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Journal article on the Internet

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Website

Cancer-pain.org [homepage on the Internet]. New York: Association of Cancer Online Resources [updated 16 May 2002; cited 9 Jul 2002]. Available from: www.cancer-pain.org

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The Intensive Care Society of Australia and New Zealand. Mechanical ventilation strategy in ARDS: Guidelines. Int Care J Aust 1996;164:282-4.

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The source of financial grants and the contribution of colleagues or institutions should be acknowledged.

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Editorial Correspondence

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Orijinal Araştırma / Original Article

The Prognostic Significant of Tumor Budding, Tumor Stroma Ratio and Tumor-Infiltrating Lymphocytes in Gallbladder Adenocarcinoma

Safra Kesesi Adenokarsinomunda Tümör Tomurcuklanması, Tümör Stroma Oranı ve Tümörü İnfiltre Eden Lenfositlerin Prognostik Önemi

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Abstract

Aim: Tumor microenvironment plays an important role in onset and progression of the cancer. Tumor budding (TB), tumor stroma and tumor-infiltrating lymphocytes are component of the tumor microenvironment. It was aim to determine the relationship of TB, tumor stroma ratio (TSR) and tumor-infiltrating lymphocytes (TILs) with clinicopathological prognostic parameters in gallbladder adenocarcinoma.

Material and Method: Thirty cholecystectomy cases that were diagnosed as adenocarcinoma between 2010 and 2020, that did not receive neoadjuvant therapy and of which archive slides could be accessed, were included in the study. TB, TSR and TILs were evaluated. A p<0.05 value was statistically significant.

Results: High TB score was significantly associated with higher histological grade (p=0.008), higher pT stage, lymphovascular invasion (LVI) (p=0.038), lymph node metastasis (p=0.046) and distant metastasis (p=0.036) . Patients with high TB scores had a shorter overall survival (p<0.001). In the high TILs group, lower histological grade (p=0.004), less LVI (p=0.029), fewer distant metastases (p=0.021) and lower TSR (p=0.008) were detected. Increased TSR was associated with higher histological grade (p=0.015) and increased distant metastasis (p=0.013). There was no significant effect of TSR on overall survival (p=0.239).

Conclusion: TB can be used as a new prognostic biomarker in gallbladder cancers due to its simple and low cost to determine and also its effectiveness in determining the prognosis. We have concluded that it is early to recommend TILs and TSR as the prognostic indicators in gallbladder cancers. In the future, further studies can be conducted on a larger number of gallbladder cancer cases with a multicenter participation to clarify the prognostic value of TILs and TSR.

Keywords: Gallbladder cancer, prognosis, stroma, tumor budding, tumor-infiltrating lymphocyte,

Öz

Amaç: Tümör mikroçevresi kanserin başlangıcında ve ilerlemesinde önemli rol oynar. Tümör tomurcuklanması (TB), tümör stroması ve tümörü infiltre eden lenfositler, tümör mikroçevresinin bileşenleridir. Bu çalışmada safra kesesi adenokarsinomunda TB, tümör stroma oranı (TSR) ve tümörü infiltre eden lenfositlerin (TILs) klinikopatolojik prognostik parametrelerle ilişkisinin belirlenmesi amaçlandı.

Gereç ve Yöntem: 2010-2020 yılları arasında adenokarsinom tanısı alan, neoadjuvan tedavi almayan ve arşiv preparatlarına ulaşılabilen 30 kolesistektomi olgusu çalışmaya dahil edildi. TB, TSR ve TILs değerlendirildi. p<0.05 değeri istatistiksel olarak anlamlı kabul edildi.

Bulgular: Yüksek TB skoru, daha yüksek histolojik derece (p=0,008), daha yüksek pT evresi, lenfovasküler invazyon (LVI) (p=0,038), lenf nodu metastazı (p=0,046) ve uzak metastaz (p=0,036) ile anlamlı ilişkiliydi. TB skoru yüksek olan hastaların genel sağkalım süreleri daha kısaydı (p<0,001). Yüksek TILs grubunda, daha düşük histolojik derece (p=0,004), daha az LVI (p=0,029), daha az uzak metastaz (p=0,021) ve daha düşük TSR (p=0,008) saptandı. Yüksek TSR, daha yüksek histolojik derece (p=0,015) ve artan uzak metastaz (p=0,013) ile ilişkilendirildi. TSR'nin genel sağkalım üzerinde anlamlı bir etkisi yoktu (p=0,239).

Sonuç: TB, hem belirlenmesi basit ve düşük maliyeti olması nedeniyle hem de prognozu belirlemedeki etkinliği nedeniyle safra kesesi kanserlerinde yeni bir prognostik biyobelirteç olarak kullanılabilir. Safra kesesi kanserlerinde prognostik göstergeler olarak TILs ve TSR'yi önermek için erken olduğu kanaatindeyiz. Gelecekte, TILs ve TSR'nin prognostik değerini netleştirmek için çok merkez katılımlı daha fazla sayıda safra kesesi kanser vakası üzerinde çalışmalar yapılabilir.

Anahtar Kelimeler: Safra kesesi kanseri, prognoz, stroma, tümör tomurcuklanması, tümörü infiltre eden lenfosit

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INTRODUCTION

Gallbladder cancer (GBC) is a rarely seen, however, the most common and aggressive malignancy of biliary tract. Its prognosis is extremely poor and its overall 5-year survival rate has not exceeded 5%.[1] American Cancer Society has reported 115,949 new cases and 84,695 deaths because of gallbladder cancer in 2020 worldwide.[2] Its prognosis depends on tumor stage and the characteristics of the tumor cells, however, it has been encountered that the patients at the same stage might have very different prognosis. This fact indicates the need for determination of additional prognostic criteria.

Tumor microenvironment plays an important role in onset and progression of the cancer. Tumor budding (TB) is the tumor infiltration encountered as a single cell or a cluster (<5 cells) at the invasive tumor margin. TB has been accepted to be associated with presence of epithelial-mesenchymal transition and plays a role as an important prognostic factor in the clinical management of the cancer patients.[3] It has been accepted as an important prognostic parameter particularly in the colorectal cancers as well as its popularity has progressively increased also in the other solid cancers. There is a limited number of studies that has investigated the impact of TB on prognosis in gallbladder cancer.[4-6] Although, TB was shown to be associated with poor prognosis in these studies, further studies are needed to confirm its clinical effect.

Tumor stroma is also one of the factors that constitute the tumor microenvironment. In the recent years, tumor stroma has drawn attention as an independent prognostic factor in some solid tumors. Another component of tumor microenvironment is the tumor-infiltrating lymphocytes. The prognostic importance of tumor-infiltrating lymphocytes (TILs) have been demonstrated in some cancer types such as breast, ovarian and colon cancers.[7-10]

In the current literature, there is only a limited number of studies that has researched the impact of TB, tumor stroma ratio (TSR) or TILs on prognosis in gallbladder carcinomas.[4,5,11,12] In the present study, it was aim to determine the relationship of TB, tumor stroma ratio (TSR) and tumor-infiltrating lymphocytes (TILs) with clinicopathological prognostic factors in gallbladder adenocarcinoma. Our study is the first that has investigated these three parameters concurrently in gallbladder carcinomas.

MATERIALS AND METHODS

Patient selection

The present study was approved by the local ethics committee (Date: 04.06.2020, Decision Number:23) and confirmed according to the ethical standards of the Helsinki Declaration.

A retrospective review was conducted on cholecystectomy specimens diagnosed with adenocarcinoma between 2010 and 2020 in our institution. Exclusion criteria were as follows: neoadjuvant therapy, histopathological diagnosis other than adenocarcinoma (e.g., adenosquamous carcinoma, neuroendocrine carcinoma and undifferentiated carcinoma) and/or unavailability of the archival haematoxylin and eosin (H&E) slides for review. As a consequence, 30 patients were included in the present study. The clinical and follow-up information was obtained from the electronic medical records.

Histopathological analysis

All archival H&E slides of the resection specimens were re-examined under the Olympus BX51 microscope (Olympus, Tokyo, Japan) by two pathologists blinded to clinical information. All pathological parameters including histological differentiation grade, invasion depth, resection margin status, lymph node (LN) metastasis, lymphovascular invasion (LVI), perineural invasion (PNI), surgical margin and distant metastasis were re-evaluated. Tumor staging was performed according to the eighth edition of the AJCC Staging Manual (pTNM, AJCC 8th Edition).[13]

TB, TSR and TILs were evaluated by two independent pathologists (IES, DG) blinded to clinicopathological data. In the case of inconsistency between the conclusions of the two pathologists, the results were evaluated by a third independent pathologist (TO) blinded to the clinicopathological data and the conclusions of the other researchers. The final outcome was approved and recorded by consensus of at least two pathologists.

Assessment of tumor budding

The following steps were followed for assessment of TB according to the ITBCC guideline:[14]

The field with the highest density of "hotspot" peritumoral budding in the 10x medium power field (10Xobjective) in the hematoxylin and eosin (H&E) slides was selected.

Following, tumor buds were counted using a 20X objective.

The count was normalized to a field measured as 0.785 mm² (counted tumor buds/normalization factor adjusted to the microscope). The features of the used microscope were as follows: Eyepiece FN Diameter: 22 mm, Specimen Area: 0.950 mm², Normalization Factor: 1.210.

Tumor buds were counted in a field of 0.785 mm² and scored as TB score1 (0-4 buds), TB score2 (5-9 buds) and TB score3 (≥10 buds).

Assessment of tumor stroma ratio

All tumor slides were scanned with a 4X objective lens to determine the field with the highest tumor depth. TSR was analyzed using a 10X objective lens. Only the fields containing both stroma and tumor within the field of view were scored to avoid scoring of the peripheral regions of the tumor margin. Since stroma-rich fields have been associated with worse prognosis, these fields were accepted to be determinant in the cases with heterogeneous TSR. In TSR, stromal ratio higher than 50% accepted to be stroma-rich while stromal ratio lower than 50% was considered to be stroma-poor.[11]

Assessment of tumor-infiltrating lymphocytes

TILs were assessed semiquantitatively using the criteria defined by Salgado et al. All the tumor slides were scanned by 100-fold and 200-fold magnification (objective ×10,×20) and mean stromal TILs (lymphocytes and plasma cells) were recorded as a continuous variable (also including the TILs on the margin of infiltration).[7]

Statistical Analysis

Our study data were analyzed using Social Sciences V.21.0 software package (SPSS Inc, Armonk, NY, US). The continuous variables were expressed as mean value and standard deviation while frequency and percentage values were given for the categorical variables. The normality was tested using Shapiro Wilk test. Chi-Square tests (Yates-corrected, likelihood ratio) were used in the analysis of the relationships between the categorical variables. Besides, Goodman and Kruskal's Gamma analysis results were taken into consideration regarding the relationships between ordinal variables. ANOVA and Kruskal Wallis tests were applied for comparison of the continuous variables. The prognostic appropriateness of TILs was assessed by means of receiver operating characteristic (ROC) analysis selecting death as the status variable and the optimal cut-off value was calculated using the Youden index for maximum of specificity and sensitivity.[8] Accordingly, ≤10% TILs and >10% TILS values were grouped as low and high, respectively. Kaplan-Meier curves and log-rank test were applied to test the differences between overall survival duration (OS) of the variables TB, TSR and TILs. Raw hazard ratios and adjusted risks for the variables TB score, TSR and TILs were analyzed by Cox regression analysis. A $p<0.05$ value was accepted to be statistically significant.

RESULTS

Totally 30 cases were included in the study. The study group comprised of 11 males (36.7%) and 19 females (63.3%). The mean ±SD age of the patients was 69.27±10.49 years. The histological grades of the tumor were low, moderate and high in 6 (20%), 19 (63.3%) and 5 (16.7%) cases, respectively. LVI and perineural invasion were detected in 19 (63.3%) and 18 (60%) cases, respectively. Totally 3 (10%), 10 (33.3%), 16 (53.3%) and 1 (3.3%) cases were evaluated as pT1, pT2, pT3 and pT4, respectively. The lymph node involvement stages were N0 and N1+N2 in 21 (70%) and 9 (30%) cases, respectively. Liver invasion at the time of diagnosis was present in 14 (46.7 %) cases. The distant metastasis at the time of diagnosis was identified in 12 (40.0%) cases (**Table 1**). The median follow-up period was 525.2±700 days. Totally 10 (33.3%) cases survived whereas 17 (56.7%) cases died, 3 cases could not be followed-up.

In this study, 13 (43.33%) tumors were TB score 1 (**Figure 1A**) and 9 (30%) tumors were score 2 (**Figure 1B**) and 8 (26.67%) tumors were score 3 (**Figure 1C**). High TB score was found significantly associated with higher histological grade (p=0.008), higher pT stage, LVI (p=0.038), LN metastasis (p=0.046) and distant metastasis (p=0.036). TB score showed no significant relationship with age (p=0.937), gender (p=0.597), presence of PNI (p=0.104), surgical margin positivity (p=0.813), liver invasion (p=0.293), TSR (p=0.461) and TILs (p=0.490) (**Table 2**). High TB score was encountered to be associated with a shorter OS ($p<0.001$). Mean OS of the patients with low TB score was 1733.4 days [95%CI: 1048.0-2418.8] whereas that of the patients with moderate and high TB scores were 283.8 days [95%CI: 136.5-431.0] and 93.1 days [95%CI:45.5-140.8], respectively (**Figure 2**).

The AUC (area under curve) value of TILs for a cutoff point of 10% was calculated as 0.80 (specificity: 80%, sensitivity: 70%, p:0.01) (**Figure 3**). In this study, 14 (46.67) tumors were TILS>10% (**Figure 4A**) and 16 (53.33%) tumors were TILS≤10%. (**Figure 4B**). No significant relationship of TILs was found with gender (p=0.631), PNI (p=0.156), liver invasion (p=1.000), pT stage (p=0.716) and lymph node metastasis (p=0.440). High TILs were significantly associated with lower histological grade (p=0.004), less LVI (p=0.029), fewer distant metastasis (p=0.021) and lower TSR (p=0.008) (**Table 3**). Mean OS of the patients with low TILs was 366.4 days [95%CI:164.2-568.5] whereas that of the patients with high TILs was 1516.4 days [95%CI: 777.2-2255.5] (p:0.051) (**Figure 2**).

Table 1. Clinicopathological characteristics of the patients

Variables	Categories	n (%)	Mean±SD
Gender	Female	19 (63.33%)	
	Male	11 (36.67%)	
Grade	1	6 (20.0%)	
	2	19 (63.33%)	
	3	5 (16.67%)	
Lymphovascular invasion	Absent	11 (36.67%)	
	Present	19 (63.33%)	
Perineural invasion	Absent	12 (40.0%)	
	Present	18 (60.0%)	
Surgical margin	Negative	20 (66.67%)	
	Positive	10 (33.33%)	
Liver invasion	Absent	16 (53.33%)	
	Present	14 (46.67%)	
pT stage	1	3 (10.0%)	
	2	10 (33.33%)	
	3	16 (53.33%)	
	4	1(3.33%)	
N stage	0	21 (70.0%)	
	1+2	9 (30.0%)	
M stage	0	18 (60.0%)	
	1	12 (40.0%)	
TSR	Stroma<%50	17 (56.67%)	
	Stroma>%50	13 (43.33%)	
TB score	1	13 (43.33%)	
	2	9 (30.0%)	
	3	8 (26.67%)	
Age			69.27±10.49
TILs			22.67±22.74

TB: Tumor budding, TSR: Tumor stroma ratio, TILs: Tumor-infiltrating lymphocytes

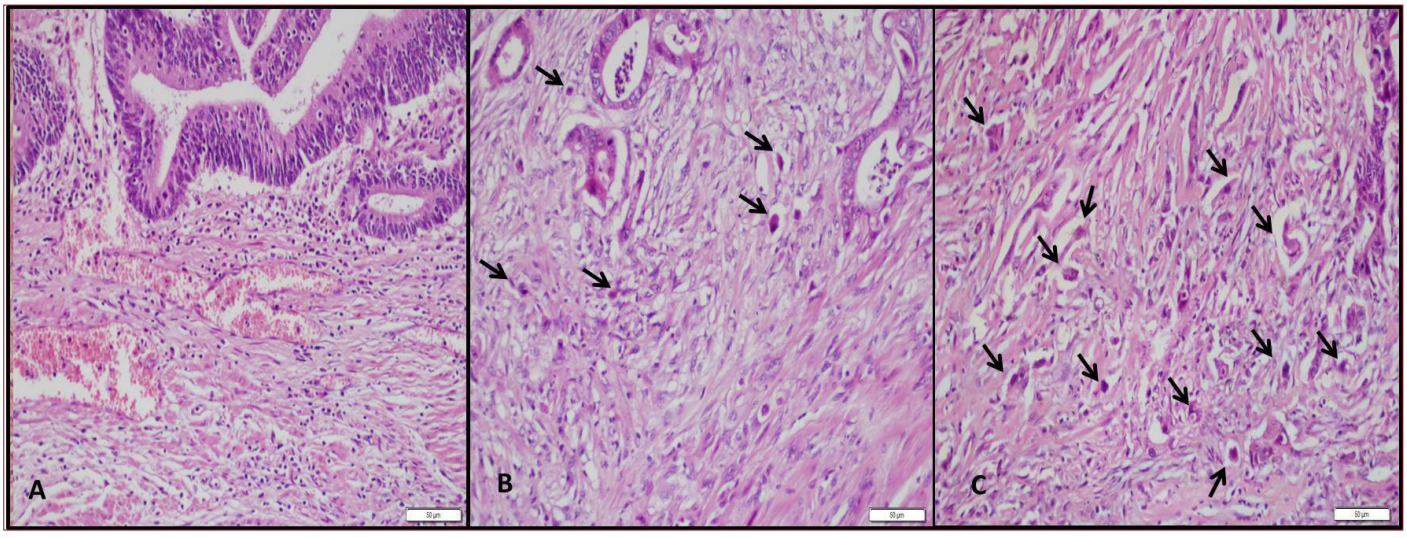

Figure 1. Tumor budding score 1 (A), score 2 (B) and score 3 (C) are seen in hematoxylin-eosin stained slides (Buds are indicated by arrows). H.Ex20

Table 2. Relationship between tumor budding score and clinicopathological findings

Variables	Categories		TB score			p value
			1	2	3	
Gender	F	n (%)	7 (36.84%)	6 (31.58%)	6 (31.58%)	0.597
	M	n (%)	6 (54.55%)	3 (27.27%)	2 (18.18%)	
Grade	1	n (%)	5 (83.33%)	1(16.67%)	0 (0.0%)	0.002*
	2	n (%)	7 (36.84%)	8 (42.10%)	4 (21.05%)	
	3	n (%)	1(20.0%)	0 (0.0%)	4 (80.0%)	
Lymphovascular invasion	(-)	n (%)	8(72.73%)	2 (18.19%)	1 (9.09%)	0.038
	(+)	n (%)	5 (26.32%)	7 (36.84%)	7 (36.84%)	
Perineural invasion	(-)	n (%)	8 (66.67%)	2 (16.67%)	2 (16.67%)	0.104
	(+)	n (%)	5 (27.78%)	7 (38.89%)	6 (33.33%)	
Surgical margin	(-)	n (%)	8 (40.0%)	6 (30.0%)	6 (30.0%)	0.813
	(+)	n (%)	5 (50.0%)	3 (30.0%)	2 (20.0%)	
Liver invasion	(-)	n (%)	9 (56.25%)	4 (25.0%)	3 (18.75%)	0.293
	(+)	n (%)	4 (28.57%)	5 (35.71%)	5 (35.71%)	
pTstage	pT1	n (%)	2 (66.67%)	1 (33.33%)	0 (0.0%)	0.001*
	pT2	n (%)	7 (70.0%)	3 (30.0%)	0 (0.0%)	
	pT3+pT4	n (%)	4 (25.0%)	5 (31.25%)	7 (43.75%)	
N	(-)	n (%)	12 (57.14%)	5 (23.81%)	4 (19.05%)	0.046
	(+)	n (%)	1 (11.11%)	4 (44.44%)	4 (44.44%)	
M	(-)	n (%)	11 (61.11%)	3 (16.67%)	4 (22.22%)	0.036
	(+)	n (%)	2 (16.67%)	6 (50.0%	4 (33.33%)	
TSR	<%50	n (%)	9 (52.94%)	4 (23.53%)	4 (23.53%)	0.461
	>%50	n (%)	4 (30.77%)	5 (38.46%)	4 (30.77%)	
Age		Mean±SD	68.62±7.96	69.22±8.32	70.38±16.30	0.937a
TILs		Mean±SD	28±25.79	16.89±15.24	20.50±25.19	0.49b

TB: Tumor budding, TSR: Tumor stroma ratio, TILs: Tumor-infiltrating lymphocytes, N: Lymph node metastasis, M: Distant metastasis, *Godman Kruskal Gamma results are given for Grade and pT stage (coefficients 0.762 and 0.742, respectively). aANOVA test. bKruskal Wallis test. Chi-square (likelihood ratio) test results were given for other analyzes

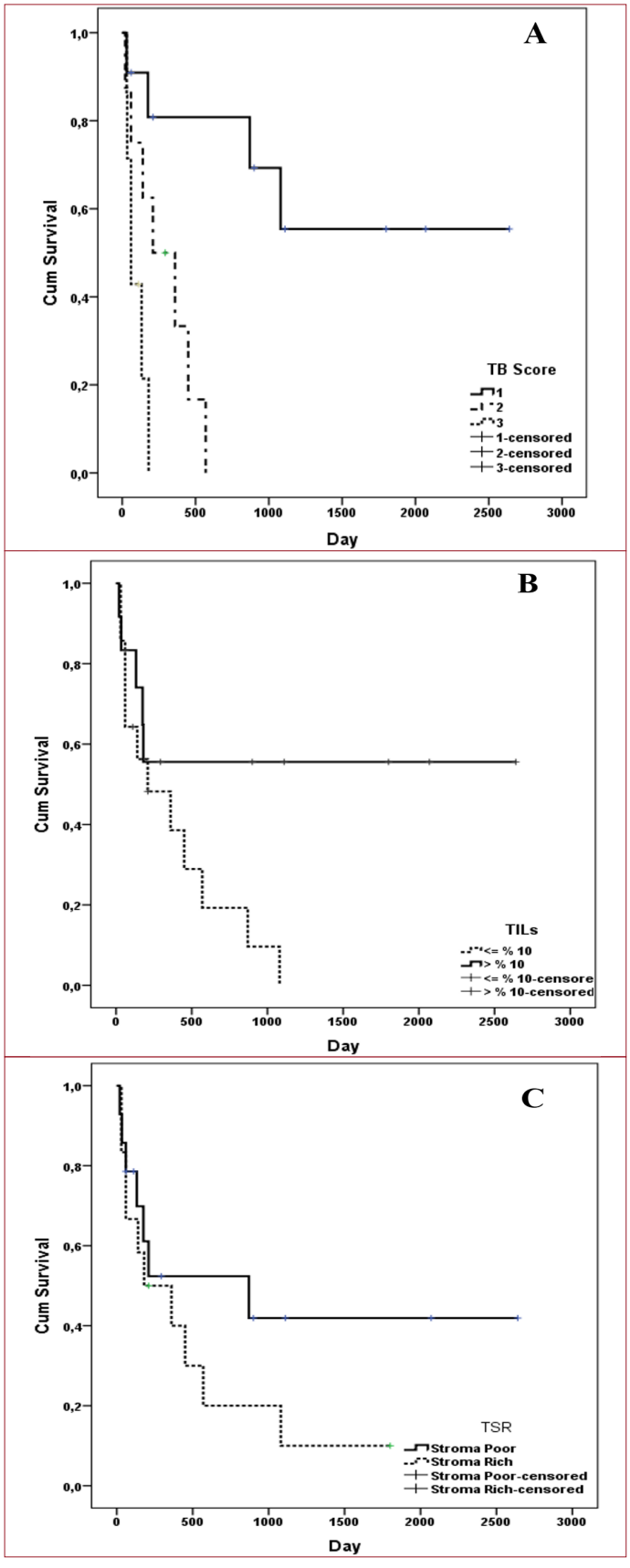

Figure 2. Kaplan-Meier curves of TB score (A), TILs (B), and TSR (C)

In the present study, 17 (56.67%) tumors were stroma poor (**Figure 5A**) and 13 (43.33%) tumors were stroma rich (**Figure 5B**). Increased TSR (>%50 stroma: stroma rich) was found associated with higher histological grade (p=0.015) and increased metastasis frequency (p=0.013). No significant relationship of TSR with gender (p=1.000), LVI (p=0.708), PNI (p=0.599), liver invasion (p=0.749), pT stage (p=0.845), lymph node metastasis (p=0.630) and surgical margin (p=1.000) was detected (**Table 3**). Stroma ratio demonstrated no significant impact on OS (p=0.239). The patients with TSR<50% (stroma-poor) had a mean of OS 1250.8 days [95%CI:559.9-1941.7] whereas that duration of the patients with TSR>50% (stroma-rich) was 467.7 days [95%CI:146.9-788.4] (**Figure 2**).

The univariate cox regression analysis of TB, TSR and TILs variables for survival status revealed that TSR and TILs posed no risk individually (p=0.250 and p=0.063, respectively). However, TB score was found significant (p=0.005). The multivariate evaluation of TB score concurrently with TILs revealed that TB score, particularly TB score3, increased the mortality risk by approximately 21-fold (95%CI: 3.25-137.82, p=0.001). However, it was determined that TILs posed no risk in the multivariate evaluation (p=0.216).

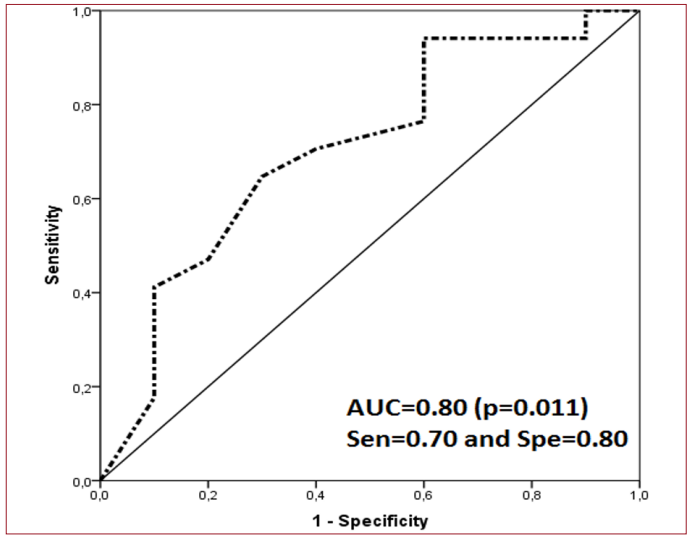

Figure 3. ROC curve relative to TILs values

DISCUSSION

Tumor cells form intact clusters using intercellular adhesion mechanisms in the first stages of carcinogenesis and they usually maintain this adhesion until undergoing sufficient dedifferentiation.[15,16] EMT (Epithelial-Mesenchymal Transition) is a phenomenon that tumor cells lose their cohesive properties and develop a tendency of separation and migration.[17] After EMT, tumor cells may enter the surrounding lymphovascular structure by detaching from the primary mass and metastasize towards distant organs. TB is accepted as an important histopathological parameter of EMT.[18,19]

Table 3. Relationship of TILs and TSR with clinicopathological findings

Variables	Categories	TILs		P Value	TSR		P Value
		≤10 n(%)	>10 n(%)		<%50 n(%)	>%50 n(%)	
Gender	F	9 (47.37%)	10 (52.63%)	0.631	11 (57.89%)	8 (42.11%)	1.000
	M	7 (63.64%)	4 (36.36%)		6 (54.55%)	5 (45.45%)	
Grade	1	0 (0.0%)	6 (100%)	0.004	6 (100%)	0(0.0%)	0.015
	2	13 (68.42%)	6 (31.58%)		8 (42.11%)	11(57.89%)	
	3	3 (60.0%)	2 (40.0%)		3 (60.0%)	2 (40.0%)	
Lymphovascular invasion	(-)	3 (27.27%)	8 (72.73%)	0.029	7 (63.64%)	4 (36.36%)	0.708
	(+)	13 (68.42%)	6 (31.58%)		10 (52.63%)	9 (47.37%)	
Perineural invasion	(-)	4 (33.33%)	8 (66.67%)	0.156	8 (66.67%)	4 (33.33%)	0.599
	(+)	12 (66.67%)	6 (33.33%)		9 (50.0%)	9 (50.0%)	
Surgical margin	(-)	11 (55.0%)	9 (45.0%)	1.000	11 (55.0%)	9 (45.0%)	1.000
	(+)	5 (50.0%)	5 (50.0%)		6 (60.0%)	4 (40.0%)	
Liver invasion	(-)	9 (56.25%)	7 (43.75%)	1.000	10 (62.5%)	6 (37.5%)	0.749
	(+)	7 (50.0%)	7 (50.0%)		7 (50.0%)	7 (50.0%)	
pTstage	pT1	1 (33.33%)	2 (66.67%)	0.716	2 (66.67%)	1 (33.33%)	0.845
	pT2	6 (60.0%)	4 (40.0%)		5 (50.0%)	5 (50.0%)	
	pT3+pT4	9 (52.94%)	8 (47.06%)		10 (58.83%)	7 (41.18%)	
N	(-)	10 (47.62%)	11 (52.38%)	0.44	13 (61.90%)	8 (38.10%)	0.630
	(+)	6 (6.67%)	3 (33.33%)		4 (44.44%)	5 (55.56%)	
M	(-)	6 (33.33%)	12 (66.67%)	0.021	14 (77.78%)	4 (22.22%)	0.013
	(+)	10 (83.33%)	2 (16.67%)		3 (25.0%)	9 (75.0%)	
TB score	1	5 (38.46%)	8 (61.54%)	0.352	9 (69.23%)	4 (30.77%)	0.461
	2	6 (66.67%)	3 (33.33%)		4 (44.44%)	5 (55.56%)	
	3	5 (62.5%)	3 (37.5%)		4 (50.0%)	4 (50.0%)	
TSR	<%50	5 (29.41%)	12(70.59%)	0.008			
	>%50	11(84.62%)	2 (15.38%)				

TB: Tumor budding, TSR: Tumor stroma ratio, N: Lymph node metastasis, M: Distant metastasis

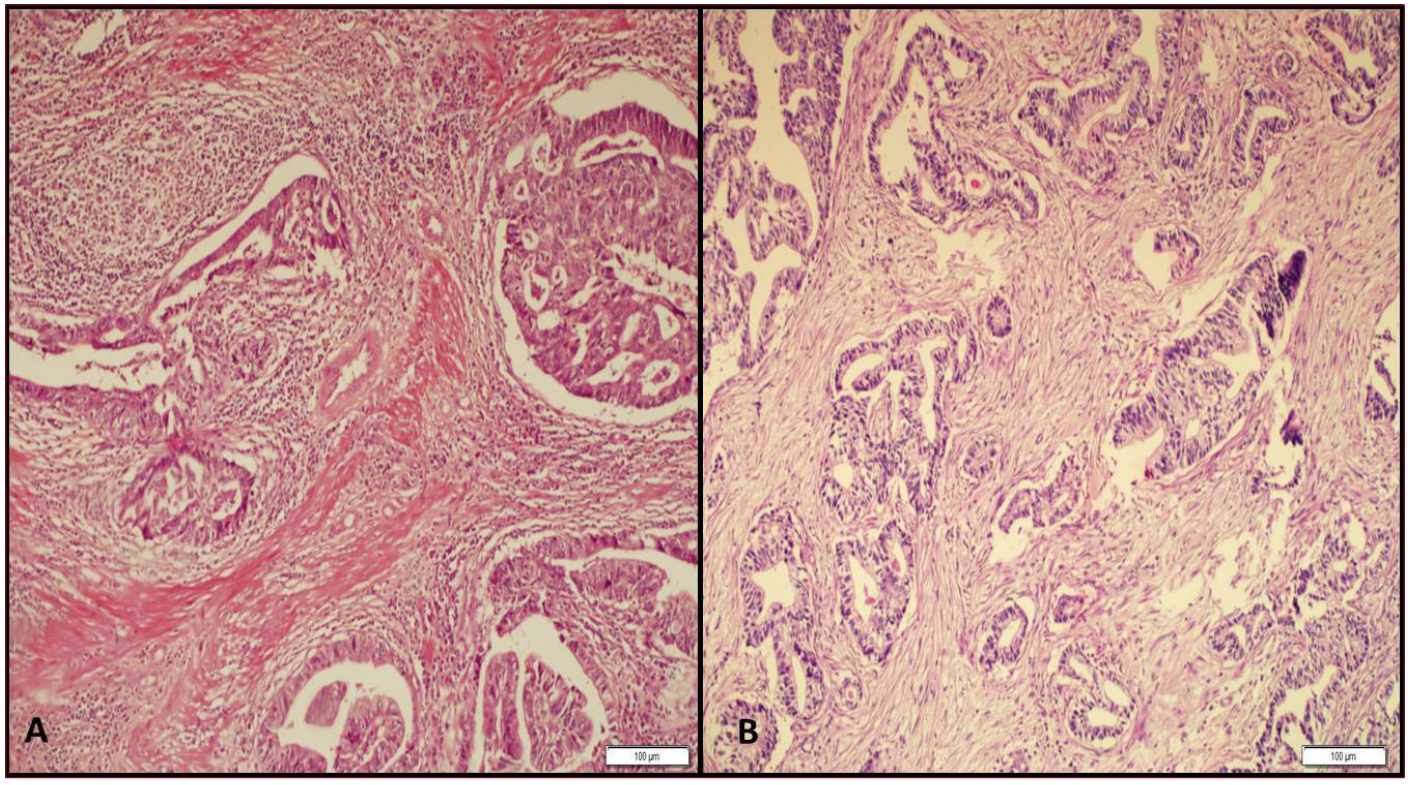

Figure 4. TILS >10% (A) and TILS ≤10% (B) are seen in hematoxylin-eosin stained slides. H.Ex10.

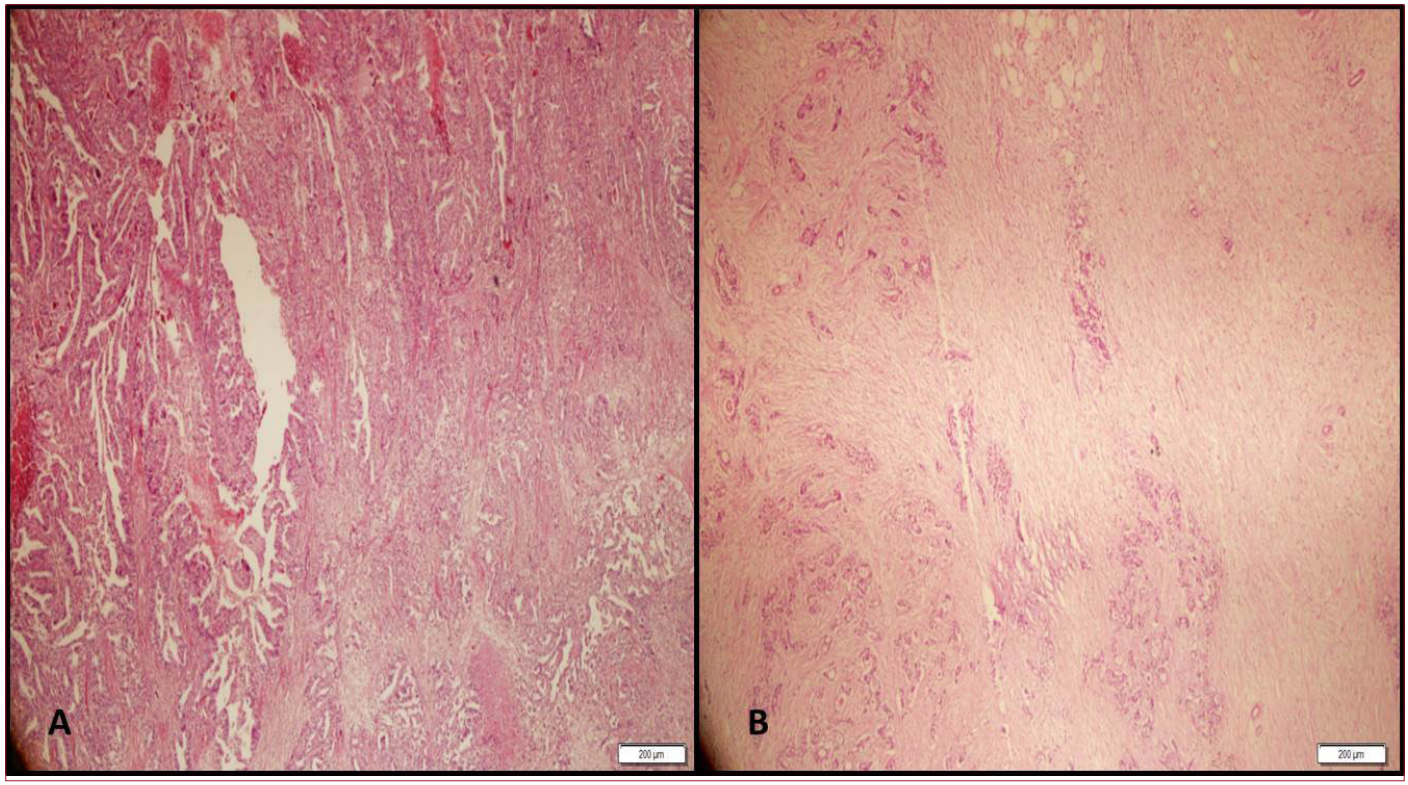

Figure 5. Tumor stroma ratio <50% (stroma poor) (A) and tumor stroma ratio >50% (stroma rich) (B) are seen in hematoxylin-eosin stained slides. H.Ex4

TB has been investigated in many cancer types such as primarily CRC (colorectal carcinoma), pancreatic ductal adenocarcinoma, oral squamous cell carcinoma, lung (adenocarcinoma+ squamous cell carcinoma), endometrial cancer, breast, stomach and esophageal cancers.[2] It has been suggested that TB was associated with poor prognosis in most of those cancer types. However, in the present time, routine reporting of tumor budding scores have been recommended only in the current protocols related with CRC reporting. The relationship of high tumor budding score with aggressive tumor characteristics such as more advanced pT, pN and AJCC stages, lymphovascular and perineural invasions, distant metastasis and local tumor recurrence in colorectal cancer has been demonstrated in many studies of the literature.[8,9,20-24] In the study of Kim et al. conducted on 78 GBC patients; a higher TB score was found associated with a poorer histological differentiation, a higher pT stage, presence of LN metastasis as well as lymphatic, venous or perineural tumor invasion.[4] Similarly, Kai et al. have also reported that presence of TB was significanly associated with advanced T stage, LN metastasis and venous invasion in GBC.[5] In our study, similarly with literature, high TB score was determined to be significantly associated with a higher histological grade (p=0.008), a higher pT stage, LVI (p=0.038), LN metastasis (p=0.046) and distant metastasis (p=0.036). High TB score was encountered to be associated with a shorter survival duration (p<0.001). The patients with a low TB score had a mean OS of 1733.4 days [95% CI: 1048.0-2418.8] whereas those with moderate and high TB scores had mean OS of 283.8 days [95% CI: 136.5-431.0] and 93.1 days [95% CI: 45.5-140.8], respectively. It was observed that particularly TB score-3 increased mortality risk by approximately 21-fold (95% CI: 3.25-137.82, p=0.001). Our results supported that TB was a significant prognostic parameter of GBC.

In the recent years, the effective role of immunotherapies in the cancer treatment has drew attention in the experimental and clinical studies. The importance of the determination of the reliable bioindicators is clearly obvious for selection of the patients with the highest probability of responsiveness to the immunotherapeutic agents. By these improvements, the importance of the evaluation of TILs has increased as the prognostic and treatment response predictive factors in various cancer types.[25] The increased rates of TILs has been associated with good prognosis in many different cancer types.[7,26-28] There is a limited number of studies that have investigated the effect of TILs in GBC and these studies have found that increased TILs was associated with better prognosis.[12,29] In this study, TILs were not significantly associated with gender, PNI, liver invasion, pT stage, and lymph node metastasis, but higher TILs were associated with lower histological grade (p=0.004), less LVI (p=0.029), less distant metastasis (p=0.021) and low TSR (p=0.008). In addition, it can be considered that the prognosis of the patients with TILs value ≤10% may worsen according to OS. The fact that TILs are not significantly associated with liver invasion and advanced pT stage, which are known as indicators of poor prognosis, seems to weaken the prognostic importance of TILs. This may be resulting from the fact that we evaluated TILs by only H&E stained slides differently from Patil et al.[12] and Lin et al.[29] This outcome suggests us that TILs

are a strong candidate to be a prognostic parameter of GBC, however, they should be supported by immunohistochemical studies such as CD3 and CD8.

TB is strongly associated with the stroma and immune system components that make up the tumor microenvironment.[3] The answer of the question that TB is a consequence of tumor microenvironment or the changes in the tumor microenvironment still remains unknown. Therefore, the relationship between TB and tumor microenvironment is interesting. Many studies in the literature have shown that TB was inversely proportional with peritumoral inflammation which is an indicator of tumor microenvironment.[20,23,24] However, Lang-Schwarz et al. have advocated that tumor budding is independent from inflammation.[9] It was found in the present study supporting the results of Lang-Schwarz et al. that there was no relationship between TB and TILs (p=0.352). Similarly, no relationship was detected also between TB and TSR (p=0.461), however, this outcome is not adequate to conclude that stroma has no impact on TB. Various stromal factors and pathways may influence TB independently from stroma ratio.

The increased tumor stroma ratio has been associated with worse survival in a series of solid cancer types including GBC.[11,30-32] However, it is not clear whether the impact of increased TSR on survival is independent from the host inflammatory responses and other components of tumor microenvironment. The relationship between tumor stroma, host and tumor characteristics has not been clarified. Li et al. have reported in their study on 51 GBC cases that TSR had an effect on OS, however, it had no independent prognostic effect on OS. It has been stated in the same research that TSR was not associated with other tumor-related parameters except pTstage.[11] It was determined in the present study that stroma-rich tumors had higher histological grade (p=0.015) and less TILs (p=0.008) while they metastasized more frequently (p=0.013). However, TSR had no relationship with other prognostic parameters of tumor (pT stage, LVI, PNI, liver invasion, TB score, lymph node metastasis) and demonstrated no effect on OS (p=0.239).

The limitations of our study were low number of cases and lack of supporting molecular studies. However, we conclude that researches conducted on limited number of case series also should be reported in the literature since gallbladder cancer is a rarely seen cancer type.

CONCLUSION

TB can be used as a new prognostic biomarker in GBCs due to its simple and low cost to determine and also its effectiveness in determining the prognosis. We have concluded that it is early to recommend TILs and TSR as the prognostic parameters in GBCs. In the future, further studies can be conducted on a larger number of GBC cases with a multicenter participation to clarify the prognostic value of TILs and TSR.

ETHICAL DECLARATIONS

Ethics Committee Approval: The present study was approved by Hatay Mustafa Kemal University Board of Ethics on Noninvasive Clinical Human Studies Ethics Committee (Date: 04.06.2020, Decision Number:23) .

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Orjinal Araştırma / Original Article

Evaluation of the COVID-19 Fear and Quality of Life in Patients with Inflammatory Bowel Disease During the Pandemic

Pandemi Döneminde İnflamatuvar Barsak Hastalığı Olan Hastalarda COVID-19 Korkusu ve Yaşam Kalitesinin Değerlendirilmesi

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Abstract

Aim: Novel Coronavirus disease (COVID-19) pandemic had caused various problems in follow up and treatment of many chronic diseases such as Inflammatory Bowel Diseases (IBD). This study aimed to determine the level of fear and anxiety of COVID-19 and evaluate the quality of life of patients with IBD during the pandemic.

Material and Method: This study was conducted as a cross-sectional study, and a total of 150 participants (IBD patient group=75, control group=75) were included. In order to evaluate the level of COVID-19 fear and anxiety, the Fear of COVID-19 Scale (FCV-19S) and Coronavirus Anxiety Scale (CAS) were used. In addition, Short Form-36 (SF-36) test was used to evaluate health-related quality of life.

Results: FCV-19S and CAS scores were significantly higher in IBD patients compared to the control group. ($p<0.05$). In IBD patients some subscores of SF-36 were significantly lower than the control group ($p<0.05$). Univariate regression analyses showed that university degree of education, having Crohn's disease, and using anti-TNF drugs were significantly correlated with the high level COVID-19 fear ($p<0.05$). FCV-19S results were found to be negatively correlated with emotional role limitation, energy, and mental health subscores of SF-36 in patients with IBD ($p<0.05$).

Conclusion: This study showed that IBD patients had higher levels of fear and anxiety regarding COVID-19. Increased levels of fear and anxiety decreased quality of life specifically mentally. One should keep in mind that the probability of nonadherence to drugs in patients with IBD during the pandemic and psychiatric support should be provided if necessary.

Keywords: COVID-19, inflammatory bowel diseases, anxiety, pandemic, anti-TNF

Öz

Amaç: Yeni koronavirüs hastalığı (COVID-19) pandemisi, İnflamatuvar Barsak Hastalıkları (İBH) gibi birçok kronik hastalığın takip ve tedavisinde çeşitli sorunlara neden olmuştur. Bu çalışma pandemi döneminde İBH'lı hastaların COVID-19 korku ve anksiyete düzeylerini ve hayat kalitelerini değerlendirmeyi amaçladı.

Gereç ve Yöntem: Bu çalışma kesitsel bir çalışma olarak yapılmış ve toplamda 150 hasta (İBH hasta grubu=75, kontrol grubu=75) çalışmaya dahil edilmiştir. COVID-19 korku ve anksiyete seviyelerini değerlendirmek için COVID-19 korku skalası (FCV-19S) ve koronavirüs anksiyete skalası (CAS) kullanıldı. Ayrıca sağlıkla ilgili yaşam kalitesini değerlendirmek için kısa form-36 (SF-36) testi kullanıldı.

Bulgular: İBH hastalarında kontrol grubuna göre FCV-19S ve CAS puanları anlamlı olarak daha yüksek, SF-36'nın bazı alt parametreleri anlamlı olarak daha düşük bulundu ($p<0,05$). Univaryant regresyon analizinde üniversite mezunu olmak, Crohn hastalığı tanılı olmak ve anti-TNF ilaç kullanmak yüksek COVID-19 korkusuyla anlamlı olarak ilişkili olduğu saptandı ($p<0,05$). İBH hastalarında FCV-19S puanları ile SF-36'nın emosyonel rol kısıtlaması, enerji ve mental sağlık parametreleri arasında negatif korelasyon olduğu görüldü ($p<0,05$).

Sonuç: Bu çalışma İBH hastalarının COVID-19 ile ilgili daha yüksek korku ve anksiyete seviyesine sahip olduğunu gösterdi. Artan korku ve anksiyete seviyeleri özellikle mental olarak yaşam kalitesini düşürmüştür. Bu dönemde İBH'lı hastalarda ilaç uyumsuzluğu olabileceği akılda tutulmalı ve gerekirse bu hastalara psikiyatrik destek sağlanmalıdır.

Anahtar Kelimeler: COVID-19, inflamatuvar barsak hastalıkları, anksiyete, pandemi, anti-TNF

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INTRODUCTION

Novel Coronavirus disease (COVID-19) had been first described in December 2019 in Wuhan province of China and spread worldwide. World Health Organization (WHO) had declared COVID-19 as pandemic in 11 March 2020 (1). After this declaration most of the countries had put restrictive regulations to prevent spread of the infection and to decrease the mortality rates. Most of the social activities like schools, shopping centers, restaurants, and entertainment centers has been suspended temporarily. Individuals had faced a great psychological stress due to both high risk of transmission and mortality of disease and social and economic problems related to lockdown (2,3). Recent studies have suggested an increase prevalence of mental diseases like anxiety, depression, and post-traumatic stress disorder during the COVID-19 pandemic (2-5).

The morbidity and mortality rates of COVID-19 have been reported to be higher in patients with chronic disease, older age or state of immunosuppression (6). COVID-19 pandemic had caused various problems in follow up and treatment of many chronic diseases for this reason. An important research area regarding chronic diseases during this time period has been inflammatory bowel diseases (IBD). Immunosuppressive drugs and biologics are used as induction and maintenance treatment in a significant number of patients with IBD (7,8). After declaration of COVID-19 as pandemic multiple studies had been reported regarding the management of patients with IBD and organization guidelines have been published. Most of the published research had been focused on information regarding incidence and mortality rates and relationship with drugs used in patients with IBD (9,10).

A few studies had been published regarding psychological effects and quality of life of patients with IBD during COVID-19 pandemic (11,12). In a study evaluating the psychological effects of pandemic on IBD patients' anxiety and depression had been found to be correlated with fear of contracting COVID-19 (11). Another study reported that patients with IBD are anxious about contracting the disease due to their diagnosis and medications they are using (12).

This study aimed to determine the level of fear and anxiety of COVID-19 and evaluate the quality of life of patients with IBD during the pandemic. As these patients suffer from chronic disease and some are using immunosuppressive drugs, we tried to shed some light on the question whether COVID-19 fear levels affect treatment adherence and follow up practices.

MATERIAL AND METHOD

Ethical Statement

This study was performed at Ankara City Hospital, Turkey which is a tertiary referral center. Ethical approval was received from the local Ethics Committee (approval number: E2-21/73) and the study was conducted in accordance with the Declaration of Helsinki guidelines. Signed informed consent was obtained from each participant prior inclusion in the study.

Study Design and Participants

This study was conducted as a cross-sectional study, and a total of 150 participants were included. Participants were divided into two groups as the IBD patient group (n = 75) and control group (n = 75). The IBD group included patients who had been diagnosed with IBD according to clinical, endoscopic and histological data and admitted to applied to gastroenterology outpatient clinic between February 1, 2021 and April 30, 2021. Control group was selected from volunteers without any clinical signs (patient relatives and clinic personnel excluding doctors and nurses). Patients with mood disorders, malignant disease, advanced organ failure, and individuals who declined to participate were not included in the study.

Data Collection

Data related to demographic characteristics such as age, gender, comorbidities, educational, and marital status were obtained by questionnaires from the participants. Information regarding the disease duration, medications, and history of operation were obtained in detail from patient files in IBD group. Disease activities were quantified by the Crohn's Disease Activity İndex (CDAI) and partial Mayo score in Crohn's and ulcerative colitis patients respectively. Clinical remission was defined as CDAI<150 and partial mayo score <2 in accordance with previous studies. In order to evaluate the level of COVID-19 fear and anxiety, the Fear of COVID-19 Scale (FCV-19S) and Coronavirus Anxiety Scale (CAS) were used. In addition, Short Form- 36 (SF-36) test was used to evaluate health-related quality of life (HRQoL).

Fear of COVID-19 Scale (FCV-19S)

FCV-19S is a short, 7-question questionnaire developed to evaluate the level of fear and anxiety related to COVID-19 infection. Patients are asked to evaluate each question with a five-point Likert type scale (1 = strongly disagree, 2=Disagree, 3=Neither agree nor disagree, 4=Agree, 5 = strongly agree) (13). Total score of this scale ranges between 7 to 35 points. The Turkish adaptation of the questionnaire was developed by Satıcı et al (14). The cut-off value in FCV-19S was determined as 16.5, and scores higher than this value have been accepted to have a significant predictive power on anxiety, health-related anxiety, and post-traumatic stress disorder (15).

Coronavirus Anxiety Scale (CAS)

CAS is a 5-question questionnaire developed by Lee, et al. to evaluate the psychological effects of the pandemic period. The validity and the reliability of the Turkish version of the questionnaire had been demonstrated. Each question regarding frequency has a range of answers from 0 to 4 (0=never, 1=rare, 2= few days, 3=more than 7 days, 4=everyday in the last 2 weeks). Total result differs from 0 to 20 (16,17).

Health-Related Quality of Life (SF-36)

Turkish version of SF-36 was used to evaluate the HRQoL (18). This questionnaire is composed of 36 questions evaluating 8 components such as physical function (PF), social function (SF),

restriction of physical function (PRL), restriction of emotional role (ERL), energy (EN), general health (GH), and mental health (MH). In the standard SF-36 scoring system each component has a range of 0 (the worst) to 100 (the best).

Statistical Analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS 22.0 for Windows) software. The variables were investigated using visuals (histograms and probability plots) and a Kolmogorov-Smirnov test to determine whether they were normally distributed. In reporting descriptive statistics, the data were expressed as mean ± standard deviation (SD) and median (minimum-maximum) for continuous variables and as frequency and percentage (%) for nominal and categorical variables. Independent samples t tests were used to compare the continuous values and Mann-Whitney U test was used to compare non-continuous and ordinal values between IBD and control groups. When necessary, Pearson's chi-square tests, Fisher's exact tests, or Likelihood tests were used to compare proportions in different groups. Logistic univariate analysis were used to confirm independent risk factors for high level of covid fear. A p-value of <0.05 was considered statistically significant.

RESULTS

Clinical characteristics of the patients in the IBD group are shown in **Table 1**. Six patients (8%) stopped using their medications without any medical advice and 12 patients (16%) either missed their colonoscopy appointment or declined colonoscopy.

Table 1. Clinical characteristics of IBD group

IBD group	n=75
IBD phenotype	
Ulcerative colitis n (%)	36 (48.0)
Crohn's disease n (%)	36 (48.0)
Unsure/unclassified n (%)	3 (4.0)
Years from diagnosis	
Median (min-max)	4 (0-20)
History of IBD related surgery	
Yes	12 (16.0)
No	63 (84.0)
Disease activity	
Remission n (%)	43 (57.3)
Active n (%)	32 (42.7)
Current medications	
Prednisolone n (%)	6 (8)
5-Aminosalicylates n (%)	19 (25.3)
Rectal therapy n (%)	28 (37.3)
Thiopurines n (%)	17 (22.6)
Budesonide n (%)	5 (6.6)
Methotrexate n (%)	1 (1.3)
Anti-TNF agents n (%)	27 (36)
Vedolizumab n (%)	9 (12)

Comparison of the demographic data of the patients in IBD group and the control group is given in **Table 2**. Accordingly no significant difference was detected in terms of age, gender, educational level, marital status, and comorbidities. (p=0.206, p=0.207, p=0.130, p=0.093, p=0.403 respectively).

Table 2. Comparison of demographic characteristics of participants between two groups

	IBD group n=75	Control Group n=75	P
Age(years) Median±SD	41.56 ±14.36	44.19±14.06	0.206*
Gender n (%)			
Female/male	32 (45.7)/43 (57.3)	38 (50.7)/37 (49.3)	0.207**
Education Status n (%)			
Illiterate	0 (0)	3 (4)	
Primary school	22 (29.3)	4 (5.3)	
Middle school	8 (10.7)	14 (18.7)	0.130***
High school	20 (26.7)	28 (37.3)	
University	25 (33.3)	26 (34.7)	
Marital status n (%)			
Married	55 (73.3)	46 (61.3)	
Single	19 (25.63	23 (30.7)	0.093***
Divorcee	1 (1.3)	6 (8)	
Comorbidities n (%)			
No	53 (70.7)	25 (80.6)	
HT	7 (9.3)	7 (9.3)	
DM	3 (4.0)	6 (8.0)	
HT+DM	2 (2.7)	0	0.403****
CAD	0 (0)	1 (1.3)	
COPD	2 (2.7)	0 (0)	
Other	8 (10.7)	6 (8.0)	

SD: standard deviation, BMI: body mass ındex, HT:hypertension, DM: Diabetes mellitus, CAD: coronary artery disease COPD: Chronic obstructive pulmonary disease*:independent sample t test, **: Fischer exact test, ***: Pearson chisquare test****:likelihood ratio test, bold values show p<0.05.

FCV-19S and CAS scores were significantly higher in IBD patients compared to the control group. (p=0.001, p=0.001, respectively) (**Figure 1**).

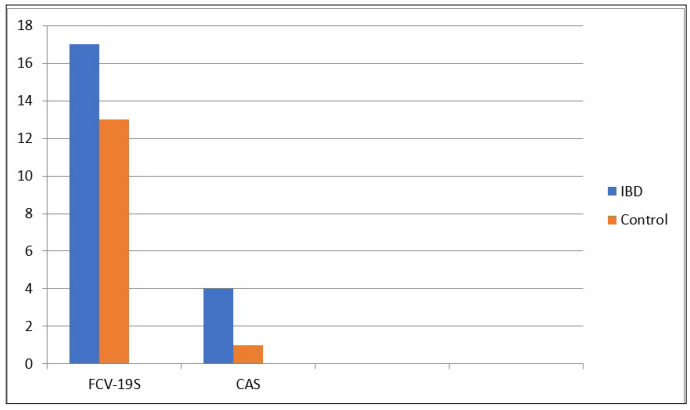

Figure 1. Comparison of COVD fear and anxiety between IBD patients and control group

In IBD patients subscores of SF-36 namely social functioning, physical role limitation, energy, mental health, general health, and body pain were significantly lower than the control group (p=0.009, p=0.001, p=0.001, p<0.001, p<0.001, p<0.001, respectively) (**Figure 2**).

Univariate regression analyses showed that university degree of education, having Crohn's disease, and using anti-TNF drugs were significantly correlated with the high level COVID-19 fear (p=0.010, p=0.022, p=0.027, respectively) (**Table 3**).

Table 3. Logistic regression analysis of factors associated with high level fear of COVID-19 scale.

	Low level	High level	OR (95%CL)	Univariate P value
Gender				
Male/Female	18 (34.4) /11 (41.9)	25 (65.6) /21(58.1)	<0.728 (0.282-1.878)	0.511
Age	44.93±14.69	43.72 ±13.79	0.894 (0.961-1.027)	0.714
Education status				
Primary school	12 (54.5)	10 (45.5)	0.394 (0.142-1.089)	0.073
Middle school	5 (62.5)	3 (37.5)	0.354 (0.077-1.620)	0.181
High school	8 (38.1)	13 (61.9)	1.029 (0.360-2.946)	0.957
University	4 (16.7)	20 (83.3)	5.00 (1.477-16.923)	0.010
IBD fenotype				
Ulcerative colitis n (%)	19 (52.8)	17 (47.2)	0.309 (0.117-0.816)	0.018
Crohn's disease n (%)	9 (25)	27 (75)	3.158 (1.183—8.427)	0.022
Unsure/unclassifed n (%)	1 (33.3)	2 (66.7)	1.273 (0.110-14.701)	0.847
Years from diagnosis	5 (0-19)	4 (0-20)	0.955 (0.859-1.060)	0.386
Disease activity				
Remission n (%)	18 (41.9)	25 (58.1)	1.375 (0.533-3.548)	0.511
Active n (%)	11 (34.4)	21 (65.6)		
History of IBD related surgery				
Yes	2 (16.7)	10 (83.3)	3.750 (0.759-18.538)	0.195
No	27 (42.9)	36 (57.1)		
Current medications				
Prednisolone n (%)	4 (66.7)	2 (33.3)	0.291 (0.050-1.702)	0.217
5-Aminosalicylates n (%)	12 (42.9)	16 (57.1)	0.782 (0.300-2.038)	0.614
Rectal therapy n (%)	10 (52.6)	9 (47.4)	0.475 (0.165-1.369)	0.168
Thiopurines n (%)	9 (52.9)	8 (47.1)	0.480 (0.160-1.439)	0.190
Budesonide n (%)	3 (60)	2 (40)	0.403 (0.063-2.575)	0.337
Anti-TNF agents n (%)	6 (22.2)	21 (77.8)	3.354 (1.148-9.803)	0.027
Vedolizumab n (%)	4 (44.4)	5 (55.6)	0.781 (0.191-3.189)	0.731

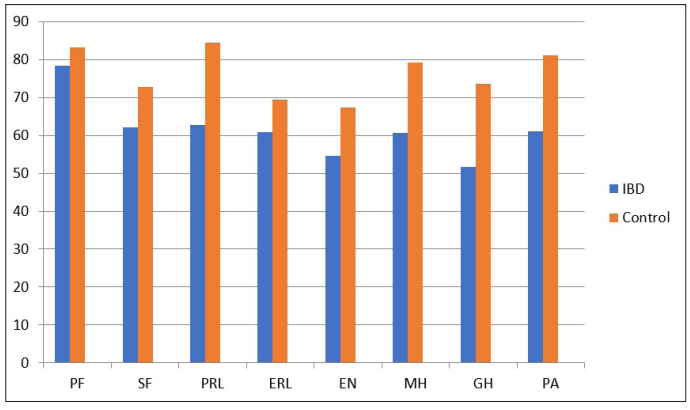

Figure 2. Comparison of SF-36 results between IBD patients and control group

The relationship of FCV-19S, CAS, and SF- 36 in IBD patients are depicted in **Table 4**. FCV-19S results were found to be negatively correlated with emotional role limitation, energy and mental health subscores of SF-36 in patients with IBD (r=-0.278, p= 0.016; r=-0.239, p=0.039; r=-0.296, p=0.01, respectively) (**Table 4**). CAS score was found to be negatively correlated with only mental health subscore (r=-0.229, p=0.048) (**Table 4**).

Table 4. Relation between Health-Related Quality of Life (SF-36) and Fear of COVID-19 Scale, Coronavirus Anxiety Scale in IBD Group

n=75	FCV-19S		CAS	
	r	p	r	p
PF	-0.119	0.319	0.038	0.746
SF	-0.219	0.059	-0.164	0.159
PRL	-0.170	0.144	-0.075	0.524
ERL	-0.278	0.016	-0.144	0.219
EN	-0.239	0.039	-0.034	0.773
MH	-0.296	0.01	-0.229	0.048
GH	-0.201	0.083	-0.150	0.198
PA	-0.224	0.053	-0.075	0.523

PF: physical funcitoning, SF: social functioning, PRL: physical role limitation, ERL: emotional role limitation, EN: energy, MH: mental health, GH: general health, PA: body pain

DISCUSSION

Our study revealed that IBD patients had higher fear and anxiety levels against COVID-19 compared to normal healthy population. Additionally, fear and anxiety level of COVID-19 were found to be correlated with some subscores of quality of life. It was determined that Crohn's disease, university degree of education, and using anti-TNF drugs were independent risk factors of shown to greater COVID-19 fear. The questionnaires were filled in peak months of COVID-19 cases and mortality in a tertiary referral center for patients with IBD. During this time frame vaccination had not reached great percentages in the population yet.

A previously published meta-analysis showed a greater degree of anxiety and depression in patients with IBD compared to the general population (19). A meta-analysis including 19 studies evaluating the quality of life showed that quality of life were significantly poorer than the healthy population (20). In fact, regarding these studies patients with IBD are expected to have lower quality of life, increased anxiety and fear actually. Poor life conditions associated with the pandemic have caused more fear of COVID-19 and decreased quality of life in patients with IBD. All parameters used in quality of life measurements except for PF and ERL were significantly lower in patients with IBD. Despite the fact that mean ERL values were lower in IBD patients no significant difference was detected between the groups. This may be due to restrictive regulations related to pandemic and lockdown being also effective on the normal population

COVID-19 fear level was significantly higher in patients with IBD with higher degree of education. Mean FCV-19S level measured in a study employed on 606 university students in Spain was a little higher than our reference cut-off level (mean:16.7). This suggests that individuals with higher education level might have higher FCV-19S levels compared to other groups (21). Another study performed on IBD patients found no significant correlation between the degree of education and the fear of COVID-19 transmission (22).

In a questionnaire study performed in 225 IBD patients in Brazil anxiety and fear of death was found in 58.2% of the patients. Additionally no significant difference regarding fear of COVID-19 was found between the patients with active disease or remission (23). Similarly we could not find any significant difference in level of COVID-19 fear between patients with active disease or patients under remission. Also the authors could not find any significant difference in terms of anxiety between patients with UC or Crohn's disease (23). Another study evaluating the effects of COVID-19 pandemic on IBD patients no significant difference was detected in terms of fear, anxiety, and depressive symptoms between UC and Crohn's disease patients (10). We found higher level of COVID-19 fear in patients with Crohn's disease compared to UC patients. This may be due to higher degree of immunosuppressive drug use especially anti-TNF drugs among patients with CD.

Another significant finding in our study was the higher level of COVID-19 fear in patients using anti-TNF drugs compared to other drug users. A study exploring the health behaviors of patients with IBD reported that patients with the highest level of fear of contracting COVID-19 were the patients using thiopurines and anti-TNF drugs (12). A cross-sectional study involving 619 IBD patients found that every 3 of 4 patients stopped taking their medicine (22). Another study found that 30% of patients stopped taking their medicine due to risk of contracting COVID-19 and 17.3 % of them missed their colonoscopy appointments (23). We found that 6 (8%) patients didn't continue their medications and 12 (16%) patients missed or refused colonoscopy procedures due to fear of contracting COVID-19. Among patients who were nonadherence to drugs 3 were using anti-TNF, 2 were using thiopurine and 1 was using vedolizumab. Our study, the rate of nonadherence to treatment was lower than previously mentioned studies.

Another important finding of our study was significant negative correlation of increased FCV-19S and CAS with some SF-36 parameters namely MH, ERL and EN. These findings imply that especially mental components of SF-36 which evaluated 2 major components such as physical and mental were negatively affected from the pandemic.

The main limitations of our study were its being a single center study involving relatively low number of patients with IBD. Another limitation might be not performing the study in the first wave of pandemic despite the fact that it was performed in a time frame with the highest COVID-19 case and mortality numbers. Finally, third limitation of the study is that changing of the disease activity compared the pre-pandemic period, which is a factor that may affect the quality of life of the patients in this period, hasn't been evaluated.

CONCLUSION

This study showed that IBD patients admitting to gastroenterology outpatient clinic during the pandemic had higher levels of fear and anxiety regarding COVID-19. Increased levels of fear and anxiety decreased quality of life specifically mentally, this was another important finding of our study. One should keep in mind that the probability of nonadherence to drugs in patients with IBD during the pandemic and psychiatric support should be provided if necessary.

ETHICAL DECLARATIONS

Ethics Committee Approval: For the study, ethical approval was obtained from the local clinical research ethics committee of our hospital (date: March 18, 2020, number: B.10.1.TKH.4.34.H.GP.0.01/62).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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Orijinal Araştırma / Original Article

Comparison of Prognostic Computed Tomography Scores in Geriatric Patients with Traumatic Brain Injury: A Retrospective Study

Travmatik Beyin Hasarı Olan Yaşlı Hastalarda Prognostik Bilgisayarlı Tomografi Skorları Karşılaştırması: Retrospektif Bir Çalışma

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Abstract

Aim: This study aimed to compare the Rotterdam and Helsinki computed tomography (CT) scoring systems for predicting the 30-day mortality after traumatic brain injury (TBI) in the geriatric population.

Material and Method: Patients aged ≥65 years presenting to the emergency department with trauma-related complaints were retrospectively scanned using International Classification of Disease codes, and patients with isolated head trauma examined using brain CT were included. Demographic data including age, gender, trauma mechanisms, Glasgow Coma Scale (GCS) score at the time of admission, light reflex information, intubation, and surgery status, and emergency department outcomes were recorded. Brain CT images were investigated to calculate the Rotterdam and Helsinki CT scores and the relationship between them was examined.

Results: Of the 890 included patients, 403 (45.3%) were male. Overall, 683 patients fell from a height of <1 m and 195 suffered injuries by hitting or direct impact. Further, the 30-day mortality rate was examined, revealing that 868 patients were alive and 22 patients died. Mortality rate was 3.7% for males and 1.4% for females. The Rotterdam and Helsinki CT scores and 30-day mortality was analyzed using receiver operating characteristic curve analysis, and the area under the curve was found as 0.564 and 0.603, respectively. The specificity of Rotterdam and Helsinki CT scoring systems in predicting 30-day mortality was 99.08% and 99.19%, respectively.

Conclusion The use of CT scoring systems such as Rotterdam and Helsinki in the geriatric population presenting with TBI allows us to predict 30-day mortality.

Keywords: traumatic brain injury, geriatrics, emergency department, tomography

Öz

Giriş: Rotterdam Bilgisayarlı Tomografi (BT) skorlama ve Helsinki BT skorlama sisteminin geriatrik popülasyonda TBH (travmatik beyin hasarı) sonrası 30 günlük mortaliteyi tahmin etme yeteneklerinin karşılaştırmasını sağlamayı amaçlamaktadır.

Gereç ve Yöntem: Acil servise travma ilişkili şikayetlerle başvuran 65 yaş ve üstü hastalar ICD kodları üzerinden retrospektif olarak tarandı ve izole kafa travması mevcut olup beyin BT ile tetkik edilmiş olan hastalar çalışmaya dahil edildi. Hastaların yaş, cinsiyet gibi demografik verileri, travma mekanizmaları, geliş muayenesinde Glasgow Koma Skalası (GKS), ışık refleksi bilgileri, entübe edilip edilmediği ve opere olup olmadığı, acil servis sonlanım bilgisi taranarak kaydedildi. Hastaların beyin BT görüntüleri incelenerek Rotterdam ve Helsinki BT skorları hesaplandı ve bunlar arasındaki ilişkiye bakıldı.

Bulgular: Çalışmamıza dahil edilen 890 hastanın 403 (%45.3) erkekti. Çalışmamızda 683 hastanın 1 metreden daha düşük yükseklikten düştüğü, 195 tanesinin çarpma veya direkt darbe alma şeklinde olduğu görüldü. Hastaların bir aylık mortalite bilgisine bakıldığında 22 hastanın öldüğü ve 868 hastanın sağ olduğu saptandı. Erkek hastalarda ölüm oranı %3,7 iken kadın hastalarda bu oran %1,4 olarak bulunmuş olup mortalite açısından cinsiyetler arasında anlamlı fark saptandı. Hastaların Rotterdam ve Helsinki BT Skorları ve bir aylık mortaliteleri ROC analizi ile incelendiğinde Rotterdam BT Skoru için eğri altında kalan alan sırasıyla 0.564 ve 0.603 olarak bulundu. Hastaların Rotterdam BT Skoru ve Helsinki BT skoru 1 aylık mortaliteyi tahmin etmede spesifitesi sırayla %99,08 ve %99,19 olarak hesaplandı.

Sonuç: TBH ile başvuran geriatrik popülasyonda Rotterdam ve Helsinki gibi BT skorlamalarının kullanımı bize 30 günlük mortaliteyi tahmin etmemizi olanak sağlamaktadır.

Anahtar Kelimeler: travmatik beyin hasarı, geriatri, acil servis, tomografi

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INTRODUCTION

Traumatic brain injury (TBI) is one of the leading causes of morbidity and mortality worldwide. TBI is the cause of many emergency department admissions, hospitalizations, and 30% of injury-related mortality.[1-3] Along with the effect of age and declined physical function, one of the most common injury mechanisms in the geriatric population is falling.[4] Although the elderly population comprised 26.7% of the total population in developed countries in 2015, this ratio is expected to reach 40% in approximately 40 years.[5] Age is one of the most important prognostic factors for TBI. The geriatric population is shown to be at higher risk than younger patients in terms of length of hospital stay, cost, survival, and functional outcome.[2,5]

Computed tomography (CT) is a routine imaging method used to evaluate lesions in patients with acute TBI and to immediately initiate diagnosis and treatment due to its easy accessibility and rapid applicability.[6] This imaging modality not only allows the diagnosis of intracranial injuries but also provides prognostic information.[6,7] Several CT scoring systems are available to predict and categorize the mortality of patients with TBI. Rotterdam CT score and Helsinki CT score are the most frequently used scoring systems.[8,9] The Rotterdam CT scoring system is based on epidural mass lesion, midline shift, basal cistern morphology, and intraventricular blood or traumatic subarachnoid hemorrhage.[10] The Helsinki CT score is calculated based on the lesion type and volume, presence of intraventricular bleeding, and suprasellar cistern status.[11]

This study aimed to compare the ability of the Rotterdam and Helsinki CT scoring systems to predict the 30-day mortality after TBI in the geriatric population.

MATERIAL AND METHOD

Patients older than 65 years who presented to the emergency department of a tertiary education and research hospital with trauma-related complaints between January 01, 2018, the same date in 2021 were retrospectively analyzed using International Classification of Disease codes, and those with isolated head trauma who were examined using brain CT were included in the study. Patients aged <65 years, without head trauma, who did not undergo brain CT examination despite having head trauma, for whom brain CT findings could not be understood whether the cause or outcome such as head trauma during syncope or epileptic seizure, and those with missing data were excluded from the study. Demographic data including age, gender, trauma mechanisms (fall from height of <1 m, fall from height of >1 m, hit or direct impact, motor vehicle collisions, pedestrian injury, motorcycle accident), Glasgow Coma Scale (GCS) on admission, light reflex information, intubation and surgery status, and emergency department outcome were recorded. Rotterdam and Helsinki CT scores were calculated by examining the patients' brain CT images. The 30-day mortality status of the patients was confirmed by checking both the Death Notification System (ÖBS, http://www.obs.gov.tr) and hospital data. The study was carried out with the permission of Umraniye Training and Research Hospital Ethical Committee (ethics committee approval number: B.10.1TKH.4.34.H.GP.0.01/294). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Statistical Analysis

The collected data were analyzed using IBM SPSS 28 (IBM Corp. Released 2021; IBM SPSS Statistics for Macintosh, Version 28.0, Armonk, NY; Analyzed using IBM Corp). Continuous data with normal distribution were presented as mean and standard deviation, whereas continuous data without normal distribution were presented as median and interquartile range (IQR). Categorical data were expressed as frequency and percentage. Categorical data were compared using Chi-squared and Fischer's exact test where applicable. Continuous data that did not fit normal distribution were compared using Mann–Whitney U test. Receiver operating characteristic (ROC) curves were compared using the DeLong test. A p value of <0.05 was considered significant in all statistical analyses.

RESULTS

Overall, 7869 patients aged older than 65 who presented to the emergency department for trauma between the study period were scanned. Of these, we excluded 3839 patients due to lack of head trauma, 1229 as they did not undergo brain CT, and 1911 due to unclear mechanism of trauma and lack of data.

Of the remaining 890 patients included in the study, 403 (45.3%) were male. Median age was 77 (IQR: 71–84) years. On examining the trauma mechanisms of the patients, we found that 683 (76.7%) patients fell from a height of <1 m, 195 (21.9%) suffered a hit or direct impact, 2 (0.2%) fell from a height of >1 meter, 6 (0.7%) were in motor vehicle collisions, 3 (0.3%) were in pedestrian injury, and 1 (0.1%) was in a motorcycle accident. Patient examination at the time of admission showed that 873 (98.1%) patients had a GCS of 15, 13 (1.5%) had a score of 14, and 4 (0.4%) had a score of ≤13. Two (0.2%) patients had negative unilateral light reflex and anisocoria at the time of admission, and four (0.4%) were intubated in the emergency department. On investigating the emergency department outcomes of the patients, we found that 1 (0.1%) patient had died in the emergency room, 28 (3.1%) had been admitted to other wards, 3 (0.3%) were moved to the intensive care unit, and 858 (96.4%) were discharged from the emergency room. Examination of the 30-day mortality of the patients revealed that 22 (2.5%) patients had died and 868 (97.5%) were alive. Brain CT findings and other data of the patients are summarized in **Table 1**.

Table 1. Descriptive characteristics of patients

	n (%)
Gender	
Male	403 (45.3)
Female	487 (54.7)
Age	77 (71 – 84)
Trauma mechanism	
Fall from height of <1 m	683 (76.7)
Fall from height of >1 m	2 (0.2)
Hit or direct impact	195 (21.9)
Motor vehicle collisions	6 (0.7)
Pedestrian injury	3 (0.3)
Motorcycle accident	1 (0.1)
Glasgow Coma Scale	
15	873 (98.1)
14	13 (1.5)
≤13	4 (0.4)
Pupil status	
Isochoric	888 (99.8)
Anisochoric	2 (0.2)
Intubation in the emergency department	4 (0.4)
Emergency department outcome	
Discharged	858 (96.4)
Admitted to a hospital ward	28 (3.1)
Admitted to the intensive care unit	3 (0.3)
Death	1 (0.1)
30-day mortality	
Alive	868 (97.5)
Dead	22 (2.5)
Brain computed tomography findings	
Subdural hematoma	17 (1.9)
Epidural hematoma	2 (0.2)
Intracerebral hematoma	3 (0.3)
Subarachnoid hemorrhage	8 (0.9)
Intraventricular hemorrhage	0 (0.0)
Compressed cistern	2 (0.2)
>5 mm shift	1 (0.1)
>25 cm³ hematoma volume	2 (0.2)
Rotterdam scores	
1	879 (98.8)
2	9 (1.0)
3	2 (0.2)
4	0 (0.0)
5	0 (0.0)
6	0 (0.0)
Helsinki scores	
–1	1 (0.1)
0	865 (97.2)
1	0 (0.0)
2	15 (1.7)
3	6 (0.7)
4	0 (0.0)
5	3 (0.3)

Table 2. Comparison of 30-day mortality in terms of age, gender, and Rotterdam and Helsinki computed tomography scores

	Mortality		p values
	Dead	Alive	
Age	81 (IQR: 76.5 – 85.8)	77.0 (IQR: 70.8 – 84.0)	0.015*
Gender			
Male	15 (3.7)	388 (96.3)	0.029**
Female	7 (1.4)	480 (98.6)	
Rotterdam CT scores			
<2	19 (2.2)	860 (97.8)	0.002***
≥2	3 (27.3)	8 (72.7)	
Helsinki CT scores			
<3	20 (2.3)	861 (97.7)	0.019***
≥3	2 (22.2)	7 (77.8)	

P values written in bold are statistically significant (p < 0.05). *Mann–Whitney U test; **Chi-squared test; ***Fischer's exact test CT, computed tomography; IQR, interquartile range

An analysis of the relationship between age and mortality revealed that the median age of the patients who had died was 81 years (IQR: 76.5–85.8) and that of the surviving patients was 77.0 years (IQR: 70.8–84.0) (Mann–Whitney U test; p=0.015). The mortality rate was 3.7% for males and 1.4% for females (Chi-squared test; p=0.029). When the Rotterdam and Helsinki CT scores and 30-day mortality of the patients were analyzed using ROC analysis, the area under the curve for the Rotterdam CT score was 0.564 and that for the Helsinki CT score was 0.603 (**Figure 1**). The difference between the two AUC values was calculated as –0.04 (95% CI: –0.101–0.021); however, this difference was not statistically significant (De-Long test; p=0.203). When the Rotterdam CT score of the patients was dichotomized at the cutoff value of 2, 879 patients were found to have a Rotterdam CT score of <2 and 2.2% of these patients died, whereas 11 patients had a score of ≥2 and 27.3% of these patients died. This difference in the mortality rates was statistically significant (Fischer's exact test; p=0.002). At this cutoff value, the specificity of the Rotterdam CT score was 99.08% (95% CI: 98.19% vs. 99.6%). When the Helsinki CT score was dichotomized at the cutoff value of 3, 881 patients had a Helsinki CT score of <3 and 2.3% of these patients died, whereas 9 had a Helsinki CT score of ≥3 and 22.2% of these patients died. The difference between the mortality rates was found to be statistically significant (Fisher's exact test; p=0.019) (**Table 2**). At this cutoff value, the specificity of the Helsinki CT score was 99.19% (95% CI: 98.35%–99.68%).

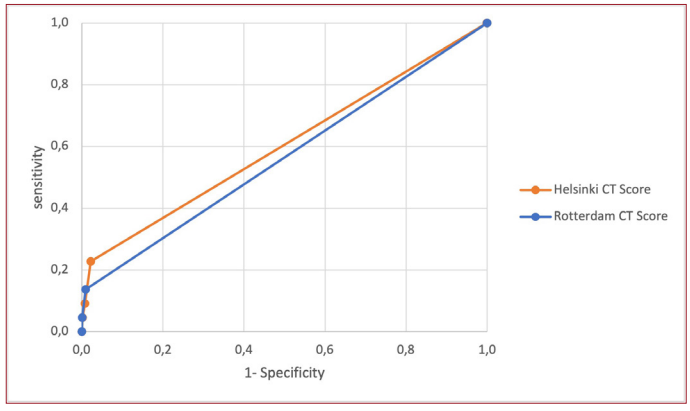

Figure 1. Receiver operating characteristic curves for Rotterdam and Helsinki computed tomography scores according to 30-day mortality

DISCUSSION

Predicting mortality is very important for patients with TBI. This helps clinicians decide the resource allocation for patients and communicate with the patient's relatives.[12] GCS is the most used scoring system to evaluate TBI and predict prognosis;.[13] however, it has some limitations, e.g., it does not consider brainstem reflexes and eye movements. GCS is not reliable for patients who consume alcohol or were given sedatives and cannot provide structural information for

intracranial lesions.[2,6,14] For these reasons, we compared the Helsinki CT scoring system with the Rotterdam CT scoring system, both of which are used to classify CT, to accurately predict prognostic values. The AUC for the Rotterdam CT scoring system was 0.564 and that for the Helsinki CT scoring system was 0.603, showing no significant differences. In mortality prediction, the sensitivity of both scoring systems was found to be >99%, which was statistically significant. When the scoring systems were individually evaluated, they were successful in predicting prognosis. No previous study in the literature includes geriatric patients.[7,11,15,16] We believe that these two scoring systems can be used to evaluate the 30-day mortality in the geriatric patient population presenting to the emergency department with TBI.

TBI-related admissions to the emergency department, ward, and intensive care units as well as mortality occur most frequently in older adults.[17] Increasing age is one of the most important prognostic factors for mortality in TBI.[2,17] In the present study, the median age of patients aged >65 years presenting to the hospital with TBI was 77 years, which is consistent with the literature.[18] It was found that the median age of the patients who died was 81 years and that of the patients who survived was 77 years. This difference was statistically significant. Differences after TBI is age-related. Morbidity and mortality increase with an increase in age,[2] which, in turn, leads to an increase in the length of hospital stay and cost of care.[2,3] Therefore, scoring systems that predict mortality may help clinicians predict the healthcare costs.

Although the number of women presenting to the emergency department with TBI was higher in the present study, the opposite was the case in terms of mortality, with a mortality rate of 3.7%, which is significantly higher compared with that for females. In the literature, some studies report that male patients more frequently present with TBI in all age groups, whereas some other studies report that the frequency of female patients is higher.[17-19]

According to our data, the most common reason for TBI in admitted patients was falling from the same level (76%). This is in accordance with previous reports, whereas one of the least common causes of TBI was motor vehicle collisions.[5,17,19]

Limitations

There are some limitations to this study. First, this is a retrospective study. Second, this was a single-center study even though 3 years of data was analyzed. This may have affected our results due to local treatment protocols. The mortality rate in the present study was very low; therefore, our results may not be applicable to other hospitals and populations with other conditions. For these reasons, the results should be validated with large-scale prospective studies.

CONCLUSIONS

In the present study, we compared the Rotterdam and Helsinki CT scoring systems. The use of such CT scoring systems for geriatric patients presenting with TBI allows us to predict the 30-day mortality. These two scoring systems have high sensitivity and can be used for geriatric patients presenting with TBI but there is no superiority to each other. Further studies are needed to support this evidence..

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Umraniye Training and Research Hospital Ethical Committee (ethics committee approval number: B.10.1TKH.4.34.H.GP.0.01/294).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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Orijinal Araştırma / Original Article

Comparisons of Treatment Protocols for SARS-CoV-2 in Early Pandemic: Single Center Experience in Turkey

Erken Pandemide SARS-COV-2 Tedavi Protokollerinin Karşılaştırılması: Türkiye'de Tek Merkez Deneyimi

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Abstract

Objective: In this retrospective observational study, we aimed to investigate the COVID-19 treatment protocols applied in our hospital in terms of side effects and 28-day mortality.

Material and Method: All 621 patients diagnosed as COVID-19 and treated with any drugs were included in the study. Inclusion criteria for patients were hospitalization with COVID-19 diagnosis and being over 18 years old. The patients were divided into 4 groups according to the treatments against COVID-19: Group 1 (only favipiravir), Group 2 (hydroxychloroquine (HQ)+ Azithromycin (AZ), Group 3 (only HQ), and Group 4 (HCQ+AZ +antibiotics). The gender, age, medications, underlying comorbidities, possible side effects due to the treatments (cardiotoxicity, hepatotoxicity, nephrotoxicity), and mortality rates were evaluated.

Results: There was no difference in terms of side effects between treatment groups. Mortality rates were lowest in the HQ+AZ group. HCQ+AZ treatment was the most effective treatment protocol.

Conclusion: It can be concluded from the study that the higher mortality rate due to favipiravir may be due to the administration of this drug only to critically ill patients during the initial period of the pandemic. Or the study may lead us to conclude that favipravir not effective in the treatment of COVID-19.

Keywords: COVID-19, favipiravir, hydroxychloroquine, azithromycin, antibiotics

Öz

Amaç: Bu retrospektif gözlemsel çalışmada hastanemizde uygulanan COVID 19 tedavi protokollerini, yan etkileri ve 28 günlük mortaliteyi araştırmayı amaçladık.

Gereç ve Yöntem: Çalışmaya COVID-19 tanısı konan ve herhangi bir ilaçla tedavi edilen 621 hastanın tamamı dahil edildi. Hastalar için dahil edilme kriterleri COVID-19 tanısı ile hastaneye yatış ve 18 yaşından büyük olmaktı. Hastalar COVID-19 tedavisine göre 4 gruba ayrıldı: Grup 1 (sadece favipiravir), Grup 2 (hidroksiklorokin (HQ)+ Azitromisin (AZ), Grup 3 (sadece HQ) ve Grup 4 (HCQ+AZ) +antibiyotikler) Cinsiyet, yaş, ilaçlar, altta yatan komorbiditeler, tedavilere bağlı olası yan etkiler (kardiyotoksisite, hepatotoksisite, nefrotoksisite) ve mortalite oranları değerlendirildi.

Bulgular: Tedavi grupları arasında yan etkiler açısından fark yoktu. Mortalite oranları HQ+AZ grubunda en düşüktü. HCQ+AZ tedavisi en etkili tedavi protokolüydü.

Sonuç: Çalışmada, favipiravire bağlı daha yüksek ölüm oranının, pandeminin ilk döneminde bu ilacın sadece kritik hastalara uygulanmasına bağlı olabileceği sonucuna varılabilir. Çalışma, favipravir'in COVID-19 tedavisinde etkisinin olmadığı sonucuna varmamızı sağlayabilir.

Anahtar Kelimeler: COVID-19, favipiravir, hidroksiklorokin, azitromisin, antibiyotikler

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) pandemic is still wreaking havoc around the world, and it's become a major cause of death and morbidity. It has caused over 2 million deaths globally since the first case was identified.[1] Patients of advanced age and comorbidities have a higher mortality rate. According to current statistics, global mortality is 6.97 percent, while mortality in our country is 2.71 percent.[2,3] For the proper treatment of the disease, successful and safe therapies with a low side effect profile are still needed. The treatment protocols are based on a small number of randomized clinical trials, experiences from the treatment of past influenza outbreaks and other coronavirus viruses, and expert opinions. Due to the need to formulate a treatment protocol in a hurry since the COVID-19 pandemic is rapidly progressing. Treatment methods are continually changing and becoming more appropriate as new research evidence and global studies become accessible.

Favipiravir and/or hydroxychloroquine (HQ) treatments have been recommended by our country's Ministry of Health since the beginning of the pandemic, according to the COVID-19 Diagnosis and Treatment Guidelines. Also, in the earliest stages of the pandemic, azithromycin (AZ) treatment was also recommended. In addition, various antibiotics were recommended for selected patients.[2] There are several studies examining the side effects of drugs used in the treatment of COVID-19 and their effects on patients' mortality, clinical course, and prognosis.[4-6] However, comparative studies on COVID-19 treatment protocols are limited to the current literature.

In this study, we aimed to retrospectively investigate the COVID-19 treatment protocols applied in our pandemic tertiary care hospital in terms of side effects and 28-day mortality.

MATERIAL AND METHOD

This retrospective, observational study included 621 confirmed COVID-19 patients from a pandemic hospital in our province. Data of the confirmed COVID-19 patients were collected from March 23 to July 1, 2020. Patients diagnosed with COVID-19 according to the World Health Organization (WHO) provisional guideline. A positive result of the SARS-CoV-2 "real-time" reverse transcriptase-polymerase chain reaction (RT-PCR) test in upper respiratory tract specimens of the patients as a definite case, although the SARS-CoV-2 RT-PCR test of the patient was negative, finding an appearance compatible with viral pneumonia in thoracic computed tomography (CT) together with appropriate clinical findings was defined as a possible COVID-19 patient.[2] Exclusion criteria were missing data, age younger than 18 years, patients who were admitted to the intensive care unit (ICU) at the time of admission, and COVID-19 diagnosis was excluded during clinical follow-up, were not included in the study. The patients were divided into 4 groups according to the COVID 19 treatment protocols: Group 1 (only favipiravir), Group 2 (HQ+AZ), Group 3 (only HQ), and Group 4 (HQ+AZ+antibiotics). The gender, age, the medications, underlying comorbidities, possible side effects due to the treatments (cardiotoxicity, hepatotoxicity, nephrotoxicity, elevation of blood uric acid levels), and mortality rates were evaluated. Data were collected from the hospital automation system and transferred to the case forms created by researchers.

Statistical Analysis

The data were analysed with the SPSS Package Program version 22.00 (IBM, Armonk, NY, USA). Number, percentage, mean, median, minimum, maximum and standard deviation were used in the presentation of descriptive data. Chi-Square test was used to compare categorical variables and Kruskal Wallis Analysis was used to compare continuous variables. For statistical significance, $p < 0.05$ was accepted.

Ethical Approval

The study was carried out in accordance with the principles of the 2013 revised Helsinki Declaration. The study was approved by COVID-19 Scientific Research Evaluation Commission of the General Directorate of Health Services of the Ministry of Health at the date of 04.05.2020 and local ethics committee of our university (dated 03.06.2020, numbered: 2020-08).

RESULTS

A total of 621 patients (256 women and 361 men) diagnosed as COVID-19 (PCR or CT positive) and treated with any drugs were enrolled in the study. The age and gender characteristics of the patients are given in **Table 1**. Most of the patients (n=341, %54,9) were in the HQ +AZ group.

The average age of in group 1 was 66.2±15.7, in group 2 was 56.4±18.8, in group 3 was 49.8±19.5 and in group 4 was 60.7±18.5 years. A statistically significant difference was found between the groups in terms of age (p=0.0001). The median age of group 3 is higher than group 1 and group 4 patients, this difference was statistically significant in the Dunn-Bonferroni corrected paired comparisons (p=0.0001, p=0.001, respectively). The median age of group 2 was lower than group 1, and this difference was statistically significant in the Dunn Bonferroni corrected paired comparisons (p=0.003).

In a comparison of treatment groups with underlying diseases, chronic obstructive pulmonary disease (COPD) and chronic renal failure (CRF) were statistically significantly higher in group 1. There was no significant difference in terms of other diseases and gender (**Table1**).

Levofloxacin (n=55), ceftriaxone (n=46), ceftazidime (n=25), piperacillin-tazobactam (n=17), meropenem (n=16) and imipenem (n=14) were the used antibiotics in group 4.

There was no difference in terms of side effects between the groups according to treatment protocols. In the only favipiravir group, mortality rates were found to be statistically significantly higher. Mortality rates were lowest in the HQ+AZ group (**Table 2**).

Table 1. Summary of demographical characteristics and comorbidities of the patients.

Variables	Total	Favipiravir only (n=49) (Group 1)	HQ+AZ (n=341) (Group 2)	HQ only (n=58) (Group 3)	HQ+AZ + antibiotics (n=173) (Group 4)	P value
	n (%)	n (%)	n (%)	n (%)	n (%)	
Gender						0.687
Female	256 (41.2)	17 (34.7)	146 (42.8)	22 (37.9)	71 (41.0)	
Male	365 (58.8)	32 (65.3)	195 (57.2)	36 (62.1)	102 (59.0)	
COPD						0.026
no	566 (91.1)	41 (83.7)	315 (92.4)	57 (98.3)	153 (88.4)	
yes	55 (8.9)	8 (16.3)	26 (7.6)	1 (1.7)	20 (11.6)	
Diabetes mellitus						0.053
no	526 (84.7)	40 (81.6)	292 (85.6)	55 (94.8)	139 (80.3)	
yes	95 (15.3)	9 (18.4)	49 (14.4)	3 (5.2)	34 (19.7)	
Hypertension						0.053
no	449 (72.3)	30 (61.2)	252 (73.9)	48 (82.8)	119 (68.8)	
yes	172 (27.7)	19 (38.8)	89 (26.1)	10 (17.2)	54 (31.2)	
Cardiac diseases						0.652
no	521 (83.9)	39 (79.6)	291 (85.3)	49 (84.5)	142 (82.1)	
yes	100 (16.1)	10 (20.4)	50 (14.7)	9 (15.5)	31 (17.9)	
Malignancy						0.021
no	593 (95.5)	45 (91.8)	330 (96.8)	58 (100.0)	160 (92.5)	
yes	28 (4.5)	4 (8.2)	11 (3.2)	0 (0.0)	13 (7.5)	
Chronic renal failure						0.029
no	601 (96.8)	45 (91.8)	335 (98.2)	57 (98.3)	164 (94.8)	
yes	20 (3.2)	4 (8.2)	6 (1.8)	1 (1.7)	9 (5.2)	
Organ transplant						1.000
no	619 (99.7)	49 (100.0)	340 (99.7)	58 (100.0)	172 (99.4)	
yes	2 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.6)	
Immunodeficiency						1.000
no	620 (99.8)	49 (100.0)	340 (99.7)	58 (100.0)	173 (100.0)	
yes	1 (0.2)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	
Chronic liver disease						0.595
no	615 (99.0)	48 (98.0)	338 (99.1)	58 (100.0)	171 (98.8)	
yes	6 (1.0)	1 (2.0)	3 (0.9)	0 (0.0)	2 (1.2)	
Rheumatic Disease						0.432
no	615 (99.0)	49 (100.0)	339 (99.4)	57 (98.3)	170 (98.3)	
yes	6 (1.0)	0 (0.0)	2 (0.6)	1 (1.7)	3 (1.7)	

*%: column percentage, p: Chi Square Test, AZ: azithromycin, HCQ: Hydroxychloroquine, COPD: Chronic Obstructive Pulmonary Disease,

Table 2. Summary of side effects and mortality.

Side effects and mortality	Favipiravir only (n=49) (Group 1)	HQ+AZ (n=341) (Group 2)	HQ only (n=58) (Group 3)	HQ+AZ + antibiotics (n=173) (Group 4)	P value
	n (%)	n (%)	n (%)	n (%)	
Cardiotoxicity					0.432
no	49 (100.0)	339 (99,4)	57 (98.3)	170 (98.3)	
yes	0 (0.0)	2 (0,6)	1 (1.7)	3 (1,7)	
Hepatotoxicity					0.358
no	49 (100.0)	328 (96.2)	56 (96.6)	163 (94.2)	
yes	0 (0.0)	13 (3.8)	2 (3.4)	10 (5.8)	
Nephrotoxicity					0.216
no	47 (95.9)	334 (97.9)	58 (100.0)	172 (99.4)	
yes	2 (4.1)	7 (2.1)	0 (0.0)	1 (0.6)	
Exitus					0.0001
no	33 (67.3)	322 (94.4)	54 (93.1)	144 (83.2)	
yes	16 (32.7)	19 (5.6)	4 (6.9)	29 (16.8)	

*%: column percentage, p: Chi-Square Test * HCQ: hydroxychloroquine.

DISCUSSION

COVID-19 is a pandemic that has been causing many deaths globally but there are still not specifically effective antiviral drugs that can currently treat COVID-19. The guidelines prepared according to preliminary results of clinical studies are rapidly changing.[1,2] Due to the variety of drugs used in the treatment of COVID-19, guiding treatment schemes have emerged with the experience in our country and in the world has been released.[7] Only favipiravir, HQ+AZ, only HQ, and HQ+AZ+antibiotics treatment protocols are among the treatment protocols used in our country in early pandemic.

In a retrospective study from Bosnia and Herzegovina; the mortality rate was 5% and the highest mortality rate was in patient over 65 years.[8] The reported COVID-19 related mortality rate was 2.4% in Turkey according to previous study results.[2] We aimed to investigate the optimal treatment by comparing the treatment protocols given, since the continuation of COVID-19 related deaths globally and the fact that the definitive treatment has not yet been found. Additionally, we aimed to compare the side effects and mortality rates of these different treatment protocols.

In our country, the treatment strategy depends on the patient's presence and it should be determined according to the course of the clinical presentation in 48-72 hours of admission. Combination treatments with HQ have a good response to therapy if there is no rapid change in O2 saturation of the patient. Favipiravir was recommended when lung parenchymal infiltration> 50% or in the group with underlying disease or in the group whose saturation is not stable such as intensive care unit patients.[2,7] Favipiravir is an antiviral which is a broad spectrum, that selectively and potently inhibits the Ribonucleic Acid (RNA)-dependent RNA polymerase (RdRp) of RNA viruses, has also been studied in various clinical studies for COVID-19 treatment.[7,9-12] Favipiravir is an intracellular phosphoribosylated precursor to form the active metabolite favipiravir ibofuranosyl-5'-triphosphate (T-705-RTP) was previously used for the treatment of pandemic influenza, has shown potent in vitro activity against SARS COV-2. Overall, favipiravir has shown promising results in clinical studies in multiple countries (such as China, Russia, Japan, the USA, UK, and India). COVID-19 treatment guidelines of many countries have included favipiravir in the treatment protocol.[10] In our country, COVID-19 patients have been treating according to the guidance of the Ministry of Health COVID-19 Guidelines. In early pandemic HQ +AZ, only HQ and HQ +AZ +antibiotics were recommended in non-severe patients' treatments. 5 days of favipiravir treatment was only recommended in severe patients. However, in the subsequent stages of the pandemic, favipiravir started to be used even in the treatment of outpatients.[2] In our study, in which only hospitalized COVID-19 patients were included, increased mortality rates were found in patients who were given only favipiravir treatment compared to the other groups. The reason for this may the treatment recommendations in the early pandemic period when the disease had more unknowns. Or it may be since these patients had already more severe underlying diseases or the clinical presentation of the patients at the time of admission was more severe.

Although there are results supporting the short-term safety of favipiravir,[7,9-15] an early study[13] reported that the most common side effects of favipiravir treatment were mild to moderate diarrhoea, asymptomatic increase in blood uric acid and transaminases, and decreased neutrophil count. In our literature research, we did not find many publications on liver toxicity due to the use of favipiravir treatment. In a controlled study, an increase in liver tests was observed in 2.8% of 35 patients using favipiravir.[13] In a retrospective study from Turkey, it was not reported that liver tests were higher in the hydroxychloroquine group, but significant increases were found in the favipiravir group.[14] We found no hepatotoxicity and cardiotoxicity in the favipiravir group, nephrotoxicity developed in 4.1% of the patients, but there was no statistically significant difference between groups. The reason for the undeveloped toxicity of the drugs may be due to the short-term treatment recommendation.

Hydroxychloroquine is a safer analog of chloroquine and has an antiviral effect against SARS-CoV-2.[7,14,16,17] HQ inhibits SARS-CoV-2's replication in vitro. HQ is a cheap and reliable drug and drug-drug interaction that is low in short-term usage.[17-20] Although it is not known clearly in the treatment of COVID-19, HQ is thought to be a safe drug. In current literature, frequently reported side effects are moderate nausea and diarrhoea, QTc prolongation.[18-21] The usage of HQ in critically ill patients may pose a risk in terms of cardiac toxicities such as ventricular arrhythmias, prolongation of the QT interval, and other cardiac toxicities.[18] In patients with a history of cardiac arrhythmia, daily side effects should be monitored according to the QT distance, and HQ and/or AZ should be discontinued when >300ms.[7]

Seyhan et al.[21] reported that post-treatment QTc measurements of both HQ +AZ group and HQ group were prolonged compared to pre-treatment measurements. In our study, no statistically significant difference was found between the groups in terms of cardiotoxicity. However, we detected cardiotoxicity in 3 patients in the HQ+AZ+antibiotics group, 2 patients in the HQ +AZ group, and in 1 patient in the only HQ group. This can be interpreted as; the possibility of cardiotoxicity increases with the number of growing treatments added to HQ therapy. Ventricular arrhythmia was not detected in our study similarly previous study.[21]

In a study from France, it was reported that HQ therapy was significantly associated with viral load reduction/ loss in COVID-19 patients, and its effect was strengthened with AZ.[2,19,20] In another study from Turkey, AZ was found effective in SARS-CoV-2 RNA-dependent RNA polymerase protein inhibition.[22] A very recently published open-label randomized controlled trial study reported that chloroquine /

HQ treatment added to standard therapy in severe COVID-19 patients caused a significant clinical deterioration, increased risk of renal dysfunction, and increased need for invasive mechanical ventilation.[23] 54.9% of our patients (n=341) were treated with HQ +AZ. With this treatment protocol, cardiotoxicity developed in 2 patients, hepatotoxicity developed in 13 patients, nephrotoxicity developed, and elevation of blood uric acid levels developed in 7 patients, and no statistically significant increase was found in terms of these side effects in comparison with other treatment groups. In addition, mortality occurred in only 5.6% of patients in this group. This rate was the lowest compared to all treatment groups. This may be due to the recommendation of HQ +/- AZ treatment in mild or moderate COVID-19 patients according to the Ministry of Health guidelines.

In addition, other several antiviral medications clinical studies involving oseltamivir, lopinavir, ritonavir, and ganciclovir are used to treat COVID-19, and the treatments recommended in the first months of pandemic in our country were the treatments included in our study. Antibiotic therapy can also be added to treatment for COVID-19 patients, depending on the severity of the concurrent disease. Among the most recommended antibiotics are cephalosporins, quinolones, carbapenems, tigecycline.[24]

In the available literature, no study examining the results of adding different antibiotic treatments to COVID-19 treatment was found. In our study, this group was not examined among themselves. There were 173 patients in this group. The most frequently added antibiotics were levofloxacin (n=55), ceftriaxone (n=46), ceftazidime (n=25). However, data on whether these antibiotics were added empirically or for the treatment of secondary infection could not be reached because the study was retrospective.

In a recent meta-analysis study conducted in 2021,[25] a total of 2702 studies and 12 clinical studies with 1636 patients were analysed. Observational studies have been found to have a moderate risk of bias, and nonrandomized studies have been found to have a significant risk of bias. These meta-analysis data showed that there was no significant difference between favipiravir treatment and standard of care in terms of mortality rate and need for mechanical ventilation in moderate to severe COVID-19 patients. Furthermore, this meta-analysis study revealed no superiority of favipiravir over the standard of care for up to 14 days or other antivirals previously shown to be ineffective for COVID-19, such as hydroxychloroquine, chloroquine, Lopinavir/Ritonavir. It is consistent with the recent meta-analysis findings and may contribute to the literature. The study demonstrated that, the higher mortality rate due to favipiravir was attributed to the administration of this drug to only critically ill patients in the first period of the pandemic. Or the study may lead us to conclude that favipiravir has no effect in the treatment of COVID-19.

CONCLUSION

The study demonstrated that, the higher mortality rate due to favipiravir was attributed to the administration of this drug to only critically ill patients in the first period of the pandemic. Or the study may lead us to conclude that favipiravir has no effect in the treatment of COVID-19. Our study was carried out in our country during the early pandemic period, when treatment protocols were not yet settled and there were many COVID 19 unknowns. Mortality rates were lowest in the HQ+AZ group but this group is not severe COVID 19 patients.

Limitations of the study: The current study has several limitations. It was a single center study and the treatments were given in the first months of pandemic examined.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by COVID-19 Scientific Research Evaluation Commission of the General Directorate of Health Services of the Ministry of Health at the date of 04.05.2020 and local ethics committee of our university (dated 03.06.2020, numbered: 2020-08).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Orjinal Araştırma / Original Article

Retrospective Analysis of Patients with Percutaneous Dilatational Tracheostomy in Intensive Care Unit

Yoğun Bakım Ünitemizde Perkütan Dilatasyonel Trakeostomi Açılan Hastaların Retrospektif Analizi

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Abstract

Aim: Tracheostomy is a method frequently applied in intensive care units with the indication of prolonged intubation.[1] Our aim in this study is to retrospectively analyze the percutaneous dilatational tracheostomy (PDT) cases performed in our clinic within 1 year.

