analysis

For statistical analysis, SPSS 15.0 for the Windows program was used. Descriptive statistics were number and percentage for categorical variables, mean, standard deviation, minimum and maximum for numeric variables. Paired samples t-test, Wilcoxon signed-ranks test, and Friedman test were used in the evaluation of the data. $P<0.05$ was considered significant.

Results

Two patients had right eye involvement and 4 patients had both eyes involved. All patients were male and the mean age was 49.5±10.59 years (34-61 years). The duration of initiating the therapy was 4.5±1.3 days (3-6 days).

BCVA values detected in the first week and the first month after the treatment were compared with those before the treatment, a statistically significant increase was detected (using Wilcoxon Signed-Ranks test; p=0.026 and p=0.042 for the right eye, p=0.038 and p=0.047 for the left eye) (Figure 1). In 80% of patients, an increase in BCVA was detected.

RNFL, in the first week, an increased thickness, which was not statistically significant (right p=0.893, left p=0.854; Wilcoxon signed-ranks test) was detected, in and in the first month, a statistically significant thinning (right p=0.028, left: 0.046; Wilcoxon signed-ranks test) was detected (Figure 2). In disc topography values, no significant difference was detected between the two eyes in the first week and the first month of the treatment (p>0.05 Wilcoxon signed-ranks test and Friedman test).

A statistically insignificant increase in GCC thickness was detected in the first week for the right eye (right p=0.109, left p=0.715; Wilcoxon signed-ranks test) and statistically significant GCC thinning was detected in the first month for both eyes (right p=0.028, left p=0.046; Wilcoxon signed-ranks test) (Figure 3).

No significant difference was found in VEP values in all controls (p>0.05, Wilcoxon signed-ranks test).

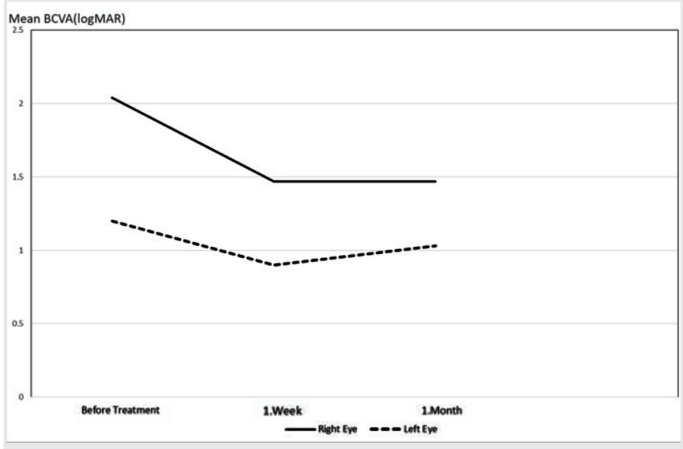

Figure 1. Mean best-corrected visual acuity (LogMAR) changes before treatment, first week and 1st month after the treatment

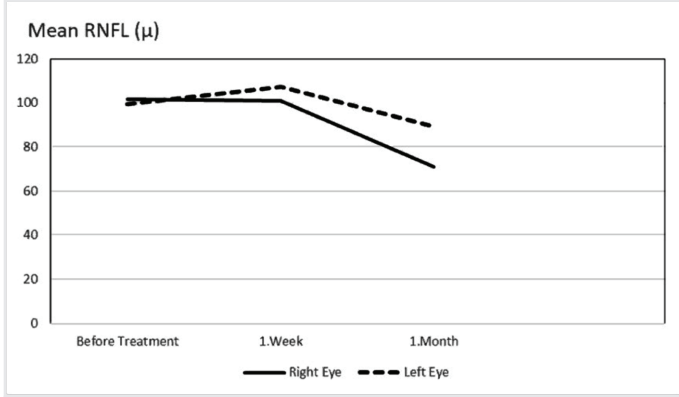

Figure 2. Mean RNFL (μ) changes before treatment, first week and 1st month after the treatment
RNFL: Retinal nerve fiber layer

No significant difference was found in CT, CMT (p>0.05, Wilcoxon signed-ranks test, and Friedman test). Ellipsoid zone was preserved before and after the treatment in all patients.

The mean ± SD of BCVA, RNFL, GCC++, CMT, and p-values (paired sample t-test) of 10 eyes before and after treatment are summarized in Table 1.