Material and Method: It's analyzed the patients who underwent PDT in Sakarya Training and Research Hospital, Anesthesia Intensive Care Unit between January 2019 and December 2019. Each patient's age, gender, diagnosis of intensive care admission, use of anticoagulant drugs, and APACHE II score were recorded. Then, the day of tracheostomy procedure, complications, total intensive care unit stay, and the patient's discharge from the intensive care unit were evaluated.

Results: A total of 79 patients were found to have undergone PDT. It was observed that the mean age of the patients was 66.56±17.83 and 48 (60.8%) were male. It was observed that 25(31.6%) of the patients were admitted to the intensive care unit with the diagnosis of postresuscitation syndrome, 17 (21.5%) cerebrovascular accident, and 15(19%) pneumonia. The mean APACHE II scores of the patients were 24.1±6.2, and 16(20.3%) patients were discharged. The median PDT procedure day was 19.5[12-30]. It was determined that only 2 of the patients had minor and 1 major and 3 (3.9%) patients did not develop any other complications apart from the bleeding related complication.

Conclusion: In our study, although 66 (83.6%) of the patients who underwent PDT procedure received anticoagulant-antiaggregant treatment, postoperative bleeding rates were observed to be quite low in accordance with the literature.

Keywords: Intubation, percutaneous tracheostomy, intensive care

Öz

Amaç: Trakeostomi yoğun bakım ünitelerinde uzamış entübasyon endikasyonu nedeniyle sıklıkla uygulanan bir yöntemdir. Entübasyon süresinin 7 günden uzun olması sonucu larengeal hasar, glottik-subglottik stenoz ve vokal kord paralizileri görülebilmektedir. Bu çalışmadaki amacımız kliniğimizde 1 yıl içinde uygulanmış olan perkütan dilatasyonel trakeostomi (PDT) olgularını retrospektif olarak analiz etmektir.

Gereç ve Yöntem: Ocak 2019 ile Aralık 2019 yılları arasında Sakarya Eğitim ve Araştırma Hastanesi, Anestezi Yoğun Bakım Ünitesi'nde PDT işlemi uygulanan hastalar incelendi. Her hastanın yaş, cinsiyet, yoğun bakıma yatış tanısı, antikoagülan ilaç kullanımı, APACHE II skoru kaydedildi. Daha sonra trakeostomi açılma günü, gelişen komplikasyonlar, toplam yoğun bakım yatış günü ve hastanın yoğun bakımdan taburculuğu değerlendirildi.

Bulgular: Toplamda 79 hastaya PDT işlemi uygulanmış olduğu saptandı. Hastaların yaş ortalamasının 66,56±17,83 olduğu ve 48 (%60,8)'inin erkek olduğu gözlendi. Hastaların, 25(%31,6)'inin postresüsitasyon sendromu, 17(%21,5)'sinin serebrovasküler olay ve 15(%19)'inin pnömoni tanısı ile yoğun bakıma kabul edildiği gözlendi. Hastaların ortalama APACHE II skorları 24,1±6,2 olup 16(%20,3) hastanın taburcu edildiği saptandı. Hastalara ortanca trakeostomi açılma günü 19,5[12-30] olup hastaların pek çoğunun antikoagülan tedavi aldığı gözlendi. Hastalardan sadece 2 sinde minör 1 inde majör olmak üzere 3(%3,9) hastada gelişen kanama ile ilgili komplikasyon dışında başka komplikasyon gelişmediği saptandı.

Sonuç: Perkütan yolla uygulanan trakeostomi işlemine bağlı ciddi komplikasyonlar gelişebilmektedir. Bizim çalışmamızda PDT işlemi uyguladığımız hastaların 66 (%83,6) tanesi antikoagülan-antiagregan tedavi almasına rağmen postoperatif kanama oranlarının literatüre uygun olarak oldukça az olduğu gözlendi.

Anahtar Kelimeler: Entübasyon, perkütan trakeostomi, yoğun bakım

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INTRODUCTION

Tracheostomy is a method frequently applied in intensive care units due to the indication of prolonged intubation.[1] Laryngeal damage, glottic and subglottic stenosis, and vocal cord paralysis can be seen with prolongation of the intubation period for more than 7 days.[2] With tracheostomy, aspiration of the airways is facilitated, a safe airway is provided, the patient's dryness and opening of the mouth are closed, the patient can be fed by the oral route, patient comfort increases, and airway resistance decreases. Absolute contraindications for percutaneous tracheostomy are cervical instability, coagulopathy, and infection at the surgical site. Relative contraindications are short neck, morbid obesity, minimal neck extension or tracheal deviation, and lung disease that cannot tolerate the apnea period.[3] Early complications of the percutaneous tracheostomy procedure are bleeding, incorrect placement of the tracheostomy tube, and obstruction. Bleeding is usually self-limiting and occurs as a result of the inability to discontinue the use of anticoagulants in intensive care patients.[4]

The tracheostomy procedure has been practiced since the 1930s, and the percutaneous dilatational tracheostomy technique was developed in the 1990s. In our clinic, percutaneous tracheostomy is performed with the technique described by Grigg et al.[5] accompanied by fiberoptic bronchoscopy. Our aim in this study is to retrospectively analyze the percutaneous tracheostomy procedures performed in our clinic in the last three years, and to analyze the success and complications of the procedure.

MATERIAL AND METHOD

Our study is a cross-sectional descriptive study and the approval of Sakarya University Faculty of Medicine Non-interventional Clinical Research Ethics Committee (Date: 09.11.2020, Decision No: 610) was obtained. The data of patients in the Anesthesiology Intensive Care Unit of Sakarya University Training and Research Hospital between January 2019 and December 2019 were analyzed retrospectively.

Inclusion criteria for the study were determined as patients aged 18-80 years who had tracheostomy during hospitalization in the anesthesia intensive care unit. Patients who had a tracheostomy procedure performed by another service or who had a tracheostomy on admission to the intensive care unit were excluded from the study.

Age, gender, diagnosis of intensive care admission, anticoagulant drug use, Acute Physiology, Assessment and Chronic Health Evaluation (APACHE II) score at admission to the intensive care unit were recorded for each patient. Then, the day of tracheostomy opening, the complications of the procedure, the total day of hospitalization in the intensive care unit, and the patient's discharge status from the intensive care unit were recorded. The final state of the patient was evaluated by dividing it into two as discharged and excitus.

Percutaneous dilatational tracheostomy is performed in our clinic with the method described by Grigg et al. in 1990. PDT procedure "Percutaneous tracheostomy kit" (Portex) set was used. The patient's shoulder was supported and the neck was extended. The FiO_2 was set to 100% in the mechanical ventilator, and the patient's peripheral oxygen saturation, blood pressure, and heart rate were closely monitored throughout the procedure. The patient was administered 1-2 mcg/kg fentanyl, 0.1 mg/kg midazolam and 0.6 mg/kg rocuronium. The surgical area was cleaned with an antiseptic solution and covered with perforated green covers. The area to be operated was determined and local anesthetic injection was performed. The intubation tube was pulled to the level of the vocal cord. Then, the fiberoptic bronchoscope was advanced through the intubation tube and the trachea was viewed from the inside throughout the procedure. Stabilizing the trachea with a nondominant hand 1.-2. Or 2.-3. Trachea was entered with a 14 G iv cannula at the appropriate place from the tracheal rings. The location of the needle was confirmed by aspiration of air, and a guide wire was inserted through the cannula. The periphery of the guide wire was dilated by visualizing the inside of the trachea with bronchoscopy. A tracheostomy tube was inserted over the guide and the cuff was inflated. The location of the tracheostomy was confirmed by bronchoscopy.

Statistical Analysis

SPSS 20 package program was used for statistical analysis of the data. Qualitative data were expressed as numbers and percentages. While quantitative data with normal distribution were expressed as mean and standard deviation, data with non-normal distribution were given as median and interquartile range. $p<0.05$ was considered significant.

RESULTS

The data of the patients who were hospitalized in the Anesthesia Intensive Care Unit of Sakarya University Training and Research Hospital between January 2019 and December 2019 were analyzed retrospectively, it was determined that a total of 79 patients underwent percutaneous dilatational tracheostomy. It was observed that 31 (39.2%) of these patients were female, 48 (60.8) were male, and the mean age was 66.56±17.83. When the diagnosis of intensive care hospitalization of the patients was evaluated, it was seen that the majority of them consisted of 25 (31.6%) postcardiopulmonary arrest patients and 17 (21.5%) patients who had had a cerebrovascular accident. Apart from these, 15 (19%) patients due to pneumonia, 9 (11.4%) patients due to trauma, 6 (7.6%) patients due to malignancy, and postoperative 4 (5.1%) patients were followed in the intensive care unit and percutaneous dilatation was performed.

The median value for hospitalization in the intensive care unit was 53.5 [32-121] days, and the patients' admission glaskow coma scale was 5 [3-8]. The mean APACHE score of the

patients was 24.1±6.2, and the expected death rate was found to be as high as 55.3±20.6% on average. When the outcome of intensive care hospitalization of the patients was evaluated, it was seen that the mortality was 63 (79.7%) and only 16 (20.3%) patients were discharged (**Table 1**).

Table 1. Demographic Data of Patients Who Had Percutaneous Dilatational Tracheostomy (n=79)

Age (years)	66.56±17.83
Gender, n(%)	
Female	31 (39.2)
Male	48 (60.8)
Hospitalization diagnosis, n(%)	
Post CPR	25 (31.6)
Cerebrovascular event	17 (21.5)
Pneumonia	15 (19)
Trauma	9 (11.4)
Malignancy	6 (7.6)
Postoperative	4 (5.1)
Other*	3 (3.9)
Intensive care day	53.5 (32-121)
Glasgow coma scale	5 (3-8)
APACHE II score	24.1±6.2
Expected death rate	55.3±20.6
Final state, n(%)	
Excitus	63 (79.7)
Discharge	16 (20.3)

*: neuroleptic malignant syndrome, Chronic renal failure, acute renal failure. Mean±SD, Median [Q1-Q3], n (%).

The PDT procedure was evaluated, it was seen that the median application day was 19.5 [12-30]. INR, PT, APTT and platelet counts, which are among the bleeding parameters evaluated on the day of the procedure, were found to be at normal levels. Before the procedure, 54 (68.4%) of the patients were using enoxaparin, 12 (15.2%) acetylsalicylic acid and 6 (7.6%) clopidogrel. 7 (8.9%) of the patients were not using any anticoagulant. Minor bleeding developed in 2 (2.6%) patients and stopped spontaneously, major bleeding developed in 1 (1.3%) patient, and bleeding control was achieved with surgical cauterization. It was observed that only 1 patient encountered a granulomatous mass during bronchoscopy during the procedure and the procedure was terminated (**Table 2**).

Table 2. Drugs used by the patients, laboratory parameters and complications

Tracheostomy procedure day	19.5 (12-30)
Anticoagulant use, n(%)	
Enoxaparin	54 (68.4)
Acetylsalicylic acid	12 (15.2)
Clopidogrel	6 (7.6)
No	7 (8.9)
INR	1.2 (1-1.2)
PT	14.4±2.7
APTT	28.9 (25-33)
Platelet count	274±121
Complication, n(%)	
Minor Bleeding	2 (2.6)
Major Bleeding	1 (1.3)
Failed operation	1 (1.3)

Mean±SD, Median [Q1-Q3].

DISCUSSION

In our study, we retrospectively analyzed 79 patients who underwent PDT procedure within 1 year. It was observed that the patients had high APACHE scores, expected death rates and ages, and were mostly composed of patients with post-cardiac arrest syndrome. The median PDT day of the patients was 19.5 [12-30], while the total intensive care unit hospitalization day was 53.5 [32-121].

While the bleeding parameters of the patients were found to be normal before the procedure, it was observed that most of them were using anticoagulants. It was found that only 1 (1.3%) of the patients had severe bleeding and 1 (1.3%) of them failed. According to the study conducted by Kırca et al., which included 442 patients, it was determined that the most common complication was early bleeding and its frequency was 1.8%.[6] In an internationally published article, bleeding rates after PDT were found to be even lower (0.6–5.0%).[7] In our study, although 66 (83.6%) of the patients who underwent PDT procedure received anticoagulant-antiaggregant treatment, postoperative bleeding rates were observed to be quite low (1.3%) in accordance with the literature.

PDT is frequently performed in patients hospitalized in the intensive care unit due to the indication of prolonged intubation. Although there is no consensus regarding the application day of the PDT procedure, it is generally recommended to open a tracheostomy for intubations longer than 14 days. Since major complications such as tracheal stenosis and ventilator-associated pneumonia may develop as a result of late tracheostomy opening after prolonged intubation, this period is tried to be kept short.[8,9]

However, this period is longer than expected due to both the process of obtaining consent from the relatives of the patient and the weaning attempts of the patient. In our study, the procedure day of tracheostomy was determined as 19.5 [12-30]. In a study conducted in our country on this subject, the opening day of tracheostomy was reported as 18±8 days, and the authors mentioned similar problems related to the prolongation of the PDT procedure.[10] On this subject, the nationwide PDT procedures performed by Gucyetmez et al, in 2018 were examined, and they reported that although PDT was applied in the 2nd and 3rd weeks of hospitalization, PDT could be applied in 15% of the patients after the 3rd week.[11] In addition, coronary angiography and stenting procedures were applied to the patients who were being followed up in our intensive care unit with the diagnosis of postresuscitation syndrome after myocardial infarction, and patients were using both ASA and clopidogrel. In these patients, the PDT application day was determined to be long, since 30 days could be waited and the PDT procedure could be applied later.

Although bleeding is the most common complication of the tracheostomy procedure, the most feared complication is the development of a tracheoesophageal fistula. In applications performed with fiberoptic bronchoscopy, posterior wall penetration is very rare, since the needle is inserted by

observing the posterior tracheal wall. When the studies reported in the literature were examined, it was reported that complications such as misplacement and airway obstruction were also encountered.[12] However, nowadays, PDT is recommended to be performed with bronchoscopy, and the incidence of mortal complications such as tracheoesophageal rupture has decreased considerably.[13]

There are also applications of PDT accompanied by ultrasonography, and one of the largest studies in the literature on this subject is the TRACHUS study, which included approximately 4,900 patients.[14] In the study, PDT procedures performed under ultrasound guidance and bronchoscopy were examined, and it was concluded that both techniques were not superior to each other. However, ultrasound-guided PDT application is more complex than bronchoscopy-guided application and the learning curve has been found to be wider.[15]

The limitation of our study is that ultrasound was not used in our study.

CONCLUSION

PDT is a procedure that is frequently applied in intensive care units due to its low complication rates and the fact that it can be performed at the bedside without the need for patient transport. Complication rates were further reduced with bronchoscopy-guided application.

ETHICAL DECLARATIONS

Ethics Committee Approval: Approval of Sakarya University Faculty of Medicine Non-interventional Clinical Research Ethics Committee (Date: 09.11.2020, Decision No: 610)

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Orijinal Araştırma / Original Article

Evaluation of Complaints Reflected to Medical Chamber of Bursa Honor Board: 1995-2005

Bursa Tabip Odası Onur Kuruluna Yansıyan Şikayetlerin Değerlendirilmesi: 1995-2005

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Abstract

Aim: To evaluate the complaints in the honor board files of a medical chamber which has an important place in determining the disruptions and violations experienced in the healthcare delivery system.

Material and Method: The study is of cross-sectional type and the files reflected in the Bursa Medical Chamber Honor Board files between the years 1995-2005 were analyzed by archive analysis method.

Results: It was found that 89% of the 121 cases obtained from the 111 files examined consisted of behaviors contrary to Turkish Medical Association Laws/decisions. The reasons for the complaints in the files were listed under three main headings and the Bursa Medical Chamber Administrative Board made the highest number of complaints with 46.3%. It was determined that 67.5% of the physicians who caused the complaint worked in a private institution and 67.6% were specialists. General surgery and gynecology and obstetrics took place in the top 2 places of specialization. A statistically significant relationship was found between the causes of complaints and age. It's found that fines were given at the highest rate. 27 of the 42 files submitted to the Turkish Medical Association High Honor Board are due to complaints of violation of the laws/decisions of Turkish Medical Association.

Conclusion: Evaluation of the complaints reflected in the medical chambers, which have an important place in the disciplinary process, is important for professional ethics and determining the place of deontology and medical ethics in medical education.

Keywords: Medical chamber, honor board, investigation/ prosecution, professional ethics

Öz

Amaç: Sağlık hizmet sunumu sisteminde yaşanan aksaklıkların ve ihlallerin belirlenmesinde tabip odası onur kurulu dosyalarındaki şikayetleri değerlendirmektir.

Gereç ve Yöntem: Çalışma kesitsel tipte olup 1995-2005 yılları arasında Bursa Tabip Odası Onur Kurulu dosyalarına yansıyan şikayetler arşiv inceleme yöntemi ile analiz edilmiştir.

Bulgular: İncelenen 111 dosyadan elde edilen 121 olgunun %89'unun Türk Tabipleri Birliği Yasa/kararlarına aykırı davranışlardan oluştuğu bulunmuştur. Dosyalardaki şikayet nedenleri üç ana başlıkta yer almış ve en fazla şikayeti %46,3 ile Bursa Tabip Odası Yönetim Kurulu yapmıştır. Şikayete neden olan hekimlerin %67,5'inin özel kurumda çalıştığı ve %67,6'sının uzman olduğu saptanmıştır. Uzmanlık alanlarında ilk 2 sırada genel cerrahi ve kadın hastalıkları ve doğum yer almıştır. Şikayet nedenleri ile yaş arasında istatistiksel anlamlı bir ilişki bulunmuştur. Dosyalarda en fazla oranda para cezası verilmiştir. Türk Tabipleri Birliği Yüksek Onur Kurulu'na iletilen 42 dosyanın 27'si Türk Tabipleri Birliği yasa/kararlarına aykırı davranış şikayet nedeniyledir.

Sonuç: Disiplin sürecinde önemli bir yere sahip olan tabip odalarına yansıyan şikayetlerin değerlendirilmesi, hem meslek ahlakı hem de eğitimde deontoloji ve tıp etiğinin yerini belirlemek açısından önemlidir.

Anahtar Kelimeler: Tabip odası, onur kurulu, soruşturma/kovuşturma, meslek ahlakı

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INTRODUCTION

Professional associations began to be established with getting together of professional members to discuss common ideas and problems and the effects of the new scientific thought movement in the 19th century. As in many professions, physicians also started to come together and organize. Following "Cemiyet-i Tıbbiye-i Şahane" (Société Impériale de Médecine de Constantinople), which was established for the first time in 1856 for the acquaintance and solidarity between the physicians of the allied armies in the Ottoman period, the first association established by Turkish physicians in 1867 was "Cemiyet-i Tıbbiye-i Osmaniye".[1-4] The first association that brought together the members of the health team was the Medical Chambers (Etıbba Odaları), which were established in accordance with the 14th article of the law dated 11.04.1928 and numbered 1219. Reasons such as the rapid increase in the number of chamber members, the increase in professional ethics problems and the impropriety in the elections revealed the necessity for the medical chambers to become a union, and a draft regulation was prepared in 1947. In order to "... protect professional deontology and solidarity among physicians and the rights and benefits of profession members…" under constitutional guarantee, it was decided to establish 23 medical chambers at the grand congress of the "Turkish Medical Association (TMA)", which was established on 23.01.1953, and Bursa Medical Chamber (BMC) was the third.[1,5-9]

The Turkish Medical Association (TMA) and Medical Chambers, which work on basic issues such as ensuring professional discipline, investigating patient complaints and determining private wage scales, apply the principles of the disciplinary regulation to investigate the unethical behaviors of physicians during their professional practices and communication with their colleagues and to determine the disciplinary penalties to be imposed.[10] If there is an objection to the decision after the decision given by the Honor Board is notified, the file is forwarded to the TMA High Honor Board (TMA HHB). After reviewing the investigation and prosecution files sent to it, the TMA HHB sends its decision to the Medical Chamber with a re-decision to approve or overturn the decision.

The studies conducted with the complaints/files of the medical chambers, which have an effective mechanism for the protection/observance of the rules of professional ethics, provided important data specific to the city and the region.[11-14] In this context, it is aimed to evaluate the complaints in the Bursa Medical Chamber Honor Board files.

MATERIAL AND METHOD

The study was cross-sectional and retrospective. The files sent to the Honor Board by the BMC Administrative Board between 1995 and 2005 were scanned with the archive analysis method to create the data of the research, and a total of 111 files were evaluated.

The files were classified with the "file evaluation form" created by the researchers and the basic data of the study were obtained. The sociodemographic characteristics of physicians (age, gender, institution/organization where they work, specialty), complainant, cause of complaint, year of complaint, punishment recommended by the honor board, objection to the punishment given, transmission to YOK, decision-making time were questioned and the data set was obtained by querying the form.

The study was approved by the local ethics committee in Uludağ University Faculty of Medicine Medical Research Ethics Committee with a decision number 2005-7/13. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Statistical Analysis: The results were presented as mean±standard deviation or median (minimum-maximum) for continuous variables. Categorical variables were described as frequency and percentage. Shapiro Wilk test was used as normality test. One-way ANOVA and Kruskal Wallis tests were used for comparisons between groups. Pearson Chi-square, Fisher-Freeman-Halton and Fisher's Exact Chi-square tests were used in the analysis of categorical data. In case of significance between the groups, Bonferroni test, one of the multiple comparison tests, was used for pairwise comparisons. A p-value <0.05 was considered as significant. All statistical analyses were performed with IBM SPSS ver.23.0 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.).

RESULTS

A total of 121 cases were evaluated because each physician in the 111 files referred to the BMC Honor Board (BMC HB) between 1995 and 2005 was considered a different case. There were 97 physicians, 89 men and 8 women, in the cases forming the research data. There are 7 files with more than one physician in the files and 13 physicians partaken in more than one file were determined. One of the files is about the BMC Administrative Board, and a total of 120 physicians were evaluated.

It was found that 89.2% (n=107) of the physicians in the cases were male and 10.8% (n=13) were female; the average age of male physicians was 41.5±9.7 years, and 48.7±18.2 of female physicians. Considering the cases with workplaces, 32.5% (n=38) were in public institutions and 67.5% (n=79) were in the private sector; 67.6% (n=75) of the physicians were determined as specialists and 32.4% (n=36) as general practitioners. Of 28 (37.3%) physicians have a specialty in internal sciences and 47 (62.7%) in surgical sciences (**Table 1**). While there was no statistically significant difference between the areas of specialization and the gender distribution, a statistically significant difference was found between the gender distributions according to the workplaces. While there was no statistical significance between the areas of specialization and the gender distribution, a statistically significant difference

was found between the gender distributions according to the workplaces (p=0.009, **Table 2**). It was determined that the reason for this significant difference was that all of the female physicians included in the complaint files were working in the private sector.

Table 1. Distribution of physicians in the files according to their specialties

	Specialties	n	%
Surgical sciences	General surgery	11	14.7
	Gynecology and obstetrics	11	14.7
	Cardiovascular surgery	7	9.3
	Otorhinolaryngology	6	8
	Ophthalmology	4	5.3
	Urology	2	2.7
	Orthopedics and traumatology	2	2.7
	Plastic and reconstructive surgery	2	2.7
	Neurosurgery	1	1.3
	Anesthesiology	1	1.3
Internal medicine	Pediatrics	5	6.7
	Internal diseases	4	5.3
	Cardiology	4	5.3
	Microbiology and infectious diseases	3	4
	Radiology	3	4
	Dermatology	3	4
	Public health	2	2.7
	Radiation oncology	1	1.3
	Physical medicine and rehabilitation	1	1.3
	Psychiatry	1	1.3
	Rheumatology	1	1.3

Table 2. Distribution of occupational characteristics by gender

		Male (n - %)	Female (n - %)	p
Specialty	Internal medicine	26 (25%)	2 (28.6%)	1.000
	Surgical sciences	44 (42.3%)	3 (42.9%)	
	General practitioner	34 (32.7%)	2 (28.6%)	
Work	Public	38 (36.2%)	0 (0%)	0.009
	Special	67 (63.8%)	12 (100%)	

When the complainants in the files were examined, it was determined that the BMC Administrative Board (46.3%, n=56) and physicians (20.7%, n=25) made the most complaints (**Figure 1**).

The causes of complaints in the determined cases are classified under 3 main headings: Behaviors contrary to the TMA Law/decisions, behaviors contrary to deontology and behaviors contrary to medical ethics. The cases were mostly included under the heading of behaviors contrary to the TMA Law/decisions (**Figure 2**). It was observed that, the highest rate of "promotion for advertising purposes" (40.5%) under the heading of acts contrary to the TMA Law/decisions; "behaving humiliating a colleague" (2.5%) under the title of behaviors contrary to deontology and "medical error and negligence" (5%) under the title of behaviors contrary to medical ethics (**Table 3**).

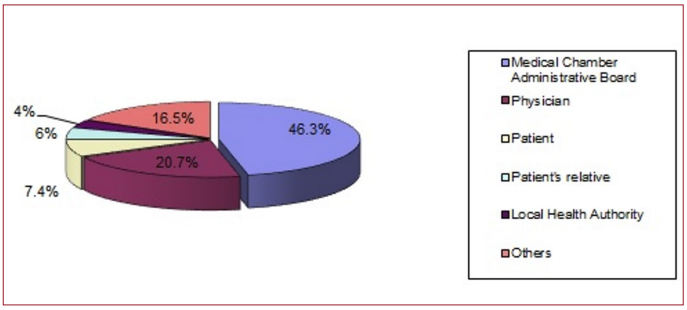

Figure 1. Complainants in cases

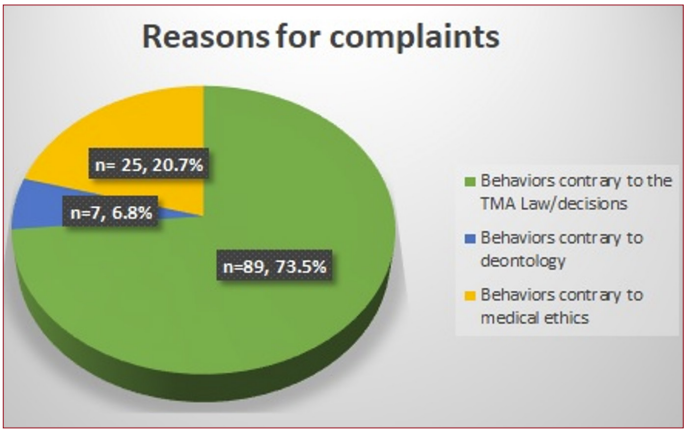

Figure 2. Reasons for complaints

Table 3. Distribution of the causes of complaints in the files of BMC Honor Board

Causes of complaints		n	%
Behaviors contrary to the Turkish Medical Association Law/ decisions	Not to pay membership fee	11	9.1
	Not to register / notice to the medical chamber	7	5.8
	Not meeting the requirements as occupational physician	4	3.3
	Making promotion for advertising purposes	49	40.5
	Working below the minimum examination fee	16	13.2
	Making signboard irregularities	2	1.7
	Writing irregular prescription	2	1.7
Behaviors contrary to deontology	Behaving humiliating a colleague	3	2.5
	Offending the dignity of medical profession	1	0.8
Behaviors contrary to medical ethics	Not showing respect for life and health	2	1.7
	Medical error and negligence	6	5
	Lack of knowledge and skills in the profession	4	3.3
	Unprofessional activities	4	3.3
	Illegal termination of pregnancy	2	1.7
	Unfair advantage	4	3.3
	Allowing illegal medical intervention	1	0.8
	Preparing false documents	1	0.8
	Revealing patient's secret	1	0.8
	Writing green' prescription for misconduct	1	0.8

When the distribution of the complaints in the cases according to the years was examined, it was found that the most complaints were between 1995 and 1999. While there was no statistically significant difference between the causes of complaints and the year distribution, it was found that the most complaints between 1995 and 1999 were behaviors contrary to the TMA Law/decisions (**Figure 3**). When the causes of complaints were examined in terms of sociodemographic characteristics, there was no statistically significant difference between gender, specialty and workplace, while the mean age of the physicians who acts contrary to the TMA Law/decisions was (39.5±8.6 years) significantly lower than the physicians who behaves contrary to deontology (51.2±12.4 years) and physicians who behaviors contrary to medical ethics (46.7±11.9 years) (p=0.001).

When the complainants and the causes of complaints were examined, it was found that the BMC Administrative Board (89.3%) and physicians (72%) complained about the behavior contrary to the TMA law / decisions, while the patients and patients' relatives (93.3%) complained about the behavior of the physicians contrary to medical ethics (p=0.001, **Table 4**). When the BMC HB decisions are examined, it is seen that 94.4% (n=68) of the physicians who were complained for behaviors contrary to the TMA Law/decisions received fines; 18.2% (n=2) of the physicians who were complained for behaviors contrary to deontology received a warning penalty; 58.4% (n=6) of the physicians who were complained for behaviors contrary to medical ethics were not deemed necessary to be punished (p<0.001). When 42 cases transmitted to TMA HHB were examined, it was seen that 81.8% (n=27) of the files forwarded with the physician's objection against decision were due to behaviors contrary to the TMA Law/decisions (p=0.005). It was determined that 51.3% (n=20) of the cases transmitted to TMA HHB ended with a fine (p=0.048).

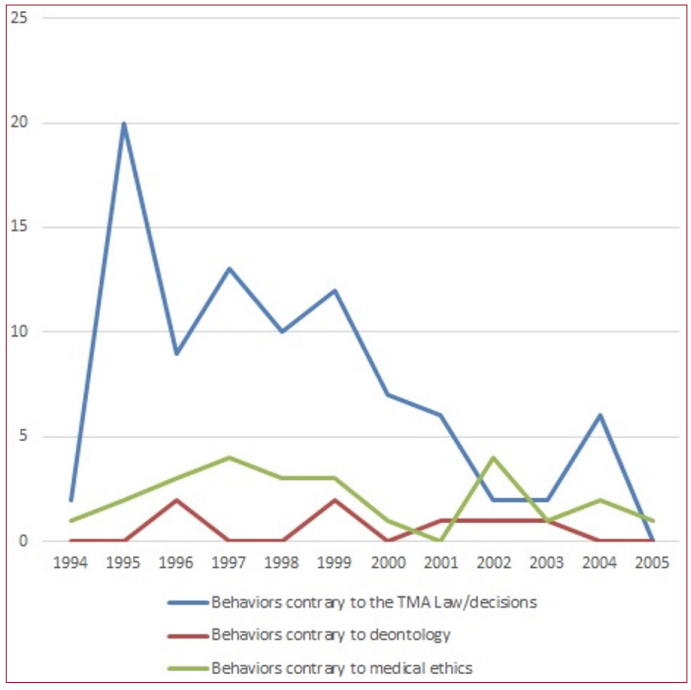

Figure 3. Reasons for complaints by year

Table 4. Distribution of complaints according to the general characteristics of the cases

		Behaviors contrary to the Turkish Medical Association Law/decisions	Behaviors contrary to deontology	Behaviors contrary to medical ethics	p
Complainant	Medical Chamber	50 (89.3%)	2 (3.6%)	4 (7.1%)	<0.001
	Physician	18 (72%)	3 (12%)	4 (16%)	
	Patient and relatives	1 (6.7%)	-	14 (93.3%)	
	Other	20 (80%)	2 (8%)	3 (12%)	
Penalty	No need	11 (44%)	2 (8%)	12 (48%)	<0.001
	Warning	6 (66.7%)	2 (22.2%)	1 (11.1%)	
	Fines	65 (94.2%)	2 (2.9%)	2 (2.9%)	
	Banned from profession	6 (50%)	-	6 (50%)	
Decision of Honor Board	No need	8 (33.3%)	2 (8.3%)	14 (58.4%)	<0.001
	Warning	6 (54.5%)	2 (18.2%)	3 (27.3%)	
	Fines	68 (94.4%)	2 (2.8%)	2 (2.8%)	
	Banned from profession	6 (54.5%)	-	5 (45.5%)	
Transmission to High Honor Board	Transmitted	30 (71.4%)	2 (4.8%)	10 (23.8%)	0.788
	Untransmitted	59 (74.7%)	5 (6.3%)	15 (19%)	
Reasons for transmission to High Honor Board	Physician objection	27 (81.8%)	2 (6.1%)	4 (12.1%)	0.005
	Other	3 (33.3%)	-	6 (66.7%)	
Decision of High Honor Board	Approval	21 (75%)	2 (7.1%)	5 (17.9%)	0.816
	Reversal	7 (70%)	-	3 (30%)	

Descriptive statistics are given as frequency (n) and percentage (%).

The total decisional time of the BMC HB was between 6.5 (1-71.5) months. The decision periods of the cases complained for the behaviors contrary to the TMA Law / decisions 5 (1-71.5 months) was determined to be more than the decision periods of behaviors contrary to deontology 9.5 (3.5-21.5 months) and the behaviors contrary to medical ethics 9.5 (1.5-24.5 months). When the decision periods were examined in terms of penalties, it was determined that the decision periods were less in cases where warning penalties 6.5 (1.5–9.5 months) were given than the decision periods in cases where money 4.5 (1–71.5 months) and ban from profession 10.75 (4.5–33.5 months) penalties were given (p=0.001).

When BMC HB decisions and TMA HHB decisions were examined in cases in terms of the reasons for transmitted to TMA HHB, it was found that there was a physician objection with a rate of 95.8% (n=23) in cases where fines were given (p<0.001, **Table 5**). 92.9% of TMA HHB decisions in the cases submitted with a physician's objection were approved by TMA HHB (p=0.008). When the approved decisions were examined, it was determined that 100% (n=10) of the decisions were approved for being banned from the profession; 70.8% (n=17) of the decisions were approved for fine and 50% (n=1) of the decisions were approved for warning (p=0.001).

Table 5. Reasons for transmission to High Honor Board according to the decisions of BMC HB and TMA HHB

		Reasons for transmission to High Honor Board		p
		Physician objection	Other	
Decision of Bursa Medical Chamber Honor Board	No need	-	5 (100%)	<0.001
	Warning	2 (66.7%)	1 (33.3%)	
	Fines	23 (95.8%)	1 (4.2%)	
	Banned from profession	8 (80%)	2 (20%)	
Decision of Turkish Medical Association High Honor Board	Approval	26 (92.9%)	2 (7.1%)	0.008
	Reversal	5 (50%)	5 (50%)	

Descriptive statistics are given as frequency (n) and percentage (%).

DISCUSSION

The medical chamber is a professional association authorized to evaluate the behavior of physicians practicing their profession in violation professional law, morality and/or ethics and to impose disciplinary punishments if necessary.[9,10,15] In addition to the studies conducted in the medical chambers in which the investigation and prosecution files were examined[7,12-14,16] the violations in the files discussed at the Supreme Health Council and the TMA HH[11,17-22] were also investigated. This study was planned to examine the files of the honor board of the medical chamber in Bursa, the fourth largest city of Turkey.

It was found that the vast majority of the physicians who complained were specialists (n=75, 67.6%). It was considered that this is due to the fact that specialist physicians can work in public institutions, as well as private hospitals, polyclinics and private practice. In addition, the fact that public employees did not have to register in the chamber may explain the excess in the number of specialist physicians. General surgery and obstetrics and gynecology took priority in their areas of expertise, and this result is in line with other studies.[7,11,12,16,17,20-24] The reasons for the high rate in two areas could be intervention in the body, consequences that may affect the quality of life, openness to possible complications and errors, etc.

When the files were evaluated in terms of the complainants, a high rate of the administrative board (46.3%) was found in parallel with the other studies.[11,12,14] Although it was seen that the complaints of patients and their relatives started to increase in the studies conducted by Civaner,[12] Öztürk et al.[13] and Akyol et al.[14] the complaints of the patients and their relatives were very few in our study. Even though it was predicted that patient complaints would increase with the right of complaint (Art. 42) defined by "Patient Rights Regulation"[25] in 1998, other studies also found higher rates of medical chamber complaints, as in our study. It was thought that this situation was caused by reasons such as the patients' lack of awareness of complaints, the fact that the disciplinary process of the physicians working in the public sector is carried out independently of the medical chambers, and the medical chambers are considered secondary in violations of medical ethics. Although the complaints were expected to increase with the "Patient Rights Regulation", the distribution between years was also inconsistent with the difference between the years investigated in other studies.[7-10]

Considering the reasons for complaints in the files, behaviors contrary to TMA Laws/decisions are seen in the first place (73.5%). This result is consistent with the studies conducted by Civaner et al.[11], Öztürk et al.[13] and Akyol et al.[14] Under this main heading it was found that "promotion for advertising purposes" ranked as 40.5% and this result was also found to be compatible with other studies.[7,12,14] Reasons such as increasing competition with the number of physicians, not knowing what to pay attention to when preparing signage to reach more patients could be the reasons for this high rate.[7,26,27]

In the statistical analysis between the causes of complaints and age, it was found that the physicians who exhibited behaviors contrary to the TTB Laws/decisions were younger and the physicians who exhibited behaviors contrary to medical ethics were older (p=0.001). This could be considered as the fact that physicians who have just started their profession do not know enough about the legislation, while elderly physicians do not have courses on medical ethics during their education.

Considering the penalties according to the reasons for the complaint, it was found that 94.4% of them were imposed

fine for the behaviors contrary to the TMA Law/decisions. Due to the physician's objection to the punishment given, the decision was forwarded to TMA HHB and it was concluded that all of the approved files were fines. Of the 42 files forwarded TMA HHB, 81.8% were because of the behaviors to the TMA Laws/decisions and 51.3% of them were fined. While this result reached the same result as the study conducted by Akyol et al.[14] it was seen that the most common punishment for being banned from the profession in the study conducted by Civaner et al.[11]

Considering the completion/determination periods of the reviewed files, it was seen that notification was generally made within 1-71.5 months. Considering the reasons for the complaint, it was found that the files investigated for the longest period of time due to the behaviors contrary to the TMA Laws/decisions; considering the punishment given, it was found that the longest period was in fines. This statistically significant result is in parallel with the results of Civaner et al.[11]

CONCLUSION

Institutions such as medical chambers, Local Health Authorities, Institution of Forensic Medicine, Supreme Health Council play an important role in the investigation/ prosecution of problems encountered in professional practices. Among these institutions, medical chambers can reach a decision on the physicians who are the subject of the complaint by conducting investigations / prosecutions within the framework of the authorities granted to them by law.[9,10] There are studies in which physicians were complained in different cities, the reasons for the complaints and the punishments given are studied.[7,11-14,16-22] In particular, the fact that physicians working in public institutions do not have to be members of the medical chamber and that not every complaint goes to the honor boards is an important limitation in making a comment in general.

As shown by the files analyzed and supported by other studies, it seems that the vast majority of physicians who cause complaints are investigated and mostly fined for behaviors contrary to TMA Laws/decisions and behaviors contrary to deontology. This result is mostly seen due to the physicians' ignorance of the legislation. However, the fact that physicians' ignorance of the legislation is not accepted as an excuse reveals the necessity of knowing the responsibilities of physicians and shows the importance of deontology and medical ethics education in pre- and post-graduate education.

Examining the investigation/prosecution files is an important resource both in discussing the effectiveness of medical chambers and in determining where physicians make the most mistakes. For this reason, conducting such researches and conducting discussions in different media will be the leading criteria in terms of making updates in the education and practice of the medical profession.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Uludağ University Faculty of Medicine Medical Research Ethics Committee (Number: 2005-7/13).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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Orijinal Araştırma / Original Article

COVID-19 Vaccine from the Perspective of University Students: Where Are We in Regards to Vaccine Decision-Making?

Üniversite Öğrencilerinin Gözünden COVID-19 Aşısı: Aşı Karar Verme Konusunda Neredeyiz?

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Abstract

Aim: Reactions against vaccines developed to combat COVID-19 are rising in all countries. Therefore, it is important to evaluate the opinions in regards to the vaccine in order to develop a positive perspective by identifying the negative opinions. This study was conducted to determine university students' attitudes towards the COVID-19 vaccine.

Material and Method: This research was conducted as a cross-sectional study with university students studying at the Health Programs Campus of Cappadocia University in the Province of Nevşehir. In this context, study data were collected from a total of 332 students to reach power of 99% based on the known sample calculation.

Results: 51.2% of the participants (n=170) in this study were between the ages of 18-20; 69.3% (n=230) were females; 24.1% (n=80) were students in Medical Laboratory Techniques Program and 52.4% (n=174) were 2nd year students. According to the results, 53.9% (n=179) of the participants believed that they could easily recover when they got sick and 76.6% of the participants (n=254) stated that they were worried about the side effects of the vaccine. Participants' total mean score from the attitudes towards the COVID-19 Vaccine Scale was found to be 3.18±0.76.

Conclusion: Students were found to have a positive attitude towards the vaccine, but they still had some concerns. It is proposed to design further comprehensive studies to eliminate students' concerns, to explain the effectiveness of the vaccine in a transparent way and to better understand the reasons underlying the vaccine hesitancy.

Keywords: Vaccine hesitancy, COVID-19, Turkey, university students, attitude

Öz

Amaç: COVID-19 ile mücadele için geliştirilen aşılara karşı tepkiler tüm ülkelerde artmaktadır. Bu nedenle aşı ile ilgili görüşlerin değerlendirilmesi, olumsuz görüşlerin tespit edilerek olumlu bir bakış açısının geliştirilmesi açısından önemlidir. Bu çalışma üniversite öğrencilerinin COVID-19 aşısına yönelik tutumlarını belirlemek amacıyla yapılmıştır.

Gereç ve Yöntem: Bu araştırma, Kapadokya Üniversitesi Nevşehir ilinde yer alan sağlık programları yerleşkesinde öğrenim gören üniversite öğrencileri ile gerçekleştirilmiştir. Araştırma kesitsel tipte bir çalışmadır. Bu kapsamda, evreni bilinen örneklem hesaplamasına dayalı olarak %99 güce ulaşmak için toplam 332 öğrenciye ulaşılarak çalışma verileri toplanmıştır.

Bulgular: Katılımcıların %51,2'sinin (n=170) 18-20 yaş arasında; %69,3'ünün (n=230) kadın, %24,1'inin (n=80) tıbbi laboratuar teknikleri programı öğrencisi olduğu ve %52,4'ünün (n=174) 2. sınıf öğrencisi olduğu tespit edilmiştir. Elde edilen sonuçlara göre, katılımcıların %53,9'u (n=179) hastalandıklarında kolayca iyileşebileceklerine inanırken, %76,6'sı (n=254) aşının yan etkilerinden endişe duyduğunu belirtmiştir. Katılımcıların COVID-19 Aşı Ölçeğine yönelik tutum ölçeğinden aldıkları toplam puan ortalamaları 3,18±0,76 olarak bulunmuştur.

Sonuç: Çalışmamızda öğrencilerin aşıya karşı olumlu bir tutum içinde oldukları tespit edilmiştir ancak yine de bazı endişeleri olduğu belirlenmiştir. Öğrencilerin endişelerini gidermek, aşının etkinliğini şeffaf bir şekilde açıklamak ve aşı tereddütlerinin altında yatan sebepleri daha iyi anlamak için daha kapsamlı çalışmaların tasarlanması önerilmektedir.

Anahtar Kelimeler: Aşı tereddütü, COVID-19, Türkiye, üniversite öğrencileri, tutum

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INTRODUCTION

Coronavirus Disease 2019 (COVID-19) outbreak, which first originated in the Wuhan province of China and identified as of January 2020, has affected the whole world in as little as three months. Due its rapid global spread, the World Health Organization (WHO) declared COVID-19 as a pandemic, which means global epidemic.[1] At the same time, the first COVID-19 case was confirmed in Turkey on this date.[2] Coronavirus is known to be transmitted through small infected droplets when people speak, sneeze or cough.[2,3] Since the virus can be transmitted so easily, all countries of the world experienced negative socio-economic and psychological effects during 2020, nearly 2.5 million deaths occurred, and as a result of COVID-19 induced depletion of healthcare systems, many countries were devastated by the crushing effects of the COVID-19 pandemic was.[1]

The most important means that can be used to control the ongoing COVID-19 pandemic is finding the effective vaccine(s) that can help reduce transmission and the demand for hospitalization and intensive care.[4] The development of the COVID-19 vaccines has been given a worldwide priority, as no effective drugs have been approved for satisfactory prevention and treatment of the disease. To date, a large number of COVID-19 vaccines are in the process of rapid development worldwide, with thirteen candidates in Phase 3 trials and 52 of these studies have been tested in clinical trials and 162 have been tested in preclinical evaluation.[5]

While all this was happening, anti-vaccine conspiracy theories spread through social media claiming that the virus was man-made and that people would be controlled by the microchips inserted into the vaccines have affected individuals' attitudes towards vaccines resulting in vaccine hesitancy.[6] In addition, vaccine hesitancy is also experienced due to rapid production process of vaccines, lack of knowledge in regards to their side effects and holding some of the vaccines that were in phase 3 due to reported side effects.[7,8] The term vaccine hesitancy is used to describe refusal or unwillingness to accept vaccination despite the availability of vaccination services.[9]

This study evaluated the attitudes of university students studying in health services programs in Nevşehir towards COVID-19 vaccines. The research aimed to the health awareness that would be formed by understanding students' perspective regarding the COVID-19 vaccine.

MATERIAL AND METHOD

Type of Research

The research was designed as a cross-sectional study to identify students' attitudes towards COVID-19 vaccine.

Research universe and sample

The research was carried out with students studying at Cappadocia University, Voccational Programs Campus in Nevsehir Province. The target universe of the study consisted of 2409 students (1412 female) studying in the health programs of Cappadocia University, Cappadocia University Vocational College during 2020-2021 academic year. In this context, a total of 332 students were reached to ensure a power ratio of 99% as a result of the sample calculation with a known universe.

Data Collection Tools

Data collection tools used in this study included a 4-item Personal Information Form developed by the researchers to assess participants' socio-demographic characteristics, a 5-item COVID-19 information form and a 9-item Attitudes towards the COVID-19 Vaccine Scale, developed by Geniş et al.[10]

Attitudes towards the COVID-19 Vaccine Scale includes 9 items and has two sub-dimensions (positive and negative attitude). Statements in the scale are rated with a 5-point Likert form: "Definitely disagree (1)", "Disagree (2)", "Undecided (3)", "Agree (4)" and "Strongly agree (5)".[10]

Items in the negative attitude sub-dimensions are scored in reverse. A value between 1-5 is obtained by dividing the total score obtained by the sum of the item scores in the scale sub-dimension by the number of items in that sub-dimension. High scores from the positive attitude sub-dimension indicate positive attitudes towards vaccination. The items in the negative attitude sub-dimension are calculated after they are reversed and the higher scores in this sub-dimension indicate less negative attitudes towards vaccination.[10]

Data Collection Method

Online data collection forms (Google Form) were sent via WhatsApp to the students who agreed to participate in the study. Via the link sent on WhatsApp, students accessed the form in the period of February 1-28, 2021. Each questionnaire took approximately 10 minutes to answer. The data were collected anonymously and confidentially and when the target number of participants was reached, further responses were enabled.

Data Analysis

SPSS 27.0 program was used in the analysis of the data. The suitability of the variables to normal distribution was evaluated with the Kolmogorov Smirnov test and statistical significance was accepted as $p<0.05$. Number, percentage, mean and standard deviation criteria were used in the evaluation of the data. Chi-square ($\chi 2$) test was employed to analyze the relationships between categorical variables

And Mann-Whitney U and Kruskal Wallis tests were performed for continuous variables (age, education level) by using the mean and standard deviation (SD) calculations.

When the reliability of the scale used in the study was examined, it was found to be 0.838 for the scale in general, indicating that the scale has a good level of reliability. Cronbach Alpha values greater than 0.60 point to reliability.[11]

Ethical Considerations

This study was approved by Cappadocia University Research Ethics Committee (Decision number: 2021.46, Date: 04.01.2021). Participation in the study was voluntary and an informed consent form was included in the introduction of the online questionnaire. All data were kept confidential.

RESULTS

Findings Regarding Participants' Socio-Demographic Characteristics

51.2% of the participants (n=170) in the study were between the ages of 18-20, 69.3% (n=230) were females, 24.1% (n=80) were students in the Medical Laboratory Techniques Program and 52.4% (n=174) were 2nd year students. 90.7% of the participants (n=301) did not have a chronic disease, 82.8% (n=275) were not infected by COVID-19 and 66.3% (n=220) had no relatives infected with COVID-19 in their families (**Table 1**).

Table 1. Distribution of the descriptive data of the participants (n=332)

Socio-Demographic Characteristics		Number (n)	Percent (%)
Age	18-20 age	170	51.2
	21-24 age	149	44.2
	25-30 age	13	3.9
Gender	Females	230	69.3
	Males	102	30.7
Educational program	Mouth and dental health	52	15.7
	Operating Room Services	28	8.4
	Audiometry	26	7.8
	First and Immediate Aid	41	12.3
	Medical Laboratory Techniques	80	24.1
	Pathology Laboratory Techniques	57	17.2
	Radiotherapy	48	14.5
Education level	1st Class	158	47.6
	2nd Class	174	52.4
Chronic illness	Yes	31	9.3
	No	301	90.7
Have you had COVID-19?	Yes	57	17.2
	No	275	82.8
Has anyone in your family had COVID-19	Yes	112	33.7
	No	220	66.3
How would you evaluate your general health status?	Very good	119	35.8
	Good	155	46.7
	Middle	43	13.0
	Bad	15	4.5

46.7% of the participants (n=155) reported their general health status as "good". 53.9% (n=179) of the participants stated that they agreed with the statement "I believe I will get over it lightly if I get sick" for the item which presented some statements about COVID-19 (**Figure 1**).

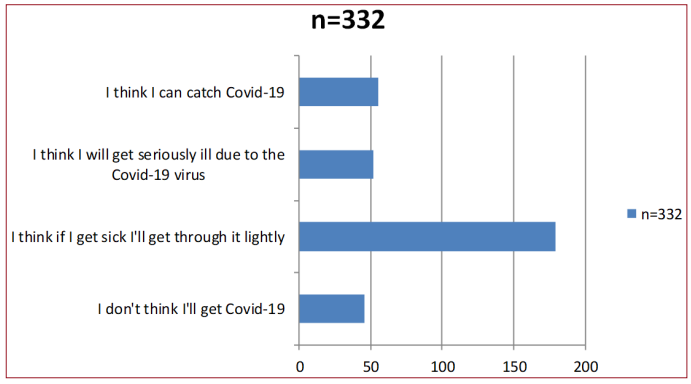

Figure 1. Participants' attitudes towards COVID-19 (n=332)

17.2% (n=57) of the participants accepted that they had COVID-19 disease and 71.9% (n=41) of them responded positively to the statement that I would like to have the vaccine to be developed/developed for this disease at the first opportunity.

76.6% (n=254) of the participants emitted that they were concerned about the side effects of the vaccine, 66% (n=219) about the content of the vaccines, and 64.5% (n=214) about the effectiveness of the vaccine. 62.3% (n=207) emitted that they were concerned about the reliability of the vaccine tests (**Figure 2**).

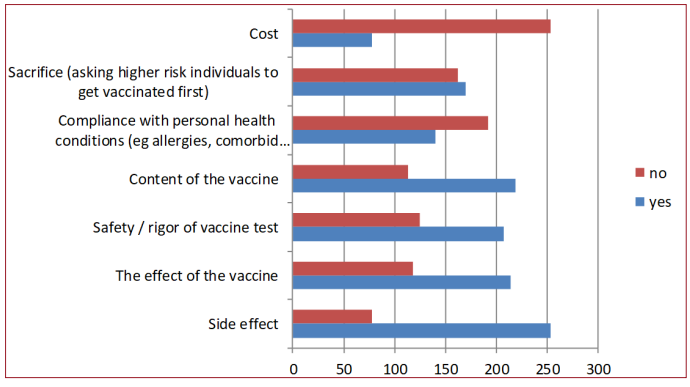

Figure 2. Distribution of participants' concerns about vaccination (n=332)

34.6% (n=115) of the participants were found to be undecided about the item "I think everybody should have the vaccine to be developed/developed for this disease", while 14.5% (n=48) said they definitely agreed with this statement. Evaluation of participants' attitudes towards the COVID-19 vaccine is given in **Figure 3** and **Table 2** presents the Cronbach Alpha values of the scale used in this study.

Table 2. Reliability Analysis of Attitudes towards Covid-19 Vaccine Scale and Its Sub-Dimensions

Scale and Sub-Dimensions	Chronbach Alfa
Positive Attitude	0.918
Negative Attitude	0.813
Total Scale	0.838

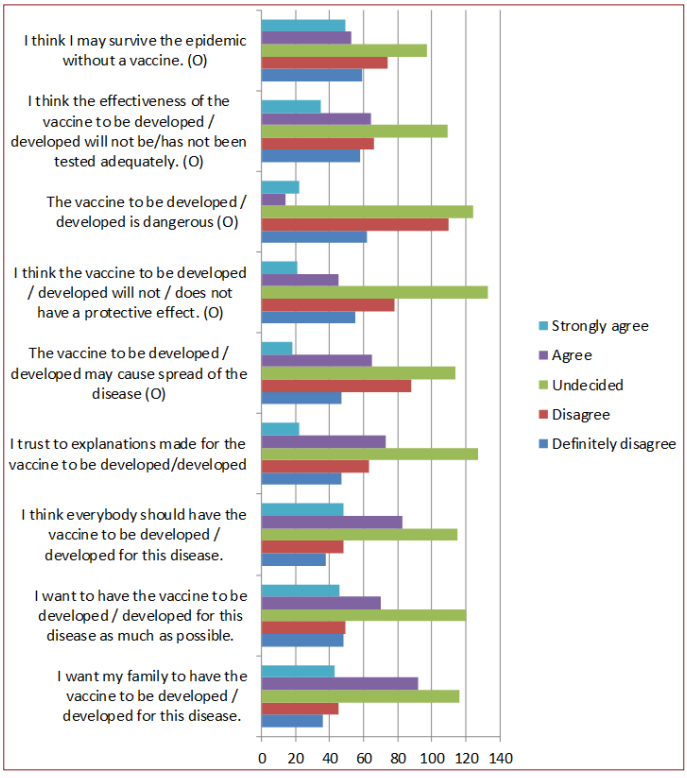

Figure 3. Attitudes of Participants towards COVID-19 Vaccine (n=332)
O: Opposite Item

Participants' total mean score from the Attitudes towards COVID-19 Vaccine Scale was found to be 3.18±0.76. Participants had a positive attitude subscale mean of 3.07±1.04 and a negative subscale mean of 3.26±0.87. This result shows that the participants had a positive attitude towards the COVID-19 vaccine.

The distribution of the data was evaluated with the Kolmogorov Simirnov test and it was identified that the data were not normally distributed (p=0.00). Mann Whitney U and Kruskal Wallis tests were used to compare scale mean scores with independent variables. A significant difference was found between the participants' departments and their scale scores (p<0.05). The difference between the groups was evaluated by the K-Independent Sample test (**Table 3**).

Radiotherapy-Operating Room (T=72.970) and Oral Dental Health-Operating Room (T=72.804) was found to cause the difference which was statistically significant (p=0.01).

DISCUSSION

The attitude of the society towards the COVID-19 vaccine can significantly affect the course of the pandemic.[12] Vaccine hesitancy and negative attitudes towards the vaccine can make it difficult to control the pandemic. Understanding the attitudes, concerns and views of university students towards the COVID-19 vaccine is important for developing an appropriate strategy for controlling the pandemic.[13,14] There are studies in the literature that examined university students' views.[13-15] This study is the first study evaluating the attitudes of health program students towards vaccination in our province.

Studies conducted with university students in different countries examining vaccine hesitancy during the pandemic demonstrated difficulties in decision-making, albeit at different levels. Barello, et al.[12] reported that 13.9% of university students in Italy (n=102) experienced vaccine hesitancy, Grech and Gauci16 found that 23.8% of university students in Malta experienced vaccine hesitancy and another study conducted with university students in Egypt by Saied

Table 3. Comparison of Independent Variables with Scale Scores

Variables	Min	Max	Median	U	p
Gender					
Female (n=230)	1	5	3.11	10476.500	0.120
Male (n=102)	1.22	4.89	3.16		
Education level					
1st Class (158)	1	5	3.11	13328.500	0.633
2nd Class (174)	1	4.89	3.22		
Educational program					
Mouth and Dental Health (n=52)	1.44	4.89	3.00	KW	p
Operating Room Services (n=28)	1.67	4.89	3.66		
Audiometry (n=26)	1.67	4.78	3.44		
First and Immediate Aid (n=41)	1.22	4.78	3.44	18.986	0.004*
Medical Laboratory Techniques (n=80)	1.28	4.76	3.16		
Pathology Laboratory Techniques (n=57)	1.21	4.67	3.22		
Radiotherapy (n=48)	1.22	4.78	2.89		
Age				KW	p
18-20 age (n=170)	1.67	4.89	3.16		
21-24 age (n=149)	2.66	4.79	3.11	0.249	0.883
25-30 age (n=13)	2.67	4.44	3.11		

U= Mann-Whitney U ; KW= Kruskal Wallis, * p<0.05

et al.[13] reported that 46.1% of the participants (n=507) also experienced vaccine hesitancy.

Studies in the literature that presented positive attitudes towards the COVID-19 vaccine addressed vaccine hesitancy as well. In a study conducted with Ethiopian university students determined that 69.3% (n=293) of the students had a positive attitude, although they had hesitations about the vaccine.[17] In this study, the mean scale scores received by the students (3.18±0.76) showed that the students had a positive attitude in general, but also revealed their hesitation. 36.1% of the participants (n=120) were undecided about the statement "I want to have the vaccine to be developed/developed for this disease at the first opportunity" included in the scale that assessed attitudes towards vaccination. This result may be related to the fact that the COVID-19 epidemic has peaked in different periods and at different times in each country due to the different prevention, treatment and vaccination policies of each country. The assessment of the population immunity level required to limit the spread of the pathogen depends on the basic reproduction number of that infectious disease agent.[18]

The most recent estimates of COVID-19 point to the fact that 60-75% immunized individuals are required to stop the spread of the virus in the community.[19-21] However, according to the results in this study, 13.9% of the participants (n=46) surprisingly did not think they would get Covid-19, while 53.9% (n=179) reported that they thought they would get over it lightly if they ever got sick.

WHO Strategic Advisory Group of Experts (SAGE) categorized the reasons for vaccine hesitancy and rejection as follows: (1) Contextual influences: historical, socio-cultural, environmental, institutional, economic or political factors. (2) Individual and group influences: personal beliefs and attitudes about previous experiences with prevention or vaccines. (3) Vaccine/vaccination specific issues: concerns about a new vaccine formulation, administration or node of administration.9 The literature also includes results supporting these groupings. In their study, Lucia et al.[22] reported that concerns about the serious side effects of the vaccine and lack of information resulted in vaccine hesitancy. Similarly, Tam et al.[23] concluded that negative circumstances such as long-term side effects, safety problems and distrust to vaccines caused vaccine hesitancy for COVID-19 vaccine. Saied et al.[13] found that 96.8% of university students (n=2065) had concerns about the side effects of the vaccine, 93.2% (n=1988) worried about the ineffectiveness of the vaccine, 80.2% (n=1711) had concerns about lack of testing in regards to the vaccine and 54.0% (n=1151) were concerned about the safety of the vaccine. Another study conducted that examined COVID-19 vaccine hesitancy with 237 university students reported the first three concerns about the vaccine as safety (37%, n=88), efficacy (24%, n=57) and limited information (16%, n=38).[24] This study the participants' concerns about the vaccine in the present study were listed, it was seen that 76.6% (n=254) were worried about side effects, 64.5% (n=214) about the efficacy of the vaccine and 62.3% (n=219) about the reliability of the tests in regards to the vaccine tests. Supporting the literature, this finding shows that the most intense concern about the COVID-19 vaccine was related to side effects. Most vaccines have side effects and since COVID-19 vaccines are new, additional side effects other than those identified in clinical trials are unknown. This fear is understandable and common. For this reason, ensuring transparency in the information provided about COVID-19 vaccines is extremely important not only in terms of vaccine effectiveness but also in terms of side effects. The foundation of vaccine acceptance is public trust, that is, trust in vaccines and vaccine manufacturers.[25] We know that the most effective way to get rid of the epidemic is through vaccination and in line with our findings, we argue that vaccine hesitancy can be reduced by supporting university students' analytical thinking via trainings that increase their health awareness and by addressing specific concerns about vaccines via provision of accurate information from the right people.

Stanley Plotkin, the author of the book "Vaccines", regarded as a bedside book by the people working in the field of vaccines and infections, says that "with the exception of safe water, the most important invention in humanity's fight against diseases, including antibiotics, has been vaccines".[26] However, in this study, it is quite striking that 40.1% of the participants (n=133) were undecided about the statement that the vaccine to be developed/developed will not/does not have a protective effect. This perspective may be related to the fact that there was only one vaccine (inactivated vaccine candidate against COVID-19 –CoronaVac- produced by Sinovac) administered in Turkey at the time of this study. Thereupon, speculations on social media and televisions also increased the confusion of public. It is also believed that types of vaccines may affect people's attitude towards vaccination. Today, it can be seen from the COVID-19 Vaccination Information Platform in Turkey that Turkish people are reluctant to get vaccinated, just like the participants in this study.[27]

Vaccine cost also appear to be the main factor for accepting vaccination.[28] A study conducted on college students in South Carolina reported that vaccination costs were one of the factors that directly affected students' vaccination behavior.[23] In our study, the ratio of the participants considering the cost in regards to vaccines was found to be 23.5% (n=78).

Supporting the literature, the current study found that the participants' attitudes towards vaccination did not differ according to their socio-demographic characteristics such as age and gender.[12,15] Although the socio-demographic characteristics did not affect the attitude towards vaccination, the type of the department where the students studied was found to be effective. In their study which they evaluated the attitudes of university students towards vaccination, Campo-Arias and Pedrozo-Pupo[15] found that 78.9% of the participants did not trust vaccination and these students were studying in departments unrelated to health.

In Malta, medical students' confidence in the COVID-19 vaccine was found to be higher compared to dental students and administrative personnel.[16] In this study, the mean scale scores of the students studying in Radiotherapy, Operating Room and Oral and Dental Health departments were found to differ compared to the mean scale scores of the students in other departments and this difference was statistically significant ($p<0.05$). This result in the study may be related to the fact that the Operating Room, Oral Dental Health and Radiotherapy departments require working with patients and the students may have thought that the risk of COVID-19 transmission could be higher.

This study has several main limitations. The first is the adoption of the convenience sampling strategy. Since the sample group is determined through a known universe, it cannot be predicted how the opinions of the individuals who did not participate in the study may have changed the results. In addition, the high number of female students in the universe resulted in higher number of responses received from the female participants in the universe, which may have affected the research results.

Another important limitation of the study is related to the use of SINOVAC, the only vaccine available in Turkey at the time of the study whose interim result report on its effectiveness had not been yet published.

CONCLUSION

When this research was conducted, Turkey was experiencing the third wave of pandemic. Turkey ranked first in Europe in the number of daily cases. Vaccination is accelerated immensely now. In light of the intense experiences of Turkish healthcare services in regards to COVID-19, we believe that the findings of this study deserve attention. We were expecting that Turkish students to be more willing to be vaccinated. Since this expectation was not supported with research data, we would like bring these results to the attention of the public health and propose conducting more comprehensive further studies in order to better understand the reasons for vaccine hesitancy among the university students in Turkey.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethiccal Issue: This study was approved by Kapadokya University Research Ethics Committee (Decision number: 2021.46, Date: 04.01.2021).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

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

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Orijinal Araştırma / Original Article

Evaluation of the Use of Breast Cancer Screening Methods among Female Patients through Champion Health Belief Model Scale

Kadın Hastalarda Meme Kanseri Tarama Yöntemlerini Kullanma Durumlarının Champion Sağık İnanç Modeli Ölçeği ile Değerlendirilmesi

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Abstract

Aim: The aim of this study is to evaluate the use of breast cancer screening methods by women in our society and its affecting factors.

Material and Method: A total of 281 women aged 40 years and older were included in the study. A sociodemographic data form, Breast Cancer Risk Assessment Form and the Champion's Health Belief Model Scale were applied to the participants through face-to-face interviews.

Results: It was found that most participants knew breast cancer screening methods but that they used the methods at a low rate. The main reason affecting their use of screening methods was whether there was a complaint. The rate of mammography was found to be significantly higher among those who performed breast self-examination (p=0.011). When the Champion's Health Belief Model Scale form was examined, it was found that the participants had the highest points from the self-efficacy subscale of breast self-examination, and the lowest points from the perceived susceptibility subscale.

Conclusion: It was observed that the use of any screening method and breast cancer risk factors affected health beliefs regarding the use of screening methods.

Keywords: Cancer screening, breast cancer, health belief model

Öz

Amaç: Çalışmamızda toplumumuzda yaşayan kadınların meme kanseri tarama yöntemlerini kullanma durumlarını ve etkileyen faktörleri değerlendirmek amaçlanmıştır.

Gereç ve Yöntem: Çalışmaya, 40 yaş ve üzeri 281 kadın dahil edildi. Katılımcılara sosyodemografik veri formu, Meme Kanseri Riski Değerlendirme Formu ve Champion Sağlık İnanç Modeli Ölçeği yüz yüze görüşme tekniği ile uygulandı.

Bulgular: Katılımcıların büyük çoğunluğunun meme kanseri tarama yöntemlerini bildiği, ancak tarama yöntemlerini düşük oranda kullandığı belirlendi. Tarama yöntemlerini kullanma durumlarını etkileyen esas sebep şikayetin olup olmaması idi. Kendi kendine meme muayenesi yapanlarda mamografi yaptırma oranları anlamlı şekilde yüksek bulundu (p=0,011). Champion Sağlık İnanç Modeli Ölçeği puan ortalamaları incelendiğinde, katılımcıların en yüksek puan kendi kendine meme muayenesi öz yeterliliği alt ölçeğinden, en düşük puanı ise duyarlılık algısı alt ölçeğinden aldıkları görüldü.

Sonuç: Herhangi bir tarama yöntemini kullanma durumu ve meme kanseri risk faktörlerinin, tarama yöntemlerini kullanma durumlarına ilişkin sağlık inançlarını etkilediği görüldü.

Anahtar Kelimeler: Kanser tarama, meme kanseri, sağlık inanç modeli

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INTRODUCTION

Breast cancer is the most common malign tumor in women worldwide and that is highly treatable with early diagnosis.[1] Breast Self-Examination (BSE), Mammography and Clinical Breast Examinations (CBE) are methods used in breast cancer screening. Individuals' beliefs, values and manners are of great importance in the use of screening methods. The Health Belief Model (HBM), which explains the reasons behind manners and behaviors, is an effective guide in explaining and measuring what motivates or prevents the patient's adherence to treatment in many health problems, alongside behaviors that protect and improve health. Studies have reported that knowing the beliefs screening methods for the diagnosis of breast cancer will be beneficial in teaching and accepting the practices.[2-4]

Based on the Victoria Champion Health Belief Model in nursing, the Health Belief Model for breast cancer screening was established in 1984. He developed the scale and revised it in 1993, 1997 and 1999. This scale, which evaluates women's beliefs about breast cancer, breast self-examination and mammography, reflects women's beliefs about breast cancer and screening behaviors in Turkey, as well as theoretically structured, valid, and reliable data collection tools on the subject within the framework of a model and makes international comparisons with the results obtained.[2-5]

The aim of this study is to determine the use of breast cancer screening methods amongst women; to identify their beliefs towards screening methods; and to research the reasons that are effective in the use of screening methods or the reasons of not having screening performed.

MATERIAL AND METHOD

A total of 281 female patients over the age of 40 who applied to the Ankara Training and Research Hospital Family Medicine district polyclinics between 01.10.2019-31.12.2019 for any reason and agreed to participate in the study were included in the study. Patients who were illiterate, had communication disabilities, were followed up for any psychiatric disorder, and those who refused to participate in the research were excluded from the study. Approval for the study was granted by the Clinical Research Ethics Committee of Health Sciences University Ankara Training and Research Hospital (Date: 12.09.2019, Decision No: E-19/55). In the study, a descriptive questionnaire prepared in accordance with the literature and the Champion Health Belief Model Scale (CHBMS) were used.[3] The questionnaire consisted of 27 questions was used to determine sociodemographic characteristics, breast cancer risk factors, and the application status of early diagnosis methods. The Breast Cancer Risk Assessment Form of the Ministry of Health was used to evaluate these questions.[4]

Our study adopted the Turkish version of CHBMS, which was adapted into Turkish by Gözüm and Aydın[5] in 2004 (cronbach's alpha: 0.69-0.83). The Champion Health Belief Model Scale includes a total of 8 subscales and 52 items evaluating an individual's judgement on their general health and breast cancer: Sensitivity, severity, health motivation, BSE barriers, BSE benefits, self-efficacy, and benefits to mammography and barriers to mammography. The statements included in the questionnaire are graded from 1 to 5 in the Likert-type scale. Higher points indicate that susceptibility and severity increase, and benefits are perceived higher for the perception of benefit and barriers are perceived high for the perception of barriers.

IBM SPSS 25.0 (Statistical Package for Social Sciences, version 25) software was used in the statistical analysis of data. Continuous variables mean±standard deviation; categorical variables were depicted as numbers and percentages. When the parametric test assumptions were met, the test of significance of the difference between two means was used to compare the differences in the independent group, while the Chi-square test was used to compare the differences in the same group when the parametric test assumptions were not met. In comparing categorical variables under the Chi-square analysis title; Pearson Chi-Square test or Fisher Exact Test, whichever is appropriate, was used according to the distribution of expected frequencies. A value of $p<0.05$ was considered statistically significant.

RESULTS

A total of 281 women aging between 40-69 participated in the study. The mean age of the participants was 48.91±7.82 years. Of the participants, 162 (57.6%) were high school or university graduates and 192 (68.3%) were actively working (**Table 1**).

Table 1. Sociodemographic Features

Sociodemographic Features	Mean	Standard deviation
Age (year)	48.91	7.82
Height (cm)	160.70	10.86
Weight (kg)	68.85	12.29
Body mass index (kg/m²)	34.96	140.64
Monthly income (TL*)	2513.81	2134.72
Number of pregnancies	2.70	1.82
Number of births	2.11	1.32
Number of children	2.04	1.16
First childbearing age	22.99	4.97
Age of first menstruation	13.28	1.25
Breastfeeding duration (months)	16.28	8.52

*TL: Turkish Lira

The rate of having mammography was statistically significantly higher in the BSE group (p=0.011). The level of education was found to be significantly higher in the group that did not have mammography (p=0.033), but it was found that the rates of BSE and CBE increased with the increase in education level (p<0.001; p=0.013, respectively).

The majority of women (43.0%) who knew how to do BSE stated that they learned it from a health worker and learning from radio-television-internet was the second most common (26.5%). When the participants were asked about their reasons for not having CBE, the most common answers were having no complaints (56.8%) and neglect (22.4%). According to the answers of the participants to the breast cancer CHBMS, it was seen that they got the highest point from "self-efficacy" and the lowest points from "sensitivity". Participants whose breast cancer risk level was calculated to be low had significantly higher sensitivity points (p<0.001; p=0.003, respectively). The number of participants who had a family history of breast cancer and who also developed breast cancer was found to be significantly higher (p<0.001). Similarly, sensitivity (p<0.001), seriousness (p<0.001), health motivation (p=0.003), BSE benefits (p=0.001), mammography benefits (p=0.034) subscales points of those with a family history of breast cancer were significantly higher. The comparison of the mean CHBMS points of the participants who know how to do BSE and those who do not are shown in **Table 2.**

Table 2. Knowing how to do BSE and CHBMS score averages

CHBMS Subscales	BSE Know Mean ± SD	BSE Do Not Know Mean± SD	p*
Sensitivity	7.73±2.78	8.53±3.19	0.121
Seriousness	19.71±5.67	22.48±5.81	**<0.001**
Health Motivation	20.82±3.73	19.76±2.89	**0.003**
BSE Benefits	15.79±3.23	15.34±2.77	0.094
BSE Barriers	18.02±5.74	20.98±5.51	**<0.001**
Self-efficacy	35.78±7.94	24.21±8.41	**<0.001**
Mammography Benefits	18.84±3.87	18.79±4.47	0.859
Mammography Barriers	24.31±8.05	27.83±8.29	**0.004**

*Statistically significant data are written in bold. SD: Standard deviation

Health motivation, BSE benefits and self-efficacy points of the participants who performed BSE were found to be significantly higher than those who did not. The health motivation, BSE benefits, self-efficacy, and mammography benefits points of the participants who had mammography were significantly higher. Health motivation (p=0.001), BSE benefits (p=0.024) points of the participants who had CBE compared to those who did not; BSE and mammography barrier points of those who did not have CBE were found to be significantly higher (p=0.015, p <0.001, respectively)

DISCUSSION

We found that most women participating in our study knew and performed BSE, a breast cancer screening method, but the rates of those who regularly applied it every month and had CBE and mammography were low. While the general sensitivity, seriousness, health motivation and benefit perceptions of the participants using breast cancer screening methods were positively correlated; perceived barriers were lower.

In our study, we aimed to evaluate the relationship between women's use of BSE, CBE, mammography, which are breast cancer screening methods, and the subscales of CHBMS and the risk of breast cancer. In various studies around the world, it has been determined that those who know and apply BSE show significant differences.[5-7] In our study, the rate of knowing BSE was 79.4%; 80.1% of women stated that they performed BSE, and 13.9% stated that they regularly perform BSE. In the previously conducted studies in Turkey, the rates of knowing BSE were found to be 25%, 49.8%, and 53.9%.[6-8] The high number of people who knew BSE in our study can be explained by the fact that the frequency of cancer screening in primary healthcare continues to increase with the current programs carried out by the Ministry of Health on this subject. The fact that most of the participants learned about BSE from health professionals supports this. The rate of obtaining information from healthcare professionals was also found to be high in other studies.[9,10] This situation reveals the importance of healthcare professionals reaching wider audiences for breast health.

In the study of Koç and Sağlam,[11] the rate of those who regularly perform BSE every month was 22.9%. According to the Ministry of Health's 2016 annual health statistics, regular BSE performance among women was reported to be 20%. In a study by Dişçigil et al.[12] BSE rates were 61.7%, but those who performed monthly regular BSE were 17.9%. Similar to that study, our study has also found regular BSE performance very low. The importance of education programs and family physicians in increasing the performance of BSE is an indisputable fact.

In our study, it was observed that as the level of education increased, the rates of performing BSE and having CBE increased significantly. In a similar study by Güner et al.[7] the rate of BSE increased as the level of education increased. In the study of Dişçigil et al.[12] similar to our study, the rate of BSE increased in direct proportion to the level of education. This emphasizes the importance of education in the use of screening methods.

In various studies, the rate of CBE among women has been reported to be between 30-80%. Başak[13] found in her study that 8.1% of women had CBE. In our study, the rate of CBE was 47.3%; the rate of regular CBE was observed to be 14.2%. Although higher rates were observed in our study when compared to the study of Başak's, it is seen that CBE was not performed at the expected level. As a result of the high difference between the rates of performing CBE and the rates of regular practice, it is thought that patients use CBE method when they have complaints, not for screening purposes.

In a study conducted by Koç and Sağlam[11] on 100 women aged 17-76 years, it was found that 97% of them did not know about mammography, and 86% of them never had a mammography. In another study, it was determined that 97.5% of nurses over the age of 40 did not have mammography.[14] In our study, the rate of having mammography was 40.9%, which seems to be

higher than that of previous studies. This can be explained by the increase in screening programs and the inclusion of women aged 40 and over in our study. Similarly, in our study, it was observed that the rate of mammography decreased as the education level increased. In many studies, it has been observed that the recommendation or guidance made by a physician, or another health professional is effective in having regular mammography.[15,16] It has been reported that the inadequacy of a physician's recommendations to encourage mammography is an important obstacle to mammography.[17] This situation shows that family physicians have a great role in promoting the use of screening methods.

When participants were evaluated based on their breast cancer risk factor according to CHBMS subscales, sensitivity and seriousness were significantly higher in the group with a low risk factor. Accordingly, emphasis must be placed on the high-risk group which was found to have lower seriousness. In addition, while calculating the risk level, the fact that sensitivity, seriousness was found to be significantly higher in those with a family history of breast cancer may suggest that it is due to the lack of information about other risk factors. With the education and information to be given on this subject, awareness of risks can be increased and susceptibility, in other words, sensitivity to the disease can be increased. Among the participants, those with a family history of breast cancer on the CHBMS subscales of sensitivity, seriousness, health motivation, BSE benefits and mammography benefits were found to be significantly higher. In a study conducted by Kılıç et al.[18] on university students, the perceived sensitivity of students with a family history of breast cancer were found to be significantly higher than students without a family history of breast cancer.

Amongst the participants who knew and perform BSE were found to have higher health motivations and self-efficacy on CHBMS subscales. In the same table, a statistically significant difference was found between not knowing, not performing BSE and barriers to BSE and mammography. In the study of Seçginli et al.[19] the rate of BSE was found to be high in women with high sensitivity to breast cancer. In another study, it is stated that the rate of BSE is higher in women with high perceived benefits of BSE and low perceived barriers.[20]

Amongst the participants who have had mammography, health motivation, perceived BSE benefits, self-efficacy and perceived mammography benefits, which are subscales of CHBMS, were found to be significantly higher. At the same time, perceived barriers to BSE and mammography were found to be significantly higher in those who did not have mammography. Likewise, various studies also have found women who do not have mammography had higher perceived barriers than women who have had mammography, in another sense, women who have had regular mammograms were found to have lower perceived barriers. It has been determined that the education and guidance provided reduces the perceived barriers.[18,21-23] Thus, perceived barriers are one of the issues that should be emphasized.

Among the CHBMS subscales, health motivation and BSE benefits of the participants who had CBE were significantly higher. At the same time, those who did not have CBE had significantly higher perceived barriers to BSE and mammography. Erbil et al.[24] have reported in their study that the group who had CBE had higher self-efficacy and perceived motivations, and low perceived barriers to BSE.

CONCLUSION

There is a need for structured, valid, and reliable data collection tools on the subject in order to examine women's beliefs about breast cancer and screening behaviors in Turkey within the framework of a theoretical model and to make international comparisons with the results obtained.

Accordingly, increasing the patients' health perceptions, seriousness and sensitivity and preventing perceived barriers will enhance the rate of using screening methods. For this purpose, each study, and education is of great importance.

ETHICAL DECLARATIONS

Ethics Committee Approval: Approval for the study was granted by the Clinical Research Ethics Committee of Health Sciences University Ankara Training and Research Hospital (Date: 12.09.2019, Decision No: E-19/55).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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Orijinal Araştırma / Original Article

Administering Geriatric Pneumonia Cases without Waiting for CRP Results, is It Practicable?

Geriatrik Pnömoni Vakalarının CRP Sonuçları Beklenilmeden Yönetimi Pratik Olur Mu?

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Abstract

Aim: C-reactive protein (CRP) is a notable marker of many diseases. Accordingly, in most cases, the clinical management of infectious diseases is revised based on CRP alterations. This study thus attempted to predict CRP alterations via immature granulocyte count (IGC) and nucleated red blood cell count (NRBC) in a geriatric population with pneumonia.

Materials and Methods: We carried out our study in the intensive care unit of a private hospital by retrospectively reviewing the laboratory findings of geriatric patients with pneumonia and an age-matched control group in the same ICU.

Results: In total, we reviewed 495 hospitalization days (the summed amount of days all 43 patients) and 221 hospitalization days (the summed amount of days all 20 controls) records. In the group comparisons, we found a statistical significance in the patient group for both IGC (p=0.001) and NRBC (p=0.002) increase. Comparing IGC to CRP measures from the following day and the day after that, there was a statistical significance in IGC increase (p=0.001) but not in NRBC (p=0.156). Further, IGCs below 0.3×103 and above 0.5×103 were better able to predict CRP alterations.

Conclusion: In geriatric patients with pneumonia, IGC is more effective than NRBC in predicting CRP variations before their actual occurrence, with the mean estimation time at least 2 days prior.

Keywords: CRP variability, geriatric pneumonia, Immature granulocyte count, Intensive care unit, Nucleated red blood cell count

Öz

Amaç: C-Reaktif Protein (CRP) birçok hastalık için önemli bir belirteçtir. Buna göre, çoğu vakada, bulaşıcı hastalıkların klinik yönetimi, CRP değişikliklerine dayalı olarak revize edilir. Dolayısıyla bu çalışma, pnömonili geriatrik popülasyonda immatür granülosit sayısı (İGS) ve çekirdekli eritrosit sayımı (ÇE) yoluyla CRP değişikliklerini öngörmeye çalışmıştır.

Gereç ve Yöntem: Özel bir hastanenin yoğun bakım ünitesinde yatan geriatrik pnömonili hastaların ve yaş uyumlu bir kontrol grubunun laboratuvar bulgularını retrospektif inceleyerek çalışmamızı gerçekleştirdik.

Bulgular: Toplamda, 495 hastanede yatış gününün (43 hastanın toplam yatış gün sayısı) ve 221 hastanede yatış gününün (20 kontrolün toplam yatış gün sayısı) kayıtlarını inceledik. Grup karşılaştırmalarında hasta grubunda hem İGS (p=0.001) hem de ÇE (p=0.002) artışı için istatistiksel anlamlılık bulduk. Ertesi gün ve ondan sonraki gün İGS ile CRP ölçümleri karşılaştırıldığında, İGS artışında (p=0.001) istatistiksel anlamlılık vardı, ancak ÇE'de (p=0.156) yoktu. Ayrıca, 0,3×103'ün altındaki ve 0,5×103'ün üzerindeki İGS'ler, CRP değişikliklerini daha iyi tahmin edebildiler.

Sonuç: Pnömonili geriatrik hastalarda, İGS, ortalama tahmin süresi en az 2 gün önce olmak üzere, CRP değişimlerini tam oluşmadan önce tahmin etmede ÇE'den daha etkilidir.

Anahtar Kelimeler: CRP değişimi, çekirdekli eritrosit sayısı, geriatrik pnömoni, immatür granülosit sayısı, yoğun bakım

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INTRODUCTION

Pneumonia is an acute, severe respiratory disease characterized by airflow limitations due to inflammation. [1] It is associated with significant morbidity and mortality in the geriatric population.[1] Besides a clinical evaluation, laboratory tests are useful for determining prognosis in pneumonia treatment. In the geriatric population, however, this may not be entirely consistent, as these patients are prone to insufficient immune responses.[2]

C-reactive protein (CRP) is an annular-shaped protein produced by the liver that indicates inflammation in the human body.[3] It was named after a matter that reacts with the somatic capsular polysaccharide antibody, and its half-life is less than 24 hours.[4] As a component of the acute phase response, CRP correlates with inflammation. Despite these qualities, elevations or reductions in CRP due to inflammation and disease severity sometimes do not follow a similar course. In these cases, precursor substances, such as procalcitonin, may evaluate disease progress instead.[5] However, the adequacy of the procalcitonin is not reliable in oncological or thrombotic events.[6]

Aside from changes in CRP, due to infection severity, there are also changes in the proportion of the granulocyte series, which can begin to appear in the peripheral blood as well. These changes are evidence that the bone marrow is under stress. Accordingly, immature granulocyte (IG) are one of the initial products of an activated immune system reaction, and it is typical to see IG in the peripheral blood in severe infectious or inflammatory processes.[7] IG count (IGC) can then allow us to have an idea of an inflammatory state like a peripheral blood smear.

Related, nucleated red blood cell count (NRBC) forms the precursor erythrocytes that respond to hypoxic stress, such as acute hemolytic crises, hematologic malignancies, and severe infections.[8] Detecting NRBC in adults is pathological and directly reflects excessive erythropoietic activity.[9] The shape of the cells in NRBC is quite similar to that of lymphocytes, though, and because of this similarity, automatic cell counting devices often add NRBC to the number of lymphocytes. These results can thus be misinterpreted as lymphocytosis. At this point, NRBC is extremely important. It can help in disease diagnosis and treatment.[10,11] Both IGC and NRBC can be obtained from a complete blood count (CBC) result.

CRP has guided us many times in the treatment of infections. However, CRP alterations may not be estimated precisely from clinical patient signs, as CRP level might have already changed by the time clinical tests take place.[12] This situation causes delays in treatment modality adjustments, mainly in geriatric patients who have impaired immunity. [13] It is therefore helpful to those patients to estimate CRP's alteration time. IGC, NRBC and CRP are similar inflammation markers, thus, we feel that IGC and NRBC can contribute to this estimation as much as clinical findings in pneumonia cases. As such, an early laboratory prediction based on IGC and NRBC can prove beneficial in the treatment of groups with delayed immune responses.

There is not enough research on geriatric pneumonia cases in the intensive care unit (ICU). Furthermore, there is not enough data on geriatric patients with pneumonia in the ICU regarding specifically IGC, NRBC, and CRP in the literature. As such, this study aims to predict CRP alterations in geriatric pneumonia ICU cases just before the actual CRP change.

MATERIAL AND METHOD

This retrospective study was conducted at a private hospital in 2019. The local university ethical committee approved the study protocol. The study was conducted according to the Declaration of Helsinki. An agreement was obtained from the private hospital to evaluate the patients' data prior to the study.

Geriatric patients with bacterial or viral pneumonia treated in the ICU and an age-matched group with normal CRP were included in this study. The patients were chosen according to the International Classification of Disease (ICD-10) codes, including J18 (Pneumonia) and A41 (other sepsis) (14). These selected codes covered the severe clinical spectrum for the patients with pneumonia in the ICU. In addition, the clinical pneumonia was confirmed by the radiological reports of the patients. Patients with oncologic, traumatic, or neurologic diagnoses were excluded from the evaluation. We also checked the patients' daily follow-up charts to determine unexpected clinical abnormalities such as intubation, fever, and hypotension. Per the follow-up charts, patients with a point of less than 5 on the Glasgow coma scale on the day of admission were excluded as well.[15] Patients receiving steroids during hospitalization were not featured in the study. Further, we were sure to include patients who used similar drugs during their treatment.

The control group consisted of patients hospitalized in the ICU due to non-infectious diseases (diabetes mellitus, cerebrovascular disease). The same exclusion criteria were applied to the control group, and daily laboratory results and medications were also noted.

The participants' laboratory tests which were studied with the Sysmex Xn-1000 AHA and Beckman Au 2700 branded devices from January to May 2019 were obtained from the hospital's archived electronic database. Initially, we chose patients who had been tested for both CBC and CRP every day. We primarily included the CRP and CBC laboratory records, which were studied more than once a day to estimate the CRP deviation time on an hourly basis. As shown in **Figure1,** the IGCs and NRBCs gathered the day before the CRPs were compared.

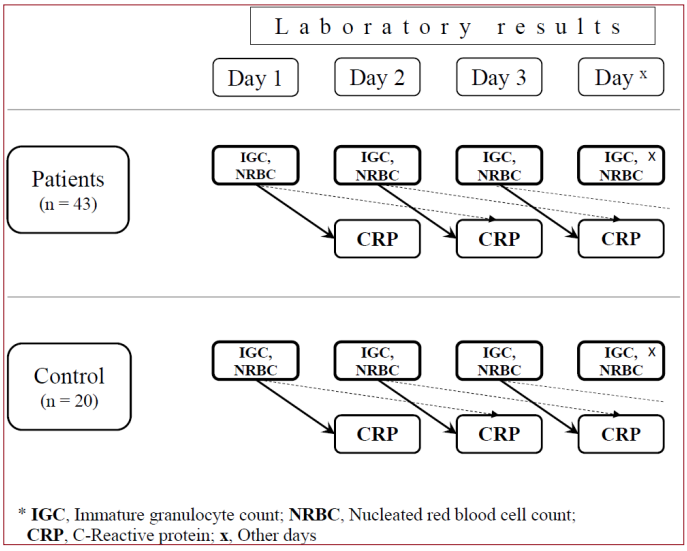

Figure 1. Study design.

Statistical Analysis

The statistical analyses were performed using SPSS ver. 21 (SPSS Inc., Chicago, IL, USA). Pearson's correlation was used to compare normally distributed data, whereas for non-normal data, the Spearman correlation was used. A one-way ANOVA test was used in the continuous multi-group analysis for normally distributed data. A post hoc (Bonferroni) test was performed to indicate the differences between participant groups. For categorical variables, we used the chi-square test. An independent samples t-test was applied to identify the significance between groups and continuous data, while A linear regression test was performed for the correlations between the patients IGCs and the CRP results of the following day (day 2) and the next day after tomorrow (day 3). We accepted a value of $p<0.05$ as statistically significant.

RESULTS

At first, we reviewed 65 files for the from the first 5 months of 2019. Nine of the records reported that the corresponding patients had been hospitalized for less than 3 days (we evaluated at least three hospitalizations days results), while 13 of them had incomplete clinical data. In the control group, 35 files were reviewed. Fifteen of them could not pass over the exclusion criteria. Finally, we reviewed 495 patient hospitalization days (the summed amount of days all 43 patients) and 221 control hospitalization days (the summed amount of days all 20 controls) records were included in the study. The patients did not use common drugs other than acetylsalicylic acid, antihypertensives, proton pump inhibitors, oral antidiabetics, analgesics, and inhalers. Additionally, none of them were given oral or intravenous steroids during treatment. All the patients' renal and liver functions were normal per their age, and their O2 saturations were at least > 80%. The patients' and controls' demographic information and laboratory results are detailed in **Table 1**.

Table 1. Demographics and laboratory results of patients and control groups

	Patients (n = 43)	Control group (n = 20)	P values
Mean age	78±9.6	76±3,4	0.121
Gender, F/M	20/23	10/10	0.210
Hospitalization day, n	11.51±6.39	5.8±3.1	0.042
Cause of hospitalization	COPD*, Pneumonia	DM†, CVD‡	NA§
Laboratory results			
WBC¶, $\times 10^9$/L	14.07±7.16	7.29±1.13	0.001
ANC†‡, $\times 10^9$/L	(0.63-91.3)	(2.09-5.82)	0.001
ALC††, $\times 10^9$/L	(0.08-11.4)	(1.55-3.31)	0.001
CRP†§, mg/L	(1.32-166.4)	(15.1-63.4)	0.001
IGC¶†, $\times 10^3$/uL	(0.01-2.96)	(0.05-0.05)	0.001
NRBC¶‡, $\times 10^3$/uL	(0-15)	(0-0.01)	0.002

P values are the comparison of patient and control groups. (Chi-Squared test or Mann Whitney U test); Data are the median, n (%), or n/N (%); *Chronic Obstructive Pulmonary Disease; †, Diabetes mellitus; ‡, Cerebrovascular disease; §, Not applicable; ¶, White blood cell; †‡, Absolute neutrophil count; ††, Absolute lymphocyte count; †§, C-Reactive Protein; ¶†, Immature granulocyte count; ¶‡, Nucleated red blood cell count.

Of the hospitalization days, only 41 days revealed normal CRP values. When the CRP variations from the remaining 454 days of total hospitalization were compared per IGC and NRBC, IGC was positively correlated with the CRP of the next day (r=0.224); NRBC was not. Further, IGC was positively correlated with the day after that as well (r=0.18). Similarly, another positive correlation existed between NRBC and both IG (r=0.158) and white blood cell (WBC) (r=0.179), as expected.

The next section of the evaluation was concerned with the comparison of the ICU patient and control groups. There was a statistical significance in the patient group for IGC (p=0.001, η=0.103) and NRBC (p=0.002, η=0.018). We compared the IGCs and NRBCs of the test day with the next days' CRP results. We found a significant difference in IGC (p=0.001, "Y=19.08*X+72.84") (**Figure 2a**), unlike NRBC (p=0.156). Even when we compared IGC with the CRP results of the day after that, they were still significant (p=0.006, "Y=15.40*X+73.63") (**Figure 2b**).

After that, we separated IGC into categories according to radio frequencies (%) and direct current (x 10^3 u/L) (16). Every category was ten times more numerous than the previous one. In brief, we formed a total of seven categories based on IGC results (**Figure 2c**). When we evaluated the IGC prediction degree of high-CRP levels (>5 mg/L), a one-way ANOVA revealed that groups 1-2 and 1-7 were more effective (F=5.049, p=0.001; **Figure 2d**). The lower IGC thus values seemed better able to predict high CRP. However, no significant differences were found at low CRP levels (<5 mg/L; p=0.121).

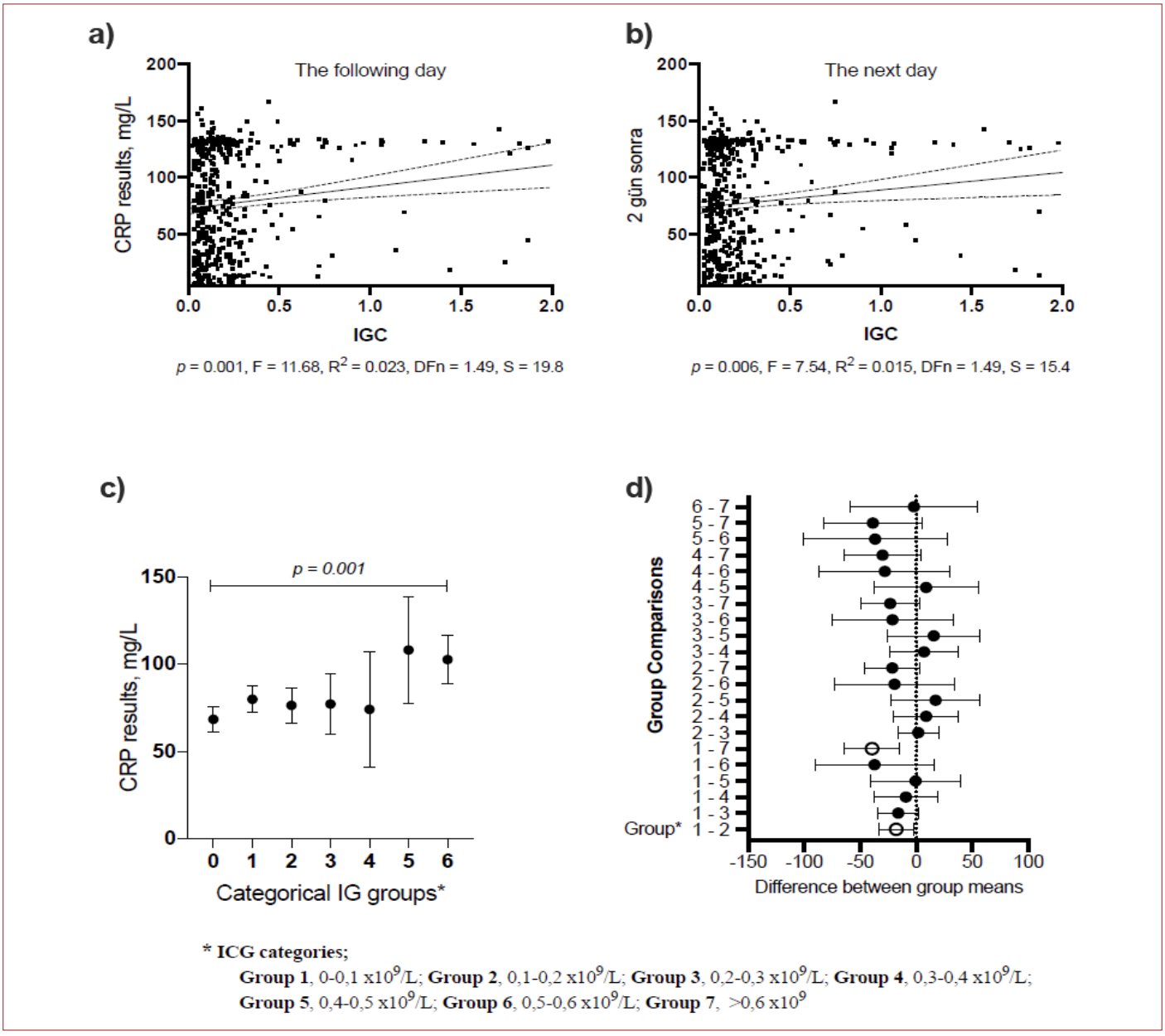

Figure 2. Comparisons between IGC subsets and C-Reactive Protein. a) Comparisons of patients' IGCs and the next day's CRP results; b) Comparison of patients' IGCs and CRP results from the next day; c) Patients' IGC categories according to radio frequencies; d) Comparisons of categorized IGC results and CRP values.

DISCUSSION

Our study's outcomes indicate that in geriatric ICU patients with pneumonia, IGC can predict CRP alterations at least one day before the actual change. Contrarily, NRBC does not make such predictions.

CRP has been used as an inflammatory marker of many diseases for almost a century.[3] However, because CRP's half-life is less than 24 hours, another inflammatory marker that can sooner alert medical professionals to a CRP alteration will improve patient treatment.[4] What is surprising from our results is that IGC not only gives information about the day it was measured, but also predicts the CRP values of the next day or even 2 days later (p=0.007). This means that IGC changes up to 2 days before the CRP alteration, and can help clinicians change patient treatment earlier than is possible through other clinical test predictions, as clinical progress predictability is vital in rapidly progressive diseases such as pneumonia.

A single-centered study showed that IGC is correlated with severe pancreatitis.[7] The study also revealed that an elevation in IGC estimates the degree of pancreatitis. The researchers confirmed IGC's estimation ability with high specificity and even labeled these cases as severe pancreatitis with increased IGC in the early hours. The use of the term hour is notable for the similarity to our present study, as one of its goals was to make inferences about CRP on an hourly basis. Our results ultimately revealed that IGC value changes predict CRP variation at least 24 hours before it actually occurs.

Another recent study also found that IGC indicates severe bacterial infection in children.[17] These researchers aimed to determine the effects of a marker in pediatric patients who came to the emergency department due to fever, and they noted that IGC was specific like WBC in bacterial infections. The inclusion of mild patients in their studies shows that IGC is important in the severity of different diseases. We did not classify the disease severity in our study, however, even a small amount of IGC in all disease levels could accurately predict the CRP variation at least 1 day in advance. This finding broadly supports the work of the related study and indicates that IGC is useful in demonstrating CRP in different age groups and disease levels.

An additional retrospective study analyzed the data of 204 patients who underwent an appendectomy and concluded that IGC was not as effective as WBC for diagnosis.[18] While IGC elevated with other infection markers, there was no correlation between these factors. However, the IGC results in the study were only registered to the first decimal unit when they should be calculated to the nearest thousandth to be considered relevant; thus, we noted our results in milliunits to observe more sensitivity. Accordingly, in our study, IGC was statistically significantly correlated to CRP predictions.

NRBC increase can be expected in bone marrow stress secondary to infection severity. Ballantine et al. compared NRBC rate, the need for blood transfusion, and the tendency for acute chest syndrome in patients with sickle cell disease.[19] In the study, an adequate number of patients were hospitalized due to vaso-occlusive crises. The patients' NRBC was found statistically significant in all compared stages. This study's importance stems from how these medical emergencies were caused by inflammation, not infection, that is, NRBC was associated with the inflammation process. In our infection-based study, the NRBC results correlated with the CRP results; however, NRBC failed to predict CRP variation. Our results are thus in agreement with this related study, indicating that NRBC does not affect infection, as it is likely to be concerned with red cell maturation.

Although the current study was based on a small patient sample, we examined how soon IGC can predict CRP deviation, not the patients' individual CRP responses. Therefore, we evaluated the number of total hospitalization days and CRP values alone, or about 500 days of data. Moreover, we evaluated patients who had three comorbidities (geriatric patients with pneumonia in the ICU), which caused the number of patients to be low. Still, our study was limited by the absence of enough blood samples on the same hospitalization day; thus, we could not reduce the CRP estimation time. Further studies can provide hourly information. Since most of the studies performed on NRBC are based on inflammation, additional NRBC research is also needed for infection cases.

According to our outcomes, we could predict changes in CRP before they occur, but not whether these changes increase or decrease at the stationary CRP states. Even so, the increase and decrease of CRP and IGC were concurrent, while for NRBC, this assumption was not clear. Overall, we can underline that the IG exchange starts at least 24 hours before the CRP exchange. This time can allow new treatment changes to take place, as geriatric patients cannot generate proper immune responses given usually insufficient CRP and WBC elevations.

CONCLUSION

This research's findings have several practical implications, though two are of particular interest. First, predicting the direction of CRP deviation sooner strengthens the current infection treatment of geriatric patients. Second, IGC can easily be integrated into a standardized method of analysis in most routine hemogram counting devices. In conclusion, the most apparent finding to emerge from this study is that IGC can detect CRP alterations at least 24 hours prior to the event actually occurring.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by the ethical committee of Karatay University School of Medicine on 20.03.2019. (2019/007 numbered).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Orijinal Araştırma / Original Article

Evaluation of Sexual Dysfunction in Hospitalized Post-Stroke Rehabilitation Patients

Hastanede Yatan İnme Sonrası Rehabilitasyon Hastalarında Cinsel İşlev Bozukluğunun Değerlendirilmesi

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Abstract

Introduction: Stroke-related factors seem to have significant effects on sexual functions in physical, biological, and psychosocial areas. This study aims to evaluate the factors affecting the sexual functions of patients after stroke.

Material and Method: This study consisted of 51 (53.1%) male and 45 (46.9%) female patients. Sociodemographics and clinical features of the patients were documented. Sexual functions evaluated with Arizona Sexual Experiences Scale (ASES), International Index of Erectile function (IIEF) and Female Sexual Function Index (FSFI).

Results: The mean age of men and women were 57.76±7.57, and 60.13±12.71 years, respectively. When the ASES cut-off point was 11, we found that 88.5% of the participants (84.3% in men and 93.3% in women) had sexual dysfunction. There was no significant difference between the frequency of sexual dysfunction in women and men (p=0.166, Pearson Chi-square Test). According to univariate ANOVA results, age (p=0.028) and BDI (p<0.001) values had a significant effect on ASES. The side of stroke (p=0.030), Brunnstrom motor evaluation (upper extremity) (p=0.028) and Beck Depression Scale (p<0.001) values had a significant effect on IIEF total values. BDS (p=0.001) values significantly affected FSFI total values.

Conclusion: The data obtained from our study showed that post-stroke sexual dysfunctions are significantly high in Turkish rehabilitation inpatient clinics. Post-stroke sexual dysfunctions are linked to multiple etiologies, both organic (hemispheric lesion side, etc.) and psychosocial (depression, etc.).

Keywords: Stroke, sexual dysfunction, function, psychology

Öz

Giriş: İnme ile ilişkili faktörlerin fiziksel, biyolojik ve psikososyal alanlarda cinsel işlevler üzerinde önemli etkileri olduğu görülmektedir. Bu çalışma inme sonrası hastaların cinsel fonksiyonlarını etkileyen faktörleri değerlendirmeyi amaçlamaktadır.

Gereç ve Yöntem: Bu çalışmaya 51 (%53,1) erkek ve 45 (%46,9) kadın hasta dahil edildi. Hastaların sosyodemografik ve klinik özellikleri belgelendi. Arizona Cinsel Deneyimler Ölçeği (ASES), Uluslararası Erektil İşlev İndeksi (IIEF) ve Kadın Cinsel İşlev İndeksi (FSFI) ile cinsel işlevler değerlendirildi.

Bulgular: Erkeklerin ve kadınların yaş ortalaması sırasıyla 57,76±7,57 ve 60,13±12,71 idi. ASES kesme noktası 11 olduğunda, katılımcıların %88,5'inin (erkeklerde %84,3 ve kadınlarda %93,3) cinsel işlev bozukluğu olduğunu bulduk. Kadınlarda ve erkeklerde cinsel işlev bozukluğu sıklığı arasında anlamlı fark yoktu (p=0,166, Pearson Ki-kare Testi). Tek değişkenli ANOVA sonuçlarına göre yaş (p=0,028) ve BDÖ (p<0,001) değerlerinin ASES üzerinde anlamlı bir etkisi vardı. İnme tarafı (p=0,030), Brunnstrom motor değerlendirme (üst ekstremite) (p=0,028) ve Beck Depresyon Skalası (p<0,001) değerlerinin IIEF toplam değerleri üzerinde anlamlı etkisi vardı. BDS (p=0,001) değerleri FSFI toplam değerlerini önemli ölçüde etkilemiştir.

Sonuç: Çalışmamızdan elde edilen veriler, Türkiye'deki rehabilitasyon yataklı kliniklerinde inme sonrası cinsel işlev bozukluklarının anlamlı derecede yüksek olduğunu göstermiştir. İnme sonrası cinsel işlev bozuklukları, hem organik (hemisferik lezyon tarafı vb.) hem de psikososyal (depresyon vb.) olmak üzere birçok etiyolojiyle bağlantılıdır.

Anahtar Kelimeler: İnme, cinsel islev bozukluğu, fonksiyon, psikoloji

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INTRODUCTION

Stroke is the primary cause of disability that can impair sexual functions and physical, linguistic, and cognitive functions.[1] Among the categories of disability after stroke, sexual dysfunctions are often overlooked. After a stroke, there is a significant decrease in sexual activity in men and women.[2-4]

Post-stroke physical problems and pain prevent some physical activities that may affect the quality of sexual activity.[5,6] In particular, hemiparesis and spasticity are physical conditions that affect sexual activity.[7] Studies show that the severity of disability due to stroke negatively affects sexual functions.[7-9] However, sexual dysfunction may develop even when physical disability is minimal or absent after stroke.[10] Various studies have shown a relationship between post-stroke depression and the occurrence of sexual dysfunction.[3] Another study found that the severity of post-stroke depression was an independent predictor of the development of sexual dysfunction in both men and women.[7] Apart from depression that develops directly due to the stroke lesion,[11] reactive depression that occurs due to the consequences of a stroke may also negatively affect sexual functions.[12] The recurrence of stroke during sexual activity is one of the biggest fears of patients. 24% of stroke patients did not engage in sexual activity due to this fear of stroke recurrence.[7] There is evidence that clinical conditions observed after stroke, such as urinary/fecal incontinence, may interfere with sexual intercourse.[13]

This study investigates whether factors such as sociodemographic characteristics, physical disability, etiology and side of stroke, presence of chronic disease, depression, stroke recurrence, and time elapsed after stroke contribute to sexual dysfunction in men and women after stroke.

MATERIAL AND METHOD

Informed consent was obtained from all the patients, and the local ethics committee approved this study of Ataturk Physical Therapy and Rehabilitation Hospital, Turkey (22.12.2014). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Participants

This cross-sectional study included hospitalized 96 post-stroke patients in inpatient Physical Therapy and Rehabilitation Clinics. A post-hoc power analysis for sexual dysfunction in stroke patients revealed 90% of the power with an 0.5% error.

The inclusion criteria included diagnosing stroke, having a sexual partner, being cooperated-orientated, and being hospitalized for rehabilitation. The exclusion criteria were diagnosis of dementia (mini-mental test <24), having pressure sore, fecal incontinence, neglect syndrome, and neurological disease other than stroke.

Assessment

Socio -demographics of the patients such as sex, age, marital status, and the number of children and clinical features (i.e., comorbidities, use of medicine, lesion site, etiology of the stroke (ischemic or hemorrhagic), recurrence of stroke, duration of time from the first stroke) were documented.

Assessment of Physical Functions and Cognition

Ambulation ability was evaluated by the Functional ambulation scale (FAS).[14] This scale comprises 0-5 stages where 0 is no ambulation and five can ambulate without any help. To scale the patient's spasticity, the modified Ashworth spasticity scale (ASS) is used with scoring from 0 to 4; a higher number indicates increased spasticity.[15] Motor staging of the stroke patients is classified by Brunnstrom motor evaluation (BME), where stage I is a flask with no motor movement, and stage VI is the isolated movement of the joint.[16] Barthel's index evaluates functional loss after stroke; higher scores indicate independence.[17] Beck Depression Scale (BDS) is applied to patients to assess the depression risk, and scores over 17 link with depression.[18] Mini-Mental test (MMT) evaluates cognitive functions quantitively; the highest point from the test is 30.[19]

Assessment of Sexuality

Arizona Sexual Experiences Scale (ASES) is developed to assess sexual dysfunctions. It is composed of five Likert types of a questionnaire for both sexes.[20] This scale aims to evaluate the sexual functions baring sexual orientation and relationship with the partner. Lower scores indicate the sexual response is strong, easy, and satisfying. Turkish validation has been executed by Soykan et al., and score ≥ 11 concludes with sexual dysfunction.[21] International Index of Erectile function (IIEF) is designed for male subjects to evaluate achievement, maintaining, and satisfaction of erection.[22] According to IIEE, erectile dysfunction (ED) is staged as mild (17-25 points), moderate (11-16 points), and severe (6-10 points), and Turkish validation has been done.[23] Female Sexual Function Index (FSFI) evaluates the sexual function of the last four weeks and is composed of desire, arousal, lubrication, orgasm, satisfaction, and pain subscales. Lower scores associated with more dysfunction, Turkish validity has been done.[24]

Statistics

Statistical Package for the Social Sciences 20.0 was used for performing the statistical analysis. Descriptive statistics (frequency, mean, and standard deviation) were used for analyzing the sociodemographic and clinical features. Categorical parameters were assessed through Chi-Square and Fisher's exact test. The Pearson and Spearman correlation was used to analyze the relationship of quantitative data to each other. Linear regression analysis and Analysis of Variance (ANOVA) were used to test factors affecting the ASES and FSFI. Logistic regression analysis was performed to test the factors on IIEE. The results were analyzed using a 95% confidence interval and a significance level of $p < 0.05$.

RESULTS

Socio-demographics Variables

This study consisted of 51 (53.1%) male and 45 (46.9%) female patients. The mean age of all cases, men and women, were 58.88±10.32, 57.76±7.57, and 60.13±12.71 years, respectively. All of the cases were married. Of the men, 15 (29.4%) were working, nine (17.7%) were unemployed, and 27 (52.9%) were retired. One (2.2%) of the women was working, 41 (91.2%) were unemployed, and three (6.7%) were retired. Of all cases, 16 (16.7%) were working, 50 (52.1%) were not working, and 30 (31.2%) were retired.

Clinical Variables

The mean time for men and women in the study after stroke was 18.27±21.79 and 19.02±24.91 months. Stroke was right-sided in 23 (45%) men and 17 (37.8%) women. The stroke etiology was ischemic in 35 (68.6%) men and 39 (86.7%) women. The presence of re-stroke was present in three men (5.9%) and eight women (17.8%). The mean FAS scores of men and women were 3.10±1.43 and 2.91±1.66, respectively. According to MMT evaluation; there was no cognitive loss in 29 (56.9%) men and 20 (44.4%) women. According to BDS evaluation; minor depression was found in 17 men (33.3%), mild depression in 11 men (21.6%), moderate depression in 18 men (35.3%), and severe depression in five men (9.8%). Minor depression was found in 10 women (22.2%), mild depression in 11 women (24.4%), moderate depression in 17 women (37.8%), and severe depression in seven women (15.6%). According to the Barthel index; one (2%) of the men was entirely dependent, 11 (21.6%) severely dependent, 22 (43%) moderately, and 11 (21.6%) mildly dependent. Three (6.7%) of the women were entirely dependent, 10 (22.1%) severely dependent, 16 (35.6%) moderately, and 12 (26.7%) mildly dependent. Clinical and demographic features of patients according to gender groups are summarized in **Table 1**.

Evaluation of Sexual dysfunction in All Cases

The mean ASES of all cases was 18.29±6.02, for women and men were 16.94±5.92 and 19.82±5.84, respectively. When the ASES cut-off point was 11, we found that 88.5% of the participants (84.3% in men and 93.3% in women) had sexual dysfunction. There was no significant difference between the frequency of sexual dysfunction in women and men (p=0.166, Pearson Chi-square Test). According to univariate ANOVA results, age (p=0.028) and BDI (p<0.001) values had a significant effect on ASES. An increase in age values and a decrease in FAS values increased ASES values. Etiology*BDI (p=0.051, η2=0.143) interaction was also predictive for ASES. The increase in ischemic etiology and BDS scores increased ASES scores (**Table 2**).

Evaluation of Sexual dysfunction in Men

Two of the men (4%) had no sexual activity. According to the IIEF ED subscale, there were seven (13.8%) men with severe, 17 (33.3%) moderate, 11 (21.6%) men with mild-moderate, and 10 (19.6%) men with mild ED. Erectile dysfunction was impaired in 45 (88.2%) of the men. The total mean of IIEF in men was 43.35±16.44, the mean of desire subscale was 5.96±1.87, the mean of orgasm subscale was 6.76±2.62, the mean of sexual satisfaction subscale was 7±3.07, and the mean of general satisfaction subscale was 5.67±2.62. According to univariate ANOVA results; side of stroke (p=0.030), BME (upper extremity) (p=0.028) and BDS (p<0.001) values had a significant effect on IIEF total values. Decreased IIEF total scores are associated with the stroke's left side, decreased BME values , and high BDS scores (**Table 3**).

Table 1. Clinical and demographic features of patients according to gender groups

	Male (n=51)	Female (n=45)
Age (years, mean, SD)	57.76±7.57*	60.13±12.71*
Time after stroke (month, mean, SD)	18.27±21.79	19.02±24.91
Side of deficit		
Right (%)	23 (45)	17 (37.8)
Left (%)	28 (55)	28 (62.2)
Type of last stroke		
Ischemic (%)	35 (68.6)	39 (69.7)
Hemorragic (%)	16 (31.4)	6 (13.3)
Recurrence of stroke (%)	3 (5.9)	8 (17.8)
Presence of urinary incontinence (%)	3 (5.9)	2 (4.4)
FAS (mean, SD)	3.10±1.43	2.91±1.66
MMT		
27-30 (normal, %)	29 (56.9)	20 (44.4)
24-27 (mild, %)	22 (43.1)	25 (55.6)
BDS (mean, SD)	2.39±1.60	2.6±1.01
Barthel's index (mean,SD)	3.20±0.98	4.98±13.01
BME		
UE (mean, SD)	3.35±1.57	3.22±1.44
Hand (mean, SD)	3.12±1.7	3.07±1.36
LE (mean, SD)	3.73±1.2	3.62±1.19
ASS		
UE (mean, SD)	1.16±1.08	0.78±0.77
LE (mean, SD)	1.06±107	0.62±0.75

ASS, Ashworth spasticity scale; BDS, Beck depression scale; BME, Brunnstrom motor evaluation; FAS, functional ambulation score; LE, lower extremity; MMT, mini-mental test; SD, standard deviation; UE, upper extremity. *Normally distributed data.

Table 2. Variance analysis of Arizona Sexual Experiences Scale

Variables	df	Mean Square	F	p	η2
Model	45	66.535	7.332	<0.001	0.868
Intercept	1	285.416	31.451	<0.001	0.386
Sex	1	10.631	1.171	0.284	0.023
Age	1	46.234	5.095	0.028	0.092
Chronic Disease	1	2.461	0.271	0.605	0.005
Side of stoke	1	1.026	0.113	0.738	0.002
Etiology	1	12.372	1.363	0.249	0.027
Reccurrence of stroke	1	7.206	0.794	0.377	0.016
Time elapsed after stroke	1	6.018	0.663	0.419	0.013
Urinary incontinence	1	16.207	1.786	0.187	0.034
BME (UE)	1	5.179	0.571	0.454	0.011
ASS (UE)	1	34.873	3.843	0.056	0.071
BDS	3	126.460	13.935	<0.001	0.455
FAS	1	0.208	0.023	0.880	0.000

ASS, Ashworth spasticity scale; BDS, Beck depression scale; BME, Brunnstrom motor evaluation; FAS, functional ambulation score; UE, upper extremity

Table 3. Variance analysis of International Index of Erectile function

Variables	Df	Mean Square	F	p	η2
Model	25	468.505	6.475	<0.001	0.866
Intercept	1	799.707	11.052	0.003	0.307
Age	1	162.323	2.243	0.147	0.082
Chronic disease	1	39.868	0.551	0.465	0.022
Side of stroke	1	383.08	5.294	0.03	0.175
Etiology	1	174.733	2.415	0.133	0.088
Reccurence of stroke	1	60.222	0.832	0.37	0.032
Time elapsed after stroke	1	166.522	2.301	0.142	0.084
Urinary Incontinence	1	120.916	1.671	0.208	0.063
BME (UE)	1	393.343	5.436	0.028	0.179
ASS (UE)	1	303.436	4.193	0.05	0.144
BDS	3	970.181	13.407	<0.001	0.617
FAS	1	170.128	2.351	0.138	0.086

ASS, Ashworth spasticity scale; BDS, Beck depression scale; BME, Brunnstrom motor evaluation; FAS, functional ambulation score; UE, upper extremity

Evaluation of Sexual Dysfunction in Women

Ten of the women (22.2%) had no sexual activity. In women, the total mean FSFI was 41.69±16.77. The mean desire, arousal, lubrication, orgasm, satisfaction, and pain subscale were 4.27±1.81, 7.11±4.71, 8.29±5.60, 4.64±3.10, 6.40±4.22, and 6.87±4.92, respectively. According to univariate ANOVA results, BDS (p=0.001) values significantly affected FSFI total values. The increase in BDS values resulted in a decrease in FSFI total score values. Age (p=0.048) and BDI (p=0.025) values had a significant effect on FSFI lubrication subscale values. The increase in age and BDI values resulted in a decrease in the FSFI lubrication subscale values. Age (p=0.041), time elapsed after stroke (p=0.035) and BDS (p=0.009) values had significant effects on FSFI satisfaction subscale values. An increase in age, decreased time after stroke, and increase in BDS values resulted in decreased FSFI satisfaction subscale values (**Table 4**).

Table 4. Variance analysis of Female Sexual Function Index

Variables	df	Mean Square	F	p	η2
Model	24	395.263	2.736	0.013	0.767
Intercept	1	2397.512	16.596	0.001	0.453
Age	1	141.965	0.983	0.333	0.047
Chronic disease	1	76.606	0.530	0.475	0.026
Side of stroke	1	10.483	0.073	0.790	0.004
Etiology	1	142.624	0.987	0.332	0.047
Reccurence of stroke	1	0.692	0.005	0.945	0.000
Time elapsed after stroke	1	9.522	0.066	0.800	0.003
Urinary incontinence	1	10.063	0.070	0.795	0.003
BME (UE)	1	9.245	0.064	0.803	0.003
ASS (UE)	1	26.194	0.181	0.675	0.009
BDS	3	813.865	5.634	0.006	0.458
FAS	1	128.741	0.891	0.356	0.043

ASS, Ashworth spasticity scale; BDS, Beck depression scale; BME, Brunnstrom motor evaluation; FAS, functional ambulation score; UE, upper extremity

DISCUSSION

Post-stroke sexual dysfunction is common in both men and women. Even in approximately 50% of stroke patients without physical disability or mild physical disability, sexual dysfunctions such as decreased libido, decreased frequency of sexual intercourse, decreased sexual arousal, orgasm problems, and sexual satisfaction problems are observed.[10] According to analyses based on ASES cut-off point, our results showed that the prevalence of sexual dysfunction after stroke was 88.5% in all participants (84.3% in men and 93.3% in women). The rates of sexual dysfunction after stroke in literature are between 20 and 75%.[25] We found a higher rate of sexual dysfunction than the results in the literature. This increase can be explained by the differences in the studies' exclusion criteria and the differences in other study patterns. Patients with depression in one of the studies were not included.[26] The fact that the patients included in our study were hospitalized, in need of rehabilitation, and were dependent or under the supervision of individuals.

ED is a significant problem in male patients after stroke. One study found that 75% of male patients had ED after stroke.[3] The same investigators objectively evaluated erectile function in male patients after stroke and found that 55% of the cases had impaired erection. Our results showed that 88.2% of men after a stroke had impaired erections. These subjects had experienced mild to severe ED within the past four weeks. This study only assessed only the last four weeks of sexual activity might help us to explain the high rate we found.

Studies have shown no independent relationship between age and gender and the presence of post-stroke sexual dysfunction.[3,8,13,26] This study showed an association between advancing age and sexual dysfunction after stroke, but gender is not effective in developing sexual dysfunction.

The results of studies evaluating the hemispheric lesion side and the frequency of development of sexual dysfunction are not consistent. Various studies have shown a positive association between sexual dysfunction and left hemisphere lesions.[8,27] In some studies, sexual dysfunction is more common with right hemispheric lesions than those with left hemispheric lesions.[28,29] Sexual reaction time is affected more significantly in right hemispheric strokes than in left hemispheric strokes.[30] The right hemisphere plays an essential role in the activation/direction of libido and erectile functions.[30] Emotional disturbances are more common in right hemisphere lesions,[11,31] and response to erotic sensations may be difficult due to sensory/perceptual neglect.[5] In addition, post-stroke sexual dysfunctions have been attributed to an imbalance of sympathetic hyperactivity and parasympathetic hypoactivity.[32,33] The high frequency of sexual dysfunctions in patients with right hemispheric stroke has drawn attention. The view of autonomic dysfunction seems plausible given the inhibition of erection by the sympathetic pathways and the pro-

erectile properties of the sacral parasympathetic pathways.[34] In this study, the left-sided (right hemispheric lesion) stroke worsened the sexual functions in mens not in women. In some other studies, no association was found between the lesion side and sexual dysfunction.[26,35] The results of these studies support our findings regarding women.

Stroke causes physical disability due to spasticity, conditions that limit proper body position and movements, and diffuse pain affect the positioning and specific sexual functions (desire, arousal, orgasm, and genital pain). In stroke cases, it becomes difficult to participate in sexual activity by hugging, caressing, touching, or other stimulating movements due to the hemiparetic extremity.[5] After stroke; numerous adverse clinical conditions such as spasticity, limb weakness, and loss of dexterity significantly affect sexual activities.[6] Fifty patients and their spouses were followed for six months after stroke in a prospective study. Those included in this study attributed their difficulties with sexual life to hemiparesis (55%) and spasticity (29%).[9] In our study, retardation of upper extremity motor development in male hemiplegic patients was associated with worsening sexual functions. However, we found that spasticity had no effect on sexual functions in men. We discovered that upper extremity motor development level or spasticity had no impact on sexual functions in women. The mean spasticity levels evaluated with the ASS were 0.98 and 0.85 for the upper and lower extremities, respectively. The fact that the spasticity level of the patients was low in general in our study may help us explain the non-adverse effects of spasticity on sexual functions.

The results of the studies support a relationship between post-stroke depression and the sexual dysfunction.[3,36] The severity of post-stroke depression was an independent predictor of the development of sexual dysfunction in both men and women.[8] A study evaluating 67 patients after stroke showed that 78% of the patients were depressed. Although this study did not evaluate not all aspects of sexual dysfunction, post-stroke depression was found to be related with sexual dysfunction.[37] We found that 71.9% of patients met the criteria for depression. Apart from depression of biological origin caused by stroke,[11, 31] physical problems due to the consequences of stroke, changes in social roles caused by disability, and severe changes in identity can exacerbate reactive depression and impair sexual functioning.[12] In this context, the contribution of depression to sexual dysfunctions in stroke patients is expected to be more pronounced than the stroke lesion itself.[8,13] This study showed that depression has a negative effect on sexual functions at almost every stage of the sexual response cycle, especially in women.

CONCLUSION

The current study showed that post-stroke sexual dysfunctions are significantly high in Turkish rehabilitation inpatient clinics. Post-stroke sexual dysfunctions are linked to multiple etiologies, both organic (hemispheric lesion side, etc.) and psychosocial (depression, etc.). Post-stroke sexual dysfunction is a condition that occurs more frequently than is thought and escapes the attention of health professionals, which patients have difficulty in bringing up. Psychosocial factors contribute significantly to the etiology. Accordingly, the use of the obtained findings in clinical practice is also limited. The natural course of post-stroke sexual dysfunction after recovery is not fully understood. Post-stroke sexual adjustment assessment tools that can be clinically meaningful should be developed. Sexual dysfunctions should be evaluated and managed with a multidisciplinary approach. Adding the definitive diagnosis and treatment of sexual dysfunctions in stroke patients to the current stroke rehabilitation protocol will contribute to the treatment outcomes of stroke patients emotionally and functionally.

Abbrevations: ANOVA: Analysis of Variance, ASES: Arizona Sexual Experiences Scale, ASS: Ashworth spasticity scale, BDS: Beck Depression Scale, BME: Brunnstrom motor evaluation, ED: Erectile dysfunction, FAS: Functional ambulation scale , FSFI: Female Sexual Function Index, IIEF: International Index of Erectile function , LE: Lower extremity, MMT: Mini-Mental test, SD: Standard deviation, UE: Upper extremity

ETHICAL DECLARATIONS

Ethics Committee Approval: The local ethics committee approved this study of Ankara Physical Therapy and Rehabilitation Hospital, Turkey (22.12.2014).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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

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Orijinal Araştırma / Original Article

Efficacy of Endoscopic Band Ligation in the Treatment of Acute Esophageal Varicose Bleeding

Akut Özofagus Varis Kanama Tedavisinde Endoskopik Band Ligasyonunun Etkinliği

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Abstract

Aim: To determine the efficacy of endoscopic band ligation (EBL) on rebleeding and mortality in the treatment of esophageal varices bleeding.

Material and Method: Fifty cirrhosis patients who applied to the emergency department with acute esophageal variceal bleeding between 2018 and 2020 and were treated with EBL within the first 12 hours were evaluated retrospectively.

Results: Twenty-seven (54%) patients were male and 23 (46%) were female. The mean hospital stay of the patients was 6.4±5.6 days, and the mean blood transfusion requirement was 3.6±2.7 units. Re-bleeding was observed within 30 days in 5 (10%) patients and within 1 year in 7 (14%) patients. Ten (20%) patients died within 30 days, and 11 (22%) patients died within 1 year. The need for blood transfusion was higher in patients with grade 3 varicose veins (4.9±3.1) than in patients with grade 2 varicose veins (2.5±1.5) (p=0.001). Mortality rate within 30 days and 1 year was significantly higher in patients with grade 3 varicose veins (p=0.001). Although the rate of bleeding within 30 days and 1 year was higher in patients with grade 3 varicose veins than in patients with grade 2 varices, the difference was not significant (p=0.087).

Conclusion: EBL is an endoscopic treatment method to be preferred in patients with acute esophageal variceal hemorrhage due to its low risk of re-bleeding and low mortality rate.

Keywords: Cirrhosis, endoscopic band ligation (EBL), esophageal varices bleeding

Öz

Amaç: Özofagus varis kanama tedavisinde endoskopik band ligasyonunun (EBL) yeniden kanama ve mortalite üzerine etkinliğini belirlemek.

Gereç ve Yöntem: 2018-2020 yılları arasında acil servise akut özofagus varis kanaması ile başvuran ve ilk 12 saat içerisinde EBL tedavisi uygulanan 50 siroz hastası retrospektif olarak değerlendirildi.

Bulgular: Hastaların 27'si (%54) erkek, 23'ü (%46) kadındı. Hastaların ortalama hastanede yatış süresi 6,4±5,6 gün, ortalama kan transfüzyon ihtiyacı 3,6±2,7 ünite idi. Beş (%10) hastada 30 gün içinde, 7 (%14) hastada 1 yıl içinde tekrar kanama görüldü. On (%20) hasta 30 gün içinde, 11 (%22) hasta 1 yıl içinde öldü. Grade 3 varisli hastalarda (4,9±3,1) grade 2 varisli hastalara (2,5±1,5) göre kan transfüzyon ihtiyacı daha fazla idi(p=0,001). 30 gün ve 1 yıl içinde ölüm oranı grade 3 varisli hastalarda anlamlı olarak daha yüksekti (p=0,001). Otuz gün ve 1 yıl içinde kanama görülme oranı grade 3 varisli hastalarda grade 2 varisli hastalara göre daha yüksek olmakla birlikte fark anlamlı değildi (p=0,087).

Sonuç: Akut özofagus varis kanama hastalarında EBL, tekrar kanama riskinin ve mortalite oranının az olması nedeniyle tercih edilecek bir endoskopik tedavi yöntemidir.

Anahtar Kelimeler: Siroz, endoskopik bant ligasyonu (EBL), özefagus varis kanaması

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INTRODUCTION

Gastroesophageal variceal bleeding is the most important complication of portal hypertension and the leading cause of death in cirrhotic cases.[1] Increased intrahepatic vascular resistance to portal flow leads to the development of splanchnic vasodilation that results in portal hypertension and an increase in hyperdynamic circulation and portal blood flow. When portal pressure rises above a threshold, gastroesophageal collaterals that develop at the site of communication between the portal and the systemic circulation enlarge with exacerbation of portal hypertension and eventually rupture.[2]

In patients with liver cirrhosis and suspected variceal bleeding, providing immediate hemodynamic stabilization, careful transfusion until the target hemoglobin is not higher than 7-8 g/dL to prevent volume-dependent increase in portal pressure, use of vasoactive drugs to reduce flow into the portal system, and use of antibiotics to eliminate inflammatory stimuli is necessary and endoscopy should be performed under careful airway protection as soon as possible.[3]

Endoscopic sclerotherapy (EST) and endoscopic band ligation (EBL) are two treatment options for esophageal varices.[4] Vasoactive drugs such as vasopressin, terlipressin, somatostatin and octreotide are effective in hemostasis by reducing portal pressure in patients with acute variceal bleeding.[5]

With the implementation of effective treatment options such as endoscopic and pharmacological treatments and transjugular intrahepatic portosystemic shunt, the death rate from esophageal variceal bleeding has decreased from 42% to 6-12% in the last two decades.[4] Therefore, prompt and appropriate treatment is important in patients with acute variceal bleeding.

The aim of our study is to determine the effectiveness of EBL on rebleeding and mortality in the treatment of esophageal varices bleeding in cirrhotic patients.

MATERIAL AND METHOD

The study included 69 cirrhosis patients who applied to the emergency department with acute esophageal variceal bleeding between 2018 and 2020 and were treated with EBL within the first 12 hours. Demographic, clinical, laboratory and endoscopic findings of the patients were obtained retrospectively by file scanning. 19 patients with incomplete information were excluded from the study. The duration of hospitalization, rebleeding rates, blood transfusion needs and mortality rates of the remaining 50 patients were analyzed. The patients' esophageal varices were classified as follows: Grade 1 (small) varices, minimally elevated veins above the surface; grade 2 (moderate) varices, convoluted veins covering <1/3 of the esophageal lumen; grade 3 (large) varices, veins in contact with each other covering >1/3 of the esophageal lumen.[6] Somatostatin treatment (250 µg IV bolus followed by 250 µg/hour continuous infusion) was started in all patients with acute esophageal variceal bleeding, and endoscopic band ligation was performed in the endoscopy unit.

The study was approved by University of Health Sciences, Gaziosmanpaşa Education and Research Hospital Ethics Committee (Date: 27.01.2021, Decision No: 219). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Statistical Analysis

The conformity of the numerical variables to the normal distribution was tested with the Shaphiro Wilk test. The Mann Whitney U test was used to compare the non-normally distributed variables in the two groups. The relationships between categorical variables were tested with the Chi-square test, and the relationships between non-normally distributed numerical variables were tested with Spearman's rank correlation coefficient. SPSS 22.0 Windows version package program was used in the analysis. $P<0.05$ was considered significant.

RESULTS

In our study, 27 (54%) patients were male and 23 (46%) were female. The mean age was 62.1±13.6. The demographic characteristics of the patients and their initial findings at the time of admission are shown in **Table 1**. According to the classification of esophageal varices, 26 (52%) patients had grade 2 varicose veins and 24 (48%) patients had grade 3 varicose veins (**Table 2**). Re-bleeding was observed within 30 days in 5 (10%) patients, within 1 year in 7 (14%) patients, and re-bleeding was not observed within 1 year in 38 (76%) patients. The mean hospital stay of the patients was 6.4±5.6 days, and the mean blood transfusion requirement was 3.6±2.7 units. Ten (20%) patients died within 30 days, and 11 (22%) patients died within 1 year. There was no significant difference between men and women in terms of rebleeding rates (p=0.800), length of hospital stay (p=0.462), need for blood transfusion (p=0.384) and death rates (p=0.093). Although the rate of bleeding within 30 days and 1 year was higher in patients with grade 3 esophageal varices compared to patients with grade 2 varicose veins, the difference between them was not statistically significant (p=0.087) (**Table 3**). However, the mortality rate within 30 days and 1 year in patients with grade 3 varices was significantly higher than in grade 2 patients (p=0.001). At the same time, the need for blood transfusion was found to be higher in patients with grade 3 varicose veins (4.9±3.1) than in patients with grade 2 varicose veins (2.5±1.5) (p=0.001). There was no significant relationship between rebleeding times and death rates (p=0.149). According to Spearman correlation analysis, there was a weak negative correlation between systolic blood pressure and the need for blood transfusion of patients (r= -0.340, p=0.016) and a weak positive correlation between systolic blood pressure and length of hospital stay (r= 0.346, p=0.014) found.

Table 1. Initial data of the patients at the time of admission (n=50)

Gender (male/female) n (%)	27 (54)/23 (46)
Age	62.12±13.6
Pulse	95.44±16.43
Systolic blood pressure	88.46±16.73
BUN	65.33±37.04
Creatinine	1.43±1.07
Hemoglobin	8.82±2.46
Glucose	143.5±65.49
AST	64.56±60.55
ALT	41.4±29.5
Sodium	138.46±9.17

Mean±SD; BUN: blood urea nitrogen; AST:Aspartate aminotransferase; ALT: Alanine aminotransferase

Table 2. Clinical features and follow-up findings of the patients

Length of stay (days) (Mean±SD)	6.4± 5.67
Blood transfusion (unit) (Mean±SD)	3.68±2.71
Esophageal varices grade	**n (%)**
Grade 1	0 (0)
Grade 2	26 (52)
Grade 3	24 (48)
Rebleeding n (%)	
Yes	12 (24)
No	38 (76)
Rebleeding time n (%)	
Bleeding within 30 days	5 (10)
Bleeding within 1 year	7 (14)
No bleeding within 1 year	38 (76)
Death n (%)	
Death within 30 days	10 (20)
Death in 1 year	11 (22)
No death in 1 year	18 (36)

Table 3. Follow-up findings according to the varicose vein sizes of the patients

	Esophageal varicose size		p
	Grade 2	Grade 3	
Length of stay /day (Mean±SD)	5.85±5.08	7.0±6.31	0.551
Blood transfusion/unit (Mean±SD)	2.54±1.56	4.92±3.15	0.001*
Death, n (%)			
Death within 30 days	1 (3.8)	9 (37.5)	
Death within 1 year	3 (11.5)	8 (33.3)	0.001*
No death in 1 year	22 (84.6)	7 (29.2)	
Rebleeding, n (%)			
Bleeding within 30 days	1 (3.8)	4 (16.7)	
Bleeding within 1 year	2 (7.7)	5 (20.8)	0.087
No bleeding within 1 year	23 (88.5)	15 (62.5)	

* Significant at p<0.05 level, Chi-square test, Mann Whitney U test

DISCUSSION

According to our study results, the rate of rebleeding within 30 days after EBL treatment was 10% and the rate of rebleeding within 1 year was 14% in patients with acute esophageal varices bleeding. In addition, death occurred within 30 days in 10 (20%) patients and within 1 year in 11 (22%) patients. As varicose size increases in patients treated with EBL, annual bleeding and mortality rates increase.

Studies have shown that esophageal varices are present in 30% to 40% of patients with compensated cirrhosis and 85% of patients with decompensated cirrhosis.[7] After the diagnosis of varicose veins, the overall incidence of variceal bleeding per year is 10-15%.[4] The most important predictive factors are the size of varicose veins and the severity of liver dysfunction.[8] Varicose size is the most useful predictor of variceal bleeding.[9] The risk of bleeding is 1-2% in patients without varicose veins in their first endoscopies, and 5% in those with small varicose veins. In those with medium and large heirs, this rate rises to 15%.[4] In our study, the annual rate of bleeding and death in patients with grade 3 (large) varicose veins after EBL treatment in acute variceal bleeding was higher than in patients with grade 2 (moderate) varices.

The two main treatment modalities available for esophageal varices are EST and EBL.[4] In a recent meta-analysis comparing these two methods, it was reported that rebleeding rates were lower and varicose eradication rate was higher in the EBL group compared to the EST group.[10] Compared to EST, EBL requires fewer treatment sessions to achieve varicose obliteration and is associated with fewer complications.[11] In another meta-analysis, the rate of rebleeding was found to be significantly lower in the EBL group than in the EST group, and the main cause of rebleeding was reported to be varicose or treatment-related ulcers. At the same time, in this meta-analysis, no significant difference was found between the EBL group and the EST group in terms of mortality.[10] EBL has replaced EST as first-line therapy in the management of esophageal varices bleeding, as it has better survival, less risk of rebleeding, and fewer side effects.[11,12]

In a recent study, in the 3-year follow-up of cirrhotic patients with acute variceal hemorrhage treated with EBL, recurrence of bleeding was reported in 28% of patients and death in 39%. Independent factors associated with rebleeding were found to be lack of EBL follow-up, BMI > 30 kg/m², Child C class, and large-grade varicose veins. Independent factors associated with mortality were reported as age >65 years, rebleeding, hepatocellular carcinoma, and lack of EBL follow-up. In this study, the reason for the high rebleeding and death rate was considered to be related to the lack of follow-up endoscopy.[13] EBL may cause rebleeding from the ulcer after banding.[14] Recurrent bleeding after emergency endoscopic ligation of acute esophageal varices bleeding in cirrhotic patients is a common complication that increases the mortality rate significantly.[13] Guidelines recommend repeated endoscopy after control of acute variceal bleeding attack until varices are eradicated.[15] In patients with acute varicose hemorrhage, the rate of rebleeding within 6 weeks after the first attack has been reported as 30-40%, and the rate of rebleeding within the first year has been reported as 60%.[16,17] In our study, the rate of rebleeding within 30 days was 10%, and the rate of rebleeding within 1 year was 14%. The reason why our rebleeding rates are lower than the results of other studies may be related to the repeated endoscopic controls we applied to our patients after a bleeding episode.

Most guidelines recommend performing endoscopy within 12 hours of admission with acute variceal bleeding, when the patient is hemodynamically stable.[18-20] In our study, endoscopy was performed in all patients after hemodynamic stabilization was achieved within 12 hours of the emergency admission. None of the patients died during endoscopic treatment. However, some studies have shown that the timing of endoscopy is not associated with mortality or rebleeding rate in patients with acute variceal bleeding.[21,22] Cheung et al. did not show a significant relationship between the time to endoscopy and mortality or rebleeding in patients with hemodynamically stable acute variceal bleeding.[23] In a meta-analysis, the timing of endoscopy did not affect the rate of mortality or rebleeding in patients with acute variceal bleeding.[24] In patients with stable hemodynamics, no significant comorbid disease, or good liver function, endoscopic intervention may be delayed until adequate medical therapy (eg, intravenous vasopressin, fluid resuscitation) is administered.[22,23] In the acute phase, 3 to 5 days of treatment with intravenous splanchnic vasoconstrictors such as terlipressin, somatostatin or somatostatin analogues may help control bleeding by reducing portal pressure.[25] In a recent meta-analysis, the use of vasoactive drugs in patients with acute variceal bleeding was associated with a significant reduction in 7-day mortality and a significant increase in hemostasis.[26] Therefore, it is recommended to start these drugs as soon as possible before endoscopy in patients with suspected acute variceal bleeding and continue for 3-5 days.[18,20] Another meta-analysis showed that the combination of endoscopic therapy (ETS or EBL) and vasoactive drugs improved initial hemostasis and reduced early rebleeding within 5 days compared to endoscopic therapy alone.[27] In our study, EBL was combined with vasoactive drugs in patients with acute esophageal variceal bleeding.

Limitations

The limitation of our study is such that the sample size is relatively small. In addition, since the data were obtained retrospectively, some of the data of the patients could not be obtained. Therefore, Child classification of the patients could not be made and MELD values could not be calculated.

CONCLUSION

In conclusion, EBL is an endoscopic treatment method to be preferred in patients with acute esophageal variceal bleeding because of the low risk of re-bleeding and the low mortality rate. At the same time, EBL should be combined with vasoactive drugs.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by University of Health Sciences, Gaziosmanpaşa Education and Research Hospital Ethics Committee (Date: 27.01.2021, Decision No: 219).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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Orijinal Araştırma / Original Article

Treatment of COVID-19-Releated Hyperinflammatory Response in Intensive Care Unit: Pulse Steroid, Anticytokines, IVIG, Plasmapheresis

COVID-19'a Bağlı Gelişen Hiperinflamatuvar Yanıtın Yoğun Bakımda Tedavisi: Antisitokinler, Plazmaferez, IVIG, Sitokin Filtresi

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Abstract

Aim: In our study, we aimed to see whether there is a difference in the survival effects of the treatments in 144 covid-19 patients who developed HIS.

Material and Method: Between Nov 2020 and Jan 2021; we retrospectively evaluated 650 patients who were admitted in to intensive care unit (ICU). Among these patients, we analyzed 144 patients whom recieved pulse steroid, anticytokine, plasmapheresis and IVIG treatment alone or in combination. The treatment planning of Covid-19 in our hospital is organized and implemented by a multidisciplinary treatment board. Accordingly, pulse was administered to patients whom had shown HIS findings after the day 7 of the initial diagnosis. If there is no contraindication; transition to anticytokine treatment and then plasmapheresis and / or IVIG was applied.

Results: When all the treatments were examined, no difference was found between the survival rates according to the application. While the mortality rate was %68 in all patients hospitalized in our ICU's with Covid-19, this rate was found to be %81 in our patients with HIS.

Conclusion: There is an obvious condition that an amount of time is needed for supposed positive results of our admitted treatments. While our mortality rate was lower in all patients we followed up; in accordance with our expectations, we can say that the mortality rate is high in patients with HIS. The fact that no superiority of treatment modalities was observed in our study; we can still attribute the fact that the clinics of Covid-19 patients are not homogeneous and that there is no definite standardization regarding treatment yet.

Keywords: Critical care, COVID-19, hyperinflamatory response, acute respiratory distress syndrome, steroids.

Öz

Amaç: Çalışmamızda, COVID-19 ilişkili hiperinflamatuvar yanıt (HIS) gelişen 144 hastamızda uyguladığımız tedavilerin sağkalıma etkilerini incelemeyi amaçladık.

Gereç Ve Yöntem: 1 Kasım 2020 ve 31 Ocak 2021 aralığında COVID-19' a bağlı ağır solunum yetmezliği ile yoğun bakımlarımızda takip ettiğimiz 650 hasta retrospektif olarak taranmıştır. Bu hastalardan 144 kişide COVID-19'a bağlı HIS varlığı düşünülerek tedavilerinde pulse steroid, antisitokin ajanlar, plazmaferez ve IVIG uygulamalarına yer verilmiştir. Bu tedavi uygulamalarının bir kısmı tek başına bir kısmı bir arada kullanılmıştır. Hastanemizde COVID-19 ilişkili hastalık tablosunun yönetimi, multidisipliner bir komite tarafından yürütülmektedir. Bu komitenin kararları doğrultusunda, tanıdan yaklaşık 7 gün geçtikten sonra hiperinflamatuvar yanıt bulguları gelişen hastalara pulse steroid verilmiştir. Daha ileri tedavi gerekliliği gösteren hastalarda, kontrendikasyon olmaması gözetilerek; antisitokin ajanlara, plazmaferez ve IVIG' e geçilmiştir.

Bulgular: Tüm tedavi ajanları değerlendirildiğinde, sağkalım üzerindeki etkilerinde farklılık gözlenmemiştir. Çalışmanın kapsadığı dönemde, yoğun bakımda takip ettiğimiz tüm COVID-19 hastalarımızın mortalite oranı %68 iken, HIS gelişmiş olan hastalarımızın mortalitesi %81 olarak bulunmuştur.

Sonuç: Takip ettiğimiz tüm hastalarda mortalite oranımız daha düşük iken; beklentilerimiz doğrultusunda HIS görülen hastalarda mortalite oranının yüksek olduğunu söyleyebiliriz. Çalışmamızda tedavi modalitelerinin birbirine üstünlüğünün görülmemesini, COVID-19 hastalarının homojen olmamasına ve kanıtlı tedavilerin henüz olmamasına bağlamaktayız.

Anahtar Kelimeler: Yoğun bakım, COVID-19, hiperinflamatuvar yanıt, akut respiratuvar distress sendromu, steroidler,

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INTRODUCTION

Physical damage due to hyperinflammatory response is one of the primary factors affecting the severity of the course of the disease. Even though the Covid-19 pandemic has been present for almost 2 years, we still lack laboratory parameters with high specificity, radiological markers, scoring systems or clinical results utilizable for predicting which patients are likely to develop severe inflammatory responses. Furthermore, there is a prevailing uncertainty regarding the development of HIS, a factor that can independently affect high mortality. Rescue treatment applied for HIS has disadvantages, possibly leading to mortal results. In this study, we aim to investigate the effects of pulse steroid, tocilizumab, anakinra, IVIG and plasmapheresis treatments in in ICU patients who developed HIS due to severe course of the disease.

MATERIAL AND METHOD

After receiving approval from the Ethical Board for Scientific Research (Decision number: KAEK/2021.03.21), we searched the hospital database for patients who received pandemic ICU-care due to Covid-19 or related syndromes (e.g. ARDS and other organ failures) in our hospital, between November 1, 2020 and January 31, 2021. Of the 650 patients turning up in the results, 144 who had developed HIS were included in the study. 144 patients who had received HIS diagnosis in the ICU were closely evaluated through the hospital database and archive files. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

HIS diagnosis was given to patients presenting at least 3 of the following criteria: persistent fever, increase in oxygen demand, increase in ferritin, d-dimer, CRP, LDH, SGOT and SGPT, and advancing lymphopenia. All the Covid-19 patients who met the criteria for HIS diagnosis were included in the study. Patients with known rheumatic or hematological diseases, patients with diagnosed malignancy and patients receiving any kind of immunosuppressant treatment were excluded.

All Covid-19 patients admitted to ICU were, as a first step, received a standart treatment consisting of favipravir, low molecular weight heparin (LMWH), acetylsalicylic acid (ASA) and metilprednizolon. Favipiravir was ordered as 2X1600 mg peroral (po) loading for the first dose, followed by 2X600 maintenance dose. The remaining drugs were prescribed according to the following regimen: Metilprednizolon 1 mg/kg/day intravenously (iv), DMAH 0,01 U/kg, acetylsalicylic acid 100 mg po. As for the ventilation, invasive and noninvasive protective mechanical ventilation strategies, high-flow nasal oxygen (HFNOT) and non-breather masks were utilized. Prone position was preferred in all patients when there were no contrindications. First choice in empirical antimicrobial treatment was moxifloxasin. D-dimer, aPTT, ferritin, CRP, procalsitoninin (PCT), fibrinogen, complete blood count, SGOT-SGPT, LDH, urea, creatinine, and bilirubin levels of all patients were monitored on a daily basis. Anteroposterior chest radiography was routinely performed 2 times a week, except for patients requiring more frequent investigation. Furthermore, patients were monitorised closely and treated when necessary in terms of fluid balance, nutrition, analgesia and sedation.

Patients who were pre-diagnosed with HIS were presented to the Covid-19 treatment committee of the hospital, which consists of a ICU specialist, a rheumatologist, a hematologist and an infectious diseases specialist. Following the decision of the committee, patients first received pulse steroid (250-1000 mg/day, for 3 days). Patients who were considered to be non-responsive to steroid within 24-48 hours were represented to the committee and were evaluated for anticytokine therapy, intravenous immunoglobulin treatment (IVIG) and plasmapheresis. Choice for further treatment was based on PCT value and surveillance cultures indicating possible secondary infections. If there were not any indicators of infection and if the PCT level was not high, patient was considered to be in a persistent hyperinflammatory condition, and received one of the anticytokine therapy options. In the anticytokine treatment regimen, patients either received IL-6 inhibitor tosulizumab 400 mg/day for consecutive 2 days or IL-1 inhibitor anakinra 3X200 mg/day (3 days), 3X100 mg/day (3 days) adding up to 10 days depending on the response. If a secondary infection was found to be most likely (PCT is high and cultures indicate growth or pre-growth), the decision was targeted antibiotic therapy usually with either plasmapheresis or IVIG. If there were findings of a secondary infection or damage in end organs consistent with septic shock, IVIG was the first choice. If the patient did not respond to an IVIG treatment regimen of 0,4 mg/kg/day after 5 days, we moved on to plasmapheresis. After 2 consecutive days of plasmapheresis, depending on the response, the treatment was continued for a maximum of 5 days, being applied every other day. Expected response in these treatments is improvement in clinical presentation and laboratory results.

We used NCSS (Number Cruncher Statistical System) Statistical Software (Utah, USA) for statistical analyses. Data were evaluated based on descriptive statistical methods (mean, standard deviation, median, frequency, ratio, IQR) as well as Shapiro Wilk test and box plot graphics to compare variables to normal distribution. For variables found to be non-normally distributed, we used Mann Whitney U test for between-group comparisons, and Wilcoxon signed-rank test for within-group comparisons. Survival evaluations were made using Kaplan Meier survival analysis and Log rank test. Significance level was determined as $p<0.05$.

RESULTS

Cases included in the study has an age range of 26 to 92 years. Demographical qualities, comorbid diseases, APACHE II scores within the first 24 hours after ICU-admission, number of intubated and not intubated patients, number of discharged patients and number of exitus cases, duration of of ICU-care were presented in **Table 1**.

Table 1. Distribution of descriptive factors		
Age	Min-Max (Median)	26-92 (65)
	Mean±SD	64.63±11.76
Gender	Female	56 (38.9)
	Male	88 (61.1)
Comorbidities	No	34 (23.6)
	Yes	110 (76.4)
Diseases (n=110)	Diabetes Mellitus	55 (50.0)
	Hypertension	70 (63.6)
	Hyperlipidemia	2 (1.8)
	COPD	17 (15.5)
	Malignancy	15 (13.6)
	CF/ACS	25 (22.7)
	Rheumatic diseases	1 (0.9)
	Cerebrovascular disease	6 (5.5)
	Dementia/Alzheimer's	4 (3.6)
	Other	35 (31.8)
APACHE-II	Min-Max (Median)	7-48 (19.5)
	Mean±SD	21.68±9.17
Intubation	No	128 (88.9)
	Yes	16 (11.1)
Result	Discharge	26 (18.1)
	Ex	118 (81.9)
Duration	Min-Max (Median)	1-71 (11)
	Mean±SD	13.63±11.38

COPD: Chronic obstrictive pulmonary disease, CF: Cardiac failure, ACS: Acute coronary syndrom.

We have found that 91.7% of our patient received pulse steroids (250 mg/day) for 3 days. Based on clinical and laboratory data, number of patients we estimate to be non-resposive to pulse steroid at the second day was 64 **Table 2**.

Table 2. Distribution based on treatment		
		Number of Patients n (%)
Treatment	Pulse	132 (91.7)
	Anakinra	40 (27.8)
	Tocilizumab	14 (9.7)
	Plazmapheresis	20 (13.9)
	IVIG	26 (18.1)

Of the total number of 144 cases, 91.7% received pulse steroids while 27.8% received Anakinra, 9.8% received Tocilizumab, 13.9% plasmapheresis and 18.1% IVIG treatment. Some of our patients were found to receive a combination of these treatments, Pulse+Anakinra being the most frequent combination (25.7%, n=37). 2.1% cases did not receive any treatment at all while 51.7% was found to use single medicine, whereas 31.9 used two medicines, 12.5% used three medicines and 2.1% used four medicines.

Among the cases not receiving pulse treatment, 3(25%) cases were observed to survive, whereas 9(75%) did not survive, and the average survival period was 17.96±2.92 days. As for the group receiving the treatment, 23(17.4%) cases survived, 109(82.6%) patients were exitus, and the average survival period was 16.32±1.53 days.

In cases not receiving Anakira treatment, 19(18.3%) cases survived, whereas 85 did not survive, and the average survival period was 17,29±1,81 days. As for the group receiving the treatment, 7(17.5%) cases survived, 33(82.5%) patients were exitus, and the average survival period was 13.85±1.49 days.

In cases not receiving Tocilizumab treatment, 23(17.7%) cases survived, whereas 107 did not survive and the average survival period was 16.69±1.56 days. As for the group receiving the treatment, 3(21.4%) cases survived, 11(78.6%) patients were exitus, and the average survival period was 14.28±2.39 days.

In cases not receiving plasmapheresis treatment, 25(20.2%) cases survived, whereas 99 did not survive and the average survival period was 17.02±1.77 days. As for the group receiving the treatment, 1(5%) cases survived, 19 patients were exitus, and the average survival period was 16.57±1.86 days.

In cases not receiving IVIG treatment, 24(20.3%) cases survived, whereas 94 did not survive and the average survival period was 17.23±1.83 days. As for the group receiving the treatment, 2(7.7%) cases survived, 24 patients were exitus, and the average survival period was 15.10±1.30 days. The relationship between survival rate and type of treatment was not significant for any of the treatments.

DISCUSSION

Covid-19-related HIS or Covid-19-related cytokine storm syndrome (CSS) is based on the former concept of cytokine storm. Cytokine storm was first observed in graft-versus-host-disease, and was later described for viral infections (e.g. influenza, SARS), autoimmune diseases (systemic lupus eritematozus and juvenile rheumatoid arthiritis) and hematological diseases (hemophagositic lymphohistiosytosis-HLH). CSS results from inappropriate activation of lymphocyte and macrophage, which causes extensive release of cytokine/chemokine, initiating systemic inflammation, and leading to multiple organ failure and high mortality(1). In Covid-19-related disease, similar symptoms and HIS develops usually by the end of the first week. Persistent fever, intensification of lymphopenia, increase in ferritin, d-dimer, LDH and CRP, worsening clinical and radiological findings (increased need of oxygen and increased pulmonary infiltrates) were evaluated as HIS-development and these patients were treated with advanced treatment agents.

Even though case series from the early days of the Covid-19 pandemic and retrospective cohort analyses are encouraging in terms of steroid use for Covid-19-associated diseases, many guidelines still suggest its use only for severe cases (2). Based on previous experiences with SARS and MERS pandemics, steroids have been among the first choices due to their systemic affects and their suppressing effect on lung inflammation. However, there are still reservations, since steroids may decrease viral clearance and increase viral load (3). A meta-analysis covering 73 studies reported that 53% of the ICU-patients received steroids, and that steroids are

favorable in severe Covid-19 patients in terms of mortality. However, there were not any significant differences between high or low doses (4). Results of the Recovery study announced on February 2021 indicate that even though patient groups were heterogenous, when patients who do nor do not use dexamethasone were compared, the dexamethasone group was found to have less mortality within 28 days (5). National Health Commission of the PRC, Surviving Sepsis Committee, WHO and Turkish Republic Ministry of Health all suggest, albeit in different evidence levels and dosages, use of steroids in severe conditions. In our study, when patients who were on a 1mg/kg/day metilprednizolon regimen developed HIS, they received pulse steroid 250 mg (IV) for 3 days, and the mortality rate was a high 82.6%. However, we cannot argue that pulse steroid treatment was the direct cause of this mortality rate. Retrospectively, we observed that number of patients who did not receive pulse steroids even though they developed HIS was very limited. If a prospective study with a matching control group could be designed, more conclusive implications could be made.

We used anticytokine treatment for patients who did not respond to pulse steroids after 48 hours, who did not present secondary infection findings, and for whom the suspicion of an infection was low. Major cytokines responsible for the cytokine storm include interleukins (IL-1, IL-6, IL-8), tumor necrosis factor (TNF-α), many of the pro-inflammatory chemokines and interferons (IFN-γ) (6). For the anticytokine treatment, we used anakinra and tocilizumab as antibodies against IL-1 and IL-6, respectively. Tocilizumab is a monoclonal antibody developed against the membrane-bound and soluble IL-6 receptor. Formerly used in chimeric antigen receptor (CAR) T-cell therapies, it was first tried on Covid-19-associated cytokine storm by Xu and colleagues in China (7). In a meta-analysis by Aziz et.al., this treatment regimen was reported to decrease mortality and need for mechanical ventilation, after which it began to appear in international guidelines (8). Covid-19 treatment guideline of Turkish Ministry of Health suggests off-treatment use of tosilizumab or anakinra in cases with macrophage activation syndrome and unresponsive to glucocorticoid treatment or cases with fast-progressing macrophage activation syndrome (9). According to the regimen prescribed in this guideline, we provided patients with 400 mg of tocilizumab as the first dose, and repeated the same dosage intravenously 24 hours later. Our data indicates that mortality rate for patients receiving tocilizumab treatment was 78.6%.

We also used another anticytokine treatment agent, the IL-1 antagonist anakinra, in the light of present literature. We could say that, during anakinra treatment, the declining trend follow-up with CRP and ferritine, compared to the late response with tocilizumab, makes it easier for us to judge the response to the drug.Iglesisas-Julian and colleagues conducted a high-dose subcutaneous anakinra study with severe Covid-19 patients who developed cytokine storm, and reported that 55.6% of the patients benefited from high-dose anakinra, that they observed decrease in CRP, ferritin and d-dimer levels, and that there were not any secondary infections. In our retrospective study, we found that patients who received anakinra in 2-10 mg/kg, mortaliy rate was 82.5%. This high mortality rare raises up questions regarding the timing of the anticytokine treatment. We have, unfortunately, failed to access any clear suggestions on this matter in the present literature. However, limited information and comments seem to suggest starting the treatment early. Another important factor is that in case of pandemics, especially during the peak periods, additional intensive care units are established. Furthermore, in these conditions, problems in standard care procedures are most possible. In the case of ICUs, even the presence of such a possibility could lead to negative results on mortality. Statistically, we have found that of the 54 patients who received tocilizumab or anakinra, 10 were discharged from the ICU. Even though this is not a significant ratio, we still consider these treatment regimen as a viable life-saving option, and think that turning to multiple anticytokine treatment combinations in the light of further research is probable.

IVIG and plasmapheresis treatments seem to fall behind anticytokines in HIS treatments. IVIG is produced from human plasma collected from general population. It is used in primary and secondary immune deficiencies and hyperinflammatory conditions as an immunomodulator. On the other hand, as we see with Covid-19, its lack of antibodies against new pathogens raises questions about its efficiency (10). In the studies on IVIG use in Covid-19, some clinicians report to use it as a prophylaxis option while others indicate to prefer it as a treatment option in various patient groups, ranging from mild symptoms to severe ICU patients (11, 12). Furthermore, some authors report better results for IVIG when it is ordered within the first 14 days after the initial symptoms of the disease, and that the response rate is not as good as expected after the 14th day. According to the hypothesis presented by these authors, viremic phase of Covid-19 is the first of the three defined phases, and it is the phase where IVIG is expected to lead to significant results. There are also studies on both IVIG and plasmapheresis treatments indicating better results for the first 10-14 days. Similarly, in our study, we have found that IVIG and plasmapheresis treatment was applied within the first 15 days.

Plasmapheresis is selective removal of the plasma from the blood. The most commonly used method of plasmapheresis, membrane filtration, has the advantage of separating especially large molecules. Due to the positive results it provides, it is preferred in diseases such as myasthenia gravis, Guillian-Barre syndrome, thrombotic microangiopathies, and some reno-vascular syndromes. Studies indicate its successful use in both MERS and SARS infections (11). Since antibodies, complementary products, lipoproteins, immune complexes, cryoglobulins, myeloma proteins, ADAMTS-13, protein-bound toxins, platelets and WBC are components removable by plasmapheresis, this method is preferred in cytokine storms

(13). Plasmapheresis have also been formerly used in Hepatitis C virus infections for reducing viral load and, therefore, the inflammatory response (14). Although there are randomized controlled trials supporting plasmapheresis use in cytokine storm/HIS development related to Covid-19, some authors still argue that the response is not significant. Faqihi and colleagues reported lower mortality rates in plasma exchange group, in comparison to standard treatments they apply in ICU, but their results were not statistically significant (15). In our study, 19 of the 20 patients who received plasmapheresis treatment after developing HIS did not survive. Convalescent plasma transfusion, which is another method of plasma exchange, has been recently on the focus of researchers in Turkey, and is expected to be a topic of further interest in the near future.

One of the major limitations of this study was its retrospective design. For this reason, factors such as start of treatment and standardization criteria are not included in the analyses. Our results are based on the data of first group patients who received advanced treatment due to Covid-19-associated HIS development. Furthermore, due to the high number of patients related to the pandemic, treatment was provided with additional units and health staff, and the problems the staff may have come across in training and practice may have led to setbacks in standard intensive care procedures. We are currently conducting a prospective design within the peak period we are still in, standardizing the treatments based on the experience we have gained from this patient group.

CONCLUSION

Covid-19 is a disease on a pandemic level, which is capable of frequent mutations, and yet lacks a standardized treatment. Due to high mortality rates it causes in ICU, search for an evidence-based treatment procedure continues. In this retrospective study, we shared our treatment plans and the results we obtained. However, based on the available data, we are currently unable to report an efficient model regarding mortality. Further research on Covid-19 and sharing the most recent information obtained is of high importance for establishing an effective treatment model..

ETHICAL DECLARATIONS

Ethics Committee Approval: This study has recieved approval from Başakşehir Çam and Sakura City Hospital's Ethical Board for Scientific Research (Decision number: KAEK/2021.03.21)

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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Orjinal Araştırma / Original Article

Does Vitamin D Supplementation Reduce Cytokine Storm and Mortality in Geriatric Intensive Care Patients Diagnosed with COVID-19

COVID-19 tanılı Geriatrik Yoğun Bakım Hastalarında D Vitamini Desteği Sitokin Fırtınasını ve Mortaliteyi Azaltır mı?

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Abstract

Introduction: Coronavirus disease progresses from an asymptomatic stage to a fatal stage characterized by a cytokine storm. The present study aimed to emphasize the therapeutic effect of vitamin-D supplementation and its potential importance in reducing the disease severity in older adults in the intensive care unit after COVID-19 diagnosis.

Materials and Method: The data of 80 patients aged ≥ 65 years who followed up in intensive care clinic. The inflammatory parameters and clinical course of 40 patients whose serum 25-hydroxyvitamin-D level was below 30 ng/ml and who received vitamin-D supplementation (case-group) were recorded on the fifth and tenth days of follow-up and compared with those of the other 40 patients 40 patients who vitamin D supplementation was not started because of high vitamin D levels (control-group).

Results: Of the 80 patients, 40 (50%) were male and 40 (50%) were female. The mean age of the patients was 72±10.8 years. The mean vitamin D level of the case group was 11.6 ng/ml. On the 10. day levels of the inflammatory markers C-Reactive Protein, Procalcitonin, D-Dimer, Ferritin, Interleukin-6 and Lactate Dehydrogenase were significantly lower and the lymphocyte count was significantly higher in the case group than in the control group. On the 5. day, the interleukin-6 level was significantly lower in the case group. Weaning was performed in nine and four patients in the case and control groups, respectively. There was no significant difference in mortality rates between the groups.

Conclusion: Vitamin-D supplementation can help reduce cytokine response. Recommended prophylactically or therapeutically at all stages of coronavirus disease.

Keywords: Elderly patients, COVID-19, cytokine release syndrome, intensive care units, vitamin D

Öz

Amaç: COVID-19 enfeksiyonunda klinik; asemptomatik durumdan, sitokin fırtınası ile karakterize ölümcül tabloya kadar değişen geniş bir yelpazede seyretmektedir. Bu makalede, tanı aldıktan sonra yoğun bakımda takibe başlanan geriatrik hasta grubunda D vitamini desteğinin terapötik etkisi ve hastalık şiddeti üzerine potansiyel önemini vurgulamak istiyoruz.

Gereç ve Yöntem: Mart ve Haziran 2021 tarihleri arasında Yoğun Bakım Kliniğimizde takip edilen COVID-19 tanısı almış 65 yaş ve üstü 80 hastanın verileri retrospektif olarak incelendi. Serum 25 (OH) D <30 ng/mL olan ve D vitamini desteği başlanan 40 hastanın, COVID-19 tanısı aldıktan sonra 5. ve 10. günlerdeki enflamatuar parametreleri ve klinik seyri kaydedilerek, Serum 25 (OH) D >30 ng/mL olan bu nedenle D vitamini desteği başlanmamış olan kontrol grubunun verileri ile karşılaştırıldı.

Bulgular: 80 hastadan 40'ı (%50) erkek ve 40'ı (%50) kadın idi. Hastaların ortalama yaşı 72±10,8 yıldı. Vaka grubunun ortalama D vitamini düzeyi 11,6 ng/mL idi. 10. gün ölçümlerinde enflamatuar belirteçlerden CRP, Prokalsitonin, D-Dimer, Ferritin, IL-6, LDH değerlerinin kontrol grubuna göre anlamlı düşük seyrettiği (P<0,05) ve lenfosit değerinin anlamlı yüksek seyrettiği gözlendi (p=0,008). Beşinci gün ölçümlerinde IL-6 düzeyi vaka grubunda anlamlı olarak daha düşüktü. Vaka ve kontrol grubunda sırasıyla 9 ve 4 hastada weaning uygulandı. Gruplar arasında weaning ve mortalite oranları açısından istatistiksel olarak anlamlı bir fark görülmedi.

Sonuç: D vitamini tedavisinin, özellikle hipovitaminoz D'nin sık görüldüğü geriatrik hastalarda sitokin yanıtını azaltmada katkı sağlayabileceği makul görünmektedir. D vitamini takviyesi, coronavirüs hastalığının tüm aşamalarında profilaktik veya terapötik olarak önerilir.

Anahtar Kelimeler: Geriatrik popülasyon, COVID-19, sitokin fırtınası, yoğun bakım üniteleri, D vitamini

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INTRODUCTION

Coronaviruses are a large family of viruses that can infect animals and humans. The world is now battling the third largest coronavirus outbreak, following the Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS) epidemics. This coronavirus has been officially named as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) by the World Health Organization (WHO) and the term coronavirus disease (COVID-19) has been used to describe the disease caused by this virus. The COVID-19 outbreak was declared a global health emergency on January 30, 2020, and was recognized as a viral pandemic on March 11, 2020.[1]

The aging of the population is an important issue at present. Aging is considered a medical and social problem. The older population is more susceptible to severe coronavirus disease and has a higher mortality rate. A large number of patients hospitalized in intensive care units with a diagnosis of COVID-19 are aged over 65 years all over the world, including Turkey.[2,3] The first COVID-19 case in Turkey, announced by the Ministry of Health on March 10, 2020, was an 89-year-old male patient. Considering that older individual stend to have at least one chronic disease, the older population is thought to be most affected by the pandemic and to have the highest mortality rate. Immuno supportive treatments have been shown to strengthen the immune system of older adults in intensive care units (ICUs) and reduce mortality and morbidity.[4]

Vitamin D plays a critical role in the immune system. It is an immunomodulatory hormone with anti-inflammatory and antimicrobial effects, in addition to anti-oxidant effects (by increasing glutathione reductase expression).[4,5] It has been reported in some studies that vitamin D deficiency may contribute to the development of viral diseases.[6] Moreover, it is emphasized that if there is vitamin D deficiency in COVID-19 patients, their sensitivity may increase in terms of complications and mortality due to infection.[7]

The serum 25-hydroxyvitamin D [25(OH)D] level stend to decrease with age.[8] Vitamin D deficiency is very common in the northern hemisphere because of low ultraviolet exposure, especially during winter months when the pandemic has been prevalent.

Vitamin D has been thought to affect prognosis by suppressing the cytokine response through the downregulation of pro-inflammatory cytokines.[9] In severe COVID-19 patients, the main problem is the inappropriate inflammatory response; therefore, it is crucial to initiate anti-inflammatory therapies that alleviate the cytokine storm in the case of high interleukin (IL)-6 expression.

Vitamin D polarizes the adaptive immune response from T helper type 1 (Th1) to T helper type 2 (Th2) response. CD4 (+) T cell production increases, and Th1 production decreases. Thus, the production of pro-inflammatory Th1 cytokines, such as tumor necrosis factor-α, interferon-γ, IL-6, IL-8, IL-12, and IL-17, is reduced.[10] In addition, vitamin D increases the expression of inflammatory cytokines by macrophages via the modulation of the innate immune response (macrophage, polymorphonuclear cell, monocyte and Toll-like receptor expression).[11]

The mechanism of COVID-19 starts with the attachment of SARS-CoV-2 to the angiotensin-converting enzyme 2 (ACE-2) receptor.[12,13] The virus gains entry into the cell and down regulates ACE-2. This causes excessive accumulation of angiotensin II.[14] The high incidence of COVID-19 in the older population, particularly in men, may be associated with the low ACE-2 expression level. On the other hand, renin is a proteolytic enzyme and a positive regulator of angiotension II. Vitamin D is a powerful renin inhibitor.[14]

The serum 25(OH)D level is one of the most widely used biomarkers to detect vitamin D deficiency.[15] A serum 25(OH) D level below 30 ng/ml is usually considered deficient. For certain patient groups, it is also advocated to maintain the serum 25(OH)D level above 40 ng/ml.[16] Vitamin D supplementation improves clinical outcomes in COVID-19 patients.[17] As the potential benefits of high-dose oral vitamin D are much more than the theoretical risks, it is thought that the use of high-dose oral vitamin D will help reach vitamin D sufficiency quickly and thus contribute to the immune response. Therefore, the present study aimed to emphasize the therapeutic effect of vitamin D supplementation and its potential importance in reducing the disease severity in older adults who were followed up in the ICU after being diagnosed with COVID-19.

MATERIAL AND METHOD

This study was carried out in a city hospital that was actively operating during the pandemic period with 70 intensive care beds. Approval was obtained from the Institutional Ethics Committee [2020/514/182/18]. However, informed consent was not obtained due to the retrospective planning of the study. The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki, Good Medical Practice Guidelines and Good Laboratory Practice Guidelines.

The study sample consisted of 80 older adults (≥65 years old). Patients (40 women and 40 men) admitted to the intensive care unit with the diagnosis of COVID-19 between March and July 2021 were included in the study. Antiviral treatment and supportive treatments were started according to the diagnostic and treatment criteria of the Turkish Scientific Committee. In our hospital, vitamin C supplementation is routinely started in all patients, and vitamin D replacement is given to patients with low vitamin D levels.

The patients were divided into two groups. Patients whose with serum 25(OH) D levels below 30 ng/ml and who received vitamin D supplementation were included in the case group (n= 40), while patients whose with serum 25(OH) D levels above 30 ng/ml and who did not receive vitamin D supplementation were included in the control group (n= 40).

Patients with comorbidities that could cause death (such as progressive Stage-4 malignancy, pulmonary embolism, diabetic ketoacidosis, advanced chronic kidney disease, acute liver failure, pregnancy, and acute myocardial infarction) were excluded from the study. Patients included in the case group were given a loading dose of 50,000 IU of vitamin D at the time of admission. A week later, a repeat dose of 50,000 IU was given once to increase vitamin D levels in the body. The laboratory data and clinical course of the two groups were recorded and compared statistically on the fifth and tenth days after the ICU admission

The patients' files were retrospectively accessed from the electronic registration system of the hospital. The demographic data (age, gender, and presence of comorbidities), treatments received, oxygenation status, presence of mortality, weaning success, discharge status, length of ICU stay, COVID-19 positivity (assessed by polymerase chain reaction), vitamin D levels, and laboratory data [ferritin, D-dimer, C-reactive protein (CRP), IL-6, lactate dehydrogenase (LDH), and procalcitonin levels and lymphocyte count]were recorded. The intubation or extubation status of the patients was stated during admission to the intensive care unit and during follow-up.

RESULTS

Eighty patients aged between 65 and 90 years (72.69±10.87 years) were included in the present study. In the case group, 21 patients were female (52.5%) and 19 were male (47.5%), while in the control group, 19 patients were female (47.5%) and 21 were male (52.5%). No significant difference was noted between the groups in terms of the hospitalization SOFA score, APACHE-II score, presence of comorbidities, and antiviral treatments used (**Table 1**). Vitamin D supplementation was given to 40 patients whose vitamin D levels were between 7 and 27 IU (mean, 11±5 IU).

The IL-6 level, which is an important marker of cytokine storms and macrophage activation syndrome (MAS), was significantly lower in the case group than in the control group on the fifth day and on the tenth day (p=0.001 and p=0.001, respectively). The measurements performed on the tenth day revealed that CRP, procalcitonin, D-dimer, ferritin, and LDH levels were significantly lower (p<0.05) and the lymphocyte count was significantly higher (p=0.008) in the case group than in the control group (**Table 2**).

No significant difference was observed between the two groups in terms of the mortality rate, length of ICU stay, hospitalization duration, and weaning success (**Table 3**).

DISCUSSION

The effect of vitamin D supplementation (which protects against SARS-CoV-2 infection) on cytokine storm development, mortality, and morbidity was retrospectively studied in patients hospitalized in the ICU after being diagnosed with COVID-19.

Table 1. Characteristics of subjects

	Control Group (n=40)	Case Group (n=40)	p
Age	65±90 (73.8)	65±87 (70.25)	0.858
Gender			0.655
0 (Male)	19 (47.5%)	21 (52.5%)	
1 (Female)	21 (52.5%)	19 (47.5%)	
DiabetesMellitus	14 (35.0%)	15 (37.5%)	0.816
Coronary Artery Dısease	18 (45.0%)	10 (25.0%)	0.059
Hypertensıon	24 (60.0%)	26 (65.0%)	0.644
Congestıve Heart Failure	9 (22.5%)	13 (32.5%)	0.316
Chronic Obstructive Pulmonary Disease	5 (12.5%)	10 (25.0%)	0.149
Cerebro vascular Dıseases	12 (30.0%)	9 (22.5%)	0.445
Malignite	5 (22.7%)	3 (7.5%)	0.087
Immun Plasma Treatment	9 (22.5%)	9 (22.5%)	1.000
AntıVıral Treatment	34 (85.0%)	34 (85.0%)	1.000
Tocilizumab Treatment	8 (20.0%)	5 (12.5%)	0.361
Positive RT-PCR Test	23 (57.5%)	19 (47.5%)	0.370
SOFA score	5.78±1.37 (6)	5.73±1.72 (5.5)	0.764
APACHE-II score	27.28±8.24	26.0±9.16	0.515

[t]Independent Samples T test: Values are given as mean±standard deviation, [m]Mann Whitney U test: Values are given as mean±standard deviation (median), [k]Ki-kare test: values are given as frequency (percentage), P<0.05: Statistically significant difference

Table 2. Measurement values of the groups

	Control Group (n=40)	Case Group (n=40)	P
P/F Admission	132.90±31.89	135.65±37.91	0.726
P/F 2 Discharge	153.5±62.96 (126.5)	187.09±89.01 (210)	0.251
CRP 1	92.55±145.42 (63)	93.63±76.88 (72.9)	0.456
CRP 2	141.66±82.50	118.56±86.74	0.232
CRP 3	196.97±128.81 (187)	80.14±76.46 (58)	0.001*
Dimer 1	4326.9±5565.4 (2320)	5073.0±7836.2 (2235)	0.546
Dimer 2	4574.5±4504.8 (2955)	3565.4±3666.8 (2400)	0.564
Dimer 3	5084.8±4957.2 (3720)	2269.9±2425.2 (1140)	0.005*
Ferritin 1	661.2±515.1 (489)	430.8±472.8 (228)	0.028*
Ferritin 2	428.5±617.4 (813)	531.4±491.8 (326)	0.061
Ferritin 3	777.4±533.8 (739.5)	430.7±395.3 (381.5)	0.013*
IL6 1	149.5±151.5 (96.85)	242.1±842.7 (42)	0.016*
IL6 2	730.9±2022.9 (147.5)	115.6±129.6 (66)	0.001*
IL6 3	1234.5±2445.9 (363)	141.9±257.8 (45)	0.001*
LDH 1	409.1±236.5 (356)	478.9±432.4 (311)	0.519
LDH 2	456.2±283.3 (408.5)	482.1±464.3 (367)	0.342
LDH 3	417.1±191.3 (410.5)	324.5±200.9 (249)	0.042*
PRC 1	1.48±2.67 (0.43)	2.34±7.12 (0.4)	0.983
PRC 2	4.05±7.58 (1.1)	2.03±3.14 (0.75)	0.265
PRC 3	3.89±5.71 (1.6)	2.43±7.36 (0.25)	0.010*
Lenfosit 1	1128.2±1107.4 (1000)	950.0±493.6 (850)	0.381
Lenfosit 2	744.7±383.2 (600)	902.6±423.3 (800)	0.110
Lenfosit 3	812.5±499.5 (650)	1165.5±530.7 (1200)	0.008*

[t] İndependent Samples T test: values are given as mean±standard deviation, [m] Mann Whitney U test: values are given as mean±standard deviation (median), * P <0.05: Statistically significant difference, 1: Admission in icu, 2: 5th day of bed, 3: 10th day of bed

Table 3. Comparison of groups

	Control Group (n=40)	Case Group (n=40)	P
İntubated AdmissionTo İcu			0.81
0	27 (67.5%)	26 (65.0%)	
1	13 (32.5%)	14 (35.0%)	
Being İntubated Stay İn İcu	30 (75%)	29 (72.5%)	0.79
Weaning	4 (12.9%)	9 (29.0%)	0.11
Length of ICU stay (days)	13.13±8.37 (11)	11.78±7.42 (10)	0.44
Hospitalization duration (days)	15.30±9.83 (11)	14.85±9.06 (12.5)	0.98
Death			
Mortality (-)	14 (35.0%)	20 (50.0%)	0.17
Mortality (+)	26 (65.0%)	20 (50.0%)	

[k] Ki-kare test: Values are given as frequency (percentage)
* P <0.05: Statistically significant difference, 1: Extubated on admission, 0: İntubated on admission

Many recent studies have revealed that vitamin D can have immunomodulatory and anti-inflammatory effects, thereby reducing morbidity and mortality in COVID-19 patients.[18,19]

In elderly patients, the risk of hypovitaminosis is higher due to the decreased time spent outdoors, increased adiposity, decreased vitamin D synthesis in the skin, decreased vitamin D absorption in the intestine, decreased 7-dehydrocholesterol level in the skin, and use of multidrug treatments.[20] Considering that the mortality rates increase with age, the importance of each intervention targeting the afore mentioned issues increases.

In their study conducted to determine the relationship between vitamin D levels and COVID-19 in advanced age Parkinson's patients, Hribar et al. found that daily vitamin D supplementation has a positive effect on the severity of COVID-19 and the disease course in older adults. It has been emphasized that vitamin D supplementation can be preferred, especially because it is cheap and reliable.[18] As a result of the study of Baktash et al. with 105 patients, it was observed that patients with vitamin D deficiency had higher peak D-dimer levels and a need for NIV support, but there was no difference in mortality between the groups.[21] Moreover, Alipio et al. demonstrated a significant correlation between serum 25(OH)D levels and clinical results ($p < 0.001$). In their study, serum 25(OH)D levels were found to be the lowest in critical cases and the highest in mild cases. As a result, they stated that an increase in serum 25(OH)D levels in the body can improve clinical outcomes.[17] In the present study, we found that although the demographic data of the groups were similar, the clinic in the case group receiving vitamin D supplementation was not as noisy as in the control group. For example, in the case group, nine patients were moved out of the intensive care unit by weaning. In the control group, weaning could be performed in only four patients. We can explain this clinical success with suppressed abnormal immune response. The Pao2/Fio2 ratio in the case group was higher than the control group, but this was not statistically significant. We can attribute this situation to the fact that the COVID-19 disease is a disease that progresses with very serious desaturation in ICU follow-up.

In a recent study, Grant et al. mentioned that supplementation with more than one micronutrient having immunosupportive roles can modulate the immune function and reduce the risk of infection. In particular, they stated that supplementation with micronutrients with the strongest evidence for immune support, namely vitamin C, vitamin D and zinc, is recommended. They emphasized that vitamin D supplementation could decrease mortality in influenza and COVID-19 patients.[22] In the present study, 26 patients died in the control group, while 20 patients died in the case group; the difference between the groups was not significant. We can attribute this numerical difference to the development of more cytokine storms in the control group. The development of cytokine storm is one of the most important causes of mortality in COVID-19 patients.

Rhodes et al. revealed that sunny countries, such as Spain and Italy, have a surprisingly high prevalence of vitamin D deficiency. Moreover, these countries have the highest rates of infection and death due to COVID-19 in Europe. They reported that the vitamin D level correlates with the severity of the immune response to COVID-19.[23]

Panarese stated that the effect of vitamin D on COVID-19 is due to the suppression of cytokine response and reduction of the severity and risk of acute respiratory distress syndrome and therefore recommended regular vitamin D supplements.[24] In a meta-analysis of 11,321 patients, Martineau et al. emphasized that vitamin D supplementation could positively change the inflammatory response and should therefore be recommended if the inflammatory response needs to be improved.[19] However, Autier et al. reviewed the publications and meta-analyses on vitamin D supplementation between 2013 and 2017 and concluded that 10–20 µg of vitamin D per day can reduce all-cause mortality; however, it does not have a significant effect on the biological markers of systemic inflammation.[25] However Wang et al. showed that vitamin d supplementation is a cost-effective approach to reduce hospitalization and/or death rates in patients newly diagnosed with COVID-19 and to prevent infection among close household contacts.[26]

In the literature, there are heterogeneous results about vitamin D supplementation. In the present study, the cytokine response on the tenth day was found to be significantly lower in the case group than in the control group. Moreover, CRP, procalcitonin, D-dimer, ferritin, and LDH levels were significantly lower and the lymphocyte count was significantly higher in the case group than in the control group. In addition, the clinical course of the patients was more benign in the case group. Although the difference in the Pao2/Fio2 ratio was not significant, it increased to a greater extent in the case group. While the number of patients who developed MAS and received tocilizumab was five in the case group, it was eight in the control group. Thus, the presence of an abnormal inflammatory response was significantly higher in the control group.

CONCLUSION

The present study revealed that vitamin D supplementation in the older population can regulate the immune system and affect the course of COVID-19 by positively contributing to the inflammatory response, clinical course, and weaning. In conclusion, vitamin D supplementation, which is safe, can be recommended as a prophylactic or therapeutic option at every stage of COVID-19.

ETHICAL DECLARATIONS

Ethics Committee Approval: Health Sciences University KartalDr.LutfiKirdar City Hospital Institutional Ethics Committee approval: [2020/514/182/18]

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Orjinal Araştırma / Original Article

The Effect of Body Weight on Sleep Quality and Sleep Duration in Adolescents

Adölesanlarda Vücut Ağırlığının Uyku Kalitesi ve Uyku Süresine Etkisi

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Abstract

Aim: The aim of the present study was to determine the effect of body weight on sleep duration and sleep quality in adolescents.

Material and Method: This cross-sectional study was performed on 14-17 year-old adolescents (n=1072) attending public and private high schools. In order to determine the sleep quality, Pittsburgh Sleep Quality Index (PSQI) was filled, and sociodemographic data were collected through a questionnaire. Body weight, height, waist, and hip circumferences were measured and body mass index (BMI), waist to hip ratio were calculated.

Results: In the least sleeping group (<8 hours/day) for both genders, the body weights were the highest ($p<0.05$). In boys, the least sleeping group had the highest BMI ($p<0.05$). The adolescents having good sleep quality had lower body weight and BMI values than the ones having poor sleep quality but the difference is not statistically significant. There was no significant relationship between sleep quality and, smoking habits, family types, self-evaluated school success, and appetite. There was a relationship between age and deterioration in the quality of sleep ($p<0.05$).

Conclusion: Sleep duration may be an important factor for obesity. In order to develop improvements on health; the adolescents, their families, and teachers should be informed more on healthy nutrition, and healthy sleep.

Keywords: Adolescent, obesity, sleep duration, sleep quality

Öz

Amaç: Bu araştırmanın amacı, adölesanlarda vücut ağırlığının uyku süresi ve uyku kalitesi üzerine etkisinin belirlenmesidir.

Gereç ve Yöntem: Kesitsel olarak tasarlanan bu araştırma, özel ve devlet liselerine devam eden 14-17 yaş adölesanlar (n=1072) üzerinde yürütülmüştür. Uyku kalitesini değerlendirmek amacıyla, Pittsburgh Uyku Kalitesi İndeksi (PSQI) kullanılmıştır. Sosyo-demografik veriler anket aracılığıyla toplanmıştır. Vücut ağırlığı, boy uzunluğu, bel ve kalça çevresi ölçülmüş, Beden Kütle İndeksi (BKİ) ve bel kalça oranı hesaplanmıştır.

Bulgular: Her iki cinsiyette de en az uyuyan (<8 saat/gün) adölesanların vücut ağırlıklarının en fazla olduğu belirlenmiştir ($p<0,05$). Erkeklerde, en az uyuyan grubun BKİ'si en yüksektir. İstatistiksel olarak anlamlı olmasa da iyi uyku kalitesine sahip olan adölesanların vücut ağırlığı ve BKİ değerlerinin, kötü uyku kalitesi olanlara göre daha düşük olduğu belirlenmiştir. Uyku kalitesi ile sigara kullanımı, aile tipi, okul başarısı ve iştah arasında bir ilişki saptanmamıştır. Yaş ve kötü uyku kalitesi arasında ilişki saptanmıştır ($p<0.05$).

Sonuç: Uyku süresi obezite için önemli bir faktör olabilir. Sağlığı geliştirmek için; adölesanlar, aileleri ve öğretmenleri sağlıklı beslenme ve sağlıklı uyku konularında daha fazla bilgilendirilmelidir.

Anahtar Kelimeler: Adölesan, obezite, uyku süresi, uyku kalitesi

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INTRODUCTION

Having a regular good night's sleep is one of the essentials of a healthy life for both children, and adults. Many somatic, cognitive, and psychological processes are strongly affected by good sleep and it seems to contribute to health improvement and survival.[1] Despite the fact that the concepts of basal sleep needs are still being studied by scientists, cumulative evidence indicates that an insufficient amount of sleep may have harsh effects on metabolism with a higher risk of obesity, diabetes, and mortality risks among populations.[2] Lately, chronic sleep duration (less than 6 hours) has been believed to be in relation to an increased risk of obesity, hypertension, diabetes, and cardiovascular diseases.[3] Various meta-analyses and reviews have just been assigned to the relation between sleep loss, and obesity or diabetes.[4,5] As accumulative evidence proposes, insufficient sleep may be connected with adverse health effects such as type 2 diabetes, obesity, hypertension and cardiovascular diseases.[6,7] Day by day, modern societies suffer more from reduced sleep duration and poor sleep quality, which are linked to changing socioeconomic environment, and lifestyle.[8]

Most studies conducted on college students put forward that they have chronic sleep deprivation. They state that their average sleep duration is around 7 hours, which is less than the recommended amount (9-10 hours) for adolescents and children.[9] In addition, adolescents may be more sensitive to the adverse effects of sleep deficit. Sleep has a crucial role in brain development. Hypothalamic mechanisms regulating appetite and energy expenditure may be modified by sleep loss at young ages. The effect of age can be expressed with another possibility. The effect of sleep duration on weight gain can change in time such that individuals with short sleep duration may not continue to gain weight linearly.[10] As observational studies show, sleep loss affect children more strongly than adults. Randomized prospective interventional trials are necessary for the clarification of the sleep duration effects on the risk of weight gain. Since depriving subjects of sleep for prolonged time periods can be unethical, extending sleeping hours of individuals with short sleep duration and obesity can be used as another way to shed a light on the relationships.[10] Sleep deprivation is linked with weight gain and obesity; however, how sleep extension could improve weight regulation is still unclear. Children and adolescents have an important issue. To observe overweight and sleep-deprived children prospectively who are encouraged to get more sleep for an adequate time period would be crucial. [10] Therefore, the aim of this study was to determine sleep duration, sleep quality, and their relations with obesity among adolescents.

MATERIAL AND METHOD

Study Design and Sample

This cross-sectional study was performed on 14-17 year old adolescents attending public and private high schools. Based on the chi-square test done for the obesity status of age variable, it was calculated by the bio-statistic expert that 1200 students needed to be involved in the study for α=0.05, power=0.80, degree of freedom (df)=8, and effect size=0.32. According to the data obtained from The Kayseri Provincial Directorate for National Education, 67 high schools located in the Kayseri city center are accepted. Five hundred twenty-six students attending 9th grade, 281 students attending 10th grade, 265 students attending 11th grade were included from every nine schools that were selected amongst the 67 high schools using the random cluster sampling method.

A total of 1072 adolescents aged 14-17 years were enrolled in the study. The objective of the research was explained, then survey forms and informed volunteer consent forms for parent permission were handed out to the students who accepted to participate in the study, and these forms were collected the following day. The study was approved by the Ethics Committee of the Faculty of Medicine, Erciyes University, Kayseri, Turkey (Approval number 2009/151). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Anthropometric Measurements

Body weight was measured using a digital scale (Tefal Premio) with an accuracy of ± 100 g. All subjects were weighed without shoes and in light clothes. Height was measured using a tape measure with the subjects standing barefoot, keeping their shoulders in a relaxed position, arms hanging freely, and held in the Frankfort horizontal plane.

Age and sex specific BMI percentiles were calculated and adolescents were classified as normal weight (≥15th-<85th percentile), overweight (≥85th-<97th percentile), and obese (≥97th percentile) according to the International Obesity Task Force (IOTF) criteria.[11] Waist circumference (WC) was obtained from the narrowest point between the lower edge of the cage framework, and the iliac crest using a flexible tape measure, but not an elastic one. Hip circumference was determined from the highest point of the side of the hip.[12] The waist/hip ratio was calculated from the values of waist and hip circumferences.

Pittsburgh Sleep Quality Index (PSQI)

The PSQI is a widely used, self-rated, standardized questionnaire assessing sleep quality in the previous month.[13] The 19 questions are grouped in seven component scores, each exploring a different sleep feature; the sum yields a global PSQI score used to define poor sleep quality when >5. On the basis of the sleep duration component of the PSQI score, self-reported short sleep duration was defined as <6 h of sleep per night. The following PSQI derived data also were analyzed: increased sleep latency (>30 min), reduced sleep efficiency (<85%), sleep disturbance (sleep disturbances component score >1), and daytime dysfunction due to sleepiness (daytime dysfunction component score >1).[13]

Statistical Analysis

All of the data obtained during the study were assessed using SPSS 25.0 (Statistical Package for the Social Sciences, SPSS Inc. Chicago, USA) software. Frequency tables and descriptive statistics were used to interpret the results. Chi-square analysis was used to compare the difference of qualitative variables between groups. The student's t-test was used to compare two independent groups in terms of quantitative variables. The one-way ANOVA was used to compare the means of more than two groups.

RESULTS

43.9% (n= 471) of the 1072 students participating the study were boys and 56.1% (n= 601) of them were girls. The mean age was 15.54±1.08. The mean body weight of the male students was 64.55±12.59 and their BMI mean was 21.5±3.58 kg/m². The mean body weight of the female students was 55.0±10.11 kg and their BMI mean was 20.80±3.52 kg/m². The mean waist circumference of the boys was 76.08±9.73 cm whereas that of the girls was 70.0±8.82. The waist/hip ratio was 0.81±0.08 in boys while it was 0.77±0.07 in girls. Body weight, height, waist circumference, hip circumference, and waist/hip ratio (p<0.001) among the anthropometric measurements were found to be significantly higher in boys than girls (**Table 1**).

Table 1. Anthropometric measurements of adolescents

	Boy (n=471) X±SD	Girl (n=601) X±SD	p
Weight (kg)	64.55±12.59	55.00±10.11	0.000*
Height (cm)	1.72±0.07	1.62±0.06	0.000*
BMI (kg/m²)	21.50±3.58	20.80±3.52	0.870
Waist circumference (cm)	76.08±9.73	70.00±8.82	0.000*
Hip circumference (cm)	93.22±9.04	90.00±8.17	0.000*
Waist/hip ratio	0.81±0.08	0.77±0.07	0.000*

*p<0.001, **p<0.05

PSQI score distributions of the adolescents are demonstrated in **Table 2**. The mean PSQI total score of the adolescents participating the study was 5.05±1.82 in boys and 5.25±1.81 in girls. PSQI subcomponent score averages were detected to be 2.11±0.67 and 2.02±0.70 in boys and girls respectively for subjective sleep quality; 19.86±14.56 and 21.15±15.42 for sleep latency; 7.35±1.54 and 7.36±1.37 for sleep duration; 93.11±6.38 and 93.92±5.01 for habitual sleep efficiency; 4.42±3.51 and 4.97±3.65 for sleep disturbance; 0.86±1.21 and 1.26±1.55 for daytime dysfunction. Subjective sleep quality was observed to be higher in boys according to their self-assesments (p<0.05). However, girls were detected to have higher levels of habitual sleep efficiency, sleep disturbance (p<0.05) and daytime dysfunction (p<0.001) compared to the boys.

Table 2. Sleep features of the adolescents according to the PSQI

PSQI	Boy (n=471) X±SD	Girl (n=601) X±SD	p
Subjective sleep quality	2.11 ±0.67	2.02±0.70	0.023*
Sleep latency	19.86±14.56	21.15±15.42	0.160
Sleep duration	7.35±1.54	7.36±1.37	0.903
Habitual sleep efficiency	93.11±6.38	93.92±5.01	0.020*
Sleep disturbance	4.42±3.51	4.97±3.65	0.013*
Day dysfunction due to sleepiness	0.86±1.21	1.26±1.55	0.000**
PSQI score	5.05±1.82	5.25±1.81	0.073

*p<0.05, **p<0.001

Table 3 indicates sleep quality evaluations of some students in the study with regards to their certain features. Age 14 group, in which older age and poor sleep quality increase in direct proportion, was observed to have the best sleep quality rate (47.0%) (p<0.05). Smokers were observed to have poorer sleep quality than non-smokers (72.0% and 59.7%, respectively). Students who are the core family members were detected to have the highest rate of good sleep quality (40.9%). On the other hand, students who have broken families were found to have the poorest sleep quality (78.4%). The relationship among the students' smoking habits, family types, school success and appetites was not statistically significant.

Table 3. Some socio-demographic characteristics of adolescents according to PSQI

	PSQI				Total		
	<5 Good sleep quality		≥5 Bad sleep quality				
	n	%	n	%	n	%	p
Age							0.030*
14	102	47.0	115	53.0	217	100.0	
15	141	41.5	199	58.5	340	100.0	
16	88	38.1	143	61.9	231	100.0	
17	98	34.5	186	65.5	284	100.0	
Smoking							0.290
Smoker	7	28.0	19	72.0	26	100.0	
Non-smoker	422	40.3	624	59.7	1046	100.0	
Family type							0.060
Core family	372	40.9	538	59.1	910	100.0	
Broken families	8	21.6	29	78.4	37	100.0	
Large families	49	39.2	76	60.8	125	100.0	
Self-evaluated school success							1.000
Unsuccessful	17	40.5	412	59.5	42	100.0	
Successful	25	40.0	618	60.0	1030	100.0	
Appetite							0.424
Very poor	3	20.0	12	80.0	15	100.0	
Poor	31	40.3	46	59.7	77	100.0	
Normal	163	39.8	247	60.2	410	100.0	
Good	139	38.9	218	61.1	357	100.0	
Very good	93	43.7	120	56.3	213	100.0	
Total	429	40.0	643	60.0	1072	100.0	

Table 4 displays the PSQI score distribution of the adolescents in terms of anthropometric features. The mean body weight of the students who have good sleep quality was 60.03±11.96 kg while that of the students who have poor sleep quality was 60.14±11.92 kg. The mean BMI was 21.46±3.61 kg/m² and 21.50±3.50 kg/m² respectively. Although poor sleep quality group was observed to have higher body weight, BMI and hip circumference averages, the difference in between was not statistically significant.

Table 4. Anthropometric measurements of adolescents according to the PSQI

	PSQI		
	<5 (Good sleep quality)	≥5 (Bad sleep quality)	p
Anthropometric measurements			
Weight (kg)	60.03±11.96	60.14±11.92	0.883
Height (cm)	1.67±0.08	1.66±0.08	0.936
BMI (kg/m²)	21.46±3.61	21.50±3.50	0.843
Waist circumference (cm)	73.03±9.62	72.64±9.72	0.513
Hip circumference (cm)	91.88±8.71	92.14±8.57	0.625
WHtR	43.73±5.33	43.52±5.51	0.544
WHR	0.79±0.07	0.78±0.08	0.195

BMI= Body mass index, WHtR= Waist to height ratio, WHR=Waist to hip ratio

The mean values of anthropometric measurements of adolescents according to their sleep duration were shown in **Table 5**. The mean body weight of boys who sleep for 8 hours or less was the highest. It was determined that the mean body weight increased as the sleep duration decreased. The difference between sleep duration groups in terms of body weight was found to be statistically significant (p<0.01). The group with the highest mean body weight in girls was determined in those who slept 8 hours or less, and the difference was statistically significant (p<0.05). The difference between height and sleep duration is statistically significant in boys (p<0.05). The group with the highest mean BMI in boys is the group that sleeps 8 hours or less. It was determined that as sleep duration increased, the mean BMI decreased, and the difference was statistically significant (p<0.05).

DISCUSSION

The major contributions of this study to the current literature were both determining the relationship between sleep deprivation, sleep quality and obesity. Sleep deprivation or short sleep occurs if sleep time lasts less than 9 hours which is the average basal level per night for adolescents. National Sleep Foundation has recently updated its guidelines to 8-10 hours for adolescents between the ages of 14 and 17.[14] Similar to a number of countries around the world, adolescents do not get enough amount of nocturnal sleep according to the studies.[15-17] This latter review concluded that in Asian studies adolescents slept for 7.64 hours, in European studies for 8.44 hours and in North American studies for 7.46 hours.[15] According to the reports of as many as one-fourth of adolescents, they sleep for 6 hours or less per night.[16] In its survey in 2006, The National Sleep Foundation stated that only 1 in 5 adolescents has 9 hours of sleep on school nights whereas 45% of them have 8 hours or less sleep. And a regular high school senior gets only 6.9 hours' sleep on such nights.[15,18] Similar to Asian and North American studies, Yılmaz et al. (2011) reported 7.42±1.48 hours sleep on school nights among adolescents in Turkey.[15,17]

Evidence strongly proposed a compatible relationship between restricted sleep and overweight/obesity in children. The shorter the sleep duration the greater the odds of overweight/obesity or weight gain.[19-23] This applies especially to preschool children. In fact, the evidence puts forward an evident dose-response association. That is to say, each unit decrease in sleep duration triggers an increase in weight or weight gain.[23] Yet, when it comes to adolescents, the

Table 5. Anthropometric measurements of adolescents according to sleep duration

Sleep duration (hour)		≤8 (n=326)	8.1-8.9 (n=58)	9.0-9.9 (n=53)	≥10 (n=34)	p
Anthropometric measurements						
Boys (n=471)	Weight (kg)	65.84±12.97	63.70±12.49	61.06±9.85	59.09±10.48	0.003**
	Height (cm)	1.73±0.07	1.72±0.07	1.70±0.07	1.70±0.08	0.028*
	BMI (kg/m²)	21.77±3.66	21.33±3.71	20.90±3.05	20.19±3.08	0.047*
	WC (cm)	75.96±9.85	75.56±8.38	76.11±9.62	78.05±11.02	0.658
	HC (cm)	93.21±9.10	94.25±8.64	92.15±8.52	93.29±10.08	0.682
	WHR	0.81±0.08	0.80±0.55	0.82±0.08	0.84±0.12	0.154
		(n=431)	(n=85)	(n=53)	(n=32)	
Girls (n=601)	Weight (kg)	57.30±10.33	55.75±9.07	53.70±7.74	54.39±12.13	0.036*
	Height (cm)	1.62±0.06	1.62±0.06	1.61±0.07	1.61±0.06	0.351
	BMI (kg/m²)	21.69±3.60	21.04±3.25	20.72±3.03	20.78±3.55	0.084
	WC (cm)	70.12±9.00	69.29±7.96	71.00±8.30	72.78±9.29	0.252
	HC (cm)	91.05±8.14	90.68±7.40	91.69±7.17	92.00±11.69	0.825
	WHR	0.77±0.07	0.76±0.08	0.77±0.05	0.79±0.05	0.307

*p<0.05, **p<0.01; BMI= Body mass index, WC= Waist circumference, HC= Hip circumference, WHR=Waist to hip ratio

evidence is unclear. One reason for this is that researches conducted on them are inadequate. Cuypers et al. (2012) have stated that inadequate amount of sleep is linked to obesity only if there is an unusual sleep range (5 or less hours of sleep).[24] Therefore, there is a stronger evidence for an inverse relationship between restricted sleep and overweight/obesity among children and adolescents than the latter age group.

Von Kries et al. (2002) state in their research on 5-6 year olds that children who sleep for 11.5 or more hours have half the risk of obesity compared to ones who sleep for 10 or less hours.[25] Similarly, Touchette et al. (2008) reported that continual short sleep in early childhood increases the risk of overweight or obesity in childhood.[26] In the research on 8234 children in England, it is found that sleeping for 10.5 or less hours at the age of 3 increases the risk of obesity by 45% in 7-year -old children.[27] According to the findings obtained from France, Tunisia, Japan, Germany, USA, Brazil, Portugal, Great Britain, Canada, Taiwan and China along with the research on 29502 children, a significant association between short sleep duration and obesity exists.[28] Another research conducted in accordance with NHANES I findings support the existence of the association between insufficient sleep duration and obesity.[29]

In the study conducted on 5358 Turkish adolescents between the ages of 6 and 17, Ozturk et al. (2009) detected that sleep duration of both sexes increases as their BMIs decrease.[30] Girls who sleep for 10 or more hours have significantly higher BMIs than the ones sleeping for 8 or less hours. On the other hand, boys who sleep for 8 or less hours have significantly higher BMIs and waist circumferences compared to the ones sleeping for 10 or more hours. The risk of overweight/obesity is lower in children who sleep for 10 or more hours than the other groups. According to research results, a decrease in sleep duration triggers the risk of overweight/obesity (statistically insignificant in girls). Consistent with Ozturk et al. (2009), in the present study, boys who sleep for 8 or less hours have the highest mean body weight. As the sleep duration decreases, mean body weight increases. Also, the difference between sleep duration groups is statistically significant with regards to body weight. Among the girls, the one belonging to the girls who sleep for 8 or less hours has the highest mean body weight. Similarly, the difference between them is statistically significant. Additionally, the difference between boys' sleep duration and height is statistically significant. The group of boys who sleep for 8 or less hours has the highest BMI average. As the sleep duration increases BMI average decreases. Likewise, the difference in between is statistically significant.

Sleep quality has a long-term impact on health among adolescent students.[31] Both biological and social factors contribute to sleep quality. Adolescents' sleep pattern requires specific attention because it may affect their academic environment.[32,33] In the study conducted on Turkish adolescents which evaluates the sleep quality of adolescents with the mean age of 15.8±0.9 years, 89.9% of the students were found to sleep 7 or more hours while this number for 1.5% of them was 5 or less. In addition, the PSQI score of 4.1% of the students was 5 or more, which was evaluated as poor.[34] According to the study results, the students' sexes, parents' educational backgrounds and jobs or school success do not affect their sleep quality. On the other hand, factors such as broken families, present or past smoking habits, falling asleep after more than 30 minutes and night sleep duration of 5 or less hours were detected to have adverse effects on the students' sleep quality.[34] Similarly in our research, among the smoking students the ratio of the ones with 5 or more PSQI scores is reported to be higher than the ones with less than 5 PSQI scores. However, the difference is not detected to be statistically significant. Furthermore, the sleep quality of 80% of the students who evaluate their own appetite as "very poor" is found to be bad. As a result, we did not find a significant relationship between the sleep quality and, smoking habits, family types, self-evaluated school success and appetite based on the PSQI score. Significant difference between sleep quality and age groups was noted among adolescents.

CONCLUSION

Sleep quality can be affected positively or negatively by eating habits, medicine usage, psychological or cognitive condition and age along with sex. Short sleep duration, especially ≤8 h, may be a risk factor of overweight or obesity. Providing ≥10 h of sleep may be recommended as a part of interventions to prevent obesity, especially for children and adolescents. However, it is necessary to assess these factors and the relation among them together to obtain more accurate results.

The limitation of this study may be self-reports of adolescents, which may interact the accuracy of reported sleep duration, and sleep quality.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by Ethics Committee of the Faculty of Medicine, Erciyes University (Date: 19.11.2009, Decision no:151)

Informed Consent: All parents signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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

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Original Article / Orijinal Araştırma

Examination of Dysphagia Status in Multiple Sclerosis Patients

Multipl Skleroz Hastalarında Disfaji Durumunun Değerlendirilmesi

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Abstract

Aim: Dysphagia is a life-threatening symptom. The present study aims to evaluate the swallowing function and dysphagia status of MS patients and to find factors that may cause dysphagia. Also, to bring attention to the importance of the early dysphagia examination in MS patients.

Material and Method: A total of 30 MS patients who applied to the neurology clinic of Mustafa Kemal University were included in the study. Dysphagia was evaluated using GUSS (Gugging Swallowing Screen) test for quantitative evaluation of swallowing function. Demographic data (age, gender) of all patients were recorded. Disease duration, if present dysphagia duration, MS type, and Kurtzke's Expanded Disability Status Scale (EDSS) indicating the patient's level of disability was all recorded.

Results: According to the GUSS test classification; while 14 patients had mild dysphagia, the remaining 16 patients did not reveal any dysphagia or aspiration risk. We found a weak correlation between EDSS and GUSS (r=-0.227), and between EDSS and Subjective Duration of Dysphagia (r=-0.227). There was a moderate and negative correlation between GUSS and duration of disease (-0.543), GUSS, and teeth status (r=-0.535) but a weak correlation between GUSS and age; GUSS and duration of dysphagia. There was a significant difference in teeth status and GUSS score

Conclusion: As a result, individuals with MS may have swallowing dysfunction due to different conditions, so these patients should be evaluated closely in terms of swallowing function from the early stages of the disease immediately upon diagnosis. Thus, serious problems related to aspiration can be prevented.

Keywords: Multiple sclerosis, dysphagia, evaluation

Öz

Amaç: Disfaji hayati risk oluşturabilen bir semptomdur. Bu çalışma, MS hastalarının yutma fonksiyonu ve disfaji durumunu değerlendirmeyi ve disfajiye neden olabilecek faktörleri bulmayı amaçlamaktadır. Ayrıca MS hastalarında erken disfaji muayenesinin önemine dikkat çekmek amaçlanmaktadır.

Gereç ve Yöntem: Çalışmaya Mustafa Kemal Üniversitesi nöroloji kliniğine başvuran toplam 30 MS hastası dahil edildi. Yutma fonksiyonunun nicel değerlendirmesi için GUSS (Gugging Swallowing Screen) testi kullanılarak hastaların disfaji durumu değerlendirildi. Tüm hastaların demografik verileri (yaş, cinsiyet) kaydedildi. Hastalık süresi, varsa disfaji süresi, MS tipi ve hastanın özürlülük düzeyini gösteren Kurtzke'nin Genişletilmiş Özürlülük Durum Skalası (EDSS) kaydedildi.

Bulgular: GUSS test sınıflamasına göre; 14 hastada hafif disfaji varken, kalan 16 hastada disfaji veya aspirasyon riski saptanmadı. EDSS ile GUSS (r=-0,227) arasında ve EDSS ile Öznel Disfaji Süresi (r=-0,227) arasında zayıf bir ilişki saptandı. GUSS ile hastalık süresi (-0,543) ve GUSS ve dişlerin durumu (r=-0,535) arasında orta ve negatif bir korelasyon saptandı ancak GUSS ile yaş ve GUSS ile disfaji süresi arasında zayıf bir korelasyon vardı. Diş durumu ve GUSS skoru arasında ise anlamlı bir fark vardı.