Optic nerve edema was detected in both the involved eyes of a patient. Optic nerve edema was not detected in the other involved eyes. At the end of the first month, all the involved eyes had optic disc atrophy.

No systemic corticosteroid-dependent side effects were observed. In the cranial MRI of all patients, brain stem, cerebellum, basal ganglia and cerebral cortices were normal.

Discussion

Formic acid formed upon methanol intoxication causes cellular damage at the mitochondrial level and demyelination of the optic nerve due to its myelinoclastic effect, thus affecting the optic nerve and retrolaminar area and leading to optic nerve edema, necrosis, myelin sheath and axon damages. Formaldehyde inhibits retinal hexokinases and causes retinal pigment epithelium, photoreceptor inner segment and optic nerve damages, as shown in an animal model (19-21).

The main objectives of the treatment are to eliminate methanol and the toxic products, treat metabolic acidosis, and to prevent the metabolization of methanol.

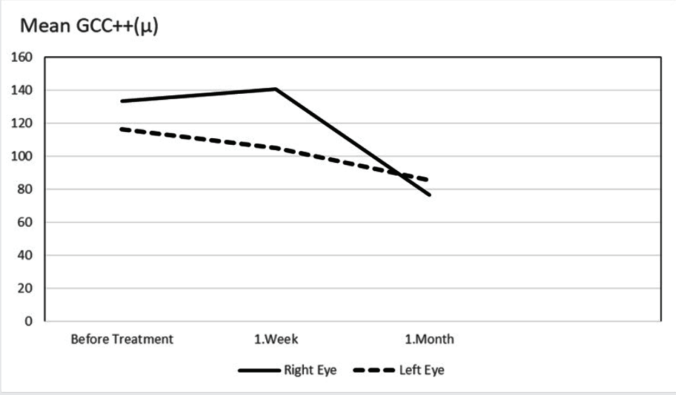

Figure 3. Mean GCC (μ) changes before treatment, first week and 1st month after the treatment
GCC: Ganglion cell complex

Antidotes (fomepizole or ethanol) are used to prevent the conversion of methanol into toxic products. In the early phase, methanol can be removed via gastric lavage. Methanol and its toxic products can be rapidly eliminated by hemodialysis. Folic acid accelerates the conversion of formic acid to carbon dioxide and water (12).

Theoretically, it is considered that optic nerve edema and axon compression in the lamina cribrosa will decrease when systemic steroids are used. The studies on the effect of high dose systemic steroid for treating methanol induce toxic optic neuropathy are mostly case series and there are studies in which increased BCVA is detected.

In the literature, the number of patients varies between 1 and 17, and the duration of starting the steroid treatment varies between 1 and 45 days. The steroid protocol used is 1 mg/kg oral prednisolone for 10-14 days, following 3 doses of 500 mg-1 g/day intravenous methylprednisolone every day or every other day. Shukla et al. (17) Discontinued steroids after 6 weeks by gradually decreasing the dose after 14 days. Our steroid protocol is in accordance with the literature (16,22-25).

In this study, at the end of the first month, an increase was detected in BCVA in 80% of the patients. Sharma et al. (16) have detected increased BCVA in 87.5% of the patients at the end of the first year, and Shukla et al. (17) detected an increased BCVA in 88% of the patients at the end of the first month. A statistically significant increase in BCVA was detected at the end of the first month, and there are studies in the literature, which detected increased BCVA after systemic steroid treatment (22,23,25).

In our study, no difference was detected between the first week and the first month before and after treatment with respect to CT and CMT. Abrishami et al. (22) Found no differences in terms of CMT, but did not specify the CMT values.

After treatment, a slight increase in RNFL was observed in the first week, but it was not statistically significant. However, at the end of the first month, a statistically significant decrease was detected. Fujihara et al. (23) Started treatment in a single case 6 days after methanol intoxication and found an increase in BCVA. This study also found that RNFL initially increased and then decreased.

In this study, differently from the other studies in the literature, GCC parameters were observed and it was found that there was been a thinning in the GCC at the first month, just like RNFL. Moreover,

Table 1. Mean best corrected visual acuity (LogMAR), retinal nerve fiber layer, Ganglion cell complex, central macular thickness values, and p-values before and after treatment of 10 eyes are shown

Parameters	Before treatment	The first week after treatment	The first month after treatment	p^1 p^2
BCVA (logMAR)	1.94±0.52	1.43±0.69	1.27±0.83	**$p=0.002^1$** **$p=0.01^2$**
RNFL	100.1±29.0	104.3±21.1	81.1±19.1	$p=0.54^1$ **$p=0.02^2$**
GCC^{++}	128.4±69.3	136.4±64.8	77.3±20.65	$p=0.06^1$ **$p=0.02^2$**
CMT	251.7±39.1	248.1±31.8	261±27.7	$p=0.19^1$ $p=0.48^2$

BCVA: Best corrected visual acuity, logMAR: Logarithm of the minimum angle of resolution, RNFL: Retinal nerve fiber layer (μ), GCC^{++}: Ganglion cell complex (μ), CMT: Central macular thickness (μ), p^1: p-values (Paired sample t-test) first week after treatment, p^2: p-values (Paired sample t-test) first month after treatment

no statistically significant difference was detected between the disc topography values identified using OCT.

We found structural and functional changes, especially in BCVA, RNFL, and GCC in the first week and month after methanol intoxication. Therefore, monitoring patients during this period may be important. Because OCT is used for monitoring many optic nerve head diseases, it may also be used for toxic optic neuropathy due to methanol intoxication. Further studies are needed on this subject.

Study Limitations

The limitations of our study are the small number of patients, retrospective structure, lack of a control group and lack of randomization. However, in our study, in addition to BCVA, OCT parameters were also included. Considering the side effects of high dose systemic steroids, more studies are required on this subject.

Conclusion

In conclusion, for treating toxic optic neuropathy due to methanol, although an increase in BCVA is observed at the end of the first month, optic nerve values such as RNFL and GCC continue to decrease.

ETHICS

Ethics Committee Approval: This retrospective study was conducted with the approval of the University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethics Committee (1183, date: 23.02.2018), in accordance with the Declaration of Helsinki.

Informed Consent: Written informed consent was obtained from all patients and/or relatives before the treatment.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept: P.S., H.G., F.Ç.; Design: P.S., H.G., F.Ç.; Data Collection and/or Processing: P.S., H.G., F.Ç.; Analysis and/or Interpretation: P.S., H.G., F.Ç.; Literature Search: P.S., H.G., F.Ç.; Writing: P.S., H.G., F.Ç.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The author declared that this study had received no financial support.

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İstanbul Med J 2022; 23(4): 310–5
DOI: 10.4274/imj.galenos.2022.74151

Post-traumatic Stress Symptoms in Health Care Professionals During the COVID-19 Pandemic

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ABSTRACT

Introduction: The severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) associated pneumonia that emerged in Wuhan, China in December 2019 and was later declared by the World Health Organization to be a pandemic has called coronavirus disease-2019 (COVID-19). Our study aims to determine the anxiety levels, post-traumatic stress disorder (PTSD) symptoms levels and psychiatric symptoms of healthcare workers working at pandemic hospital and effects of these symptoms on psychological adjustment to healthcare professionals during the COVID-19 pandemic in Turkey.

Methods: This study was cross-sectional survey study and conducted between March 2020-June 2020 with 973 consenting participants working at the pandemic hospital. For the study, we used an online questionnaire, which consisted of three parts: an online-informed consent, basic sociodemographic information and a set of online questions. The data were collected by the researchers. All procedures were approved by our hospital's Ethics Committee. Traumatic Stress Symptom Scale (TSSS) was used for the study.

Results: Nine hundred and seventy-three persons participated in the study. Among the three groups, nurses also had the highest fear of dying during the COVID-19 pandemic ($p<0.001$); the highest feelings of hopelessness about the future during the COVID-19 pandemic ($p<0.001$); the highest increase in level of anxiety ($p<0.001$), and the highest experience of recent sleep disturbances ($p<0.001$). Women had a statistically significantly higher mean TSSS score and mean TSSS score of participants with doctors or medical specialization was lower than participants with other levels of education ($p<0.001$).

Conclusion: Although the rate of PTSD was significantly higher in nurses in our study, PTSD was also seen in the other two groups. Indeed, it was much higher in people working in environments at high risk for COVID-19 than in the other groups. This may be the consequence of nurses' having greater exposure to COVID19-infected patients. This situation may be related to long working hours, inadequate rest and burnout. We recommend that healthcare workers work in the shift.