Sonuç: MS'li bireylerde farklı koşullara bağlı olarak yutma güçlüğü görülebilmektedir, bu nedenle bu hastalar tanı konulduktan hemen sonra hastalığın erken evrelerinden itibaren yutma fonksiyonu açısından yakından değerlendirilmelidir. Böylece aspirasyonla ilgili ciddi sorunların önüne geçilebilir.

Anahtar Kelimeler: Multipl skleroz, disfaji, değerlendirme

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INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system. The etiology is still unknown, both genetic and environmental factors play a role in the development of the disease.[1,2] MS is more common in women and young adults. The prevalence is very variable in different geographical regions.[3] According to the localization of the lesions in the central nervous system, a variety of symptoms are seen. The most common symptoms are vision problems, imbalance, weakness, urinary incontinence, loss of sensation, speech and swallowing problems.[2]

Swallowing is a complex function realized through voluntary and involuntary movements with oral, pharynx, larynx, esophagus and respiratory muscles and other anatomical structures.[4] Swallowing disorder is defined as dysphagia. Lesions of the cerebral cortex associated with swallowing function and problems due to neuromuscular transmission can cause dysphagia.[5] Dysphagia is a life-threatening symptom in patients with MS.[6] Incidence varies between 33% and 43% in MS patients.[7] Aspiration pneumonia due to dysphagia is the leading cause of mortality in MS patients.[8] Malnutrition and dehydration due to dysphagia also contribute to mortality.[7,9] If dysphagia can be determined by a quick and easy applicable screening method, these complications can be prevented. Therefore, for dysphagia in the subclinical period, early diagnosis is critical.[9] However, dysphagia in MS usually receives limited attention. Therefore, it is important for neurologists to recognise minor symptoms of dysphagia and to be aware of the new methods of evaluation.[8,10] If swallowing disorders in MS patients, are detected early and treated appropriately in early term of the disease, many of the complications caused by dysphagia, including aspiration pneumonia, can be avoided. The present study aims to evaluate the swallowing function and dysphagia status of MS patients and to find factors may cause dysphagia. Also, to bring attention to importance of the early dysphagia examination in MS patients.

MATERIAL AND METHOD

This study was approved by the Clinical Study Ethics Committee of Mustafa Kemal University Tayfur Ata Sökmen Medical Faculty (Date: 26.09.2019, Decision No: 02). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Thirty MS patients who applied to the neurology clinic of Mustafa Kemal University between 15th September 2019-15th October 2019 were included in the study. All of the patients included in the study were diagnosed as MS according to the Mc Donald diagnostic criteria. Patients were informed about the study procedure and consent forms were obtained. Demographic data of all patients were recorded. The disease duration and if present, dysphagia duration is recorded. The patients were asked to evaluate their swallowing status subjectively and they were asked to give a score between 1 and 10 to their swallowing status and, high scores mean healthy swallowing status. Patients were asked about the condition of their teeth and were asked whether they used dental prosthesis or not. Patients were evaluated for weight loss over the last 1 year. Patients were asked which way they are currently feeding; oral, nasogastric tube or percutaneous endoscopic gastrostomy. Patients questioned in terms of diet types; solid, semisolid, or liquid. The neurological examination of all patients was performed and MS type determined by the neurologist conducting the study. Kurtzke's Expanded Disability Status Scale (EDSS) was used to quantify the disability of the patients. Facial muscle weakness was evaluated by Manuel Muscle Test.

To determine the risk of dysphagia and aspiration in MS patients, easy and fast applicable tests are needed at the bedside of the patient. Gugging Swallowing Screen test (GUSS) is an easy and fast applicable test and helps to evaluate the degree of dysphagia gradually, allows the patient to make dietary recommendations after assessment. Dysphagia was evaluated using GUSS test for quantitative evaluation of swallowing function.[11] This test consists of two main parts. The first section includes a preliminary assessment (indirect swallowing test) and evaluates saliva swallowing. The second part is the direct swallowing test and it consists of 3 sub-groups that evaluate the ingestion of food firstly semi-solid, then liquid and finally solid consistency. The most successful performance is noted when applying subgroups. A maximum of 5 points can be reached in each subgroup. If 5 points are reached, switch to the other subgroup, if not, the test is terminated and further investigation by videofluoroscopy or fiberoptic endoscopy is recommended. A maximum of 20 points can be obtained from the test. The patient with a score of 20 is considered to have normal swallowing ability without aspiration risk and dysphagia. 0-9 points considered as severe,10-14 points as moderate and 15-19 points as mild dysphagia. A score of 14 or fewer points carries a risk of aspiration.

RESULTS

The demographic characteristics of the patients are presented in **Table 1**. A total of 30 patients with MS were included in the study. 22 (73.3%) of the participants were female, 8 (26.7%) were male. The mean±SD age of the participants was 41.16±12.58 years (range 20-63 years). Thirteen of them had tooth bridge and 9 had a dental filling. All of them have oral feeding and can eat semisolid, liquid, and solid. The duration of the MS disease was 95.13±70.56 months and subjective dysphagia duration was 5.56±22.62 months. The mean±SD EDSS was 2.83±2.19 (range 1-7). All of the patients had relapse-remitting MS: 30 (100 %).

Table 1. Demographic characteristics of the patients

Characteristics		n	%
Sex	Male	8	26.7
	Female	22	73.3
Working Condition	Employed	13	43.3
	Unemployed	17	56.7
Feeding Type	Semisolid	0	0
	Liquid	0	0
	Solid	30	100
Teeth Status	Tooth filling	9	30
	Prosthesis	10	33.33
	Bridge	3	13.6
	Nothing	8	26.7
		X±SD	
Age(Years)		41.16±12.58	
Disease duration (Months)		95.13±70.56	
Subjective dysphagia duration (Months)		5.56±22.62	
Subjective swallowing status (0-10)		9.25±1.05	

There was a significant difference in teeth status and GUSS score (p=0.043, x2=6.284).

According to muscle test results, most of them have 5 degrees of muscle test. We realized that smiling muscles were weaker than other muscles, this may be caused because they do not smile so much and do not use these muscles very much. Also, most of their tongue muscle strength is not in the best degree. There was a weak correlation between GUSS and muscle test (**Table 2**).

Table 2. Muscle test results

	Muscle Test Degree						GUSS	
	5		4		3			
Muscle	n	%	n	%	n	%	r	p
Orbicularis oculi	28	93.3	2	6.7	0	0	-0.236	0.210
Zygomaticus major	10	33.3	15	50	5	16.7	0.218	0.474
Buccinator	26	86.7	4	13.3	0	0	-0.33	0.916
Risorius	17	56.7	10	33.3	3	10	0.040	0.832
Masseter	29	96.7	1	3.3	0	0	0.082	0.667
Suprahyoid	30	100	0	0	0	0	-	-
Tongue protrusion	24	80	5	16.7	1	3.3	0.249	0.184
Tongue Down	20	66.7	8	26.7	2	6.7	0.157	0.408
Tongue Up	23	76.7	2	6.7	5	16.7	0.311	0.095
Tongue Right	17	56.7	7	23.3	6	20	0.097	0.751
Tongue Left	16	53.3	7	23.3	7	23.3	0.002	0.996

According to GUSS test results, no dysphagia was detected in 16 (53.3%) patients and mild dysphagia was detected in 14 (46.7%) patients. All the patients' scores were over 14 so none of them have aspiration risk (**Table 3**).

We found a weak correlation between EDSS and GUSS (r=-0.227), and between EDSS and Subjective Duration of Dysphagia (r=-0.227). There was a moderate and negative correlation between GUSS and duration of disease (-0.543), GUSS, and teeth status (r=-0.535) but a weak correlation between GUSS and age; GUSS and duration of dysphagia (**Table 4**).

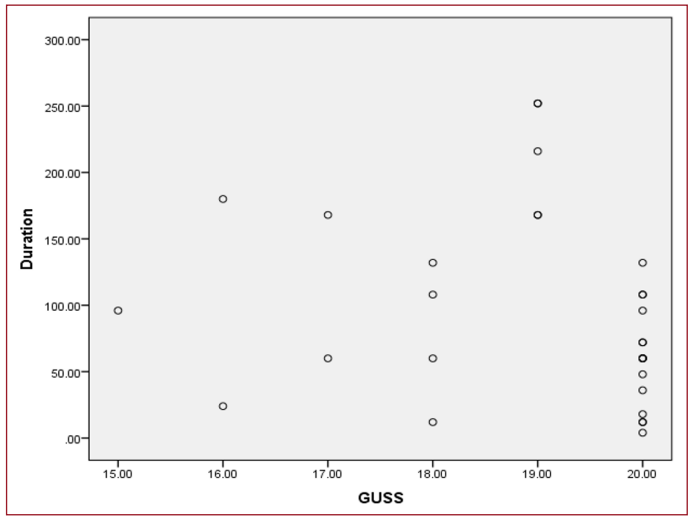
Table 3. Swallowing tests results

Gugging Swallowing Screen (GUSS)	n	%
20 (Semisolid / liquid and solid textures successful)	16 (x=20)	53.3
15-19 (Semisolid and liquid texture successful and solid unsuccessful)	14 (x=17.71±1.32)	46.7
10-14 (Semisolid swallow successful and liquids unsuccessful)	0	0
0-9 (Preliminary investigation unsuccessful or semisolid swallow unsuccessful)	0	0

Table 4. Correlation between GUSS and characteristics

	GUSS	
	r	p
EDSS	-0.227	0.228
Age	-0.349	0.028
Duration of the disease	-0.543	0.002
Duration of dysphagia	0.163	0.389

There was a weak and negative correlation between GUSS and age (r=-0.349), a moderate and negative correlation between GUSS and duration of the disease (r=-0.543), (**Graph 1**). Also, there was a moderate and negative correlation between subjective swallowing status- duration of the disease (r=-0.44) and subjective swallowing status-duration of the dysphagia (r=-0.40).



Graph 1. Correlation between GUSS and duration of the disease. r=-0.543, p=0.002

DISCUSSION

MS is a chronic, progressive and neurodegenerative disease that can affect swallowing functions. In this study, we aimed to examine swallowing status in MS patients. We found that 16 of the patients had healthy swallowing function and 14 of them had mild dysphagia. It was concluded that duration of the disease affect swallowing function negatively, so clinicians should consider dysphagia in MS patients and routine swallowing function examining should be included to the neurological examination of the MS patients.

In a meta-analysis evaluating the frequency of dysphagia in MS patients, the frequency of dysphagia was 43.33% and this rate was similar to our study results.[12] The prevalence of dysphagia in MS patients varies between 10% and 90%.[13,14] This result showed that dysphagia is a common problem in MS patients. As the reason for this variability in dysphagia prevalence of MS patients, it might because of evaluation methods, data collection procedures, and different sample sizes. In our study, according to GUSS test results, no dysphagia was detected in 16 of the (53.3%) patients and mild dysphagia was detected in 14 of the (46.7%) patients. This rate is substantial. Especially considering the patient's life is in question, it appears that dysphagia is one of the important problems of MS patients.

Poorjavad et al. found a significant relationship between disease duration and the frequency of dysphagia.[9] In our study patients' disease duration is not long as much as it may cause severe dysphagia. But the correlation that we found between dysphagia and disease duration shows us that MS patients have a risk of swallowing problems in the future and they are a candidate for dysphagia.

In our study, we found a weak correlation between EDSS and dysphagia and this was not consistent with the literature.[4,7,13,15] This may be probably due to low EDSS scores of our patients and a low number of patients.

Chewing ability is dependent on teeth status. Thus, the presence of prosthetic teeth, filled teeth, or tooth loss is expected to indirectly disturb the coordinated execution of pre-swallow and swallowing behaviors. In our study, we revealed that there was a significant difference in teeth status and GUSS score. Revealing that significant difference between dental status and swallowing functions of patients may show that dental problems can trigger dysphagia in individuals with MS.

In this study, there were no patients with moderate or severe dysphagia, patients' dysphagia status were mild (46.7%) and this was consistent with the literature found by Fernandes at all (40.8%).[13] However, we think that there may be changes in the results by increasing the number of participants with future studies. The limited number of samples can be considered as one of the limitations of our study. Another limitation is that the GUSS test results could be checked with further examinations such as videofluoroscopy or fiberoptic endoscopy to make fewer mistakes. And the last limitation of the study is that a control group could have been included in the study to evaluate the significance of the test results. Further studies are needed to reveal the relationship between MS and dysphagia more clearly.

We did not find a significant correlation between muscle test degree and dysphagia. Patients have mild dysphagia or healthy swallowing so, muscle test degree did not affect significantly. Also, muscle test degree was in good status except for zygomaticus major and tongue muscles. The zygomaticus major and Risorius muscles are muscle of facial expression which draws the angle of the mouth superiorly and posteriorly to allow one to smile.[14] Their muscle test degree was not 5, this means that MS patients are not smiling so much and this caused weakness in smiling muscles. So MS patients should have support from a psychologist.

CONCLUSION

As a result, individuals with MS may have swallowing dysfunction due to different conditions, so these patients should be evaluated closely in terms of swallowing function from the early stages of the disease immediately upon diagnosis. Thus, serious problems related to aspiration can be prevented.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by the Clinical Study Ethics Committee of Mustafa Kemal University Tayfur Ata Sökmen Medical Faculty (Date: 26.09.2019, Decision No: 02).

Informed Consent: Patients were informed about the study procedure and consent forms were obtained.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article / Orijinal Araştırma

Predictors of Binge Eating Disorder and the Impact on the Quality of Life in Patients with Severe Obesity Before Bariatric Surgery

Bariatrik Cerrahi Öncesi Şiddetli Obezitesi Olan Hastalarda Tıkınırcasına Yeme Bozukluğunun Belirleyicileri ve Yaşam Kalitesi Üzerine Etkileri

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Abstract

Aim: Binge eating disorder (BED) is the most common eating disorder among bariatric surgery candidates. BED may pose a risk to postsurgical outcomes. This study aims to determine the predictors of BED and the impact on the psychiatric comorbidity and quality of life for patients with severe obesity who underwent bariatric surgery.

Material and Method: A total of 207 patients with severe obesity who underwent bariatric surgery were included. Face-to-face psychiatric interviews were performed to diagnose BED according to the DSM-5 diagnostic criteria. A sociodemographic and clinical form, Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), Body Image Scale (BIS), and Short Form-36 Health Survey were administered to the participants.

Results: The rate of BED was determined as 30.9%. BED was associated with being female, lifetime suicidal ideation, previous suicide attempts, age of onset of obesity and the age of onset of dieting. Patients with BED presented with worse symptoms in BDI, BAI, BIS, and most domains of quality of life.

Conclusion: Decreased BIS score, younger ages of onset for dieting, and previous suicide attempts predicted BED. The recognition of factors involved in the development of BED in patients with severe obesity will improve the effectiveness of treatment options for these patients.

Keywords: Binge eating disorder, obesity, bariatric surgery, quality of life, psychiatric

Öz

Amaç: Tıkınırcasına yeme bozukluğu (TYB), obezite cerrahisi adayları arasında en sık görülen yeme bozukluğudur. TYB, ameliyat sonrası sonuçlar için risk oluşturabilir. Bu çalışma, bariatrik cerrahi uygulanan şiddetli obezitesi olan hastalarda TYB'nin yordayıcılarını ve psikiyatrik komorbidite ve yaşam kalitesine etkisini belirlemeyi amaçlamaktadır.

Gereç ve Yöntem: Bariatrik cerrahi uygulanan toplam 207 şiddetli obezite hastası çalışmaya dâhil edildi. DSM-5 tanı ölçütlerine göre TYB tanısı için yüz yüze psikiyatrik görüşmeler yapılmıştır. Katılımcılara sosyodemografik ve klinik form, Beck Depresyon Envanteri (BDE), Beck Anksiyete Envanteri (BAE), Beden İmajı Ölçeği (BİÖ) ve Kısa Form-36 Sağlık Anketi uygulandı.

Bulgular: TYB oranı %30,9 olarak belirlendi. TYB kadın cinsiyet, yaşam boyu intihar düşüncesi, önceki intihar girişimleri, obezite başlangıç yaşı ve diyete başlama yaşı ile ilişkiliydi. TYB'li hastaların BDE, BAE, BİÖ ölçekleri ve yaşam kalitesinin çoğu alanında düşük puanlar saptandı.

Sonuç: Düşük beden algısı, daha genç diyete başlama yaşı ve önceki intihar girişimleri TYB'nin yordayıcı faktörleridir. Şiddetli obezitesi olan hastalarda TYB gelişiminde rol oynayan faktörlerin tanınması, bu hastalar için tedavi seçeneklerinin etkinliğini artıracaktır.

Anahtar Kelimeler: Tıkınırcasına yeme bozukluğu, obezite, bariatrik cerrahi, yaşam kalitesi, psikiyatrik eştanı, yordayıcılar

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INTRODUCTION

In recent years, increasing studies have shown bariatric surgery (BS) is an effective treatment for severe obesity.[1,2] However, although surgery has an important role in the care of patients with severe obesity, some psychopathological features, specifically disordered eating behaviors, may pose a risk to postsurgical outcomes.[2,3] Binge eating disorder (BED) may cause such a hazard.[4] BED is defined as repeated and persistent periods of excessive eating accompanied by a feeling of loss of control. The lifetime prevalence of BED is 2.22% in worldwide[5] and the most common comorbidity (40%) is obesity.[6]

Health related quality of life (HRQoL) refers to the effect a medical condition, such as obesity, has on one's well-being and physical function.8 Many researches have documented the relation between extreme obesity and quality of life impairment, and found that obesity is associated with reduced mental and physical HRQoL.[7,8] Impairment in quality of life is therefore an important problem affecting emotional and physical health for bariatric surgery candidates. Besides obesity, eating disorders in general may reduce quality of life.[9] Studies have shown that BED specifically, is related with reduced quality of life. Moreover BED is related with significant impairment in aspects of HRQoL relating to both mental and physical health[10] and obese patients with BED experience impairments to psychosocial aspects of quality of life.[11]

BED is correlated with increased psychiatric comorbidity, health problems, and psychosocial impairment.[12] There may be a higher risk for psychological problems in some subgroups of the obese population (e.g., female patients seeking BS and the patients with severe obesity).[13,14] This study aims to identify predictors of BED and its impact on psychiatric comorbidity and quality of life in patients with severe obesity who seek BS. Reports from randomized controlled trials for BS have shown positive long-term outcomes in terms of weight loss, resolution of comorbidities, and improved life expectancy.[1,2] The results of this study are important in terms of recognizing BED and psychiatric comorbidity that may disrupt this positive course. In this study, the predictors of BED, its effects on psychiatric comorbidity and quality of life will be investigated in patients with severe obesity that have undergone bariatric surgery.

MATERIAL AND METHOD

This research was approved by the İstanbul Bağcılar Education and Research Hospital's ethical committee (reference 2012-60) and was conducted in accordance with the Declaration of Helsinki.

Participants and procedure

The data were collected at the İstanbul Bağcılar Education and Research Hospital. A total of 207 patients with severe obesity (body mass index [BMI] ≥ 40 kg/m^2) who underwent bariatric surgery between January 1st, 2014 and December 31st, 2014 were included. Patients obtaining pre-surgical consultation from the psychiatry clinic were consecutively included in the study. Patients over 18 years old and diagnosed with severe obesity (BMI ≥ 40 kg/m^2) met the inclusion criteria. Reasons for exclusion were pregnancy, illiteracy, substance abuse, declared inability to complete questionnaires, and serious psychiatric disorders that hindered judgement. The aim of the study was explained to the participants and informed consent forms were obtained before they were included in the study. Face-to-face interviews were carried out by a psychiatrist who was well trained in eating disorders to diagnose BED according to DSM-5-TR criteria. A sociodemographic and clinical data form, Beck Depression Inventory, Beck Anxiety Inventory, Body Image Scale and Short Form-36 Health Survey were administered to the participants.

Measures

Sociodemographic and clinical data form was prepared by the researchers to collect sociodemographic data (age, gender, marital status, education level, employment, smoking, and alcohol consumption) and clinical data (additional medical diseases, lifetime suicidal ideation, previous suicide attempts, BMI, obesity onset age, and first diet onset age) to aid in analysis.

Beck Depression Inventory (BDI) is one of the most commonly used inventories in depression-related investigations. The scores range from 0–63, with higher scores indicating greater symptoms of depression. The Turkish version of the scale was adapted by Hisli (1989).[15,16] The reliability score for the scale is 0.92.

Beck Anxiety Inventory (BAI) is a self-report scale that aims to measure the frequency of anxiety symptoms. The scores range from 0–63, with higher scores indicating greater symptoms of anxiety. The Turkish validity and reliability study of the scale was conducted by Ulusoy, Şahin, and Erkman (1998).[17,18] The reliability score for the scale is 0.95.

Body image scale (BIS), formerly known as the body cathexis scale, was developed by Secord and Jourard in 1953and determines a person's satisfaction with forty different body parts or functions using a five-point Likert system.[19] The minimum score received is 40 and the maximum score is 200. Higher scores point to an increased level of satisfaction. In Turkey, the validity and reliability studies of this scale were conducted by Hovardaoglu and Özdemir (1993).[20] It was calculated as 0.86 in the current study.

Diagnostic psychiatric interview, a face-to-face clinical interview was carried out by a psychiatrist to screen BED diagnostic criteria according to the DSM-5-TR.[21]

Short Form-36 Health Survey (SF-36) is a 36-item self-assessment scale that evaluates HRQoL based on eight health-related dimensions: mental health, social

functioning, physical functioning, energy/vitality, role limitations associated with physical or emotional problems, and general perception of pain or health.[22] The reliability and validity of the Turkish translation has been established.[23]

Statistical Analysis

The collected data were analyzed using the Statistical Package for the Social Sciences version 20.0 (SPSS 20.0, Chicago, IL, USA). The descriptive statistics were presented as frequency, percentage, mean, and standard deviation. The chi-square test was used to determine possible differences between groups in terms of categorical variables. The student's t-test was used for comparing continuous variables. The normality of distribution for continuous variables was investigated using the Kolmogorov–Smirnov test. Comparisons of non-normally distributed variables were made with the Mann-Whitney U test. A binary logistics regression model was generated with the BIS score, first diet onset age(years), and previous suicide attempts. The variables evaluated were determined as significant variables derived from our results and literature review, in accordance with clinical experience.[24]

RESULTS

Among all participants, 154 (74.4%) were women and 53 (25.6%) were men. The mean age was 36.2±9.91 and the mean BMI was 47.2±5.50. The range of additional medical disease was 75.4%, lifetime suicidal ideation 23.7%, and previous suicide attempts 13.5%.

After a detailed psychiatric interview using DSM-IV-TR diagnostic criteria, 64 (30.9%) participants were diagnosed with BED. There were no differences between those diagnosed with BED and not diagnosed with BED in terms of marital status, education level, employment, smoking, alcohol consumption, or additional medical diseases. However, the relationship between BED diagnosis and gender (female), lifetime suicidal ideation, and previous suicide attempts was found to be statistically significant (p values=0.038, 0.006, 0.002, and 0.005, respectively). There was no significant difference between those diagnosed with BED and not diagnosed with BED in terms of age (current BED: 35.0±9.82, no BED: 36.81±10.01, p= 0.241) and BMI (current BED: 48.2 ± 6.11, no BED: 46.7±5.22, p= 0.109), while those diagnosed with BED had a significantly lower obesity onset age (current BED: 14.63±8.07, no BED: 17.38±10.55, p= 0.041) and first diet onset age (current BED: 20.37±7.08, no BED: 24.25±10.07, p= 0.002). **Table 1** presents the sociodemographic and clinical data of all participants diagnosed with BED and not diagnosed with BED.

A comparison of the BDI, BAI, BIS, and SF-36 scores are summarized in **Table 2**. Participants diagnosed with BED reported significantly higher mean BDI (p<0.001) and BAI (p=0.030) scores and lower mean BIS scores (p<0.001) than those not diagnosed with BED. Participants diagnosed with BED reported lower mean scores on physical role limitation, general health, vitality, social function, and mental health than those not diagnosed with BED (p values= 0.017, 0.001, <0.001, 0.041, and 0.004, respectively).

Binary logistic regression was performed and showed that BIS scores decreased, first diet onset age (years) decreased, and previous suicide attempts increased participants' likelihood of having BED. The logistic regression model was statistically significant, $\chi 2$ (3)=27.28, p <0.001. The model explained 17.6% (Nagelkerke R2) of the variance in BED and predicted 72.7% of cases (**Table 3**).

Table 1. Comparison of the sociodemographic and clinical characteristics of diagnosed with or without BED, and their relation to BED

	Overall (n=207) n (%)/ mean±SD	Current BED (n=64) n (%)/ mean±SD	No BED (n=143) n (%)/ mean±SD	p
Gender				0.038*
Females	154 (74.4)	54 (84.4)	100 (69.9)	
Males	53 (25.6)	10 (15.6)	43 (30.1)	
Marital Status				0.875
Married	137 (66.2)	43 (67.2)	94 (65.7)	
Single	70 (33.8)	21 (32.8)	49 (34.4)	
Education Level				0.462
Primary	74 (35.7)	26 (40.6)	48 (33.6)	
Secondary	94 (45.4)	25 (39.1)	69 (48.3)	
High	39 (18.8)	13 (20.3)	26 (18.3)	
Employment				0.655
No	54 (26.1)	18 (28.1)	36 (25.2)	
Yes	153 (73.9)	46 (71.9)	107 (74.8)	
Smoking				0.985
No	113 (54.6)	35 (54.7)	78 (54.5)	
Yes	94 (45.4)	29 (45.3)	65 (45.5)	
Alcohol consumption				0.463
No	140 (67.6)	41 (35.9)	99 (69.2)	
Yes	67 (32.4)	23 (64.1)	44 (30.8)	
Additional medical disease				0.789
No	51 (24.6)	15 (23.4)	36 (25.2)	
Yes	156 (75.4)	49 (76.6)	107(78.4)	
Lifetime suicidal ideation				0.002*
No	158 (76.3)	40 (62.5)	118 (82.5)	
Yes	49 (23.7)	24 (37.5)	25 (17.5)	
Previous suicide attempt				0.005*
No	179 (86.5)	49 (76.6)	130 (90.9)	
Yes	28 (13.5)	15 (23.4)	13 (9.1)	
Age (years)	36.2±9.91	35.0±9.82	36.81±10.01	0.241
Weight (kg)	128.0±17.2	127.3±17.2	128.3±17.3	0.694
BMI (kg/m2)	47.2±5.50	48.2 ± 6.11	46.7±5.22	0.109
Ages of onset for obesity (years)	16.53±9.91	14.63±8.07	17.38±10.55	0.041*
Ages of onset for dieting (years)	23.05±9.41	20.37±7.08	24.25±10.07	0.002*

* p<0.05. Mann Whitney U tests, Student t and chi-squared (X^2) tests were used.
BED: Binge Eating Disorder; BMI: Body mass index.

Table 2. BDI, BAI, BCS and SF-36 scale scores comparison

	Overall (n=207) mean±SD	Current BED (n=64) mean±SD	No BED (n=143) mean±SD	p
BDI	16.46±9.56	20.58±11.08	14.62±8.18	<0.001**
BAI	14.67±10.54	17.03±11.65	13.61±9.86	0.030*
BIS	121.86±27.08	111.34±26.10	126.57±26.26	<0.001**
SF-36				
Physical Function	47.65±23.12	43.82±20.58	49.37±24.05	0.092
Physical Role Limitation	42.63±41.03	32.42±37.44	47.20±41.86	0.017*
Pain	62.60±24.11	58.96±21.56	64.23±25.07	0.204
General health	46.85±19.06	40.25±17.78	49.81±18.93	0.001**
Vitality	50.74±21.31	42.65±20.94	54.37±20.52	<0.001**
Social Function	66.06±26.01	60.54±28.62	68.53±24.45	0.041*
Emotional Role Limitation	50.56±42.16	46.87±40.15	52.21±43.07	0.401
Mental Health	59.65±18.18	54.18±18.57	62.09±17.52	0.004**

*p<0.05. **p<0.01.Student's t-test and Mann–Whitney U Test were used. BED: Binge Eating Disorder; BDI: Beck Depression Inventory; BAI: Beck Anxiety Inventory; BIS: Body Image Scale; SF-36: SF-36 quality of life scale.

Table 3. Multivariate Binary Regression Analysis for BED Predictors

	B	SE B	Wald χ2	p	OR	95% C.I.for EXP(B)
BIS	-0.024	0.007	12.54	<0.001**	0.97	(0.96, 0.99)
Ages of onset for dieting (years)	-0.043	0.44	5.03	0.025*	0.95	(0.92, 0.99)
Previous suicide attempt	0.918	0.31	4.27	0.039*	2.50	(1.04, 5.98)

*p < .05. **p < .001. OR: odds ratio; BED: Binge Eating Disorder; BIS: Body Image Scale.

DISCUSSION

In the current study, BED rate was determined as 30.9%. BED had a significant relationship with sociodemographic and clinical features such as being female, lifelong suicide ideation, previous suicide attempts, and early onset ages of obesity and dieting. The patients diagnosed with BED demonstrated more significant depression and anxiety symptoms as well as poor body image (dissatisfaction). Patients diagnosed with BED had a lower quality of life, particularly in terms of mental health. Reduced body image, early onset age of dieting and previous suicide attempts were determined as predictors of BED and were anticipated in 72.7% of the model cases.

BED rate was determined as 30.9% among participants. This rate was 26.3% in the USA studies done among patients with severe obesity who wanted to undergo a bariatric surgery.[25] In a community-based study with the participants from 14 countries on 4 continents, the BED prevalence rate was noted as 1.4%.[26] BED prevalence is 13%–27% in obese people who want to lose weight with treatment in primary care setting and is between 2% and 53% in bariatric surgery candidates. 27It was thought that the wide range in BED rates among bariatric surgery candidates was caused by methodological defaults such as the specifications of the participants, BED evaluation scales, and insufficient sample and option biasness.[2] However, the data from the present study and findings in the literature demonstrate that patients with severe obesity who will undergo bariatric surgery have a high rate of BED.

The current study concurs with the literature that the BED rate is higher in women compared to men.[13,26] There are few studies that research suicide ideation or attempts specifically related to BED. Those studies suggest that suicide ideation and/or suicide attempts are related to the BED, in accord with the current study.[28,29] However, whether the relation between suicidal behaviors and BED is caused by psychiatric comorbidity in patients with obesity is a subject for future studies.[24] In a study with 98 participants diagnosed with BED, it was shown that starting to diet at an early age could lead to BED.[30] In another study with 537 participants who sought treatment for obesity, it was suggested that an early dieting onset age and obesity are related to eating disorders and highlights the relation between anorexia nervosa and BED.[31] In the current study, patients diagnosed with BED have more symptoms of depression, anxiety, and poor body image. There was a higher rate of psychopathology such as depression, anxiety and substance abuse in patients with obesity diagnosed with BED compared with those who were not diagnosed with BED.13 Besides, a positive correlations were found between adipose tissue and depressive symptoms.[32] Further, anxiety and depression symptoms may contribute to the continuance of eating disorder symptoms and developing BED.[33,34] The obesity-psychopathology-BED relation frequently seen in the literature is repeated in the findings of the current study. It emphasizes the importance of mental health support in patients with obesity. Reduced body image is frequently seen in patients with obesity and is a common finding in patients with an eating disorder.[35] There are few studies which describe the relation between BED and body image in patients with obesity. The results of these studies show that body image satisfaction in patients diagnosed with BED is lower, which concurs with this study.[35,36]

In this study, the HRQoL of patients without BED was significantly higher compared to the patients with BED. This result is consistent with studies concerning eating disorders in general[37,38] and BED in particular.[9,39,40] We observed impairment in the mental health quality of life in patients with BED and it was associated with greater impairment of mental HRQoL, which indicates that BED affects mental health independently from obesity itself in extremely obese individuals. Researchers have found that extreme obesity is related with poor HRQoL.[41] A 2013 meta-analysis found that physical HRQoL decreased in overweight and obese groups in comparison to individuals with anormal weight, and only in extremely obese individuals was mental HRQoL impaired.[42] Moreover, in a study among patients with severe obesity, Hsu et al. (2002) found that both mental and physical health was reduced in patients with BED compared to those without BED.[39] However, a 2013 study found differences only in the mental component.[43] On the contrary, no differences were found in the mental component of HRQoL in other studies. The existence of an eating disorder may contribute to impairment

in HRQoL by creating an additional burden.[9] Before surgery, psychiatric comorbidity is common in patients with obesity[44] and can influence HRQoL scores. In the current study, patients with BED presented lower scores in anxiety and depressive symptoms compared to those without BED. Compared with the previous literature, the low ratio of psychiatric comorbidity in the present study could be attributed to only patients mentally healthy enough to seek treatment being referred to the medical center.[30] However, it is difficult to determine whether the lower mental HRQoL results are from an eating disorder or another psychiatric cause.[45]

In a two-year observational study, increased dieting, pressure to be thin, eating disturbances, appearance overvaluation, body dissatisfaction, depressive symptoms, emotional eating, body mass, low self-esteem, and little social support predicted the onset of binge eating with 92% accuracy.[46] In a another study the authors describe a risk factor model for BED, in which external and internal stressors such as interpersonal conflicts, exposure to food, impulsiveness, low self-esteem, tension, and concern with one's weight as triggers for binge eating episodes.[47] Two other studies showed that body dissatisfaction or the increase thereof predicted binge eating during adolescence and young adulthood.[48,49] In a recent three-year follow-up study, thin-ideal internalization, body dissatisfaction, dieting, overeating, and mental health care predicted the onset of subthreshold/threshold BED.[50] Therefore, the current study and findings in the literature are consistent.

Study limitations and strengths

There are several limitations to this study. First, the sample was comprised of patients with severe obesity who were already seeking treatment. These findings cannot be generalized to different groups such as community samples or people uninterested in participating in research. Second, the study used a cross-sectional design; however, to determine relationships between the explored variables a longitudinal study must be conducted. Third, the lack of a non-obese comparison group can be another relative limitation. However, the strength of the present study was the use of a clinical psychiatric interview conducted by a psychiatrist who was well trained in eating disorders. We have sought to explore predictors of BED in this study, more research is needed to understand BED in individuals suffering from severe obesity.

CONCLUSIONS

The results of this study showed that BED has a high rate, affects HRQoL, increases anxiety and depressive symptoms, and deepens body image dissatisfaction in patients with severe obesity. In addition, it was observed that predictors for BED may be related to gender, lifelong suicide ideation, previous suicide attempts, early onset of obesity and dieting, and reduced body image satisfaction. BED should be considered as an important factor which may affect the treatment process in patients with severe obesity.

ETHICAL DECLARATIONS

Ethics Committee Approval: This research was approved by the İstanbul Bağcılar Education and Research Hospital's ethical committee (reference 2012-60).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Orijinal Araştırma / Original Article

Risk Factors Associated with Severe Disease in COVID-19

COVID-19'da Ciddi Hastalıkla İlişkili Risk Faktörleri

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Abstract

Aim: This study aimed to determine the characteristics and risk factors associated with severe illness from COVID-19.

Material and Method: A total of 186 adult patients (97 female) hospitalized with a diagnosis of COVID-19 (laboratory-confirmed cases, SARS-CoV-2-RNA detected with the molecular method) between March 2020 and May 2020 were included in the study. The possible risk factors evaluated were age, gender, comorbidities, smoking, symptoms, and laboratory parameters at the time of admission to the hospital.

Results: A total of 186 patients were included in the final study; 43 (23.1%) were evaluated as having severe COVID-19 and 143 (76.9%) as having non-severe COVID-19. Multivariate logistic regression analysis identified risk factors for severe COVID-19 to be age >65 years (odds ratio [OR]=5.289, 95% confidence interval (CI):1.680–16.651, p=0.004), elevated levels of lactate dehydrogenase (LDH; OR=8.521, 95% CI:2.445–29.702, p=0.001), ferritin (OR=7.436, 95% CI:2.171–25.468, p=0.001), D-dimer (OR=10.076, 95% CI: 2.758–36.813, p<0.001), creatine kinase myocardial band (CK–MB; OR=5.916, 95% CI:1.833–19.089, p=0.003), and troponin (OR=9.201, 95% CI:11.886–44.888, p=0.006).

Conclusion: The results of this study examining possible risk factors for severe COVID-19 demonstrated that age >65 years and elevated LDH, ferritin, D-dimer, CK-MB, and troponin levels are independent risk factors. Clinicians should consider these potential risk factors for progression to severe illness when treating COVID-19 patients.

Keywords: COVID-19, pandemic, risk factor, severe illness

Öz

Amaç: Çalışmamızın amacı COVID-19'da şiddetli hastalık ile ilişkili özellikler ve risk faktörlerinin belirlenmesidir.

Gereç ve Yöntem: Mart 2020-Mayıs 2020 tarihleri arasında COVID-19 (moleküler yöntemle SARS-CoV-2-RNA tespit edilen olgular) tanısı ile hastaneye yatırılan toplam 186 yetişkin hasta (97 kadın) çalışmaya dahil edildi. Olası risk faktörleri olarak yaş, cinsiyet, komorbidite, sigara kullanımı, semptomlar ve yatış sırasındaki bazı laboratuvar parametreleri irdelendi.

Bulgular: Hastaların 97'si (%52,2) kadın olup, 43 (%23,1) olgu şiddetli COVID-19 ve 143 (%76,9) olgu şiddetli olmayan COVID-19 olarak değerlendirildi. Çoklu değişkenli lojistik regresyon analizinde; 65 yaş üzeri (odds oranı (OR)=5.289, %95 güven aralığı (CI) 1.680-16.651, p=0.004), artmış LDH (OR=8.521, 95% CI:2.445-29.702, p:0.001), ferritin (OR=7.436, 95% CI:2.171-25.468, p:0.001), D-dimer (OR=10.076, 95% CI: 2.758-36.813, p<0.001), CK-MB (OR=5.916, 95% CI:1.833-19.089, p:0.003) ve troponin seviyesi (OR=9.201, 95% CI:11.886-44.888, p:0.006) şiddetli COVID-19 için risk faktörleri olarak tanımlandı.

Sonuç: Ciddi COVID-19 için olası risk faktörlerini incelediğimiz bu çalışmada 65 yaş üstü, yükselmiş LDH, ferritin, D-dimer, CK-MB ve troponin düzeylerinin bağımsız risk faktörleri olduğunu bulduk. Klinisyenler, COVID-19 hastalarının tedavisi sırasında ciddi hastalığa ilerleme için bu potansiyel risk faktörlerini dikkate almalıdır.

Anahtar Kelimeler: COVID-19, pandemi, risk faktörü, şiddetli hastalık

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) first recorded in December 2019 in Wuhan, China; the virus then rapidly spread throughout the world.[1] The disease is highly contagious, and its primary clinical symptoms are fever, dry cough, fatigue, myalgia, and shortness of breath. While COVID-19 often presents with only upper respiratory tract symptoms, it may also manifest itself through a broad spectrum of symptoms, such as mild pneumonia, severe pneumonia, acute respiratory failure, and multiple organ damage.[2] In a large cohort study conducted in China, the clinical status of the cases was evaluated as 81% mild, 14% severe, and 5% critical, and the overall case fatality rate (CFR) was reported to be 2.3%.[3] In most patients, the disease is mild and even asymptomatic, usually resolving spontaneously without the need for hospitalization. Although severe cases are rare, they are difficult to treat, and the mortality rate is high.[4] Identifying risk factors for COVID-19 progression is crucial to help diagnose severe cases early and improve prognosis. This study aimed to determine the characteristics and risk factors associated with severe illness in COVID-19. The results of this research will help in the early detection of patients at risk of developing severe illness and improve the outcomes of these patients.

MATERIAL AND METHOD

Study Setting

The retrospective cross-sectional study was conducted in the Health Sciences University Konya Training and Research Hospital, a 1200-bed tertiary hospital located in an area with a high prevalence of COVID-19 and accepted as a reference center for COVID-19 care. Patients over 18 years of age hospitalized in the Infectious Diseases Clinic and General Intensive Care Unit (ICU) of our hospital between March and May 2020 were included in the study.

Study Design

The study sample comprised a total of 186 adult patients (97 female) hospitalized with a laboratory-confirmed (RNA SARS-CoV-2 detected by molecular method) diagnosis of COVID-19 (World Health Organization confirmed case definition). Patients were excluded from the study if they were aged <18 years, were pregnant, had any hematological disease, had a history of thromboembolic events, or were using anticoagulant or antiaggregant treatments for any reason. According to the National Institutes of Health (NIH) COVID-19 Treatment Guidelines, patients with COVID-19 were categorized into groups: Mild illness defines those individuals who have any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but who do not have shortness of breath, dyspnea, or abnormal chest imaging; moderate illness defines those individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have an oxygen saturation (SpO_2) ≥94% on room air at sea level; and severe illness define those individuals who have SpO_2 <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) <300 mm Hg, respiratory frequency >30 breaths/min, or lung infiltrates >50%.[5] In accordance with this classification, 43 patients were included in the severe COVID-19 group and 143 in the non-severe (mild or moderate) group. The possible risk factors evaluated were age, gender, comorbidities, smoking history, symptoms, and laboratory parameters during hospitalization. Among the comorbidities considered were diabetes mellitus (DM), malignancy, chronic lung disease, hypertension (HT), and cardiovascular (CV) disease. The symptoms analyzed were fever, sore throat, headache, dizziness, weakness, myalgia, cough, shortness of breath, chest pain, palpitations, anorexia, abdominal pain, diarrhea, decreased sense of smell and taste, and nasal congestion. The laboratory parameters examined during hospitalization included neutrophil count, lymphocyte count, platelet count, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), ferritin, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), D-dimer, troponin, and creatine kinase myocardial band (CK–MB). Comparisons were made between the severe and non-severe COVID-19 patient groups with respect to age, gender, smoking history, comorbidities, symptoms, and laboratory parameters.

Ethical Approval

Approval for the study was granted by the Local Ethics Committee of the Health Sciences University Konya Training and Research Hospital (Decision no: 08.05.2020/38-07). In addition, permission was obtained from the Ministry of Health on 05/01/2020 (Application no: 2020-04-30T14_23_49). The study was conducted in accordance with the principles of the Declaration of Helsinki 2013.

Statistical Analysis

Data obtained in the study were analyzed statistically using SPSS V22.0 software (IBM Corp., Armonk, NY, USA). Continuous variables were presented as mean ± standard deviation (SD) values and categorical variables as number (n) and percentage (%). In the comparisons between the severe and non-severe COVID-19 patients, the independent samples t-test was applied to evaluate continuous data and the chi-square test to evaluate categorical data. Univariate and multivariate logistic regression analyses were performed to identify risk factors for severe COVID-19. All variables with a p value <0.1 on univariate analysis were entered into forward, stepwise multivariate logistic regression analysis. A value of < 0.05 was considered statistically significant.

RESULTS

According to the inclusion criteria (**Figure 1**), 186 patients hospitalized for laboratory-confirmed COVID-19 were included, and 97 (52.2%) were female. The severe COVID-19 group included 43 (23.1%) patients, and the non-severe COVID-19 group included 143 (76.9%) patients. The patient outcomes were recorded as recovery in 169 (90.9%) and death in 17 (9.1%). Comorbidities of the patients were recorded as 59 (31.7%) with HT, 19 (10.2%) with CV disease, 42 (22.6%) with DM, 18 (9.7%) with chronic lung disease, and 3 (1.6%) with malignancy. The three most common symptoms were cough (63.4%), weakness (55.9%), and anorexia (50.5%). Other symptoms were fever (37.6%), sore throat (34.9%), dyspnea (29%), headache (25.3%), myalgia (16.1%), nasal stuffiness (15.6%), loss of smell (14.5%), palpitations (12.9%), loss of taste (12.4%), dizziness (10.8%), diarrhea (9.7%), chest pain (8.1%), and abdominal pain (3.8%). In the examination of the antiviral and antibacterial treatments administered to patients for COVID-19, all patients received hydroxychloroquine and azithromycin, 155 (83.3%) received oseltamivir, 64 (34.4%) received favipiravir, and 8 (4.3%) received lopinavir/ritonavir. The demographic data and clinical characteristics of all patients with COVID-19 are summarized in **Table 1**.

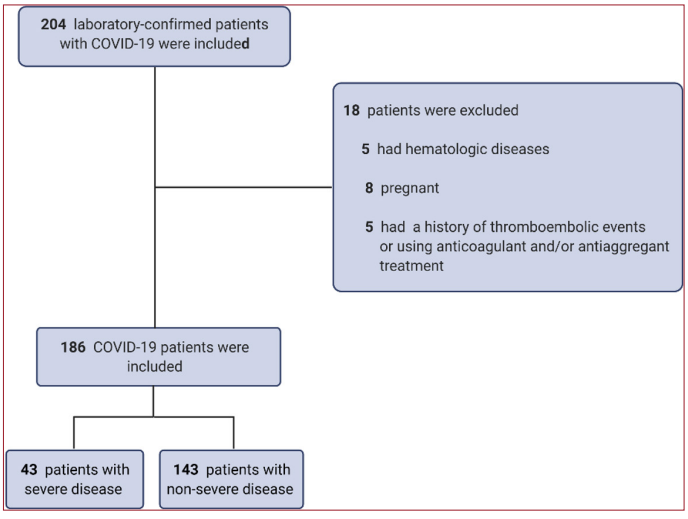

Figure 1. The study population.

Table 1. Demographics and clinical characteristics of patients with COVID-19 (n=186)

Characteristics	n (%)
Sex	
Male	89 (47.8)
Female	97 (52.2)
Disease severity	
Severe	43 (23.1)
Non-severe	143 (76.9)
Outcome	
Healing	169 (90.9)
Exitus	17 (9.1)
Comorbidity	
Malignancy	3 (1.6)
Chronic pulmonary disease	18 (9.7)
Cardiovascular disease	19 (10.2)
Hypertension	59 (31.7)
Diabetes mellitus	42 (22.6)
Symptoms at admission	
Fever	70 (37.6)
Sore throat	65 (34.9)
Headache	47 (25.3)
Dizziness	20 (10.8)
Weakness	104 (55.9)
Myalgia	30 (16.1)
Cough	118 (63.4)
Dyspnea	54 (29.0)
Chest pain	15 (8.1)
Palpitation	24 (12.9)
Anorexia	94 (50.5)
Abdominal pain	7 (3.8)
Diarrhea	18 (9.7)
Loss of smell	27 (14.5)
Loss of taste	23 (12.4)
Nasal stuffiness	29 (15.6)
Treatment	
Hydroxychloroquine	186 (100)
Favipiravir	64 (34.4)
Lopinavir/ritonavir	8 (4.3)
Oseltamivir	155 (83.3)
Azytromicin	186 (100)

No significant difference was determined between the severe and non-severe COVID-19 groups with respect to gender (p=0.882). When the two groups were compared in terms of age, the mean age of the severe patients was significantly higher than that of the non-severe patients (p=0.001). When the hemogram parameters were compared, the neutrophil count was considerably higher in the severe group than in the non-severe group (p=0.006). Lymphocyte and platelet counts were significantly lower in the severe versus non-severe group (p<0.001 and p=0.031, respectively). There was no significant difference between the two groups in terms of creatinine (p=0.184). The ALT, AST, and LDH levels were significantly higher in the severe group (p=0.040, p=0.005, and p=0.038, respectively). The ferritin level was determined to be significantly higher in the severe group (p=0.008). No significant difference was observed between the two groups in terms of ESR (p=0.255). CRP was found to be significantly higher in the severe group (p<0.001). There was no significant difference between the two groups in terms of CK–MB (p=0.197). Troponin and D-dimer were significantly higher in the severe group than in the non-severe group (p=0.029 and p=0.002, respectively). The demographic data and laboratory parameters of the severe and non-severe patients with COVID-19 are summarized in **Table 2.**

Table 2. Demographics and laboratory parameters between severe and non-severe patients with COVID-19

Characteristics (n, %/mean±SD)	Non-severe n=143	Severe n=43	P value
Demographics			
Age (years)	56.0±14.7	64.9±14.1	0.001
Sex (male)	68 (47.6)	21 (48.8)	0.882
Laboratory parameters			
Neutrophils (1800-6980/mm³)	3929±1924	5732±3926	0.006
Lymphocytes (1260-3350/mm³)	1723±663	1059±520	<0.001
Platelets (150000-450000/mm³)	214000±69953	186814±77689	0.031
Creatinine (0.84-1.25 mg/dl)	0.9±0.5	1.2±1.6	0.184
Alanine aminotransferase (0-50 U/L)	23±16	29±21	0.04
Aspartate aminotransferase (0-50 U/L)	29±15	40±24	0.005
Lactate dehydrogenase (0-248 U/L)	273±230	352±153	0.038
Ferritin (18.5-306.5 µg/L)	144±212	473±633	0.008
C reactive protein (0-5 mg/L)	23±34	70±72	<0.001
Erythrocyte sedimentation rate (mm/h)	32±23	40±29	0.255
D-dimer (0-2 mg/L)	0.5±0.4	2.0±2.7	0.002
Creatine kinase –MB (0-3.6 U/L)	16±8	13±9	0.197
Troponin (0-60 mg/L)	7±17	41±94	0.029

Risk Factors for Severe COVID-19

The results of univariate and multivariate logistic regression analyses associated with severe COVID-19 are shown in **Table 3**. In univariate regression analysis, risk factors for severe COVID-19 were found to be age >65 years and the presence of chronic pulmonary disease, DM, decreased lymphocyte count, and elevated levels of AST, LDH, ferritin, CRP, ESR, D-dimer, CK-MB, and troponin. All the variables with p-values <0.1 in univariate analysis were entered into the forward step-wise multivariate logistic regression analysis. As a result of the multivariate logistic regression analysis, the risk factors for severe COVID-19 were determined to be age >65 years (odds ratio (OR)=5.289, 95% confidence interval (CI) 1.680–16.651, p=0.004), elevated levels of LDH (OR=8.521, 95% CI 2.445–29.702, p=0.001), ferritin (OR=7.436, 95% CI 2.171–25.468, p=0.001), D-dimer (OR=10.076, 95% CI 2.758–36.813, p<0.001), CK–MB (OR=5.916, 95% CI 1.833–19.089, p=0.003), and troponin (OR=9.201, 95% CI 11.886–44.888, p=0.006; **Table 3**).

Table 3. Logistic regression analysis results of risk factors for severe COVID-19 (n=186)

	Univariate Analysis			Multivariate Analysis		
Variables	OR	95% CI	p	OR	95% CI	p
Gender (male vs. female)	1.053	0.532–2.082	0.882			
Age >65 y	3.441	1.697–6.978	0.001	5.289	1.680–16.651	0.004
Smoking	1.231	0.371–4.082	0.734			
Chronic pulmonary disease	3.040	1.117–8.276	0.030	3.220	0.509–20.388	0.214
Diabetes mellitus	2.546	1.206–5.373	0.014	2.136	0.642–7.108	0.216
Cardiovascular disease	1.814	0.642–3.698	0.122			
Hypertension	1.348	0.576-4.154	0.461			
Lymphocyte count decreased	3.754	1.845–7.640	<0.001	1.388	0.461–4.177	0.560
Creatinine increased	2.560	1.060–6.187	0.037			
Alanine aminotransferase increased	1.436	0.476–4.333	0.520			
Aspartate aminotransferase increased	3.308	1.316–8.317	0.011	0.599	0.118–3.045	0.537
Lactate dehydrogenase increased	4.389	2.048–9.408	<0.001	8.521	2.445–29.702	0.001
Ferritin increased	8.727	3.868–19.689	<0.001	7.436	2.171–25.468	0.001
C reactive protein increased	6.445	2.941–14.124	<0.001	1.664	0.454–6.102	0.442
Erythrocyte sedimentation rate increased	2.961	1.468–5.974	0.002	2.123	0.714–6.312	0.176
D-dimer	7.200	3.133–16.544	<0.001	10.076	2.758–36.813	<0.001
Creatine kinase myocardial band increased	3.192	1.537–6.629	0.002	5.916	1.833–19.089	0.003
Troponin increased	11.023	3.908–31.090	<0.001	9.201	1.886–44.888	0.006

DISCUSSION

The results of the current study demonstrated that the clinical features of age >65 years and elevated levels of LDH, ferritin, D-dimer, CK-MB, and troponin according to laboratory tests were associated with severe COVID-19. The clinical spectrum of COVID-19 may vary from asymptomatic to severe; respiratory failure requiring mechanical ventilation, sepsis, septic shock, metabolic acidosis, coagulation disorder, and multiorgan failure may be seen.[6] It is critical to analyze the clinical features of COVID-19 in different regions and identify risk factors to reduce severe and critical illness incidence at an early stage.

In light of data from many countries, the elderly population is known to be at a higher risk of severe consequences of COVID-19 and has the most significant risk of death.[7] In a series of multivariable-adjusted analyses based on COVID-19 patient cohorts, more severe illness cases have been associated with advanced age.[8-10] Physiological changes that develop with aging, such as the disruption of the barrier systems in the skin, the respiratory system, and the gastrointestinal system, and a decrease in mucociliary clearance create a predisposition to infections. The age-related weakening of the immune systems of elderly patients leads to more severe infections than that in younger individuals.[11] Elderly patients have a higher prevalence of frailty and comorbidity, which reduces their functional reserve. Furthermore, their capacity and flexibility against diseases and infections are decreased.[12] The results of this study allowed the conclusion that being over the age of 65 years increased the risk of serious COVID-19 5.2-fold.

Previous studies have shown that a high LDH level is a risk factor for mild patients to progress toward critical illness.[13] According to a meta-analysis of 3117 hospitalized COVID-19 patients, the mean LDH value of severe patients was 1.54-fold higher than in non-severe cases.[14] High basal LDH levels were significantly associated with the risk of acute respiratory distress syndrome (ARDS) and mortality.[15] According to the results of the current study, elevated LDH levels increase the risk of serious COVID-19 8.5-fold. High LDH levels in severe COVID-19 patients are thought to be associated with lung damage and tissue damage.[16,17]

Many studies have associated elevated serum ferritin levels with mortality and the development of severe consequences in COVID-19.[18] A meta-analysis of 25 studies and 5350 patients showed that high ferritin is associated with a poor outcome and ARDS development in COVID-19 patients.[19] Active ferritin production occurs during inflammatory diseases. Cytokine-producing macrophages, which make up most immune cells in the lung parenchyma, are thought to be responsible for serum ferritin secretion. In addition, ferritin synthesis can be induced by many inflammatory stimuli, including cytokines such as IL-6.[20] The results of the current study demonstrated that elevated ferritin levels increased the risk of serious COVID-19 7.4-fold.

A meta-analysis that included 5872 COVID-19 patients showed that higher D-dimer concentrations were associated with severe illness and death in these patients.[21] Another study of 343 hospitalized COVID-19 patients concluded that D-dimer levels >2.0 µg/mL at hospital admission were an independent predictor of in-hospital mortality.[22] Viral infections are usually accompanied by an aggressive pro-inflammatory response and an inadequate anti-inflammatory response. This can cause the dysfunction of endothelial cells, resulting in excess thrombin formation. Moreover, severe COVID-19 can increase blood viscosity and induce thrombosis via a hypoxia-inducible transcription factor-dependent signaling pathway. Coagulopathy and even diffuse intravascular coagulation may develop in some patients due to sepsis.[22] The results of the current study found that a high D-dimer level increased the risk of severe illness 10-fold.

COVID-19 is associated with many direct or indirect cardiovascular complications, such as myocarditis, myocardial damage, arrhythmia, and venous thromboembolism.[23] Troponin and CK-MB have been identified as biomarkers of cardiac injury. In a study examining 416 cases, the troponin level was significantly higher in COVID-19 patients who were followed up in the intensive care unit (ICU) than in those who were not.[24] The results of multivariate logistic regression analysis determined elevated troponin levels to be an independent risk factor for critical illness.[25] In a retrospective study conducted with 138 patients, troponin and CK-MB were significantly higher in all patients requiring ICU hospitalization, and it was suggested that CK-MB has predictive value.[26] A meta-analysis including 4189 patients found that troponin and CK-MB were significantly increased in those with severe illness compared to those with mild illness.[27] In the current study, it was concluded that elevated troponin increased the risk of serious COVID-19 9.2-fold, and elevated CK-MB increased the risk 5.9-fold. Different theories about the cardiac injury mechanism in COVID-19 have been proposed, and further studies are needed for clarification.

Limitations

This study had some limitations, primarily because the data of the two groups were not balanced, and the sample size of the severe group was relatively small. A second limitation was that no further examination was made to reveal the relationship between elevated laboratory parameters and related organ injury. Finally, only the values of the examined laboratory parameters on presentation were considered, and the changes in the following days were not evaluated.

CONCLUSION

In this study, which examined possible risk factors for severe COVID-19, the results showed that age >65 years and elevated levels of LDH, ferritin, D-dimer, CK-MB, and troponin were independent risk factors. Clinicians should consider these potential risk factors for progression to severe illness when treating COVID-19 patients. The determination of possible severe patients at early stages will influence the treatments to be applied and reduce the morbidity and mortality of these patients.

ETHICAL DECLARATIONS

Ethics Committee Approval: Approval for the study was granted by the Local Ethics Committee of the Health Sciences University Konya Training and Research Hospital (Decision no: 08.05.2020/38-07).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article / Orijinal Araştırma

Ultrasound-Guided Intermediate Cervical Plexus Block for Postoperative Analgesia in Patients Undergoing Carotid Endarterectomy Under General Anesthesia: A Case-Control Study

Genel Anestezi Altında Karotis Endarterektomi Uygulanan Hastalarda Postoperatif Analjezi İçin Ultrason Eşliğinde İntermediate Servikal Pleksus Bloğu: Vaka Kontrol Çalışması

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Abstract

Aim: The aim of this study is to compare intravenous analgesia (IVA) and intermediate cervical plexus block (ICPB) in terms of acute pain scores and opioid consumption in patients undergoing carotid endarterectomy (CEA) under general anesthesia.

Materials and Method: Following the induction of anesthesia, dexketoprofen trometamol 50 mg was administered before the surgical incision, and paracetamol 1 g was given at the end of the surgery and continued at 6 hour intervals for group IVA. Whereas, ultrasound-guided intermediate cervical plexus block was performed in ICPB group. VAS scores, morphine consumption, length of stay, and patient satisfaction status were compared.

Results: A total of 109 patients (57 in the IVA group and 52 in the ICPB group) between January 2015 and June 2021 were enrolled. The mean VAS score after extubation was significantly lower in the ICPB group (4.1±1.4 vs 1.2±0.8, p=0.005). Total morphine consumption was found to be significantly lower in the ICPB group (13.1±4.4 mg vs 3.9±2.4 mg, p<0.001). The hospital stay was 3.1±1.3 days in the IVA group, while it was 2.2±0.9 days in the ICPB group (p=0.0014). The patients in the ICPB group were found to be significantly more satisfied (3.4±1.4 vs 1.2±0.8, p<0.001).

Conclusion: Intermediate cervical plexus block provides lower acute pain scores and lower opioid consumption compared to intravenous analgesia in patients undergoing CEA under general anesthesia. In addition, this combined technique shortens the ICU and hospital length of stay and improves patient satisfaction.

Keywords: Carotid endarterectomy, intermediate cervical plexus block, analgesia

Öz

Amaç: Bu çalışmanın amacı, genel anestezi altında karotis endarterektomi (KEA) uygulanan hastalarda intravenöz analjezi (IVA) ve intermediate servikal pleksus bloğunu (ICPB) akut ağrı skorları ve opioid tüketimi açısından karşılaştırmaktır.

Gereç ve Yöntem: Anestezi indüksiyonunu takiben, Grup IVA'ya cerrahi kesi öncesi deksketoprofen trometamol 50 mg, operasyon bitiminde 1 gr parasetamol verildi ve 6 saat arayla devam edildi. ICPB grubuna ise ultrason eşliğinde ara servikal pleksus bloğu yapıldı. VAS skorları, morfin tüketimi, hastanede kalış süresi ve hasta memnuniyeti karşılaştırıldı.

Bulgular: Ocak 2015 ile Haziran 2021 arasında toplam 109 hasta (IVA grubunda 57 ve ICPB grubunda 52) dahil edildi. Ekstübasyon sonrası ortalama VAS skoru ICPB grubunda anlamlı olarak daha düşüktü (4,1±1,4'e karşı 1,2±0,8, p=0,005). Toplam morfin tüketimi ICPB grubunda (13,1±4,4 mg vs 3,9±2,4 mg, p<0,001) anlamlı olarak daha düşük bulundu. Hastanede kalış süresi IVA grubunda 3,1±1,3 gün iken, ICPB grubunda 2,2±0,9 gündü (p=0,0014). ICPB grubundaki hastaların anlamlı olarak daha fazla memnun oldukları bulundu (3,4±1,4'e karşı 1,2±0,8, p<0,001).

Sonuç: İntermediate servikal pleksus bloğu, genel anestezi altında KEA uygulanan hastalarda, intravenöz analjeziye kıyasla daha düşük akut ağrı skorları ve daha düşük opioid tüketimi sağlar. Ayrıca bu kombine teknik, yoğun bakım ve hastanede kalış süresini kısaltır ve hasta memnuniyetini artırır.

Anahtar Kelimeler: Karotis endarterektomi, intermediate servikal pleksus bloğu, analjezi

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INTRODUCTION

Carotid endarterectomy (CEA), which was first described by Eastcott et al. in 1954, continues to be performed frequently.[1] Although carotid artery stenting is an alternative, there are studies indicating that the rate of periprocedural stroke is higher.[2] Therefore, it has not completely replaced endarterectomy. According to current guidelines, symptomatic internal carotid artery stenosis greater than 50% and asymptomatic internal carotid artery stenosis greater than 60% are stated as indications for CEA.[3]

The anesthesia techniques used for CEA are still controversial. Although general anesthesia and cervical plexus blocks are the most commonly used methods, their superiority to each other has not been proven yet. While cervical plexus blocks provide effective neurological follow-up during surgery, general anesthesia provides airway safety and ventilation control.[4] In addition, general anesthesia may be somewhat advantageous in terms of patient satisfaction.[5] On the other hand, cervical plexus blocks may provide effective postoperative analgesia and stable hemodynamics.[6] However, in almost all of these comparisons, analgesia was provided with oral and/or intravenous medications in the general anesthesia groups.

In this context, the aim of this study is to compare intravenous analgesia and intermediate cervical plexus block (ICPB) in terms of acute pain scores and opioid consumption in patients undergoing CEA under general anesthesia. The secondary objective is to compare length of stay and patient satisfaction.

MATERIAL AND METHOD

Ethics Committee was obtained from Ankara University, Faculty of Medicine, Clinical Research Ethics Committee (Date: 09.09.2021, Decision No: 2021/317). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The records of patients who underwent CEA under general anesthesia between January 2015 and June 2021 were evaluated. Patients who could not use patient-controlled analgesia and could not cooperate for pain assessment were excluded. In addition, patients whose all data could not be accessed due to deficiencies in the registration system were excluded from the study.

The patients were taken to the operating room without any premedication. In addition to routine anesthesia monitoring, bispectral index (BIS) and bilateral cerebral near infrared spectroscopy (NIRS) monitoring was performed. Anesthesia induction was provided with lidocaine 1 mg/kg, propofol 3 mg/kg, remifentanil 1 µg/kg and rocuronium 0.6 mg/kg. After tracheal intubation, anesthesia was maintained with sevoflurane 1-2% and remifentanil 0.1 - 0.2 µg/kg/min to keep the BIS between 50-60. Invasive radial artery monitoring was performed in all patients for close hemodynamic follow-up. Patients were placed in a supine position with the head facing the opposite side of the surgery.

In intravenous non-opioid analgesia (IVA) group, dexketoprofen trometamol (Metadem, IE Ulagay-Menarini, Turkey) 50 mg was administered before the surgical incision, except for patients with chronic renal failure. In addition, Paracetamol (Partemol, Vem Ilac, Ankara, Turkey) 1 g was given 30 minutes before the end of the surgery and continued at 6 hour intervals. Whereas, ultrasound-guided intermediate cervical plexus block was performed in ICPB group, according to the technique described by Choquet et al.[7] The ultrasound probe was placed in the transverse plane at the level of the fourth cervical vertebra using GE Vivid T8 portable US machine (GE Healthcare, Fairfield, CT, USA) with a 3 to 8 MHz linear probe. Then, a 22 gauge 50 mm needle (Stimuplex A, B-Braun, Melsungen, Germany) was advanced in-plane with a posterior approach, from the posterior border of the sternocleidomastoid muscle to the posterior cervical space. After hydrodissection to test the appropriate injection site, 10 mL of 0.025% bupivacaine was injected under ultrasound control. 5 mL of the same local anesthetic solution was injected in the same plane while the needle was withdrawn (**Figure 1**). Finally, the last 5 mL was injected into the subcutaneous tissue at the posterior border of the sternocleidomastoid muscle.

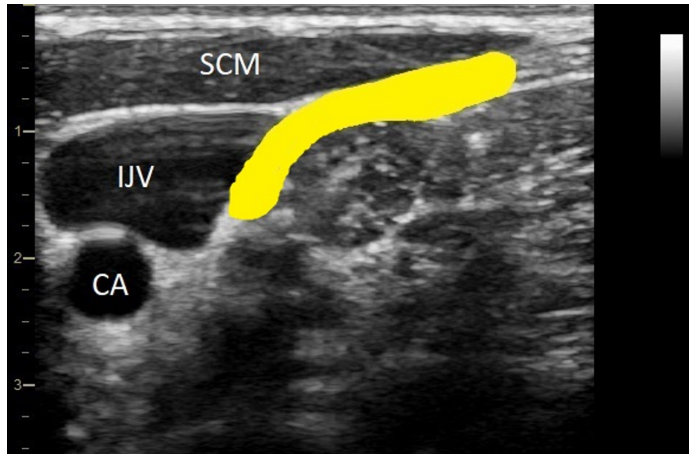

Figure 1. Transverse axis sonogram of the lateral side of the neck at the level of the fourth cervical vertebra. The yellow area shows the local anesthetic infiltrated area for ICPB. CA: carotid artery; IJV: internal jugular vein; SCM: sternocleidomastoid muscle.

After the surgery, the patients were extubated and transferred to the cardiovascular surgery intensive care unit (ICU) for close follow-up. Patient-controlled analgesia was set as a 1 mg bolus of intravenous morphine and a five-minute lock out time without a continuous rate. Visual Analogue Scale (VAS) from 0 to 10 (0=no pain and 10=the worst pain imaginable), which was explained to the patients before surgery, was used for self-assessment of postoperative pain. Morphine requirement and VAS scores were recorded every 15 minutes for the first four hours after surgery. Then, 30-minute follow-ups were taken. Patients with a VAS score below 4 and who were deemed appropriate by the surgical team to go to ward were transferred. Patient satisfaction status was measured on a 5-point scale before discharge (1, very satisfied; 2, satisfied; 3, average; 4, poor; 5, very poor).

Statistics

In the analyzes performed using IBM SPSS 20.0 software, the distribution of the data was evaluated with the Kolmogorov-Smirnov test. Normally distributed variables were compared using Student's t-test, while non-normally distributed variables were evaluated with Mann-Whitney U-test. Intergroup categorical data were compared using the Pearson chi-square test. Variables specified as mean ± SD, if indicated. P values of less than 0.05 were regarded as statistically significant.

RESULTS

A total of 109 patients, 57 in the IVA group and 52 in the ICPB group, were enrolled. There was no difference between groups in terms of demographic data. Surgical sides were also similar between the groups (p=0.17). The duration of surgery was 136±31 minutes in the IVA group, while it was 144±34 minutes in the ICPB group (p= 0.31) (**Table 1**).

Table 1. Demographic and surgical data

	IVA (n: 57)	ICPB (n: 52)	p value
Age, y, mean±SD	67.1±7.3	65.8±8.5	0.52
Sex (M/F), n	33/24	31/21	0.36
Body mass index, kg/m^2, mean±SD	23.6±3.2	24.1±2.9	0.47
ASA II / III, n (%)	24 (42.1)/33 (57.9)	18 (34.6)/34 (65.4)	0.41
Comorbidities, n (%)			
Hypertension	46 (80.7)	43 (82.6)	0.51
Diabetes mellitus	15 (26.3)	12 (23)	0.32
Coronary artery disease	18 (31.5)	16 (30.7)	0.44
COPD	7 (12.2)	6 (11.5)	0.39
Chronic renal failure	5 (8.7)	4 (7.6)	0.27
Side of surgery (L/R), n	30 / 27	28 / 24	0.37
Duration of surgery (min), mean±SD	136±31	144±34	0.31

IVA: intravenous analgesia; ICPB: intermediate cervical plexus block; COPD: chronic obstructive pulmonary disease.

The mean VAS score after extubation was significantly lower in the ICPB group (4.1±1.4 vs 1.2±0.8, p=0.005). In addition, VAS scores at the first, second and sixth hours were significantly lower in the ICPB group than in the IVA group. On the other hand, there was no difference between VAS scores after 24 hours (1.4±0.4 vs 0.7±0.3, p=0.134). Moreover, total morphine consumption was found to be significantly lower in the ICPB group (13.1±4.4 mg vs 3.9±2.4 mg, p<0.001) (**Table 2**).

While the length of stay in the ICU was 5.7±1.9 hours in the IVA group, it was 2.4±1.1 hours in the ICPB group (p<0.001). Similarly, the hospital stay was 3.1±1.3 days in the IVA group, while it was 2.2±0.9 days in the ICPB group (p=0.0014). Furthermore, considering the patient satisfaction score, the patients in the ICPB group were found to be significantly more satisfied (3.4±1.4 vs 1.2±0.8, p<0.001) (**Table 3**).

Table 2. Visual analog scale (VAS) scores [0-10], total morphine consumption (mg)

	IVA (n: 57)	ICPB (n: 52)	p value
VAS scores, mean±SD			
After extubation	4.1±1.4	1.2±0.8	0.005
1st hour	3.8±1.1	0.9±0.6	0.004
2nd hour	3.7±1.6	1.0±0.6	0.004
6th hour	3.1±2.1	1.1±0.5	0.006
24th hour	1.4±0.4	0.7±0.3	0.134
Total morphine consumption (mg), mean±SD	13.1±4.4	3.9±2.4	<0.001

IVA: intravenous analgesia; ICPB: intermediate cervical plexus block; VAS: visual analog scale.

Table 3. Length of ICU and hospital stay, and patient satisfaction scores

	IVA (n: 57)	ICPB (n: 52)	p value
Length of ICU stay (hour), mean±SD	5.7±1.9	2.4±1.1	< 0.001
Length of hospital stay (day), mean±SD	3.1±1.3	2.2±0.9	0.014
Patient satisfaction score (1-5), mean±SD	3.4±1.4	1.2±0.8	< 0.001

IVA: intravenous analgesia; ICPB: intermediate cervical plexus block; ICU: intensive care unit.

DISCUSSION

ICPB resulted in lower acute pain scores and lower opioid consumption compared to intravenous analgesia in patients undergoing CEA under general anesthesia. In addition, ICPB provided shorter intensive care and hospital stays and higher patient satisfaction.

CEA continues to be practiced frequently, but there are uncertainties regarding the superiority of anesthesia techniques applied for this surgery.[8] Although regional techniques come to the fore, general anesthesia is also frequently applied due to the preferences of both the physicians and the patients.[9] After the GALA trial, which could not find a difference between local anesthesia and general anesthesia, many studies have been carried out on this subject.[10] Cervical plexus blocks have become popular and applied by anesthesiologists frequently. Hasde et al. stated that there was no difference between regional anesthesia and general anesthesia in terms of mortality and cerebral complications in CEA. On the other hand, they emphasized that regional anesthesia is more advantageous in terms of hemodynamic stabilization, postoperative pulmonary complications and length of hospital stay.[11] In addition, Kim JW et al. determined that since awake neurological monitoring can be performed under regional anesthesia, it reduces the rate of shunt usage, and also shortens operation time and the length of hospital stay.[12] However, the general anesthesia methods used in all these studies are not standard and show differences. These differences may be important in terms of hemodynamics and postoperative outcomes. There are also deficiencies in techniques used for effective pain control, which have a serious impact on perioperative complications. Therefore, in order to demonstrate an enhanced general anesthesia technique, we aimed to reveal the difference of regional block used in combination for analgesia in patients who underwent standardized general anesthesia for CEA.

A wide range of nerve blocks are used for the treatment of acute pain in anesthesia practice. The effectiveness of nerve blockades applied in combination in patients undergoing general anesthesia has been demonstrated. It is recommended to be applied because it both contributes to a more balanced anesthesia and provides a serious reduction in acute pain scores.[13] In recent years, especially USG guided deep, intermediate or superficial cervical plexus blocks has been widely used for CEA. Alilet et al. compared the efficacy of superficial and intermediate cervical plexus blocks for CEA, but could not find a significant difference between these two techniques.[14] Whereas, Kavaklı et al. stated that ultrasound-guided combined deep and superficial cervical plexus block resulted in less additional analgesic use and lower pain scores compared to the ICPB.[15] Samanta et al. applied this blockade, which is used for regional anesthesia, as a combination therapy in a patient who underwent CEA under general anesthesia and noted that they encountered a better hemodynamic response and improved postoperative outcome.[16] Based on this, we used ICPB as a combination therapy in patients undergoing CEA under general anesthesia.

Acute pain is one of the most important factors affecting hemodynamics and patient comfort after CEA. Opioids are often used in the treatment to avoid any complications caused by pain. Even when ultrasound did not enter anesthesia practice that much, cervical block was used using the landmark technique to reduce opioid consumption. Messner et al. demonstrated that superficial cervical plexus block with the landmark technique decreased opioid consumption in patients who underwent CEA under general anesthesia in 2006.[17] In fact, Cherprenet et al. stated that even local anesthetic wound infiltration before closure reduces opioid consumption and decreases pain scores.[18] In a more recent study, Do et al. mentioned that ultrasound-guided cervical plexus block leads to both a more stable hemodynamic and lower pain scores compared to general anesthesia.[19] As expected, in our study, patients who had ICPB in addition to general anesthesia presented with lower acute pain scores and reduced opioid consumption. Based on this, we think that it would be more appropriate to review the standardization of general anesthesia technics for CEA in the literature and to make comparisons accordingly.

The effective use of health resources is very important in today's medicine, as it has become a current issue again during the pandemic period. Shortening the length of stay of patients in intensive care or hospital is one of the most important parts of this perspective. There are studies indicating that the anesthesia technique used for CEA is a feature that makes difference in terms of hospital stay. Lobo et al. stated shorter length of stay in patients who underwent locoregional anesthesia when compared with general anesthesia.[20] In line with this data, Gürer et al. mentioned that the duration of hospitalization is shorter in surgery completed under local anesthesia.[21] However, it is controversial how general anesthesia is standardized in these studies. In our study, we found that the addition of ICPB shortened the hospital stay in patients who underwent general anesthesia. Therefore, we think that it should be kept in mind that effective analgesia methods are effective on this period. In addition, it is known that the patient satisfaction is higher than regional anesthesia in patients who underwent CEA under general anesthesia.[22] Our study, in which both groups were under general anesthesia, revealed that the addition of ICPB further increased patient satisfaction.

This study has some limitations. First, randomization could not be done because the study plan was retrospective. Second, the sociocultural and educational levels of the patients may have created a difference in the perception of pain, but no record was kept for this subject. Third, postoperative complications and the long term results of the applied techniques on the patients could not be examined. It can be described as a deficiency in order to reveal the effects of nerve blocks on chronic pain. Better planned and large-scale studies are needed to reveal the effectiveness and differences of anesthesia and analgesia methods applied in patients who have undergone carotid endarterectomy.

CONCLUSION

Intermediate cervical plexus block provides lower acute pain scores and lower opioid consumption compared to intravenous analgesia in patients undergoing CEA under general anesthesia. In addition, this combined technique shortens the ICU and hospital length of stay and improves patient satisfaction. Better standardized studies are needed to reveal the effect of anesthesia techniques on CEA outcomes..

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethics Committee was obtained from Ankara University, Faculty of Medicine, Clinical Research Ethics Committee (Date: 09.09.2021, Decision No: 2021/317).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article / Orijinal Araştırma

The Clinical Importance of C-Reactive Protein to Albumin Ratio (CAR) in Patients Diagnosed with COVID-19

COVID-19 Tanılı Hastalarda C-Reaktif Protein Albumin Oranının (CAR) Klinik Önemi

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Abstract

Aim: The course of COVID-19 infection due to SARS-CoV-2 is manifested by viral replication in the upper respiratory tract with or without lung involvement and extrapulmonary systemic hyperinflammation syndrome. Because it has a wide clinical spectrum ranging from asymptomatic cases to multiorgan failure, early identification of prognostic biomarkers is crucial to distinguish patients at risk of developing more serious disease. Our aim is to investigate the relationship between the C-reactive protein to albumin ratio (CAR), a biomarker which has both prognostic and diagnostic importance, and COVID-19 infection.

Material and Method: Between 1 June 2021 and 1 September 2021, 215 patients who were followed up in the pandemic service and intensive care unit for COVID-19 pneumonia were retrospectively analyzed. The demographic and routine laboratory data of the patients and the parameters accepted as new inflammatory biomarkers such as neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR) lymphocyte to monocyte ratio (LMR), and CAR were compared between the patient groups in the service and intensive care unit, and the groups of patients who died and were discharged.

Results: A total of 205 patients with a diagnosis of COVID-19 pneumonia, 113 (55.1%) male and 92 (44.9%) female, were included in the study. When CAR, known as a new inflammatory biomarker, was compared between both groups, it was found to be statistically significantly higher in patients hospitalized in the intensive care unit ($p<0.001$). In addition, this biomarker was shown to be significantly associated with mortality ($p=0.001$). The presence of Hypertension (HT) and malignancy was found to be statistically significant in terms of the risk of hospitalization and mortality in the intensive care unit ($p<0.001$, $p<0.001$, respectively).

Conclusion: The CAR can be a reliable, inexpensive and easily accessible parameter that can be used both in clinical classification and in determining the prognosis in COVID-19 infection causing the pandemic.

Keywords: C-reactive protein, albumin, CAR, COVID-19, prognosis

Öz

Amaç: SARS-CoV-2'ye bağlı gelişen COVID-19 enfeksiyonun seyri, akciğer tutulumu olan veya olmayan üst solunum yollarında virüs çoğalması ve ekstrapulmoner sistemik hiperinflamasyon sendromu ile kendini gösterir. Asemptomatik vakalardan multiorgan yetmezliğine kadar değişen geniş bir klinik yelpazeye sahip olduğundan, prognostik biyobelirteçlerin erken tanımlanması, daha ciddi hastalık geliştirme riski olan hastaları ayırt etmek için çok önemlidir. Amacımız, hem prognostik hemde diagnostik önemi olan C-reaktif protein albumin oranı (CAR) adlı biyobelirtecin, COVID-19 enfeksiyonu ile ilişkisini araştırmaktır.

Gereç ve Yöntem: 1 Haziran 2021-1 Eylül 2021 tarihleri arasında pandemi servisi ve yoğun bakım ünitesinde COVID-19 pnömonisi nedeniyle takip edilmiş 215 hasta retrospektif olarak incelendi. Hastaların demografik ve rutin laboratuvar verileri ile nötrofil lenfosit oranı (NLR), platelet lenfosit oranı (PLR), lenfosit monosit oranı (LMR) ve CAR gibi yeni inflamatuar biyobelirteçler olarak kabul edilen parametreler, servis ve yoğun bakımda yatan hasta grupları ile exitus ve taburcu olan hasta grupları arasında karşılaştırıldı.

Bulgular: Çalışmaya 113 (% 55.1)'ü erkek, 92 (% 44.9)'si kadın olmak üzere toplam 205 COVID-19 pnömoni tanılı hasta dahil edildi. Yeni inflamatuar biyobelirteç olarak bilinen CAR, her iki grup arasında karşılaştırıldığında, yoğun bakımda yatan hastalarda istatiksel olarak anlamlı yüksek bulundu ($p<0.001$). Ayrıca bu biyobelirteçin mortalite ile anlamlı ilişkili olduğu gösterildi ($p=0.001$).Yoğun bakım yatış ve mortalite riski açısından Hipertansiyon (HT) ve malignite varlığı istatiksel olarak anlamlı bulundu (sırasıyla; $p<0.001$, $p<0.001$).

Sonuç: CAR, pandemiye neden olan COVID-19 enfeksiyonunda hem klinik sınıflamada hemde prognozu belirlemede kullanılabilecek güvenilir, ucuz ve kolay ulaşılabilir bir parametre olabilir.

Anahtar Kelimeler: C-reaktif protein, albümin, CAR, COVID-19, prognoz

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INTRODUCTION

SARS-CoV-2 was defined as a viral pneumonia agent which was first seen in China on December 31, 2019.[1] This virus, which later spread all over the world, caused a global pandemic. The clinical picture caused by this virus ranges from asymptomatic cases to acute respiratory failure, diffuse intravascular coagulopathy, septic shock and multiorgan failure.[2] Therefore, early identification of prognostic biomarkers is crucial to distinguish patients at risk of developing more serious disease.

The course of viral infection is manifested by viral replication in the upper respiratory tract with or without lung involvement and an extrapulmonary systemic hyperinflammation syndrome.[3] A cytokine storm characterized by significant elevations of interleukin- (IL-) 2, IL-6, tumor necrosis factor-α, C-reactive protein (CRP), ferritin, d-dimer, and low level of albumin is observed usually during the advanced stages of infection in patients who develop this abnormal inflammatory response.[4-6]

C-reactive protein to albumin ratio (CAR) is a newly defined systemic inflammatory marker that combines both CRP (positive acute phase reactant) and albumin (negative acute phase reactant) levels. In various studies, it has been emphasized that CAR can be a biomarker with both prognostic and diagnostic importance in different diseases, including COVID-19.[7-9] In this study we aimed to investigate the relationship between COVID-19 infection and CAR and make a scientific contribution to the studies on this topic.

MATERIAL AND METHOD

Ethics committee approval for this study was obtained for this study (Approval Number: HRU/21.10.18 and Approval Date: 24.05.2021). A written informed consent was obtained from each participant. The study was conducted in accordance with the principles of the Declaration of Helsinki.

215 patients, who were followed up in the pandemic service and intensive care unit for COVID-19 pneumonia between 1 June 2021 and 1 September 2021, were retrospectively analyzed. Patients over the age of 18, patients with pneumonic infiltration on chest X-ray or Chest computed tomography (CT), patients without evidence of active inflammation due to different organs, patients with biochemical and hematological blood tests taken before treatment on the first day of hospitalization, and patients with positive COVID-19 PCR result were included in this study. Patients under the age of 18, patients without radiological pneumonic infiltration, and patients without laboratory data on the first day of hospitalization (ten patients) were not included in the study. In the end, a total of two hundred and five (205) patients were included in this study. Demographic and laboratory information of the patients were obtained from the recorded data. Age, gender, comorbidities, hospitalization location, clinical status after treatment, biochemical and hematological laboratory data of all patients were recorded. While 27 patients given 10-15 lt/min O_2 with a reservoir (non-rebreathing) mask, with oxygen saturation (SO_2) <90%, respiratory rate/min >30 and/or bilateral diffuse infiltration in Chest CT were followed in the intensive care unit, the remaining 178 patients were followed up in the service. Patients were divided into two groups according to the location of hospitalization as service and intensive care unit. Complete blood count was evaluated with an automated blood cell counter (Coulter LH, 780 Hematology Analyzer, Beckman Coulter Corp, Hileh, Florida) and the ratio of neutrophil to lymphocyte count was calculated as NLR, the ratio of lymphocyte to monocyte count was calculated as LMR, and the ratio of platelet to lymphocyte count was calculated as PLR. The level of albumin and CRP was measured using the Roche Diagonistics Cobas 8000 c502 analyzer and CAR (mg/g) was calculated as the ratio of CRP to level of albumin. Demographic and routine laboratory data and parameters accepted as new inflammatory biomarkers such as NLR, PLR, LMR and CAR were compared between two groups. Besides, the patients were divided into two different groups, as discharged and exitus, according to their clinical status. Laboratory data and comorbidities were compared to determine the mortality risk.

Statistical Analysis

Descriptive statistics are presented as mean±standard deviation or median (25-75 quartile range). The Kolmogorov-Smirnov test was used to determine whether the data were normally distributed. Student's t test was used to compare normally distributed data, and Mann-Whitney U test was used to compare not normally distributed data. Cut-off values were determined using ROC curve analysis to predict ICU admission and mortality according to level of CAR. Statistical significance level was accepted as $p < 0.05$.

RESULTS

A total of 205 patients, including 113 (55.1%) male and 92 (44.9%) female patients, with a diagnosis of COVID-19 pneumonia were included in the study. While 86.8% (178) of these patients were followed in the service, 13.2% (27) were followed in the intensive care unit. 184 patients were discharged with recovery and 21 patients died.

Demographic and laboratory data of the patients are shown in **Table 1**. All data were compared between two groups. Compared to those followed in the service, patients followed in the intensive care unit had a statistically significant higher male sex ratio and the age ($p=0.003$, $p=0.008$, respectively). There were statistical differences in serum albumin, CRP, White blood cell (WBC), neutrophil, lymphocyte, lactate dehydrogenase (LDH), aspartate aminotransferase (AST) values between two groups. Lymphopenia, hypoalbuminemia, leukocytosis, and the high level of NLR and PLR were more significant in patients who were followed in the intensive care unit.

When CAR, known as the new inflammatory biomarker, was compared between two groups, it was found to be statistically significantly higher in patients hospitalized in the intensive care unit (p<0.001) (**Table 1**). Besides, a significant relationship was shown between this biomarker and mortality (**Table 2**).

Table 1. Demographic and laboratory data of patients followed for Covid 19 pneumonia

	Service (n=178)	Intense care unit (n=27)	P
Age, years	53.5 (34.7-87.0)	73.0 (63.0-84.0)	0.008
Gender, F/M	87/91	5/22	0.003
Urea, mg/dl	29.9 (23.5-39.4)	78.0 (35.3-100.0)	<0.001
Creatine, mg/dl	0.7 (0.8-1.0)	0.9 (0.8-1.8)	0.001
Albumin, mg/dl	4.2±0.5	3.4±0.5	<0.001
AST, U/dL	29.0 (24.0-38.7)	44.0 (25.0-63.0)	0.028
ALT, U/dL	27.0 (20.0-38.2)	29.0 (18.0 -53.0)	0.975
LDH, U/L	239.5 (188.0-309.7)	385.0 (188.0-563.0)	0.021
Sodium, mg/dl	138.9±3.8	138.7±7.4	0.873
Potassium, mg/dl	4.1±0.7	4.3±0.9	0.101
CRP, mg/dl	9.2 (2.7-45.0)	59.9 (48.1-131.7)	<0.001
WBC, x10^3/mL	5.6 (4.5-7.8)	9.2 (5.0-12.0)	0.005
Neutrophil, x10^3/mL	3.5 (2.5-5.4)	7.9 (3.9 -10.2)	<0.001
Lymphocyte, x10^3/mL	1.4 (0.8-1.9)	0.6 (0.5-1.1)	<0.001
Monocyte, x10^3/mL	0.5 (0.3-0.6)	0.6 (0.2-0.7)	0.902
Platelet, x10^3/mL	205.5 (170.2-256.7)	166.0 (131.0-307.0)	0.239
MCV, fL	79.2±16.3	85.3±7.5	0.136
MPV, fL	10.4 (9.6-11.0)	10.5 (10.0-11.0)	0.334
RDW, %	12.8 (12.2-13.7)	18.6 (12.9-47.6)	<0.001
NLR	2.6 (1.6-4.8)	10.2 (3.8-15.8)	<0.001
PLR	155.7 (105.1-214.5)	284.1 (138.3-472.9)	<0.001
LMR	2.5 (1.6 -3.9)	1.6 (1.0-4.0)	0.115
CAR	2.1 (0.6 -11.0)	20.3 (13.3-38.7)	<0.001

ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactat dehydrogenase; CRP, C-reactive protein; WBC, white blood cell; MCV, mean corpuscular volume; MPV, mean platelet volume; RDW, red cell distribution width; NLR, Neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; LMR, lymphocyte to monocyte ratio; CAR, C reactive protein to albumin ratio.

Table 2. Comparison of laboratory data according to clinical status after treatment

	Discharged (n=184)	Exitus (n=21)	P
Urea, mg/dl	31.0 (21.5-40.2)	87.7 (64.2-106.5)	<0.001
Creatine, mg/dl	0.8 (0.7-1.0)	1.2 (0.8-1.2)	<0.001
Albumin, mg/dl	4.2±0.5	3.3±0.3	<0.001
AST, U/dL	29.0 (24.0- 34.0)	37.0 (20.5 -64.0)	0.178
ALT, U/dL	27.0 (20.0-37.5)	26.8 (15.0-15.0)	0.513
LDH, U/L	241.0 (188.0-316.2)	303.0 (11.0-612.5)	0.200
Sodium, mg/dl	138.7±3.8	140.0±7.9	0.490
Potassium, mg/dl	4.1±0.7	4.4±1.0	0.034
CRP, mg/dl	10.0 (2.9-49.7)	86.5 (49.5-179.5)	<0.001
WBC, x10^3/mL	5.6 (4.4-7.4)	11.0 (6.5-13.7)	<0.001
Neutrophil, x10^3/mL	3.5 (2.5-5.2)	9.9 (5.4 -10.9)	<0.001
Lymphocyte, x10^3/mL	1.3 (0.8-1.9)	0.6 (0.4-1.0)	<0.001
Monocyte, x10^3/mL	0.4 (0.3-0.6)	0.6 (0.2-0.7)	0.921
Platelet, x10^3/mL	205.0 (169.0-256.2)	227.0 (137.5-317.0)	0.986
MCV, fL	79.4±16.4	85.3±7.5	0.155
MPV, fL	10.4 (9.7-11.0)	10.5 (10.0-11.0)	0.372
RDW, %	12.8 (12.2-13.7)	41.1 (13.1-48.7)	<0.001
NLR	2.7 (1.6-4.8)	12.7 (7.0-20.8)	0.001
PLR	155.7 (105.1-217.8)	335.0 (172.9-548.4)	0.001
LMR	2.5 (1.6-3.9)	1.6 (1.0-4.0)	0.109
CAR	2.2 (0.6-11.7)	22.7 (13.7-57.4)	0.001

ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactat dehydrogenase; CRP, C-reactive protein; WBC, white blood cell; MCV, mean corpuscular volume; MPV, mean platelet volume; RDW, red cell distribution width; NLR, Neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; LMR, lymphocyte to monocyte ratio; CAR, C reactive protein to albumin ratio.

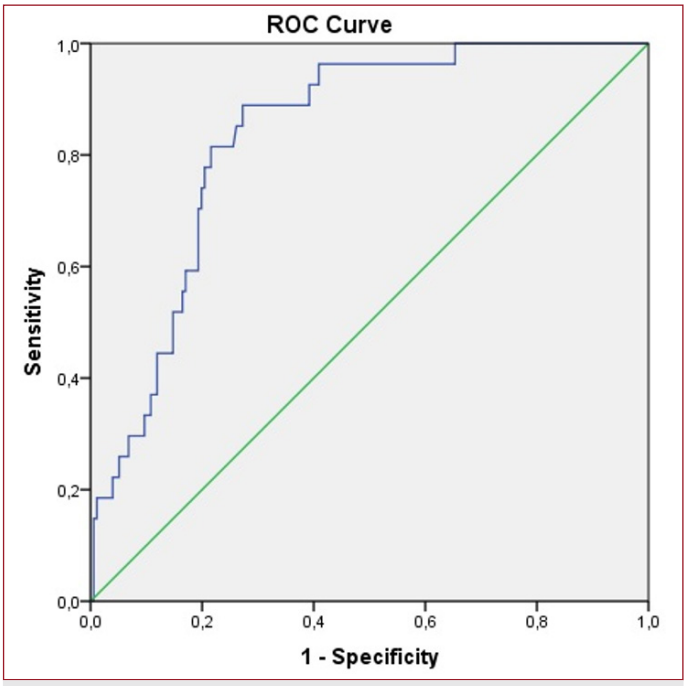
The comorbidities of the patients included in the study are shown in **Table 3**. Presence of hypertension (HT) and malignancy were found to be statistically significant factors in terms of hospitalization at intensive care unit and mortality.

Table 3. Comparison of comorbidities with hospitalization and mortality status

	DM	HT	CAD	Asthma	COPD	Malignancy
Patient location						
Service (n=178)	17	14	8	7	3	0
Intensive care unit (n=27)	4	8	2	1	2	2
P	0.401	0.001	0.513	0.954	0.072	<0.001
Mortality status						
Discharge (n=184)	17	14	8	7	3	0
Exitus (n=21)	4	8	2	1	2	2
P	0.160	<0.001	0.297	0.830	0.026	<0.001

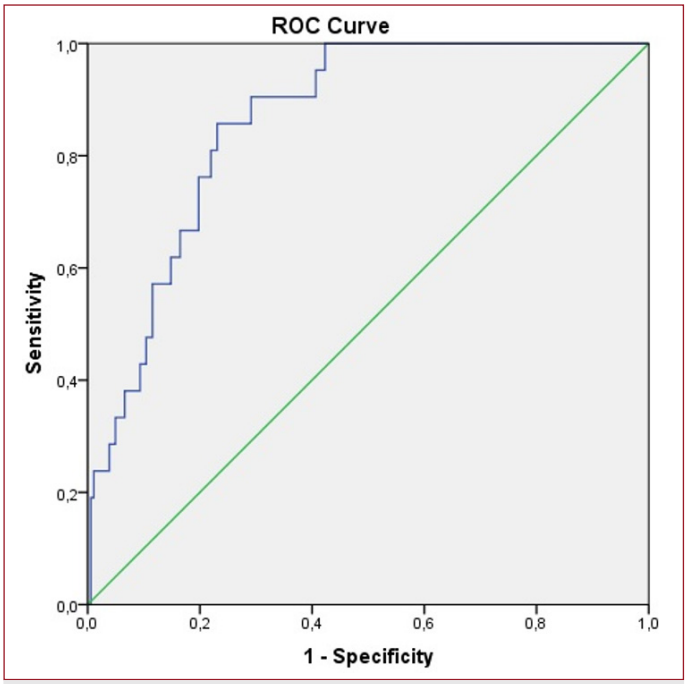
DM; Diabetes Mellitus, HT; Hypertension, CAD; Coronary Artery Disease, COPD; Chronic Obstructive Pulmonary Disease

ROC curve analysis was performed to determine the cut-off values of CAR in predicting the hospitalization at intensive care unit and mortality. The optimal cut-off value of CAR for intensive care admission was determined as ≥ 12.6% with a sensitivity of 81% and a specificity of 79% (**Figure 1**). On the other hand, the optimal cut-off value of CAR for mortality was found as ≥ 13.9 with a sensitivity and specificity of 76% and 81, respectively (**Figure 2**).



Variables	AUC	95%CL	P
CAR	0.835	0.769-0.901	<0.001

Figure 1. ROC curve of CAR level for predicting ICU admissions



Variables	AUC	95%CL	P
CAR	0.862	0.800-0.924	<0.001

Figure 2. ROC curve of CAR levels for predicting mortality

DISCUSSION

As a result of our study, we found that CAR is a significant prognostic parameter in estimating the risk of intensive care unit admission and mortality due to COVID-19 infection, and that HT and malignancy are important comorbidities that affect the prognosis.

The clinical manifestation of COVID-19 infection is generally mild. However, patients may sometimes rapidly develop an acute respiratory failure, diffuse intravascular coagulopathy, septic shock which may result in mortality. Age, gender, and comorbidities (HT, Diabetes mellitus (DM), Coronary Arterial Disease (CAD), chronic lung diseases, malignancies, etc.) are among the most important factors affecting the prognosis in COVID-19 patients. In many studies, advanced age and male gender predominance and accompanying comorbidities such as DM, HT, CAD, and malignancy have been observed in patients with severe PCR (+) COVID-19 diagnosis.[10-13] Similar to the literature data, the patients followed in the intensive care unit were older and mostly male in our study and the mortality risk was statistically significantly higher, especially in those with a history of HT and malignancy.

Hematological and biochemical parameters are of great importance in the evaluation of clinical picture of patients with COVID-19 diagnosis. While the severity of patient clinic is generally in a positive correlation with increases in leukocyte and neutrophil counts, and the level of LDH, AST, and alanine aminotransferase (ALT); it has been observed that there is a negative correlation with a decrease in lymphocyte and eosinophil counts.[11,14] In our current study, we found a significant difference in terms of leukocytosis, neutrophilia, lymphopenia, high LDH and AST levels in patients followed-up in the intensive care unit compared to those hospitalized in the service.

CRP has been used as a systemic marker for tissue damage, infection, and inflammation since it was first defined as an acute phase protein.[15] Various studies reported that the level of CRP is an independent predictor for severe COVID-19 infection, malignancies, neurological and cardiac diseases.[16-19] The concentration of albumin is negatively related to systemic inflammatory response which is caused by down-regulation of hepatic synthesis due to the increased catabolism and cytokines such as TNF-α.[20] Systemic inflammation due to viral infections, including COVID-19 infection, might cause a decrease in the level of albumin. In a recent study, low serum albumin levels were found to be significantly related with worsened clinical status and longer hospital stay in COVID-19 patients.[21] However, albumin might not be a specific parameter alone in determining the inflammation since low albumin levels may develop due to reasons such as advanced age and nutritional deficiencies. In our study, we found that high CRP and low albumin levels were statistically significant in patients who were followed in the intensive care unit and were exitus. We think that the CRP and albumin levels of the patients are important in terms of determining inflammation, since these are the results of the examinations obtained within the first 24 hours of hospitalization.

The scientific community is in urgent need of reliable, new biomarkers of COVID-19 disease progression to classify high-risk patients. The CRP to albumin ratio (CAR), which is considered as a new inflammatory biomarker, reflects the balanced relationship between the severity of inflammatory reactions and immune status more accurately. In literature, it has been stated that CAR is an important biomarker that can be used in clinical follow-up and prognosis prediction for different malignancies, cardiac, neurological, and systemic inflammatory diseases.[22-25] In recent studies, it has been emphasized that CAR may be a promising prognostic biomarker for risk stratification and clinical management of patients with severe COVID-19 and can be an early predictor of disease progression.[26,27] In this study, we assumed that CAR alone can be a stronger prognostic parameter than CRP and albumin in predicting clinical severity and mortality in hospitalized patients with a diagnosis of COVID 19. We determined that the level of serum CAR, both in patients who are hospitalized in the intensive care unit and who died after treatment due to COVID-19 infection, was significantly higher than patients who were followed-up in service and who were alive. Besides, we predicted the risk of hospitalization and death in the intensive care unit in ROC analysis with high sensitivity and specificity in the presence of increased CAR levels in patients with a diagnosis of COVID-19.

The limitations of this study include its single-center and retrospective design, exclusion of patients with mild clinical course with PCR(+) and no lung involvement on Chest CT

due to hospitalization and lack of recorded laboratory data, and inclusion of patients with malignancies and chronic comorbidities that may affect the inflammatory response.

CONCLUSION

The CAR is a new biomarker that has been widely used because of its diagnostic and prognostic importance in different clinical pathologies. We can conclude that this biomarker is a reliable, inexpensive, and easily accessible parameter that can be used to determine the clinical classification and prognosis of COVID-19 infection.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethics committee approval for this study was obtained from the Dean of Harran University Faculty of Medicine (Approval Number: HRU/21.10.18 and Approval Date: 24.05.2021).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Orjinal Araştırma / Original Article

CRP/Lymphocyte Ratio in Patients with COVID-19 with Headache

Baş Ağrısı Olan COVID-19 Hastalarında CRP/Lenfosit Oranı

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Abstract

Aim: One of the most common neurologic symptoms observed in COVID-19 is headache. The pathogenesis of this headache is still not clearly defined. In our study, we aimed to reveal the relationship between headache observed in patients with COVID-19 and the C-reactive protein CRP/lymphocyte ratio, an indicator of inflammation.

Material and Method: The demographic, clinical, and laboratory characteristics of patients followed up with a diagnosis of COVID-19 were recorded. The clinical and laboratory findings of patients with and without headache were compared.

Results: A total of 106 patients were included in the study. The mean age of all patients was 60.81±15.03 years and 50.9% were male. The mean age of the patient group with headache (57.77±15.42 years) was significantly lower than the mean age of the group without headache (64.22±13.95 years) (p=0.027). The smoking rate was also higher in this group (p=0.003). Smell and taste disorders were also found to be significantly higher in patients with headache compared with patients without headache (p=0.003). When the groups were compared in terms of the CRP/lymphocyte ratio, no significant difference was found (p<0.05).

Conclusion: Our study is important in that it is the first to examine the CRP/lymphocyte ratio in patients with headache. It can be a guide for future studies with larger patient groups.

Keywords: COVID-19, SARS-CoV-2 infection, headache, C-reactive protein, inflammation, CRP/lymphocyte ratio

Öz

Amaç: COVID-19'da izlenen en sık nörolojik semptomlardan birisi baş ağrısıdır. Bu baş ağrısının patogenezi halen net olarak tanımlanamamıştır. Çalışmamızda COVID-19 enfeksiyonunda izlenen baş ağrısının bir enflamasyon göstergesi olan CRP/Lenfosit oranı ile ilişkisini ortaya koymayı amaçladık.

Gereç ve Yöntem: COVID-19 tanısı ile izlenen hastaların demografik, klinik ve laboratuvar özellikleri kaydedildi. Baş ağrısı olan ve olmayan hastaların klinik ve laboratuvar bulguları karşılaştırıldı.

Bulgular: Çalışmaya toplam 106 hasta dahil edildi. Tüm hastaların yaş ortalaması 60.81 (± 15.03) ve %50.9'u erkekti. Baş ağrısı olan hasta grubun yaş ortalaması (57.77±15.42) baş ağrısı olmayan grubun yaş ortalamasına (64.22±13.95) göre anlamlı düşük bulundu (p=0.027). Bu grupta sigara kullanma oranı da yüksekti (p=0.003). Yine baş ağrısı olanlarda koku ve tat alma bozukluğu semptomu baş ağrısı olmayan hastalara göre anlamlı oranda yüksek bulundu (P=0.003). Gruplar CRP/Lenfosit oranı açısından karşılaştırıldığında anlamlı fark saptanmadı (p<0.05).

Sonuç: Çalışmamız baş ağrısı olan hastalarda CRP/Lenfosit oranını irdeleyen ilk çalışma olması bakımından önemlidir. Daha büyük hasta grupları ile yapılacak ileriye dönük çalışmalar için yol gösterici olabilir.

Anahtar Kelimeler: COVID-19, SARS-CoV-2 Enfeksiyonu, Baş ağrısı, C-Reactive Protein, İnflamasyon, CRP/Lenfosit Oranı

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) was defined as a global pandemic by the World Health Organization (WHO) in early March 2020. It has been demonstrated that the novel coronavirus, which is a single-stranded RNA virus, is primarily effective on the lungs, but can also affect multisystems, especially the renal, hematologic, and neurologic systems.