Keywords: COVID-19, post-traumatic stress disorder, healthcare workers

Introduction

The severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) associated pneumonia that emerged in Wuhan, China in December 2019 and was later declared by the World Health Organization (WHO) to be a pandemic has been called coronavirus disease-2019 (COVID-19) (1). Respiratory droplets are the main ways in which COVID-19 spreads. This can make healthcare workers a high-risk population at the beginning of the pandemic. Healthcare personnel are forced to perform their jobs under challenging conditions. Moreover, COVID-19 spreads, they are under enormous psychological pressure. Not only do they generally experience traumatic events, they frequently witness patient deaths.

Previous studies have shown that post-traumatic stress disorder (PTSD) develops in healthcare personnel in such epidemics as SARS and middle east respiratory syndrome (MERS) (2). Reasons for such trauma are to living in isolation, work in high-risk environments and to being in contact for treatment of infected patients (3). Healthcare workers encountering traumatic events begin seeing their environment negatively and to lose a sense of security. Consequently, they may become increasingly isolated as they try avoiding situations that remind them of the traumatic events they have experienced (4). Given that the psychosocial effects of the pandemic on people are so immense, healthcare workers will come up against similar difficulties even more intensely. A study conducted in Italy in the COVID-19 situation there showed that physicians and nurses had greater levels of stress and anxiety than the non-health care worker population (5). Ourstudy aims to determine PTSD symptoms levels and psychiatric symptoms of healthcare workers working at pandemic hospital during the COVID-19 pandemic.

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Cite this article as: Kalaycı İG, Canbek Ö, Bağ S. Post-traumatic Stress Symptoms in Health Care Professionals During the COVID-19 Pandemic. İstanbul Med J 2022; 23(4): 310-5.

Received: 02.09.2022
Accepted: 31.10.2022

Method

This study was conducted between March 2020-June 2020 with 973 consenting participants working at the pandemic hospital. All participants studied in the pandemic services. For study we used an online questionnaire, which consisted of three parts: an online-informed consent, basic sociodemographic information and a set of online questions. This questionnaire was sent to all hospital workers (total number of 2703) with the permission of the head physician and the participants were doctors, nurses and the other healthcare workers. A total of 973 (36.0%) people completed all survey. These data were collected by the researchers. All procedures were approved by University of Health Sciences Turkey, İstanbul Training and Research Hospital's Ethics Committee (approval number: 2276, date: 08.05.2020). Approval was also obtained from Scientific Committee.

The sociodemographic data form was created considering the participants' position, sex, age, educational level, marital status, number of children, psychiatric illness status, use of psychiatric medications, alcohol-tobacco use, occupational status and working conditions at the hospital.

The second part of the questionnaire asked the participants to assess the COVID-19 risk in their workplace. It also asked if an elderly person lived in their home, as well as if they had received a diagnosis of COVID-19. The participants were asked to indicate the degree to which they had been psychologically affected by the pandemic and the extent to which they were afraid of transmitting COVID to other people and relatives. They were also asked how long they thought the current situation will last. Through these questions, healthcare workers' behavior vis-à-vis the COVID-19 situation and the differences between them in terms of stress and anxiety was analyzed. To uncover the worries and fears of participants about COVID-19, the following statement was used: "I am very concerned about COVID-19" (COVID-19 anxiety).

Traumatic Stress Symptom scale: This self-report scale was developed by Başoglu et al. (6) to determine the possibility of PTSD and depression accompanying PTSD over the course of the previous month. Ton this 23-point scale, there are 17 traumatic stress symptom-related statements and six depression symptom-related statements (6).

Statistical Analysis

Statistical analyses were performed using SPSS version 17.0. To determine the extent to which the variables were normally distributed, histogram graphs and the Kolmogorov-Smirnov test were used. Descriptive analyses were performed using means, median and standard deviations. Categorical variables were compared using Pearson chi-square test. When assessing non-parametric (non-normally distributed) variables, the Mann-Whitney U test was used for 2 categories and the Kruskal-Wallis test for more than 2 categories. When analyzing ordinal data, the Spearman correlation test was used. Results containing a value less than 0.05 were considered statistically meaningful.

Results

A total of 973 persons 352 men and 621 women participated in the study. The sociodemographic characteristics of the participants who completed the questionnaire are shown in Table 1.

Table 2 contains the responses of nurses, doctors and other personnel to items that make up the Traumatic Stress Symptom scale (TSSS). The TSSS scores of nurses were significantly higher than those of doctors and other participants. Based on these results, of the three groups, it can be said that nurses constitute the group most traumatized by the perception of severity of the COVID-19 situation. Infact, the fear of doctors about transmitting COVID-19 to people at home was less than this fear in the other two groups ($p<0.001$). Among the three groups, nurses also had the highest fear of dying during the COVID-19 pandemic ($p<0.001$); the highest feelings of hopelessness about the future during the COVID-19 pandemic ($p<0.001$); the highest increase in the level of anxiety ($p<0.001$), and the highest experience of recent sleep disturbances ($p<0.001$). Women had a statistically significantly higher mean TSSS score and mean TSSS score of participants with doctors or medical specialization was lower than participants with other levels of education ($p<0.001$) (Table 3). Mean TSSS score of those working in high COVID-19 risk environments was higher than of those working in moderate COVID-19 risk environments ($p<0.001$).

The finding of low COVID positivity (8.4%) among the healthcare workers participating in our study may be attributable to the quarantine measures that were in place at the time. However, 785 (80.7%) of them had had a relative or colleague test positive for COVID-19. Fear of transmitting COVID-19 to people at home, fear of dying, feelings of hopelessness about the future, increasing anxiety levels, and experiencing recent

Table 1. Sociodemographic variables

		n	%
Sex	Male	352	36.2%
	Female	621	63.8%
Education	Primary school	11	1.1%
	High school	93	9.6%
	Two-year college	151	15.5%
	Four-year college	410	42.1%
	PhD or medical specialization	308	31.7%
Marital status	Single	478	49.1%
	Married	495	50.9%
Position	Doctor	343	35.3%
	Nurse	338	34.7%
	Other	292	30.0%
Do you have children?	Yes	409	42.0%
	No	564	57.1%
Is there an elderly person living at home?	Yes	155	15.9%
	No	818	84.1%
Do you smoke?	Yes	252	25.9%
	No	721	74.1%
Do you drink alcohol?	Yes	158	16.2%
	No	815	83.8%
Do you have a history of psychiatric illness or treatment?	Yes	71	7.3%
	No	902	92.7%
Age		36±8.3	-

Table 2. Differences between the items of Traumatic Symptom Scales among doctors, nurses, and others

	Doctor		Nurse		Other		p
	n	%	n	%	n	%	
When you encounter situations that remind you of events, do you get physical reactions such as trembling and heart palpitations?	60	17.5	101	29.9	59	20.2	**<0.001**
Have you avoided or unwanted to go to places reminiscent of the COVID-19 pandemic?	170	49.6	232	68.6	201	68.8	**<0.001**
Do you have unpleasant dreams about the COVID-19 pandemic?	59	17.2	92	27.2	43	14.7	**<0.001**
Do you ever have unwanted thoughts that aren't related to the COVID-19 pandemic?	116	33.8	157	46.4	94	32.2	**<0.001**
Do you feel distant or cut off from the people around you?	206	60.1	244	72.2	204	69.9	**0.002**
Do you feel every morning as if the COVID-19 pandemic is happening over again?	91	26.5	167	49.4	121	41.4	**<0.001**
Do you have difficulty experiencing emotions like love or happiness?	146	42.6	182	53.9	132	45.2	**0.009**
Do you feel at the edge with what's going on around you even though there is no clear reason?	177	51.6	220	65.1	172	58.1	**0.002**
Have you experienced difficulty in focusing or concentrating on your work?	178	51.1	190	56.2	129	44.2	**0.010**
Have you got extremely impatient or angry during this period?	172	50.2	230	68.1	165	56.5	**<0.001**
Do you feel distressed when you encounter things that remind you of the COVID-19 pandemic?	167	48.7	228	67.5	159	54.5	**<0.001**
Do you get unwanted disturbing thoughts about the COVID-19 pandemic?	116	33.8	157	46.5	94	32.4	**<0.001**
Have you tried to not think about the COVID-19 when it's entered your mind?	173	50.2	190	56.2	130	44.2	**0.010**

Mann-Whitney U test- Spearman correlation test, COVID-19: Coronavirus disease-2019

sleep disturbances were all higher in women than in men (p<0.001). More men predicted that the COVID-19 pandemic would last 6 months, whereas more women said that it would last one or more years (Table 4). The participants who were working in a department at high risk of COVID-19 was 54.3%. More persons working in such departments reported feelings of hopelessness about the future and increased anxiety during the pandemic than those working in departments at moderate risk of COVID-19 (p<0.001). Likewise, more reported having recently experienced sleep disturbances than those working in environments at low and moderate risk of COVID-19 (p<0.001). Previous psychiatric treatment history was reported less among persons working in departments at moderate risk of COVID-19 (p<0.001). The number of people working in environments at high risk of COVID-19 stating that it would last more than one year was higher than people working in other risk environments (p<0.001).