Headache is one of the common neurologic manifestations observed in patients with COVID-19, and it has been shown to occur at rates of 6.7% to 40%.[1, 2] The pathogenesis of headache observed in COVID-19 has not been fully explained. The first possibility may be that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) directly invades the trigeminal nerve endings in the nasal cavity.[3] This situation has been associated with angiotensin-converting enzyme 2 (ACE2) expression in neurons.[4] The second possibility is trigeminovascular activation based on vascular pathogenesis with the participation of endothelial cells known to have ACE2 expression. Another possible mechanism is related to proinflammatory mediators and cytokines released due to the virus.[3]

The S1 subset of the SARS-CoV-2 surface spike protein binds to the ACE2 receptor, triggering the production of angiotensin-1. ACE then converts angiotensin-1 to angiotensin-2, which binds to the angiotensin receptor and raises endothelin-1 (ET-1) levels. This results in a diffuse inflammatory response with the release of pro-inflammatory cytokines and interleukins (IL).[5, 6] Large-scale unregulated production of ILs, particularly IL-6, activate multiple pathways. They increase the production of acute-phase reactants such as C-reactive protein (CRP) and the mobilization of neutrophils.[7] Thus, together with stress-induced neutrophilia, relative lymphopenia seen in severe manifestations of SARS-CoV2 infection develops.[8-10] This indicates that the parameter expressed as the CRP/lymphocyte ratio may be an indicator of the severity of inflammation. Typically, the CRP/lymphocyte ratio is used as a prognostic marker for various types of cancer, including gastric carcinoma and colon cancer.[11, 12] The rationale behind this is that the CRP/lymphocyte ratio also serves as a good representative of the complex host-tumor immunologic interactions that result in the systemic inflammatory process believed to contribute to the pathogenesis and progression of these carcinomas.[13] It can be concluded that the CRP/lymphocyte ratio may be a good marker in this disease process and have prognostic value because COVID-19 triggers different immunologic mechanisms and accelerates a systemic inflammatory response.[14]

Studies showing that the CRP/lymphocyte ratio is associated with COVID-19–associated pneumonia and can be used as a biomarker in predicting prognosis suggest that this parameter is a strong indicator of inflammation. In this study, we aimed to reveal the relationship between the CRP/lymphocyte ratio and headache, considering that the headache observed in COVID-19 was related to the severity of inflammation.

MATERIAL AND METHOD

Study Design and Patients

In this retrospective observational study, patients who were admitted to our hospital between April and November 2020 and were diagnosed as having COVID-19 according to the WHO guide[15] were included. The study was conducted in accordance with the ethical standards of the responsible institution on human subjects and the Declaration of Helsinki. Approval was obtained from the Local Ethics Committee (Protocol No: 2021/025) and the Ministry of Health for this retrospective study.

Clinical, demographic, and laboratory data were extracted from electronic medical records using a standardized data collection form. The records of a total of 122 patients aged over 18 years were analyzed for the study. A total of 106 patients were included in the analyses after excluding those with a history of head trauma, malignancy or cerebrovascular disease, those who were diagnosed as having COVID-19 in their follow-up, and those who were pregnant. Headache was diagnosed according to the International Classification of Headache Disorders.[16]

The diagnosis of COVID-19 was made using respiratory tract swab samples (throat swabs) with real-time qualitative polymerase chain reaction (RT-qPCR). Among the data regarding the main comorbidities, a history of diabetes mellitus (DM), hypertension (HT), chronic obstructive pulmonary disease (COPD), and coronary artery disease (CAD) were recorded. Routine blood work, complete blood count, serum biochemical tests CRP, D-dimer, myocardial enzymes (troponin), and serum ferritin values were recorded.

Statistical Analysis

Whether the continuous variables were normally distributed was evaluated using the Shapiro-Wilk test. Student's t-test (for data with normal distribution) and the Mann-Whitney U test (for data without normal distribution) were used to compare the two groups. The Chi-square test was used to investigate the relationship between categorical variables. A general linear model was applied to adjust for the possible effect of age and smoking. Statistical analysis was performed using the SPSS for Windows version 24.0 software package. A significance level of 0.05 was used in the analyses.

RESULTS

A total of 106 consecutive patients with a confirmed diagnosis of COVID-19 were included in our study. Just over half the patients (50.9%) were male. The mean age was 60.81±15.03 years and the most common comorbidities were HT (19.8%) and DM (18.9%). Of the patients, 15.1% were smokers (**Table 1**). The mean white blood cell (WBC) count was 7.63±3.5 (normal range, 4.49-12.68) 109/L, the neutrophil count was 5.56±3.07 (normal range 2.1-8.89) 109/L, the monocyte count was 0.54±0.27 (normal range 0.25-0.84) 109/L, the

platelet count was 242.43±97.21 (normal range 173-390) 109/L, the ferritin level was 280.05±262.81 (normal range, 23.9-336.2) ng/mL, the D-dimer level was 0.69±1.18 (normal range 0-0.5) µg/mL, and the troponin level was 11.05±16.12 (normal range 0-19.8) ng/L (**Table 2**).

Table 1. Descriptive Characteristics of the Patients

	n (%)
Sex (male)	54 (50.9)
Contact history	23 (22.6)
Hyposmia-hypogeusia	41 (38.7)
Headache	56 (52.8)
Comorbidity	52 (49.1)
Diabetes mellitus	20 (18.9)
Hypertension	21 (19.8)
Coronary artery disease	4 (3.8)
Chronic obstructive pulmonary disease	6 (5.7)

Table 2. Laboratory Parameters of the Patients

Variables (n=106)	Median (Min-Max)
WBC (109/L)	6.66 (3.35-23.8)
Neutrophil (109/L)	4,54 (1.65-15.9)
Lymphocyte (109/L)	1.15 (0.46-5.64)
Monocyte (109/L)	0.5 (0.18-1.74)
Platelet (109/L)	223 (71-624)
CRP (mg/L)	63.6 (1.5-407)
Ferritin (ng/mL)	169.9 (7.6-1368)
D-dimer (µg/mL)	0.37 (0.02-9.68)
Troponin (ng/L)	7 (1.3-99.7)
CRP/lymphocyte ratio	50 (0.78-536)

WBC: White Blood Cell, CRP: C-reactive protein.

The mean lymphocyte count was 1.28±0.67 (normal range 1.26-3.35) 109/L, and the mean CRP level was 75.56±66.74 (normal range 0-8) mg/L. The mean CRP/lymphocyte ratio of the patients was 77.23±86.17.

The patients were divided into two groups as those with and without headache (n=56 and n=50, respectively) and compared. The groups were similar in terms of sex distribution ($p<0.05$). The mean age of the patient group with headache (57.77±15.42 years) was significantly lower than the mean age of the group without headache (64.22±13.95 years) ($p=0.027$). The smoking rate was also higher in this group ($p=0.003$). Smell and taste disorders were also found to be significantly higher in patients with headache compared with patients without headache ($p=0.003$). When the groups were compared in terms of the CRP/lymphocyte ratio, no significant difference was found ($p<0.05$). There was no significant difference when the CRP/lymphocyte ratio was compared again after the effect of age and smoking, which were different between the groups, was eliminated using a linear model ($p=0.343$) (**Table 3**)

Table 3. Comparison of laboratory parameters of patients with and without headache

Variables (Mean±SD)	Headache (+) (n=56)	Headache (-) (n=50)	P	$P_{adjusted}$
WBC (10^9/L)	7.85±3.99	7.38±2.86	0.962	0.415
Neutrophil (10^9/L)	5.95±3.59	5.14±2.32	0.613	0.203
Lymphocyte (10^9/L)	1.32±0.8	1.24±0.5	0.955	0.370
Monocyte (10^9/L)	0.55±0.3	0.54±0.23	0.621	0.790
Platelet (10^9/L)	243.84±98.3	240.86±96.94	0.766	0.949
CRP (mg/L)	67±53.38	85.14±78.54	0.346	0.219
Ferritin (ng/mL)	274.46±239.72	286.31±288.83	0.747	0.657
D-dimer (µg/mL)	0.5±0.58	0.91±1.59	0.330	0.156
Troponin (ng/L)	8.78±13.33	13.59±18.58	0.058	0.340
CRP/lymphocyte ratio	69.27±73.59	86.15±98.37	0.268	0.345

*WBC: white blood cell, CRP: C-reactive protein. † Significant at 0.05 level; Student t-test for age, Mann-Whitney U test for other numerical variables, Padjusted: General linear model; results adjusted by age and smoking.

DISCUSSION

COVID-19 is a rapidly spreading, pandemic infection. It was first identified with an outbreak that began in December 2019 in Wuhan, China. In their study with 138 patients, Wang et al. reported the mean age of the patients as 56.0 years.[17] Of the patients in that study, 54.3% were male and 45.7% were female. In the study of Huang et al. in which 1733 patients were included, 52% of the patients were male and the median age was 57.0 years.[18] In our study, 50.9% of the patients were male. The mean age was 60.81±15.03 years.

The clinical course in COVID-19 may vary according to underlying diseases. Huang et al. reported that 32% of 41 patients had an underlying disease; that they found DM in 20%, HT in 15%, and cardiovascular disease in 15% of patients.[19] In another study, Lai et al. found that the most common underlying diseases in adult patients were HT, cardiovascular disease, and DM.[20] In our study, HT and DM were found to be the most common underlying diseases.

Headache was detected in 52.8% of the patients in our study, and the mean age of patients with headache was found to be lower than those without headache. In a large, multicenter, prospective European study by Lechien et al. in which 1420 patients with COVID-19 were evaluated, it was reported that headache was more common in young people compared with the elderly.[21] Although this finding was explained by the low mean age of the patients (mean age 39 years), similar findings in our study indicated that more comprehensive and detailed studies were needed on this subject.

Another finding of our study was that the rate of smoking was higher in the group with headache compared with those without headache. The functional similarity between the nicotinic acetylcholine receptor (nAChR) and ACE2 suggests that smoking may promote cellular entry of SARS-CoV2 via nAChR signaling.[22] The higher prevalence of COVID19-related neurologic symptoms such as headache in smokers can be explained by the same cells expressing nAChR and ACE2 in the central nervous system (CNS).[22]

Giacomelli et al. showed that postviral smell and/or taste disorders were detected in 33.9% of individuals infected with SARS-CoV-2.[23] This rate was shown to increase up to 68% in different studies.[24] The source of this dysfunction in COVID-19 may be the transneural penetration of SARS-CoV through the olfactory bulb.[25] Another possible mechanism is the presence of the transmembrane ACE2 receptor, which is detected in the cranial nerves related to smell and taste and is a necessary component for SARS-CoV2 binding.[4] Smell and/or taste disorders were detected in 38.7% of the patients included in our study. The frequency of hyposmia/hypogeusia in patients with headache was significantly higher than in patients without headache. Our findings support the view that CNS involvement in COVID-19 may be mediated by transneural penetration or the ACE2 receptor.

CRP is known to play an important role in innate immunity as an early defense mechanism against infections. It was shown in previous studies that the level of CRP was high in patients with COVID-19 and that this level was even correlated with the severity of pneumonia.[26, 27] In our study, the mean CRP value of all patients was 75.56±66.74 mg/L, which was above the reference range (0-8 mg/L), as expected. There was no significant difference in mean CRP levels between patients with and without headache ($p<0.05$).

One of the common hematologic findings in patients with COVID-19 is lymphopenia.[19, 28] Ni et al. showed that severe lymphopenia was correlated with the severity of COVID-19 and that the number of T lymphocytes (especially CD8+ and CD4+ subset) increased significantly with effective treatment, and this increase was associated with a decrease in proinflammatory cytokines in the serum after treatment.[29] In our study, the mean lymphocyte count of the patients was 1.28±0.67 109/L and was within the normal range. Due to the nature of our study design, this could be explained by the fact that the blood samples studied were those of patients under treatment; blood samples at the time of admission were not studied. There was no difference in terms of mean lymphocyte count between patients with and without headache.

In our study, the CRP/ymphocyte ratio was used as an inflammation marker based on the possible effects of the severity of inflammation on the secondary headache mechanism. There was no significant difference in terms of CRP/lymphocyte ratios between patients with and without headache ($p<0.05$). It should be considered that current approaches used in the treatment of COVID-19, especially steroid therapy [30] and immunotherapies [31], may affect the CRP/lymphocyte ratio.

Our study had some limitations. The most important limitation of our study is that the treatments used by the patients were not examined. The relatively small number of patients is another limitation.

CONCLUSION

Our findings are important because this is the first study to examine the relationship between the CRP/lymphocyte ratio and headache in patients with COVID-19. The higher incidence of COVID-19 headache in smokers and the frequency of olfactory-taste disorder association in those with headache may be a guide for studies to elucidate the pathogenesis of pain. Prospective studies with larger patient groups are required to reveal the pathogenesis of headache in SARS-CoV2 infections.

ETHICAL DECLARATIONS

Ethics Committee Approval: Approval was obtained from the Local Ethics Committee (Protocol No: 2021/025) and the Ministry of Health for this study.

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Orijinal Araştırma / Original Article

Clinical and Demographic Evaluation of Patients Admitted to the Pediatric Intensive Care Unit

Çocuk Yoğun Bakım Ünitesine Yatan Hastaların Klinik ve Demografik Değerlendirilmesi

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Abstract

Purpose: This study aimed to evaluate the patients who received health services in the pediatric intensive care unit (PICU) of Ankara City Hospital's Pediatrics Department in a 2-year period and the outcomes of these cases by examining their clinical and demographic characteristics.

Material and Method: This retrospective study was carried out in the 32-bed tertiary PICU of xxxxxx Hospital. The records of 2280 patients between the ages of 1 month and 18 years who were hospitalized in the PICU between September 1, 2019, and September 1, 2021, were retrospectively analyzed. Age, sex, presence of chronic disease, reason for hospitalization in the intensive care unit, length of stay, status and duration of respiratory support, and mortality rates were evaluated.

Results: The mean age of the patients was 5.16±5.12 years and the mean PICU stay was 12.47±20.16 days. Bronchiolitis, sepsis, pneumonia, trauma, congenital heart disease, status epilepticus, hematological diseases, oncological diseases, diabetic ketoacidosis, and metabolic diseases were found to be the most common reasons for hospitalization in the PICU. The most frequent underlying diseases were neurological, respiratory, hematological, cardiological, endocrinological, nephrological, gastrointestinal system, oncological, and metabolic diseases. The mortality rate of these patients was 10.8%. Underlying oncological or hematological diseases and immunodeficiency, higher susceptibility to infection, longer hospital stay, and longer duration of mechanical ventilation were found to be statistically significantly higher in deceased patients compared to survivors.

Conclusion: The profile of patients admitted to PICUs is expanding day by day. A significant decrease in mortality was observed in all patient groups as a multidisciplinary approach was implemented. It was also observed that most of the patients had an underlying chronic disease and this condition was associated with mortality.

Keywords: Pediatric Intensive Care Unit, Mortality, Respiratory Support Devices

Öz

Amaç: Bu çalışmada Ankara Şehir Hastanesi Çocuk Sağlığı ve Hastalıkları Anabilim Dalı, Çocuk Yoğun Bakım Ünitesi'ne (ÇYBÜ)'ne 2 yıl içinde yatan hastaların klinik ve demografik özellikleri incelenerek hangi hastalara hizmet verildiğinin ve sonuçlarının değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Bu retrospektif çalışma xxxxxx Hastanesi 32 yataklı 3. basamak çocuk yoğun bakım ünitesinde yapıldı. Merkezimiz ÇYBÜ'ne 01.09.2019-01.09.2021 tarihleri arasında yatırılmış olan 1 ay ile 18 yaş arası 2280 hastanın dosya kayıtları retrospektif olarak incelendi. Yaş, cinsiyet, kronik hastalık varlığı, yoğun bakım ünitesine yatırılma nedeni, yatış süresi, solunum destek cihazına bağlanma durumu ve süresi, mortalite oranları değerlendirildi.

Bulgular: Olguların ortalama yaşları 5,16±5,12 yıl ve ortalama yoğun bakım yatış süreleri 12,47±20,16 gündü. ÇYBÜ'ne bronşiolit, sepsis, pnomoni, travma, konjenital kalp hastalığı, status epileptikus, hematolojik hastalıklar, onkolojik hastalıklar, diabetik ketoasidoz, metabolik hastalıklar en sık yatış nedeni olarak bulundu. En fazla altta yatan hastalıklar norolojik, solunumsal, hematolojik, kardiyolojik, endokrinolojik, nefrolojik, gastrointestinal sistem (GIS) hastalıkları, onkolojik hastalıklar, Mmetabolik hastalıklar gözlendi. Hastaların %10.8'u kaybedildi. Ölen hastalarda altta yatan onkolojik, hematolojik hastalıklar ve immün yetmezliği olan hastalarda enfeksiyona duyarlılıklarının fazla olması, yatış süresinin ve mekanik ventilatörde kalış süresinin uzun olması sağ kalanlara göre istatistiksel olarak anlamlı derecede fazla bulundu.

Sonuç: Çocuk yoğun bakıma kabul edilen hasta profili her geçen gün artmaktadır. Bütün hasta gruplarında multidisipliner olarak yaklaştıkça mortalitede önemli oranda azalma görülmüştür. Hastaların bir çoğunda altta yatan kronik bir hastalık olduğu ve bu durumun mortalite ile ilişkili olduğu gözlendi.

Anahtar Kelimeler: Çocuk yoğun bakım ünitesi, Mortalite, Solunum destek Cihazları

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INTRODUCTION

Although pediatric intensive care units (PICUs) represent a new subbranch of medical treatment, they have developed rapidly and their importance is increasing day by day. Today, patient mortality rates are decreasing rapidly thanks to the treatment of critically ill patients in PICUs. Especially with extracorporeal membrane oxygenation (ECMO), there has been a noticeable decrease in mortality rates. The vital signs of patients in intensive care units are monitored more closely, the patients are supported as necessary, and multidisciplinary treatment approaches are applied.

The first PICU was established in Sweden in 1955, which was followed by the establishment of PICUs in important centers in Europe, Australia, and North America in the 1960s (1). While the number of general pediatric service beds in hospitals in the United States decreased by 40% between 1980 and 2000, the number of pediatric intensive care beds increased by 70% (2). About half of the units in Turkey were opened between 2000 and 2004 (3). This study was designed to evaluate the diagnosis, treatment, and mortality outcomes of patients admitted to a PICU by examining the retrospective clinical and demographic characteristics of the patients hospitalized in our center over the course of 2 years.

MATERIALS AND METHODS

This retrospective study was carried out in the 32-bed tertiary PICU of xxxxxxxxxxx Hospital. The demographic characteristics of children aged 1 month to 18 years who were hospitalized in the PICU between September 1, 2019, and September 1, 2021, were evaluated. For this purpose, records of 2280 patients hospitalized within these 2 years were retrospectively analyzed. Age, sex, presence of chronic disease, reason for hospitalization in the intensive care unit, length of stay, status and duration of respiratory support, and mortality rates were evaluated.

This study was authorized by the Ministry of Health (Ethics Committee E2-22-1245) and local ethics committee approval was received on January 5, 2022 (Ethics Committee No: 1245).

Information obtained from the data was analyzed using the SPSS 17.0 software program. Categorical data were expressed as percentages. Medians and interquartile ranges were used for quantitative data. Differences between categorical variables were evaluated with chi-square tests and differences between continuous variables were evaluated with non-parametric tests (Mann-Whitney U). Values of $p<0.05$ were considered to be statistically significant.

RESULTS

Over the course of 2 years, 2280 patients were hospitalized in the PICU. While 60% of the patients were hospitalized directly in the PICU, 20% of them were transferred to the PICU with a sudden worsening of their general condition while they were hospitalized in the pediatric ward. The rate of patients admitted to the PICU for postoperative patient care was 20% and 20% of the patients admitted to the PICU had been referred by ambulance. While 2% came to the hospital by air ambulance, 18% came by land ambulance. Fifteen percent of the patients admitted to the PICU were the children of immigrants. While 52% of the patients were male, 48% were female. Furthermore, 22% of the patients were between 1 month and 1 year old, 36% were 1 year to 5 years old, 10% were 6 years to 10 years old, and 32% were 11 years to 18 years old. The demographic data of the patients hospitalized in the PICU are given in Table 1.

Table 1. Demographic data of patients hospitalized in the pediatric intensive care unit (PICU)

Demographic data, n=2280	n (%) or mean±SD	p
Age (years) of all patients	5.16±5.12	
Average age of patients discharged from PICU	9.23±8.15	0.160
Average age of patients who died in PICU	3.45±7.60	
Sex		
Male	1186 (52%)	0.630
Female	1094 (48%)	
Hospitalization rates by age		
1 month to 1 year	502 (22%)	
1 year to 5 years	820 (36%)	
6 years to 10 years	228 (10%)	
11 years to 18 years	730 (32%)	
Mean length of stay of all patients	12.47±20.16	
Total length of stay of patients discharged from PICU	7.6±12.16	0.001
Total length of stay of patients who died in PICU	23±15.82	
Duration of mechanical ventilation for all patients	9±15.04	
Duration of mechanical ventilation for patients discharged from PICU	3±4.13	0.001
Duration of mechanical ventilation for patients who died in PICU	17.25±24.82	
High-flow nasal cannula	752 (33%)	
NIV/CPAP/BiPAP	798 (35%)	
Tracheostomy	116 (5.1%)	
Use of inotropes	807 (35.4%)	
Extracorporeal membrane oxygenation	13 (0.6%)	
Bed occupancy rate	2166 (95%)	
Mortality rate	246 (10.8%)	
Sequelae rate	109 (4.8%)	
Immigrant children	250 (11%)	
Use of central venous catheter	729 (32%)	

NIV/CPAP/BiPAP: Non-invasive positive airway pressure/continuous positive airway pressure/bi-level continuous positive airway pressure

The mean age of the patients was 5.16±5.12 years (range: 1 month to 18 years). The mean length of stay of all patients admitted to the PICU was found to be 12.47±20.16 days (range: 1-280). Bed occupancy rate was 95% for these 2 years in the unit. The main reasons for hospitalization in the PICU were as follows: infections, 28% (12% bronchiolitis, 10% sepsis, 4% pneumonia, 2% other causes of infection); trauma, 14%; congenital heart disease, 12%; status epilepticus, 12%;

hematological diseases, 10%; oncological diseases, 7%; diabetic ketoacidosis, 3%; and metabolic diseases, 2%. The most common reasons for hospitalization are given in Table 2. The rate of underlying disease of all patients hospitalized in the PICU was 66%. The most common underlying diseases were neurological diseases at 17%, respiratory diseases at 14%, hematological diseases at 13%, cardiological diseases at 11%, endocrinological diseases at 8%, nephrological diseases at 8%, gastrointestinal system (GIS) diseases at 7%, oncological diseases such as solid organ cancers at 7%, and metabolic diseases at 5% (**Table 2**). Nearly one-fourth (24%) of the patients were treated with mechanical ventilation during their hospitalization. The mean duration of mechanical ventilation was 9±15.04 days (range: 1-280) for all patients hospitalized in the PICU. While 87% of the patients were subsequently transferred to pediatric clinics, 2.2% were referred to other centers, 10.8% of the patients died, and 4.8% recovered with sequelae.

Table 2. Diagnoses of patients admitted to the pediatric intensive care unit (PICU)

	n	%
Diagnoses of admitted patients, n=2280		
Infections	638	28
Bronchiolitis	272	12
Sepsis	228	10
Pneumonia	92	4
Other infection causes	46	2
Trauma	319	14
Congenital heart disease	273	12
Seizures	273	12
Hematological diseases	228	10
Oncological diseases	160	7
Diabetic ketoacidosis	68	3
Metabolic diseases	46	2
Intoxication	46	2
Gastrointestinal system (GIS) diseases	46	2
Kidney diseases	46	2
Other*	137	6
Total	2280	100
Underlying diseases, n=1485 (66% of total patients)		
Neurological	253	17
Respiratory	207	14
Hematological	194	13
Cardiological	163	11
Endocrinological	119	8
Nephrological	119	8
GIS diseases	104	7
Oncological diseases such as solid organ cancers	104	7
Metabolic diseases	74	5
Other**	148	10
Total	1485	100

*: Hypertension, bronchial asthma attack, urticaria, primary immunodeficiency, endocrinological emergencies, choking, **: Infectious diseases, immunological diseases, hereditary diseases

The mean age of the patients transferred from the PICU to pediatric clinics or discharged from the PICU was 9.23±8.15 years (range: 1 month to 18 years), and 8% of the patients who left the PICU had been treated by mechanical ventilation during their hospitalization in the PICU. The total length of hospital stay was calculated as 7.6±12.16 days (median: 1-280). When only patients who were discharged from the PICU were considered, the duration of mechanical ventilation was 3±4.13 days (range: 1-55 days) (Table 1).

The mean age of the patients who died in the PICU was found to be 3.45±7.60 years (range: 1 month to 18 years). Their total hospitalization duration was calculated as 23±15.82 days (range: 1-280). It was determined that 100% of the deceased patients had been treated by mechanical ventilation (Table 1). The duration of mechanical ventilation among deceased patients was 17.25±24.82 days (median: 1-280). In the PICU, approximately 41% of the patients were found to have died due to underlying leukemia, lymphoma, or solid organ cancers, while 22% died due to heart diseases.

Length of hospital stay and duration of mechanical ventilation among deceased patients were statistically significantly longer compared to those of surviving patients ($p<0.05$). The rate of mortality in cases of hemato-oncological diseases was also statistically significant ($p<0.05$).

One-third (33%) of the patients were treated by high-flow nasal cannula (HFNC) and 35% received non-invasive positive airway pressure (NIV) treatment. Furthermore, 5.1% of the patients who were intubated for an extended period had tracheostomy. Single or multiple inotropic therapy was administered to 35.4% of the patients hospitalized in the PICU. Eleven patients underwent ECMO (4.8%) (Table 1).

DISCUSSION

In recent years, PICUs have developed rapidly in Turkey as well as in the world. This has resulted in a significant reduction in mortality with swift and appropriate interventions for many children. The variety of patients admitted to PICUs has increased with each passing day. Mortality has also significantly decreased thanks to the use of extracorporeal therapies in PICUs. This study was conducted to examine the clinical and demographic characteristics of patients hospitalized in a PICU over the course of 2 years and the respiratory support treatments that they received.

In developed countries, PICU beds constitute 10% of the total hospital beds (4). The total number of beds in Ankara City Hospital is 3633. The number of beds in the children's hospital is 555. The ratio of the number of beds in the PICU to the total number of beds is 6% (32/555). When others studies conducted in Turkey are examined, it is seen that the length of stay in PICUs varies between 2 and 5.3 days (5,6). In various studies conducted outside of Turkey, it was reported that the length of stay in the PICU varied between 4.5 and 8.1 days (7). In the present study, the duration of hospitalization was 12.47±20.16 days for all patients hospitalized in the PICU. The reason why hospital stay was longer in the present study compared to others is that Ankara City Hospital is a referral hospital, and patients with high mortality risk have to be hospitalized without indication, similarly to patients in the

terminal stage. It was thought that this situation was also due to the presence of all branches of medicine in Ankara City Hospital, the follow-up of many chronically ill patients in the relevant departments, the need for intensive care during the treatment of patients with underlying chronic diseases, and the fact that since this is a referral hospital, patients requiring long-term intensive care treatment are admitted to the PICU.

The reasons for and rates of hospitalization of patients in PICUs vary in different studies. In the studies conducted by Arias et al. and Khilnani et al., it was suggested that the most important reasons for hospitalization in PICUs were related to respiratory system disorders, while some studies showed that congenital heart disease was the leading cause of hospitalization (8,9). In the present study, respiratory system diseases ranked first among the reasons for hospitalization.

Different mortality rates were stated in various studies conducted in PICUs. Mortality in PICUs generally varies between 3% and 7% worldwide (10,11). In the present study, the mortality rate in the PICU was 10.8%, and 14% of the patients who died did so within the first 48 hours. In a developing country like Turkey, the fact that the mortality rate in the PICU is over 10% is considered an indicator of the fact that intensive care is applied for patients with no prognosis or indications (12). In a study by Tutanç et al., it was reported that there was a negative correlation between age and length of stay in the PICU, that treatment by mechanical ventilation statistically significantly prolonged the length of stay, and that treatment by mechanical ventilation also increased the probability of mortality by 30% (13). In the present study, the increase in length of stay due to mechanical ventilation is seen to be a reason for the high mortality rate. In univariate analyses, similar to the findings in the literature, longer duration of mechanical ventilation and longer hospitalization duration of deceased patients were found to be statistically significant (p=0.001).

Since this hospital is both a referral and pandemic hospital, it serves all of Turkey and also neighboring countries. Therefore, the mortality rate is higher than that in the referring hospitals due to admission of patients with poor general condition and critical diseases. In this evaluation, it was observed that very different patient groups were treated in the PICU, most of the patients had an underlying chronic disease, and the duration of mechanical ventilation was related to mortality. Long-term complications develop as the hospital stay is prolonged. There are studies showing that the use of inotropic or vasoactive drugs also increases the risk of mortality. The use of these drugs is generally associated with disease severity and mortality (14,15). In the present study, the rate of inotrope use was 35% among all patients. Use of central venous catheters (CVCs) and mechanical ventilation are associated with high mortality and complication rates (16,17). In the present study, the rate of patients with CVCs was 32%, and 24% of the total patients were intubated and treated with mechanical ventilation. In Ankara City Hospital, the use of NIV or HFNC is preferred to the use of mechanical ventilators as much as possible. The NIV application rate was 35% and the HFNC application rate was 33% in the present study. Two previous studies showed that the use of NIV significantly reduced mortality (18,19).

CONCLUSION

In the present study, it was seen that the main factors affecting mortality and longer hospitalization in the PICU were mechanical ventilation and the presence of chronic diseases. The fact that children with surgical problems are not followed in PICUs and that terminal patients with no prognosis are transferred to intensive care show that the indications for admission to PICUs should be reconsidered. Necessary studies should be carried out in order to develop treatment services in PICUs and make plans in this regard.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was authorized by the Ministry of Health (Ethics Committee E2-22-1245) and local ethics committee approval was received on January 5, 2022 (Ethics Committee No: 1245).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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Original Article / Orijinal Araştırma

Perceptions of Intern Nurses Regarding the Coronavirus (COVID-19) Pandemic: A Qualitative Study

İntörn Hemşirelerin Koronovirüs (COVID-19) Salgınına İlişkin Algıları: Niteliksel Bir Çalışma

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Abstract

Aim: The Covid-19 pandemic has affected the individual and professional lives of all people, especially health professionals. For this reason, this study aimed to qualitatively determine the perceptions of intern nurses regarding the Covid-19 pandemic.

Material and Method: This phenomenological study was conducted with intern students receiving education at the final year of the nursing department of a state university in the Marmara Region of Turkey between November 1, 2020, and January 15, 2021. An in-depth face-to-face interview method was used in the study. In the interviews, four semi-structured interview questions developed by the researchers were directed to the participants, the answers were audio-recorded and the interviews were analyzed by content analysis by the researchers. The codes obtained as a result of the solution were collected under the main theme and sub-themes, which were created in a way that would provide meaning integrity.

Results: As a result of the data analysis, three main themes, seven sub-themes, and twenty-four codes were determined for the perceptions of the participants regarding the Coronavirus (Covid-19) pandemic. It was determined that many factors affected intern nurses' daily lives negatively and positively during the pandemic process and that participants resorted to some physical, psychological, and social methods to cope with the pandemic process. A group of intern nurses who performed clinical practice during the pandemic stated that this process had a positive effect on their individual development, their approach to patients, and their professional attitudes. Nevertheless, another group stated that their professional commitment decreased, that they felt worried and worthless, and that they avoided participating in the practices.

Conclusion: It was determined that intern nurses, the closest group to the nursing profession, were affected by the pandemic process in many positive and negative aspects, that their professional perceptions changed due to their concerns about the current situation and future, and that they used different techniques that supported and restrained their development in coping with the process. Educational institutions are recommended to provide motivation, counseling, and psychological support programs in order for student nurses to be able to manage their concerns, negative affections, and changing professional perceptions.

Keywords: Covid-19, intern nurse, nursing student, pandemic.

Öz

Amaç: Covid-19 pandemisi tüm insanların olduğu gibi özellikle sağlık profesyonellerinin bireysel ve mesleki yaşamlarını etkilemiştir. Bu nedenle bu çalışma intörn hemşirelerin COVID-19 pandemisine ilişkin algılarının niteliksel olarak belirlenmesi amacıyla gerçekleştirilmiştir.

Gereç ve Yöntem: Fenomolojik (Olgu bilimi) bir çalışma olarak 1 Kasım 2020-15 Ocak 2021 tarihleri arasında Türkiye'nin Marmara Bölgesi'nde yer alan bir devlet üniversitesinin hemşirelik bölümü son sınıf intörn öğrencilerinin katılımı ile gerçekleştirilmiştir. Araştırmada yüz yüze derinlemesine görüşme yöntemi kullanılmıştır. Görüşmelerde araştırmacılar tarafından geliştirilen dört adet yarı yapılandırılmış görüşme sorusu katılımcılara yöneltilmiş, yanıtlar ses kaydına alınmış ve görüşmeler araştırmacılarca içerik analizi yapılarak çözümlemeye gidilmiştir. Yapılan çözümle sonucunda elde edilen kodlar anlam bütünlüğü sağlayacak şekilde oluşturulan ana tema ve alt temalar altında toplanmıştır.

Bulgular: Katılımcılardan toplanan verilerin analizi sonucunda koronovirüs (Covid-19) pandemisine ilişkin algılarına yönelik üç ana tema, yedi alt tema ve yirmi dört kod belirlenmiştir. Pandemi sürecinde intörn hemşirelerin günlük yaşamların olumsuz ve olumlu yönde etkileyen birçok unsur olduğu, pandemi süreciyle baş etmede fiziksel, psikolojik, sosyal bazı yöntemlere başvurdukları belirlenmiştir. Pandemi süresince klinik uygulama yapan bir grup intörn hemşire bu sürecin bireysel gelişimlerini, hastaya yaklaşımlarını, profesyonel tutumlarını olumlu etkilediğini ifade ederken, diğer bir grup intörn hemşire ise mesleki bağlılıklarının azaldığını, kendilerini kaygılı ve değersiz hissettiklerini ve mesleki uygulamalara katılmaktan kaçındıklarını belirtmişlerdir.

Sonuç: Hemşirelik mesleğini gerçekleştirmeye en yakın grup olan intörn hemşirelik öğrencilerinin pandemi sürecinden olumlu ve olumsuz birçok yönden etkilendiği, geleceğe ve anlık duruma ilişkin kaygıları nedeniyle mesleki algılarının değiştiği ve süreç ile baş etmede gelişimlerini destekleyen ve engelleyen farklı teknikler kullandıkları belirlenmiştir. Öğrenci hemşirelerin kaygılarını, olumsuz etkilenişlerini ve mesleğe ilişkin değişen algılarını yönetebilmeleri için eğitim kurumlarınca motivasyonu arttırıcı, danışmanlık ve psikolojik destek programlarını sağlamaları önerilmektedir.

Anahtar Kelimeler: Covid-19, intörn hemşire, öğrenci hemşire, pandemi.

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INTRODUCTION

The coronavirus (COVID-19) infection has affected the entire world and became a pandemic. The virus manifests itself as an acute respiratory syndrome in humans.[1] COVID-19 emerged in late 2019 and spread to almost all over the world. According to the World Health Organization (WHO), it caused thousands of people to die.[2]

Home stays and decreased social relations for protection against the pandemic may cause psychological problems such as depression, fear, concerns of inadequate and inefficient healthcare services, sleep problems, and anxiety.[3,4] In a study conducted during the COVID-19 pandemic period, it was determined that 7% of individuals in the most affected regions of China developed post-traumatic stress symptoms one month after the onset of the pandemic.[5] Furthermore, a study conducted with first-year nursing students reported that 85.9% of students experienced fear due to the COVID-19 pandemic.[6]

The COVID-19 pandemic has led to individual, national, and international intense effects.[7] It has caused significant changes by affecting the economy, social life, and education, and especially the health system all over the world.[8] Nurses fighting on the front line. The WHO declared 2020 as the "Year of the Nurse and Midwife". Due to the COVID-19 pandemic, the nursing profession has been on the world agenda, worthy as declared. Nurses have started to show that they are the "Nurses: A Voice to Lead in World Health" in 2020.[9-11] During the COVID-19 pandemic, the education process in all higher education institutions has been affected as well as health institutions. Countries have taken some measures in order to keep the spread of the virus under control and protect public health. Among these measures, education was temporarily suspended in many countries, including Turkey, and many educational institutions were temporarily closed. Many educational institutions have ensured the continuity of education with distance education.[10] In this process, the Council of Higher Education (CoHE) declared that the spring semester of the 2019-2020 academic year would be given by distance education in universities.[8,12] Although distance learning had not been frequently used before the COVID-19 pandemic, it has been used as an alternative learning method due to the inability to provide face-to-face education during the pandemic period.[8]

Some nursing students, the health professionals of the future, had their practical courses in health institutions during the onset of the COVID-19 pandemic period. This may have caused fear and anxiety. As a matter of fact, according to the relevant studies, nursing students experience stress, fear, and anxiety during the pandemic process.[6,13-16]

While the COVID-19 pandemic was continuing, clinical practice courses were continued with the distance education method for lower grades in the fall semester of 2020 whereas final-year intern nursing students received their clinical practice courses in the hospital. Therefore, this may have led intern students to concerns, changed professional attitudes, and some mood changes. In this sense, it is necessary to determine the perceptions of intern nursing students regarding the COVID-19 pandemic. According to the literature, qualitative research approaches provide the opportunity to obtain detailed information about the attitudes, beliefs, motivations, and behaviors of society members.[17,18] Based on this idea, this study aimed to qualitatively determine the perceptions of intern nurses, who are the prospective health professionals of the future, regarding the COVID-19 pandemic. It is thought that the findings of this study will contribute to the literature, determine the factors affecting the perceptions of intern nurses and how they are affected, and provide the opportunity to make developmental interventions when necessary.

MATERIALS AND METHOD

In order to conduct the research, necessary legal permissions were received from the Scientific Research Commission of the Ministry of Health, General Directorate of Health Services (Permission number: 2020-05-02T04-41-52) and the ethics committee of the university where the study was conducted (Dated: 1 June 2020, Decision number: 2020-05). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Research Type and Time

This research was planned as a qualitative phenomenological study. Phenomenology is not only a philosophical approach but also a research method in which certain methods are used in order to understand the perceptions, interests, and experiences of an individual.[19] The research was carried out with final-year intern students at the nursing department of a state university in the Marmara Region of Turkey between November 1, 2020, and January 15, 2021.

Research Population and Sample

The population of the research consisted of students receiving education in the final year of the nursing department (arastirmanin evreni?). The sample consisted of 21 intern nurses who voluntarily agreed to participate in the study.

Data Collection

Students who agreed to participate in the study were informed about the study and their consent was taken. The students were told that all data would be used for scientific research. In addition, the researchers explained that the answers of the students will not affect the course grades in any way. In the study, a semi-structured interview form developed by the researchers was used as a data collection tool. In order to reveal the perceptions of the students regarding the COVID-19 pandemic, an in-depth interview method was used and 4 open-ended questions were asked in the interview. The clarity of the interview form and the suitability of the questions were rearranged after receiving the opinion of five faculty members who are specialists in their fields. Accordingly, the following questions were asked to the students.

- How has the COVID-19 pandemic effected your daily life?

- What methods have you used to cope with the COVID-19 pandemic?

- How do you think performing your clinical practice in a pandemic hospital during the COVID-19 pandemic affects your practices?

- If you give care to an individual diagnosed with COVID-19 when you start working after graduation, what feelings do you think you would experience?

On the basis of confidentiality, the opinions of the participants were coded without using their names. Each student was given a code name (S1, S2, S3 …….. S21). In the interviews, questions were asked to the students using the face-to-face interview technique and verbal communication and listening skills. The interviews were audio-recorded with a voice recorder and notes were taken by the researcher at the same time. All interviews with the students were held in the same environment (teaching staff's office). Interviews lasted an average of 10-12 minutes for each student. The students were informed about the audio recordings; their written consent was taken and the interviews were recorded on a voice recorder.

Data Analysis

After the completion of the interviews, the audio recordings and the notes were transcribed and manual content analysis was performed by the researchers. The outputs generated after the analysis were read many times and a code list was created. During coding, the researchers reached a consensus on thematic explanations describing the findings. Sub-themes and main themes were determined by classifying the generated codes according to their content integrity.

RESULTS

As a result of the content analysis, three main themes, seven sub-themes, and twenty-four codes were determined for the perceptions of intern nurses regarding the coronavirus (COVID-19) pandemic (**Table 1**).

Theme 1. Effects of the Pandemic Process on Daily Life

Expressions of intern students regarding the effects of the pandemic process on their daily lives were discussed in two sub-themes: "Positive Effects" and "Negative Effects".

Sub-Theme 1. Positive Effects

Intern students mentioned the positive effects on their daily lives during the pandemic and emphasized the codes of "development of planned work habits", "strengthening of family ties", "finding opportunities for personal development", "reduction in noise pollution". Below are examples of interviews statements about the codes that positively affected their daily lives.

"…I started doing everything… in a planned way." (S1)

"…noise pollution is less since there are fewer people outside…" (S10)

"…our family ties have become stronger. You know, we spend more time together because of the fear that something would happen to one of us." (S13)

"…I learned to value … the time I spent at home. I learned to spend time at home instead of going out. I read a book, take time for myself. I dedicate myself to personal development and I am happy at the same time…" (S16)

Table 1. Main Themes, Sub-Themes, and Codes for the Perceptions of Intern Nurses Regarding the Coronavirus (COVID-19) Pandemic.

MAIN THEMES	SUB-THEMES	CODES
1- Effects of the pandemic process on daily life	1-Positive effects	Development of planned working habits Strengthening of family ties Finding opportunities for personal development Reduction in noise pollution
	2-Negative effects	Psychological problems Physical problems Social problems Family problems Problems related to the education process
2- Methods used to cope with the pandemic process	1-Physical methods	Using protective materials Using antiseptics and disinfectants Enhancing immunity
	2-Psychological methods	Avoidance of information Keeping up with up-to-date information Developing repetitive behaviors
	3-Social methods	Social distance Social isolation
3- Effects of professional clinical practices during the pandemic process	1-Positive effects	Increased awareness Ability to empathize with patients Improvement in professional behavior skills
	2-Negative effects	Decreased commitment to the profession Feeling worthless Increased anxiety Avoidance of participating in practices

Sub-Theme 2. Negative Effects

Intern students mentioned the negative effects on their daily lives during the pandemic and emphasized the codes of "psychological problems", "physical problems", "social problems", "family problems", "problems related to the education process". Below are examples of interviews statements about the codes that negatively affected their daily lives.

"…In my family, my mother and sister work. We, three people, live at home. For example, I cannot hug them. We have always started to keep a distance, even in family relations, due to the fear of getting infected at any moment…" (S1)

"…I was going out to cafes, spending time with my friends. If I didn't do any of them, I would come to school. In other words, there was an environment where I could meet with my friends. They all stopped at once and we stayed at home." (S3)

"…I can say it changed a routine. It changed my school schedule, my living conditions. I stayed away from education. We would have a five-month internship; I would be able to improve myself even more. Right now, I'm trying to do what I can in a two-week period." (S4)

" ..I am very worried. Because my anxiety is high in general. I used to have panic attacks sometimes, …It affects me. However, I can adapt after a while. Of course, I will do everything I can. Because I will be a health professional. I will try to do my job even if I am anxious." (S6)

"…I used to wear a single mask, now I started wearing two masks. I normally wash my hands a lot and I started to wash them even more. I even had dermatitis on my hands." (S8)

Theme 2. Methods Used to Cope with the Pandemic Process

The methods that intern students used to cope with the pandemic process were addressed in three sub-themes: "Physical Methods", "Psychological Methods", and "Social Methods".

Sub-Theme 1. Physical Methods

Intern students mentioned the physical methods they used to cope with the pandemic process and emphasized the codes of "using protective materials", "using antiseptics and disinfectants", and "enhancing immunity". Below are examples of interviews statements about the codes regarding the physical methods they used to cope with the pandemic.

"…I wear a mask; I wash my hands more, and so on. I try to stay away from people, but I know that it will infect everyone... Most importantly, I try to keep my immune system strong. I pay attention to my diet." (S4)

"…not going out without a cologne, having spare masks, having gloves… not accepting guests, not entering public areas, not going to places such as cafes unless necessary. We only use public transportation only when necessary…" (S5)

"…I had a blood test to know if there is anything wrong. I take supplementary vitamins so that my body resistance does not decrease… My vitamin D level was low. I also take 2000 or 4000 units of Magnesium a day. Apart from that, I pay attention to what I eat; I also try to exercise." (S10)

Sub-Theme 2. Psychological Methods

Intern students mentioned the psychological methods they used to cope with the pandemic process and emphasized the codes of "avoidance of information", "keeping up with up-to-date information", and "developing repetitive behaviors". Below are examples of interviews statements about the codes regarding the psychological methods they used to cope with the pandemic.

"… for example, when I come home, I wash my hands for at least one or two minutes, even I am at home. For example, I go out on the balcony at home; I get fresh air; I use cologne or something when I go back to the room… As soon as I feel that I am in contact with the outside, I wash my hands for at least one or two minutes." (S6)

"…we do research, of course. We do research online. We look at the news to learn. This is how we try to adapt." (S11)

"…at first I was avoiding learning about COVID-19. As if there was no such thing. In my normal routine, I had been reading books or watching movies or TV shows. And then, after getting into life so much, I started researching COVID-19; I started learning." (S16)

Sub-Theme 3. Social Methods

Intern students mentioned the social methods they used to cope with the pandemic process and emphasized the codes of "social distance" and "social isolation" codes. Below are examples of interviews statements about the codes regarding the social methods they used to cope with the pandemic.

"We had to impose restrictions on our daily lives. We started to do less of the things we normally do routinely. We started to pay more attention, not to go out unless necessary, and to reduce social activities." (S5)

"…for example, I go out, but I go to the seaside; I sit alone; I do not get involved with anyone." (S2)

"Now I had to limit my social activities. …I try to use public transportation very little; if the distance is short so that I can walk, I try to walk or try to use a taxi. I used to go to cafes a lot; I used to go to astro pitch football games; now I try to reduce them. I don't go to cafes. I don't go to crowded restaurants." (S7)

"…I always pay attention to social distance. I like to follow the rules. You know, when I walk on the road, I always keep my distance with people." (S8)

Theme 3. Effects of Professional Clinical Practices During the Pandemic Process

Expressions of intern students regarding how they were affected by clinical practices during the pandemic process were discussed in two sub-themes: "Positive Effects" and "Negative Effects".

Sub-Theme 1. Positive Effects

The positive effects of clinical practice that intern students had during the pandemic were discussed under three codes: "increased awareness", "ability to empathize with patients", and "improvement in professional behavior skills". Below are examples of student interview statements regarding the relevant codes.

"…in fact, how careless we were about hygiene in our previous lives. For example, when I left a patient room, I had not washed my hands. Right now, I immediately say 'No! We are in the pandemic process...' Then I said that this is what should have happened" (S16)

"…we are nurses, so everyone employed in the health sector must have taken all kinds of things into consideration when choosing this profession. Anything can happen. It is a pandemic today; it could end; it could start again, or it could be something else." (S2)

"…we empathize…I think of my family. It could have been my mother in this place; it could have been my father. Everyone deserves good health care, a good care." (S17)

"…Of course, but I provide care professionally." (S9)

"…after I started working in the field, I wanted to start by learning something better. … not just because of the pandemic, there are many diseases that are contagious, that can be transmitted through droplets. It seems like we will be more prepared; If I had started working right now without experiencing this internship, maybe I would have been more afraid. Now I have both got used to it and better learned and understood the measures. I can put it into practice in a better way." (S12)

Sub-Theme 2. Negative Effects

The negative effects of clinical practice that intern students had during the pandemic were discussed under four codes: "decreased commitment to the profession", "feeling worthless", "increased anxiety", "avoidance of participating in practices". Below are examples of student interview statements regarding the relevant codes.

"...I will be assigned next year and I don't even think about assignment. Because if I get sick in the future…" (S1)

"…I have fear, anxiety. It is for my family more than myself because I still live with my family. I mean, I'm afraid for them more than myself. Frankly, I don't want to infect them, even if I get infected… I try to avoid contact as much as possible, but I still have to provide care…" (S3)

"…I wouldn't want to do the clinical practice. Why should I risk myself? You also have the potential to harm your loved ones; that's why I wouldn't want to work." (S4)

"…I feel worthless. Because … doctors try not to contact as much as possible. I always have to, others can avoid, but everyone knows that I will have to contact… because you act as a bridge. In other words, the value given to patients is not given materially, spiritually, or in terms of position…, in no way." (S18)

DISCUSSION

The COVID-19 pandemic, which started in Wuhan, China at the end of 2019, disturbed both the personal and professional lives of people all around the world.[20,21] Nursing students were among the most affected groups due to the changing experiences, organizational differences, uncertainties about their competencies, uncertainties about the education process.[22] For this reason, the study was carried out to examine the perceptions of intern nursing students who went into clinical practice during the pandemic process regarding the COVID-19 pandemic. In line with the results obtained, it was determined that the students were affected by the pandemic process both positively and negatively. It was seen that social solidarity was at a high level in our country especially during the pandemic and that our solidarity ties were tested due to the pandemic.[23] The students who participated in the study stated that the ties within the family, the smallest building block of society, got stronger and that they spent more time together. Likewise, Felaza et al. (2020) stated in their study that medical students strengthened their family ties during the pandemic process.[24] On the other hand, since carbon emissions in various parts of the world decreased, the atmosphere was cleaned, nature began to recover, and the pollution of the seas stopped. The deteriorated environmental balance has begun to be reestablished.[23] Participants in the study similarly mentioned a reduction in noise pollution. Students, who could evaluate the COVID-19 pandemic positively despite its negative effect on life, stated that this traumatic process offered opportunities to study in a planned way, read books, and spend time for personal development. Similarly, Asıcı and Günlü (2020) obtained positive findings in their study that the pandemic process increased personal development and awareness among students.[25] Thus, the COVID-19 pandemic may have positively contributed to the growth, development, and empowerment of some young individuals, the improvement of family ties, and the compensation for the damage humanity has done to the world.

The pandemic process has negatively affected health professionals in physical, psychological, and social aspects.[26] The students who participated in the research also mentioned many negative physical, psychological, social, familial, and educational effects on their daily lives during the pandemic process. In the interviews, the students stated that they decreased their contact even in the family due to the fear of infection, stayed away from the environments such as schools and cafes where they got social, stayed away from the education system they were accustomed to, had less clinical practice in the professional field, had psychological problems such as panic attacks and repetitive behaviors, and developed dermatitis due to the increase in washing frequency. According to the literature, nursing students are afraid of the COVID-19 pandemic and have psychological problems.[26,27] It is obvious that social relations will not be the same as before after the COVID-19 pandemic, at least for a certain period of time. This can increase social alienation since people

can see each other as potential virus carriers.[23] Furthermore, there are shortcomings in the practice training of final-year students who will provide one-to-one nursing care in health institutions, creating pressure on students. The social distance rule that requires being away from friends and home stays are difficult for young people to tolerate; therefore, it can be suggested that nursing students are under intense stress in terms of academic, familial, health, and social relations during the pandemic process.

Coping with anxiety and stress during outbreaks is very important in order to improve the effects of anxiety and stress on health.[28] Strategies for coping with this process are multidimensional and include many different ways such as problem solving, information seeking, avoidance, support seeking, social isolation.[28,29] When the literature was examined, it was seen that the viral COVID-19 infection affects people with low immunity more easily.[30] The guidelines of the WHO and the Turkish? Ministry of Health have recommended paying attention to adequate and balanced nutrition, preferring healthy foods, regular exercise, adequate sleep, and meditation in order to reduce susceptibility and long-term complications caused by the coronavirus.[31] Moreover, social isolation, which is one of the most effective weapons in coping with this process, includes individuals staying away from crowded environments and paying attention to the physical distance between people.[32] In the study, intern students mentioned hygiene practices (handwashing, use of masks, gloves, disinfectants), immune-supportive activities (proper nutrition, physical activity, vitamin supplement, health examinations), social distance, and social isolation (staying away from the crowded, not leaving the house, not accepting guests, moving by opening the distance between people) as the methods they used to cope with the pandemic process. In addition, some participants stated that they suppressed their anxiety by avoiding getting information about the disease in coping with this process whereas other participants stated that they could continue the process by keeping up with up-to-date information and tried to adapt. It was thought that this negative process, which has caused mandatory life changes such as quarantine, might be an opportunity to gain habits such as proper nutrition, exercising, hygiene habits, compliance with the rules, and obtaining information from the right sources.

Nurses as a health professionals fighting COVID-19 on the frontline and will be key players in ending the pandemic with appropriate support.[9] For this reason, it is desired result to continue to train nurses in higher education institutions in order to solve the global nurse demand in case of increasing crisis.[33] Clinical practice is a critical yet complex and challenging component of the professional development of nursing students.[34] Therefore, distance education and mixed methods have created opportunities to complete this challenging education process component in the COVID-19 pandemic.[35] In other words, in order to overcome this crisis period with the least damage, nursing students received their practical courses in the hospital environment and their theoretical lessons with distance education during the COVID-19 pandemic.[9] This process had both positive and negative effects on students. The participants stated that they were able to better implement many protective measures that they had not paid attention to before, that this process increased their awareness, that they could now better empathize with patients, and that they felt prepared for negative health conditions that may occur in the future. In a qualitative study conducted by Swift et al. (2020)[36] with undergraduate nursing students, students stated that they could be useful during the pandemic process and that the society's positive response to their effort would also positively affect their career preferences. However, the literature also includes negative feedback from students in clinical practice. Ulenaers et al. (2021)[22] stated that only 49.47% of students could establish a balance between clinical practice and private life. Yılmaz and Büyüköztürk (2021) determined that nursing students had concerns about getting infected by COVID-19 [37], being in contact, and infecting their family members, patients, or health professionals, being a carrier, and about an interruption of their education. Slettmyr et al. (2019)[38] and Sampaio et al. (2021)[39] also determined in their studies that students experienced noncompliance between self-protection or protecting their loved ones and the urge to "do their part". Studies also mentioned that the anxiety levels of students who live with their families and who have chronic diseases increase.[40-42] Çalışkan et al. (2020) [43] also showed in their study that the fear of COVID-19 negatively affects the level of attitude towards the nursing profession. In the study conducted by Kızıltepe and Yılmaz (2021), students stated that nurses had fear/anxiety of being sick, that they did not want to enter the patient's room, that communication with patients was limited due to the necessity of working with protective equipment, that they spent less time with patients, that they paid less attention to contact with patients, that the care provided to patients was severely interrupted, and that the quality of care decreased.[41] Likewise, intern students participating in our study stated that their professional commitment decreased due to being involved in clinical practice during the pandemic, that they were hesitant about working after graduation, that they were worried about their and their families' health, that being on the front line made them feel worthless, that they felt uncomfortable about not having the right to withdraw from care while everyone had it, and that they were not supported financially and morally. Although the research findings are consistent with the literature, it makes us question how the motivation resources will support students' commitment to the profession during the education process.

CONCLUSION

This study aimed to examine the perceptions of intern nursing students who have been in clinical practice during the pandemic process, regarding the COVID-19 pandemic.

In line with the results obtained, it was determined that the students were able to find opportunities to support their personal development during the pandemic process, but they also had negative psychological, physical, social, familial, and educational experiences. Although some students developed healthy lifestyle behaviors in coping with the process, it was observed that they encountered psychological problems due to the anxiety they experienced. During the pandemic, intern nursing students who went to clinical practices were affected both positively and negatively in professional, emotional, and familial aspects. However, at the end of the research process, it was thought that students need more motivation support in an ominous process such as a pandemic and that the current support mechanisms should be reconsidered by educational institutions. Educational institutions are recommended to increase professional ties with improved counseling services regarding the pandemic process and all future extraordinary situations. A psychological support program to be provided along with the distance education process is thought to help students in this regard.

ETHICAL DECLARATIONS

Ethics Committee Approval: In order to conduct the research, necessary legal permissions were received from the Scientific Research Commission of the Ministry of Health, General Directorate of Health Services (Permission number: 2020-05-02T04-41-52) and the ethics committee of the university where the study was conducted (Dated: 1 June 2020, Decision number: 2020-05).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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

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Orijinal Araştırma / Original Article

The Relationship of the Number of Pregnant in the Labor Room to Perception of Support, Fear of Childbirth and Satisfaction

Travay Odasındaki Gebe Sayısının Doğumdaki Destek ve Kontrol Algısı, Doğum Korkusu ve Anne Memnuniyeti ile İlişkisi

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Abstract

Aim: This descriptive study aimed to determine the relationship of the number of pregnant women in the labor room to mothers' perception of support and control during labor and their postnatal fear and satisfaction levels.

Material and Method: The research is descriptive type. The study was carried out at the postnatal care clinics of two public hospital in Turkey. The sample consisted of a total of 686 women. The data were analyzed using the SPSS 23.0 program. The level of spread was accepted to be 0.05.

Results: The postnatal women who had stayed at single labor rooms, had spontaneous delivery, had delivery standing up, did not have intervention during delivery had higher perceptions of support/control at labor and care satisfaction levels and lower fear of childbirth levels. It was found that high perceptions of support and control at labor reduced fear of childbirth, while increasing satisfaction with the care in normal delivery ($p<0.05$).

Conclusion: It was determined that pregnant women having their deliveries in single rooms had high levels of support/control perceptions at labor and care-related satisfaction, as well as low levels of fear of childbirth.

Keywords: Fear of childbirth, labor room, mother satisfaction, perception of support and control, pregnancy

Öz

Amaç: Bu çalışma travay odasındaki gebe sayısının doğumdaki destek ve kontrol algısı, doğum korkusu ve anne memnuniyeti ile ilişkisini belirlemek amacıyla planlanmıştır.

Gereç ve Yöntem: Araştırma tanımlayıcı tiptedir. Çalışma Türkiye'de iki devlet hastanesinin doğum sonu servislerinde yapılmıştır. Araştırmaya toplam 686 kadın dahil edilmiştir. Veriler SPSS 23.0 programı kullanılarak analiz edilmiştir. Yanılma düzeyi 0,05 olarak alınmıştır.

Bulgular: Tek kişilik travay odasında kalan, doğumu spontan gerçekleşen, ayakta doğum yapan, doğum sırasında müdahalede bulunulmayan lohusaların doğumda destek / kontrol algısının ve bakıma ilişkin memnuniyet düzeylerinin yüksek, doğum korkusunun düşük olduğu belirlenmiştir. Doğumda destek ve kontrol algısının yüksek olmasının doğum korkusunu azalttığı bununla birlikte normal doğumda bakıma ilişkin memnuniyet duyma düzeylerini de arttırdığı belirlenmiştir ($p<0,05$).

Sonuç: Tek kişilik odada doğum eylemi gerçekleştirilen gebelerin doğumda destek / kontrol algısının ve bakıma ilişkin memnuniyet düzeylerinin yüksek; doğum korkusunun düşük olduğu belirlenmiştir.

Anahtar Kelimeler: Doğum korkusu, travay, anne memnuniyeti, destek ve kontrol algısı, gebelik

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INTRODUCTION

The mothers who receive quality care before and during childbirth and whose physiological, psychological and social needs are met have reduced fear of childbirth.[1] Low levels of fear of childbirth lead mothers to have a positive labor experience and increase the mother's satisfaction.[2,3] A high level of mother satisfaction is also highly important in the start and maintenance of the mother-infant interaction after birth and in terms of the mother's healthy satisfaction of her own and her baby's needs.[3]

Today, the necessity for pregnant women to be in single rooms for the process of labor and have labor in such rooms is among the important factors that increase mothers' satisfaction, reduce fear of childbirth and provide a supportive approach in care.[4] Still, at some hospitals, prenatal monitoring and labor do not take place in single rooms, and the delivery process takes place not in the room of monitoring but in a separate room. On the other hand, it was reported that mothers experience a positive delivery experience, and interventions with delivery are reduced at hospital and home births where one-person monitoring is carried out, and labor takes place in the same room.[5] As a result of the comprehensive literature review, no study was encountered to have investigated the effects of the number of pregnant women in the labor room on mothers' perception of support and control during labor and their postnatal fear and satisfaction levels.

MATERIAL AND METHOD

Study design

This descriptive study was planned to examine the relationship of the number of pregnant women in the labor room to mothers' perception of support and control during labor and their postnatal fear and satisfaction levels. The study was carried out at the postnatal care service of two public hospitals in Turkey. In one of the hospitals prenatal monitoring is carried out in double rooms, and delivery takes place in a separate room. In other hospital prenatal monitoring is carried out in single rooms, and delivery takes place in the same room. The population of the study consisted of 5069 women who gave vaginal birth at the postnatal care service of two public hospitals in 2018. The sample size was calculated by power analysis. The p ratio was taken as 0.50 to keep the sample size on the maximum level. The sample size to represent the population was determined as 686 with a significance level of α=0.05, confidence interval of 1-α=0.95, error rate of β=0.20 and power of 1-β=0.80.

Data collection tools

The data were collected by the researchers in line with the literature by using a "Puerperal women information form", "The perception of support and control in birth scale", "The Wijma delivery expectancy / experience questionnaire – version b", and "The scale for measuring maternal satisfaction in vaginal birth".

Puerperal women information form: This form included 18 questions in order to determine the puerperal women's ages, educational, and past and present obstetric information.[1-3]

The perception of support and control in birth scale (SCIB): The lowest one can score on the scale[6] is 33, and the highest score is 165. A high score on the scale indicates that the perception of support and control during delivery is strong. In this study, the Alpha coefficient of the SCIB was 0.95.

The Wijma delivery expectancy / experience questionnaire – version b (W-DEQ B): The minimum score on the scale[7] is 33, while the maximum score is 198. High scores show that women have strong fear of childbirth.[8] In the present study, the Alpha coefficient of the W-DEQ B was 0.94.

The scale for measuring maternal satisfaction in vaginal birth (SMMS-VB): The overall raw score varies between 43 and 215. As the overall score one scores on the scale increases, the levels of satisfaction from the care that mothers receive in the hospital during normal delivery increase. The cut-off score of the scale was set at 150.5 (≥150.5=high satisfaction, <150.5=low satisfaction).[8] In the present study, the Cronbach alpha coefficient of the SSMMS-VB was 0.95.

Research application and ethical approval

Prior to the study, written permission was obtained from authors's university ethics review board (Decision No: 2019-05/37). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Written permission has been obtained from two public hospitals to conduct the study. People who met the criteria of the study (those with no psychiatric and physical diseases, and so forth) were informed about the purpose and scope of the study, and written consent forms were obtained for their participation. The forms were administered at the hospital by the researcher using the face-to-face interview technique to the women who gave written consent indicating that they participated in the study voluntarily (approximately within 24 hours for vaginal delivery).

Statistical analysis

The data obtained from the study were analyzed using the SPSS 23.0 program. Data providing parametric conditions were analyzed by carrying out independent-samples t-tests for pairs of independent groups and Pearson correlation analyses for evaluating relationships, as well as descriptive statistical analyses. The level of spread was accepted to be 0.05.

RESULTS

Of the puerperal women participating in our study, 82.9% were between 19 to 35 years old, and they were 30.10±6.29 years old on average; 42.1% had a pregnancy history. Among the postnatal women, 34.4% stayed in single rooms during labor, 85.3% gave vaginal births that started spontaneously, only 5.8% used the "standing" position during delivery, and

55% received interventions (episiotomy / sutured delivery, fundal pressure, vacuum application). Perineal trauma occurred in 46.9%. The puerperal women's mean overall scores on SCIB, W-DEQ B B, and SMMS-NB were found to be 112.84±23.68; 97.31±29.55 and 151.47±25.04, respectively.

There was moderate fear of childbirth in 16.3% of the puerperal women severe fear of childbirth in 25.5%, and fear of childbirth at a clinical level in 58.2% (**Table 1**).

Table 1. Experiencing fear of childbirth according to W-DEQ B (n=686).

W-DEQ B*	Mild (≤37) n(%)	Middle (38-65) n(%)	Serious (66-84) n(%)	Clinic (≥85) n(%)
Fear level of childbirth	0 (0)	112 (16.3)	175 (25.5)	399 (58.2)

* W-DEQ B: The Wijma Delivery Expectancy / Experience Questionnaire Versiyon B

The postnatal women who had stayed at single labor rooms, had spontaneous delivery, had delivery standing up, did not have intervention during delivery and did not have perineal trauma had higher perceptions of support/control at labor and care satisfaction levels and lower fear of childbirth levels ($p<0.05$), (**Table 2**).

There were a negative significant relationship between the mean SCIB and W-DEQ B scores of the participants and a positive significant relationship between their mean SCIB and SSMS-NB scores ($p<0.05$). It was determined that high perceptions of support and control at labor reduced fear of childbirth, while increasing satisfaction with the care in normal delivery (**Table 3**).

Table 3. The correlation of scale total scores.

Scales**	SCIB	
	r*	p
W-DEQB	-0.883	0.000
SSMS-NB	0.696	0.000

*Pearson'sKorelasyonAnalysis;**SCIBScale:ThePerceivedSupportandControlinBirthScale;W-DEQB:TheWijmaDeliveryExpectancy/ExperienceQuestionnaireVersiyonB;SSMS-NB:ScalesforMeasuringMaternalSatisfactioninNormalBirth;SSMS-NB

DISCUSSION

Whatever their form of delivery may be, the delivery experience they have has an important place in women's lives.[9] An important factor that affects women's experience of a positive delivery is the characteristics of the labor room in the intrapartum period. The positive experiences of mothers increase in hospital deliveries where a single person is monitored in a room, and the delivery is performed in the same room.[4,5,10] In our study, 34.4% of the women stayed in single rooms at labor. Single rooms where labor is monitored increase the autonomy and privacy feelings of women the most.

The process of delivery is a highly stressful event for all women, and women need increased levels of support in this period. This support is usually provided by midwives and doctors.[11] While the mean total SSMS-NB score in our study was moderate (112.84±23.68), Colley et al.[12] found the perceptions of labor support and control of women to be on a low level. A study has determined that women who are supported at delivery by receiving quality care and whose physiological, psychological

Table 2. Distribution of scale total score means according to some features of puerperal women.

Characteristics	SCALES***		
	SCIB $\bar{x}$±sd	W-DEQB $\bar{x}$±sd	SMMS-NB $\bar{x}$±sd
Labor room			
Single room (n=236)	139.61±5.33	66.40±5.14	177.91±7.53
≥ Double room (n=450)	98.80±16.32	113.52±23.51	137.62±19.17
t / p*	37.372/0.000	30.387/0.000	31.038/0.000
Type of childbirth			
Vaginal delivery (n=585)	115.66±23.52	94.58±29.83	154.32±25.02
Induction vaginal delivery (n=101)	96.49±17.10	113.13±22.09	135.02±17.89
t / p*	7.837/0.000	5.970/0.000	7.429/0.000
Birth position			
Lithotomy (n=474)	103.77±20.58	107.96±26.78	142.12±22.22
Squatting (n=172)	131.59±17.77	75.19±21.82	171.05±18.48
Standing (n=40)	139.75±5.40	66.20±4.68	178.28±6.38
F / p**	171.587/0.000	143.058/0.000	158.275/0.000
Intervention in birth			
Yes (n=377)	104.93±19.69	107.69±26.72	142.14±22.67
No (n=309)	122.50±24.56	84.64±27.88	162.87±23.04
t / p*	10.393/0.000	11.021/0.000	11.830/0.000
Perineal trauma			
Yes (n=377)	106.31±20.44	104.63±26.25	143.95±22.99
No (n=309)	118.62±24.84	90.84±30.80	158.14±24.92
t / p*	7.027/0.000	6.265/0.000	7.714/0.000

* Independent sample t test; ** ANOVA; *** SCIB Scale: The Perceived Support and Control in Birth Scale; W-DEQ B: The Wijma Delivery Expectancy / Experience Questionnaire Versiyon B; SSMS-NB: Scales for Measuring Maternal Satisfaction in Normal Birth

and social necessities are met have reduced fear of childbirth.[1] In our study, 58.2% of the women were found to have clinical levels of fear of childbirth. According to a meta-analysis by Deliktas and Kukulu[13] on fear of childbirth, 21 in every 100 women experience tokophobia. High mother's satisfaction levels are dependent on women to have a positive delivery experience.[3] The mothers' satisfaction levels in normal delivery in our study were high (151.47±25.04).

Delivery environments are important especially in reducing fear of childbirth, providing a positive delivery experience and in increasing mother's satisfaction levels.[14] In our study, the women who stayed in single rooms and double rooms received care from midwives. The ones who stayed in single rooms had higher labor support and control perceptions and satisfaction levels and lower fears of childbirth. Single rooms where privacy increases, and better attention is paid to women may explain the differences among the women's perceived support and control levels, fear of childbirth levels and satisfaction levels.

Interventions that are made unnecessarily during delivery (induction, episiotomy, etc.) reduce the control perceptions[15], satisfaction levels[15,16] and increase the fear of childbirth levels of women.[17] Similar results were also obtained in our study. The labor support and control perceptions were high, fears of childbirth were low, and satisfaction levels were high among the women who were not intervened with and had spontaneous vaginal deliveries.

The physical characteristics of labor rooms must be in a structure that will support the position (support a vertical position, etc.) needed by the mother.[11] Thies-Lagergren et al.[18] reported that women who gave birth in a sitting position had increased control feelings and reduced pain levels. Usage of the crouching position from among vertical positions at labor is associated with less perineal injury.[19] In our study, the women who gave birth standing up or in a crouching position and did not have perineal or cervical tearing had higher labor support and control feelings and lower fear of childbirth levels. Previous studies and our study appear to support the usage of vertical positions for delivery at labor rooms and the idea that this situation reduces the rate of perineal trauma.

The significant predictors of perceptions of control at labor, delivery experience and satisfaction are the delivery environment, the healthcare personnel monitoring the delivery and providing care and their levels of informing the woman. A study determined a positive relationship between labor control perceptions and satisfaction. In women with high labor control feelings, delivery satisfaction levels are also high.[15] A study have shown that the control feelings perceived by women during labor affect the delivery experience of women and their satisfaction with the delivery.[20] In similarity to other studies, in our study, it was determined that a high perception of support and control at labor reduced fear of childbirth, and in addition to this, it increased the levels of satisfaction with care in normal delivery.

CONCLUSION

It was determined that the pregnant women staying in single rooms and having their deliveries in the same rooms had high levels of support / control perceptions at labor and care-related satisfaction, as well as low levels of fear of childbirth. In line with these results, it may be recommended to monitor all pregnant women in single rooms and perform delivery procedures in these same rooms.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethical approval has been provided by the Ethics Committee from the Faculty of Medicine, Cumhuriyet University (2019-05/37).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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Orijinal Araştırma / Original Article

Evaluation of Patients Diagnosed with Ileus in the Emergency Department

Acil Serviste İleus Tanısı Alan Hastaların Değerlendirilmesi

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Abstract

Purpose: In emergency department, a delayed diagnosis and treatment of ileus causes a substantial increase in morbidity and mortality.

Material and Method: In this study we aimed to determine the major risk factors of mortality and hospital stay length in patients with ileus.

Results: It was determined that blood transfusion requirement, lactate, total bilirubin, and C-reactive protein levels, presence of colon cancer, and mean arterial pressure were among the parameters that can be used for predicting mortality in patients with ileus. In addition, qSOFA value and potassium, sodium, and total protein levels were determined to be among the parameters that are effective for determining the need for surgery in patients with ileus.

Conclusion: Considering the study findings, it is possible to reduce both morbidity and mortality and to achieve cost reduction by determining parameters that have effect on mortality, length of hospitalization, and surgical decision in patients with ileus.

Keywords: Abdominal pain, emergency room, ileus, mortality, surgery

Öz

Amaç: Acil serviste ileus tanı ve tedavisindeki gecikme ciddi mobidite ve mortalite artışıyla sonuçlanmaktadır.

Gereç ve Yöntem: Bu çalışmada ileus hastalarında hastanede kalış süreleri ve mortaliteyi etkileyen ana faktörlerin tespiti amaçlanmıştır.

Bulgular: Kan transfüzyonu ihtiyacı, laktat, total bilirubin ve C-reaktif protein seviyelerinin yüksekliği ile kolon kanseri varlığı ve ortalama arter basıncı düşüklüğünün ileus hastalarında mortaliteyi belirlemede etkili olduğu tespit edildi. İlave olarak qSOFA değeri ile sodyum, potasyum ve total protein seviyelerinin ileus hastalarında cerrahi ihtiyacını belirlemede etkili olduğu görüldü.

Sonuç: İleus hastalarında hastanede kalış süreci, cerrahi kararı, mortalitenin tespiti, mortalite ve morbiditenin azaltılması ve tedavi maliyetlerinin azaltılmasında çalışmada tespit edilen parametrelerin kullanımının faydalı olabileceğini düşünmekteyiz.

Anahtar Kelimeler: Acil servis, cerrahi, ileus, karın ağrısı, mortalite

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INTRODUCTION

Abdominal pain is one of the most common conditions that results in the admission of adult patients to the emergency department (ED) with a rate of 4%-8%.[1] Among these types of pain, those that require surgery are referred to as acute abdomen. The term acute abdomen typically refers to the clinical condition that manifests as a complaint of prominent abdominal pain occurring in the past week due to non-traumatic reasons and possibly requiring urgent treatment.[2]

The most common causes of acute abdomen in EDs include acute appendicitis, acute cholecystitis, diverticulitis, intestinal obstruction, pancreatitis, and perforated peptic ulcer.[3] Approximately 15% of all such hospital admissions are caused by ileus.[2] Ileus refers to a slowdown or delay in the distal progression of the intestinal contents in the gastrointestinal system owing to a functional or mechanical reason. Ileus can be divided into two groups: ileus associated with mechanical factors and not associated with mechanical factors. Ileus associated with non-mechanical factors can be classified into two types: adynamic ileus and dynamic ileus. Mechanical factors involved in ileus include extraintestinal pathologies (hernia etc.), intestinal wall pathologies (malignancy etc.), and intraintestinal pathologies.[4] Previously, the most common cause in the etiology of ileus was inguinal hernia, whereas currently the most common reason is the condition caused by postoperative adhesions.[5,6] Delay in diagnosis and treatment in ED can lead to a critically increase in mortality.[7]

In the present study, we aimed to retrospectively examine the sociodemographic characteristics, comorbid diseases, and etiology of patients with ileus in the adult ED and to determine the parameters that can be used in the surgical decision-making, and mortality prediction.

MATERIAL AND METHOD

The study was approved by the ethics committee (protocol number TÜTF-BAEK 2018/168 dated 07.05.2018). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. The patients who were admitted to the Emergency Department of tertiary hospital during a 2-year period and were clinically and radiologically diagnosed with ileus. Data were retrospectively collected from the hospital registry system and ED patient records of the hospital and documented in the previously prepared study form.

During the study period, 316 patients who were clinically and radiologically diagnosed of ileus. In this period a total of 306 patients were diagnosed with ileus. Of these, 64 patients aged <18 years and previously diagnosed with ileus and 55 patients whose complete information was unavailable were excluded from the study. Finally, a total of 197 patients were included in the study. Age, sex, vital signs at the time of admission (systolic–diastolic blood pressure, heart rate, body temperature, respiratory rate), laboratory tests, duration of admission complaints, detailed background information, risk factors (such as malignancy and surgical history), length of hospitalization (for inpatients), type and amount of blood products administered, and quick Sepsis-Related Organ Failure Assessment (qSOFA) scores of the patients were retrospectively reviewed from the records and documented. The hospital registry system was used to evaluate the 30-day mortality rates of patients. For patients who were not discharged within 30 days, mortality was inquired by contacting the patient or their relatives.

Data Analysis

Shapiro–Wilk test was used to examine compliance to normal distribution. Univariate and multivariate logistic regression (Backward 29 Wald method) analyses were used to determine risk factors. First, the effects of all factors were examined using univariate logistic regression, and factors with a p-value of <0.200 were included in the multivariate logistic regression model. ROC analysis (Youden index) was used to evaluate the model performance and determine cut-off points. Simple and multiple linear regression analyses were used to determine the factors affecting a quantitative variable. Multiple linear regression analysis was applied on factors with a p-value of <0.200 in simple linear regression analysis. To avoid the issue of multiple linear correlation in both linear regression and logistic regression, variables that showed high correlation (e.g., r > 0.9) were investigated. Among variables with high correlation with each other, the variable with a lower p-value in the univariate model was included in multiple linear regression and/or multivariate logistic models. In terms of descriptive statistics, in addition to minimum and maximum values for quantitative variables, mean and standard deviation were determined for those that conformed to the normal distribution, median and interquartile range were determined for those that did not conform to the normal distribution, and number and percentage were determined for qualitative variables. The significance level for all statistical analyses was determined as 0.05, and all analyses were conducted using IBM SPSS 23.0 package program, R program gplots package, easyROC, and TURCOSA (Turcosa Analytics Ltd Co, Turkey, www.turcosa.com.tr) statistical software (52).

Group comparisons were performed using Mann–Whitney U test and Student's t-test for quantitative variables that did not conform to the normal distribution. Relationships between qualitative variables were investigated using the Pearson's chi-square test and Fisher's exact test.

RESULTS

Of the patients, 90 (45.7%) were women and 107 (54.3%) were men. Mean patient age was 64.10±15.02 years (min-max:19-97). Although the mean age of men was higher than that of women, a significant difference was not observed (p=0.077). Details regarding mean patient age is provided in **Table 1**.

Table 1. Mean age of patients with ileus

	Mean age (years)	Minimum–maximum (years)
Female	64.3±18.92	19-94
Male	61.6±17.83	20-95
Total	64.10±15.02	19-97

When the history of abdominal surgery of patients was assessed, it was found that 129 (65.5%) patients had previously undergone an abdominal surgery. When the patients were examined in terms of presence of cancer, 87 (44.2%) patients were found to have a previous cancer diagnosis. Of the patients, 29 (14.7%) were previously diagnosed with colon cancer, 14 (7.1%) with liver cancer, and 13 (6.6%) with rectal cancer.

On the examination of qSOFA scores at the time of admission, the score was found to be ≥1 in 28 (13.8%) patients and 0 in 169 (86.2%) patients. Evaluation of the vital and laboratory findings of patients revealed that the mean body temperature was 37°C (min-max: 36°C-38.4°C), mean heart rate was 92 beats/min (min-max:72-148 beats/min), mean systolic arterial blood pressure was 125 mmHg (min-max:70-150 mmHg), mean diastolic arterial blood pressure was 70 mmHg (min-max:40-95 mmHg), and mean arterial blood pressure (MAP) was 90 mmHg (min-max: 50-113 mmHg). The mean values of other laboratory parameters are presented in **Table 2**.

Mortality Prediction Model

It is determined that 25 (12.7%) of the patients died within the 30 days of admission. Statistical models were analyzed to determine parameters that could influence mortality in patients with ileus. In the model analyses, the model created by considering the accuracy rates obtained in predicting mortality with McFadden, Cox, and Snell and Nagelkerke R2 measurements.

According to the Hosmer–Lemeshow test result, the model was found to conform to the data (p=0.266). The logistic regression model results revealed that the parameters such as blood transfusion (p<0.001), lactate level (p=0.029), presence of colon cancer (p=0.001), total bilirubin (TBIL) level (p=0.025), and MAP (p=0.001) showed a significant effect on mortality. Although the effect of C-reactive protein (CRP) level was not significant (p=0.065), it was included in the model owing to its substantial contribution to the model. When the remaining parameters in the model were maintained constant, one unit increase in the number of blood transfusions was found to increase the mortality risk by 1.25 times (95% confidence interval (CI):1,106-1,412), whereas CRP and lactate level increased the mortality risk by 1.068 times (0.1-1.15 and 1.01-1.14, respectively). Similarly, when the other parameters in the model were maintained constant, one unit increase in TBIL level increased the mortality risk 3.521 times (1.171-10.588) and MAP increased this risk by approximately 10%.[odds ratio: 0.9 times (0.848-0.955). Colon cancer is the most important factor that increases mortality risk. It was observed that the mortality risk of patients with colon cancer was approximately 35 times (4.6-171) higher than those without colon cancer.

Table 2. Mean values of vital and laboratory parameters of patients with ileus

Qualitative Variables	Mean (±SD)	Minimum	Maximum
Temperature (°C)	37 (0.5)	36	38.4
Heart rate (beats/min)	92 (14)	72	148
SAP (mmHg)	125 (26.5)	70	150
DAP (mmHg)	70 (12)	40	95
MAP (mmHg)	90 (17)	50	113
HGB (g/dL)	12.5 (2.1)	6.9	19.6
Hematocrit (%)	37.4 (6.5)	19.5	58.2
WBC (10^3/uL)	10.7 (6.4)	1.1	31.8
PLT (10^3/uL)	282 (156)	70	881
AST (U/L)	27 (20.5)	8	239
ALT (U/L)	15 (12)	4	112
Total protein (g/dL)	6.7 (1.0)	4.2	9.5
Albumin (g/dL)	3.6 (0.6)	2.0	5.3
Total bilirubin (mg/dL)	0.7 (0.7)	0.2	7.2
Direct bilirubin (mg/dL)	0.2 (0.3)	0.1	3.4
Indirect bilirubin (mg/dL)	0.5 (0.5)	0.1	3.8
Urea (BUN) (mg/dL)	46 (38.5)	13	247
Creatinine (mg/dL)	0.9 (0.7)	0.2	11.6
Na (mmol/L)	136.6 (4.6)	123.0	151.0
K (mmol/L)	4.3 (0.6)	2.1	5.6
Cl (mmol/L)	101.4 (5.1)	83	116
CRP (mg/dL)	3.1 (2.8)	0.2	53
ALP (U/L)	84 (44)	11	675
GGT (U/L)	24 (25)	7	982
Amylase (U/L)	49 (38)	4	489
Lipase (U/L)	18 (19)	1	297
Glucose (mg/dL)	119 (41)	55	358
pH (blood gas)	7.4 (0.1)	7.2	7.56
HCO_3 (blood gas)	23 (6)	12	44
PO_2 (mmHg)	96 (3)	37	99
Lactate (mg/dL)	13 (11)	2	109
INR	1.13 (0.2)	0.89	4.28

SAP: Systolic arterial pressure, DAP: Diastolic arterial pressure, MAP: Mean arterial pressure, HGB: Hemoglobin, WBC: White blood cell count, PLT: Platelet, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, BUN: Blood urea nitrogen, Na: Sodium, K: Potassium, Cl: Chlorine, CRP: C-reactive protein, ALP: Alkaline phosphatase, GGT: Gamma glutamyl transferase, pH: pH of blood gas, HCO_3: Bicarbonate in blood gas, PO_2: Oxygen in blood gas, LACTATE: Lactate level in blood gas, INR: International normalized ratio

Using the probability estimates obtained as a result of the logistic regression model, it was examined whether the model shows significant difference for distinguishing between the two groups (dead and alive) by ROC analysis. In addition, the performances of the variables MAP and TBIL, CRP, and lactate levels in the final model for distinguishing between both groups (dead and alive) individually were examined.

On examining the area under the curve (AUC) value obtained, it was observed that the prediction model significantly separated the groups (AUC=0.965, p<0.001). Therefore, it is possible to state that the model shows a successful performance in determining mortality. According to the ROC analysis, the cutoff point for probability prediction using the Youden index was determined as 0.588. Performance measures according to this cutoff point were determined as follows: sensitivity was 80% (20/25), selectivity was 100% (172/172), positive predictive value was 100% (20/20), and negative predictive value was 97.2% (172/177).

AUC values of the variables MAP and TBIL, CRP, and lactate levels in the model were obtained as 0.788, 0.766, 0.766, and 0.743, respectively; the AUC values obtained for these variables were significant (p<0.001 for all variables). The cutoff points for the variables MAP and TBIL, CRP, and lactate levels were 80, 0.9, 3.7 and 18, respectively, according to the Youden index. Patients with MAP value of <80 mmHg can be expected to be in the risk group for mortality. According to these cutoff points, sensitivity, selectivity, positive predictive value, and negative predictive value measures were 64%, 87%, 41%, and 95% for MAP; 76%, 60%, 22%, and 95% for TBIL level; 0, 88%, 60%, 25%, and 98% for CRP, and 72%, 74%, 29%, and 95% for lactate, respectively.

Considering these results, the variables MAP and TBIL, CRP, and lactate levels exhibited lower performance in determining risk groups for mortality (range of AUC values:0.70-0.79) when considered individually. However, an AUC value of 0.965 was obtained in the multivariate logistic regression model that included the variables blood transfusion and presence of colon cancer along with the above variables.

In multivariate logistic regression model, it was observed that both AUC value and other performance measures (selectivity, positive predictive value, and negative predictive value) were higher than measures observed individually for the variables. Considering this finding, it can be concluded that instead of using the variables individually for mortality prediction, the use of a prediction model derived from these variables can provide an increase in diagnostic performance. ROC analysis results on mortality prediction are shown in **Table 3**.

Additionally, according to the results of the logistic regression model, blood transfusion, lactate level, presence of colon cancer, TBIL level, MAP, and CRP level were significant variables for mortality prediction. However, the categories of the dependent variable used in the model remain quite unbalanced (dead: 25 (12.7%) and alive: 172 (87.3%).

It should be considered that this unbalance may have negative effects on coefficient prediction and variable selection. It is recommended that the study be repeated with an evenly distributed dependent variable in the future.

Factors affect the length of hospitalization

Overall, 97 (53.3%) of the inpatients were women, and 85 (46.7%) were men. And it was observed that gender did not have a significant effect on the length of hospitalization (p=0.838). The length of hospitalization of patients with blood transfusion was observed to be 3-32 days (median:14 days), whereas the length of hospitalization in those who did not receive blood transfusion was 1-35 days (median:5 days). The length of hospitalization of the patients with a history of cancer diagnosis was 1-35 days (median:10 days), whereas the length of hospitalization for those without a cancer diagnosis was 1-30 days (median:6 days). The length of hospitalization of patients who underwent surgery for ileus was 2-35 days (median:13.5 days), whereas the length of hospitalization in patients who underwent no surgery was 1-21 days (median:4.5 days). The median length of hospitalization of patients with a lactate level of <14 mg/dL was 6 days and ranged between 1 and 35 days, whereas that of patients with a lactate level of >14 mg/dL was 9 days and ranged between 1 and 32 days. The length of hospitalization in patients with a creatinine level of <1.2 mg/dL was 1-35 days (median:7.25 days), whereas that in patients with a level of <1.2 mg/dL was 2-29 days (median:7.5 days).

In the quantitative descriptive statistical evaluation of hospitalized patients, the median age was found to be 64 years (min-max:19-97); however, it was not a significant factor (p=0.201). On evaluating the vital signs of hospitalized patients, the median temperature was 36.9°C (min-max:36°C-38.4°C) but it was not a significant factor (p=0.986). However, the median heart rate of the hospitalized patients was 92 beats/min (min-max:72-148 beats/min) and it was found to be a significant factor (p=0.030). Similarly, the median systolic arterial blood pressure value of hospitalized patients determined as 125 mmHg (min-max:70-150 mmHg) was concluded to be a significant factor (p=0.034). Further, the median albumin level of hospitalized patients 3.6±0.7 g/dL (min-max: 2-5.3 g/dL)) was found to be a significant factor (p<0.001). The median value of TBIL level in hospitalized patients was 0.8 mg/dL (min-max:0.2-7.2 mg/dL); it was found to be a significant factor (p=0.043). The median urea level of hospitalized patients (47 mg/dL (min-max:13-247 mg/dL)) was found to be a significant factor (p=0.003). Likewise, the median creatinine level.[1 mg/dL (min-max:0.2-11.6 mg/dL)] and median CRP level (3.3 mg/dL (minimum-maximum:0.2-53 mg/dL)) of the hospitalized patients were found to be a significant factors (p=0.012 and 0.002, respectively). Further, the median lactate level of the hospitalized patients was determined as 13 mg/dL (min-max:2-109 mg/dL); it was a significant factor (p=0.005). The results of statistical analysis affecting the length of hospitalization of the patients according to other laboratory parameters and their presence are presented in **Table 4**.

Table 3. ROC analysis results for mortality prediction

	AUC	P	Cutoff point	Sensitivity	Selectivity	Positive predictive value	Negative predictive value
MAP	0.788	<0.001	80	0.640	0.866	0.410	0.943
TBIL	0.700	<0.001	0.9	0.760	0.593	0.213	0.944
ROC	0.766	<0.001	3.7	0.880	0.599	0.242	0.972
Lactate	0.743	<0.001	18	0.720	0.733	0.281	0.947
Model	0.965	<0.001	0.588	0.800	1	1	0.972

MAP: Mean arterial pressure, TBIL: Total bilirubin (mg/dL), ROC: Reciever operator characteristics curve

Table 4. Quantitative descriptive statistics of hospitalized patients with ileus

	Mean (± SD)	Min	Max	R2	P
Age	65 (20.3)	19	97	0.009	0.201*
Temperature (°C)	36.9 (0.5)	36	38.4	<0.001	0.986
Heart rate (beats/min)	92 (14)	72	148	0.026	0.030*
SAP (mmHg)	125 (25)	70	150	0.025	0.034
DAP (mmHg)	70 (12)	40	95	0.008	0.221
MAP (mmHg)	90 (16.3)	50	113	0.017	0.084
HGB (g/dL)	12.5±2.1	6.9	19.6	0.017	0.081*
Hematocrit (%)	37.4±6.2	19.5	58.2	0.011	0.167
WBC (10^3/uL)	10.8 (6.7)	1.1	31.8	<0.001	0.938
PLT (10^3/uL)	281 (161.5)	70	881	<0.001	0.991
AST (U/L)	27.5 (22.3)	8	239	<0.001	0.783
ALT (U/L)	16 (12)	4	112	0.003	0.438
Total protein (g/dL)	6.7±1	4.2	9.5	0.004	0.369
Albumin (g/dL)	3.6±0.7	2	5.3	0.081	<0.001*
Total bilirubin (mg/dL)	0.8 (0.7)	0.2	7.2	0.022	0.043*
Urea (BUN) (mg/dL)	47 (37.5)	13	247	0.047	0.003*
Creatinine (mg/dL)	1.0 (0.7)	0.2	11.6	0.035	0.012*
Na (mmol/L)	136.5±4.6	123	151	<0.001	0.565
K (mmol/L)	4.2±0.7	2.1	5.6	<0.001	0.663
Cl (mmol/L)	101.3±5.2	83	116	<0.001	0.166*
CRP (mg/dL)	3.3 (8.3)	0.2	53	0.053	0.002*
ALP (U/L)	83.5 (43.3)	11	675	<0.001	0.448
GGT (U/L)	24 (24.5)	7	982	<0.001	0.780
Amylase (U/L)	48.5 (38)	4	489	<0.001	0.639
Lipase (U/L)	18 (19.3)	1	297	<0.001	0.362
Glucose (mg/dL)	119 (41)	55	358	<0.001	0.813
pH	7.4 (0.1)	7.2	7.56	<0.001	0.431
HCO_3 (mEq/L)	22 (6)	12	44	<0.001	0.457
PO_2 (mmHg)	96 (3)	37	99	<0.001	0.392
Lactate (mg/dL)	13 (10.3)	2	109	0.044	0.005*
Blood transfusion	0 (5)	0	42	0.261	<0.001

SAP: Systolic arterial pressure, DAP: Diastolic arterial pressure, MAP: Mean arterial pressure, HGB: Hemoglobin, WBC: White blood cell count, PLT: Platelet, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, BUN: Blood urea nitrogen, Na: Sodium, K: Potassium, Cl: Chlorine, CRP: C-reactive protein, ALP: Alkaline Phosphatase, GGT: Gamma glutamyl transferase, pH: pH of blood gas, HCO_3: Bicarbonate in blood gas, PO_2: Oxygen in blood gas, LACTATE: Value Checked in Blood Gas, * Indicates a significance difference at p<0.05.

Further statistical analyses were performed to determine the factors affecting the decision of whether patients require surgery following diagnosis. It was observed that 82 of 197 patients (41.6%) had undergone a surgery following diagnosis, whereas 115 (57.4%) of them had not undergone surgery. Of patients who underwent surgery, 43 were men and 39 were women. Of patients who did not undergo a surgery, 64 were men and 51 were women. The effect of gender on the operation status (i.e., operated vs. non-operated) of patients was not significant (p=0.655).

The mean age of the operated patients was 65±20 years, whereas that of the non-operated patients was 65±19.7 years; the effect of age on the operation status was not significant (p=0.266). It was determined that 56 (14.7%) of the operated patients and 73 (60.1%) of the non-operated patients had a history of abdominal surgery; its effect on the operation status was not significant (p=0.484).

Because the use of the length of hospitalization as the dependent variable provided discrete values and the linear regression assumptions (assuming normal distribution of errors) were not achieved, a logarithmic transformation was applied to the variable length of hospitalization to determine the factors affecting this variable. The model created by multiple linear regression analysis was significant (p<0.001) and explained the difference of 46.4% in the length of hospitalization (with logarithmic transformation). Based on the multiple linear regression analysis results shown in Table 10, the factors that can affect the length of hospitalization with 95% CI were a history of cancer diagnosis (p=0.005), creatinine level (p=0.005), blood transfusion status (p<0.001), and operation status following ileus (p<0.001). Although lactate level (p=0.066) was not significant, it was not excluded from the model owing to its positive contribution to the model. High R2 values in simple linear regression analysis showed that the factors blood transfusion status (R2=0.315) and post ileus status (R2=0.255) demonstrated the greatest effect on the length of hospitalization (**Table 5**). In addition, when the standardized coefficients in the multiple linear regression model were examined, it was determined that blood transfusion status (B=0.561) and post ileus status (B=0.533) were the most important factors that increased the length of hospitalization. Further, the presence of cancer.[R2=0.052; B=0.252) and increased creatinine level (R2=0.035; B=0.089) in a patient were the other important factors that increased the length of hospitalization. Increased lactate level (R2=0.044; B=0.007) also prolonged the length of hospitalization.

Table 5. Model for length of hospitalization in patients with ileus

	Coefficient prediction (B)	Standard error	P
Creatinine level	0.089	0.032	0.005
Lactate level	0.007	0.004	0.066
Blood transfusion status	0.561	0.098	<0.001
Surgery following ileus	0.533	0.094	<0.001
Presence of cancer	0.252	0.089	0.005

In terms of the laboratory findings that affect the operation status of patients, the mean total protein level of operated and non-operated patients was 6.5±1.0 g/dL and 6.9±1.0 g/dL, respectively, and its effect on the operation status was significant (p=0.006). Further, the mean albumin level of operated and non-operated patients was 3.4±0.6 g/dL and 3.7±0.7 g/dL, respectively; the effect of albumin level on the operation status was significant (p=0.002). The mean potassium level of operated and non-operated patients was 4.1 mmol/L and 4.4 mmol/L, respectively; its effect on the operation status was significant (p=0.042). The mean CRP level of operated and non-operated patients was 4.7 mg/dL and 2.6 mg/dL, respectively; the effect of CRP level on the operation status was significant (p=0.023).

Table 6. Multivariate logistic regression analysis results for operation status following diagnosis

	Coefficient prediction	Standard error	Odds ratio	95% Confidence interval		p
				Lower limit	Upper limit	
qSOFA (1)a	1.018	0.459	2.768	1.125	6.810	0.027
K level	-0.462	0.242	0.630	0.392	1.013	0.057
Na level	-0.080	0.035	0.923	0.862	0.989	0.023
Total protein level	-0.362	0.160	0.696	0.509	0.953	0.024

The Hosmer–Lemeshow test was used to determine the goodness of fit of the model; it was observed that the model fit was achieved in the final model (p=0.258). The results of multivariate logistic regression analysis for the operation status following diagnosis are shown in **Table 6.**

Patients with a qSOFA score of 1 have higher risk of requiring surgery than those with a score of 0.[odds ratio: 2.77 (1.13-6.81)] qSOFA score of 1 or higher causes a significant increase in the risk of requiring surgery (p=0.027). In addition, potassium, sodium, and total protein levels have a significant effect on the risk of requiring surgery following ileus (p=0.057, 0.023, and 0.024, respectively). An increase in potassium. [odds ratio: 0.630 (0.392-1.013)], sodium.[odds ratio: 0.923 (0.862-0.989)], and total protein.[odds ratio: 0.696 (0.509-0.953)] levels reduces the risk of requiring surgery.

DISCUSSION

The recent study findings revealed that 25 (12.7%) patients died and 172 (87.3%) survived during their 30-day follow-up period. In the study of Karabulut et al.[7], the mortality rate of the patient who underwent surgery due to ileus was 12.5%, whereas in the study of Çalışkan et al.[8], 4.1%. This variation was attributed to the small number of patients in that study and the difference in age groups. Based on various studies, mortality due to intestinal obstruction was found to be 20%-25% during the 1960s-1970s; however, currently, it has decreased to 3%-7%.[9]

The mean age of patients with ileus varies in the studies. It was 64.1 (19-97) years in our study. The high mean age observed in this study was considered attributable to the inclusion of an elderly population who were diagnosed with cancer in ED, had a history of surgery, experienced chronic diseases, and were followed up in our hospital. A significant effect of age on mortality was observed as a result of the analysis, and it was concluded that the increase in age increases the mortality risk (odds ratio=1.034, p=0.040).

In our study, models that can determine the 30-day mortality of patients diagnosed with ileus in ED were studied. In the literature review, although studies have evaluated the factors affecting mortality, no studies examining models were found. Analysis of the qSOFA score of inpatients revealed that this score significantly affected the length of hospitalization (p<0.001). It was observed that age of the hospitalized patients was not a significant factor (p=0.201).

According to the logistic regression model results, blood transfusion status, lactate level, presence of colon cancer, TBIL level, MAP, and CRP level were found to be significant variables for predicting mortality in our model. However, the categories of the dependent variable used in the model were quite unbalanced (dead: 25 and alive: 172). It should be considered that this situation may have a negative impact on coefficient prediction and variable selection. In the study by Uludağ et al.[10], it was found that male sex, age, presence of comorbid diseases, occurrence of intestinal necrosis, previous abdominal surgery, and malignancy increased the frequency of complications; the development of intestinal necrosis was a factor that increased mortality. In the study of Karabulut et al.[7], it was determined that the patient group with the highest mortality experienced colorectal cancers; hernia was the second most frequent malignancy.

According to the model generated in present study, factors affecting the operation status were the qSOFA score (p=0.027), potassium level (p=0.057), sodium level (p=0.023), and total protein level (p=0.024). A comparative analysis could not be performed because no model for the factors affecting the need for surgery among patients in ED was found in the literature. We expect our model to serve as an example for studies with larger patient groups and to help reduce the number of surgeries; we believe that the use of our model can reduce the cost by decreasing mortality and length of hospitalization.

There are some limitations of the recent study. First of all this study was designed and carried out as a single center format. So data could be supported more centered and comprehensive studies. The second one is demographic characteristics of the patients. In this study most of the patients have comorbid diseases, and isolated ileus cases were limited. It may affect the results.

CONCLUSION

We believe that the parameters obtained as a result of the study can be used in predicting the need for surgery, length of hospitalization, and mortality in patients diagnosed with ileus in ED. Further, these parameters can be used as a scoring system with additional comprehensive studies and will thus contribute to the literature.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by the clinical research ethics committee of Trakya university. Date: 07.05.2018, number: 08/02.

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article / Orijinal Araştırma

Patient Safety Attitudes of Nurses Working in Surgical Clinics: A Cross-Sectional Study

Cerrahi Kliniklerde Çalışan Hemşirelerin Hasta Güvenliği Tutumları: Kesitsel Bir Araştırma

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Abstract

Aim: This study conducted to investigate the attitudes of nurses working in surgical clinics towards patient safety.

Material and Method: The descriptive and cross-sectional study sample consisted of 100 nurses working at the surgical clinics of a hospital in the Marmara region of Turkey. The data were collected between March 2020 and June 2020 by using a Nurse Identification Form and The Safety Attitudes Questionnaire. Median, percentage distribution, independent t-test and analysis of variance (ANOVA) test were used for statistical evaluation. A written permission was obtained from the Scientific Ethics Board where the study was conducted for the investigation to be carried out.

Results: The mean total attitude score of the nurses included in the study was found 155.88±20.77. No statistically significant difference was found to exist between the mean total scores of the Safety Attitudes Questionnaire, and the variables of the nurses' gender, education level or place of work ($p > 0.05$). A statistically significant difference was found between the marital status of nurses, working position and the mean total score of the of the Safety Attitudes Questionnaire.

Conclusion: It was concluded from this study that nurses working in surgical units had a positive attitude toward patient safety. Nursing leaders should therefore endeavor to maintain nurses' work motivation and improving working conditions to maintain patient safety.

Keywords: Nurse, surgical clinics, nursing, patient safety, attitude

Öz

Amaç: Bu araştırma cerrahi kliniklerde çalışan hemşirelerin hasta güvenliğine yönelik tutumlarını araştırmak amacıyla yapılmıştır.

Gereç ve Yöntem: Tanımlayıcı ve kesitsel tipteki araştırma örneklemini Türkiye'nin Marmara bölgesindeki bir hastanenin cerrahi kliniklerinde çalışan 100 hemşire oluşturdu. Veriler Mart 2020 ile Haziran 2020 arasında Hemşire Tanıtım Formu ve Hasta Güvenliği Tutum Ölçeği kullanılarak toplanmıştır. İstatistiksel değerlendirme için medyan, yüzde dağılımı, bağımsız t testi ve varyans analizi (ANOVA) testi kullanıldı. Araştırmanın yapılabilmesi için araştırmanın yapıldığı Bilim Etik Kurulu'ndan yazılı izin alındı.

Bulgular: Araştırmaya dahil edilen hemşirelerin ölçek toplam puan ortalamaları 155.88±20.77 olarak bulundu. Hasta Güvenliği Tutum Ölçeği toplam puan ortalamaları ile hemşirelerin cinsiyet, eğitim düzeyi veya iş yeri değişkenleri arasında istatistiksel olarak anlamlı fark bulunmadı ($p > 0.05$). Hemşirelerin medeni durumu, çalışma pozisyonu ve Hasta Güvenliği Tutum Ölçeği toplam puan ortalamaları arasında istatistiksel olarak anlamlı fark bulundu.

Sonuç: Bu çalışmada cerrahi birimlerde çalışan hemşirelerin hasta güvenliğine yönelik olumlu tutuma sahip oldukları sonucuna varılmıştır. Hemşirelik liderleri, hasta güvenliğini sağlamak için hemşirelerin çalışma motivasyonunu korumaya ve çalışma koşullarını iyileştirmeye çalışmalıdır.

Anahtar Kelimeler: Hemşire, cerrahi klinikler, hemşirelik, hasta güvenliği, tutum

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INTRODUCTION

Patient safety is one of the most important issues in health care delivery. It is one of the basic patient rights for an individual to receive health care in a safe environment.[1,2] The World Health Organization (WHO) has defined patient safety as "the absence of preventable harm to a patient during the process of health care and reduction of risk of unnecessary harm associated with health care to an acceptable minimum".[3] Patient safety is the crucial aspect of quality in health services, and avoidance of medical errors at every stage of care by health care providers to prevent the harm that health care services may cause to individuals.[2] According to Robertson and Long[4], preventable medical errors in related to patient safety commonly included errors related to surgical medication, hospital infections, falls, communication problems and errors related to material use. Nurses play a key role in reducing medication errors, reducing infection rates, and ensuring safe transitions from the hospital to the home in hospital settings. Patient safety in nursing practise also mandates that a professional healthcare provider support the patient in obtaining optimal health while ensuring that all required safety measures are taken to avoid or minimise risk.[4,5]

One of the places where medical errors related to patient safety occur the most is surgery clinics.[2] In a retrospective study in which medical errors were observed in clinics, it was found that 43.6% of the preventable errors were made in the surgical department.[6] In the study conducted by Özata and Altunkan[7], in which they evaluated the types of medical errors in terms of internal and surgical clinics, it was determined that the wrong route of drug administration was higher in surgical clinics than in internal clinics. Surgical clinics are settings where interventional procedures are frequently performed and where the workload is considerable. As a result, errors may occur more frequently, and medical error tendencies are increasing as nurses working in surgical services perform under stress. A recent study by Karacabay et al.[7] found that most of nurses who working in surgical clinical faced medical errors during the clinical interventions. Increases in workload may also pose a risk to patient safety by reducing the nurse's ability to perceive and respond to clinical situations.[7-9] To determine medical errors in surgical clinics, identify interventions that may threaten patient safety, it is critical to examine the attitudes of the nurses working in these clinics. Determining the patient safety attitudes of nurses working in surgical clinics will enable the prediction of medical errors and the determination of the approaches to be developed to prevent them. Therefore, this study conducted to investigate the attitudes of nursing working in surgical clinics towards patient safety.

MATERIAL AND METHOD

Written permission was obtained by email from the authors of the Turkish validity and reliability study of the scale in order to conduct the research. This study was approved by Uludağ University Faculty of Medicine Clinical Research Ethics Committee (Date: 19.02.2020, Decision No: 2020-3/2), and from each of the nurses who voluntarily participated in the research. All the participants were provided verbal information about the study, and written informed consent was obtained from each participant. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design

This descriptive cross-sectional design study was conducted in surgical units of hospitals in the Marmara region of Turkey between March and June 2020.

Participant and Data Collection

The population of the study was 130 nurses employed in the surgical clinics of a large hospital in the Marmara region of Turkey. The research sample consisted of 100 nurses who were actively working in these units and who were willing to participate in the current study (Participation rate: %76.92).

Data were collected using with a Nurses' identification form and The Safety Attitudes Questionnaire.

Nurses' Identification Form

The form was prepared by the researchers and consisted of eight questions aimed at determining the participant nurses' sociodemographic and professional characteristics.

The Safety Attitudes Questionnaire (SAQ)

The scale was developed by Sexton et al.[10] with the basic aim of measuring patient safety attitudes of nursing. Turkish validity and reliability of the scale was performed by Baykal et al. (2010).[11] The scale consists of 46 items, structured as 5-point, Likert-type: (5)" I strongly disagree," (4)" I disagree," (3) "I have no opinion, " (2) "I agree, " and (1) "I strongly agree." The scale consisted of six subscales as Teamwork Climate, Safety Climate, Perceptions of Management, Job Satisfaction, Working Conditions, and Stress Recognition. The minimum score obtainable on the scale is 46 and the maximum is 230. The higher scores indicate that greater patient safety attitudes. In a previous study conducted in Turkey, the Cronbach's alpha was found to be 0.90 for the scale.[11] The Cronbach alpha coefficient in the current study was 0.92. After consenting to participate in the current study, data were collected through face-to-face interviews conducted with the participant nurses in their clinics. This process was taken into consideration in order to ensure that the duration of the research did not negatively impact upon the participants' working hours. The time taken to complete each questionnaire was approximately 15-20 minutes.

Statistical Analysis

In evaluating the collected research data, IBM's Statistical Package for Social Science (SPSS, Version 22.0) was employed. There was no data found to be missing from the current study. Continuous variables are presented as median (min–max), whilst categorical variables are described using frequencies and percentages. Shapiro-Wilk normality test was applied in order to examine whether or not the numerical data

were distributed normally. Since the data were found to be normally distributed, independent t-test and analysis of variance (ANOVA) test were used to compare the scores of the sociodemographic information of the nurses.

RESULTS

The mean age of the participant nurses included in the research was 36.85± 7.51 years. In addition, 20.0% worked in the general surgery, 80.0% held a bachelor's degree, 94.0% were female, and 68.0% were married. The mean length of time that they had worked in the surgical clinic was 8.55±7.55 years, they worked for 41.53±3.04 hours per week, and 93.0% of them working as a clinical nurse (**Table 1**).

Table 1. Distribution of nurses' descriptive characteristics (n= 100)

Characteristics	n	%
Age (Mean ± SD)	36.85± 7.51 years	
Weekly work time (Mean ± SD)	41.53 ± 3.4 hours	
Length of employment in surgical clinic (Mean ± SD)	8.55±7.55 years	
Gender		
Female	94	94.0
Male	6	6.0
Marital status		
Married	68	68.0
Single	32	32.0
Highest educational qualification		
Health Vocational High School	4	4.0
Associate degree	6	6.0
Bachelor's degree	80	80.0
Postgraduate degree	10	10.0
Service of work		
Thoracic surgery	10	10.0
Ophthalmology	7	7.0
General surgery	20	20.0
Ears, nose, throat, head and neck surgery	6	6.0
Pediatric surgery	12	12.0
Urology	9	9.0
Orthopedic surgery	11	11.0
Gynecological surgery	7	7.0
Working position		
Clinical nurse	93	93.0
Administrator nurse	7	7.0

The mean total score from the scale of the nurses included in the study was found to be 155.88±20.77, from the sub-dimension mean scores; teamwork climate was 44.61±6.97, safety climate was 19.14±3.38, perceptions of management was 25.65±5.00, job satisfaction was 34.05±7.73, working conditions was 17.47±2.85, stress recognition was 14.96±3.88 (**Table 2**).

Table 2. Mean scores of nurses' SAQ and sub-dimensions

SAQ and sub-dimensions	Mean±SD	Min-Max Score
Teamwork climate	44.61±6.97	12-57
Safety climate	19.14±3.38	5-25
Perceptions of management	25.65±5.00	7-35
Job satisfaction	34.05±7.73	11-53
Working conditions	17.47±2.85	6-25
Stress recognition	14.96±3.88	5-25
Total SAQ	155.88±20.77	46-199

SAQ: Nurses' Safety Attitudes Questionnaire

No statistically significant difference was found between the variable of the nurses' gender, education level or place of work and the mean total scores of the Safety Attitudes Questionnaire ($p > 0.05$). However, a statistically significant difference was found between the marital status of nurses, working position and the total score of the of the Safety Attitudes Questionnaire ($p < 0.05$) (**Table 3**).

DISCUSSION

This study was conducted with the aim of examining the patient safety attitudes of nurses working in surgical clinics. In this study, which was carried out on nurses who working in the surgical clinics of a university hospital in Turkey, the effect of variables including age, gender, educational status, marital status, place of work and working position on patient safety attitude is determined. The findings obtained from the current study are discussed against the findings of the existing literature.

According to the results obtained from this study; it was revealed that nurses had highest average among with the sub-dimensions of "working conditions" and "safety climate". It was determined that the lowest average was obtained to the "job satisfaction" sub-dimension. One of the essential factors influencing workforce productivity is job satisfaction. Preserving high level of job satisfaction among nurses is critical for achieving the appropriate high quality medical service.[12] Although these results revealed that the nurses were satisfied with the management actions related to safety aspects, the low level of job satisfaction might negatively affect the quality of the nurses' interventions. In study conducted with nurses working in surgical clinics, the motivation levels of nurses were examined, and it was reported that their willingness to work in the clinic may be related to their motivation.[12]

In the study by Özer et al.[13] on nurses working in a public hospital in Turkey, nurses had the highest average to the sub dimension of the working conditions and safety climate as in our study while the lowest average was given to the sub-dimension of stress recognition. Other studies found different findings in terms of sub-dimensions average of nurses.[13-15] The inconsistencies between the results of current study and previous studies could be related to differences in sample characteristics, sample size and the health institutions delivery system.

Several studies were examined some nursing characteristics to assess their relations with perception of patient safety. In the current study, it was revealed significant relations between marital status and working position and nurses' perception of patient safety. In contrast, some studies did not establish any significant relations between marital status or working position and scores of attitudes of patient safety.[13,16]. In the current study, it was obtained no significant relations between gender, education level or place of work and nurses' perception of patient safety.

Table 3. Distribution of nurses' some descriptive characteristics and mean scores of nurses' SAQ and sub-dimensions

Characteristics	Safety climate Mean ± SD	Teamwork climate Mean ± SD	Perceptions of management Mean ± SD	Job satisfaction Mean ± SD	Working conditions Mean ± SD	Stress recognition Mean ± SD	SAQ Mean ± SD
Gender							
Female	19.29±3.27	44.76±6.91	25.73±4.94	34.09±7.81	17.43±2.89	14.88±3.95	156.22±20.92
Male	16.66±4.36	42.00±8.07	24.33±6.28	33.33±6.91	18.00±2.28	16.16±2.48	150.50±19.05
Statistical test*	t = 1.869	t = 0.944	t = 0.663	t = 0.233	t = -0.467	t = -0.782	t = 0.653
p	p=0.650	p=0.347	p=0.509	p=0.816	p=0.641	p=0.436	p=0.506
Marital status							
Married	19.51±2.78	45.51±5.39	26.30±4.28	35.25±6.34	17.60±2.51	15.20±3.54	159.39±16.59
Single	18.34±4.33	42.68±9.32	24.25±6.10	31.50±9.71	17.18±3.49	14.43±4.55	148.40±26.41
Statistical test*	t = 1.627	t = 1.915	t = 1.946	t = 2.310	t = 0.677	t = 0.921	t = 2.535
p	p=0.107	p=0.058	p=0.054	p=0.023	p=0.500	p=0.359	p=0.036
Highest educational qualification							
Health Vocational High School	17.25±1.70	41.50±5.50	21.00±3.55	31.00±1.82	15.25±3.59	14.50±2.08	140.50±6.24
Associate degree	21.00±2.44	47.83±3.86	27.83±2.78	37.00±6.00	17.16±1.47	13.83±2.99	164.66±9.54
Bachelor's degree	19.10±3.42	44.38±7.25	25.53±4.98	33.96±7.88	17.55±2.92	15.28±3.80	155.82±21.98
Postgraduate degree	19.10±3.87	45.70±6.51	27.10±5.76	34.20±9.01	17.90±2.51	13.20±5.24	157.20±16.77
Statistical test**	F= 1.025	F= 0.795	F= 1.874	F= 0.495	F= 0.923	F= 1.060	F= 1.106
p	p=0.385	p=0.500	p=0.139	p=0.687	p=0.433	p=0.370	p=0.351
Service of work							
Thoracic surgery	19.00±1.49	44.50±2.87	24.30±3.46	33.30±15.04	18.10±1.28	14.80±2.97	154.00±15.04
Ophthalmology	21.33±4.27	46.66±7.31	27.33±5.46	36.50±10.36	17.83±2.48	13.00±5.93	162.66±18.01
General surgery	18.40±3.54	42.80±7.14	25.25±4.79	34.45±6.51	18.10±2.67	15.55±2.89	154.55±16.58
Ears, nose, throat, head and neck surgery	21.00±2.44	47.50±4.72	23.00±6.08	34.16±5.26	136.8±2.22	16.33±2.58	164.16±11.07
Pediatric surgery	20.33±1.77	48.75±4.57	28.16±4.38	37.58±6.20	16.16±2.28	14.58±3.80	165.58±12.39
Urology	20.66±2.34	47.33±3.57	26.77±3.63	35.55±7.41	16.63±1.56	12.77±5.44	161.55±12.81
Orthopedic surgery	18.54±2.69	42.18±4.23	22.36±3.61	32.18±5.94	18.44±1.81	14.54±2.54	146.45±14.18
Gynecological surgery	15.85±1.34	39.85±10.12	23.00±6.08	26.85±8.85	16.57±4.64	17.00±3.69	139.14±20.78
Statistical test**	F= 1.995	F= 1.737	F= 1.914	F= 1.319	F= 0.893	F= 0.994	F= 1.550
p	p=0.056	p=0.100	p=0.067	p=0.244	p=0.526	p=0.446	p=0.151
Working position							
Clinical nurse	19.01±3.44	44.18±6.95	25.29±4.86	33.44±7.54	17.57±2.90	15.15±3.77	154.66±20.75
Administrator nurse	20.62±2.19	49.50±5.58	29.75±5.03	41.00±6.80	16.25±1.90	12.75±4.77	169.87±15.98
Statistical test*	t = -1.298	t = -2.102	t = -2.248	t = -2.734	t = 1.264	t = 1.691	t = -2.018
P	p=0.197	p=0.038	p=0.015	p=0.007	p=0.209	p=0.094	p=0.046

SAQ: Nurses' Safety Attitudes Questionnaire; *: Independent t test; **: One-way Anova

In our study, it was determined that female nurses had higher scores than male nurses in sub-dimension of safety climate, teamwork climate, perceptions of management and job satisfaction. Female nurses had also higher scores in terms of total score of patient safety attitudes. According to these results, it may show that female nurses are more satisfied with their jobs, show a strong organisational commitment to safety, and are satisfied with managerial actions. In a study by Özer et al.[13], female nurses had higher scores than male nurses in all dimensions. The present study found that nurses who had associate degree of nurses had higher scores in total score of patient safety attitudes. Other studies found different relationships between educational level and total or sub-dimensions average of nurses. According to these results, it is recommended to review the training curriculum in all levels of nursing program in terms of improvements in attitude toward patient safety. When evaluating the total and subscale scores according to the working units of the nurses, results showed no difference. Nurses who working pediatric surgery had higher scores in total score of patient safety attitudes. A cross-sectional and descriptive study by Unver and Yenigun[17] investigated the attitudes of nurses working in surgical departments toward patient safety. The authors found that the patient safety culture was similar among the surgical units of the study hospital.

Limitations

The current study was conducted with nurses working in surgical clinics at a single health institution. Therefore, these conclusions cannot be generalized, although the current study's findings could be retested according to other contexts.

CONCLUSIONS

In conclusion of the current study, it was found that the nurses' attitudes regarding patient safety were moderate, but that their independent variables other than marital status and working position did not significantly affect their attitudes. Nursing and healthcare managers should consider the training and education of nurses with respect to the maintain of patient safety and to also improve the quality of nursing interventions. In line with these results, it is recommended that future studies be conducted with a larger sample, and to include nurses working in other clinical fields to potentially elicit results that consider a different perspective.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by Uludağ University Faculty of Medicine Clinical Research Ethics Committee (Date: 19.02.2020, Decision No: 2020-3/2).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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

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Orijinal Araştırma / Original Article

Relationship Between Myalgia and Laboratory Parameters in Hospitalized Patients with COVID-19

COVID-19 Tanılı Hospitalize Hastalarda Miyalji ve Laboratuvar Parametreleri Arasındaki İlişki

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Abstract

Aim: Myalgia is among the first and most common symptoms in patients with COVID-19. A limited number of studies have been found evaluating the frequency of myalgia and the laboratory findings associated with this condition. In this study, we aimed to evaluate the prevalence of myalgia and the relationship between myalgia and laboratory parameters in patients who were hospitalized due to COVID-19.

Material and Method: Three hundred fifty-eight patients with confirmed diagnoses of COVID-19 who were hospitalized between March 2020 and January 2021 were included in the study. The patients were divided into two groups according to the presence and absence of myalgia. Demographic characteristics, medical history, symptoms, clinical findings, and laboratory findings were evaluated retrospectively.

Results: A total of 358 patients, 192 (42.9%) females and 166 males, were included in the study. The mean age of the patients was 60.3±15.2 years. When the laboratory findings of the 166 patients with myalgia and 192 patients with no myalgia were compared, no difference was found between the groups in terms of white blood cell, neutrophil, lymphocyte, monocyte, and platelet counts, C-reactive protein, ferritin D-dimer, and troponin levels. However, creatine kinase (CK) levels were found to be significantly higher in the group with myalgia compared with the group without myalgia ($p<0.001$). In 92 (25.6%) of 358 patients, the CK level was found to be higher than 200 U/L. The median value for CK was 55 U/L in the group without myalgia and 221 U/L in the group with myalgia.

Conclusion: Myalgia is one of the most common symptoms in COVID-19. In patients with myalgia, the CK level is higher than in patients without myalgia. These patients should be closely monitored in terms of the risk of rhabdomyolysis because high CK is an indicator of muscle damage.

Keywords: COVID-19, myalgia, creatine kinase, rhabdomyolysis

Öz

Amaç: COVID-19 hastalarında miyalji ilk ve en yaygın semptomlar arasında yer almaktadır. Miyalji sıklığını ve bu durumla ilişkili laboratuar bulgularını değerlendiren sınırlı sayıda çalışmaya rastlanılmıştır. Bu çalışmada hastalığı daha şiddetli olması sebebiyle hospitalize takip edilen hastalarda miyalji sıklığını ve miyalji ile laboratuar parametreleri arasındaki ilişkiyi değerlendirmeyi amaçladık.

Gereç ve Yöntem: Bu çalışmaya Mart 2020- Ocak 2021 tarihleri arasında hastanede yatırılarak takip edilen COVID-19 tanısı doğrulanmış 358 hasta dahil edilmiştir. Miyalji varlığı ve yokluğuna göre hastalar 2 gruba ayrılmıştır. Demografik özellikler, tıbbi geçmiş, semptomlar, klinik bulgular ve laboratuvar bulguları retrospektif olarak değerlendirildi.

Bulgular: Bu çalışmaya 192'si (% 42,9) kadın, 166'sı erkek olmak üzere toplam 358 hasta dahil edildi. Hastaların yaş ortalaması 60,3±15,2 idi. Miyalji tarifleyen 166 hasta ve tariflemeyen 192 hastanın laboratuar bulguları karşılaştırıldığında, white blood cell (WBC), neutrophil, lymphocyte, monocyte, platelet değerleri, C reactive protein (CRP), ferritin D-dimer, troponin düzeyleri arasında gruplar arası fark saptanmadı. Ancak miyalji olan grupta olmayan gruba göre creatine kinase (CK) düzeyleri anlamlı yüksek saptandı ($p<0.001$). 358 hastanın 92'sinde (%25,6) CK düzeyi 200 U/L 'den yüksek saptanmıştır. CK için ortanca değer miyaljisi olmayan grupta 55 U/L iken miyaljisi olan grupta 221 U/L olarak elde edilmiştir.

Sonuç: COVID-19'da miyalji en sık gözlenen bulgulardan biridir. Miyalji tarifleyen hastalarda CK düzeyi miyalji olmayan hastalara göre yüksektir. CK yüksekliği kas hasarı göstergesi olduğundan bu hastalar rabdomiyoliz riski açısından yakın izlenmelidir.

Anahtar Kelimeler: COVID-19, kreatin kinaz, miyalji, rabdomiyoliz

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INTRODUCTION

The infection that was first detected in December 2019, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was named coronavirus 2019 (COVID-19) by the World Health Organization (WHO) and declared a pandemic. As of April 2021, COVID-19 has infected more than 153.1 million people in 216 countries and killed more than 3.2 million people worldwide.[1]

The clinical manifestations of patients infected with COVID-19 range from mild symptoms to severe pneumonia and multiorgan failure. Although COVID-19 specifically targets the respiratory system, neurologic symptoms may also frequently accompany.[2] These include central nervous system involvement such as encephalitis, acute disseminated encephalomyelitis (ADEM), encephalopathy, steroid-sensitive encephalopathy, posterior reversible encephalopathy syndrome (PRES), and meningitis, as well as peripheral findings such as hyposmia/agusia, ophthalmoparesis, facial paresis, and Guillain-Barre syndrome. Neuromuscular findings such as neuropathy, critical illness myopathy, myalgia, myositis, and rhabdomyolysis have also been described.[3]

Myalgia, in particular, may be among the first and most common symptoms. In a meta-analysis evaluating 1995 patients with COVID-19 from 10 countries, the prevalence of myalgia was found as 35.8%.[4] The presence and severity of myalgia can adversely affect activities of daily living and prevent patients from maintaining their quality of life during the illness.[5] In addition, studies are showing that the presence of myalgia is closely related to disease severity and respiratory distress.[6,7] A limited number of studies have been found evaluating the frequency of myalgia and the laboratory findings associated with this condition.

In this study, we aimed to evaluate the prevalence of myalgia and the relationship between myalgia and laboratory parameters in hospitalized patients.

MATERIAL AND METHOD

This study was a single-center retrospective study, and patients with confirmed COVID-19 diagnoses who were hospitalized between March 2020 and January 2021 were included. It was planned to include 400 patients in the study, but 358 patients were included in the study; 42 patients were excluded because they did not meet the inclusion criteria. The patients were divided into two groups according to the presence and absence of myalgia. All patients with COVID-19 in this study were diagnosed according to the WHO guideline.[8] The inclusion criteria were as follows: age over 18 years, positive SARS-CoV-2 real-time reverse transcription-polymerase chain reaction (rRT-PCR) in a nasopharyngeal swab, lung tomography compatible with viral pneumonia, and hospitalization. Patients with a history of malignancy, a history of rheumatologic disease, and patients transferred to the intensive care unit (ICU) due to the need for intensive care were not included in the study.

Demographic characteristics, medical history, comorbid diseases, initial symptoms, clinical, laboratory, and imaging findings of hospitalized patients were evaluated retrospectively from electronic medical records. Approval was obtained from the Local Ethics Committee (Protocol No: 2021-026) and the Ministry of Health for this study.

Statistical Analysis

Data were analyzed using the IBM Statistical Package for the Social Sciences V23 software (SPSS Inc.; Chicago, IL, USA). Normal distribution of the laboratory values according to the presence of myalgia was examined using the Kolmogorov-Smirnov test. The difference between the groups was examined using the Mann-Whitney U test because the quantitative data did not show normal distribution. The Chi-square test was used to analyze categorical data. The independent samples t-test was used to compare the ages. Univariate and multivariate binary logistic regression analyses were used to determine the risk factors affecting the presence of myalgia. The cut-off values for creatine kinase (CK) values in diagnosing myalgia were analyzed using receiver operating characteristics (ROC) curve analysis. The level of significance was accepted as $p<0.05$.

RESULTS

A total of 358 patients, 192 (42.9%) females and 166 males, were included in the study. The mean age of the patients was 60.3±15.2 years. The most common presenting symptom was fatigue (n=176, 49.1%), followed by myalgia, cough, fever, shortness of breath, and headache. The most common comorbidity in patients was hypertension (HT) with 31.2%, followed by diabetes mellitus (DM) with 29.6%, and asthma with 9.5%. Of the patients, 42 (11.7%) were smokers (**Table 1**).

Patients were grouped according to the presence of myalgia. Demographic characteristics and laboratory findings of 166 patients with myalgia and 192 patients with no myalgia were compared. No difference was found between the groups in terms of age, gender and comorbid diseases (**Table 2**). No difference was found between the groups with and without myalgia in terms of steroid use during hospitalization ($p = 0.078$). All patients included in the study were discharged, and the mean hospital stay was 8.1±3.52 days.

When the groups were compared in terms of laboratory findings, no difference was found between the groups in terms of white blood cell (WBC), neutrophil, lymphocyte, monocyte, and platelet counts, C reactive protein (CRP), ferritin D-dimer, and troponin levels. However, creatine kinase (CK) levels were found to be significantly higher in the group with myalgia compared to the group without myalgia ($p<0.001$) (**Table 2**).

Table 1. Demographic and Clinical Features

Characteristics	Results (n=358)	
	Mean± SD	Median (min-max)
Age (years)	60.3±15.2	61 (20-88)
	n	%
Sex		
Male	192	53.6
Female	166	46.4
Symptom at admission		
Cough	130	36.3
Fever	104	29
Myalgia	166	46.3
Fatigue	176	49.1
Headache	70	19.5
Dyspnoea	80	22.3
Loss of taste and smell	30	8.3
Diarrhea	14	3.9
Comorbid diseases		
Hypertension	118	31.2
Diabetes mellitus	112	29.6
Asthma	36	9.5
Chronic obstructive pulmonary disease (COPD)	26	7.2
Cardiovascular diseases	28	7.8
Other Diseases	36	10.1
Smoking	42	11.7
Discharge from the hospital	358	100
Steroid treatment during hospitalization	278	77.6
Length of stay (days), mean±SD (min-max)	8.1± 3.52	4-29

*Significant at 0.05 level; Chi-square test for categorical variables, Student's t-test for age. Abbreviations: SD, standard deviation.

In 92 (25.6%) of 358 patients, the CK level was found to be higher than 200 U/L. In patients describing myalgia, this rate was 31.9% (53/166). The median value for CK was 55 U/L in the group without myalgia and 221 U/L in the group with myalgia. The cut-off value for CK was 123.5 U/L and the area under the ROC curve (AUC) was determined as 88.5%. According to the cut-off value of 123.5 U/L, the sensitivity was 85.4%, the specificity was 87.9%, the positive predictive value (PPV) was 89.1%, the negative predictive value (NPV) was 83.9%, and the correct classification rate was 86.6%. The ROC curve analysis is presented in **Figure 1**.

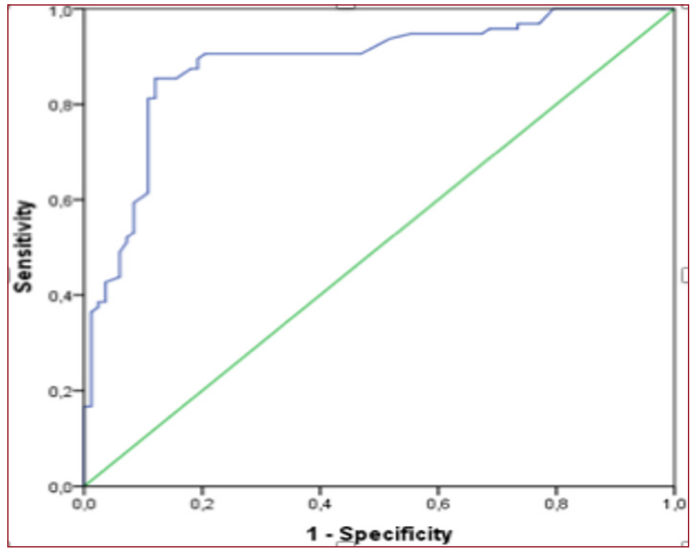

Figure 1. ROC curve analysis of CK value

Table 2. Comparison of demographic characteristics and laboratory parameters in the groups with and without myalgia

	With myalgia (n=166)		Without myalgia (n=192)		P
Age (Mean±SD)	60.4±14.8		60.3±15.7		0.960
Sex-Male, n (%)	104 (55.9)		110 (64)		0.302
Female	62 (36)		82 (44.1)		
Comorbid disease					
Hypertension	44 (26.5)		74 (38.5)		0.088
Diabetes mellitus	60 (36.1)		52 (27.1)		0.192
Asthma	20 (12)		16 (8.3)		0.243
Chronic obstructive pulmonary disease (COPD)	12 (7.2)		14 (7.3)		0.999
Cardiovascular diseases	14 (8.4)		12 (6.3)		0.785
Other Diseases	15 (9)		21 (10.9)		0.656
Smoking	20 (12)		22 (11.5)		0.862
Steroid treatment during hospitalization	122 (73.4)		156 (81.2)		0.078
Laboratory findings	**Mean±SD**	**Median (Min-Max)**	**Mean±SD**	**Median (Min-Max)**	
White blood cells, ×103/μL	7.8±3.1	6.8 (3.3 - 17.2)	7.5±3.3	6.7 (3.3 - 23.8)	0.379
Neutrophils, ×103/μL	5.7±3	4.9 (1.7 - 15.7)	5.4±2.9	4.4 (1.7 - 15.9)	0.456
Lymphocytes, ×103/μL	1.3±0.6	1.2 (0.3 - 2.8)	1.4±0.7	1.3 (0.3 - 5.6)	0.319
Monocytes, ×103/μL	0.9±2.9	0.5 (0.1 - 27)	1.5±6.8	0.5 (0.1 - 57)	0.706
Platelets ×103/μL	238.9±93.6	220 (97 -624)	239.9±88.5	212.5 (71 -581)	0.808
C-reactive protein (CRP), mg/L	91.8±119.6	56 (3.1 - 869)	65.3±59.3	49.5 (1.5 - 322)	0.292
Ferritin, ng/mL	322±304.6	197 (7.6-1500)	227±215.9	149 (7.6-1146)	0.061
D-dimer, ng/mL	1.4±4.1	0.4 (0.1-29.3)	0.9±2.7	0.3 (0 - 25.4)	0.115
Troponin, ng/mL	14.7±32.9	6.8 (1.3-255)	11.5±21.5	5.3 (0.4 - 175)	0.617
Creatine kinase (CK), U/L	77.6±80.9	55 (4 - 540)	364±459.8	221 (25 - 3550)	<0.001

*Significant at 0.05 level; Mann-Whitney U test for numerical variables; SD, standard deviation

Risk factors affecting the presence of myalgia were determined as a result of univariate analysis (**Table 3**). According to the analysis, the increase in the CK value indicated the presence of myalgia (p<0.001). No other variables were determined as risk factors (p>0.05). In multivariate analysis, the increase in CK value increased the presence of myalgia 1.016 times (p<0.001). No other variables were identified as risk factors for the presence of myalgia (**Table 3**).

DISCUSSION

In this study, among 358 patients who were hospitalized over a 10-month period and whose diagnoses of COVID-19 were confirmed clinically, and whose laboratory tests were evaluated, the frequency of myalgia was found as 46.3% (166/358). When the literature was reviewed, the prevalence of myalgia was found as 37.5% in a study in which 294 hospitalized patients with COVID-19 were evaluated,[9] and the prevalence of myalgia was found as 59% in a study examining the data of 417 patients with COVID-19 from 12 European hospitals.[10] In a study on the function of smell and taste in patients with COVID-19, myalgia was found in more than 50% of the patients.[11] The rate found in our study was similar to the literature consisting of large case series.

In a study conducted on 1420 European patients with COVID-19, myalgia was found at a higher rate in older patients compared with younger patients with prominent ear, nose, and throat symptoms.[12] However, when the groups with and without myalgia were compared in our study, no difference was found in terms of age.

The mechanism of muscle-joint pain in viral diseases has not yet been revealed, and when the possible myalgia mechanisms due to COVID-19 are evaluated, the angiotensin-converting enzyme 2 (ACE2) receptor used by the virus to enter the cell has been highlighted. It is thought that SARS-coV-2 may cause skeletal muscle damage via ACE2 receptors in muscles or due to proinflammatory cytokine increase.[13,14] It is thought that interferon (IFN)-γ, interleukin (IL)-1β, IL-6, IL-17, and tumor necrosis factor (TNF)-α, which are known to be elevated in patients with COVID-19, can directly induce muscle fiber proteolysis and decrease protein synthesis.[15] Satellite cells, thought to be important in the recovery process of COVID-19, are progenitor cells that directly contribute to muscle fiber growth. It is thought that IL-1β and TNF-α can inhibit the proliferation and differentiation of these cells, and IL-1β and IL-6 can induce muscle fibroblast activity and lead to fibrosis.[16,17]

There are a limited number of studies evaluating musculoskeletal symptoms and parameters related to infection and inflammation. In a meta-analysis performed by Cipollaro et al.[18] it was recommended to evaluate the relationship between musculoskeletal symptoms and inflammatory and infection-related parameters (IL-6, C-reactive protein) and laboratory findings. In a study evaluating laboratory parameters associated with myalgia and fatigue in patients with COVID-19, a higher lymphocyte count was observed in the group with myalgia compared with those without myalgia.[19] In our study, however, no difference was found between the groups with and without myalgia in terms of inflammatory parameters such as white blood cell counts, lymphocyte and neutrophil counts, and C-reactive protein.

Table 3. Logistic regression analysis results of risk factors affecting the presence of myalgia

	Univariate		Multivariate	
	OR (95% CI)	p	OR (95% CI)	p
Age	0.999 (0.98 - 1.019)	0.959	0.968 (0.929 - 1.008)	0.115
Sex, Female	2.250 (1.234 - 4.1059)	0.088	1.064 (0.369 - 3.066)	0.908
Sex, Male	1.476 (0.769 - 2.833)	0.242	1.964 (0.655 - 5.894)	0.229
Comorbid disease	1.007 (0.553 - 1.836)	0.981	0.449 (0.09 - 2.228)	0.327
Diabetes mellitus	0.656 (0.348 - 1.238)	0.193	0.863 (0.263 - 2.83)	0.808
Hypertension	1.739 (0.919 - 3.29)	0.089	3.849 (1.081 - 13.7)	0.057
Cardiovascular diseases	1.009 (0.325 - 3.132)	0.987	0.56 (0.094 - 3.349)	0.525
Asthma	0.724 (0.233 - 2.246)	0.576	0.907 (0.132 - 6.248)	0.921
COPD	1.182 (0.654 - 2.138)	0.580	0.53 (0.185 - 1.52)	0.238
Other additional diseases	1.269 (0.606 - 2.659)	0.527	1.251 (0.336 - 4.655)	0.738
White blood cell, $\times10^3/\mu L$	0.971 (0.886 - 1.064)	0.530	0.904 (0.594 - 1.376)	0.638
Neutrophil, $\times10^3/\mu L$	0.963 (0.871 - 1.065)	0.465	1.106 (0.687 - 1.783)	0.678
Lymphocyte , $\times10^3/\mu L$	1.278 (0.782 - 2.09)	0.328	0.757 (0.225 - 2.548)	0.653
Monocyte, $\times10^3/\mu L$	1.028 (0.959 - 1.101)	0.435	1.029 (0.874 - 1.211)	0.735
Platelet $\times10^3/\mu L$	1 (0.997 - 1.003)	0.941	0.998 (0.993 - 1.004)	0.561
CRP, mg/L	0.996 (0.992 - 1)	0.073	0.995 (0.987 - 1.003)	0.232
Ferritin, ng/mL	0.999 (0.997 - 1)	0.021	0.999 (0.997 - 1.001)	0.283
D-dimer, ng/ml	0.952 (0.863 - 1.05)	0.326	1.008 (0.898 - 1.133)	0.888
Troponin, ng/mL	0.996 (0.984 - 1.007)	0.441	0.998 (0.976 - 1.021)	0.887
Creatine kinase (CK), U/L	1.016 (1.011 - 1.021)	<0.001	1.016 (1.011 - 1.022)	<0.001

* Abbreviations: COPD, chronic obstructive pulmonary disease; CRP, C reactive protein; SD, standard deviation.

If striated muscle cells are damaged and membrane integrity changes, CK begins to rise in the blood after about 2-12 hours and decreases to baseline values within 3-5 days. In conclusion, high CK is closely related to the intensity of striated muscle damage.[20] In studies, an increase in CK levels has been reported, varying between 9.6% and 27%.[21,22] In our study, the CK level was found to be higher than 200 U/L in 92 (25.6%) of 358 patients. This rate was found to be 31.9% in patients describing myalgia. The high percentage of CK in our study can be explained by the inclusion of hospitalized patients with a more severe course, similar to the study of Pitscheider et al.[22] It was reported that patients with COVID-19 with very high CK levels developed rhabdomyolysis following viral myositis.[23] Patients with rhabdomyolysis can present with elevated CK levels without myalgia and typical COVID-19 symptoms. Although very high CK levels were detected in only three patients in our study, a rapid decrease was observed in the follow-up and renal functions remained within normal limits. Careful monitoring of kidney functions and muscle enzymes in SARS-CoV-2 infection, and closer follow-up of patients with myalgia and high CK for the development of rhabdomyolysis have been recommended.[23]

In another study involving 161 adults with COVID-19, 17 patients had CK levels higher than 190 U/L and 18 had myalgia. However, no association was found between CK levels and myalgia.[24] In another study investigating the relationship between myalgia and CK levels in patients with COVID-19, a significant relationship was found between high CK results and myalgia in 140 of 239 patients.[25] In our study, the median value for CK was 55 U/L in patients without myalgia and 221 U/L in patients with myalgia, and a significant increase was found in CK values in patients with myalgia symptoms compared with patients without myalgia symptoms. The cut-off value for CK was 123.5 U/L, with a sensitivity of 85.4% and a specificity of 87.9%.

The presence of muscle-joint pain has been associated with the severity of the disease. In one study, increased CK was observed in 40% of severely affected patients (for example, those admitted to the ICU) and only 24% of patients with mild disease.[26] In another study, it was reported that CK was higher in patients with abnormal findings on lung imaging.[26] It has been stated that CK can indicate the severity of the disease, but it is not a prognostic indicator. No comment can be made on this issue because patients who were followed in the ICU or transferred to the ICU during the follow-up were not included in our study.

It is known that corticosteroids used in the treatment of COVID-19 affect the musculoskeletal system negatively and it is recommended that patients who receive corticosteroid treatment should be monitored in terms of musculoskeletal symptoms.[27] There is no study in the literature searching the relation between steroid use and myalgia in patients with COVID-19. In our study, steroid use was evaluated in groups with and without myalgia. In our study, our patients were mostly followed up with moderate-to-severe pneumonia, so they were receiving corticosteroids. However, there was no difference between the groups with and without myalgia in terms of steroid use.

This study had some limitations such as being a single-center study, having a limited number of patients, being a retrospective study, not being able to perform advanced etiologic examinations such as electromyoneurography (ENMG) and muscle biopsy, not including patients in the ICU, and not being able to perform advanced laboratory investigations such as measuring IL levels. It is thought that more data are needed in this area to determine the contribution of processes involved in the pathogenesis of myalgia in patients with COVID-19, and multicenter clinical studies with a larger number of patients are needed.

CONCLUSION

Myalgia is one of the most common symptoms in COVID-19. The CK level in patients describing myalgia is higher than in patients without myalgia. These patients should be closely monitored in terms of the risk of rhabdomyolysis because high CK is an indicator of muscle damage. In addition, cohort studies focusing on the health of the musculoskeletal system of recovering patients will make an important contribution to more clearly determining the long-term consequences of this devastating disease..

ETHICAL DECLARATIONS

Ethics Committee Approval: Approval was obtained from the Local Ethics Committee (Protocol No: 2021-026) and the Ministry of Health for this study.

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article / Orijinal Araştırma

Evaluation of the Efficacy of Colistin Therapy with or without Loading Dose in the Treatment of Multi Drug Resistant Gram-negative Bacterial Infections

Çoklu İlaca Dirençli Gram-negatif Bakteriyel Enfeksiyonların Tedavisinde Yükleme Dozlu veya Yüklemesiz Kolistin Tedavisinin Etkinliğinin Değerlendirilmesi

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Abstract

Aim: Colistin (Col) is an agent used in the treatment of multidrug-resistant gram-negative (MDRGN) bacterial infections. This drug has been administered with a loading dose in recent years to provide rapid clinical response and therapeutic blood levels. In our study, we aimed to evaluate whether there is a relationship between the efficacy of the loading dose of Col treatment, mortality, microbiological clearance during treatment, nephrotoxicity, and neurotoxicity side effects for the treatment of MDRGN bacterial infections.

Material and Method: In this retrospective study, which included a control group, 6-years data was analyzed. Totally, 323 patients who received Col treatment with or without loading dose (LD) were included in the study. Patients were divided into two groups; I: without Col-LD regimen (those who were hospitalized in 2011-2014), II: with Col-LD regimen (those who were hospitalized in 2015-2017). Demographic characteristics such as age, gender, microbiological cultures, laboratory results, side effects, and mortality of the patients were evaluated.

Results: A statistically significant relationship was found between with Col-LD regimen and nephrotoxicity. However, it was determined that there was no statistically significant relationship between microbiological clearance without a Col-LD regimen. Nephrotoxicity was found to be decreased with the Col-LD regimen. Neurotoxicity was observed more frequently (3.7%) in with Col-LD regimen. Initial and final C-reactive protein (CRP) and procalcitonin (PCT) levels were statistically significantly lower in with Col-LD regimen.

Conclusion: It was found that with Col-LD regimen had a statistically significant effect on nephrotoxicity, neurotoxicity, and treatment outcome, but had no effect on microbiological clearance. In addition, with Col-LD regimen was effective in decreasing CRP and PCT values.

Keywords: Colistin, colistin loading therapy, multiple resistant, gram negative bacterial infection.

Öz

Amaç: Kolistin (Col), çok ilaca dirençli gram-negatif (MDRGN) bakteriyel enfeksiyonların tedavisinde kullanılan bir ajandır. Bu ilaç hızlı klinik yanıt ve terapötik kan seviyeleri sağlamak için son yıllarda yükleme dozu ile uygulanmaktadır. Çalışmamızda MDRGN bakteriyel enfeksiyonlarının tedavisinde Col tedavisinin yükleme dozunun etkinliği ile mortalite, tedavi sırasındaki mikrobiyolojik klirens, nefrotoksisite ve nörotoksisite yan etkileri arasında bir ilişki olup olmadığını değerlendirmeyi amaçladık.

Gereç ve Yöntem: Kontrol grubu içeren bu retrospektif çalışmada 6 yıllık veriler analiz edildi. Toplamda yükleme dozu (LD) olan veya olmayan Col tedavisi alan 323 hasta çalışmaya dahil edildi. Hastalar iki gruba ayrıldı; I: Col-LD rejimi almayanlar (2011-2014'te hastaneye yatırılanlar), II: Col-LD rejimi uygulananlar (2015-2017'de hastaneye yatırılanlar). Hastaların yaş, cinsiyet, mikrobiyolojik kültürler, laboratuvar sonuçları, yan etkiler ve mortalite gibi demografik özellikleri değerlendirildi.

Bulgular: Col-LD rejimi ile nefrotoksisite arasında istatistiksel olarak anlamlı bir ilişki bulundu. Ancak Col-LD rejimi olmadan mikrobiyolojik klirens arasında istatistiksel olarak anlamlı bir ilişki olmadığı belirlendi. Col-LD rejimi ile nefrotoksisitenin azaldığı bulundu. Nörotoksisite, Col-LD rejiminde daha sık (%3.7) gözlendi. İlk ve son C-reaktif protein (CRP) ve prokalsitonin (PCT) seviyeleri Col-LD rejiminde istatistiksel olarak anlamlı derecede düşüktü.

Sonuç: Col-LD rejiminin nefrotoksisite, nörotoksisite ve tedavi sonucu üzerinde istatistiksel olarak anlamlı bir etkiye sahip olduğu, ancak mikrobiyolojik klirens üzerinde hiçbir etkisinin olmadığı bulundu. Ayrıca Col-LD rejimi ile CRP ve PCT değerlerinin düşürülmesinde etkili olmuştur.

Anahtar Kelimeler: Kolistin, kolistin yükleme tedavisi, çoklu dirençli, gram negatif bakteriyel enfeksiyon.

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INTRODUCTION

The antimicrobial resistance of Gram-negative (GN) bacteria is globally threatening. The United States (USA) Center for Disease Control and Prevention (CDC) reported that amongst multidrug-resistant (MDR) GN, extended-spectrum beta-lactamase (ESBL) organisms, carbapenemase-producing *Enterobacteria*ceae, carbapenem-resistant Acinetobacter species, multi-resistant *Pseudomonas aeruginosa* are emerging and spreading globally.[1] Infections caused by MDR GN bacteria are among the main causes of mortality, especially for critically ill patients hospitalized in intensive care units (ICUs).[2] In addition, these infections are associated with increased healthcare costs and length of hospital stay.[1]

Colistin, also called polymyxin E, was used clinically in the late 1950s, but was shelved in the early 1970s due to its nephrotoxicity and neurotoxicity side effects and the presence of less toxic antibiotics.[3] Since there were no new antibiotics at a level to respond to the increasing antibiotic resistance, colistin was accepted as a last-resort treatment option.[4] On the other hand, the increasing use of colistin has resulted in the increasingly widespread use of colistin resistance worldwide, and the increasing trend of resistance rates has gradually reduced the treatment options of clinicians.[5]

The low post-antibiotic effect of colistin may cause unsuccessful clinical response and development of resistant subpopulations in critically ill patients due to insufficient dose.[6] In addition to providing therapeutic blood levels, the rapid and effective clinical response has been recommended to be given with a loading dose of colistin in recent years.[6,7] For these reasons, it has been reported that there is a higher clinical success with the loading dose, and no significant change is found in terms of side effects.[6,8]

This study aimed to evaluate whether there is a relationship between the efficacy of the loading dose of colistin treatment, mortality, microbiological clearance during treatment, nephrotoxicity, and neurotoxicity side effects for the treatment of MDRGN bacterial infections. And also, to reveal whether there is a change between reactive protein (CRP) and procalcitonin (PCT) levels were aimed.

MATERIAL AND METHOD

Study Design and Patients

In our retrospective study, which included a control group, 6-years data was analyzed. Since colistin treatment was given without loading before the year 2015 in our hospital, no additional intervention was made to differentiate the groups. Totally, 323 patients who received colistin treatment with a loading dose (LD) or without LD, were included in the study. Patients were divided into two groups; I: without Col-LD regimen (those who were hospitalized in 2011-2014), II: with Col-LD regimen (those who were hospitalized in 2015-2017). Demographic characteristics such as age, gender, microbiological cultures, laboratory results, side effects, and mortality of the patients were evaluated.

In those who did not take the loading dose, colistin was used intravenously (IV) 150 mg every 12 hours. In patients who received a loading dose; 300 mg colistin was administered as a maintenance dose of 150 mg 12 hours after IV loading dose, then 150 mg every 12 hours.

Definations

Microbiological clearance was defined as the absence of the same type of bacterial growth or control culture negativity which was taken after the 3rd and 7th days of colistin treatment. The clinical response was defined as a decrease in CRP and PCT values at the beginning and end of treatment.

RIFLE (Risk-Injury-Failure-Loss-Endstage) scoring (8) was used for nephrotoxicity determination. For neurotoxicity, it was accepted that neurotoxicity developed in patients who were evaluated as drug-induced neurotoxicity after neurology consultation due to symptoms during hospitalization.

Data Collection and Microbial Identification

The data of patients who received colistin therapy were retrospectively scanned on the Probel Patient Information Management System program. Demographic characteristics such as age, gender, microbiological cultures, laboratory results, side effects, and mortality of the patients were evaluated. Microbiological cultures were studied with the VITEC 2 Compact 15 (bioMérieux) device in the microbiology laboratory of our hospital and verified by E-test when necessary.

Statistical Analysis

IBM SPSS Statistics for Windows (v21.0; IBM Corp) program was used to analyze the data. After testing the frequency analysis, firstly, a normal distribution test was performed for all variables. Cross-tabular descriptive statistics analysis was performed to determine the composition of possible subgroups resulting from the variables within the whole. The Chi-square (Chi-Square) test was used to find the explanatory power of the independent variable on the dependent variables, and the Wilcoxon test, which is a Two-Related Sample Test, was used to determine the relationship between the variables. The Wilcoxon test was used to check whether there is a significant difference between the observed values of the two covariates that are related to each other. Variables, mean standard error, categorical variables were given as numbers or %. In all statistical comparisons, $p \leq 0,05$ values were considered statistically significant.

The study was conducted in accordance with the approval of Manisa Celal Bayar University Faculty of Medicine Clinical Research Ethics Committee (Date: 04.06.2016, Decision No: 32).

RESULTS

Totally, 323 patients, 123 (67.9%) of with LD regimen, 93 (65.5%) of the patients were without Col-LD regimen, were included in the study. 216 of them (66.9%) were male and the average age of the patients in the study group was 62.21±19.28, 112 (61.8%) of with Col-LD regimen and 84 (59.2%) of the group without Col-LD regimen were over 65 years old.

When the homogeneity of the variances of the group distributions is evaluated with the F Levene's test for both subgroups of the study in terms of age, gender and accompanying risk factors, underlying diseases; It was observed that age, gender, and presence of diabetes were homogeneous in both groups (p> 0.05). It was observed that there was no homogeneity between other dimensions such as neurological disorder, hematological malignancy, previously antibiotic usage, presence of a peripheral catheter, and mechanical ventilation (p <0.05) (**Table 1**).

Table 1. Homogeneity test of variances.

Variable	With Col-LD (n=181)	Without Col-LD (n=142)	p
Gender (M)	123	93	.721
Gender(F)	58	49	.364
>65 years	112	84	.628
Diabetes mellitus	33	21	.251
Neurological disorder	36	50	.002
Hematological malignancy	26	6	.002
Solid organ malignancy	29	20	.374
Previously antibiotic usage	168	141	.004
presence of peripheral catheter	168	142	.000
Presence of mechanical ventilation	95	99	.001

In the evaluation of a total of 323 patients included in the study according to their department; the majority of the patients (39.9%) were hospitalized in the Anesthesia Intensive Care Unit (ICU). The other clinics where the patients are hospitalized are surgical ICU (7.7%), internal medicine ICU (17%), hematology (4%), infectious diseases (1.5%), oncology (0.6%), other (Plastic surgery, Orthopedics) Cardiology, etc.) wards (29.1%). The most common reasons for using colistin therapy were NP / VAP (Nosocomial pneumonia / ventilator-associated pneumonia) (48.9%) and sepsis (25%). 99 (30.7%) of the patients who received colistin therapy had colistin monotherapy. It was found that 168 of them (52.0%) received their treatment in combination with at least one antibiotic. It was found that double or triple antibiotic combination therapy was used in 56 (17.3%) patients.

To examine the relationship between Col- LD regimen and mortality, a bivariate Chi-Square test (Chi-Square independence test) was used. The chi-square test value was found to be 4.944 (p=0.04). Since the p-value was less than 0.05 at the 95% confidence interval, a significant relationship was found between Col- LD regimen and mortality (**Table 2**).

A Chi-square test was used to examine the relationship between with Col-LD regimen and nephrotoxicity. According to the analysis results, the Chi-square value was calculated as 15,256 and the p-value was calculated as 0,000, and a statistically significant relationship was found between colistin loading and nephrotoxicity (**Table 3**). Nephrotoxicity was less common in the Col-LD regimen. The relationship between colistin loading and neurotoxicity was found to be significant as the type (p=0.011) (**Table 4**).

Table 2. Evaluation the relationship between mortality and colistin loading dose regimen.

			Non survivors	Survivors	Total
Col-LD	With	existing	103	78	181
		% Among those Col LD	56.9%	43.1%	100.0%
		Total %	31.9%	24.2%	56.0%
	Without	existing	92	50	142
		% Among those Col LD	64.8%	35.2%	100.0%
		Total %	28.5%	15.4%	44.0%
Total		existing	195	128	323
		% Among those Col LD	60.4%	39.6%	100.0%
		Total %	60.4%	39.6%	100.0%

Chi-Square test	Value	Sd	Full Significance (2 tails)
Pearson Chi-Square	4.944[a]	2	.004
Probability Ratio	5.241	2	.007
Linear Relationship	.907	1	.041

[a]0 cells (0,0%) have expected count less than 5. The minimum expected count is 9,67, *Chi-Square test

Table 3. Evaluation of the relationship between colistin loading dose, nephrotoxicity and neurotoxicity.

			nephrotoxicity		Total
			yes	no	
nephrotoxicity	Col- LD With	existing	79	102	181
		% Among those Col LD	43.6%	56.4%	100.0%
		Total %	24.5%	31.6%	56.0%
	Col- LD Without	existing	93	49	142
		% Among those Col LD	65.5%	34.5%	100.0%
		Total %	28.8%	15.2%	44.0%
	Total	existing	172	151	323
		% Among those Col LD	53.3%	46.7%	100.0%
		Total %	53.3%	46.7%	100.0%

			neurotoxicity		Total
			yes	no	
neurotoxicity	Col- LD With	existing	11	170	181
		% Among those Col LD	6.1%	93.9%	100%
		Total %	3.4%	52.6%	56.0%
	Col- LD Without	existing	1	141	142
		% Among those Col LD	0.7%	99.3%	100.0%
		Total %	0.3%	43.7%	44.0%
	Total	existing	12	311	323
		% Among those Col LD	3.7%	96.3%	100.0%
		Total %	3.7%	96.3%	100.0%

Chi-Square test	Value	Sd	Full Significance (2 tails)
Pearson Chi-Square	6,422[a]	1	.011
Probability Ratio	5,008	1	.025
Linear Relationship	7,739	1	.005

[a]0 cells (0,0%) have expected count less than 5. The minimum expected count is 5,28.

There was no statistically significant relationship between colistin loading and microbiological clerance (p=0,393) (**Table 4**).

Table 4. Evaluation of the relationship between colistin loading dose and microbiological clearance

			Col LD		Total
			without	with	
microbiological clearance	yes	existing	68	60	128
		Expected value	71.7	56.3	128.0
		among microbiological clearance existed %	53.1%	46.9%	100.0%
		% Among those Col LD	37.6%	42.3%	39.6%
	no	Gözlenen Değer	113	82	195
		Expected value	109.3	85.7	195.0
		among microbiological clearance existed %	57.9%	42.1%	100.0%
		% Among those Col LD	62.4%	57.7%	60.4%
Total		existing	181	142	323
		Expected value	181.0	142.0	323.0
		among microbiological clearance existed %	56.0%	44.0%	100.0%
		% Among those Col LD	100.0%	100.0%	100.0%

Chi-Square Test

	Value	Sd	Full Significance (2 tails)
Pearson Chi-Square	.730[a]	1	.393
Probability Ratio	.547	1	.459
Linear Relationship	.729	1	.393

[a]0 cells (0,0%) have expected count less than 5. The minimum expected count is 56,27

The Wilcoxon test is used to check whether there is a significant difference between the observed values of two covariates that are related to each other. In this study, the nonparametric Wilcoxon test was used to investigate whether there was a difference between the first and last CRP PCT values of patients loaded with colistin. The first and last C-reactive protein (CRP) values of 177 out of 323 patients (100 from those who were loaded and 77 from those who did not) could be reached in the study. In the evaluation of the difference between the first and last CRPs of the patients who were loaded with colistin, the mean of the first CRP was 41.83 and the standard deviation was 67.82. The average the last CRP of the patients who were loaded with colistin was 30.98, and the standard deviation was 48.62. As can be seen, there is a decrease in the CRP of the same patients with colistin loading. These findings show that the difference between the first CRP and the last CRP is significant at the 95% confidence interval (Z=-2.077, p <0.05). The average of the first CRP of the evaluation of the difference between the first and last CRPs of the patients without colistin loading is 31.61, the standard deviation is 39.39. The average the last CRP of the patients who cannot be loaded with colistin is 29.22, and the standard deviation is 36.02. As can be seen, there is a very low decrease in CRP of patients who are not loaded with colistin. However, these findings showed that the difference between CRP at the beginning of treatment and CRP at the end of treatment was not significant (Z=-1.953, p=0.06). In other words, while there was a great decrease in the CRP of the patients who were loaded with colistin, the decrease in the CRP of the patients who were not loaded was evaluated as significant. This shows that colistin loading has a high level of effect on CRP.

Table 5. Evaluation of CRP and procalcitonin values by Wilcoxon test.

		Results	n	mean	sd	Z	P
CRP	With	First CRP	100	41,83	67,82	-2,077	0,03
		Last CRP	100	30,98	48,62		
	Without	İlk CRP	77	31,61	39,39	-1,953	0,06
		Last CRP	77	29,22	36,02		
prokalsitonin	With	First PCT	49	15,52	27,82	-3,492	0,00
		Last PCT	49	5,90	17,63		
	Without	First PCT	51	31,61	24,82	-,682	0,49
		Last PCT	51	26,22	21,76		

Chi-Square Test

	Value	Sd	Full Significance (2 tails)
Pearson Chi-Square	15,256[a]	1	,000
Probability Ratio	14,391	1	,000
Linear Relationship	15,425	1	,000

[a]0 cells (0,0%) have expected count than 5. The minimum expected count is 66,38
* sd: standard deviation, CRP: C reactive protein.

The first and last PCT values of a total of 100 patients, 49 of whom were taken as a sample in the study, and 51 of whom were not loaded with colistin, were reached. In the evaluation of the difference between the first and last PCT of the patients who were loaded with colistin, the mean of the first PCT was 15.52 and the standard deviation was 27.82. The mean of the final PCT of the same patients is 5.90, the standard deviation is 17.63. As can be seen, a significant decrease is observed in the PCT of the same patients with colistin loading. It is seen that the difference between the first PCT and the last PCT of these patients is significant at a 95% confidence interval (Z=-3.492, p <0.05). The mean of the first PCT of the evaluation of the difference between the first and last PCTs of the patients without colistin loading is 31.61 and the standard deviation is 24.82. The average of the last PCT of the patients who cannot be loaded with colistin is 28.22, and the standard deviation is 22.76. As can be seen, although there is a decrease in the PCT of patients without colistin loading, it is seen that the difference between PCT at the beginning of treatment and PCT at the end of treatment is not statistically significant (Z=-1.953, p> 0.05).

DISCUSSION

In the GN bacterial infections that develop in hospitalized patients; since *Enterobacteria* (especially *Klebsiella spp.* and *Escherichia coli*), *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* are frequently encountered as causative agents and they can develop resistance, colistin continues to be one of the limited number of antibiotics we have.[9] Usage and doses of colistin may differ from country to country. The main reason for this is the existence of different formulations in the market and the dosage of some products using milligrams (mg) and others using international unit (IU) units. This situation may cause a difficult understanding of the pharmacokinetic and pharmacodynamic properties of colistin. Therefore, as new researches and studies are conducted, the colistin dose is

revised. It can be seen that this situation delays compliance with new dose recommendations and even causes different dosing administrations even in the same hospital. The optimal dose of colistin has not been defined. Although there are small descriptive studies evaluating the loading dose of colistin, very few of them included a control group. Because colistin is an old drug; It has not been developed with modern drug development procedures, and data to guide its use are limited.[10,11]

It has been hypothesized that the colistin loading dose is an improvement in treatment.[12] In the Sanford Antimicrobial Treatment Guideline published in November 2012, it was stated that colistin initially increased the efficacy of 5 mg/kg loading dose.[12,13] Recent guidelines recommend an IV loading dose of 300 mg of colistin base activity followed by a daily.[14] maintenance dose of 2 mg/mg target plasma concentration adjusted according to renal function However, it has been reported that more evidence is needed regarding the risks and benefits of the loading dose, and strategies are urgently needed.[10,11,15] In our hospital, colistin has been used with a loading dose since 2015.

Nazer et al.[11] reported that there are no randomized controlled studies among the clinical studies evaluating colistin, only two studies by Trifi[16] and Elefritz[17] were the control group. Also in the same review; It has been reported that there are only 3 studies on the pharmacokinetics of colistin.[3,10,18]

Pharmacokinetic modeling showed that the loading dose reduced the time to reach therapeutic concentrations in patients with infections due to CD-GN pathogens; however, clinical data on this dosing approach are limited.[3,19]

In the literature, it is stated that an important risk factor for the development of colistin resistance is the long-term use of colistin, but there is no clear information about the duration. As the most effective strategy to prevent colistin resistance formation, the use of colistin in combination with other antimicrobials has been recommended.[20] In our study, 99 (30.7%) of the patients used only colistin, while 168 (52.0%) received their treatment in combination with an antibiotic. The double or triple antibiotic combination was administered to 56 (17.3%) patients.

Meropenem was mostly used in the combination. Our patients with colistin resistance also received combined therapy. Because, in addition to reducing colistin resistance, combination therapies are recommended to increase the clinical efficacy of colistin.[21] One of the important reasons why colistin is preferred in combination therapy is that although the microorganism is only sensitive to colistin, the partial destruction of the bacterial cell wall as a result of the use of carbapenem and the increase in colistin activity on the cell membrane over time.[22] Studies have been conducted on its combined use with a carbapenem, tigecycline, sulbactam, and colistin, and it has been shown that combined therapy is more effective.[20] In our study, colistin monotherapy was found to be homogeneous in both groups. Abdelsalam et al.[23] reported that the combination of meropenem-colistin caused a significant decrease in mortality compared to cases where colistin was used alone; the association of combination therapy with significant hepatoxicity, nephrotoxicity, and neurotoxicity has not been established. In our study, no significant difference was found between colistin monotherapy and combination therapy in terms of clinical, biochemical response, and mortality side effects.

One concern with using the loading dose regimen of colistin is its potential for nephrotoxicity. Colistin-associated nephrotoxicity rates range from 6% to 48%.[19,24] Colistin-related nephrotoxicity is usually mild and returns to normal when the drug is discontinued. Most cases of nephrotoxicity shown in this study are mild and reversible. Patients receiving colistin therapy with hypertension or chronic kidney disease should be closely monitored and the administration of neurotoxic agents should be avoided in all patients whenever possible.[25]

Pogue et al.[26] retrospectively evaluated risk factors for the development of colistin-related nephrotoxicity using RIFLE criteria and reported that ARF developed in 43% of the patients, and ARF developed depending on the dose of colistin. Independent risk factors in multivariate analysis are; simultaneous use of rifampicin and concomitant administration of 3 or more nephrotoxic agents. Although Doshi et al.[27] had a 6.5 times higher risk of nephrotoxicity in critically ill patients who received at least 2 nephrotoxic agents, no relationship was found between total daily dose or total cumulative IV colistin dose and nephrotoxicity. Similarly, Elefritz et al.[17] reported that ARF developed in 50% of the patients in the pre-application period and 58% (p=0.59) in the post-application period, and there was no statistical difference. However, in the same study; it was thought that the nephrotoxicity rates were higher than previously reported in both groups, but this result was determined because only critically ill patients were evaluated in this study[17] Katip et al.[27] in the prospective cohort study; 102 cancer patients diagnosed with multiple resistant A.baumanii infections were evaluated. In this study; 75 patients were given a loading dose of colistin; There was no significant clinical and microbiological response in patients in the loading dose group or patients in the unloading dose group. However, nephrotoxicity according to RIFLE criteria developed in 38 (50.67%) patients in the loading dose group and 6 (22.22%) patients in the unloaded dose group (p=0.013). Independent predictors of nephrotoxicity were reported as colistin administration with a loading dose and age> 60 years.

Alp et al.[15] in their half experimental study; MDR A. baumannii infected ventilator-associated pneumonia patients who received and did not receive Col LD were compared. For those who take the loading dose; on the 14th day of treatment, the clinical improvement rate increased from 47.6% to 56.7%, but bacteriological clearance (80% versus 81%), ICU mortality (50% versus 54.2%), or the duration of stay in the ICU (median: 32 versus 36 days) found no significant difference. It was found

that mortality increased in patients with nephrotoxicity and age was the only risk factor for nephrotoxicity. Also; overall, he reported that nephrotoxicity was more severe in those receiving the loading dose according to the RIFLE criteria. Bellos et al.[28] eight (three prospective and five retrospective cohorts) studies consisting of 1115 patients were included in the meta-analysis study. In this study; it has been reported that administration of colistin loading dose does not change the clinical, treatment response, mortality, or nephrotoxicity risk (28). In our study; it was found that nephrotoxicity decreased with the LD (p=0.000).

The most common side effects of colistin therapy are nephrotoxicity and neurotoxicity. Although there are numerous case reports of nephrotoxicity, little literature information is available on the neurotoxicity of the drug. There are limited reports, especially on psychiatric side effects.[29-32] Dai et al.[33] reported that colistin administration (15 mg/kg/day for 7 days) can cause significant mitochondrial dysfunction in central and peripheral nerve tissues. In our study, neurotoxicity was observed more frequently (3.7%) in patients who received a loading dose of colistin. Since we only see neurotoxicity in 12 of all patients in total, it is thought that it will not be statistically significant to evaluate this statistically. In other studies, no data related to these were found.

Grégoire et al.[34] reported that colistin loading dose is associated with less exposure to subtherapeutic colistin concentration, thus limiting the emergence of bacterial resistance. Trifi et al.[16] reported that, the Col LD group had a higher maintenance dose than the group without Col LD, and it is difficult to evaluate the clinical treatment response in this study. In another study, no significant difference was found between patients with and without colistin loading. [16] In a study conducted on 30 patients with MDR-associated VIP infection, clinical and microbiological usefulness was not found.[15] Bellos et al.[28] reported that administration of Col LD was associated with higher microbiological response rates, especially in A. baumannii infections. Katip et al.[27] reported that there was no statistically significant clinical and microbiological difference between the patients in the loading dose group or the patients in the non-loading dose group. Also; In multivariate logistic regression analysis, it has been reported that the presence of septic shock is associated with both a poor clinical and microbiological response, rather than the application of colistin.[27] In our study; in terms of microbiological response, there was no significant relationship with colistin loading.

In the available literature; data on the relationship between colistin loading dose and CRP and PCT could not be reached. In our study, the decrease in CRP values above was found to be statistically significant between patients with and without colistin loading, whose initial and final CRP values could be reached. However, there was a very low decrease in CRP value without colistin loading and it was not statistically significant. Also again between the two groups; The written PCT value is given to the patient decreases and a significant decrease was not observed in the absence of loading.

CONCLUSION

Colistin loading therapy; It was found that its effect on nephrotoxicity, neurotoxicity and treatment outcome was statistically significant (95% CI, p <0.05), but it had no effect on microbiological response. In addition, when the loading dose of colistin therapy was compared with the load-free treatment; It was found to be effective in decreasing CRP and PCT values. There is a need for randomized controlled studies involving more patients evaluating colistin loading therapy.

Limitations of the study: Only the patient data belonging to our own hospital were evaluated retrospectively, so the number of cases is insufficient.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was conducted in accordance with the approval of Manisa Celal Bayar University Faculty of Medicine Clinical Research Ethics Committee (Date: 04.06.2016, Decision No: 32).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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Orijinal Araştırma / Original Article

How Important are Arterial Blood Gas Parameters for Severe Head Trauma in Children?

Çocuklarda Ağır Kafa Travmalarında Arter Kan Gazı Parametreleri Ne Kadar Önemlidir?

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Abstract

Aim: Our aim in this study is to consider the relationship between arterial blood gas (ABG) parameters and prognosis in severe head trauma in children.

Material and Method: Patients younger than 17 years of age with a Glasgow Coma Scale (GCS) of 8 and below with a history of head trauma were retrospectively analyzed. The relation of ABG parameters taken at the time of admission with mortality was examined. Independent sample T-test was used for pH, PCO_2 and base extract (BE) parameters in ABG, and Mann Whitney U test was used for PO_2 and lactate parameters.

Results: 48 patients were included in the study. Gender, age, admission blood pressure arterial values, GCS and Abbreviated Injury Scale (AIS) scores, length of stay in intensive care, and the surgical application did not differ statistically between the patient groups who died and survived. Ph and PO_2 values were lower, PCO_2, lactate, and BE values were found to be higher in the deceased patient group compared to the living patient group. The presence of acidosis, hypercapnia, or hyperlactatemia according to ABG values in the patient group who died was statistically significantly higher.

Conclusion: In our study, we found that the presence of acidosis, hypercapnia, and hyperlactatemia in patients according to ABG values increased mortality. We found that high PCO_2 and lactate values are specific indicators of poor prognosis. We think that PCO_2 and lactate measured in arterial blood may be biomarkers that can determine the prognosis.

Keywords: Traumatic brain injury, blood gas, child, lactate

Öz

Amaç: Bu çalışmadaki amacımız, çocuklarda şiddetli kafa travmasında arteriyel kan gazı (AKG) parametreleri ile prognoz arasındaki ilişkiyi ele almaktır.

Gereç ve Yöntem: Glasgow Koma Skalası (GKS) 8 ve altında olan ve kafa travması öyküsü olan 17 yaşından küçük hastalar geriye dönük olarak incelendi. Başvuru anında alınan AKG parametrelerinin mortalite ile olan ilişkisi incelendi. AKG'da pH, PCO_2 ve baz ekstraktı (BE) parametreleri için bağımsız örnek T- testi, PO_2 ve laktat parametreleri için ise Mann Whitney U testi kullanıldı.

Bulgular: Çalışmaya 48 hasta alındı. Ölen ve yaşayan hasta grupları arasında cinsiyet, yaş, başvuru tansiyon arter değerleri, GKS ve Kısaltılmış Yaralanma Skalası (AIS) skorları, yoğun bakımda kalış süresi ve cerrahi uygulama istatistiksel olarak farklılık göstermedi. Ölen hasta grubunda yaşayan hasta grubuna göre Ph ve PO_2 değerleri daha düşük, PCO_2, laktat ve BE değerleri daha yüksek bulundu. Ölen hasta grubunda AKG değerlerine göre asidoz, hiperkapni veya hiperlaktatemi varlığı istatistiksel olarak anlamlı derecede yüksekti.

Sonuç: Çalışmamızda AKG değerlerine göre hastalarda asidoz, hiperkapni ve hiperlaktatemi varlığının mortaliteyi artırdığını bulduk. Yüksek PCO_2 ve laktat değerlerinin kötü prognozu gösteren spesifik göstergeler olduğunu saptadık. Arter kanında ölçülen PCO_2 ve laktatın prognozu belirleyebilecek biyobelirteçler olabileceğini düşünüyoruz.

Anahtar Kelimeler: Travmatik beyin hasarı, kan gazı, çocuk, laktat

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INTRODUCTION

Traumatic injuries cause 50% of deaths under the age of 18.[1] Head trauma is the most common type of trauma seen in childhood and is responsible for 80% of trauma-related deaths.[2,3] Up to 80% of head traumas are mild (GCS 14), 10% are moderate (8 <GCS <14) and about 10% are severe (GCS ≤ 8).[4] Mortality rates, especially in patients with severe head trauma, are around 30% despite all treatments.[5]

The pathological processes that occur in the brain tissue after head trauma is called traumatic brain injury (TBI). TBI is defined as primary, and secondary according to its physiopathology. Primary TBH, with the effect of mechanical forces, occurs as a result of damage to neuronal and vascular tissue. After physical damage to cell membranes, neuronal edema, hypoperfusion, and neurotoxicity occur. Secondary TBI is defined as the result of processes such as ischemia, reperfusion, and hypoxia in the damaged areas of the brain after the first injury.[6] Treatment aims to correct intracranial and extracranial factors that cause secondary TBI.[7]

Knowing the biomarkers that affect the prognosis in head trauma makes it easier to identify patients who may be at risk, determine treatment methods, and predict the clinical outcome.[8] To determine the TBI level and prognosis after head trauma, studies with glucose, S100 calcium-binding protein B and thiol have shown that they can be biomarkers.[9-11]

Arterial blood gas (ABG) is an examination that provides an overview of acid-base balance and can show the oxygen need and requirements of tissues.[12] Studies on the effects of parameters in ABG on prognosis have been mostly conducted on cardiovascular and respiratory system diseases.[13-14] There is an insufficient number of studies on this subject in Head Trauma. Our aim in this study is to evaluate ABG parameters after severe head trauma in children, as well as to find their prognostic effects and their relationship with mortality.

MATERIAL AND METHOD

The study was conducted in accordance with the Declaration of Helsinki after the approval of the Kafkas University Medical Faculty Non-interventional Ethics Committee dated 25.06.2020 and numbered 2020/233. Patients between the ages of 0-17 who were admitted to the emergency service of the Kafkas University Health Research and Application Hospital after severe head trauma between 2014 and 2019, were examined.

Children with proven intracranial pathology with computed tomography and having a GCS score of 8 or less, were included in the study. Demographic characteristics of the patients, Blood Pressure Arterial (TA) measurements at the time of admission, GCS, AIS values, pH, PCO_2, PO_2, lactate and BE values in ABG, the number of days of hospitalization in the intensive care unit, and the data regarding the application of surgery, were all obtained by scanning the patient files. Patients with diabetes, electrolyte disturbances, chronic lung diseases, severe hypovolemia, anemia, and infections that may affect blood gas results, as well as severe multiple trauma (thoracic, abdominal organ injuries, major bone fractures, and cardiac injuries) accompanying head trauma, were excluded from the study.

In ABG parameters, pH: 7.35-7.45, PaO_2: 80-100 mmHg, $PaCO_2$: 35-45 mmHg, lactate level up to 2 mmol/L and BE: up to±3 mmol/L were taken as normal values.[15] In analyzing ABG data, the"Medcalc: Acid-base Calculator" calculation software was used. Ph<7.35 value was defined as acidosis, PaO_2 <80 mmHg value as hypoxia, $PaCO_2$> 45 mmHg value hypercapnia, lactate> 2 mmol/L value hyperlactatemia and BE ≥±3mEq/L values as base deficit.

Statistical Analysis

The data obtained were analyzed with the IBM SPSS Statistics 22 program. Quantitative data were calculated as mean±standard deviation. Categorical variables were presented as numbers and percentages. Statistically, the Chi-square test was used in the analysis of categorical variables. The Shapiro Wilk test was used to find the quantitative values showing homogeneous distribution. The independent sample T-test was used for the analysis of the parameters showing homogeneous distribution among the quantitative variables, and the Mann Whitney U test was used for the analysis of the parameters not showing homogeneous distribution. ROC Curve (receiver process characteristic curve) analysis was performed for ABG parameters. P <0.05 was considered significant in all statistical tests.

RESULTS

In our study, the data of a total of 48 patients were examined. The most common intracranial pathologies were intracerebral hematoma (22.9%), subdural hematoma (16.6%), and traumatic subarachnoid hemorrhage (14.5%), respectively (**Figure 1**). There were 16 (33.3%) female patients, and 32 (66.6%) male patients, according to their gender. No statistically significant difference was found between the patient groups who died and survived in terms of gender and surgical application in **Table 1.** The mortality rate among all patients was 35.41%.

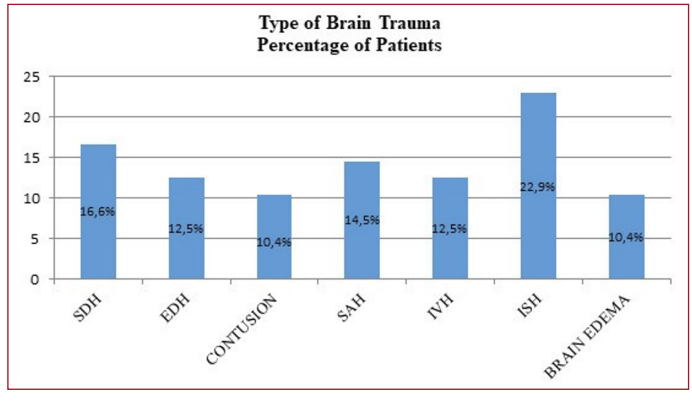

Figure 1. Type of brain trauma percentage of patients
(SDH: Subdural hematoma (8), EDH: Epidural hematoma (6), Contusion (5), SAH: Subarachnoid hemorrhage (7), IVH: Intraventricular hemorrhage (6), ICH: Intracerebral hemorrhage (11), Brain Edema (5))

Table 1. Demographic and clinical data

	All (n=48)	Exitus(n=17)	Surviving (n=31)	p value
Boys	32 (66.7%)	13 (40.6%)	19 (59.4%)	0.350
Girls	16 (33.3%)	4 (25%)	12 (75%)	
Intracranial Operation				
Yes	14 (29.2%)	6 (42.9%)	8 (57.1%)	0.478
No	34 (74.8%)	11 (32.4%)	23 (67.6%)	

The mean age of the patients included in the study was 7.56±4.28 years. The mean age of the deceased patient group was 6.29±4.57 years and the average age of the surviving patient group was 8.25±4.02 years. No statistically significant difference was found between the mean age, TA values measured at hospital admission, several days of intensive care hospitalization, GCS and AIS values, of the patient groups who died and survived (**Table 2**).

It was observed that the mean values of Ph, PO_2 were lower, the mean values of PCO_2, lactate, and BE were higher in the patient group who died, compared to the living patient group, and the difference between the groups was found to be statistically significant (p <0.05) in **Table 3**.

Table 2. T test results of the difference in Age, GCS, AIS, mean TA and IC days between the fatal and surviving cases

	Groups	n	$\bar{x}$	Ss	sd	t	p
Age	Exitus	17	6.294	4.579	29.593	1.482	.149
	Surviving	31	8.258	4.024			
GCS	Exitus	17	5.941	1.390	29.187	1.677	.104
	Surviving	31	6.612	1.202			
AIS	Exitus	17	17.647	6.918	31.928	0.156	.877
	Surviving	31	17.967	6.645			
TA	Exitus	17	108.529	12.344	31.657	0.093	.926
	Surviving	31	108.871	11.740			
Hospitalized days to ICU	Exitus	17	5.470	3.299	28.714	1.516	.140
	Surviving	31	6.903	2.797			

(GCS: Glasgow Coma Scales, AIS: Abbreviated Injury Scale, TA: Tension Arterial, ICU: Intensive Care Units)

Table 3. Proportions and p values of ABG results in living and deceased patient groups

	All	Exitus (n=17)	Surviving (n=31)	OR	%95 CI	p value
Acidosis						
Yes	26 54.2%	14 29.2%	12 25.2%	7.389	1.748-31.225	0.004
No	22 45.8%	3 6.3%	19 39.6%			
Hypoxia						
Yes	17 35.4%	8 16.7%	9 18.8%	2.173	0.636-7.420	0.212
No	31 64.6%	9 18.8%	22 45.8%			
Hypercapnia						
Yes	21 43.8%	13 27.1%	8 16.7%	9.344	2.352-37.123	0.001
No	27 56.3%	4 8.3%	23 47.9%			
Hyperlactataemia						
Yes	19 39.6%	14 29.2%	5 10.4%	24.267	5.039-116.865	0.000
No	29 60.4%	3 6.3%	26 54.2%			
BD						
Yes	10 20.8%	6 12.5%	4 22.9%	3.682	.867-15.640	0.068
No	38 79.2%	4 8.3%	27 56.3%			

(BD: Base Deficit, OR: Odds Ratio)

According to ABG values, 14 (53.8%) of 26 patients with acidosis, 13 (61.9%) of 22 patients with hypercapnia, and 14 (73.7%) of 19 patients with hyperlactatemia died. Acidosis, hypercapnia, and hyperlactatemia were higher in the patient group who died, and this difference was statistically significant (p <0.05). In our study, 8 (47.1%) of 17 patients with hypoxia and 6 (60.0%) of 10 patients with BE (20.8%) died. The presence of hypoxia and BE did not show a statistically significant difference between the groups who died and survived (p> 0.05) (**Table 4**).

Table 4. Average values in ABG

	All	Exitus	Surviving	P value
Ph	7.56±0.13	7.15±0.12	7.35±0.08	0.00
PO_2 (mmHg)	81.66±15.38	71.17±17.12	87.41±10.86	0.02
PCO_2 (mmHg)	40.89±8.03	49.29±5.59	36.29±4.75	0.00
Lactate (mmol/L)	3.54±2.52	6.25±2.05	2.06±1.12	0.00
BD (mmol/L)	2.52±1.56	3.75±1.07	1.85±1.36	0.00

By performing ROC analysis, sensitivity, specificity, 95% confidence interval of sensitivity, 95% confidence interval (CI) of specificity, 95% confidence interval of AUC, and AUC were examined in terms of mortality of parameters measured in ABG. According to the ROC analysis results, AUC values for Ph, PCO_2, and lactate were above 0.500. (**Figure 2**), (**Table 5**). We obtained significant results for PCO_2 and lactate in the analysis performed to find out at what values each of Ph, PCO_2, and lactate is associated with mortality. For PCO_2, the sensitivity of 49 mmHg and above for mortality was 58.8%; the specificity of 96.8% and for lactate above 4.5 mmol/L, the sensitivity for mortality was 82.4%: we found that its specificity was 93.6%.

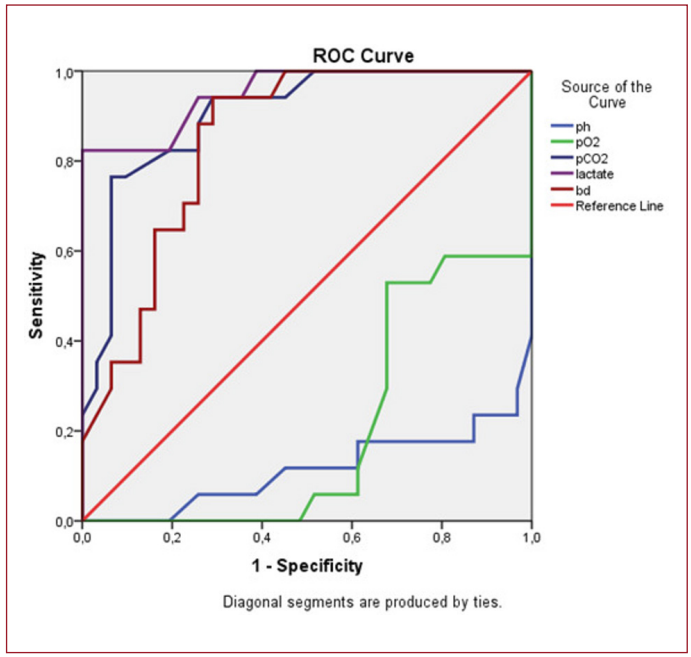

Figure 2. ROC curve for the values of ABG parameters

Table 5. AUC values of ABG parameters in patients who died

Area Under the Curve					
Test Result Variable(s)	Area	Std. Errora	Asymptotic Sig.b	Asymptotic 95% CI	
				Lower Bound	Upper Bound
PH	0.114	0.058	0.000	0.000	0.228
PO_2 (mm Hg)	0.203	0.064	0.001	0.077	0.329
PCO_2 (mm Hg)	0.954	0.027	0.000	0.900	1.000
Lactate (mmol/L)	0.952	0.030	0.000	0.892	1.000
BD (mmol/L)	0.847	0.054	0.000	0.741	0.954

The test result variable(s): ph, PO_2, PCO_2, lactate, be has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased. a. Under the nonparametric assumption b. Null hypothesis: true area=0.5

For the simplest in-group and between-group comparisons, at alpha=0.05, the sample size needed for the effect value determined for a statistical power of 0.50 is approximately n=46. Within the scope of this study, the sample size is above the sufficient number for the study. The Cohen's d scores of the power analysis performed for all quantitative values resulted above 0.90.

DISCUSSION

TBI after head trauma is one of the main causes of morbidity and mortality in the pediatric age group.[16] Since brain development continues in children, axonal myelination is not fully formed and brain tissue has a higher water content than adults. While focal damage is frequently seen in adults after head trauma, this is common damage in children. Although children after TBI have a higher survival rate than adults, sequelae are more devastating in children.[17]

Acidosis may cause neural death by disrupting acid-base homeostasis in brain tissue.[18] Therefore, the presence of acidosis has been accepted as an important indicator of morbidity and mortality.[19] Kushi stated that jugular venous blood pH levels are useful as an early prognostic indicator in the evaluation of neurological function in patients with TBI.[20] In our study, the mean pH value was 7.15 in the patients who died and 7.35 in the survivors, and the presence of acidosis in the patients who died was statistically significantly higher, which shows us that acidosis is an important indicator for mortality.

There are studies on the increasing effect of hypoxia after head trauma on secondary brain injury.[21] Adequate oxygenation is important to reduce brain damage, with or without surgery. Rapid intubation and mechanical ventilation are recommended to achieve this.[22] In children with severe head trauma with oxygen saturation <90% or PaO_2 <60 mmHg, the importance of correcting hypoxia and increasing cerebral perfusion pressure was initially mentioned in the literature.[23,24] Studies showing that the presence of hypoxia after head trauma negatively affects the prognosis are common.[25-27] But some studies have stated that hypoxia is not seen as a factor affecting poor prognosis.[28,29] Although one study conducted on patients with severe head trauma indicated that those with normal PO_2 levels showed a better prognosis, no statistically significant result was found.[30] In our study, PO_2 values were lower in patients who died, but the presence of hypoxia did not show a statistically significant difference between the groups and was not seen as a factor affecting prognosis.

Since it is known that low PCO_2 levels in the blood in patients with severe head trauma increase blood flow and volume through cerebral vasodilation, it is important to bring PCO_2 to normal levels as soon as possible.[31] Dumont studied 65 adult patients with a severe head injury to determine the effect of PCO_2 levels on mortality: it was reported that the survival rate in patients with normocapnia was better than in patients with hypercapnia, and stated that blood PCO_2 levels could be used as a prognostic biomarker.[32] In addition, Rahimi et al. reported that there was no relationship between blood PCO_2 levels and mortality in children with severe head trauma.[28] In our study, blood PCO_2 mean values and the presence of hypercapnia were statistically significantly higher in the group of patients who died. In the ROC analysis, it was found that PCO_2 values of 49 mmHg and above in arterial blood had 58.8% sensitivity for mortality. Our study showed that the presence of hypercapnia negatively affects the prognosis and increases mortality.

Lactate is a by-product of anaerobic metabolism, and blood lactate level also reflects the degree of tissue hypoperfusion and hypoxia.[8] There are studies with varying results about the role of lactate levels in brain damage. Some studies indicate that high lactate levels in the blood increase the use of lactate as cerebral energy and this protects cerebral glucose in the damaged brain.[33,34] It has been reported that with the increase of lactate level in the blood, vasodilation occurs in the cerebral vessels, and cerebral blood flow increases and this situation has a neuroprotective effect on cerebral cell metabolism.[35] On the other hand, studies are reporting that brain damage and mortality increase with impaired cerebral blood flow regulation in cases where lactate levels in the blood are too high.[36-38] Therefore, the role of lactate in TBI is not clear yet. Although Ramanathan et al. and Shah et al. reported that blood lactate levels were high in children after trauma, they did not address the relationship between lactate and prognosis.[39,40] In our study, the mean blood lactate values and the presence of hyperlactatemia were statistically significantly higher in the patient group who died. In the results of ROC analysis, it was found that lactate values of 4.5 mmol/L and above in ABG had 82.4% sensitivity for mortality.

In patients with general body trauma, BE has been reported as an important indicator of tissue perfusion and hypoxia and blood BE values have been reported to be a prognostic biomarker in such traumas.[41,42] There is an insufficient number of clinical studies regarding the effect of blood BE values on brain injury after head trauma. In our study, although blood BE values were high in the patient group who died, they did not give statistically significant results in terms of mortality.

Limitations

Our study has some limitations, the first of which is that our patient population was small. The other limitation is that it is a retrospective study. In addition, patients with multiple trauma accompanying severe head injuries were excluded from the study. Finally, there is an arterial condition for blood gas and venous blood gas was not accepted in the sample.

CONCLUSION

It is very important to identify and measure some prognostic biomarkers beforehand to prevent secondary brain damage. ABG measurement is an advantageous method with its widespread use and rapid results. Our study showed that the presence of acidosis, hypercapnia, and hyperlactatemia according to ABG values, are associated with poor prognosis in children with severe head trauma, and their presence increases mortality. Our study has shown that PCO_2 and lactate levels in ABG can be a biomarker for prognosis

ETHICAL DECLARATIONS

Ethics Committee Approval: Approval of the Kafkas University Medical Faculty Non-interventional Ethic Committee dated 25.06.2020 and numbered 2020/233.

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Orijinal Araştırma / Original Article

Prevalence of Enchondromas of the Hand in Adults as Incidental Findings on Magnetic Resonance Imaging

Erişkinlerde Başka Sebeplerden Ötürü Çekilen Manyetik Rezonans Görüntülemede Saptanan El Enkondromlarının Prevalansı

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Abstract

Purpose: To determine the prevalence of enchondromas (EC) in adults as incidental findings in the long bones of the upper extremities and the bones of the hand on magnetic resonance imaging (MRI).

Material and Method: A retrospective review of upper extremity MRI scans for the presence of incidental EC in patients older than 18 years was performed. EC location, size, and appearance were defined. Age, gender, MRI region, side, most common symptom, eccentric or central location in the bone, affected finger, presence of biopsy, presence of trauma history,and size of enchondroma were evaluated.

Results: A total of 9713 upper extremity MRIs were evaluated. In our study, the prevalence of EC in the entire upper extremity was 1.2% with MRIs that performed for upper extremity bones only. EC was most commonly seen in MR imaging of the hand. The proximal phalanx was the most commonly affected bone. Often presentin the third and fourth decades of life and the ulnar side of long bones were affected. In our study, the overall prevalence of hand EC was 4.8%. While the incidence of hand enchondromas was 5.8% in females, it was 4.1% in males. The incidence of enchondromas in the hand was approximately 5.77 times higher than in the shoulder.

Conclusion: This study suggests that with the prevalence of EC, as determined by MR imaging, the hand should continue to be considered the most common site for enchondromas.

Keywords: Prevalence of enchondromas, hand, incidental findings, upper extremities, magnetic resonance imaging

Öz

Amaç: Manyetik rezonans görüntülemede (MRG) üst ekstremite uzun kemikleri ve el kemiklerinde tesadüfi bulgular olarak erişkinlerde enkondrom (EK) prevalansını belirlemek.

Gereç ve Yöntem: 18 yaşından büyük hastalarda tesadüfi EC varlığı için üst ekstremite MRG taramalarının retrospektif bir incelemesi yapıldı. EC konumu, boyutu ve görünümü tanımlandı. Yaş, cinsiyet, MRG bölgesi, taraf, en sık görülen semptom, kemikte eksantrik veya santral yerleşim, etkilenen parmak, biyopsi varlığı, travma öyküsü varlığı ve enkondrom boyutu değerlendirildi.

Bulgular: Toplam 9713 üst ekstremite MRG'si değerlendirildi. Çalışmamızda sadece üst ekstremite kemikleri için yapılan MRG'lerde tüm üst ekstremitede EC prevalansı %1.2 idi. EC en sık elin MR görüntülemesinde görüldü. Proksimal falanks en sık etkilenen kemikti. Genellikle yaşamın üçüncü ve dördüncü dekatlarında ortaya çıkar ve uzun kemiklerin ulnar tarafı etkilenir. Çalışmamızda el EC'nin genel prevalansı %4.8 idi. El enkondromlarının insidansı kadınlarda %5,8 iken erkeklerde %4,1 idi. Eldeki enkondrom insidansı omuzdakinden yaklaşık 5.77 kat daha fazlaydı.

Sonuç: Bu çalışma, MR görüntüleme ile belirlenen EC prevalansı ile birlikte, elin enkondromlar için en yaygın bölge olarak düşünülmeye devam etmesi gerektiğini düşündürmektedir.

Anahtar Kelimeler: Enkondrom prevelansı, el, kısa tubuler kemik, üst ekstremite, MR

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INTRODUCTION

Enchondromas (EC) are generally solitary, inactive, and asymptomatic benign cartilage neoplasms occurring in the bone marrow.[1] According to classic information based on radiographs, EC occurs most frequently in the hand.[2,3] The World Health Organisation's classification of soft tissue and bone tumors indicates a high prevalence for enchondromas.[4] This classic information is based on simple radiologic data. Advanced imaging techniques such as magnetic resonance imaging (MRI) to identify other pathologies for different skeletal regions do not account for incidentally detected enchondromas. EC can often be found incidentally on MRI scans for various pathologies.[5] One of the most important problems of our time is the incidental discovery of EC on MRI performed at the time of diagnosis of any pathology.[1,2,6] As MRI becomes more common in these studies, knowledge of the prevalence of incidental EC in these studies will contribute to the literature.[1,6,7] In EC prevalence calculation, the fact that MRI scans for another pathology are very easy and cost-effective makes it necessary to re-evaluate these prevalence values.

Detection of EC on radiographs is generally based on destruction of bone[3] or the presence of intralesional cartilage calcifications. Because EC is clinically asymptomatic and does not cause massive bone destruction, most EC are difficult to detect on direct radiographs. Recent publications in the literature answering the question of whether the long bones of the hand are indeed the most common site for EC[3] conclude that the hand should no longer be considered the most common body part for EC. It is thought that this is because radiographs are relatively insensitive compared with MRI in detecting small lesions in larger bones such as the proximal humerus and around the knee.

Our hypothesis is that despite the results of recent MRI studies in the literature, the hand remains the most common site for EC even when high-resolution imaging is used. The purpose of this study is to investigate whether the hand is the most common site for EC among upper extremity enchondromas incidentally detected on upper extremity MRI imaging, which is a more sensitive imaging modality that can show small enchondromas, and the prevalence of EC in the upper extremity.

MATERIAL AND METHOD

We retrospectively analyzed 9713 upper extremity MRI scans performed consecutively for any reason between 2011 and 2020 for the presence of enchondromas (**Figure 1**). Approval was obtained from the local ethics committee of the Faculty of Medicine at …….University. The study was conducted in accordance with the Declaration of Helsinki. The exclusion criteria for the study were patients whose image quality was insufficient to assess the presence of enchondromas, patients younger than 18 years of age, and patients with orthopedic implants at the MRI application area.

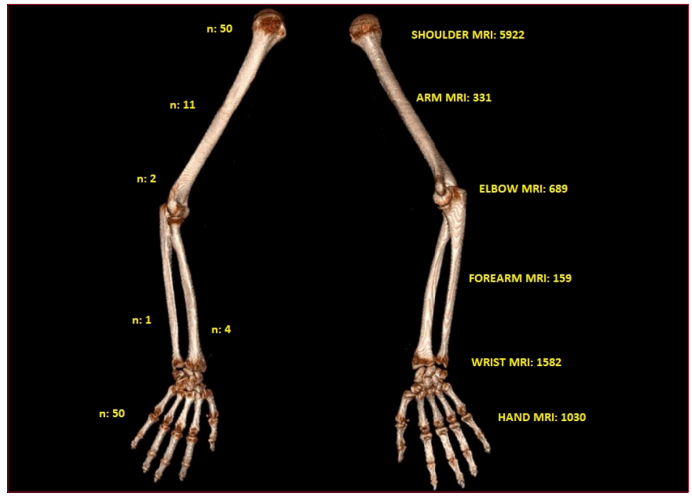

Figure 1. Upper Arm distribution of all MR evaluated and all detected enchondromas.

Low and medium signals in T1 on MRI, chondroid matrix, calcification foci with low signal intensity; cartilage matrix and septal appearance with high signal intensity and low signal intensity in T2, calcification foci with low signal intensity were evaluated in favor of enchondroma. Cases with subchondral lesions, subchondral cysts, intraosseous ganglia, or subchondral edema were not included in the study.

All lesions that met the criteria for a cartilage tumor and were agreed upon by two orthopaedic and traumatology physicians with more than 10 years of experience to determine lesion characteristics were included in the study(OB , ECZ).

MR images from these cases were analyzed using the Image Archiving and Communication System (PACS Sectra Workstation Ids7, Version 21.2.11.6289; ©2019 Sectra Ab). The length and width of all ECdetected in the PACS system were measured. Age, sex, and the bone region in which EC were detected were recorded. For subsequently discovered hand EC, an additional examination was performed using the ENLIL system(ENLIL hospital information management system, version v2.19.46 20191118). Symptoms of EC in the hand at the time of admission, whether there was previous trauma, whether a biopsy was performed, whether surgery was required, on which side they occurred, which bone and finger were affected, and whether they were centrally or eccentrically located were recorded.

All MRI examinations were performed on a 1.5 scanner (1.5T and 3T Siemens, Erlangen, Germany) at a single facility.

Statistics

Data obtained were analyzed using IBM SPSS Statistics software (software version 23.0). Main data were analyzed using the Kolmogorov-Smirnov test. However, a smaller group of patients with hand chondromas was analyzed with the Shapiro-Wilk test. Descriptive statistics were presented as mean ± SD and categorical values. The Student T test and

Mann-Whitney U test were used to compare data between groups. The chi-square test, Fisher exact test, and Fisher-Freeman-Halton test were used to evaluate the categorical variables. A p value of <0.05 was considered statistically significant for all tests.

RESULTS

In our study, EC were detected in 71 female and 47 male patients. The prevalence of EC in the upper extremity in females was 1.19%. The prevalence of upper extremity enchondromas in men was 1.27%. The most common age range was 41-50 years (24.7%) (**Table 1**).

Table 1. Descriptive statistics of individuals with enchondromas

	Count	%
Gender		
Female	71	60.2
Male	47	39.8
Extremity MR area		
Hand	44	10.6
Wrist	7	16.3
Forearm	4	1.6
Elbow	2	7.1
Upper Arm	11	3.4
Shoulder	50	61
Location of Enchondroma		
Proximal Phalanx	22	18.6
Metacarpal	18	15.3
Middle Phalanx	10	8.5
Distal Ulna	1	0.8
Distal Radius	4	3.4
Humerus Proximal Metaphysis-Diaphysis	10	8.5
Humerus Anatomical Neck	8	6.8
Head of Humerus	13	11.2
Humerus Surgical Neck	15	12.7
Tuberculum Majus	3	2.5
Humerus Distal Metaphysis-Diaphysis	1	0.8
Humerus Distal Metaphysis	2	1.6
Humerus Proximal 1/3 Diaphysis	6	5.1
Humerus Shaft	5	4.2
Zone of the Enchondroma		
Hand	50	42.4
Radius	4	3.4
Ulna	1	0.8
Distal Humerus	2	1.6
Humerus Shaft	11	3.4
Proximal Humerus	50	42.4
Age Groups		
11-20	3	2.5
21-30	18	15.3
31-40	20	16.9
41-50	29	24.7
51-60	15	12.7
61-70	28	23.7
71-80	5	4.2

MRI was performed mostly on the shoulder in both women and men (**Figure 2**). In our study, the prevalence of enchondroma was found to be 1.2% in the entire upper extremite (**Figure 2**).

The mean both length and width of the tumor were highest in enchondromas detected in the humeral diaphysis (**Figure 3**).

The median age of patients with enchondroma was 44 (**Table 2**). The mean tumor length was 26.7 (range 2-85) mm, and its width was 12.0 mm (range 2-25) (**Table 2**).

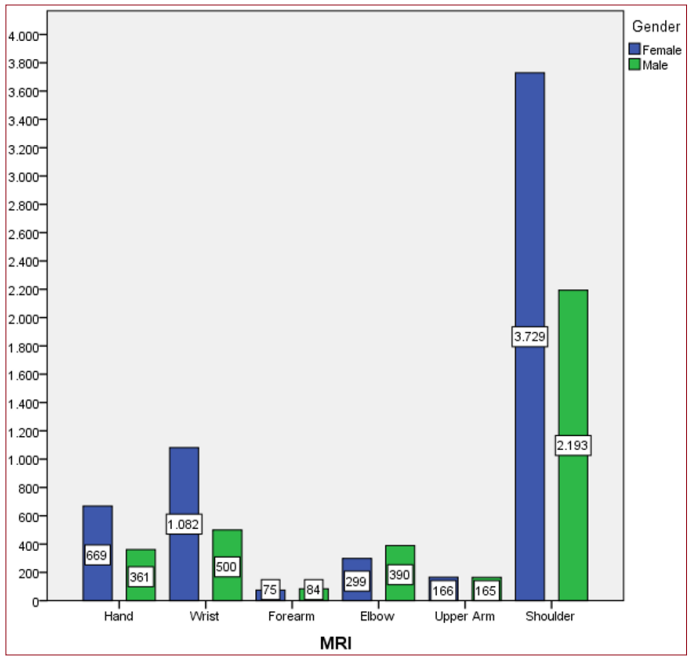

Figure 2. Distribution of all evaluated MRs by gender.

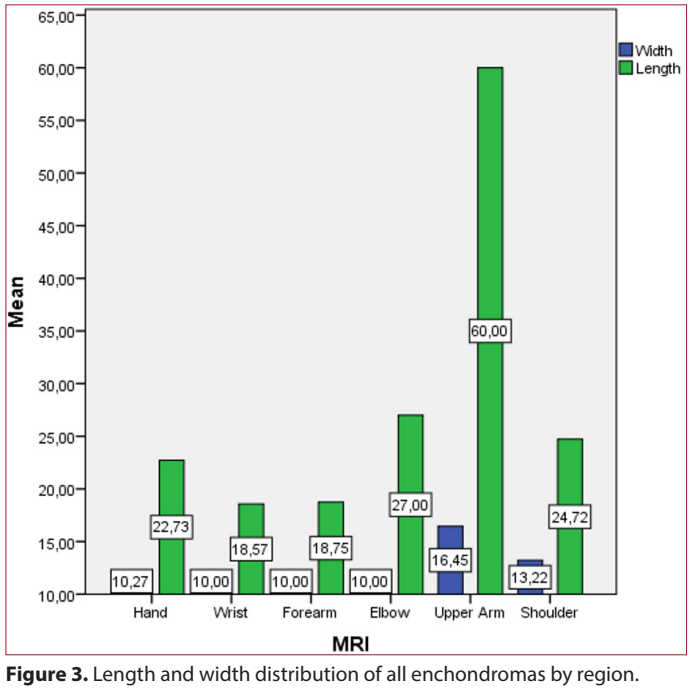

Figure 3. Length and width distribution of all enchondromas by region.

Table 2. Age of the patients and size of the all EC.

	N	Mean	Median	SD	Min	Max	IQR
Age	118	46.7	44	15.3	18	78	35-61
Length	118	26.7	20	19.2	2	85	15-32
With	118	12	10	5.2	2	25	8-16

A total of 50 patients were found to have EC on hand MRI. Of these EC, 22 were located in the proximal phalanx, 18 in the metacarpal, and ten in the middle phalanx. Most EC were located in the hand bones on the ulnar side. EC were found in the radius in four patients and in the ulna in one patient (**Figure 4**). None of the patients had Ollier disease or Maffucci syndrome.

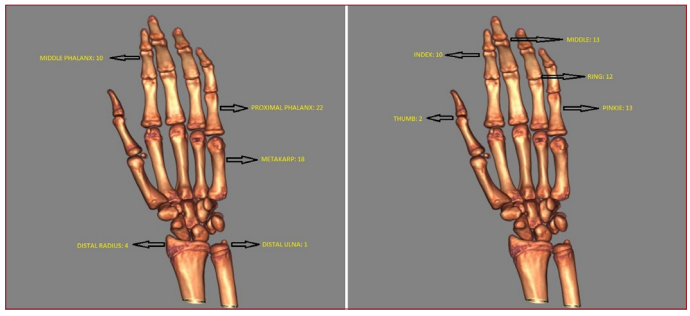

Figure 4. Hand distribution of enchondromas

None of the lesions had evidence of an endosteal scalloping, associated soft tissue mass, or surrounding bone marrow edema suggestive of chondrosarcoma. The overall incidence of hand EC was 4.85% in all hand MRI. While the incidence of hand EC was 5.8% in women, it was 4.15% in men. Hand EC occurred most frequently in the age group 31-40 years (6.46%), followed by the age group 18-30 years (6.28%).

EC was found in the proximal humerus in 50 patients, in the humeral shaft in 11 patients, and in the distal humerus in two patients (**Figure 5**). The incidence of enchondroma on MRI of the shoulder was 0.84%. The likelihood of enchondroma in the hand was approximately 5.77 times higher than in the shoulder. While the probability of enchondroma in the shoulder was 0.75% in women, this rate was 1% in men. The highest incidence of shoulder enchondromas was between 61 and 70 years of age (1.19%), followed by the age groups 41-50 (1.07%) and 31-40 years (0.84%).

Six patients with hand chondromas whose records could not be fully retrieved through our hospital's ENLIL system were excluded from the study. Twenty-eight (63.6%) of the 44 hand enchondroma patients whose hand MRIs could be evaluated in detail and clinical examination could be achieved were female (**Table 3**). The dermographic data of the hand EC patients whose clinical data were fully accessible are shown in **Table 1**.

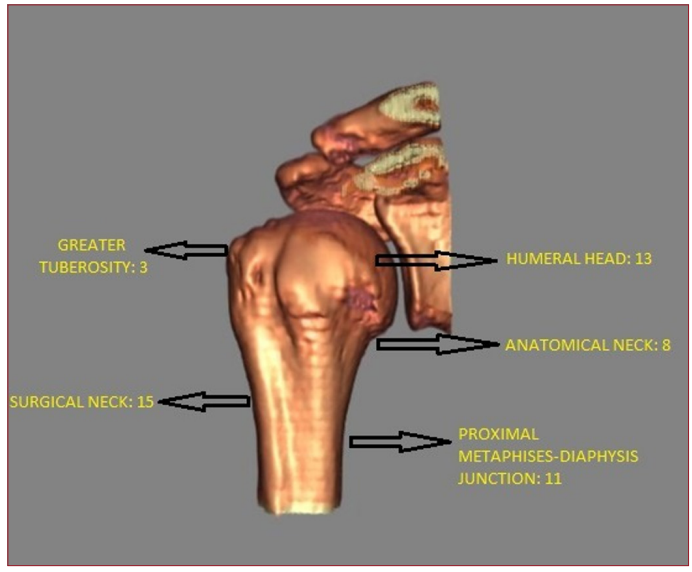

Figure 5. Distribution of enchondromas in the proximal humerus.

Table 3. Comparison of hand EC between genders.

	Female (n=28)	Male (n=16)	p
Side			0.864
Right	13	7	
Left	15	9	
Most Common Symptom			0.668**
Swelling	14	10	
Pain	11	4	
Pathological Fracture	3	2	
Location in bone			0.039
Eccentric	12	12	
Central	16	4	
Bone of hand			0.560**
Proximal Phalanx	11	9	
Metacarpal	11	4	
Middle Phalanx	6	3	
Finger			0.470**
Thump	2	0	
Index	6	4	
Middle	6	7	
Ring	8	2	
Pinky	6	3	
Biopsy			0.227
Present	14	5	
Absent	14	11	
Trauma			>0.999*
Present	3	2	
Absent	25	14	
Operation			0.314*
Present	10	3	
Absent	18	13	

Chi-square test was performed. * Fisher's Exact test was performed**Fisher-Freeman-Halton test was performed.