Discussion

Our aim in this study was to analyze the post-traumatic stress symptoms of healthcare workers. It is crucial that healthcare institutions provide psychosocial support and intervention to their healthcare employees. Concern about infection, fatigue, burnout at the workplace and PTSD may be seen in healthcare workers (7). A study reported that PTSD was seen in 25% of healthcare workers during the SARS and Ebola epidemics (8). Our study found that the mean PTSD score in women was significantly higher than in men. Similarly, the mean TSSS score of nurses was higher than that of doctors and other healthcare workers. The reason for this may be that nurses constitute a group of healthcare workers having the greatest contact with patients. Nurses report a higher degree of physical reactions such as heart palpitations, trembling and sweating-when confronting environments reminding them of previous events than doctors and other healthcare workers do (p<0.001) (29.9%). Additionally, nurses report a higher degree (68.6%) of avoidance behavior than do doctors and other healthcare workers.

The loss of a sense of security is closely related to PTSD. An earlier study reported that one of the greatest fears healthcare workers had during the SARS and MERS epidemics was that they would transmit infection to family and friends (4). The rapidity and ease at which COVID-19 spreads have also been a major stressor negatively affecting the mental health of healthcare workers. This stressful situation has been reported to be a critical risk factor for PTSD in healthcare workers (9). In our study, the fear of transmitting COVID-19 to others at home was less in doctors (83.7%) than in nurses (89.1%) and the other groups (91.4%). However, the difference between the groups was not statistically significant (p=0.008). The fear of transmitting the disease was quite high in all three groups. The fear of death, hopelessness about the future, an increase in anxiety levels, and recently having experienced sleep disturbances during the COVID-19 pandemic was higher in nurses than in doctors and the other groups. The virus is a cause of illness and death and involves uncertainty, which may produce unrealistic fear and panic (10). The greatest psychological impact of the COVID-19 pandemic on the mental health of society can be seen in the rise of extreme stress or anxiety in individuals (WHO, 2020). Sleep disturbances may explain the high rate of PTSD in nurses. In addition to having severe negative impacts on physical health, COVID-19 may cause mental health problems such as stress, insomnia, high anxiety and chronic depression (11).

While there is no monitoring system systematically tracking COVID-19-related deaths of healthcare workers in the world, according to statistics compiled by Amnesty International, more than 3,000 healthcare workers

Table 3. PTSD scores between groups

		Median ± SD	p
Sex	Male	16.8±13.8	**<0.001**
	Female	23.1±12.1	
Education	Primary school	25.1±18.4	**<0.001**
	High school	21.2±13.1	
	Two-year college	23.5±13.3	
	University	21.7±13.3	
	PhD or medical specialization	18.1±13.8	
Marital status	Single	21.1±13.7	0.455
	Married	20.6±13.5	
Position held	Doctor	17.1±13.6	**<0.001**
	Nurse	24.2±13.4	
	Other	20.4±12.1	
Do you have children?	Yes	20.6±13.7	0.551
	No	20.1±13.6	
Is there an elderly person living at home?	Yes	22.1±13.5	**0.035**
	No	20.4±13.6	
Do you smoke?	Yes	22.5±14.1	**0.025**
	No	20.2±13.4	
Do you drink alcohol?	Yes	22.1±14.1	**0.031**
	No	20.4±13.5	
Do you have a history of psychiatric illness or treatment?	Yes	26.1±14.1	**0.001**
	No	20.4±13.5	
Do you work at a center where COVID-19 patients are being actively treated?	Yes	21.1±13.7	0.194
	No	19.3±12.8	
Please assess the risk of being exposed to COVID-19 risk in the department where you work	Low	20.3±14.8	**0.001**
	Moderate	18.9±12.5	
	High	22.3±14.1	
To what extent have you been psychologically affected by this pandemic?	Not at all	6.1±9.3	**<0.001**
	Somewhat	16.7±11.9	
	Excessively	29.8±11.2	
Before the COVID-19 pandemic, to what extent were you anxious?	Not at all	18.3±13.2	**<0.001**
	Somewhat	21.2±13.3	
	Excessively	29.6±13.3	
Have you received a COVID-19 diagnosis?	Yes	23.4±14.8	0.078
	No	20.6±13.5	
Has a relative or a colleague been diagnosed with COVID-19?	Yes	21.7±13.5	**<0.001**
	No	17.4±13.7	

Mann-Whitney U test-Spearman correlation test, PTSD: Post-traumatic stress disorder, COVID-19: Coronavirus disease-2019

in 79 countries have died from COVID-19 (12). This situation increases the fear of death among healthcare workers. In our study, the fear of death was greater than the fear of transmitting COVID-19 to others at home. It was also greater in people who had children.