The hand EC is more eccentrically located in the male sex. The most common complaint of patients with hand chondromas (54.5%) was swelling, followed by pain (34.1). 11.4% of patients had pathologic fractures. On radiographic examination, the tumor was eccentrically located in 54.5%. Enchondromas in the hand were most common in the proximal phalanx (45.5%), followed by the metacarpal (34.1%). The third finger was most commonly affected (29.51%) and the first finger was least commonly affected (4.6%). 11.4% of patients had a history of trauma. The comparison of quantitative data are shown in **Table 4**. The mean age of the 44 patients was 40 SD14.4 years. The median age was 39 years. The length was 22.7 SD8.2 mm, and the width averaged 10.2 SD3.8 mm. Although length and width were greater in men, they were not statistically significant.

Table 4. Comparisonof variables for hand EC between genders

	Female (n=28)	Male (n=16)	p
Age	42.2±14.5	37±14.0	0.247
Lenght (mm)	22.6±8.1	22.8±8.7	0.959
Width (mm)	9.9±3.6	10.8±4.2	0.311

DISCUSSION

Although most cartilage tumors are clinically inconspicuous, studies of their epidemiology are mostly based on classic radiologic evaluations. One of the most important problems is the incidental detection of EC on magnetic resonance imaging (MRI), which is observed on MRI of the extremities and performed in the diagnosis of other joint pathologies.[6,8-10] It is a problem that is increasing in importance day by day and may lead to different conclusions about its prevalence. Therefore, it is important to know the true prevalence of enchondromas in MRI examinations of the extremities.

To our knowledge, our study is the first to determine the incidental prevalence of EC in MRI of all upper extremity bones. When we look at the literature, it is seen that the studies conducted on the evaluation of incidental prevalence are insufficient. The study of EC of the hand that we found in the literature was performed by Davies et al.[3] Based on the MRI study and the fact that MRI is more sensitive than radiographs in identifying EC, Davies et al.[3] found in this study that EC in the hand are relatively rare in contrast to classic findings. Davies et al.[3] In their study, they found that the incidence of EC in the hand should be 5% in trauma series, as the incidence in the proximal humerus and knee is approximately 2.5% in routine MRI examinations.[3] However, in their study, they found a lower rate. In our study, a total of 9713 MRIs of the upper extremities were examined. In MRI examinations that included all upper extremity bones, our study found a prevalence of 1.2% for enchondromas in the entire upper extremity. The EC was mostly seen in the MR imaging of the hand region. The prevalence of upper extremity EC in women was 1.19%. The prevalence of upper extremity EC in men was 1.27%. Hong et al. His studies have shown that EC is a relatively common incidental finding in the proximal humerus (2.1%)(6). In our study, the incidence of EC on MRI of the shoulder was 0.84%. The incidence of EC in the hand was approximately 5.77 times higher than in the shoulder. In our study, the incidence of shoulder enchondromas in women was 0.75%, whereas this rate was 1% in men. The results of our study corresponds with studies that performed with classic radiography rather than the results of MRI-based studies that Davies et al. conducted.

In a retrospective study by Simon et al.[11] EC was the most common tumor on the hand (47.1%). In our study, we included only cases in which EC was found in the hands and upper extremities. In our study, the overall incidence of hand EC was 4.85%. While the incidence of hand EC in women was 5.8%, it was 4.15% in men. Gaulke at al investigated 327 solitary EC of the hand in their study, and the incidence of proximal phalanx and little finger involvement was quite high. In our MRI-based study, enchondromas were detected in a total of 50 patients. Of these enchondromas, 22 were located in the proximal phalanx, 18 in the metacarpal, and ten in the middle phalanx. Gaulke et al.[12] reported that the proximal phalanx of the little finger was the most commonly affected bone.[12] The proximal phalanges (48.9%) and little fingers (34.3%) were the most commonly affected. In our MRI-based study, the EC were mostly located in the hand bones on the ulnar side. In the study by Gaulke et al.[12] these lesions often develop in the third and fourth decades of life and prefer long bones with ulnar borders. In our study, hand EC occurred most frequently in the age group of 31-40 years (6.46%), followed by the age group of 18-30 years (6.28%).

Most EC are asymptomatic and are not discovered until they show symptoms such as swelling, pain, and deformity. Tang et al.[13] noted that EC were discovered as incidental findings on radiographs without obvious symptoms or pain. Bauer et al.[14] noted a low risk of pathologic fractures in their study. In contrast, in the series reported by Sassoon et al.[15] 102 patients with hand EC had a pathologic fracture rate of 40% (n=41). In our study, the most common complaint of patients with hand EC (54.5%) was swelling, followed by pain (34.1%) and 11.4% of patients had pathologic fractures.

In studies of EC, incidental EC were found in 0.8% to 2.9% of routine examinations with a wide range of different results.[8-10] After examination of shoulder pain with plain radiographs, computed tomography (CT), and magnetic resonance imaging (MRI), incidental chondral tumor findings are estimated to be 2% to 4%.[16] The higher detection rates in MRI studies likely reflect the higher sensitivity of MRI to detect small lesions. Davies et al.[17] the prevalence of incidentalEC from the proximal femur on MRI is 0.7%. In their study determining the stromal prevalence of cartilage tumors as incidental findings on MRI of the

knee, they found a 2.8% prevalence of EC.[9] In an autopsy case series, a prevalence of EC of only 0.2% was observed.[18] The reported prevalence for MRI examinations of the knee performed because of pain ranged from 2.3% to 2.9% (8-10). In 601 healthy subjects, the prevalence of knee was only 0.8%.[8] Incidentally, cartilage tumors detected in the knee were most commonly found in the distal femur (approximately 2%), followed by the proximal tibia (0.5-0.7%) and proximal fibula (0.1-0.2%), and were generally small.[9,10] Hong et al.[6] reported that the prevalence of cartilage tumors found incidentally on MRI of the shoulder was 2.1%. Walden et al.[10] reported a 2.9% prevalence of EECs on clinical knee MRI. The prevalence of enchondromas in skeletally immature children undergoing knee MRI for various reasons was also 2.9%.[19]

Stomp et al.[9] reported that among the 1285 MRI examinations of the knee, 86% of 49 tumors were smaller than 2 cm. In Walden's study, which included 449 knee MRI examinations, 57% of 23 tumors were smaller than 1 cm.[10] In the shoulder extension study (which included 477 MRI examinations), seven of the ten incidentally detected ECs were smaller than 1 cm, and the three larger ones measured 1.2 cm or less.[6] In our study, the mean tumor length was 26.7 (range 2-85) mm and width was 12.0 mm (range 2-25).

An important limitation of our study is its retrospective nature. Although most MR scans are performed with 1.5 T protocols, the protocols are not uniform. In addition, not all EC diagnosed in this study underwent pathologic confirmation. However, we believe that the criteria established for the diagnosis of an EC are sensitive enough. Subchondral lesions and subchondral cysts were excluded in this study. Therefore, we believe that the prevalence of enchondromas was correctly reported in this article.

Accordingly, EC of the hand most commonly affects the proximal phalanx. The characteristic clinical findings and the easily recognizable findings on imaging studies make this diagnosis straightforward. Radiographically, enchondromas appear as well-demarcated, expansive, lytic lesions with varying degrees of striated or punctate, annular and arctal calcification. However, annular and arctic calcification is not seen in all cases.[20] Calcification foci on MRI have low signal intensity in all sequences. Low to moderate signal intensity on T1-weighted images shows signal intensity of a cartilage tumor and inhomogeneous high signal intensity with septa with low signal intensity onT2-weighted images shows signal intensity of a cartilage tumor. MRI is better for the evaluation of bone marrow and soft tissue edema.[21]

CONCLUSION

Enchondromas of the hand are still most common, although radiographs have become relatively insensitive in detecting small lesions in larger bones such as the proximal humerus and around the knee compared with MRI.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was initiated with the approval of the Gaziosmanpaşa Universty Hospital Ethics Committee (Protocol No: 21-KAEK-235).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Orijinal Araştırma / Original Article

Does The COVID-19 Pandemic Have an Effect on Perioperative Intra-Abdominal Wound Culture in Patients Undergoing Appendectomy? A Retrospective Cohort Study

COVID-19 Pandemisinin Apendektomi Geçiren Hastalarda Perioperatif Karın İçi Yara Kültürüne Etkisi Var Mı? Retrospektif Bir Kohort Çalışması

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Abstract

Aim: The aim of this study is to examine the effect of the changing microbiota structure during the pandemic period on the bacterial aerobic culture profile of the wound taken from patients operated for acute appendicitis, together with clinical variables.

Material and Method: Our study included 125 patients who underwent an appendectomy in the General Surgery Clinic between 01.03.2019-01.02.2021 and whose wound culture was taken during an appendectomy. The patients were divided into two groups; group1 (pre-pandemic) and group2 (during a pandemic). Both groups were compared in terms of age, gender, clinical, laboratory and wound culture data.

Results: There was no significant difference between the groups in terms of age, clinical symptoms, surgical method, laboratory and radiological data (p>0.05). In the pre-pandemic group, there was growth of Escherichia coli in 35 (53%) patients, Klebsiella pneumoniae in 3 (4.5%) patients, and Pseudomanas aeruginosae in 2 (3) patients from Gram-negative bacteria while Streptecoccus anginosus and Strep. constellatus growth were most common from Gram-positive bacteria. In the pandemic group, there was the growth of E. coli in 29 (49.2%) patients, P. aeruginosae in 5 (8.5%) patients, K. pneumoniae in 2 (3.4%) patients from Gram-negative bacteria, Citrobacter freundii and Strep. anginosus growth were the most common from Gram-positive bacteria. E. coli is the most common bacteria in both groups.

Conclusion: Although E. coli was found to be the most frequently identified microorganism in patients with acute appendicitis, an increase in the density and resistance of Pseudomonas group bacteria were detected, possibly due to the effect of the COVID-19 pandemic.

Keywords: COVID-19 pandemic, appendectomy, wound culture, antibiotic resistance

Öz

Amaç: Yaptığımız bu çalışmada amaç pandemi döneminde değişen mikrobiyota yapısının akut apandisit nedeni ile opere edilen hastalardan alınan yara yeri bakteriyel aerobik kültür profiline olan etkisini klinik değişkenlerle birlikte incelemektir.

Gereç ve Yöntem: Çalışmamıza 01.03.2019-01.02.2021 tarihleri arasında Genel Cerrahi Kliniğinde apendektomi yapılan ve apendektomi esnasında yara yeri kültürü alınan 125 hasta dahil edildi. Hastalar iki gruba ayrıldı; grup1(pandemi öncesi) ve grup2 (pandemi süreci). Her iki grup; yaş, cinsiyet, klinik, laboratuvar ve yara yeri kültür verileri açısından karşılaştırıldı.

Bulgular: Gruplar arasında yaş, klinik semptomlar, ameliyat yöntemi, laboratuvar ve radyolojik verileriler açısından anlamlı fark yoktu(p>0,05). Pandemi sürecindeki grupta perfore apendisit, apendokolit, hastanede kalış ve antibiyotik kullanım süresi daha fazla oduğu tespit edildi(p<0,05). Pandemi öncesinde Gram negatif bakterilerden 35 (%53) hastada Escherichia coli, 3 (%4,5) hastada Klebsiella pneumoniae, 2 (%3) hastada Pseudomanas aeruginosae üremesi olurken Gram pozitif bakterilerden en çok Streptecoccus anginosus ve Strep.constellatus üremesi olmuştur. Pandemi döneminde ise Gram negative bakterilerden 29 (%49,2) hastada E. coli, 5 (%8,5) hastada P. aeruginosae, 2 (%3,4) hastada K. pneumoniae üremesi olurken Gram pozitif bakterilerden en çok Citrobacter freundii ve Strep. anginosus üremesi olmuştur. Her iki grupta da en yaygın üreyen bakteri E.coli'dir.

Sonuç: Akut apandisitli hastalarda en sık tanımlanan mikroorganizma E. coli olarak bulunmuş olsa da muhtemel olarak COVID-19 pandemi sürecinin etkisi ile Pseudomonas gurubu bakterilerin yoğunluğunda ve direnç durumunda artış tespit edilmiştir.

Anahtar Kelimeler: COVID-19 pandemisi, apandektomi, yara yeri kültürü, antibiyotik direnci

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INTRODUCTION

COVID-19 (SARS-CoV-2) virus, which was first seen in Turkey in March 2020, first appeared in Wuhan, China in December 2019 and was declared a pandemic by the World Health Organization on March 11, 2020, as it spread all over the world.[1] It has been determined that SARS-CoV-2 has corona virus characteristics and is a virus of the Betacoronavirus 2B family, and bats and seafood have been accused as intermediate hosts, although it is not certain.[2,3] The virus spreads between humans by droplets and close contact, with an average incubation period of 2 to 14 days. The virus affects many organs, especially respiratory system organs.[2] Although it is transmitted mainly by droplet infection, it has been reported in studies that it can also be transmitted by fecal-oral and environmental ways.[4] It has been reported that corona patients in Wuhan, China, where the virus first originated, have gastrointestinal symptoms such as diarrhea, abdominal pain and vomiting in up to 10% of patients as well as fever, fatigue, and cough complaints.[5] However, in recent studies, this rate was much higher and Tian et al. found it to be 39.9% in their study.[6]

Acute appendicitis is the most common cause of admission to the emergency department with acute abdomen in approximately 7% of adults, slightly more in males.[7] Although various causes are held responsible for its etiology, it is not known precisely.[8] While surgical treatment was used in previous years in the treatment of acute appendicitis, this has changed in recent years depending on whether the appendix is complicated or not. If it is complicated, surgery is recommended, if not, medical treatment is recommended.[9] It has been reported that taking an interoperative culture during an appendectomy in patients with acute appendicitis is important in terms of preoperative and medical treatment regulation.[10] Routine intra-abdominal culture is recommended for appropriate antibiotic therapy since many bacteria grow in wound cultures especially during complicated appendicitis.[11] Although the appendicitis microbiota is richer, it is similar to the rectum microbiota, so it has been suggested that changes in the rectum microbiota will guide the diagnosis and treatment of acute appendicitis.[12] It has been put forward that in the COVID-19 pandemic, the disease itself, the drugs and the changes in habits lead to changes in the intestinal microbiota.[13]

The gastrointestinal system flora has been affected due to the changes in eating, sleeping and travel habits during the COVID-19 pandemic. Therefore, considering that the appendix may also be affected, it was the aim of this study to determine possible changes in the treatment protocol of the appendix by examining the wound culture in acute appendicitis.

MATERIAL AND METHOD

The study included 125 patients who were admitted to Niğde Ömer Halisdemir University Faculty of Medicine Training and Research Hospital General Surgery Clinic between March 1, 2019, and March 1, 2021, taken to emergency operation with the diagnosis of acute appendicitis, who met the study criteria, and whose intraoperative wound culture was taken during an appendectomy. The study was carried out in accordance with the Declaration of Helsinki, after the approval of the ethics committee with the decision dated 22.04.2021 and numbered 2021/53.

Patients who met the research criteria and agreed to participate in the study, who underwent appendectomy and whose wound culture was taken, were included in the study. Inclusion criteria for the study were defined as patients who had an open appendectomy and had a wound culture taken during the COVID-19 pandemic period and in the previous year with the diagnosis of acute appendicitis, and being between the ages of 18-80. Exclusion criteria were defined as patients who were diagnosed with lymphoma and leukemia, who did not undergo open appendectomy, who used antibiotics during the culture period, and who received chemotherapy and radiotherapy in the last 6 months.

Patients who underwent open appendectomy and whose intraoperative wound cultures were taken were divided into two groups as before and after the COVID-19 pandemic. Patients underwent open appendectomy and their wound culture was taken; Group 1 consisted of those who underwent these interventions between 01 March 2019-28 February 2020, and Group 2 were between 01 March 2020 and 01 March 2021. Age, gender, radiological diagnosis, laboratory results (WBC, Lymphocyte, PLT neutrophil and CRP), the surgery, histopathological results, complications, length of stay in the hospital, duration of antibiotics used, bacteria grown in wound culture and antibiotic sensitivity data of all participants in the study were recorded one by one. These data were compared between the two groups. All patients in the study were diagnosed and operated on by the same physician in the same general surgery clinic. Patients were taken into operation with the diagnosis of preoperative acute appendicitis after evaluating the diagnosis of acute appendicitis physical examination, radiological (Ultrasonography and Computed Tomography) and laboratory results. Open appendectomy operation was performed in all patients. Wound cultures were taken intraoperatively in a sterile environment just after appendectomy was performed, and were then transferred to the storage medium with a sterile swab from the infected area by opening the lumen of the appendix by the general surgery specialist. The culture samples were sent to the medical microbiology laboratory within one hour at the latest. Preoperative and peroperative antibiotics were not given to the patients, and metronidazole and ampicillin + sulbactam antibiotics were given just after the operation. Ciprofloxacin was given to those allergic to ampicillin + sulbactam.

The samples sent to the medical microbiology laboratory were inoculated on 5% sheep blood agar and EMB (Eosin Methylene Blue) media and incubated at 35±1°C for 24 hours. The grown samples at the end of the incubation were pre-evaluated according to gram staining, colony morphology,

and catalase and oxidase test results. Identification of the isolates and antibiotic susceptibility were performed with the Vitek 2 Compact (Biomerieux, France) device as well as by using classical microbiological methods. The susceptibility rates were interpreted by a medical microbiologist according to EUCAST (European Committee on Antimicrobial Susceptibility Testing) criteria.[14]

Data were analyzed by IBM SPSS V23. Conformity to normal distribution was evaluated by the Kolmogorov-Smirnov test. Independent samples t test and Mann Whitney U test were used to compare quantitative data according to groups. Categorical data were analyzed with the Chi-Square Test. The significance level was taken as $p<0.05$.

RESULTS

The median values of age did not differ between the groups (p=0.231). While the median value was 40 in Group 1, it was 33 in Group 2. Gender distributions differed between the groups (p=0.008). While the proportion of women in Group 1 was 57.6%, it was 33.9% in Group 2. Median values of hospital stay differed between the groups (p<0.001). While the median value was 4 in Group 1, it was 5 in Group 2. The median values of antibiotic duration differed between the groups (p<0.001). While the median value was 9 in Group 1, it was 10 in Group 2 (**Table 1**).

WBC average values did not differ between the groups (p=0.845). While the average value was 14 in Group 1, it was 13.9 in Group 2. Lymphocyte median values did not differ between the groups (p=0.74). While the median value was 2 in Group 1, it was 2 in Group 2. The median values of platelets did not differ between the groups (p=0.095). While the median value was 271.5 in Group 1, it was 250 in Group 2. The median values of CRP did not differ between the groups (p=0.365). While the median value was 19.5 in Group 1, it was 27 in Group 2. The median values of neutrophils did not differ between the groups (p=0.686). The median value was 11.2 in Group 1, and it was 11 in Group 2 (**Table 2**).

The presence of appendicolith differed between the groups (p=0.030). While the rate was 21.2% in group 1, it was 40.7% in group 2. While the perforation rate was 11.1% in group 1, it was 30.5% in group 2, and there was a statistical difference between them (p=0.015). Other categorical variables did not differ between the groups (p>0.05) (**Table 1**).

Table 1. Comparison of categorical data according to groups

	Group 1 (n=66) (Non-pandemic)	Group (n=59) (Pandemic)	Total (n=125)	p
Age*	38.2±14.1/40 (47.25)	36.8±16.8/33 (43)		0.231[b]
Gender, n (%)				0.008[a]
Male	28 (42.4)	39 (66.1)	67 (53.6)	
Female	38 (57.6)	20 (33.9)	58 (46.4)	
ASA**, n (%)				0.486[a]
I	17 (25.8)	21 (35.6)	38 (30.4)	
II	38 (57.6)	29 (49.2)	67 (53.6)	
III	11 (16.7)	9 (15.3)	20 (16)	
Surgery (Open appendectomy), n (%)	66 (100)	59 (100)	125 (100)	
Appendicolith (yes), n (%)	14 (21.2)	24 (40.7)	38 (30.4)	0.030[a]
Perforation (no), n (%)	8 (11.1)	18 (30.5)	26 (20.8)	0.015[a]
Residential, n (%)				0.199[a]
Intraperitoneal	60 (90.9)	43 (81.1)	66 (55.5)	
Retrocecal	6 (9.1)	10 (18.9)	53 (44.5)	
Post-Op Complication, n (%)				0.234[a]
No	53 (80.3)	41 (69.5)	94 (75.2)	
Yes	13 (19.7)	18 (30.5)	31 (24.8)	
Ileus	4 (30.8)	4 (22.2)	8 (25.8)	
Ileus+Reoperation	0 (0)	1 (5.6)	1 (3.2)	
Ileus+Wound Inf.	0 (0)	1 (5.6)	1 (3.2)	
Diarrhea	2 (15.4)	2 (11.1)	4 (12.9)	
Wound Inf.	6 (46.2)	6 (33.3)	12 (38.7)	
Wound Inf.+ Hernia	0 (0)	2 (11.1)	2 (6.5)	
Wound Inf+Diarrhea	1 (7.7)	2 (11.1)	3 (9.7)	
Pathology, n (%)				0.067[a]
Acute Appendicitis	47 (73.4)	32 (54.2)	79 (64.2)	
Acute Suppurative Appendicitis	3 (4.7)	6 (10.2)	9 (7.3)	
Appendix Mucocele (L)	1 (1.6)	1 (1.7)	2 (1.6)	
Gangrenous Appendicitis	5 (7.8)	2 (3.4)	7 (5.7)	
Perforated Appendicitis	8 (12.5)	18 (30.5)	26 (21.1)	
Hospital Stay *	4.5±1.9/4 (5)	6.3±3.3/5 (8)		<0.00[b]
Antibiotic Duration *	9.4±1.6/9 (10)	11.4±3.2/10 (13)		<0.00[b]

aChi-Square test, n (%), bMann Whitney U test, * average±standard deviation/median,**American Society of Anesthesiologists

Table 2. Laboratory and radiological data according to groups

	Group 1 (n=66) Non-pandemic (IQR)	Group 2 (n=59) Pandemic (IQR)	p
WBC*	14±4.8/14 (17)	13.9±3.8/14 (17)	0.845[a]
Lymphocyte *	1.9±0.9/2 (2)	2.2±1.4/2 (2)	0.740[b]
Platelets *	274.6±71.4/271.5(302.75)	249.2±65.5/250 (300)	0.095[b]
CRP*	47.2±67.5/19.5 (59)	62.3±76.4/27 (101)	0.365[b]
Neutrophil *	11.2±4.7/11.5 (14)	11±3.8/11 (13)	0.686[a]
USG, n (%)			0.775[c]
Acute Appendicitis	17 (77.3)	7 (77.8)	
Appendix Mucocele	1 (4.5)	0 (0)	
Intra-abdominal Abscess	3 (13.6)	2 (22.2)	
Perforated Appendicitis	1 (4.5)	0 (0)	
BT, n (%)			0.500[c]
Acute Appendicitis	52 (88.1)	52 (91.2)	
Appendix Mucocele	1 (1.7)	0 (0)	
Intra-abdominal Abscess	0 (0)	1 (1.8)	
Perforated Appendicitis	6 (10.2)	4 (7)	

[a]Independent samples t-test, [b]Mann Whitney U test, [c]Chi-square test, * average±standard deviation / median (min-max), IQR: the interquartile range

Bacteria grown in bacterial culture according to groups are summarized in **Table 4**. Gram-negative bacteria grew more intensely than gram-positive bacteria in both groups. Escherichia coli was most frequent in 35 (53) patients, Klebsiella pneumoniae in 3 (4.5) patients, Pseudomanas aeruginosae in 2 (3) patients from Gram-negative bacteria in Group-1, Streptecoccus anginosus and Strep.constellatus were the most common growth among Gram-positive bacteria. While E. coli in 29 (49.2) patients, P. aeruginosae in 5 (8.5) patients, K. pneumoniae in 2 (3.4) patients from Gram-negative bacteria in Group-2, Citrobacter freundii and Strep. anginosus were the most common among Gram-positive bacteria. While the most growth rate from Gram positive bacteria was Strep. spp. (21.2%) in Group 1, Staphylococcus spp. (15.3%) growth was more in Group 2. The most commonly grown bacteria in both groups was E. coli (**Table 3**).

Table 3. Bacteria isolated from wound culture according to groups.

	Group 1 (Non-pandemic)	Group 2 (Pandemic)	Total
Culture			
Acinetobacter spp.	1 (1,5)	0 (0)	1 (0,8)
Citrobacter braakii	2 (3)	0 (0)	2 (1,6)
Citrobacter freundii	3 (4,5)	4 (6,8)	7 (5,6)
E. coli	35 (53)	29 (49,2)	64 (51,2)
Enterococcus avium	0 (0)	1 (1,7)	1 (0,8)
Klebsiella oxytoca	0 (0)	1 (1,7)	1 (0,8)
Klebsiella pneuoniae	3 (4,5)	2 (3,4)	5 (4)
Lactobacillus spp.	2 (3)	0 (0)	2 (1,6)
Pseudomons aeruginosa	2 (3)	5 (8,5)	7 (5,6)
Staph. lentus	0 (0)	1 (1,7)	1 (0,8)
Staph. cohnii	0 (0)	1 (1,7)	1 (0,8)
Staph. hominis	2 (3)	4 (6,8)	6 (4,8)
Staph. lugdinensis	2 (3)	3 (5,1)	5 (4)
Strep. anginosus	5 (7,6)	4 (6,8)	9 (7,2)
Strep. constellatus	5 (7,6)	0 (0)	5 (4)
Strep. intermedius	2 (3)	4 (6,8)	6 (4,8)
Strep. mitis	2 (3)	0 (0)	2 (1,6)

Table 4. Antibiotic susceptibility of bacteria isolated from wound culture according to groups

	Group 1 (Non-pandemic)		Group 2 (Pandemic)		Total		p1
	R	S	R	S	R	S	
AMC	14 (46,7)	16 (53,3)	14 (48,3)	15 (51,7)	28 (47,5)	31 (52,5)	1,000
ETP	1 (5,6)	17 (94,4)	0 (0)	31 (100)	1 (2)	48 (98)	0,367
GN	3 (8,1)	34 (91,9)	3 (8,3)	33 (91,7)	6 (8,2)	67 (91,8)	1,000
CEF	8 (36,4)	14 (63,6)	5 (13,9)	31 (86,1)	13 (22,4)	45 (77,6)	0,059
CFM	3 (12,5)	21 (87,5)	0 (0)	5 (100)	3 (10,3)	26 (89,7)	1,000
CRO	8 (33,3)	16 (66,7)	6 (20)	24 (80)	14 (25,9)	40 (74,1)	0,425
LEV	1 (50)	1 (50)	1 (16,7)	5 (83,3)	2 (25)	6 (75)	0,464
CIP	9 (24,3)	28 (75,7)	9 (25)	27 (75)	18 (24,7)	55 (75,3)	1,000
AZT	---	2 (100)	---	5 (100)	---	7 (100)	---
AMP	22 (66,7)	11 (33,3)	17 (53,1)	15 (46,9)	39 (60)	26 (40)	0,389
AK	1 (4,8)	20 (95,3)	0 (0)	36 (100)	1 (1,8)	56 (98,2)	0,368
TGC	---	10 (100)	---	31 (100)	---	41 (100)	---
SXT	17 (43,6)	22 (56,4)	11 (35,5)	20 (64,5)	28 (40)	42 (60)	0,658
IMP	---	11 (100)	---	14 (100)	---	24 (100)	---
PIP	2 (66,7)	1 (33,3)	4 (66,7)	2 (33,3)	6 (66,7)	3 (33,3)	1,000
TZP	5 (23,8)	16 (76,2)	0 (0)	37 (100)	5 (8,6)	53 (91,4)	0,004
MEM	0 (0)	15 (100)	1 (2,7)	36 (97,3)	1 (1,9)	51 (98,1)	1,000
TOB	---	1 (100)	---	6 (100)	7 (100)	---	---
NET	1 (50)	1 (50)	1 (20)	4 (80)	2 (28,6)	5 (71,4)	1,000
F	---	10 (100)	---	---	---	10 (100)	---
FOS	---	18 (100)	---	---	---	18 (100)	---
CAZ	7 (43,8)	9 (56,3)	7 (20)	28 (80)	14 (27,5)	37 (72,5)	0,099
CXM	9 (69,2)	4 (30,8)	7 (21,9)	25 (78,1)	16 (35,6)	29 (64,5)	0,005
CZ	7 (77,8)	2 (22,2)	7 (22,6)	24 (77,4)	14 (35)	26 (65)	0,004
FOX	1 (10)	9 (90)	2 (7,4)	25 (92,6)	3 (8,1)	34 (91,9)	1,000
VA	---	8 (100)	---	9 (100)	---	17 (100)	---
ESBL*	---	---	---	2 (100)	---	2 (100)	---

[1]Chi-square test, n (%), *Extended-Spectrum Beta Lactamases
(AMP: Ampicillin, AMC: Amoxicillin + clavulanic acid, AK: Amikacin, AZT: Aztreonam, CAZ: Ceftazidime, CEF: Cefepime, CFM: Cefixime, CRO: Ceftriaxone, FOX: Cefoxitin, CIP: Ciprofloxacin, CXM: Cefuroxime, CZ: Cefazolin, ETP: Ertapenem, FOS: Fosfomycin, GN: Gentamicin, IPM: Imipenem, LEV: Levofloxacin, MEM: Meropenem, F: Nitrofurantoin, NET: Netilmicin, PIP: Piperacillin, SXT: Trimethoprim / sulfamethoxazole, TZP: Piperacillin + tazobactam, VA: Vancomycin, TGC: Tigecyclin, TOB: Tobramycin)

The antibiotic resistance profiles of the isolated bacteria are summarized in **Table 4** in general according to the groups. In group-1 patients, resistance was found to be 77.8% for cefazolin, 69.2% for cefuroxime, 10% for cefoxitin, 33.3% for ceftriaxone, 24.3% for ciprofloxacin, 50% for levofloxacin. In Group-2, resistance was found to be 22.6% for cefazolin, 21.9% for cefuroxime, 7.4% for cefoxitin, 20% for ceftriaxone, 25% for ciprofloxacin, and 16% for levofloxacin. While the susceptibility and resistance statuses of Piperacillin/Tazobactam, cefuroxime and cefazolin differed statistically according to the groups, the sensitivity and resistance against the others did not differ (**Table 4**). The resistance to antibiotics of the two most common bacteria is summarized in **Figure 1**.

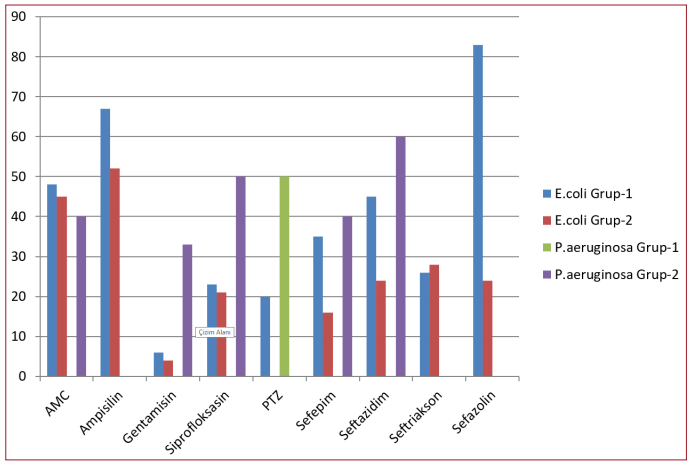

Figure 1. The resistance to antibiotics of the two most common bacteria

DISCUSSION

Gastrointestinal microbiota is generally described as a postpartum organ that can affect both systemic and intestinal physiology, and whose composition and activity is composed of a wide variety of bacteria.[15] The microbiota promotes the maturation of immune cells and the development of immune system functions in disease and health conditions.[16] While the mutualistic relationship between the host and intestinal bacteria is called symbiosis, the imbalance in the gut microbiota or decrease in diversity is called dysbiosis. Microbiota is associated with various pathologies such as constipation, obesity, inflammatory bowel disease, depression, diabetes, colon cancer, coronary artery diseases.[17-19] Although the normal GIS microbiota is composed of bacteria belonging to the Bacteroides and Firmicutes phyla intensely, a very small portion of them is potentially pathogenic bacteria such as the Proteobacteria phylum.[20]

Some studies have reported a bidirectionally functioning axis called the 'gut-lung axis'.[21] In other words, just like respiratory infections can affect the gut microbiota, the gut microbiota can affect the lung immunity and microbiota by affecting the immune system. In a study on the influenza virus, it was reported that as a result of therapy regulating the gut microbiota, the replication of viruses in the pulmonary epithelium decreased, thus the severity of the disease reduced. It was thought that this situation may also be valid for COVID-19 patients.[22] SARS-CoV-2 can change the commensal microorganism composition in the gut and lead to gut dysbiosis; and dysbiosis can cause increased cytokine levels, systemic inflammation, and exaggerated immune responses.[23] Although studies on COVID-19 and microbiota are limited, it has been reported that opportunistic pathogens (Peptostreptococcaceae, Enterobacteriaceae, Staphylococcaceae, etc.) increase and beneficial bacteria (Faecalibacterium, etc.) decrease.[22,24] In addition, Angiotensin Converting Enzyme 2 (ACE2) receptors, which are the main receptors of SARS-CoV-2, are highly present both in the respiratory tract and in the GIS.[25] In this case, it is thought that the COVID-19 virus may affect the gastrointestinal system and microbiota. In this study, the effect of the changing microbiota structure during the pandemic period on the bacterial aerobic culture profile of the wound taken from the patients who were operated on for acute appendicitis was examined together with the clinical variables.

Appendicitis is thought to be the result of bacterial overgrowth as a consequence of an obstruction of the appendix lumen for various reasons.[26] Anaerobic species such as Bacteriodes fragilis and Fusobacterium nucleatum have been reported to be the most common bacterial agents in appendicitis. E. coli has been reported as the most common bacteria detected by aerobic culture method; however, bacteria such as K. pneumoniae, Strep. spp., Enterococcus spp. and P. aeruginosa have also been shown to be a factor.[27,28] Our study was found to be compatible with the literature in this respect. It is difficult to explain the effects of these agents on infection, since the species identified in appendicitis were found to be compatible with the gastrointestinal microbiota, according to studies conducted with both new generation sequencing and culture methods.[28] In addition, microbiota profiles vary from person to person. Although factors such as diet, geography, medicines (antibiotics, etc.), surgeries, chronic diseases and genetic structure affect the microbiota structure, Peeters et al. and Arlt et al. have shown that there is a significant decrease in microbial richness and diversity in inflamed appendix tissue in two different studies.[29,30] The COVID-19 pandemic, which is thought to be one of the factors affecting these changes in the microbiota structure, is also the main subject of this study.

While E.coli (53%), K.pneumoniae (4.5%) and P.aeruginosae (3%) from gram-negative bacteria were the most common, respectively in cultures made before the pandemic, it was observed in the pandemic period that the growth of E.coli (49.2%), P.aeruginosae (8.5%) and K.pneumoniae (3%), respectively were the most common. It is noteworthy that the rate of P.aeruginosa increased during the pandemic period compared to the pre-pandemic period. Because P.aeruginosa is resistant to physical environments, antiseptics and antibiotics, and is fond of humid environments, and even grows in disinfectants, this microorganism can easily live in outdoor environments and especially in hospital

environments. P.aeruginosa, which progresses with high mortality and morbidity, ranks the first among the factors of nosocomial infections.[31,32] It made us think that the reason for this change in P.aeruginosae may be the drugs used during the pandemic process and the prolongation of hospital stay.

It has been reported to prolong the hospital stay and duration of antibiotic use of the patients and the number of non-perforated acute appendicitis decreased significantly while the number of perforated acute appendicitis increased during the pandemic period.[33-35] Our study was found to be compatible with the literature in this respect. This situation makes us think that the increase in the incidence of hospital-acquired infectious agents in public due to prolonging of hospital stay may be a result of the pandemic.

On the other hand, while Strep. spp. (21.2%) and Staph. spp. (%6) were the most prevalent in Gram-positive bacteria before the pandemic, the balances changed during the pandemic period; and it was observed that the growth of Staph. spp. (15.3%) and Strep. spp. (13.6%) were the most. In our study, similar to the studies conducted before the pandemic, it has been observed that the growth of Strep. spp. type bacteria was more than Gram-positive bacteria.[11,36,37] The reason for this change in Gram-positive bacteria can be interpreted as an effect of the pandemic period, just like in P.aeruginosa, but more studies are needed for this.

In some studies, only the place of antibiotic therapy in patients with non-perforated appendicitis was studied. In one of these studies, appendectomy and antibiotic groups were compared in the seven-year follow-up of 423 patients. According to this study, there was no difference in satisfaction compared to appendectomy in patients who received only antibiotic treatment, and in seven years, 39 percent of those in the antibiotic group required appendectomy.[38] For non-perforated appendicitis, international authors recommend appendectomy in adults.[39,40] Our study is compatible with the literature in this respect. The aim of prophylactic antibiotic therapy is to prevent wound infection and complications such as intra-abdominal abscesses that may occur following an appendectomy. The treatment to be given should be a group of antibiotics that affect gram-negative aerobes and anaerobes.[41] While the antibiotics chosen for the recommended antibiotic treatment for non-perforated appendicitis are the first and second-generation antibiotics such as cefoxitin, cefotetan, cefazolin and metronidazole, it is clindamycin, ciprofloxacin, levofloxacin, gentamicin or aztreonam for those allergic to the cephalosporin group.[42] In patients with perforated appendicitis, antibiotic therapy should be therapeutic rather than prophylactic, and should consist of broad-spectrum therapy. Antibiotic treatment should be rearranged according to the culture results after the first empirical treatment. In empirical treatment, second and third-generation cephalosporins such as cefuroxime, ceftriaxone, and cefotaxime, ciprofloxacin or levofloxacin are mostly used, each of them in combination with metronidazole.[43]

There are also some limitations to our study. First, although only aerobic bacteria were identified and interpreted in our study, anaerobic bacteria, which constitute the majority of gut bacteria, could not be identified because our laboratory conditions were not suitable. Another limitation is that the study was conducted only within a single geographical region. Since geography is one of the factors affecting the gut microbial structure, larger-scale multicenter studies are needed to generalize the results. The strength of our study is that it is the first wound culture study to compare the pre-pandemic and during a pandemic.

CONCLUSION

As a result, although the most frequently identified microorganism in patients with acute appendicitis was E. coli, an increase in the density and resistance of Pseudomonas group bacteria was detected, possibly due to the effect of the COVID-19 pandemic. Therefore, these changes should be considered in the empirical treatment to be selected. Additional studies are needed to better understand the changes caused by the pandemic process to the microbiota and its effect on the acute appendicitis process.

ETHICAL DECLARATIONS

Ethics Committee Approval: Approval was obtained with the decision of the Ethics Committee of Niğde Ömer Halisdemir University, dated 22.04.2021 and numbered 2021/47.

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Orijinal Araştırma / Original Article

Results of Adjustable Intragastric Balloon Use According to Body Mass Index Values

Vücut Kitle İndeksi Değerlerine Göre Ayarlanabilir İntragastrik Balon Kullanım Sonuçları

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Abstract

Aim: In our study, it was aimed to compare the results of the adjustable intragastric balloon (AIGB) in patients according to body mass index (BMI).

Material and Method: We recorded the data of 82 patients that we performed the AIGB procedure in the last four years retrospectively. During the initial implantation of the balloon, inflating was performed with 300-350 cc saline and methylene blue. BMI and excess weight loss ratios (EWL) of the patients and at the time of the balloon removal were noted. Patients' complaints and complications arising after balloon application or additional inflation were reported.

Results: It was determined that there was a statistically significant decrease between weight, BMI, and EWL values measured at the 4th, 8th, and 12th months after the first application was performed (p <0.001). The weight and EWL values were evaluated in two groups as morbidly obese (BMI ≥40) and patients with BMI <40.İt was determined that there was a statistically significant decrease in weight and EWL values in both groups depending on time (p <0.001), in further analysis, the difference between the 8th and 12th months for EWL values was not statistically significant (p>0.05) in morbidly obese patients (BMI≥40), all other differences were statistically significant (p<0.001).

Conclusion: AIGB treatment has satisfactory results in morbidly obese patients. AIGB can be preferred as an alternative method to bariatric surgery in patients where bariatric surgery may be high risk due to comorbidities and in cases where patients do not prefer bariatric surgery.

Keywords: Obesity, intragastric balloon, weight loss

Öz

Amaç: Çalışmamızda hastalarda ayarlanabilir intragastrik balonun sonuçlarının (AIGB) vücut kitle indeksine (VKI) göre karşılaştırılması amaçlandı.

Gereç ve Yöntem: Son dört yılda AIGB uygulaması yaptığımız 82 hastanın verilerini retrospektif olarak incelendi. Balonun ilk implantasyonu sırasında 300-350 cc salin ve metilen mavisi ile şişirme yapıldı. Hastaların ve balonun çıkarıldığı anki VKİ ve kilo verme oranları (EWL) not edildi. Hastaların balon uygulaması veya ek şişirme sonrası oluşan şikayetleri ve komplikasyonları kaydedildi.

Bulgular: VKİ ve EWL değerleri arasında ilk uygulama yapıldıktan sonra 4., 8. ve 12. aylarda ölçülen kilolarla istatistiksel olarak anlamlı azalma olduğu belirlendi (p<0,001). Ağırlık ve EWL değerleri morbid obez (VKİ ≥40) ve VKİ <40 olan hastalar olmak üzere iki grupta değerlendirildi. Her iki grupta da zamana bağlı olarak ağırlık ve EWL değerlerinde istatistiksel olarak anlamlı azalma olduğu belirlendi (p<0,001). İleri analizde, morbid obez hastalarda (BMI≥40) EWL değerleri için 8. ve 12. aylar arasındaki fark istatistiksel olarak anlamlı değildi (p>0.05), diğer tüm farklılıklar istatistiksel olarak anlamlıydı (p<0.001).

Sonuç: AIGB tedavisi morbid obez hastalarda tatmin edici sonuçlara sahiptir. Bariatrik cerrahinin ek hastalıklar nedeniyle yüksek riskli olabileceği hastalarda ve hastaların bariatrik cerrahiyi tercih etmediği durumlarda, AIGB obezite cerrahisine alternatif bir yöntem olarak tercih edilebilir.

Anahtar Kelimeler: Obezite, intragastrik balon, kilo kaybı

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INTRODUCTİON

Despite all the precautions taken, obesity is a rapidly increasing health problem worldwide. Metabolic disorders caused by obesity affect the whole body and lead to many chronic diseases. Current treatments accompanied by diet and sports in the struggle against obesity include medical therapy, endoscopic methods, bariatric surgery, acupuncture, and psychiatric behavior therapy. Bariatric surgery procedures are the treatments that have the fastest effect and in which the maintenance of weight control is possible for a long time.[1,2]

Endoscopic bariatric treatment methods, which may be an alternative to bariatric surgery procedures and have become very popular in recent decades, seem to be preferred more because of their low-risk rates. Endoscopic interventions include intragastric balloons and botulinum toxin applications performed in the last decade.[3-5] There are also opinions that the adjustable intragastric balloons (AIGB) are more useful and efficient than the other types of intragastric balloons.[6]

An important feature of AIGB application is that it can be applied endoscopically under mild sedation. Intragastric balloons allow patients to reduce their food intake by creating a feeling of fullness in their stomachs. It is assumed that intragastric balloons provide peripheral saturation by preventing food intake, reducing intragastric volume, and delaying gastric emptying.[7] In this study, we will present the results of patients who underwent intragastric balloon administration.

MATERIAL AND METHOD

The recorded data in the files of 82 patients who underwent AIGB in XXXXXXX General Surgery Clinic between 2016-2020 were collected and analyzed. Ethics committee approval was obtained from Keçiören Training and Research Hospital Clinical Research Ethics Committee (2012-KAEK-15/1596) for our retrospective study. Our study was carried out in accordance with the principles of the Declaration of Helsinki.

82 patients over the age of 18 who applied to the general surgery clinic for gastric balloon treatment for obesity between January 2016 and January 2020 were included in the study. Inclusion criteria were: Morbid obesity (Body mass index (BMI) >40), patients preparing for bariatric surgery to decrease surgical risk, BMI 35-40 and with obesity-related diseases; BMI 35 and who have failed many attempts to lose weight with psychological indications in a multidisciplinary treatment program. The existence of an organic disease of the upper digestive tract, Crohn's disease, anti-inflammatory medicines, anticoagulants, or steroids, drunkenness, or drug addiction were all considered exclusion factors. A hiatus hernia with a diameter of more than 5 cm was recognized as an exclusion criterion.

An adjustable balloon system (Spatz Medical, Great Neck, NY, USA) was administered to the patients. All procedures were performed under sedation by intravenous propofol administration by an anesthesiologist under operating room conditions.

The esophagus and stomach of the patients were examined endoscopically before the implantation of AIGB for the first time. The procedure was terminated in patients with esophagitis, gastritis, or peptic ulcer, and three months after the necessary medical treatments were applied, AIGD was implanted in patients without any pathology. AIGB application was abandoned for two patients who were not included in the study and whose gastritis condition continued after medical treatment.

In patients who underwent AIGB application for the first time, Spatz balloon was first implanted in the stomach fundus with the help of an endoscope. Subsequently, the balloon was inflated with the previously prepared 300-350 cc S.F. + Methylene Blue (MB). The first procedure was completed after no leak or pathology was observed. A second 150 cc or 120 cc SF+MB administration was performed for 19 patients. Thirteen patients were administered 100 cc SF+MB for the third time.

The BMI and excess weight loss ratios (EWL) of the patients during the balloon implantation were recorded. BMI, weight losses, EWL ratios during the second, and if applied, the third procedure and during balloon removal were also recorded. Complaints and complications of patients after balloon implantation or additional inflation were reported. Comorbid disease states, medications used by patients, changes in these conditions were noted. The patients were divided into two groups; morbidly obese group of BMI≥ 40 kg/m^2 and BMI <40 kg/m^2 overweight-obese group which consisted of moderately obese, slightly obese, overweight.

Statistical analysis

Continuous variables, mean±standard deviation, and categorical data were expressed as numbers and percentages. Normality analyses were performed with the Shapiro-Wilk normality test in the intergroup analysis of continuous variables. Repeated Measures ANOVA Test was used to analyze the time-dependent changes of the variables that are suitable for normal distribution. Bonferroni was used as the post-hoc test after the ANOVA test, as the variances were homogeneously distributed. Further analyzes of the dependent groups were performed with the Paired Samples T-test. Based on the difference in the postoperative percent of excess weight loss rates between the groups, a power analysis was performed considering a 5% alpha error, 80% power, and a bilateral hypothesis. Adequate sample size was determined as 27 patients per group. Actual power was 0.812, while effect size d was 1.4372. Analyzes were performed with IBM SPSS Package Program version 24.0 (IBM Corporation, Armonk, NY, USA). P values of <0.05 were considered as statistically significant.

RESULTS

Intragastric balloon implantation was performed in all 82 patients included in the study. The mean age of the patients was 50.86±13.48 years, 68.2% were women, their mean weight was 117.6±27.5 kg, and the mean BMI values were 42.9±10.4 kg/m2. It was determined that there was a statistically significant decrease between weight, BMI, and EWL values measured at the 4th, 8th, and 12th months after the first application was performed (p <0.001). When examining the EWL percentage averages in detail; after the intragastric balloon application, it was found that a decrease of 28±14.2% in EWL percent averages occurred in the first four months, whereas the values between 4 and 8 months had a decrease of 15%±11.8, and between the 8th and 12th months the decrease was only 6%±8.6 (p <0.001). A total change of 51.3%±30.1 in EWL was found between the pre-procedure period and the 12-month post-balloon application. In further analysis, the difference between the 8th and 12th months between weight and BMI values was found to be not statistically significant (p> 0.05), and all other differences were significant (p <0.001) (**Table 1**).

When weight and EWL values were evaluated in two groups as morbidly obese (BMI ≥ 40) and overweight-obese patients (BMI <40); although it was determined that there was a statistically significant decrease in weight and EWL values in both groups depending on time (p <0.001), in further analysis, the difference between the 8th and 12th months for EWL values was not statistically significant (p> 0.05) for morbidly obese patients (BMI ≥40), and all other differences were significant (p <0.001). It was observed that EWL percentage means changed by 18.5%±7.2 in the morbidly obese group and 41%±10.6 in the overweight-obese group in the first four months after application and this change was determined to occur in both groups at the eighth month as 7.6%±3.6 vs. 23.5%±12.4 and at 12th months as 1.5%±7 vs. 11.1%±7.6. (**Table 2**).

When evaluated in terms of comorbid diseases, twenty-two patients had Type 2 Diabetes Mellitus (T2DM), eleven patients had hypertension, and three patients had sleep apnea syndrome at the time of treatment onset. After an average of 1-year after AIGB application treatment, we found that four patients with diabetes were discontinued from oral antidiabetic treatment, and two patients switched to oral antidiabetic treatment instead of insulin treatment and two patients under antihypertensive treatment discontinued the treatment due to hypertension. Although a patient with T2DM and sleep apnea syndrome lost 22 kg of weight, we could not find an improvement in both diseases.

Complications

Procedural complications were observed, especially during initial implantation. After balloon implantation, nausea, vomiting, and epigastric pain occurred in four patients, weakness occurred in one patient, only pain occurred in one patient, and melena occurred in one patient. In one patient, the silicone balloon had to be removed 22 days after the procedure due to erythematous urticarial plaques, which appeared on the tenth day after the procedure and did not regress despite medical treatment. The patient recovered from the allergic rash within three days after the balloon was removed. Allergic rashes that occurred in a patient with nausea and vomiting regressed rapidly with antihistaminic treatment.

After the second procedure, in other words, after inflating 120 ccs, nausea and vomiting developed in one patient, and melena developed in another patient. Both patients were discharged after two days of medical follow-up and treatment. In two patients, nausea and vomiting developed after the third inflation, which was 100 cc, and their complaints regressed after three days in one patient and seven days in one patient.

Table 1. Comparison of weight, BMI, EWL and volume changes in patients treated with intragastric balloon according to the months of treatment

	Pre-operative (n=82)	Postoperatif 4th month (n=79)	Postoperatif 8th month (n=80)	Postoperatif 12th month (n=82)	Preop. - Postop. total change between 12 months (n=82)	p
Weight (kg)	117.6±27.5	108.5±25.8	102.8±28.1	98.4±26.6 †	19.2±8.3	<0.001*
BMI (kg/m^2)	42.9±10.4	39.7±9.8	37.9±10.4	35.8±9.7 †	7±3.2	<0.001*
EWL (% average)	-	28%±14.2	15%±11.8	6%±8.6	51.3%±30.1	<0.001*
Balloon volume (cm^3)	-	322.3±25.1	448.9±25.8	538.7±50.4	209.3±41.8	-
Balloon time(month)	-	4.1±0.9	3.9±1.2	4.9±2.7	12.9±3	-

* Repeated Measures ANOVA Test, † Paired Samples T Test, BMI: Body mass index; EWL= Percent of excess weight loss

Table 2. Weight, EWL changes in patients treated with intragastric balloon according to the BMI values

		Pre-operative (n=82)	Post-operative 4th month (n=79)	Post-operative 8th month (n=80)	Post-operative 12th month (n=82)	Preop. - Postop. total change between 12 months (n=82)	p
BMI <40 (n=41)	Weight (kg)	99.7±21.2	88.7±20.1	82.7±20	82.7±17.8	16.8±7.6	<0.001*
	EWL (% average)	-	41%±10.6	23.5%±12.4	11.1%±7.6	68.7±31.4	0.001*
BMI ≥40 (n=41)	Weight (kg)	135.4±20.8	122.9±19.3	120.4±22	114.1±25	16.3±6.5	<0.001*
	EWL (% average)		18.5%±7.2	7.6%±3.6	1.5%±7	33.9±15.8	0.001*

* Repeated Measures ANOVA Test, BMI: Body mass index; EWL= Percent of excess weight loss

The female patient, whose BMI was <30 kg/m^2 and who wanted to continue balloon treatment for 17 months, complained especially of halitosis in the last two months. The most common complication seen in total was nausea in 7 patients, vomiting in 5 patients, pain in 5 patients, weakness in 2 patients, allergic reaction in 2 patients, and melena in 2 patients.

DISCUSSION

Due to excessive calorie intake as a result of more accessible nutrients and a sedentary lifestyle, the prevalence of obesity increases rapidly. Current treatment approaches to fight obesity are lifestyle changes, medical treatment, endoscopic methods, and bariatric surgery. Together with lifestyle changes and medical treatment, 3-9% weight loss in 1 year can be achieved.[8] The disadvantages of pharmacological treatment are the incidence of side effects and cost. Also, many studies proved that weight loss was put back after the drug use is discontinued. Although the most effective method is surgery, many patients do not accept it because of its risks and high cost.

Adjustable intragastric balloon application, which is one of the most popular endoscopic methods in recent years, is superior to other balloon applications and surgical procedures regarding both cost and complications. Early and late complications are reported between 11% to 23% after surgical operations.[9] Nausea constitutes the majority of the complication rates that appear to be high in the intragastric balloon and adjustable intragastric balloon application, and this complaint can be resolved by medical treatment or spontaneously resolve within the first 3-7 days.[10] In our study, similar to the literature, the most frequently encountered problem in terms of complications was nausea, which occurred in 7 patients. However, nausea and vomiting rates were lower compared to other studies. The most undesirable complication was an allergic reaction, which resulted in the removal of the balloon on the 20th day. No complication in the form of balloon collapse or perforation developed in any of our patients.

In obese patients (BMI ≥ 30 kg/m^2) and especially in patients with a high cardiovascular risk profile and high overall mortality risk due to comorbid diseases, intragastric balloon application is recommended in preventive treatment.[11] Also, it has been stated that intragastric balloon implantation can be indicated in selected patients who have a BMI <30 kg/m^2 and who cannot achieve weight loss with a controlled diet program or pharmacotherapy.[12] In our study, BMI of two patients was <30 kg/m^2, BMI of nine patients was between 30 and 40 kg/m^2, and in total, 50% of our patients were below the morbid obesity limit. It was observed that the AIGB application was statistically significantly efficient in weight loss and EWL levels in both morbid obese patients and patients with a BMI <40 kg/m^2. It was found that the effect was better in patients who are under morbid obesity levels (BMI <40 kg/m^2) than patients with morbid obesity levels.

One of the critical features of intragastric balloons is their duration of use. While AIGB can be used for almost a year, other disposable balloons have a usage period of 3 to 6 months. The literature also reveals the importance of the duration of the intragastric balloon in the body in terms of lost weight. In the study of Mion et al.[13] performed with swallowable Obalon®, patients lost an average of 5 kg in 12 weeks period. Weight loss between 8.7 and 17.4 kg were reported in different studies performed with Orbera balloon, while the average weight loss was 16.9 kg.[14-16] The average weights of our patients to whom we applied AIGB were 117.6±27.5, according to the values recorded in Table 1. In the 4th month, an average weight loss of approximately 9.1 kg was found, while the amount of weight loss was 14.8 kg in the 8th month. The average weight loss of the patients at the end of the 12th month was recorded as 19.2 kg. This result shows that the amount of weight loss increases with increasing time. However, it was observed that patients lost weight at a much faster rate in the first four months, the weight loss acceleration slowed down between 4 and 8 months and decreased to lower rates between 8 and 12 months. Although the balloon was inflated in the fourth and eighth months, it could be mentioned that patients developed tolerance to the balloon over time. From this point of view, it can be estimated that shortening the balloon inflation time intervals, shortening the balloon's remaining duration in the body in parallel with this finding will yield better results.

In the data published by Usuy et al.[10] regarding Spatz AIGB, it was observed that the weight loss rate obtained in patients with a BMI rate > 40 kg/m^2 was higher than patients with a BMI < 40 kg/m^2. However, according to our data, although both patient groups benefited statistically significantly, it stands out that patients with BMI <40 kg/m^2 benefit more from AIGB when these two patient groups are compared. This result may be since the stomachs of morbidly obese patients develop a tolerance to the balloon more quickly.

Because of our belief that surgical approaches generally give better results in morbidly obese patients, we generally recommend surgical treatment to morbidly obese patients in our clinic. The patients included in this study consisted of either surgically high-risk patients due to their comorbidities, or patients who did not want surgical treatment because of their fear of surgery. We have seen that AIGB treatment is a statistically significant method for weight loss in morbidly obese patients. However, this effect was higher in the non-morbid obese patient group.

Despite the low rates of the regression of comorbid diseases, the AIGB application had satisfactory results, compared to surgical treatment.

The most significant limitation of this study was the low number of patients. The main reason was that our hospital was located in an economically lower area of our city, and patients did not have the financial power to supply AIGB.

CONCLUSIONS

Endoscopic treatment methods applied for obesity yield results just as successful as surgical techniques. It is observed that it is effective, especially in increasing the quality of life of patients who are not suitable for surgery and suffering from comorbid diseases.

Quite satisfying results are obtained in obese patients with AIGB treatment. In the morbidly obese patient group, AIGB is an advantageous method for weight loss when surgery may be risky due to comorbid diseases or surgery is not preferred by patients. In our opinion, the point to be considered in AIGB is that by keeping the balloon inflation frequencies shorter, without allowing the patients to develop tolerance to the balloon and adjusting the duration of the balloon in the body of patient not to exceed one year, we believe that it will provide optimum benefit for the patients. We think that we will be more enlightened about this subject with further studies that will be conducted with a randomized, prospective design and include a higher number of patients under these conditions.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethics committee approval was obtained from Keçiören Training and Research Hospital Clinical Research Ethics Committee (Date: 28.02.2018, Decision No: 2012-KAEK-15/1596).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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Orijinal Araştırma / Original Article

Are the Effects of Old and New-Generation Antiepileptic Drugs on Hemogram Parameters Different?

Eski ve Yeni Kuşak Antiepileptik İlaçların Hemogram Parametrelerine Etkileri Farklı Mı?

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Abstract

Introduction: There are different comments related to hematological side effects caused by antiepileptic drugs (AEDs). In our study, we investigated the effects of AEDs on hemogram parameters.

Material and Method: Hemogram values of 293 patients including 156 women, who used AEDs for at least six months, were compared with the values of 36 healthy control participants group who did not. In addition, the hemogram values of the patients using old-generation AEDs such as phenytoin (PHT), carbamazepine (CBZ), valproic acid were compared with those using new-generation AEDs as levetiracetam, oxcarbazepine, pregabalin (PGB), gabapentin and two AEDs in combination.

Results: Comparison of the patients using AEDs with the control group revealed that white blood cell (WBC) values of only PHT users were lower than the control group (p=0.045). Red cell distribution width (RDW) values were found to be higher in healthy controls than those using AEDs (p<0.001). When the groups using AEDs were compared among themselves, it was found that the WBC values of the users of old- generation AEDs as PHT and CBZ were significantly lower than those using PGB (p=0.006; P=0.005, respectively).

Conclusions: As hematological side effects, AEDs may decrease WBC counts. The WBC decreasing effects of PHT and CBZ, which are older generation antiepileptics, are more pronounced than pregabalin, which is a new-generation AED. The effects of AEDs on hemogram parameters of the patients should be taken into consideration while choosing appropriate AEDs and also while following the patient.

Keywords: Antiepileptic drugs, hemogram, white blood cells, RDW

Öz

Amaç: Antiepileptik ilaçların (AEİ) neden oldukları hematolojik yan etkilerle ilişkili farklı sonuçlar vardır. Çalışmamızda AEİ'ların hemogram parametrelerine olan etkilerini araştırdık.

Gereç ve Yöntem: En az altı ay AEİ kullanan 156'sı kadın 293 hastanın hemogram değerleri AEİ kullanmayan 36 sağlıklı kontrol grubunun değerleri ile karşılaştırıldı. Ayrıca AEİ olarak eski kuşak antiepileptik ilaçlardan fenitoin (PHT), karbamazepin (KBZ), valproik asit, daha yeni kuşak antiepileptik ilaçlardan levetirasetam, okskarbazepin, pregabalin (PGB), gabapentin ve ikili AEİ kullanan hastaların hemogram değerleri birbirleri ile karşılaştırıldı.

Bulgular: AEİ kullanan hastaların kontrol grubu ile karşılaştırmalarında sadece PHT kullananların beyaz kan hücre değerleri kontrol grubuna göre düşük bulundu (p=0.045). Sağlıklı kontrollerde "red cell distribution width" (RDW) değeri AEİ kullananlara göre daha yüksek bulundu (p<0.001). AEİ kullanan gruplar kendi aralarında karşılaştırıldığında eski kuşak AEİ'lardan olan PHT ve KBZ kullananların PGB kullananlara göre beyaz kan hücre değerlerinde anlamlı düşüklük tespit edildi (sırasıyla p=0.006; P=0.005).

Sonuç: AEİ'lar hastalarda hematolojik yan etki olarak özellikle beyaz kan hücre düşüklüğüne neden olabilirler. Daha eski kuşak AEİ'lardan olan PHT ve KBZ'in yeni kuşak AEİ'lardan pregabaline göre beyaz kan hücre değerlerinde azalma yapıcı etkileri daha belirgindir. Hastalar için ilaç seçimi yapılırken ve takipleri süresince AEİ'ların hemogram parametreleri üzerine etkileri göz önüne alınmalıdır.

Anahtar sözcükler: Antiepileptik ilaçlar, hemogram, beyaz kan hücreleri, RDW

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INTRODUCTION

Antiepileptic drugs (AEDs) play an important role in controlling seizures and increasing the quality of life of patients with epilepsy. AEDs are also used for a long time in cases such as neuropathic pain, movement disorders, psychiatric diseases. Therefore, it is important to monitor closely their clinical and biochemical side effects. As is known, AEDs can have hematological side effects.[1] It has been reported that they may cause many side effects such as thrombocytopenia, leukopenia, neutropenia, pancytopenia, pure red cell aplasia, aplastic anemia, macrocytosis, megaloblastic anemia, and bone marrow depression.[2,3] However, data on which AEDs have more of these side effects differ. Although AEDs have been reported to cause thrombocytopenia and a decrease in white blood cells, leukocytosis has been reported in some case reports.[4] Hematological effects are more common in patients who use more than one antiepileptic drug (AED).[3] In the hemograms of the patients, white blood cell (WBC), red blood cell (RBC), and platelet (PLT) counts; hemoglobin (HB), hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC)), red blood cell distribution width (RDW), mean platelet volume (MPV), plateletcrit (PCT), platelet distribution width (PDW) values are important for monitoring the hematological effects of the drugs. Changes in these blood parameters may sometimes convey vital importance. Limited number of studies have been performed on hematological side effects of AEDs. In our study, we examined the changes in hemogram parameters of patients using AEDs.

MATERIAL AND METHOD

Ethics committee approval was obtained for the study (Yıldırım Beyazıt University Faculty of Medicine Non-Pharmaceutical Clinical Research Ethics Committee. No: 09, Date: 11.06.2012). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients who had been using only AEDs for at least six months, and older than 18 years of age without known any oncological, rheumatological, immunological, hematological, allergic, infectious and granulomatous diseases; metabolic disease other than diabetic polyneuropathy, and bleeding diathesis were included in this retrospective study. A total of 293 patients using AEDs, including 156 women, were included in the study. The average age of the patient population was 42 (range 18-88) years. The control group consisted of 36 healthy volunteers who did not use AEDs. The study population consisted of patients using valproic acid (VPA) (n=97), levetiracetam (LEV) (n=29), oxcarbazepine (OXC) (n=14), phenytoin (PHT) (n=12), carbamazepine (CBZ) (n=37), pregabalin (PGB) (n=40), gabapentin (GBP) (n=34), other AEDs (n=9) and two AEDs in combination (n=21). The control group consisted of healthy individuals who did not use any antiepileptics or any other drugs. WBC, RBC, HB, HCT, MCV, MCH, MCHC, RDW, PLT, MPV, PCT, PDW values detected in the final control hemograms performed when the patients came to the neurology outpatient clinic were recorded.

All data were processed using Microsoft Excel for Windows and SPSS programs. Patients' gender, age, hematological parameters, and AEDs used were recorded as variables. Means, ranges, frequencies, and ratios were used for descriptive statistics and assessments of categorical variables. One-way analysis of variance (Anova) was used for the relationship of AEDs with hematological data, and Tukey post-hoc test was used for paired comparisons. The effect of age and gender was investigated with Bonferroni test. The value of $p < 0.05$ was accepted for statistical significance.

RESULTS

When the hemogram parameters (WBC, RBC, HB, HCT, MCV, MCH, MCHC, RDW, PLT, MPV, PCT, PDW) were compared in patients using any AED with those in the control group not using AEDs, a statistically significant difference between only WBC counts ($p < 0.001$) and RDW values ($p < 0.001$) was detected. When paired comparisons of WBC counts were made between the control group and the each group using AEDs separately, the significant difference was found only between the patients in the control group and those using PHT ($p=0.045$) (**Table 1**). When paired comparisons of RDW measurements between the control group and the groups using AEDs were made, a significant difference was detected for each drug group ($p < 0.001$) (**Table 2**). This significant difference did not change when Bonferroni corrections were calculated for the parameters of age and gender. When the patient groups using AEDs were compared among themselves in terms of hemogram parameters, only WBC values were found to be significantly different ($p < 0.001$) (**Table 3**). In paired comparisons between groups, this difference was found to be between PGB and PHT ($p=0.006$) and between PGB and CBZ ($p=0.005$) (**Table 4**). In these comparisons, when Bonferroni corrections were made for age and gender, the significance of this difference further increased. However, the risk of decrease in white blood cell counts did not increase with the use of two AEDs in combination ($p > 0.05$).

Table 1. Comparisons between groups that used and did not use AEDs in terms of WBC counts

	N	Mean ±SD	P value*
Control	36	7.40±2.15	
VPA	97	6.62±1.57	0.525
LEV	29	7.08±2.41	1.000
OXC	14	6.07±1.68	0.441
PHT	12	5.36±1.40	0.045**
CBZ	37	6.07±1.70	0.086
PGB	40	7.70±1.87	1.000
GBP	34	6.53±1.54	0.662
Dual AEDs	21	6.82±2.29	0.984

*Comparison with the control group, Valproic acid (VPA), levetiracetam (LEV), oxcarbazepine (OXC), phenytoin (PHT), carbamazepine (CBZ), pregabalin (PGB), gabapentin (GBP), antiepileptic drugs (AEDs), standart deviation (SD), white blood cell (WBC).

Table 2. Comparisons between groups that used and did not use AEDs in terms of RDW values

	N	Mean ±SD	P value*
Control	36	36.65±10.73	-
VPA	97	15.14±6.96	<0.001
LEV	29	16.50±9.32	<0.001
OXC	14	13.44±1.08	<0.001
PHT	12	13.19±1.12	<0.001
CBZ	37	15.37±8.34	<0.001
PGB	40	15.27±6.06	<0.001
GBP	34	13.89±1.01	<0.001
Dual AEDs	21	16.27±9.41	<0.001

Comparison with the control group, Valproic acid (VPA), levetiracetam (LEV), oxcarbazepine (OXC), phenytoin (PHT), carbamazepine (CBZ), pregabalin (PGB), gabapentin (GBP), antiepileptic drugs (AEDs), standart deviation (SD), red cell distribution width (RDW).

Table 3. Comparisons of hemogram parameters among AED users (Anova) (n=284 patients

	Mean±SD	p-value
WBC	6.73±1.95	<0.001**
RBC	6.50±28.71	0.492
HB	13.95±1.60	0.330
HCT	41.50±4.18	0.240
MCV	87.32±6.35	0.420
MCH	29.45±2.63	0.060
MCHC	33.62±1.42	0.052
RDW	15.06±6.71	0.737
PLT	231.38±68.74	0.207
MPV	10.88±6.66	0.930
PCT	0.25±0.07	0.376
PDW	13.38±2.31	0.174

*Patients using other AEDs were not included in the analysis. **Statistically significant. Antiepileptic drugs (AEDs), standart deviation (SD), white blood cell (WBC), red blood cell (RBC), platelet (PLT), hemoglobin (HB), hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC)), red blood cell distribution width (RDW), mean platelet volume (MPV), plateletcrit (PCT), platelet distribution width (PDW).

DISCUSSION

In our study, we examined whether there were any changes in the hemogram parameters of patients using AEDs. When the group using any AED was evaluated with the control group, the WBC counts of those using AEDs were found to be lower than the control group. When the groups using AEDs were compared with the control group, it was seen that this difference was caused by the group using PHT. When AEDs were compared among themselves, WBC counts significantly decreased in patients using PHT and CBZ, which are old-generation AEDs, compared to patients using PGB, which is a new AED.

It has been stated that the hematological side effects of AEDs may range from thrombocytopenia to neutropenia, anemia, red cell aplasia, and bone marrow failure.[5,6] In some studies, it has been reported that old-generation AEDs such as CBZ, PHT, phenobarbital, VPA induce frequent hematological changes when compared with new-generation AEDs (such as PGB, GBP, LEV, LTG, OXC, TPM, ZA), comparable to our results.[5]

The causes of hematological side effects of AEDs have not been fully understood, yet. These effects may be related to many different mechanisms such as direct toxic effects of the drugs on bone marrow, increased levels of toxic metabolites, and homocysteine, decrease in folic acid levels, direct effects of drugs on cells or their immunological effects. Neutropenia due to AEDs usually occurs in the first weeks after exposure to the drug and resolves within the first days after the drug is discontinued.[5] It is known that CBZ can cause moderate leukopenia, eosinophilia, and rarely leukocytosis.[7] Patients with low leukocyte or neutrophil counts prior to CBZ treatment may experience transient leukopenia and less frequently neutropenia.[5] Neutropenia is a rare side effect of GBP therapy.[5] Leukopenia, neutropenia, and pancytopenia have been described with LEV.[5] PHT can cause thrombocytopenia, leukopenia, neutropenia, pancytopenia, pure red cell aplasia, aplastic anemia, macrocytosis, and megaloblastic anemia.[5] Monotherapy or combination therapies with CBZ, PHT, phenobarbital and VPA decrease platelet counts more significantly when compared to treatments with newer

Table 4. Comparisons of AEDs among themselves as for their effects on WBC counts (Tukey test)

Drugs	WBC mean±SD	p-value							
		VPA	LEV	OXC	PHT	CBZ	PGB	GBP	Dual- AEDs
VPA (n=97)	6.62±1.57	-	0.95	0.882	0.405	0.842	0.060	1.000	1.000
LEV (n=29)	7.09±2.41		-	0.754	0.151	0.401	0.925	0.958	1.000
OXC (n=14)	6.07±1.67			-	0.989	1.000	0.119	0.997	0.962
PHT (n=12)	5.35±1.40				-	0.967	0.006*	0.635	0.430
CBZ (n=37)	6.06±1.70					-	0.005*	0.981	0.864
PGB (n=40)	7.70±1.87						-	0.164	0.728
GBP (n=34)	6.53±1.54							-	1.000
Dual –AEDs (n=21)	6.82±2.29								-

Valproic acid (VPA), levetiracetam (LEV), oxcarbazepine (OXC), phenytoin (PHT), carbamazepine (CBZ), pregabalin (PGB), gabapentin (GBP), antiepileptic drugs (AEDs), standart deviation (SD), white blood cell (WBC).

AED combinations.[8,9] Thrombocytopenia observed in some patients using CBZ or OXC has been attributed to excessive destruction of peripheral blood platelets.[10] It has been shown that the mechanism of thrombocytopenia is not directly related to the toxicity of CBZ, OXC or their metabolites.[10] Routine monitoring of platelet counts is recommended in patients treated with CBZ and OXC.[10] VPA may cause cytopenia by directly affecting the bone marrow or acting on one or more cell lines (pancytopenia, neutropenia, leukopenia).[11,5] The effects of VPA on the normal hematopoietic system are still largely unknown. It has been reported that in vitro VPA treatment affects the composition of hematopoietic progenitor cells, myeloid progenitor compartment, resulting in a significant and concentration-dependent inhibition of neutrophil differentiation.[12] VPA can change the membrane matrix by affecting the sphingomyelin and phosphotidylserine content in erythrocytes.[13] It has been reported that there is an increase in MCV and MCH values in patients who received VPA as mono or polytherapy.[14] Most frequently VPA induces thrombocytopenia.[15,16] Available data report a prevalence of thrombocytopenia between 5% and 54% of patients treated with VPA (12-18% in studies with sample size > 150). The risk of thrombocytopenia increases in elderly female patients, especially those who receive VPA above a dose of 1g/day.[17] The mean age of our patients using VPA was 34.2±15.8 years. In one study, when hematological changes were compared in patients treated with VPA, CBZ, LEV, and LTG, lower platelet counts were found in those treated with LEV monotherapy compared to healthy controls, and no difference was detected in HB and WBC values.[1] In our study, we did not find decreased platelet counts in patients using VPA, LEV and other AEDs. Megaloblastic anemia has been reported as potential side effect of PHT.[18] In one study leukopenia and lymphopenia were detected n PHT users, and in this study an inverse correlation was found between serum folate and PHT levels which was directly attributed to the toxic effects of the drug.[19] PHT monotherapy in children with epilepsy can significantly increase serum homocysteine levels and cause a significant decrease in serum folate and vitamin B12 levels.[20,21] Contrary to these data, some researchers reported that AEDs do not have a significant effect on biochemical and hematological parameters of epileptic patients.[22]

In our study, we found that the WBC counts were lower in patients using the old- generation AEDs especially PHT and CBZ compared to those using PGB which is one of the new-generation AEDs. In addition, we could not find any reduction in white blood cell counts in patients using two AEDs. We found no difference in the PLT, RBC, HB, HCT, MCV, MCH, MCHC, RDW, MPV, PCT, PDW values of our patients depending on the AEDs they used. In our study, RDW values of the healthy group were higher than those using AEDs, compared to the control group, while the RDW values did not differ among AED users. RDW is an index that measures the heterogeneity in the dimensions of erythrocytes.[23] As a simple and inexpensive test, RDW provides valuable information about general health status, different diseases, clinical results, complications, and mortality regardless of the underlying disorder.[24]

The shortcomings of our study can be specified as the low number of patients enrolled in the study groups for each drug; the failure to perform peripheral smear; the absence of the levels of blood AED concentrations, blood iron, ferritin, iron binding capacity, sedimentation, CRP, homocysteine, folic acid and vitamin B12; and also the absence of the counts of leukocytes' subtypes.

CONCLUSION

In conclusion, as a hematological side effect, AEDs may decrease WBC counts. The effects of PHT and CBZ, which are among the old-generation AEDs, on WBC counts are more pronounced than PGB, which is one of the new-generation AEDs. It is important to check and monitor the hemogram parameters while selecting AEDs for patients and also in the follow-up of patients using these drugs.

The effects of antiepileptic drugs on hematological parameters are still controversial. In particular, the WBC profiles of patients using old-generation antiepileptic drugs should be followed more closely..

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethics committee approval was obtained for the study (Yıldırım Beyazıt University Faculty of Medicine Non-Pharmaceutical Clinical Research Ethics Committee. No: 09, Date: 11.06.2012).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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Orijinal Araştırma / Original Article

The Effect of Epileptic Seizure Occurring After Intracranial Hemorrhages on Early Mortality

İntrakraniyal Kanamalar Sonrasında Oluşan Epileptik Nöbetin Erken Dönem Mortalite Üzerine Etkisi

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Abstract

Introduction: Intracranial hemorrhages (ICH) are at high risk for long-term morbidity and morbidity in terms of complications such as epilepsy. In our study, we aimed to determine the effect of epileptic seizure seen after ICH on early mortality and to provide information to the literature.

Material and Method: My study was done retrospectively. A total of 238 patients with a confirmed diagnosis of ICH who met the inclusion criteria were included in the study. In the classification of the seizure as early and late; early seizure up to the 14th day after bleeding; Seizures observed on the 14th day and above were classified as late seizures.

Results: In the demographic data There was no significant difference between the groups in terms of age. Seizure + 57.7% of cases were male; seizure – 52.7% of the cases were male and the groups were not different in terms of gender. When the effect of seizure type on 30-day mortality was examined, it was observed that mortality was significantly higher in cases with late seizures.

Conclusions: We determined that the epileptic seizure seen after ICH has an effect on mortality. Therefore, it is necessary to be careful in terms of mortality in cases with seizures. Especially in cases with late seizures, mortality is higher than in cases with early seizures, so it is necessary to be careful in terms of mortality in cases with late seizures. In addition, we found that the use of antiepileptic drugs did not affect mortality.

Keywords: Epileptic seizure, intracranial hemmorage, mortality, antiepileptic drugs

Öz

Giriş: İntrakraniyal kanamalar (İKK) akut fazda genellikle hematomun ve çevreleyen ödemin nöronal iletim üzerindeki yıkıcı etkisini gösteren epilepsi gibi komplikasyonlar açısından uzun dönem morbidite ve morbidite için yüksek risk altında kalmaktadır. Epileptik nöbet, İKK sonrasında akut ve uzun dönemde sık görülen durumlardan biridir. Çalışmamızda, İKK sonrasında görülen epileptik nöbetin erken dönem mortalite üzerine etkisini tespit edip literatüre bilgi sağlamayı amaçladık.

Gereç ve Yöntem: Çalışmamı retrospektif olarak yapıldı. Çalışmaya dahil edilme kriterlerini karşılayan 238 kesinleşmiş İKK tanılı hasta çalışmaya dahil edildi. Nöbetin erken dönem ve geç dönem olarak sınıflandırmasında; kanama sonrası 14. güne kadar erken nöbet; 14. gün ve üzeri süreçte görülen nöbet ise geç dönem nöbet olarak sınıflandırıldı.

Bulgular: Olguların demografik verilerinde; nöbet + olanlarda yaş ortanca değeri 69,0 yıl; nöbet – olgularda yaş ortanca değeri 69,0 ve tüm olgularda ise yaş ortanca değeri 69 yıl olup; gruplar arasında yaş açısından anlamlı fark tespit edilmedi. Nöbet + olguların %57,7'si erkek; nöbet – olguların %52,7'si erkek olup cinsiyet açısından da gruplar farklı değildi. Nöbet tipinin 30 günlük mortalite üzerine etkisi incelendiğinde ise geç dönem nöbet geçiren olgularda mortalitenin anlamlı olarak yüksek olduğu görüldü

Sonuç: İKK sonrasında görülen epileptik nöbetin mortalite üzerine etkisinin olduğunu tespit ettik. Bu nedenle nöbet geçiren olgularda mortalite açısından dikkatli olmak gerekmektedir. Özellikle geç dönem nöbet görülen olgularda mortalite erken dönem nöbet geçiren olgulara göre daha fazla olduğundan geç dönem nöbet görülen olgularda mortalite açısından dikkatli olmak gerekmektedir. Ayrıca antiepileptik ilaç kullanımının mortalite üzerine etki etmediğini tespit ettik. Daha kapsamlı çalışmalar yapılması ile bu konuda daha net bilgilerin elde edileceğini düşünmekteyiz.

Anahtar Kelimeler: Epileptik nöbet, intrakraniyal kanama, mortalite, antiepileptic ilaç

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INTRODUCTION

The World Health Organization (WHO) defines stroke as "a focal or global deficit that occurs suddenly, lasts for 24 hours or more, or results in death, with no other cause other than a vascular cause".[1] Intracranial hemorrhages (ICC) constitute 10-15% of all strokes and cause morbidity and/or mortality in 60% of cases.[2,3] A case of ICH remains at high risk for long-term morbidity and morbidity in terms of complications such as epilepsy, which generally shows the devastating effect of hematoma and surrounding edema on neuronal transmission in the acute phase.[4,5]

Epileptic seizure is one of the most common acute and long-term conditions after ICH.[6] Seizures that begin after ICH are classically divided into early seizures (from 1-2 hours to 1-2 weeks after bleeding) and late-stage seizures (seizures that occur after 3 weeks or more).[7]

Our study investigating the effect of epileptic seizure seen after ICH on early mortality is one of the few studies conducted on this subject as far as we have researched.[8] In our study, we aimed to determine the effect of epileptic seizure seen after ICH on early mortality and to provide information to the literature.

MATERIAL AND METHOD

Ethics committee approval was obtained from the ethics committee of İzmir Katip Çelebi University Ataturk Research and Training Hospital (with the decision of the ethics committee dated 18.02.2021 and numbered 0071). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Setting

Our study was conducted retrospectively between January 1, 2020 and January 1, 2021. For the study, 238 patients with a confirmed diagnosis of ICH who applied to the emergency department of our hospital and met the inclusion criteria were included in the study.

Study Population

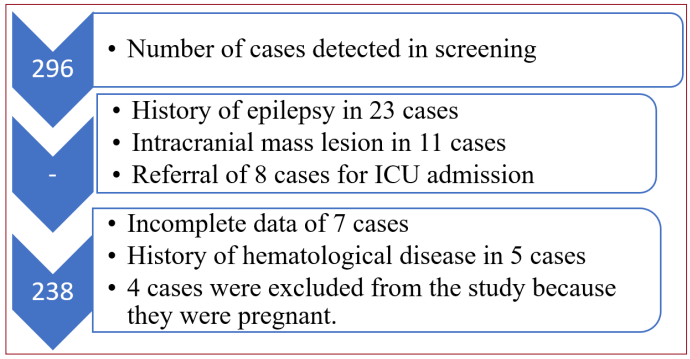
The study was planned to be performed in the emergency department of a tertiary hospital. The number of admissions to the emergency department is an average of 800 patients per day. Our hospital has a bed capacity of 1100 and is one of the largest hospitals in the region. It has units that require all critical interventions, such as aortic dissection, cerebrovascular infarction, coronary angiography laboratory, and is the region's important critical patient care and stroke center.

Patients with a definitive diagnosis of ICH and no history of trauma were included in the study. Patients under the age of 18, pregnant patients and patients with missing data were excluded from these patients. Patients who died without imaging studies, whose outcome could not be followed, and whose medical history was unknown were not included in the study. Patients with a history of any intracranial mass or space-occupying lesion in their medical history, history of epileptic disease and drug use were also excluded from the study.

Patients who were in shock when they applied to our clinic and whose vital data were unstable were not included in the study.

Data collection

For the study, patients were identified by scanning the file and automation system (Enlil Hospital Automation System). "I61.0-9, I63.0-9, I64.0-9, I65.0-9, I66.0-9, I67.0-9 and I68.0-9) ICD10 diagnostic codes from the automation system for ICH used. As a result of the scan, 196 patients were identified. Of the 296 detected cases, 23 had a history of epilepsy, 11 had a history of intracranial space-occupying mass lesion, 8 were referred to another health center due to lack of space in the intensive care unit (ICU), 7 had missing data were not included in the study because 5 of them had a history of hematological disease and 4 of them were pregnant patients.



Study Group

Demographic data of the cases, the way they came to the hospital (outpatient and ambulance), whether they had epileptic seizures, duration of epileptic seizures (prehospital, emergency service and hospitalization service), number of seizures, bleeding sites of the cases (frontal, parietal, temporal, occipital and brain stem). classified) as well as bleeding sites (supratentorial, infratentorial and intraventricular hemorrhages), the glaskow coma scale of the cases (GCS), the National Institutes of Health Stroke Scale score (NIHSS), admission vitals, whether antiepileptic therapy was initiated, response to epileptic medication, hospitalization or discharge status, outcomes, and 30-day mortality were evaluated. The cases of seizures after discharge were obtained from the medical records of the cases (e-pulse system) and mortality information was obtained from the T.C. It was evaluated from the death notification records of the Ministry of Health.

Bleeding areas and epilepsy evaluation of the cases were evaluated by a neurologist and a neurosurgeon. No electroencephalogram (EEG) or test was performed for epilepsy of the cases. A diagnosis of epileptic seizure was made with a complete clinical evaluation. The diagnosis of epilepsy was made according to the ILAE 2007 study (9). In the classification of the seizure as early and late; early seizure up to the 14th day after bleeding; Seizures observed on the 14th day and above were classified as late seizures.

Statistical Analyzes

It was done using SPSS 28.0 for Windows® statistical program (IBM Inc. Chicago, IL, USA). Number, percentage, mean, standard deviation, median, minimum and maximum were used in the presentation of descriptive data. The conformity of the data to the normal distribution was evaluated with the Kolmogorov-Smirnov Test. Pearson chi-square test and Fisher's Exact test were used to compare categorical data. T Test was used to compare two independent numerical data and Kruskal Walles Test was used to compare triple numerical data.

In our study, we first performed a regression analysis of the factors that have an effect on mortality from epilepsy. We then included the significant factors in the multiple regression analysis.

Results were considered significant at $p<0.05$, with a 95% confidence interval.

RESULTS

Our study was conducted with 238 people. 186 of these cases did not have seizures after ICH, both before and after hospitalization. Of the 52 cases, 9 had epileptic seizures before the hospital and 43 had epileptic seizures after the hospital, in the early and late period. In this way, the cases were classified as having seizures (seizure +) and non-seizure (seizure -) and data were presented.

In the demographic data of the cases; median age was 69.0 (80.75-58.25) years in those with seizure +; seizure – median age in cases was 69.0 (77.25-58) years and median age in all cases was 69 (78-58) years; There was no significant difference between the groups in terms of age. Seizure + 57.7% of cases were male; seizure – 52.7% of the cases were male and the groups were not different in terms of gender. There was no significant difference between seizure + and - groups in terms of hypertension, diabetes, coronary artery disease and dyslipidemia history. A history of ICH was found to be significantly higher only in cases with seizures + (p=0.044). There was no significant difference between the groups in the way of admission to the hospital, admission hours, admission vital signs, median values of admission GCS and NIHSS scores, and use of anticoagulant/antiaggregant (**Table 1**).

Table 1. Comparison of demographic and disease data of cases according to seizure status

Parametre	All patients (n=238)	Seizure - (n=186)	Seizure + (n=52)	p
Demographic				
Age (years)	69 (78-58)	69.0 (77.25-58)	69.0 (80.75-58.25)	.698**
Gender				.522*
Boy	128 (53.8)	98 (52.7)	30 (57.7)	
Woman	110 (46.2)	88 (47.3)	22 (42.3)	
Hypertension	142 (59.7)	111 (59.7)	31 (59.6)	.992*
diabetes	74 (31.1)	56 (30.1)	18 (34.6)	.428*
Coronary Artery Disease	44 (18.5)	30 (16.1)	14 (26.9)	.074*
ICH disease history	13 (5.5)	9 (4.8)	4 (7.7)	.048*
dyslipidemia	28 (11.8)	23 (12.4)	5 (9.6)	.114*
Disease				
Admission time				.224*
00:00-06:00	76 (31.9)	58 (31.2)	18 (34.6)	
06:00-12:00	58 (24.4)	49 (26.3)	9 (17.3)	
12-00-18:00	29 (12.2)	19 (10.2)	10 (19.2)	
18:00-00:00	75 (31.5)	60 (32.3)	15 (28.8)	
Application Form				.420*
ambulatory	36 (15.1)	30 (16.1)	6 (11.5)	
by ambulance	186 (78.2)	144 (77.4)	42 (80.8)	
Enthusiasm	16 (6.7)	12 (6.5)	4 (7.7)	
Vitals at the Time of Application				
Systolic Blood Pressure	144 (166.25-129)	145.5 (167-130.75)	137.5 (164.25-122)	.101**
Diastolic Blood Pressure	89 (100-77.75)	90 (100-78)	85 (99.5-68.25)	.181**
Heart rate	95 (115-76)	95 (114-78)	98.5 (116.75-76)	.976**
Respiratory rate	16 (18-14)	15 (18-13.75)	16 (20-14)	.242**
GCS	13 (14-12)	13.0 (14.0-12.0)	13.0 (14.0-10.0)	.210**
NIHSS	8 (16-5.75)	8.0 (16.0-5.0)	10.5 (17.5-6.0)	.113**
Anticoagulant/antiaggregant use				.109*
yes	34 (14.3)	23 (12.4)	11 (21.2)	
no	204 (85.7)	163 (87.6)	41 (78.8)	

*: Pearson $\chi 2$ Testi; **: Kruskal Wallis Test used. GCS: Glasgow coma scale, NIHSS: National Institutes of Health Stroke Scale

Bleeding was detected in the near cranial computed tomography imaging after the cases were admitted to the hospital, and the areas and amounts of bleeding were recorded. In the light of these data; In cases with seizures, the most bleeding was observed in the temporal, parietal and brain stem, respectively; In cases without seizures, it was observed that it was most common in the temporal, brain stem and parietal regions. In addition, while seizure + is not observed in cases with bleeding in other regions; seizure – bleeding was observed in the frontal region, occipital and cerebellar regions of the cases. This situation was found to be statistically significant. When classified as tentorial, there was no significant difference between bleeding sites in terms of seizures. There was no significant difference between the two groups in terms of the amount of bleeding. The relationship in terms of seizures was examined in the cases in which prophylactic antiepileptic treatment was started, and no significant difference was found. Again, no significant difference was found in terms of 7-day or 30-day mortality with the initiation of antiepileptic treatment. In terms of hospitalization, it was observed that the hospitalization status was significantly higher in cases with seizures; Again, it was observed that the rate of exitus in seizure + cases was significantly higher than in seizure - cases. Again, this significant difference was also reached when the 7-day and 30-day mortality data were compared with the seizure + and - groups. While no significant difference was found between the seizure groups in terms of hospitalization; In terms of follow-up times, the median values of the follow-up periods in seizure + cases were the same, but there was a significant difference between quartiles (p<0.001) (**Table 2**).

Table 2. Evaluation of the results of the patients' disease states and outcomes

Parameter	All (n=238)	Seizure - (n=186)	Seizure + (n=52)	p
Bleeding Site				0.003
frontal	14 (5.9)	14 (7.5)	0 (0.0)	
parietal	25 (100.0)	18 (9.7)	7 (13.5)	
temporal	164 (68.9)	121 (65.1)	43 (82.7)	
occipital	5 (2.1)	5 (2.7)	0 (0.0)	
cerebellar	7 (2.9)	7 (3.8)	0 (0.0)	
Brainstem	23 (9.7)	21 (11.3)	2 (3.8)	
Bleeding Site (tentorial)				.365
supratentorial	179 (75.2)	136 (73.1)	43 (82.7)	
infratentorial	12 (5.0)	10 (5.4)	2 (3.8)	
intraventricular	47 (19.7)	40 (21.5)	7 (13.5)	
Amount of Bleeding (mL)	10 (12-8)	10 (12-8)	10 (13.75-8)	.509
Presence of Seizure				-
No Seizure	186 (78.2)	-	186 (78.2)	
Early Seizure	25 (10.5)	-	25 (10.5)	
Late Seizure	27 (11.3)	-	27 (11.3)	
History of Prehospital Seizure				-
yes	9 (3.8)	-	9 (17.3)	
no	229 (96.2)	-	43 (82.7)	
Prophylactic Antiepileptic Use				.109
yes	34 (14.3)	23 (12.4)	11 (21.2)	
no	204 (85.7)	163 (87.6)	41 (78.8)	
Hospitalization Status				0.044
Discharge	5 (2.1)	5 (2.7)	0 (0.0)	
Service Admission	164 (68.9)	134 (72.0)	30 (57.7)	
ICU Admission	58 (24.4)	38 (20.4)	20 (38.5)	
Self-desired exit/treatment refusal	11 (4.6)	9 (4.8)	2 (3.8)	
outcome				<0.001
Discharge	172 (72.3)	145 (78.0)	27 (51.9)	
exit	66 (27.7)	41 (22.0)	25 (48.1)	
Mortality (7 Days)				.001
yes	26 (10.9)	14 (7.5)	12 (23.1)	
no	212 (89.1)	172 (92.5)	40 (76.9)	
Mortality (30 Days)				<0.001
yes	66 (27.7)	41 (22.0)	25 (48.1)	
no	172 (72.3)	145 (78.0)	27 (51.9)	
Hospitalization Time (mean / day)	8 (14-5)	8 (14-5)	11.5 (15-5)	.303
Follow-up Time (average / day)	30 (30-21)	30 (30-30)	30 (30-11.25)	<0.001

*: Pearson $\chi 2$ Testi; **: Kruskal Wallis Test used. ICU: Intensive Care Unit

Table 3. Regression analysis of parameters affecting mortality

Parameter	7 Day Mortality			30 Day Mortality		
	OR (%95 CI)	Wald test	p	OR (%95 CI)	Wald test	p
Gender	0.578 (0.223-1.498)	1.273	0.259	0.527 (0.260-1.067)	3.167	0.075
Age	1.021 (0.984-1.058)	1.212	0.271	1.002 (0.975-1.029)	0.019	0.890
Amount of Bleeding	0.940 (0.810-1.090)	0.676	0.411	0.917 (0.819-1.027)	2.231	0.135
Seizure	0.269 (0.101-0.717)	6.898	0.009	0.249 (0.112-0.553)	11.649	<0.001
Arrival NIHSS	0.862 (0.801-0.928)	15.739	<0.001	0.834 (0.788-0.883)	38.458	<0.001

NIHSS: National Institutes of Health Stroke Scale, OR: Odds Ratio, CI: Confidence interval

When the effect of seizure type on 30-day mortality was examined, it was observed that mortality was significantly higher in cases with late seizures (44% vs 51.9%; p<0.001).

The effects of age, gender, amount of bleeding, seizure + and admission NIHSS score, which are thought to be effective on mortality, on 7-day and 30-day mortality were investigated. It was observed that the increase in seizure and presentation NIHSS scores had a significant positive effect on both 7-day and 30-day mortality (**Table 3**).

DISCUSION

In this study, we aimed to investigate whether seizures have an effect on early mortality in patients who develop epileptic seizures after ICH. In the data of our study, we found that both the 7-day and 30-day mortality rates of cases with epileptic seizures were significantly higher when compared to cases without seizures.

Similarly, in the study of Szaflarski et al.[10] investigated the incidence of epileptic seizures and the effect of seizures on mortality in stroke patients; reported that seizures in hemorrhagic stroke cases cause a significant increase in 30-day mortality. Again, in a study by Vespa et al.[11] There are data that the presence of seizures in patients after hemorrhagic stroke causes an increase in mortality.

In some studies in the literature, there are publications stating that there is no significant relationship between seizure status and mortality in patients with intracranial hemorrhage. In the study of Claessens et al.[8] it was stated that epileptic seizures were not associated with mortality. In the study of Labovitz et al.[12] it was found that epileptic seizure was not associated with 30-day mortality in both ischemic and hemorrhagic stroke cases. In addition to these, some studies have shown that mortality is reduced in patients with ICH who have had seizures. In the prospective cohort study of Brüning et al.[13] It has been reported that mortality is reduced in ICH patients with seizures. Again, in the study of Mehta et al.[14] It has been reported that mortality is reduced in ICH patients with seizures.

It has been stated that there are many factors affecting mortality in ICH patients. In the study of Claessens et al.[8] high NIHSS score was associated with mortality; In addition, advanced age, high male gender, peripheral vascular disease, and the presence of anticoagulant/antiplatelet drug use were reported to be risk factors for mortality. In our study, we found that high NIHSS scores were associated with mortality; We could not detect a significant relationship between age, gender, location of bleeding and mortality. In this respect, although our study was found to be compatible with the literature in terms of NIHSS, our study did not find any significance in terms of the increased risk of mortality in terms of age, gender and anticoagulant use, and different results were found in the literature. We think that this difference may be due to the number of samples in our study.

There is no clarity in the literature on the use of prophylactic and therapeutic antiepileptic drugs for epilepsy after ICH. In some studies, there are studies reporting that long-term use of antiepileptic drugs benefits neurological recovery and survival. In their study, Claessens et al. reported that it reduced mortality and improved survival, independent of seizure frequency, in cases using antiepileptic drugs for 10 years.[8] In the study of Gilad et al. with patients with ICH; reported positive results in neurological recovery after valproate treatment given to patients.[15] In our study; It was seen that the use of antiepileptic in the cases did not have a significant effect on mortality. We think that more comprehensive and long-term prospective studies on this subject will provide clarity on this issue in the literature.

When the effects of early and late seizures on mortality were examined; Mortality was found to be significantly higher in late-stage seizures at 30-day follow-up. Therefore, as a result of our study; We think that mortality and morbidity will be prevented by making the follow-up periods of seizure patients more carefully and with shorter intervals.

Limitations of study

Our study has several limitations. One of our limitations is that the data obtained because our study was conducted retrospectively were within the scope of the information received by the physicians of the patients. Another limitation of ours is; Although there was not a large enough population to change the study data, the cases that could not be followed up in this process and were excluded due to missing data were still considered as a limitation.

CONCLUSION

We determined that the epileptic seizure observed after ICH had an effect on mortality. Therefore, it is necessary to be careful in terms of mortality in cases with seizures. Especially in cases with late seizures, mortality is higher than in cases

with early seizures, so it is necessary to be careful in terms of mortality in cases with late seizures. In addition, we found that the use of antiepileptic drugs did not affect mortality. We think that with more comprehensive studies, more clear information will be obtained on this subject.

ETHICAL DECLARATIONS

Ethics Committee Approval: İzmir Katip Çelebi University Non-Interventional Clinical Studys Institutional Review Board (date: 18.02.2021 number: 071).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Orijinal Araştırma / Original Article

An Approach to Pediatric Breast Masses in View of the Current Literature

Güncel Literatür Eşliğinde Çocuk Yaş Grubu Meme Kitlelerine Yaklaşım

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Abstract

Aim: Although breast masses are uncommon in children and adolescents, it is a worrying phenomenon for families when diagnosed. Breast masses in this age group are generally benign and most of them are seen in adolescents. In this retrospective study, it was aimed to discuss the treatment approach to breast masses in the pediatric age group.

Material and Method: The patient information was obtained from the hospital records and automation system. The patients were retrospectively analyzed with regards to age, complaints and their duration, family history, association with menstruation, location and size of the breast mass, methods of diagnosis, histopathological findings, and postoperative complications.

Results: There was no difference between neoplastic group (NG) and non neoplastic group (NNG) with respect to median age, body mass index, side and location of the mass, reason for admission, association with puberty, and follow-up time (p>0.05). When both groups were compared in terms of the size of the mass, the mass size was measured to be 2.2 cm (1.4-3) in NNG and 3.8 cm (3-8) in NG. There was no statistically significant difference between the two groups (p=0.12).

Conclusion: Surgical excision will be appropriate when a pediatric breast mass is detected in the neoplastic group, there is a family history, the size of the mass does not change or increase during follow-up, and malignancy is suspected on imaging.

Keywords: Breast, mass, child

Öz

Amaç: Meme kitleleri çocuk ve ergen yaş grubunda ender görülmesine rağmen tespit edildiğinde aileler için oldukça endişe verici bir durumdur.Bu yaş grubunda ki meme kitleleri genelde iyi huyludur ve büyük bir kısmı ergenlik döneminde görülür.Bu geriye dönük çalışma ile çocuk yaş grubunda meme kitlelerine tedavi yaklaşımının tartışılması amaçlanmıştır.

Gereç ve Yöntem: Hastalara ait bilgiler hastane kayıtları ve otomasyon sisteminden elde edildi. Olgular yaş, başvuru yakınmaları ve süresi, aile öyküsü, menstruasyonla ilişkisi, meme kitlesinin yeri, büyüklüğü, tanıda kullanılan yöntemler, histopatolojik bulgular ve cerrahi sonrası komplikasyonlar bakımından geriye dönük olarak değerlendirildi.

Bulgular: Neoplastik grup (NG) ile neoplastik olmayan grup (NOG) arasında ortanca yaş, beden kitle indeksi, tespit edilen kitlenin tarafı ve lokalizasyonu, başvuru nedeni, puberte ile ilişki ve takip süresi bakımından fark saptanmadı (p>0,05).Her iki grup tespit edilen kitlenin boyutları açısından karşılaştırıldığında NOG da kitle boyutu 2,2 cm (1,4-3), NG da kitle boyutu 3,8 cm (3-8) ölçüldü. Her iki grup arasında istatistiksel olarak anlamlı bir fark saptanmadı (p=0,12).

Sonuç: Çocuk yaş grubunda memede neoplastik grup içerisinde değerlendirilen bir kitle tespit edildiğinde, aile hikayesinin olması, kitlenin takip boyunca boyutlarında değişiklik olmaması veya artması, görüntüleme de malignite şüphesi bulunması durumunda cerrahi eksizyon uygun olacaktır.

Anahtar Kelimeler: Meme, kitle, çocuk

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INTRODUCTION

Although breast masses are uncommon in children and adolescents, it is a worrying phenomenon for families when diagnosed. Breast masses in this age group are generally benign and most of them are seen in adolescents.[1] The probability of pediatric breast masses becoming malignant is reported as 0.3%. Malignant breast masses constitute less than 1% of all childhood cancers.[2] Ultrasonography is the most commonly used imaging method in the differential diagnosis of breast masses in children, unlike adults. Mammography is not preferred in pediatric cases due to high breast density and exposure to ionizing radiation.[3] Breast masses that are benign may regress spontaneously in children. Therefore, most of the cases may require close follow-up.[4] There are very few studies in the literature conducted on the algorithm that can be used in the follow-up and treatment of pediatric breast masses. The present study aimed to retrospectively analyze the data of patients who were admitted to the pediatric surgery clinic due to breast mass, and to present the results by discussing them in view of the current literature.

MATERIAL AND METHOD

The study included patients younger than 18 years of age who were admitted to the Pediatric Surgery Clinic between January 2015 and June 2020 due to complaints of breast mass. The patient information was obtained from the hospital records and automation system. The patients were retrospectively analyzed with regards to age, complaints and their duration, family history, association with menstruation, location and size of the breast mass, methods of diagnosis, histopathological findings, and postoperative complications. As a result of examination, and laboratory, imaging and histopathological evaluation, cases diagnosed with ductal ectasia, fibrocystic disease, mastitis and abscess secondary to trauma are included in the non-neoplastic group (NNG) and those diagnosed with fibro adenoma, haemangioma, juvenile papillomatosis, intraductal papilloma in the neoplastic group (NG). Categorical variables were reported as frequency and percentage. Continuous variables were analyzed to see whether they show normal distribution using histogram, and they were reported as median and range. Ordinal and continuous variables were compared using the Mann-Whitney test and the chi-square test. SPSS software (IBM SPSS Statistics, version 25, IBM Corp, Armonk, NY, USA, 2017) was used for statistical analysis. A P value <0.05 was considered statistically significant. The study was approved by the Ethics Committee of Health Sciences University, Kocaeli Derince Training and Research Hospital with the decision no. 2020/170. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

RESULTS

63 patients were included in the study and all cases were female. As a result of the analysis, 41 cases were evaluated as NNG and 22 cases as NG. The median age of the non-neoplastic group (NNG) was 13.4 (0-18 years) and the median of the neoplastic group (NG) was 13.5 years (10-18 years). The most common reason for admission in NNG and NG was palpable breast mass (56%, 59% respectively). The median duration of complaint in NNG before the admission was 1.4 months (0.5-6 months), and it was determined to be 1.3 months for NG (0.5-6 months). Thirty-four cases (82.9%) were in post pubertal period when mass was diagnosed in NOG while 15 cases (59%) were in post pubertal period when mass was detected in NG. Family history was detected in three cases in NG. There was a history of breast trauma in four cases in NOG. The median follow-up time was 2.1 months (1-4) for NOG while it was 1.5 months (0-4) for NG.

There was no difference between NNG and NG with respect to median age, side and location of the mass, reason for admission, association with puberty, and follow-up time (p>0.05) (**Table 1**).

Ultrasonography was performed in all cases as the first imaging examination. MRI was used for differential diagnosis in 16 (25.3%) patients with masses more than 3cm in size, multiple masses, and increase in size during follow-up.

When both groups were compared in terms of the size of the mass, the mass size was measured to be 2.2 cm (1.4-3) in NNG and 3.8 cm (3-8) in NG. There was no statistically significant difference between the two groups (p=0.12).

When 22 cases who underwent mass excision were examined, the size of the mass was bigger than 3cm in nine cases (40.9%), an increase in mass size was detected in seven cases (31.8%) after menstrual period during follow-up, and six cases (27.2%) were suspected of malignancy with imaging methods, and total surgical excision was performed for histopathological diagnosis of breast masses.

In the final postoperative histo pathology reports, the histo pathological diagnosis of 14 patients (63.6%) was reported to be fibro adenoma, four cases (18.1%) to be hamartoma, and four cases (18.1%) to be juvenile papillomatosis.