Although the rate of PTSD was significantly higher in nurses in our study, PTSD was also seen in the other two groups. Indeed, it was much higher in people working in environments at high risk for COVID-19 than in the other groups. A systematic study of the mental health of the general population showed that individuals experience the following mental health issues at the rates indicated: anxiety (6.3-50.9%), depression (14.6-48.3%), PTSD (7-53.4%), and stress (8.1%-81.9%) (12). In our study, the rate of anxiety among healthcare workers, which has increased, was 71.2%. They experienced feelings of hopelessness at a rate of 62.8% and PTSD at a rate of 75%. The difficulties that health care workers have in feeling safe at work may be due to the psychological distress that health care workers experience. The virus not being fully understood, the lack of

Table 4. Differences questionnaire items between groups

n		Doctor		Nurse		Other		p
		%	n	%	n	%		
Are you afraid of transmitting COVID-19 to people who live in your home?	Yes	287	83.7	301	89.0	267	91.4	**0.008**
	No	56	16.3	37	10.1	25	8.6	
Have you experienced a fear of death during the COVID-19 pandemic?	Yes	144	41.98	171	50.59	112	38.4	**0.006**
	No	199	58.0	167	49.4	180	61.6	
Have you experienced hopelessness about the future during the COVID-19 pandemic?	Yes	211	61.5	232	68.6	168	57.5	**0.013**
	No	132	38.5	106	31.4	124	42.5	
Has your anxiety level increased during the COVID-19 pandemic?	Yes	235	68.5	264	78.1	194	66.4	**0.002**
	No	108	31.5	74	21.9	98	33.6	
Have you experienced sleep disturbances lately?	Yes	183	53.4	261	77.2	171	58.6	**<0.001**
	No	160	46.7	77	22.8	121	41.4	
How long do you think the COVID-19 pandemic will last?	3 months	11	3.21	18	5.33	14	4.8	0.305
	6 months	50	14.6	44	13.02	35	11.1	
	1 year	70	20.4	75	22.2	80	27.4	
	More than 1 year	212	61.8	201	59.5	163	55.8	
Have you received psychiatric treatment during the COVID-19 pandemic?	Yes	15	4.4	15	4.4	15	5.1	0.883
	No	328	95.6	323	95.6	277	94.9	

Mann-Whitney U test- Spearman correlation test, COVID-19: Coronavirus disease-2019

information on how to prevent and control it, long heavy workloads, the high risk of being exposed to COVID-19 patients, shortages of protective medical equipment, insufficient rest, and being exposed to critical life event like death may contribute to this feeling of being unsafe at work.

Study Limitations

Our study is not sustainable. We cannot predict what will happen one year later because most of the workers who participated in our research left our hospital. Also our study was conducted only one pandemic hospital. Future studies will be conducted different hospitals.

Conclusion

PTSD has occurred in all healthcare workers during the COVID-19 pandemic, which claimed many lives of healthcare workers in Turkey since February 2021. It occurs more in nurses than in doctors and other healthcare workers. PTSD is also higher in women, who work in a risky setting or who have elderly people or children living at home. Anxiety levels in healthcare workers are high. This can be attributed to the length of work hours and insufficient rest, so it is recommended that healthcare workers should work on well-designed shifts and psychological support should be provided whenever it is necessary.

Ethics Committee Approval: All procedures were approved by University of Health Sciences Turkey, İstanbul Training and Research Hospital's Ethics Committee (approval number: 2276, date: 08.05.2020).

Informed Consent: It was obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions: Concept: İ.G.K., S.B.; Design: İ.G.K., Ö.C., S.B.; Data Collection or Processing: İ.G.K., S.B.; Analysis or Interpretation: İ.G.K., Ö.C., S.B.; Literature Search: İ.G.K., Ö.C., S.B.; Writing: İ.G.K., Ö.C., S.B.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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