No complications or recurrence were detected in the patients who underwent surgery during the postoperative follow-up.

Eight cases with breast rash, erythema, pain and tenderness on physical examination of NOG who were evaluated as mastitis and breast abscess were treated with antibiotic and anti-inflammatory agents without drainage or aspiration. The complaints of breast abscess and mastitis were disappeared at the follow-up one week later (**Table 1**).

Table 1. Characteristics of pediatric breast masses

Variable			NNG (n,%)	NG(n,%)	p
Number of Cases (n,%)	(63, 100%)		41 (65%)	22 (35%)	0.22
Age (median,years)			13.4 (0-18)	13.5 (10-18)	0.67
Admission Symptoms	Palpable Mass		23 (56.0%)	13 (59%)	0.26
	Pain		7 (17.0%)	6 (27.2%)	0.42
	Swelling and Rash		8 (19.5%)	0	
	Discharge		3 (7.3%)	3 (13.6%)	0.46
Menstrual Condition	Postpubertal		34 (82.9%)	13 (59.0%)	0.23
	Prepubertal		7 (9.7%)	9 (41.0%)	0.36
Family History	Yes		5 (12.1%)	3 (13.6%)	0.86
	No		36 (87.8%)	19 (86.3%)	0.75
Location of the Breast Mass	Right (25, 39.6%)	Upper external	7	3	0.32
		Upper internal	5	3	
		Lower external	3	1	
		Bottom internal	2	1	
	Left (32, 50.7%)	Upper external	9	4	0.45
		Upper internal	7	3	
		Lower external	4	2	
		Bottom internal	1	2	
	Multiple (4, 6.3%)		3	1	
Imaging	USG		40 (97.5%)	21 (95.4%)	0.57
	MRI		7 (17.0%)	9 (40.9%)	0.64
Size (cm)			2.2 (1.4-3)	3.8 (3-8)	0.22

DISCUSSION

Pediatric breast masses are mostly benign, and current literature supports the safety of clinical observation in this population, at least as an initial management step.

Tea et al. have reported that operation occurs due to breast mass at an average age of 16.[5] Our study found the median age to be 13.4 years in NNG, and the median age of the patients in NG to be 13.5 years, which is similar to the results in the literature.

When the literature was reviewed, no significant difference was reported between right and left breast involvement.[6,7] In our study, the most common location was the left upper quadrant while no significant difference was found between the right and left breast.

A complete and detailed history and physical examination are crucial for the diagnosis of pediatric breast masses. Ultrasonography is important among imaging methods and the best diagnostic tool for any palpable breast mass in this age group. Ultrasound enables accurate measurements of breast masses and helps to monitor increase in size. However, the place of the BI-RADS classification has not yet been proven in the pediatric population. Koning et al. concluded that this classification may increase the risk of malignancy or surgical procedure in the pediatric age group.[8]

Mammography is not used routinely in the young as the pediatric breast is denser than that of an adult, which may limit the sensitivity of mammography. Mammography also uses ionizing radiation and the principle of exposure to radiation in a young population is to maintain the radiation level as low as reasonably achievable. Computed tomography and magnetic resonance imaging (MRI) are helpful in that they can be utilized in characterizing breast masses when sonography is not suitable and in evaluating the extent of metastatic disease or primary tumour for surgical planning.[9] The present study used MRI for differential diagnosis in 16 (25.3%) patients with masses more than 3 cm in size, multiple masses, and increase in size during follow-up.

As known from the literature, the most common benign breast tumour in adolescents is fibro adenoma, which accounts for 68% of all breast masses.[10] In our study group, 81.7% of all breast masses that were completely removed were reported to be fibro adenoma and juvenile fibro adenoma.

Neoplastic breast masses should be suspected to be benign if they show smooth, well-defined circumscribed hyper echoic or slightly hypo echoic, thin echogenic capsule, ellipsoid or less lobulation in imaging studies. Malignant breast masses were evaluated as those that are larger, elongated masses with micro calcification, posterior acoustic shadowing, and hypo echoic nodular lesions.[11]

When the literature was examined, no significant difference was observed between sizes in studies conducted on the size of breast masses undergoing surgery.[5-7] The smallest mass in our study was measured to be 3cm while the largest one to be 8 cm in NG who underwent surgery.

Ezer et al.[7] reported the period of admission to the clinic due to breast mass to be one month. In our study, the admission period for NG was determined to be 1.3 months.

Some researchers advocate removing all the fibro adenomas while some others argue that fibro adenomas can be followed up in periods considering the low incidence of breast cancer in adolescents.[14] When the literature is reviewed, surgery is recommended for patients who experience increase in size rather than decrease during follow-up, have complicated USG findings, have a family history of breast cancer, and have a history of malignancy.[6,7,15,16] The average follow-up period of cases with breast masses is 7.4 months. Among the indications for surgery, the most common reason is suspicion of malignancy (65%). This is followed by the mass that did not disappear in the follow-up (25%), increase in mass size (5%), and multiple masses (5%).

Although the risk of malignancy in pediatric breast masses is very low, this possibility should be kept in mind during follow-up due to the risk of developing carcinoma from the epithelial region reported as 0.1-0.3%.[18] The present study detected no malignant mass in NG cases that underwent surgery, and observed no recurrence or complications during the follow-up.

Although the treatment of giant fibro adenomas and juvenile fibro adenomas is recommended to be carried out without surgery, the epithelium of juvenile fibro adenomas being sometimes shown at the border suggests that benign pediatric breast masses should be treated surgically. It should note that the follow-up of mass is not a form of treatment.[19]

This study has certain limitations. The study was conducted by scanning records retrospectively and the number of patient groups is low. There is a need for prospective studies with a wider patient group on this subject.

CONCLUSION

In children, it is of almost importance to avoid unnecessary surgical intervention in order not to damage the developing breast tissue and not to adversely affect the patient's psychology. On the other hand, surgical excision will be appropriate when a pediatric breast mass is detected in the neoplastic group, there is a family history, the size of the mass does not change or increase during follow-up, and malignancy is suspected on imaging.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the Ethics Committee of SBÜ Kocaeli Derince Training and Research Hospital with the decision no. 2020/170.

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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Orijinal Araştırma / Original Article

The Effect of Vitamin B12 Levels on Prognosis in COVID-19 Patients

COVID-19 Hastalarında Vitamin B12 Düzeyinin Prognoz Üzerine Etkisi

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Abstract

Objectives: It is known that vitamins have some effects such as suppressing viral replication, developing anti-inflammatory responses and that they increase immunity in COVID-19. This study aimed to investigate the correlation between the vitamin B12 (Vit B12) serum levels and the prognosis of the disease in patients with COVID-19.

Material and Method: A total of 408 participants were included in the study. Sociodemographic information such as age, educational status, serum vitamin B12 levels, hemogram parameters, and clinical findings of the patients who were admitted for follow-up after the end of COVID-19 infection was evaluated retrospectively. Serum vitamin B12 level between 150-200 pg/mL was assessed as mild deficiency, the value between 100-150 pg/mL as severe deficiency and the value under 100 pg/mL as extremely severe deficiency.

Results: It was determined that the clinical progression of COVID-19 patients with vitamin B12 deficiency was worse than those without vitamin B12 deficiency. Therefore, we think that Vit B12 supplementation may have a positive effect in COVID-19 patients. However, longer-term and more comprehensive studies with more patients are needed on this subject.

Conclusion: The clinical progression was worse in COVID-19 patients with Vit B12 deficiency than those who had no Vit B12 deficiency. Therefore, it has been concluded that Vitamin B12 supplement can have positive effects on COVID-19 patients; however, more comprehensive further studies with longer duration and higher number of patients are needed.

Keywords: COVID-19, vitamin B12, inflammation, prognosis

Öz

Amaç: Vitaminlerin, Koronavirüs Hastalığında (COVID-19) viral replikasyonu bozma, anti-inflamatuar yanıt geliştirme gibi etkileri olduğu ve immüniteyi artırdıkları bilinmektedir. Bu çalışmada, COVID-19 hastalarında Vitamin B12 (Vit B12) serum seviyeleri ve hastalığın prognozu arasındaki ilişkiyi görmeyi amaçladık.

Gereç ve Yöntem: Çalışmaya COVID-19 enfeksiyonu geçiren 408 katılımcı dâhil edildi. Hastaların yaş, eğitim durumu gibi sosyodemografik bilgileri, serum Vit B12 düzeyleri, hemogram parametreleri, klinik bulguları retrospektif olarak incelendi. Serum B12 vitamini düzeyi 200-2000 normal, 150-200 pg/mL arası hafif eksiklik, 100-150 pg/mL arası ağır eksiklik 100 pg/mL'nıın altı ise çok ağır eksiklik olarak gruplandırıldı.

Bulgular: Katılımcıların yaş ortancası 44.51(18-88), Vit B12 düzeyi ortancası ise 179.50 ng/L (75-641) idi. Hastaların 248 (%60.78)'inde Vit B12 eksikliği vardı. Ağır Vit B12 eksikliği olan hastalarda ve çok ağır Vit B12 eksikliği olanlarda ateş, diğer gruplardan daha fazlaydı. Benzer şekilde öksürük, tat ve koku kaybı, baş ağrısı, pnömöni ve hospitalizasyon oranı daha yüksekti (P<0.01). Gruplar arasında platelet ve nötrofil sayıları açısından anlamlı farklılık vardı. Vit B12 düzeyi normal oranlara göre hafif ve ağır olan hastaların platetet sayısından daha yüksekti (p<0.01).

Sonuç: Vit B12 düzeyi eksikliği olan COVID-19 hastalarının klinik progresyonunun Vit B12 eksikliği olmayanlardan daha kötü olduğu belirlendi. Bu nedenle COVID-19 hastalarında Vit B12 takviyesinin olumlu etkisi olabileceğini düşünmekteyiz. Fakat bu konuda daha uzun süreli ve daha fazla hasta ile kapsamlı çalışmaların yapılması gerekmektedir.

Anahtar Kelimeler: COVID-19, vitamin B12, inflamasyon, prognoz

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INTRODUCTION

COVID-19 causes a wide clinical spectrum of diseases such as asymptomatic infection, mild upper respiratory tract infection and severe lower respiratory tract infection with respiratory failure.[1]

Vit B12 is an important immunomodulator that has a supportive function for hematopoietic, nerve and immune systems.[2] It can suppress viral replication in the host cell.[3] In Vit B12 deficiency, lymphopenia, decrease in the number of CD8 cells and dysfunction of natural killer cells can be observed.[4] In addition, Vit B12 deficiency increases oxidative stress by increasing methylmalonic acid and homocysteine, which results in endothelial dysfunction, thrombocyte activation, elevated tissue factor expression, and activation of the coagulation cascade.[5,6]

Nutritional deficiencies such as vitamin D, Vit B12 and selenium deficiency are seen in patients with COVID-19 and it is known that these deficiencies can affect the host immune responses against viral infections and inflammatory activity. Moreover, nutritional deficiencies can be effective in the onset of COVID-19 infection and the clinical severity of the disease.[7,8] Optimal levels of vitamins and trace elements known as immunomodulators and stimulators for the immune system to function in optimal conditions are important in the struggle against COVID-19.[9] Vit B12 is predicted to increase immunity with the effects of suppressing viral replication, developing anti-inflammatory responses and decreasing proinflammatory responses in COVID-19.[10] However, according to the authors' knowledge the correlation between serum Vit B12 levels and clinical results of Vit B12 deficiency in patients with COVID-19 has not been clarified yet.

This study aimed to reveal the effect of Vit B12 level and Vit B12 deficiency on the clinic and symptoms in patients with COVID-19.

MATERIAL AND METHOD

This is a retrospective study performed on patients who were diagnosed with COVID-19 by a PCR test and admitted to the Pandemic Outpatient Clinic of XXXX State Hospital between February-June 2020 for follow-up examination within the 14 days after the end of quarantine. The study sample was obtained from the files of all patients who were Turkish citizens diagnosed with COVID-19 and admitted to XXXX State Hospital Internal Diseases Outpatient Clinic for post-COVID follow-up and who were tested for serum Vit B12 level. A total of 408 patients were included in the study. Sociodemographic characteristics such as age and educational status, serum Vit B12 levels, laboratory parameters, neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were accepted as inflammatory markers, and clinical results of the patients diagnosed with COVID-19 were obtained with file scanning. The data obtained were recorded in a form prepared by the researchers. Demographic characteristics and comorbidities of the patients were assessed between those with and without Vit B12 deficiency. The patients were classified according to their Vit B12 levels in order to determine the differences between clinical and laboratory results. For Vit B12 levels, the values between 200-2000 ng/L as normal, 150-200 ng/L were accepted as a mild deficiency, values between 100-150 ng/L as severe deficiency and values under 100 ng/L as very severe deficiency.[11]

Setting and sampling

A total of 425 patients admitted between June 2020 and November 2020 were included in the study. Seventeen patients who did not meet the inclusion criteria were excluded from the study. The study was completed with 408 patients. The exclusion criteria were as follows; being under the age of 18, pregnancy or lactation, having a significant liver, renal or hematologic dysfunction during screening, and having heart failure or psychiatric disease.

Statistical analysis

The study's statistical evaluation was made using the SPSS version 22.0 (IBM Corp., Armonk, NY, USA) computer package program. Mean, standard deviation, median, minimum and maximum values as descriptive statistics were calculated for continuous variables among the emphasized features and categorical variables were expressed as numbers and percentiles. Whether the numerical data of the variables were normally distributed or not was determined with one sample Kolmogorov Smirnov test. The chi-square test was used to determine between the groups and categorical variables. The intergroup differences were assessed with ANOVA. Tukey test was used in values with difference. Statistical significance level was accepted as $p<0.05$.

RESULTS

A total of 408 participants were included in the study. The median Vit B12 level of all the patients was 179.50 (75-641). The median age of the participants was 44.51 years (18-88) Of the patients, 69 (16.92%) had at least one chronic disease. Fifty patients (12.25%) had hypertension; 38 (9.31%) had diabetes mellitus; 29 (7.10%) had pulmonary disorder; 12 (2.94%) had heart failure; 2 (0.50%) had neurological disorder; and 2 (0.50%) had malignancy. Of the patients, 248 (60.78%) had Vit B12 deficiency. When those with deficiency were categorized very severe deficiency was recorded in 16 (3.92%), severe deficiency in 105 (25.73%) and deficiency in 127 (31.12%) (**Table 1**). The groups with and without Vit B12 deficiency were similar in terms of age, gender and presence of at least one comorbid disease (p: 0.057, p: 0.168 and p: 0.426 respectively) (**Table 2**). The symptoms and their distributions were presented in the **Table 3** in detail. The rate of fever was higher in patients with severe Vit B12 deficiency and those with extremely severe

Vit B12 deficiency. Similarly pneumonia, cough, rate of hospitalization, loss of taste and smell (p<0.01), headache, sore throat and dyspnea were higher (p<0.05). The groups were different in terms of platelet and neutrophil counts. Platelet count was higher in the patients with mild and severe Vit B12 deficiency than in those with normal Vit B12 levels (p<0.01). Neutrophil levels were higher in the patients with severe Vit B12 deficiency than in those with normal Vit B12 levels (p<0.01) (**Table 4**).

Table 1. Vitamin B12 Levels of Study Group

Vitamin B12 Levels (Median, min-max)	
179.50 (75-641) ng/L	
Variables	**n (%)**
Normal Vitamin B12 (200-2000 ng/L)	160 (39.21)
Vitamin B12 Deficiency (<200 ng/L)	248 (60.78)
Mild (150-200 ng/L)	127 (31.12)
Severe (100-150 ng/L)	105 (25.73)
Very Severe (<100 ng/L)	16 (3.92)

Table 2. Socio-Demographic Information of Patients According to Their Vitamin B12 Status

Variables	Normal n (%)	Vitamin B12 Deficiency n (%)	p
Gender			0.168
Male	65 (40.62)	118 (47.58)	
Female	95 (59.37)	130 (52.41)	
Age	47.2±15.2	44.1±16.1	0.057
Marital Status			0.019
Single	25 (15.62)	63 (25.40)	
Married	135 (84.37)	185(74.60)	
Educational Status			0.135
Illiterate	20 (12.50)	18 (7.25)	
Primary / Secondary School	76 (47.50)	112 (45.16)	
High School	35 (21.87)	53 (21.37)	
Associate's/Bachelor's Degree	21 (13.12)	54 (21.77)	
Postgraduate	8 (5.00)	11 (4.43)	
Presence of Chronic Disease			0.426
Yes	30 (18.75)	39 (15.72)	
No	130 (81.25)	209 (84.27)	

*Pearson chi-square tests were used in the analysis of the data, and corrections were made with Fisher's exact test in the cells with small numbers (p<0.05)

DISCUSSION

This study was conducted with the aim of revealing the effect of Vit B12 level and deficiency on the clinics and symptoms in COVID-19 patients, it was found that pulmonary involvement and hospitalization rates were higher and the difference between the clinics and severity of the deficiency increased in the patients with Vit B12 deficiency. Vit B12 is a vitamin with an immunomodulation effect and plays an important role in our immune system. Vit B12 can decrease the severity of COVID-19 by suppressing viral replication.[12] As far as we reviewed literature we could not find many studies assessing Vit B12 level in COVID-19 patients and its relationship with clinical progression. Shakeri et al. found the serum Vit B12 levels of the hospitalized COVID-19 patients as 465.4±35.70 ng/L in their third day of hospital stays and Im et al. found Vit B12 levels of the COVID-19 adult patients admitted to Inha University Hospital in North Korea as 727 (535.5-962.8) ng/L in the seventh day. In the current study, Vit B12 level of the participants was 179.50 (75-641) ng/L, which was lower than those in the previous studies.[6,13] This may be due to race, gender and sociocultural differences.

Table 3. Comparison of Symptoms and Clinics of Patients According to the Status and Severity of Vitamin B12 Deficiency

	Normal n (%)	Mild n (%)	Severe n (%)	Very severe n (%)	p
Symptoms					
Fever	42 (26.25)	29 (22.83)	37 (35.24)	13 (81.25)	<0.001
Cough	56 (35.00)	39 (30.71)	42 (40.00)	15 (93.75)	<0.001
Sore Throat	48 (30.00)	27 (21.25)	23 (21.90)	9 (56.25)	0.010
Dyspnea	25 (15.62)	17 (13.38)	25 (23.81)	3 (18.75)	0.0184
Muscle and joint pain	80 (50.00)	62 (48.81)	61 (58.09)	10 (62.50)	0.386
Loss of taste/smell	82 (51.25)	71 (55.90)	73 (69.52)	15 (93.75)	<0.001
Lack of appetite	68 (42.50)	38 (29.92)	32 (30.47)	3 (18.75)	0.641
Backache	62 (38.75)	55 (43.30)	42 (40.00)	8 (50.00)	0.880
Fatigue	89 (55.62)	62 (48.81)	64 (60.95)	13 (81.25)	0.056
Headache	42 (26.25)	43 (33.85)	30 (28.57)	10 (62.50)	0.042
Clinics					
Hospitalization	9 (5.62)	9 (7.08)	15 (14.28)	7 (43.75)	<0.001
Pneumonia	8 (5.00)	7 (5.51)	15 (14.28)	7 (43.75)	<0.001

*Pearson chi-square tests were used in the analysis of the data, and corrections were made with Fisher's exact test in the cells with small numbers (p<0.05)

Table 4. Comparison of Laboratory Findings Data of Patients According to According to The Status and Severity of Vitamin B12 Deficiency

Laboratory Findings	Normal X±SS	Mild X±SS	Severe X±SS	Very Severe X±SS	p
Platelet, $\times10^9$/L	250.46±59.00	287.57±103.08	280.64±78.33	253.68±32.78	<0.001
Neutrophil, $\times10^9$/L	3.76±1.42	3.97±1.29	4.16±1.31	3.34±1.37	0.039
Lymphocyte, $\times10^9$/L	3.49±2.08	3.42±2.07	3.37±2.10	2.43±1.07	0.274
MPV f/L	8.39±2.64	8.43±2.86	8.76±2.51	9.08±2.37	0.555
PDW %	11.64±7.11	12.01±4.48	13.25±10.65	15.39±9.67	0.136
NLR	1.37±0.72	1.50±0.72	1.59±0.81	1.48±0.50	0.113
PLR	95.73±54.15	113.28±79.36	103.91±46.81	115.67±29.99	0.093

MPV: mean platelet volüme, PDW: platelet distribution width, NLR: neutrophil-to-lymphocyte ratio, PLR platelet-to-lymphocyte ratio, *ANOVA test was used to examine the differences in quantitative data between groups (p<0.05). The significant difference in PLT values is due to the differences between normal – severe (p=0.014) and normal - mild (p<0.001) groups. The significant difference in neutrophil values is due to the difference between the normal and very severe groups (p=0.047).

It can be assumed that Vit B12 supplement in the patients infected with COVID-19 will provide faster recovery, decrease oxidative stress, improve clinical progression and minimize the conditions caused by the disease such as lung infection, multiple organ dysfunction and mortality by acting as an anti-inflammatory and analgesic agent.[5,6] In a study assessing the levels of the hospitalized COVID-19 patients during admission and their clinical results (length of hospital stay, intensive care unit stay and mortality), Vit B12 levels of the death COVID-19 patients were lower than those of the patients staying in the intensive care unit and wards and Vit B12 levels did not affect the need for intubation or length of hospital stay.[13] However, it was reported in another study that Vit B12 supplement for COVID-19 patients reduced the length of hospital stay.[14] When we consider that Vit B12 supplement provides faster recovery and can decrease pulmonary involvement it is possible to expect higher rates of hospitalization and lung infection in COVID-19 patients with Vit B12 deficiency like in our study. In addition, our study had similar results with the other studies in terms of the increasing clinical deterioration with the increasing severity of the deficiency of Vit B12.

It is known that COVID-19 causes severe disruptions in the quality of life.[15] Although clinical findings of COVID-19 are various the most common symptoms are fever and cough. Sore throat and fatigue can accompany these symptoms.[16] In addition, loss of smell has a very high rate and it has been reported in some studies that its incidence ranges from 5% to 68%.[17] Loss of taste and smell tends to happen together. The mechanism under the loss of smell in COVID-19 patients is not clearly known. However, it is considered to be due to neurological damage.[18] Additionally, Vit B12 deficiency can cause disruptions in respiratory, gastrointestinal and central nervous systems as well.[19] In our study, those with extremely severe Vit B12 deficiency had a higher rate of loss of taste. Further studies are needed to understand whether Vit B12 deficiency has an effect on loss of taste in COVID-19 patients.

The information about between the severity of Vit B12 deficiency and COVID-19 symptoms is insufficient in the literature. It has been revealed in studies that Vit B12 supplements have the potential to decrease the symptoms associated with COVID-19.[8,10] In our study, the rates of fever, cough, and loss of taste/smell were higher, which suggests that the symptoms and quality of life can be affected by the increasing Vit B12 deficiency.

Lymphopenia is one of the common hematologic changes in COVID-19.[20] A significant systemic increase occurs in inflammatory mediators and cytokines about 7-14 days after the onset of the symptoms and lymphopenia becomes significant.[21] The increased NLR and PLR levels, markers of inflammation, are associated with the clinical severity of COVID-19.[22,23] There is no study assessing the hematologic parameters in Vit B12 deficiency in COVID-19 patients. Therefore, it is one of the rare studies revealing the correlation between Vit B12 deficiency and clinics and laboratory results in COVID-19 patients, which is the strength of our study. Vit B12 deficiency can cause hematologic changes as well.[19] The group with Vit B12 deficiency had a higher rate of lymphopenia and high NLR and PLR, which may be caused by the disease process and Vit B12 deficiency which is an immunomodulator. Moreover, when it is considered that Vit B12 supplement decreases inflammation it can be expected that the inflammation markers increase in case of its deficiency.

The limitations of the present study were being retrospectively performed and the analyses could not be performed during the quarantine period when the disease was active.

CONCLUSION

The clinical progression of COVID-19 patients with Vit B12 deficiency is worse. The specific symptoms such as fever, loss of taste/smell and cough were more common in patients with Vit B12 deficiency. In addition, the inflammation markers of the patients with Vit B12 deficiency were higher. Therefore, it is considered that Vit B12 has effects on the prognosis and symptoms in COVID-19 patients. Moreover, Vit B12 supplements in COVID-19 patients can have a positive effect on the clinics during the infection period. More comprehensive basic and clinical studies on the effect of Vit B12 deficiency on the pathology and Vit B12 supplement in COVID-19 patients should be performed..

ETHICAL DECLARATIONS

Ethics Committee Approval: The institutional consent to perform the study was obtained from Kayseri Provincial Directorate of Health and the study was approved by the Ethics committee of Nuh Naci Yazgan University (Decision number: 1/711 and Date: 19.02.2021).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Orijinal Araştırma / Original Article

A Comparative Prospective Study with Depression, Anxiety and Quality of Life Scales in Women with Induced Abortion and Miscarriage before Pregnancy Termination

İsteyerek Düşük Yapan ve Spontan Düşük Yapan Kadınlarda Depresyon, Anksiyete ve Yaşam Kalitesi Ölçekleri ile Karşılaştırmalı Prospektif Bir Çalışma

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Abstract

Aim: We aimed to compare the pre-termination quality of life (QoL) domains, depression and anxiety symptoms of women whose pregnancy will be terminated due to induced abortion and miscarriage (spontaneus abortion).

Material and Method: This prospective case-control study included women hospitalized for pregnancy termination less than 10 weeks old at a university hospital between January 2020 and December 2020. Self-evaluation questionnaires were presented to 35 women in the induced abortion group and 35 women in the miscarriage group. Women with chronic systemic diseases, those with known psychological disorders and therefore taking medication, women who were offered an abortion with the decision of the health board and who did not want to fill out the questionnaire were excluded from the study. For this, WHOQOL-BREF short-form quality of life questionnaire, Beck Depression and Anxiety Inventory were used to determine psychological stress levels before termination.

Results: Moderate-severe depression symptoms were found to be statistically higher (31.4%, 5.7%, respectively) in induced abortion group than miscarriage group ($p<0.05$). Similarly moderate-severe anxiety sypmtoms were 34.3% in the induced abortion group and 8.6% in the miscarriage group, and a statistical difference was observed ($p<0.05$). We found the lowest percentages in the environmental domain of QoL in both group. In terms of the psychological domain of QoL and the physical domain of QoL, we obtained statistically significantly lower results in the induced abortion group compared to the miscarriage group ($p<0.05$).

Conclusion: It was observed that women who had induced abortion were more prone to depression and anxiety before pregnancy termination than those who had miscarriage . The low level of environmental domain of QoL was noted in both groups, and the physical and psychological domains of QoL were found to be lower in the induced abortion group. Whether they have a pregnancy plan or not, we believe that supporting women of reproductive age with self-efficacy-enhancing strategies and increasing their psychological resilience will benefit them in the early pregnancy problems and management they will encounter in the future.

Keywords: Induced abortion, miscarriage, depression, anxiety, quality of life

Öz

Amaç: Çalışmamızda isteyerek düşük ve spontan düşük nedeniyle gebeliği sonlandırılacak olan kadınların, gebelik terminasyonu öncesi yaşam kalitesi (YK) düzeyleri, depresyon ve anksiyete belirtileri açısından karşılaştırılmasını amaçladık.

Gereç ve Yöntem: Prospektif vaka-kontrol çalışmamıza, Ocak 2020 ile Aralık 2020 arasında bir üniversite hastanesinde, gebelik yaşı 10 haftadan küçük olan ve gebelik terminasyonu nedeniyle hastaneye yatırılan kadınlar dahil edildi. İsteyerek düşük grubundaki 35 kadına ve spontan düşük grubundaki 35 kadına öz değerlendirme anketleri sunuldu. Kronik sistemik hastalığı olan, daha önce psikolojik rahatsızlığı bilinen ve bu nedenle ilaç kullananlar, sağlık kurulu kararı ile kürtaj önerilen ve anketi doldurmak istemeyen kadınlar çalışma dışı bırakıldı. Terminasyon öncesi yaşam kalitesini değerlendirmek için WHOQOL-BREF kısa form yaşam kalitesi anketi, psikolojik stres düzeyini belirlemek için Beck Depresyon ve Beck Anksiyete envanteri kullanıldı.

Bulgular: İsteyerek düşük grubunda orta-ağır depresyon belirtileri istatistiksel olarak spontan düşük grubuna göre daha yüksek bulundu (sırasıyla %31,4, %5,7, $p<0,05$). Benzer şekilde, isteyerek düşük grubunda orta-şiddetli anksiyete belirtileri %34,3, spontan düşük grubunda %8,6 idi ve istatistiksel olarak anlamlı fark gözlendi ($p<0.05$). Yaşam kalitesi ölçeğinin fiziksel ve psikolojik alanı açısından, isteyerek düşük grubunda spontan düşük grubuna göre istatistiksel olarak anlamlı derecede daha düşük sonuçlar elde ettik ($p<0.05$).

Sonuç: İsteyerek düşük yapan kadınların, gebeliği sonlandırmadan önce, spontan düşük yapanlara göre depresyon ve anksiyeteye daha yatkın oldukları gözlendi. İsteyerek düşük grubundaki düşük psikolojik YK skorları ve her iki gruptaki düşük çevresel YK skorları, üreme çağındaki kadınların öz yeterliklerini ve psikolojik dayanıklılıklarını artıracak stratejilerle desteklenmelerinin, ileride yaşanacak erken gebelik sorunlarının yönetiminde onlara fayda sağlayacağını düşündürmektedir.

Anahtar Kelimeler: Isteyerek düşük, spontan düşük, depresyon, anksiyete, yaşam kalitesi

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INTRODUCTION

Induced abortion is common worldwide, but its incidence is not known precisely due to legal differences between countries. It has been reported as 40 per 1000 women between 1990 and 2014, and this rate may differ according to societies and regions. Between 2010 and 2014, approximately 56 million abortions were performed worldwide each year.[1] Therefore, there are studies examining the relation between induced abortion and psychological and psychiatric disorders, since it is widely related to public health. Studies and their results are likely to be contradictory for local, social and legal reasons. In a study of over 5000 women from China, induced abortion was shown to be associated with increased suicidal ideation.[2] On the other hand, in a subject conducted for women in the USA, it was noted that there was no relation between induced abortion after the first unwanted pregnancy and symptoms of depression.[3] It is also stated in the ESHRE workup that it is a safe practice for induced abortion. Evidence is sufficient and reassuring that it does not pose a risk for subsequent fertility, breast cancer, and mental health.

Clinical miscarriage accounts for 12% of all pregnancies, and one out of every four women miscarries by age 39.[4] After miscarriage follow-up, 34.1 percent of women have positivity in depression screening. Among the risk factors; young age, low education level, advanced gestational age at the time of miscarriage, and the presence of previous miscarriage have been reported.[5] Although studies are mostly conducted on depression and anxiety screening in the monthly periods after miscarriage, it is reported that there is a 41% increase in anxiety levels immediately after miscarriage as well as women and their partners face clearly increased depression and anxiety.[6] Women who report adverse life events prior to miscarriage are twice as likely to have a chromosomally normal miscarriage. There are meta-analyses that report an increase in miscarriage in women with a history of exposure to psychological stress, even after adjusting for lifestyle factors, suggesting that psychological stress before and during pregnancy is associated with miscarriage.[7,8] Although chromosomal abnormalities underlie many cases of early pregnancy loss, psychological stress factors before and during pregnancy have been reported to increase the risk of miscarriage. In the same study, there are suggestions for psychological counseling in routine prenatal care and inferences that it can prevent misscariage.[9] In the study of quality of life in women who had miscarriage, there was no deterioration in the general quality of life, but they reported poor results in terms of the psychological domain of quality of life after the miscarriage.[10]

As mentioned above, studies mostly focused on psychological health problems following early pregnancy loss. However, there is insufficient data on the relationship between symptoms of psychological deterioration and quality of life during pregnancy and prior to termination. We hypothesized that deterioration of pre-pregnancy psychological status and quality of life may be seen at a higher rate in women who decided to induced abortion during early pregnancy. The primary aim of our study is to compare the women who decided to terminate the pregnancy (induced abortion) and the women who experienced spontaneous abortion (miscarriage) in terms of variables such as quality of life, depression and anxiety symptoms.

MATERIAL AND METHOD

Study Design

This study was designed prospectively and approved by BBBBBB University Institutional Review Board and Ethics Committee (Project no: KA: 18/303). Written informed consent was obtained from the participants. Two-tailed power analysis of two independent groups was performed using the G Power computer program,[11] and the total number of samples required to detect large effects was 70 using chi-square with 90% power.

Inclusion and exclusion criterias

Women whose pregnancy was terminated between January 2020 and December 2020 were included in the study by dividing them into two groups (induced abortion and miscarriage). Women who had a pregnancy less than 10 weeks and wanted to terminate the pregnancy voluntarily constituted the induced abortion group, and women who resulted in spontaneous pregnancy loss under 10 weeks constituted the miscarriage group. According to country rules, our termination week was up to 10 weeks and therefore those with gestational weeks between 6 and 10 weeks were included. Gestational terminations were performed by applying dilatation and curettage procedures in all patients included in the study.

Women with chronic systemic diseases (chronic renal failure, hypertension, severe endocrine disorders, known diagnosis of thrombosis) or who were recommended to terminate pregnancy (teratogen drug use, radiation exposure, teratogen infections) were excluded from the study. In addition, patients with a diagnosis of psychiatric disease and using medication for this reason were also excluded from the study.

The questionnaires listed below were filled in for the patients who met the inclusion criteria, after their consent was obtained. All patients were literate. Foreign language support was not needed for any patient. 6 patients in the study group and 3 patients in the control group did not fill in the questionnaires and gave up answering the questionnaires.

Questionnaires

The World Health Organization Quality of Life Short Form Turkish Version questionnaire (WHOQOL-BREF-TR): The World Health Organization Quality of Life (WHOQOL) is questionnaire including different domains to evaluate quality of life. This material is modified for diverse societies. WHOQOL-BREF is a short form of the initial material.[12] WHOQOL-

BREF-TR is specific for Turkey, which was verified by studies.[13] WHOQOL-BREF-TR consists of 26 items related to the various aspects of life and is related to the following domains; overall (2 items), physical (7 items), psychological (6 items), environmental (8 items) and social ties (3 items). Quality of life score cannot be defined by adding scores from all domains. All areas are evaluated separately and independently reflect different aspects of the quality of life. Scores range from 1 to 5 for each question. The raw score calculated for each domain is converted into computerized scores ranging from 0 to 100. Higher scores indicate better quality of life. This is designed for comparison. There is no cutoff value.

Beck Depression Inventory-Turkish (BDI II-TR): BDI-II is a 21-item self-report inventory designed to assess depressive symptoms as cited in DSM-IV. It was formed for the purpose of evaluating the symptoms, not for diagnosis.[14] Each item is classified on a 4-point scale ranging from 0 to 3. The total score ranges from 0 to 63, with higher scores indicating more severe depressive symptoms . Cutoff values specific to our society have been determined. Accordingly, a total score of 0-12 is considered to be minimal, 13-18 mild, 19-28 moderate, and 29-63 severe depression.[15]

Beck Anxiety Inventory (BAI): BAI is designed to assess the level of anxiety symptoms. It is a self-report inventory consisting of 21 items. It measures the physical, emotional and cognitive aspects of anxiety and the fear of losing control.[16] It has been shown to be valid for the Turkish population. Each item is graded on a 4-point scale ranging from 0 (not at all) to 3 (severely disturbed). The total score ranges from 0 to 63. Higher scores represent higher intensity of anxiety. A total of 0-7 points is interpreted as the minimal anxiety level, 8-15 as mild, 16-25 as moderate and 26-63 as severe anxiety levels.[17]

Domain scores of QoL were counted as percentiles. Depression and anxiety scales were classified as minimal , mild, moderate-severe.

Statistical Analysis

The Statistical Package for the Social Sciences software package (SPSS version 25.0, IBM,United States, licensed by Baskent University) was used. Shapiro-Wilk test was used to determine whether the data conformed to normal distribution and Levene test was used for variance homogeneity. Independent Sample t test and Mann-Whitney U test was used to compare variables of two independent groups. Pearson's Chi-square test (with exact results) was used to compare categorical variables and Cramer's V for Pearson's Chi square test was calculated to assess effect size. Reliability analysis was performed for the internal consistency of the items in the questionnaires, and Cronbach's alpha was calculated for each scale. Quantitative variables were shown as mean ± SD (standard deviation) and median (25% Percentile/75% Percentile), and categorical variables as n (%). Variables were analyzed at a 95% confidence level, and a p value of less than 0.05 was considered significant.

RESULTS

There was no statistically significant difference between the two groups in terms of age, parity and educational status (p>0.05 for all).

When the domains of quality of life scale (QoL) were examined (Cronbach a coefficients=0,89) there was no statistical difference in the overall domain of QOL , social domain of QoL (SDQoL) and environmental domain of QoL (EDQoL), (p>0.05 for all). In terms of psychological domain of QoL (PDQoL), the result was 67% in the induced abortion group, while it was 75% in the miscarriage group, and a statistically significant difference was observed (p<0.05). Likewise, a statistically significant decrease was observed in the induced abortion group compared to the miscarriage group for physical domain of QoL (PhDQoL), (69.5±14.4 and 75.4 ±12.9, respectively, p<0.05)(**Table 1**). A weak but significant negative correlation was observed between PDQoL and induced abortion (CC: 0.312, p<0.05)(**Table 2**).

Table 1. Comparison of depression score, anxiety score, quality of life domains and other examined variables according to type of abortion

	Type of Abortion		P Value
	Miscarriage (n=35) Mean±SD or Median (Q1-Q3)	Induced Abortion (n=35) Mean±SD or Median (Q1-Q3)	
Age	31.4 ±5.4	32 ±4.9	0.605
Parity	2 (1/3)	2 (2/3)	0.121
Educational status			0.546
Less than high-school	7 (20)	6 /17.6)	
High-school	11(31.4)	15 (44.1)	
University	17 (48.6)	13 (38.2)	
General QoL (%)	75 (63/83)	75 (50/79))	0.150
Physical domain of QoL (%)	75.4 ±12.9	69.5±14.4	0.046
Psychological domain of QoL (%)	75(67/83)	67 (58/75)	0.019
Social domain of QoL (%)	75 (58/75)	75 (50/83)	0.972
Enviromental domain of QoL	63.4 ±15.7	57±16.5	0.935
Depression (score)	5 (2/9)	10 (5/24)	0.014
Anxiety (score)	6 (4/10)	10 (5/26)	0.016
	n(%)	n(%)	
Depression			<0,01
Minimal	27(77.1)*	15(42.9)	
Mild	6 (17.1)	9 (25.7)	
Moderate-Severe	2 (5.7)	11 (31.4)*	
Anxiety			0.032
Minimal	25 (71.4)	18 (51.4)	
Mild	7 (20)	5 (14.3)	
Moderate-Severe	3 (8.6)	12 (34.3)*	

Independent Sample t test / Mann Whitney U test (Monte Carlo)/Pearson Chi-Square Test (Exact)/ Q1: %25 Percentile, Q3:%75 Percentile, SD.:Standard Deviation, bold values means p<0.05, * significant to compare the other group

Table 2. Correlation between induced abortion and depression score, anxiety score and quality of life domains

Variables	Induced	abortion
Psychological Domain of QoL	r:-0,312	p:0.013
Physical Domain of QoL	r:-0,218	p:0.070
Anxiety score	r:0,336	p:0.013
Depression score	r:0.410	p:0.001

Spearman's rho Test (two-tailed), r: Correlation coefficient, bold value means p<0.05, QoL: Quality of Life

In this study BDI-II-TR questionnaires showed high consistency with cronbach coefficients (0,85). Depression scores as pure score median values were statistically significantly higher in the induced abortion group than the miscarriage group (10 points, 5 points, respectively, p<0.05). When categorically analyzed according to depression scores, moderate-severe depression was found to be statistically higher (31.4 %, 5.7%, respectively) and minimal depression was found to be statistically lower (42.9 %, 77.1%, respectively) in induced abortion group than miscarriage group (p<0.01, Cramer's V=0.313)(**Table 1**). A weak but significant positive correlation was observed between depression scores and induced abortion (CC: 0.410, p<0.05)(**Table 2**).

Anxiety scores were statistically significantly higher in the induced abortion group, similar to the results of depression scores, when the median values of the pure score were examined (p<0.05). When the anxiety scores are examined according to categorized BAI questionnaires (cronbach a coefficients=0.80) while moderate-severe anxiety was 34.3% in the induced abortion group, it was 8.6% in the miscarriage group, and a statistical difference was observed (p<0.05). Although the result of minimal axiety in miscarriage group was higher than induced abortion group, it was not statistically significant (71.4%, 51.4%, respectively). A weak but significant positive correlation was observed between anxiety scores and induced abortion (CC: 0.336, p<0.01) (**Table 2**).

There was no statistically significant relationship between depression scores, anxiety scores, quality of life domains and variables such as age, parity, and educational status.

DISCUSSION

Early pregnancy loss is often accompanied by various psychological problems.[6,7,9] This situation can sometimes be in the form of an anxiety disorder due to a desired baby, or sometimes it can be due to the inability to easily overcome the stress experienced during miscarriage. On the other hand, women who want to terminate their pregnancy voluntarily also may experience psychological stress, depression and anxiety symptoms. Considering the social, legal and regional changes, while this rate is high in women who decide to have an abortion in some parts of the world, it is said that it does not affect mental health in the publications made in some other countries.[2,3,18]

Our results report that there is a statistically significant increase in the raw score of depression and anxiety symptoms in the induced abortion group, and in addition, high results such as 31.4% and 34.3% in the percentages of moderate-to-severe depression and anxiety, respectively. Different authors from different countries have reported conflicting results on this issue. In a study involving 57770 women from 2013 to 2017 in Germany, a significant positive association was found between psychiatric disorders and spontaneus (OR 2.16 -2.60) and induced abortion (OR 1.75 - 2.01).[19] In the strong evidence study by Munk-Olsen et al., it was reported that the incidence of first psychiatric contact per 1000 person-years in women with first induced abortion was similar before abortion (14.6%) and after abortion (15.2%), but increased compared to women with first birth (3.9% before delivery and 6.7% postpartum).[20]

From a different perspective, Steinberg et al.[21] reported that induced abortion did not increase mental disorder and that higher incidences were due to some pre-existing psychological problems in women who had abortions. They provided strong evidence against the claim that abortion significantly harms women's mental health after adjusting for confounding factors (anxiety, mood, impulse control, substance use, eating disorders, and suicidal ideation). Our results agree with those of Steinberg et al for induced abortion. The significant increase in depression and anxiety levels in this group before termination suggests that the negative psychological outcomes in women after induced abortion mentioned in the literature may be related to a pre-existing psychological stress. However, our moderate-severe depression and anxiety rates are quite low in the miscarriage group compared to the induced abortion group. Therefore, psychological negativities before termination may have an effect on decisions in women in the induced abortion group. Steinberg et al.[22] stated in another study that pre-abortion psychological health was the best predictor of post-abortion psychological health. They also stressed that helping women feel less stigmatized about having an abortion may be important for reducing pre-abortion symptoms of depression, anxiety, and stress. They also reported younger age, higher education, and childhood problems as predictors of increased pre-abortion depression, anxiety, and stress. In our study, age, educational status and parity were not correlated with pre-termination depression and anxiety symptoms.

It is clear that the quality of life of women is as important as the need for medical treatment during both unwanted pregnancies and miscarriages. Previous studies in this area have reported low post-abortion PDQoL levels, but high results in terms of SDQoL and PhDQoL.[10,23,24] While the studies covered the post-abortion period, we submitted pre-abortion quality of life questionnaires to women's self-assessment. Results for all quality of life domains were not above 75 percent on average. We found the lowest percentages in the EDQoL domain in both group. This result made us think that women had a lack of environmental support and an inability to feel safe in this process. In addition, considering that the PDQoL and PhDQoL levels, which we found even lower in the induced abortion group, are added to the symptoms of anxiety and depression, it is clear that women who decide to abort should receive psychological support primarily before termination. Because this deterioration in psychological health can be challenging in their decision process and worsening of these results can be observed after termination. It has been reported that the quality of life of women who receive support in coping with health-related problems or

who develop self-efficacy with their previous experiences is positively correlated, especially in terms of PDQoL.[10] Strategies to increase the self-efficacy of women with low quality of life, which can be considered as a general health problem, may be important in terms of having a higher quality of life during a miscarriage or termination period they will experience in the future.

There is a need to report some limitations of our study. Although our aim in this prospective study was to evaluate pre-termination psychological health criteria and compare them between the two groups, it would be useful to include them in the long-term outcomes after abortion. In addition, this research is in the form of a symptom study as a result of the self-assessment of the patients, not on a diagnostic basis.

CONCLUSION

As a result, we report higher depression and anxiety scores, increased rate in terms of moderate-severe depression and anxiety symptoms , lower psychological and physical quality of life results in women who have induced abortion due to unwanted pregnancy compared to miscarriage in the pre-termination period . We also draw attention to the low environmental quality of life in both groups. With these results, we emphasize the importance of pre-pregnancy psychological counseling and increasing self-efficacy with the support to be provided during pregnancy, especially for women who decide to have abortion.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was design prospectively and approved by Baskent University Institutional Review Board and Ethics Committee (Project no: KA: 18/303)

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Orijinal Araştırma / Original Article

The Effects of Thyroid-Stimulating Hormone, Free Thyroxine Levels, and Thyroid Antibodies on Mean Platelet Volume: Original Research

Tiroid Uyarıcı Hormon, Serbest Tiroksin Seviyeleri ve Tiroid Antikorlarının Ortalama Trombosit Hacmi Üzerindeki Etkileri: Orijinal Araştırma

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Abstract

Background: Coagulation abnormalities have been reported in patients with impaired metabolism of thyroid hormones. Platelets play an important role in coagulation and Mean Platelet Volume (MPV) has been considered as an inflammatory biomarker in multiple diseases.

Objectives: The aim of this study was to investigate whether any relationship exists between the values of thyroid-stimulating hormone (TSH), free thyroxine,(FT4) anti-thyroid peroxidase (Anti TPO), anti-thyroglobulin (Anti TG) and those of the MPV.

Material and Method: Patients who were admitted to the Endocrinology outpatient clinic between October 2013 and July 2019 with a pre-diagnosis of thyroid disease were included in the study. The data were analyzed with IBM SPSS V23. Compatibility with normal distribution was examined with the Shapiro Wilk test. The relation between the variables was evaluated with Spearman rank correlation.

Results: Records of 1098 patients were examined. There is a very weak positive relationship between TSH and MPV (r: 0,07), there is no significant relationship between FT4, Anti TPO, Anti TG and MPV.

Conclusion: Patients have high TSH values display a increased MPV should hence be acknowledged in risk prediction of thrombotic events.

Keywords: Thyroid hormones, mean platelet volüme, thyroid diseases

Öz

Giriş: Tiroid hormonlarının metabolizması bozulmuş hastalarda pıhtılaşma anormallikleri bildirilmiştir. Trombositler pıhtılaşmada önemli bir rol oynar ve Ortalama Trombosit Hacmi (MPV), birçok hastalıkta inflamatuar bir biyobelirteç olarak kabul edilir.

Amaç: Bu çalışmanın amacı, tiroid uyarıcı hormon (TSH), serbest tiroksin, anti-tiroid peroksidaz (Anti TPO) ve anti-tiroglobulin (Anti TG) değerleri ile MPV değerleri arasında herhangi bir ilişki olup olmadığını araştırmaktı.

Gereç ve Yöntem: Endokrinoloji polikliniğine Ekim 2013 - Temmuz 2019 tarihleri arasında tiroid hastalığı ön tanısıyla başvuran hastalar dahil edildi. Veriler IBM SPSS V23 ile analiz edildi. Normal dağılıma uyumluluk Shapiro Wilk testi ile incelendi. Değişkenler arasındaki ilişki Spearman sıra korelasyonu ile değerlendirildi.

Bulgular: 1098 hastanın kayıtları incelendi. TSH ile MPV arasında çok zayıf bir pozitif ilişki vardı (r: 0,07), ST4, Anti TPO, Anti TG ve MPV arasında anlamlı bir ilişki yoktu.

Sonuç: Yüksek TSH değerlerine sahip hastalarda yüksek MPV değerleri görülmekte olup trombotik olayların risk tahmini yapılabilir.

Anahtar Kelimeler: Tiroid hormonları, ortalama trombosit hacmi, tiroid hastalığı

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INTRODUCTİON

Platelets play a significant role in the pathogenesis of cardiovascular diseases by promoting the complication of an injured atherosclerotic lesion into thrombus. The rupture of an atherosclerotic plaque cause release of a variety of prothrombotic factors in the bloodstream and exposes the subendothelial matrix to the contact with blood elements. This leads to platelet activation, adhesion and aggregation and hence thrombus formation initiates.[1,2]

Platelet activation typically represented by shape change from discoid to spherical and volume increase.[3] This phenomenon can be easily identified with modern hemocytometers and shown with the increase of the mean platelet volume (MPV).[4]

MPV is a machine-calculated measurement of the average size of platelet found in blood and is typically included in blood test as part of the complete blood count. Since the average platelet size is larger when the body is producing increased numbers of platelets, the MPV test results can be used to make inferences about platelet production in bone narrow or platelet destruction problems.[5]

In the literatüre, coagulation abnormalities has been reported in patients with impaired metabolism of thyroid hormones. These typically range from mild laboratory anomalies[6-8] to clinically relevant thrombotic episodes like cardiovascular disease and venous thrombosis.[9]

Also hypothyroidism results in the decrease of cardiac output and cardiac contractility. Studies suggested that accelerated atherosclerosis and thrombosis are the causes of cardiovascular morbidity in hypothyroidism patients.[10,11]

The study of MPV can provide important information on the course and prognosis in many inflammatory conditions.[12]

MPV is a useful index to reflect platelet activation, and has been considered as an inflammatory biomarker in multiple diseases.[13]

Furthermore, increased MPV has been detected in a variety of malignancies.[14-16]

Bayhan et al. studied with patients who underwent total thyroidectomy because of benign or malignant diseases of the thyroid.MPV was significantly higher in patients with malignant thyroid diseases than in those with benign thyroid diseases.[17]

Since an increased MPV is broadly acknowledged as a risk marker for platelet function and activation[18] and fluctuations of thyroid hormones are frequently associated with thrombotic complication, we planned a retrospective study to find the effects of thyroid-stimulating hormone (TSH), free thyroxine (FT4), anti-thyroid peroxidase (Anti- TPO), anti-thyroglobulin (Anti-TG) on MPV values.

MATERIAL AND METHOD

Ethical approval with the number of 2019 /0024 was taken from the KTO Karatay University Faculty of Medicine date of October, 25, 2019. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study was designed as a retrospective descriptive study. Patients who were admitted to the Endocrinology outpatient clinic between 1st of October 2013 and 31st July 2019 with a pre-diagnosis of thyroid disease and who underwent MPV test were included in the study.

We retrospectively reviewed the files of patients and recorded age, gender, TSH, FT4, Anti- TPO, Anti-TG and MPV values. Any patient who did not perform any of these tests with MPV was excluded from the study. The first laboratory results of patients were taken into account.

TSH, FT4, Anti-TPO, Anti-TG were measured on the ARCHITECT i2000SR immunoassay analyzer (Abbott Diagnostics).

MPV levels were measured in venous blood samples placed in EDTA-standard tubes using Abbott Cell-Dyn 3700 Hematology Analyzer with the flow cytometry method.

The data were analyzed with IBM SPSS V23. Compatibility with normal distribution was examined with the Shapiro Wilk test. The relation between the variables was evaluated with Spearman rank correlation. The significance level was taken as $p < 0.05$.

RESULTS

File records of 1098 patients were examined. 849 of them were women (77.30%) and 249 of them were men (22.70%). (**Table 1**).

Table 1. Frequency distribution of gender

	N	%
Gender		
Female	849	77.30
Male	249	22.70

N : number

The mean age was 47.10, standard deviation was 15.90 (minimum 15, maximum 93 years).

Through these patients 1092 had TSH results, 1084 had FT4 results. Anti TPO was analysed in 1016, anti TG was analysed in 1073 patients.

The laboratory reference ranges provided by the manufacturer used in this study were as follows: MPV: 7.50-12 fl, TSH 0.35–4.94 µIU/ml, FT4 0.7-1.4 ng/dl, TPOAb < 5.61 IU/ml, and TgAb < 4.11 IU/mL.

The mean value of TSH, FT4, Anti TPO, Anti TG and MPV were 2.80 µIU/ml, 1.30 ng/dl, 151.90 IU/ml, 70.50 IU/ml and 7.50 fl respectively. While the standart deviations were 24.30 for TSH, 1.80 for FT4, 357.50 for Anti TPO, 184.10 for Anti TG and 1.20 for MPV.

The median value of TSH, FT4, Anti TPO, Anti TG and MPV were 0.40 µIU /ml, 1.10 ng/dl, 1.10 IU/ml, 3.40 IU/ml and 7.30 fl respectively (**Table 2**).

Table 2. Descriptive statictics

	N	Mean	Std. Deviation	Median	Minimum	Maximum
Age	1098	47.10	15.90	45	15	93
TSH	1092	2.80	24.30	0.40	0	734
FT4	1084	1.30	1.80	1.10	0.10	57
Anti TPO	1016	151.90	357.50	1.10	0	6000
Anti TG	1073	70.50	184.10	3.40	0	1000
MPV 0	1098	7.50	1.20	7.30	0	16.10

N: number, Std. Deviation: Standard Deviation, TSH: Thyroid-stimulating hormone, FT4:Free thyroxine, Anti TPO: Anti thyroid peroxidase, Anti TG: Anti thyroglobulin, MPV: Mean platelet volüme

While there is a very weak positive relationship between TSH and MPV (r: 0.07), there is no significant relationship between ST4, Anti TPO, Anti TG and MPV (**Table 3**).

Table 3. Correlation analysis results

		TSH	ST4	Anti TPO	Anti TG	MPV 0
TSH	r					
	p	---				
ST4	r	-0.567				
	p	0.000	---			
Anti TPO	r	0.103	0.000			
	p	0.001	0.990	---		
Anti TG	r	0.038	0.044	0.672		
	p	0.209	0.151	0.000	---	
MPV 0	r	0.075	-0.045	0.006	-0.013	
	p	0.013	0.137	0.843	0.664	---

r: Spearman rank correlation, N: number, Std. Deviation: Standard Deviation, TSH: Thyroid-stimulating hormone, FT4:Free thyroxine, Anti TPO: Anti thyroid peroxidase, Anti TG: Anti thyroglobulin, MPV: Mean platelet volüme

DISCUSSION

Strengths of the study: Our study covers a period of 6 years and the data of 1098 people have been reached. This is a very good number if we compare with the literature.

Limitations of the study: Data loss is one of our limitations. For example the MPV value of 1098 people has been studied but 6 people with MPV values could not have been compared with other values. Our analyses is limited. We have performed only one analysis according to our aim of the study.

MPV is a precise measurement of their dimension, calculated by hematological analyzers on the basis of volume distribution during routine blood morphology test. MPV ranges between 7.50 and 12 fl, whereas the percentage of large platelets should amount to 0.20-5% of the whole platelet population. In physiological conditions, MPV is inversely proportional to the platelet count, which is associated with hemostasis maintenance and preservation of constant platelet mass.[12]

MPV can be affected by multiple factors. The study of MPV can provide important information on the course and prognosis in many inflammatory conditions. Increased MPV was observed in cardiovascular diseases, peripheral diseases, cerebral stroke, respiratory diseases, chronic renal failure, intestine diseases, rheumatoid diseases, diabetes and various cancers. Decreased MPV was noted in tuberculosis during disease exacerbation, ulcerative colitis, SLE in adult, and different neoplastic diseases.[12,19] Because of these factors MPV should be assessed in parallel with other inflammatory markers.

The results of the present study demonstrated a very weak positive relationship the TSH level and MPV. In our study patients were not questioned for other chronic diseases. So it may be argued that an elevated MPV is secondary to other factors that are affected with the MPV.

But the number of samples in the study is quite high since 6-year patient data is scanned.

In the literature there were studies investigating the association between MPV and thyroid diseases.

In the study of Lippi et al. a significant association was found between MPV and TSH values in both simple ($r = 0.12$; $p < 0.001$) and multivariable regression analysis (beta coefficient, 0.07; $p < 0.001$.[20]

Erikci et al. studied patients with subclinical hypothyroidism and euthyroidic healthy control group, and reported that the MPV values were significantly higher in cases than in controls.[21]

Carlioglu et al found significantly higher MPV values in patients with euthyroid Hashimoto thyroiditis than in healthy controls. And there was also positive correlation between anti-TPO, anti-tiroglobulin and MPV levels.[22]

Kim et al. retrospectively studied 6893 asymptomatic Korean adults who were 20 years of age or older and who underwent voluntary regular health check-ups. They found that MPV was positively correlated with the TSH level.[23]

Our study is compatible with the literature. But it seems reasonable to suggest that MPV plays a role in the thrombotic process and that elevated TSH levels are not only a causal factor.

Although in hypothyroidism patients atherosclerosis and thrombosis are accelerated and this results in increase in MPV levels[10-11], there are studies that showed increase in MPV levels with hyperthyroidism.

Platelet changes, such as lower platelet count increased MPV together with the shortened platelet lifespan, were observed in Graves disease previously.[24] Bagir et al. compared recurrent Graves disease with remission and found MPV significantly higher in the recurrent group and attributed this state to hypermetabolism.[25]

In the study of Erem et al. a significant association was only found between MPV and anti-thyroid peroxidase (TPO) antibodies in patients with Graves disease.[26]

In our study, we found a very weak positive relationship significant relationship between TSH and MPV. The results of this study may have some clinical implications. Regardless of the fact that an increased MPV may be considered as a risk factor or a simple marker of thrombosis.[27,28]

As such, it seems reasonable to suggest that platelet activation, as reflected by an increased MPV, may be an important mediator of thrombotic complications in patients with fluctuations of thyroid hormones.[29]

CONCLUSION

The observation that patients have high TSH values display a increased MPV should hence be acknowledged in risk prediction of thrombotic events and also in the clinical management or antithrombotic prophylaxis of subjects in the euthyroid state. But still further and comprehensive studies are needed. The other factors that affect MPV levels can be questioned thus the relationship between MPV and TSH levels can be specifically evaluated.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethical approval with the number of 2019 /0024 was taken from the KTO Karatay University Faculty of Medicine date of October,25,2019.

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Orijinal Araştırma / Original Article

Retrospective Analysis of Hepatitis B and Hepatitis C Viruses and HIV Infections in Patients Presenting to the General Surgery Clinic and Evaluated Preoperatively

Genel Cerrahi Kliniğine Başvuran ve Ameliyat Öncesi Değerlendirilen Hastalarda Hepatit B, Hepatit C Virüs ve HIV Enfeksiyonlarının Retrospektif Analizi

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Abstract

Aim: Hepatitis B (HBV), Hepatitis C (HCV) and Human Immunodeficiency Virus (HIV) infections are important parenterally transmitted infections. The aim of this study is to determine the seroprevalence of HBsAg, anti-HBs, anti-HCV and anti-HIV in patients with preoperative preparation.

Material and Method: Anti-HBs, HBsAg, anti-HCV, anti-HIV tests with chemiluminescent enzyme immune-assay method in a total of 900 patients applied to the General Surgery Clinic and were evaluated preoperatively by Abbott Architect i1000 immunoassay analyzer (Abbott Diagnostics, Illinois, USA) operated according to the manufacturer's instructions. Anti-HBs titer above 10 IU/mL, serum optical density/"cut-off" control optical density (S/Co) ≥1 in HBsAg, anti HCV and anti-HIV tests were accepted as positive. HBV-DNA and HCV-RNA tests were performed with real-time PCR method.

Results: Anti-HBs test was found to be reactive in 34.11% and nonreactive in 65.89%. HBsAg positivity was 1.0% (9/900), and anti-HCV positivity was 0.33% (3/900). Anti-HIV positivity and HBsAg-anti-HCV association were not detected. Six patients with HBsAg positivity and one patient with anti-HCV positivity were found incidentally during preoperative examinations.

Conclusion: As a result of these data, it can be concluded that cost-effective serological tests for HBV and HCV infections performed in the preoperative period are extremely important in the detection of asymptomatic patients. Preoperative screening is important in terms of early diagnosis of patients before complications such as cirrhosis and HCC develop, enabling treatment, as well as enabling healthcare professionals to increase infection control measures while intervening with infected patients, to be more careful in terms of percutaneous injuries, and to reduce the risk of transmission.

Keywords: Preoperative preparation, hepatitis B (HBV), hepatitis C (HCV), HIV, seroprevalence

Öz

Amaç: Hepatit B (HBV), Hepatit C (HCV) ve İnsan Bağışıklık Yetmezliği Virüsü (HIV) enfeksiyonları parenteral yolla bulaşan önemli enfeksiyon etkenleridir. Bu çalışmanın amacı, preoperatif hazırlık yapılan hastalarda HBsAg, anti-HBs, anti-HCV ve anti-HIV seroprevalansını belirlemektir.

Gereç ve Yöntem: Genel Cerrahi Kliniğine başvuran ve ameliyat öncesi değerlendirilen toplam 900 hastada anti-HBs, HBsAg, anti-HCV, anti-HIV testleri kemilüminesan enzim immun-assay (KMIA) yöntemi ile Abbott Architect i1000 (Abbott Diagnostics, Illinois, USA) cihazında üretici talimatlarına göre çalışıldı. Anti-HBs titresi 10 IU/mL üzeri olması, HBsAg, anti HCV ve anti-HIV testlerinde serum optik yoğunluk/"cut-off" kontrol optik yoğunluk (S/Co) ≥1 olması pozitif olarak kabul edildi. HBV-DNA ve HCV RNA testleri gerçek zamanlı (real-time) PCR yöntemi ile çalışıldı.

Bulgular: 900 hastanın (ortalama yaş= 51.8±16.5) 501'i kadın (%55.7), 399'u erkek (%44.3) hastalardan oluşmakta idi. Anti-HBs testi hastaların %34.11'inde reaktif, %65.89'unda nonreaktif olarak saptanmıştır. HBsAg pozitifliği %1.0 (9/900), anti-HCV pozitifliği %0.33 (3/900) olarak belirlenmiştir. Anti-HIV pozitifliği ve HBsAg-anti-HCV birlikteliği saptanmamıştır. HBsAg pozitifliği saptanan altı hasta ve anti-HCV pozitifliği olan bir hasta preoperatif tetkikler sırasında tesadüfen saptanmıştır.

Sonuç: Sonuç olarak asemptomatik hastaların saptanmasında preoperatif dönemde yapılan HBV ve HCV enfeksiyonlarına yönelik maliyeti düşük serolojik testlerin son derece önemli olduğu sonucuna varılabilir. Preoperatif tarama hastaların siroz, hepatosellüler karsinom (HCC) gibi komplikasyonlar gelişmeden erken dönemde tanı konması, tedaviye olanak sağlaması açısından önemli olduğu kadar, sağlık çalışanlarının da enfekte hastaya müdahale ederken enfeksiyon kontrol önlemlerini artırması ve perkütan yaralanmalar açısından daha da dikkatli olunmasına, bulaş riskinin azalmasına olanak sağlamaktadır.

Anahtar Kelimeler: Preoperatif hazırlık, hepatit B (HBV), hepatit C (HCV), HIV, seroprevelans

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INTRODUCTION

Hepatitis C (HCV) and Hepatitis B virus (HBV) infections are important public health problems worldwide due to their serious risks such as chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC). It is estimated that 80 million (64-103 million) people are HCV-viremic around the world and the prevalence of HCV RNA is 1.1% (0.9-1.4%).[1] The number of HCV-infected individuals in Turkey is 1.0–1.3 million and the prevalence of HCV is approximately 1.0%.[2] 75-80% of individuals exposed to HCV develop chronic infection. The risk of developing cirrhosis in patients with chronic HCV infection is between 2-5% annually.[3]

In 2016, approximately 292 (251–341) million people were identified as infected with chronic hepatitis B virus (HBV), which corresponds to a prevalence of 3.9% (3.4-4.6%).[4] In terms of HBV infection, Turkey is among the moderately endemic (2-7%) regions, which include the Mediterranean, Eastern Europe, and Latin America.[5] Among the factors contributing to the development of HCC in Turkey, HCV comes first (49% of cases), followed by HBV (26%), alcohol (19%), and other factors (11%).[6] Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death. HCC has a poor prognosis and low survival rate, due to its low resectability rate, high recurrence rate after resection, and poor response to conservative treatment.[7]

In 2016, World Health Organisation (WHO) adopted a global hepatitis strategy to eliminate viral hepatitis as a public health threat by 2030, targeting a 90% reduction in hepatitis B and hepatitis C cases and a 65% reduction in deaths.[8] Therefore, comprehensive studies including prevention, screening, and treatment of HBV and HCV infections are required to achieve these goals.[8,9]

The availability of HBV vaccines is important in preventing HBV infection. Direct-acting antivirals (DAAs), highly effective in the treatment of HCV infection, make a significant contribution to the elimination of the disease.[9] However, protection and prevention strategies, as well as diagnosis of these infectious diseases, are very important. It is worrying that only 12 out of 194 countries were able to meet the WHO 2030 elimination targets as of June 2018. Reducing healthcare-associated transmission remains an important preventative measure in elimination programs. Recognizing viral hepatitis as a health priority and prevention, screening and diagnostic programs are extremely important to achieve the WHO 2030 elimination targets.[8,9]

Prior to surgery, HBsAg, anti-HCV, and anti-HIV screening are frequently performed. Because these infections are likely to be asymptomatic in the beginning, the probability of detection by chance in screening is high. This study aims to determine the seroprevalence of HBsAg, anti-HBs, anti-HCV, and anti-HIV in patients in the preoperative preparation stage and to analyze it together with the results of the molecular test in patients with positivity. In addition, we aimed to investigate whether the patients with reactivity were previously informed about this condition, whether it was detected during the preoperative examination, possible transmission route, treatment, and follow-up information.

MATERIAL AND METHOD

This study was carried out with the approval of Balikesir University Non-Interventional Research Ethics Committee (Date:24/03/2021 and Decision no:2021/89). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. HBV, HCV, and HIV infections were investigated in a total of 900 patients who presented to the General Surgery Clinic and were evaluated preoperatively. Repeated results of the same patient were not included. Anti-HBs, HBsAg, anti-HCV, and anti-HIV serological test results were evaluated retrospectively. Molecular test results, medical histories, risk factors for transmission, disease treatment, and follow-up information of patients with reactivity were analyzed via their file records.

Anti-HBs, HBsAg, anti-HCV, anti-HIV tests were performed using the chemiluminescent enzyme immune-assay (CMIA= "Chemiluminescent Microparticle Immunoassay") method on the Abbott Architect i1000 (Abbott Diagnostics, Illinois, USA) device according to the manufacturer's instructions. Anti-HBs titer above 10 IU/mL and serum optical density/"cut-off" control optical density value (S/Co) ≥1 in HBsAg, anti-HCV, and anti-HIV tests were considered positive. HBV-DNA and HCV-RNA tests were performed with the real-time PCR method.

Statistical Analysis

The data obtained in the study were recorded to the SPSS 22.0 (SPSS INC, Chicago, IL, USA) program and statistical analyzes were conducted. Categorical variables were given as percentages and mean±standard deviation.

RESULTS

A total of 900 patients (mean age= 51.8±16.5, age range= 18-88) were included in the study. 501 patients (55.7%) were female (mean age= 50.3±15.9) while 399 (44.3%) were male (mean age= 53.7±17.1). Anti-HBs test was found to be reactive in 34.11% and nonreactive in 65.89% of the patients. HBsAg positivity was found as 1.0% (9/900) and anti-HCV positivity was 0.33% (3/900). Anti-HIV positivity and HBsAg, anti-HCV association were not detected (**Table 1**).

Table 1. Anti-HBs, HBsAg, anti-HCV, anti-HIV test results

Serological parameters	Positive n (%)	Negative n (%)
HBsAg	9 (1.0)	891 (99.0)
Anti-HCV	3 (0.33)	897 (99.67)
Anti-HIV	-	900 (100.0)
Anti-HBs	307 (34.11)	593 (65.89)

Eight of the HBsAg positive patients had an S/Co value of ≥10, while one patient had a <10. The HBV DNA PCR test of the patient with HBsAg S/Co: 1.36 was found to be negative, which was evaluated as false positive. Two of the patients with HBsAg reactivity were registered patients and HBV was transmitted to one of them after giving birth and to the other from her partner. The other six patients were identified as a result of preoperative examinations (**Table 2**).

Table 2. Analysis of S/Co values of HBsAg positive patients

HBsAg (+) (n=9)	S/Co	Mean±SD	Minimum - Maximum
8 patients	≥10	3186±2279.53	108 - 5945
1 patient	<10	1.36	1.36

SD: Standard deviation, S/Co: serum optical density/"cut-off" control optical density

While two of the anti-HCV positive patients had an S/Co value of ≥10, one patient had <10 (**Table 3**). One of the patients with anti-HCV reactivity was operated on due to rectal cancer, but detailed information could not be reached because he died. HCV RNA positivity was also detected in a patient with anti-HCV positivity. A patient in whom positivity was found incidentally one year ago and source of transmission was unknown is being followed up by the Gastroenterology department due to HCV infection. HCV RNA was negative in a patient with anti-HCV positivity (S/C:6.29). Anti-HCV positivity in this patient was determined during preoperative examinations.

Table 3. Analysis of S/Co values of anti-HCV positive patients

Anti-HCV (+) (n=3)	S/Co	Mean±SD	Minimum - Maximum
2 patients	≥10	13.23±2.58	11.40 - 15.06
1 patient	<10	6.29	6.29

SD: Standard deviation, S/Co: serum optical density/"cut-off" control optical density

DISCUSSION

Infections are one of the most important occupational risk factors to which healthcare professionals are exposed. HBV, HCV, and HIV infections, which are especially at risk of parenteral transmission, are the leading causes. These agents can be transmitted by contact with infected blood and body fluids of patients with impaired skin and mucous membranes (10).

In our country, serological tests for HBV, HCV, and HIV infections are performed preoperatively for patients who will undergo surgical intervention. In a study examining the results of 37675 patients in our country, HBsAg positivity was determined as 3.27% and anti-HCV positivity was determined as 0.65% (11). In 3731 patients whose serological markers were investigated prior to septoplasty, HBsAg positivity was found to be 3.6%, anti-HCV positivity was 0.3%, and anti-HIV positivity was 0.2% (12). In the study of Erbay et al. (13), 0.6% of 25424 patients who underwent surgical intervention were anti-HCV-positive. To be brief, in different studies conducted in our country, preoperative HBsAg seropositivity rates ranged between 0.25-7.7% (11,12,14-16). In our study, HBsAg positivity was 1.0%, which was consistent with studies conducted in our country. Anti-HCV positivity was between 0.3-2.3 in literature (11-16). In our study, anti-HCV positivity was determined as 0.33%, which was in line with the data of our country. Anti-HIV positivity was reported between 0.0-0.2 in studies (12,14-16). However, no anti-HIV positivity was found in our study.

Centers for Disease Control and Prevention (CDC) emphasizes that HBV infections can be easily diagnosed with cost-effective serological tests even in the asymptomatic period. Thus, advanced liver diseases such as cirrhosis and HCC can be prevented with early initiation of treatment (17). Similarly, DAAs, which are new generation HCV drugs, are very effective in HCV elimination, so it is extremely important to detect and treat the disease with screening tests at an early stage before complications develop (9). The success of antiviral drugs (especially DAAs) is very high and they are effective in approximately 95% of people with HCV infection. However, the delay or lack of diagnosis also reduces the rates of access to treatment. The fact that the vaccine, which provides a great advantage in preventing HBV infections, does not exist for HCV infections suggests that medical treatment is very important to prevent this infection. At this point, early diagnosis is critical (9,18). In our study, two of the patients with HBsAg positivity were registered patients and six were found incidentally during preoperative examinations. One of the patients with anti-HCV positivity was also diagnosed with preoperative examinations during the scans. Accordingly, it can be concluded that the tests for HBV and HCV infections that are performed in the preoperative period are extremely important in the detection of asymptomatic patients.

There is a direct relationship between the prevalence of infection in the community and the risk of transmission. Therefore, the risk of infection is higher in healthcare professionals in underdeveloped and developing countries (19). The risk of exposure is even higher, especially among healthcare professionals working in surgical departments. Screening for HCV, HBV, and HIV infections raises the awareness of healthcare professionals working in the surgical departments, ensures that the surgical procedure is reviewed, and allows more intensive infection control measures (such as face shield-visor, double gloves) (20,21). Preoperative screening is thought to be cost-effective in countries with high HCV and HBV seroprevalence (21-24).

CONCLUSION

Although our study was conducted retrospectively, it is worth emphasizing the importance of preoperative screening for HBV, HCV, and HIV infections. Therefore, a considerable number of patients were diagnosed by chance and were referred for follow-up or treatment. Preoperative screening is very important in terms of early diagnosis of patients

before complications develop and enabling the treatment. Additionally, it helps to increase infection control measures when intervening with infected patients, to be more careful in terms of percutaneous injuries, and to reduce the risk of transmission.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was carried out with the approval of Balikesir University Non-Interventional Research Ethics Committee (Date:24/03/2021 and Decision no:2021/89).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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Orijinal Araştırma / Original Article

Detection and Endoscopic Treatment of Foreign Bodies in the Upper Gastrointestinal System of the Geriatric Patients

Geriatrik Hastalarda Üst Gastrointestinal Sistemdeki Yabancı Cisimlerin Tespiti ve Endoskopik Tedavisi

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Abstract

Introduction: Ingestion of foreign bodies is a worldwide problem associated with severe morbidity and mortality. The incidence of foreign body ingestion increases in the elderly population due to impaired intraoral sensitivity and swallowing reflex, visual problems, tooth loss, and mental disorders.

Material and Method: All patients admitted with foreign body ingestion were retrospectively screened between January 2016 and May 2020. The patients over 65 years of age were included for the study. All patients were managed by a flexible endoscope.

Results:49 patients referred with the diagnosis of foreign body ingestion Geriatric population consisted of 24 (49%) patients, mean age was 77.4±7.8 years and 15 (62.5%) were male. The most common symptom at admission was dysphagia in 41.7% of patients. The most common ingested foreign bodies are meat and food in 58.3% of the patients ($p<0.01$). Foreign bodies were most often stuck at the upper esophageal sphincter level (50%). Our average time to perform endoscopic intervention was approximately 3 hours after patients were admitted to the emergency room. Perforation due to chicken bones was detected in 2 patients, and both patients recovered after follow-up without the need for surgical intervention, and additive endoscopic intervention. Our success rate is 100% after endoscopic procedures, and no complications or death secondary to the procedure were observed in none of the patients.

Conclusion: Endoscopic foreign body removal is a highly effective procedure with relatively low complication and mortality rates. Immediate endoscopic intervention should be performed in patients who ingest foreign body to reduce the risk of complications.

Keywords: Elderly, foreign bodies, endoscopy, upper gastrointestinal tract

Öz

Giriş: Yabancı cisimlerin yutulması, ciddi morbidite ve mortalite ile ilişkili olup, dünya çapında bir sorundur. Yaşlı popülasyonda ağız içi hassasiyet ve yutma refleksinin bozulması, görme sorunları, diş kaybı ve ruhsal bozukluklar nedeniyle yabancı cisim yutma insidansı artmaktadır.

Gereç ve Yöntem: Yabancı cisim yutulması ile başvuran tüm hastalar retrospektif olarak Ocak 2016-Mayıs 2020 tarihleri arasında tarandı ve 65 yaş üstü hastalar çalışmaya dahil edildi. Tüm hastalara fleksibl endoskopi uygulandı.

Bulgular: Yabancı cisim yutulması tanısı ile başvuran 49 hasta tarandı. Geriatrik popülasyon 24 (%49) hastadan oluşmaktaydı, ortalama yaş 77.4±7.8 yıl ve 15'i (%62.5) erkekti. Hastaların en sık başvuru semptomu disfaji (%41.7) idi. sık yutulan yabancı cisimler et ve yiyeceklerdi (%58.3, $p<0.01$). Yabancı cisimler en sık üst özofagus sfinkter seviyesinde (%50) sıkışmıştı. Endoskopik müdahale için ortalama süremiz, hastaların acil servise başvurusundan yaklaşık 3 saat sonradır. İki hastada tavuk kemiğine bağlı perforasyon saptandı ve her ikisi de cerrahi müdahaleye ve ilave endoskopik müdahaleye gerek kalmadan düzeldi. Endoskopik işlemler sonrası başarı oranımız %100 olup, hiçbir hastada işleme bağlı komplikasyon veya ölüm görülmedi.

Sonuç: Endoskopik yolla yabancı cisim çıkarılması, nispeten düşük komplikasyon ve mortalite oranları ile oldukça etkili bir işlemdir. Yabancı cisim yutan hastalarda komplikasyon riskini azaltmak için acil endoskopik müdahale yapılmalıdır.

Anahtar Kelimeler: Yaşlı, yabancı cisim, endoskopi, üst gastrointestinal sistem

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INTRODUCTION

Ingestion of foreign bodies (FB) is a worldwide problem associated with severe morbidity and mortality.[1] The most (80%-90%) ingested FB pass through the esophagus easily and come out from the gastrointestinal (GI) system spontaneously in less than 7 days.[1,2] However, an endoscopic procedure is required to remove FB in 10% to 20% of cases, and a surgical procedure is required in less than 1% of cases. Severe complications may occur due to FB ingestion. Approximately 1500 deaths/year occur in USA due to foreign body ingestion.[1]

FB are common in children, mentally retarded people, alcoholics, obese people who swallow food without chewing, and especially geriatric patients using dental prosthesis.[3] The incidence of FB ingestion increases in the elderly population due to impaired intraoral sensitivity and swallowing reflex, visual problems, tooth loss and mental disorders. In the pediatric group and in the patients with psychiatric disorders, metallic objects (safety pins, coins, and disc batteries) are commonly ingested as foreign bodies. FB ingestion often occurs during meals in the geriatric group. Therefore, fish bones, chicken bones, and impacted foods are commonly found in this group.[2,4]

The esophagus is the narrowest part of the upper gastrointestinal system. Therefore, FBs are most commonly detected in the esophagus, especially at the level of cricopharyngeal muscle.[2,5] Diagnosis of FB in the esophagus by physical examination is difficult. The sudden onset of complaints in a patient who was normal before is the most important sign to consider foreign body ingestion. Symptoms generally vary by the shape, size, stuck location, local complication of the FB, and the age of the patient. [5] The complaints are variable; however, the most common symptoms are dysphagia and odynophagia.[3,5]

In most of the cases, ingested foreign bodies are radio-opaque, and may be detected radiologically. Two-way cervical X-ray, lung X-ray, and direct abdominal X-ray should be applied for diagnosis. However, absence of FB in direct radiography does not rule out the diagnosis. Therefore, asymptomatic patients with suspected FB should be evaluated by endoscopic examination even if the radiological findings are normal.[6] In these patients, endoscopic examination of the esophageal lumen is recommended in order to evaluate the mucosal damage and underlying predisposing factors (i.e. malignancy, eosinophilic esophagitis) after FBs are removed.[3]

The best treatment method to remove FB is controversial. The treatment option is associated with several factors including the patient's age, clinical condition, anatomical location of the foreign body, the size and sharpness of the FB, and the experience of the physician.[5,7] The success rate of flexible endoscopes in the management of FB in the upper GI system is over 95% with minimal incidence of complication. Therefore, the flexible endoscope is the ideal choice for both diagnosis and treatment.[4] Because of the risk of severe complications, European Gastrointestinal Endoscopy Association (ESGE) recommends immediate therapeutic esophagogastroduodenoscopy (EGD) for pointed objects, batteries, and FBs causing complete esophageal obstruction (preferably within 2 hours to most lately within 6 hours). For other esophageal FBs which do not cause complete obstruction, therapeutic EGD is recommended within 24 hours.[8] Different endoscopic methods (removing out or pushing distal) and equipment are used depending on the type and location of the FBs.[2,4] Prolonged stuck of FB in esophagus or difficult esophagoscopy procedure increases the risk of esophageal perforation. Life-threatening complications including sepsis, retropharyngeal abscess, tracheoesophageal fistulas, and mediastinitis secondary to perforation may develop.[3,9] The scientific studies reported that the incidence of complications is 1-5% during removal of FB or in prolonged cases.[10]

There is limited number of studies on FB ingestion in the geriatric population in the literature. Predisposing factors (i.e. malignancy, stricture, and motility disorder) that may cause FBs to be stuck in the esophageal lumen are common in geriatric patients with FB obstruction. Therefore, these conditions should be considered very carefully in the endoscopic examination and management of geriatric patients.[2] In our study, we evaluated the outcomes of geriatric cases that were admitted to our emergency outpatient clinic, and then examined and treated by flexible endoscope because of FB ingestion.

MATERIAL AND METHOD

The study was conducted in accordance with the principles of the Helsinki Declaration. This retrospective study was approved by the institutional review board and ethics committee (Number: 15386878-044) of Amasya University Sabuncuoğlu Şerefeddin Training and Research Hospital.

Patients

The patients who were admitted to our hospital (emergency room, outpatient clinic or inpatients) due to the complaint of FB ingestion between January 2016 and May 2020, and underwent endoscopic examination were screened retrospectively. Among 49 patients with the complaint of FB ingestion, 24 patients over 65 years of age were included in the study. Written informed consent was obtained from the geriatric patients with good cognitive functions, and from first-degree relatives of patients with impaired cognitive functions before endoscopic interventions. Patients with FB ingestion were examined radiologically through plain X-ray or computed tomography (CT) methods before the digital esophagogastroduodenoscopy (EGD) examination by a flexible endoscope (Fujinon VP-4450HD video-endoscope ve FujinonEG-590WR fiber-endoscope). In addition, patients were examined by an otolaryngologist. Depending on the nature and location of FB, several endoscopic devices (Medwork BAS1-A2-30-23200 retrieval baskets, Medwork

GmbH BIO1-c4-23-230 biopsy forceps, Medwork pol2-B1-30-23-220-OL polypectomy snare, Galena FG-28U-30D2 endoscopic foreign body forceps, and Foreign Body Retrieval Hood 40mm at Distal end, 8.3mm at proximal end, length of 75mm) were used for the procedures.

The clinical variables analyzed included the age, sex, type and location of the FB, relevant upper gastrointestinal diseases, endoscopic methods, accessory device usage, symptoms, and intervention and complications during the procedure. The mean duration of endoscopic intervention for FBs was defined as the period from the moment when the patients were admitted to the emergency service or outpatient clinics to the moment when the endoscopy procedure was performed.

Statistical Evaluation

NCSS (Number Cruncher Statistical System) Statistical Software (NCSS LLC, Kaysville, Utah, USA) program was used for statistical analysis of the data. Descriptive statistical methods (mean, standard deviation, median, frequency, and ratio) as well as the one-eye chi square test, and Fisher Freeman Halton test were used to compare qualitative data when the study data were evaluated. A p value below 0.05 (p <0.05) value was considered as statistically significant.

RESULTS

In our study; geriatric patients who were are admitted with the diagnosis of FB ingestion and were treated by flexible EGD between January, 2016 and May, 2020 were analyzed retrospectively. Among 49 patients evaluated by endoscopic examination for FB ingestion, 24 (49%) patients were in the geriatric population. The time from admission to the emergency room to endoscopic intervention is between 40 minutes and 22 hours and 50 minutes; the average time is 2.55±4.5 hours. The most common symptom at admission is dysphagia in 10 (41.7%) patients. Besides, 7 (29.2%) patients developed aphagia, 5 (20.8%) patient developed odynophagia, 1 (4.2%) patient developed vomiting, and 1 patient (4.2%) was asymptomatic. When they were examined according to the ingested FBs, a statistically significant difference was found (p <0.01). Most common FBs detected by endoscopic examination were meat and food with an incidence of 58.3% (n:14), followed by bone with an incidence of 29.2% (n:7). Furthermore, herbal substance was detected in 8.3% (n:2) and drug in 4.2% (n: 1) of the patients. The endoscopic examination performed to remove FB showed that the foreign body stuck in the upper esophagus in 50% (n:12), in the middle esophagus in 16.7% (n: 4), and in the distal esophagus in 20.8% (n: 5) of the patients. In addition, foreign body was detected in the stomach in 1 (4.2%) patient, and in the duodenum in 1 (4.2%) patient; no foreign body was detected in 1 (4.2%) patient. Detection of FB in the upper esophagus was found to be statistically significant (p <0.01). The results of the endoscopic examination of the patients are presented in **Table 2**.

Table 1. Demographic data of geriatric patients ingesting foreign body

Age (years)	Median (Min-Max)	71 (66-93)	
	Mean±Sd	77.4±7.8	
Sex, n (%)	Female	9	(37.5)
	Male	15	(62.5)
Personal history, n (%)	none	4	(16.7)
	Dementia	3	(12.5)
	CVA*	2	(8.3)
	Parkinson	1	(4.2)
	İHD¥, HT£	5	(20.8)
	Asthma – COPD**	2	(8.3)
	Malignancy	4	(16.7)
	Other	3	(12.5)
Endoscopy time	Min - Max (hours)	40 min-22 hrs 50 min	
	Mean±Sd	2 hrs 55 min ±4 hrs 54 min	
Symptoms, n (%)	Asymptomatic	1	(4.2)
	Aphagia	7	(29.2)
	Odynophagia	5	(20.8)
	Dysphagia	10	(41.7)
	Vomiting	1	(4.2)

*CVA: Cerebrovascular accident, ¥,İHD: İschemic Heart Disease, £HT: Hypertension, **COPD: Chronic obstructive pulmonary disease

Table 2. Endoscopic findings of patients ingesting foreign body

		n	%	p
Foreign body	Meat, Food	14	58,3	0,001**
	Bone	7	29,2	
	Medicines	1	4,2	
	Herbal	2	8,3	
	None	1	4,2	0,001**
Stuck location	Upper Esophagus	12	50	
	Middle Esophagus	4	16,7	
	Distal Esophagus	5	20,8	
	Stomach	1	4,2	
	Duodenum	1	4,2	
Foreign body intervention	No foreign body was detected	1	4,2	
	Removed	21	87,5	
	pushed into the stomach	2	8,3	
Esophageal injury	No Damage	16	66,7	0,001**
	Laceration	3	12,5	
	Perforation	2	8,3	
	Erosion	3	12,5	
Predisposing pathology of the esophagus	Normal	20	83,3	
	Malignancy	2	8,3	
	Achalasia	1	4,2	
	Benign stenosis	1	4,2	

The endoscopic examination of a patient who has consistently ingested olive seed and was referred from the emergency department with a hematemesis pre-diagnosis revealed 33 olive seeds obstructing the duodenal lumen completely (**Figure 1**).

The FBs detected by endoscopic examination were removed from GI system in 21 (91.3%) of 23 patients, and were pushed into the stomach in 2 (8.7%) patients. After FBs were removed, endoscopic investigation of esophageal mucosa showed no injury in 16 (66.3%) patients, mucosal erosion in 3 (12.5%) patients, laceration in 3 (12.5%) patients, and perforation in 2 (8.3%) patients (**Figure 2**). There was not any statistically

significant association found between esophageal injury and ingested FBs (p> 0.05) (**Table 3**). However, the incidence of esophageal injury induced by FBs such as bone is remarkable, and it is suggested that larger series would yield significance. We had two cases with perforation on computerized tomography (CT) before the procedure, and the FB were chicken bones in both cases. One of these patients had ingested the FB 3 days ago, and the ingested chicken bone was stuck perpendicular to the lumen at the level of the upper esophageal sphincter, and ulcers developed on both walls of the lumen (**Figure 3**). Endoscopic hemoclips was inserted in 3 (12.5%) patients with lacerations in the esophageal wall secondary to FB. Two patients with perforation were consulted with thoracic surgery. These patients were hospitalized in the gastroenterology department since surgical intervention was not considered to be required. Oral nutrition of the patients was discontinued; total parenteral nutrition and broad-spectrum parenteral antibiotic treatment were initiated. Both patients recovered without the need for surgical intervention and additive endoscopic procedure after follow-up. Our success rate was 100% after endoscopic procedures. No complications or mortality was observed associated with the procedure (**Table 4**).

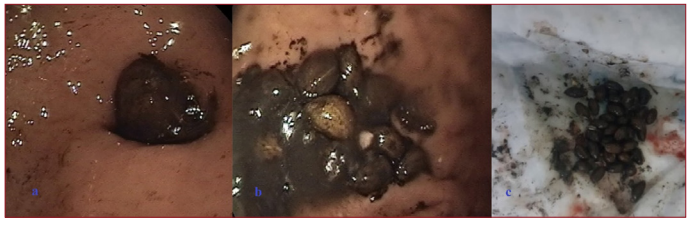

Figure 1: Olive seeds stuck in the pylorus (a), pulling olive seeds into the gastric corpus (b), removing out olive seeds (c)

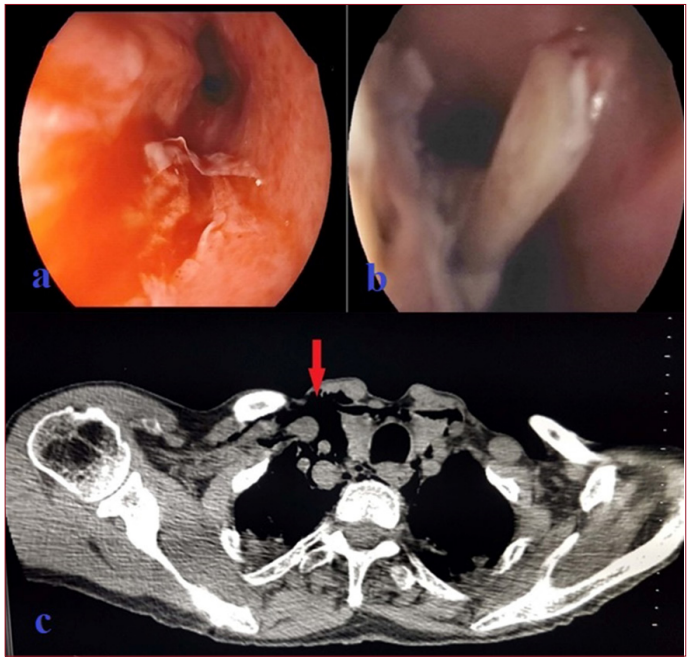

Figure 2: Endoscopic image of chicken bone stuck in the mucosa in the esophageal lümen and damage to the mucosa (a, b), appearance of free air secondary to perforation in the mediastinum by CT (c) (red arrow)

Table 3: Relationship between damage status and ingested foreign body

		No Esophageal Injury; n (%)	Esophageal injury is present; n (%)	P
Foreign body	Meat, Food	10 (62,5)	4 (50)	> 0.05
	Bone	3 (18,8)	4 (50)	
	Medicines	1 (6,3)	0	
	Herbal	2 (12,5)	0	

Fisher Freeman Halton Test

Table 4: Findings after endoscopic intervention

		n	%
Endoscopic intervention	None	21	87,5
	Hemoclips	3	12,5
Hospitalization	None	22	91,7
	Yes	2	8,3
Success rate	None	0	0
	Yes	24	100
Complications secondary to procedure	none	24	100
	Present	0	0
Mortality	None	24	100
	Present	0	0

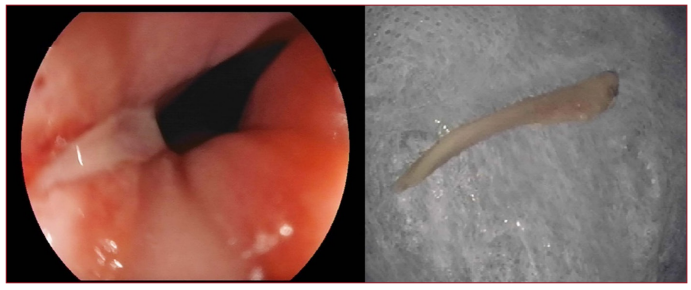

Figure 3: Foreign body and ulcer secondary to FB waited for a long time (3 days) in esophagus.

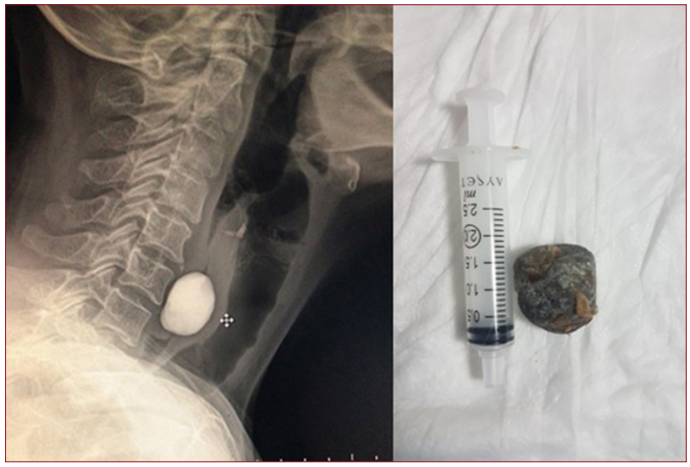

Figure 4: Foreign body swallowed at higher density than bone structures on x-ray. In the endoscopic examination, it was seen that the stone found by the patient on the ground was stuck at the level of the upper esophageal sphincter.

DISCUSSION

Geriatric age is a life period associated with multiple pathologies and relevant common signs and symptoms.[11] Ingestion of FB is a common global problem. Older people frequently ingest foreign bodies due to decreased intraoral sensitivity, swallowing disorders, visual and mental disorders, tooth loss, and problems with dental prostheses.[2] If ingested FBs are not managed promptly, severe complications including mucosal inflammation, deep neck abscess, mediastinitis, and esophageal perforation may occur.[12] Therefore, these complications may be prevented by early diagnosis and effective treatment of patients admitted to hospital due to FB ingestion.[2]

In the study of Yao et al.[4] the most common symptoms after FB ingestion were odynophagia (36.5%) and dysphagia (27%). They detected FBs in the stomach and duodenum in most of asymptomatic patients. The most common symptoms in our study were dysphagia (41.7%), aphagia (29.2%), and odynophagia (20.8%), respectively.

Most of the FBs are stuck in the upper esophagus in most of the studies.[1] In the study of Yao et al.[4] FBs were mostly detected in the esophagus (75.6%). Other locations included the stomach (12.5%), pharynx (8.3%), anastomoses (2.4%), and duodenum (1.2%). In our study, 87.5% of foreign bodies were detected in the esophagus, 4.2% in the stomach, and 4.2% in the duodenum. In a study on geriatric patients performed by Hsin-Chang et al.[2] 51.1% of foreign bodies were detected in the upper esophagus, 13.3% in the middle esophagus and 28.9% in the lower esophagus. In line with the literature, 50% of foreign bodies were detected in the upper esophagus, 16.7% in the middle esophagus, and 20.8% in the distal esophagus in our study; and a statistically significant difference was found ($p < 0.01$).

Several ingested FBs may be detected through cervical and lung X-rays. CT is much more sensitive than plain X-rays to detect any foreign bodies before endoscopic interventions.[4] The role of CT scanning does not aim to localize esophageal foreign bodies only, but also to evaluate relevant local complications including perforation, fistulization, and pleural empyema.[13] In our study, 14 (58.3%) patients had undergone cervical and lung X-rays before endoscopic intervention. FBs were detected in 4 (16.7%) patients through X-ray (**Figure 4**). The CT was performed on 4 patients in total; 3 of them had no visible object by X-ray and 1 patient had suspected perforation. FBs were detected in all of these patients through the CT.

The most common FBs detected in the studies of Wu[4] and Yao[14] were food-meat boluses (64.3%, 41.6%, respectively). In the study conducted by Hsin et al.[3] the most common FBs in the geriatric population were chicken and fish bones (37.8%); however, the most common FBs in our study were food-meat bolus (56.5%), and bone by 30.4%. When they were examined by the type of ingested foreign bodies, a statistically significant difference was found ($p < 0.01$). Hsin et al. also found dental prostheses by 17.8%, and drug packages by 8.8% in geriatric patients. The use of dental prostheses due to tooth loss and visual impairment in the elderly may be the reason of this condition.[2] However, in our study, endoscopic intervention was performed due to the use of herbal substances (garlic and olive seed) in 2 patients (8.7%), and due to drug misuse in 1 patient (vitamin D ampoule was ingested).

The success rate of FB removal from the esophagus by flexible endoscope was 83.8% in the study performed by Wu et al., 94.1% in the study performed by Li et al.[8,14] In the study performed by Hsin-Chang et al.[2] FBs were removed by primary method in 88.8% (40/45) of the patients. FBs were removed by alternative methods in 5 patients (4 patients by rigid endoscope under general anesthesia, and 1 patient by surgical method). In our study, the foreign body was removed in 21 (87.5%) patients; FB was pushed into the stomach from the esophagus in 2 (8.3%) patients. Our success rate was 100%.

The total incidence of complications induced by foreign bodies in the upper GI system is 15% to 42%.[14] These are localized complications such as erosions, superficial lacerations, edema, hematoma, and mild respiratory complications in general. The incidence of severe complications such as perforation or bleeding is 0.5-7.5%, and the mortality rate is 0-3.5%.[14] In our study, the incidence of complications due to foreign body was 20.8% during endoscopic procedures (mucosal laceration in 3 (12.5%) patients, perforation in 2 (8.3%) patients. Endoscopic hemoclips was inserted in 3 patients with deep esophageal lacerations. The chicken bone caused perforation in both cases. Two patients with perforation were consulted by thoracic surgery. Surgical intervention was not considered in these two patients, and conservative treatment was planned. Oral nutrition of the patients was discontinued; total parenteral nutrition and broad-spectrum parenteral antibiotic treatment were initiated. Both patients recovered without the need for surgical intervention and additive endoscopic procedure after close follow-up. No statistically significant association was found between the incidence of esophageal injury and type of ingested foreign bodies ($p > 0.05$). However, the incidence of esophageal injury induced by foreign bodies such as bone is remarkable, and it is suggested that the larger series would yield significance.

In the study of Hsin-Chang et al.[2] the initial success rate in FB removal was approximately 88.8%, and no mortality was found. Our success rate after endoscopic interventions was 100% in our study, and no complications or mortality due to endoscopic interventions were observed. After FB removal, routine endoscopy control is recommended in order to detect predisposing factors (i.e. malignancy, benign stenosis, achalasia, eosinophilic esophagitis) that may cause stuck in the GI system.[8] The studies performed by Yao et al.[4] found underlying predisposing pathologies in 29.2% of the patients. In the study conducted by Hsin et al.[2] on geriatric patients,

a predisposing pathology was found in the esophagus in 26.6% of the patients. In our study, an underlying pathology (malignancy, achalasia and stricture) was found in 16.7% of the patients.

Endoscopic strategy in the management of FB ingestion varies by FB type, symptoms, and ingestion duration. The timing of endoscopic management after FB ingestion is an important factor affecting the outcome.[1] Because of the possible severe complications, ESGE recommends immediate therapeutic EGD (preferably within 2 hours, latest within 6 hours) for pointed objects, batteries and FBs causing complete esophageal obstruction, and recommends therapeutic EGD within 24 hours for other esophageal foreign bodies that do not cause complete obstruction.[10] Wu et al.[14] reported in their study that esophageal ulcerations and odynophagia were more common if endoscopic intervention was delayed more than 24 hours from the ingestion moment in adult patients with suspected FB ingestion or food-meat bolus effect. In our study, endoscopic intervention was performed as soon as possible (mean endoscopy time is approximately 3 hours) after the patients were admitted to the emergency department. Only one patient was admitted to our hospital after 3 days following the FB ingestion. Endoscopic intervention was performed in a short time (40 minutes) following his admission to emergency department. However, chicken bone stuck for a long time in the esophageal lümen caused ulceration and microperforation in the upper esophagus. This finding supports the importance of timing for endoscopy.

Hsin et al.[2] followed up the patients who underwent endoscopic intervention due to FB for at least 3 days (2). However, the ESGE guidelines state that the patient may be discharged after successful and uncomplicated endoscopic removal of the ingested FBs.[10] Therefore, 22 patients without complications in our study were discharged after the endoscopic procedure.

Limitations of our study were the retrospective design and limited number of the cases. However, this kind of study is difficult to be conducted prospectively, and there are few studies on FB ingestion in geriatric patients. In addition, the age range of geriatric patients was considered to be 60 years in the studies.[2]

Patients in the geriatric population have multiple chronic diseases, and therefore use multiple drugs. Elderly people also commonly use over-the-counter medicines and herbal preparations. In the literature, the most common herbal preparations were reported as gingko biloba and garlic.[15] Furthermore, folkloric beliefs suggest that ingestion of olive seeds improves gastric disorders and stomach wounds, so this method is frequently used by patients in our country.[16] However, obstruction developed in 2 patients due to the use of herbal substances in our study, and endoscopic intervention was performed. One of the patients tried to ingest a whole piece of garlic with approximately 25x20 mm diameter, and it was stuck at the level of the upper esophageal sphincter. Another patient was admitted to our emergency department due to black colored vomiting. Endoscopic examination revealed 33 olive seeds were stuck between the duodenal bulbus and the pylorus. Olive seeds were initially pulled into the stomach from the duodenum and then completely removed out in a single session. Anamnesis of the patient revealed that the patient always ingested olive seeds for stomach complaints, and an obstruction due to an ulcer scar in the duodenal bulbus was detected by the endoscopic examination after removing out all the seeds.

Akan et al.[11] pointed to studies on drug use in geriatric patients that, the physician should instruct the details of the treatment to the patient not only verbally, but also in a written document. It is necessary to instruct prescriptions to the relatives or caregivers of the patients with cognitive impairment. Besides, it is recommended that the elderly patients with dementia or previous cerebrovascular disease should be closely followed up by their caregivers, ground/puree food should be given to patients with chewing problems; and if not contraindicated, the drug tablets or capsules should be crushed and mixed with sufficient drinking water.[2] In our study, a patient whom vitamin D ampoule was for oral use has ingested the ampoule directly. The ampoule was removed from the stomach by endoscopic procedure in this patient.

CONCLUSION

Endoscopic FB removal is a highly effective procedure with relatively low complication and mortality rates. Immediate endoscopic intervention should be applied in patients who ingest FB in order to reduce the risk of complications. Caregivers of geriatric patients with cognitive disorders should be warned and trained to be cautious about FB ingestion..

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by the institutional review board and ethics committee (Number: 15386878-044) of Amasya University Sabuncuoğlu Şerefeddin Training and Research Hospital.

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Orijinal Araştırma / Original Article

The Early-Term Adverse Effects in Healthcare Personnel after CoronaVac Vaccination

CoronaVac Aşısı Sonrası Sağlık Personelinde Erken Dönem Olumsuz Etkileri

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Abstract

Objectives: Among the various Covidien-19 vaccine, Sinovac vaccination program in Turkey is carried out by coronavac vaccine developed by Chinese firms. Our aim was to determine the early side effects of CoronaVac vaccine in Turkish healthcare professionals.

Material and Method: Volunteer healthcare personnel vaccinated with CoronaVac were evaluated four weeks after the first dose. Demographic, clinical characteristics, and post-vaccination side effects were recorded. Statistical analysis was performed with SPSS 15.0 software.

Results: The study was conducted with 516 volunteers. The mean age was 34.53±7.80 years, and the majority of the participants (58.1%) were women. The most common occupational nursing (34.8%) and smoking rate in the study was 27.1%. Approximately one third (31%) of the participants had a previous COVID-19 infection and antibody positivity (27.9%). The most common side effects were determined to be arm pain (55.8%) followed by headache (24.8%), fatigue (18.6%) and joint pain (7.8%). On the third day after vaccination, the diagnosis of COVID-19 was reported in one person. Four (0.8%) stated that they took a break from their daily routine due to syncope and one person due to COVID-19.

Conclusion: In this study, no life-threatening side effects were reported in the early period after CoronaVac. Among the early side effects of CoronaVac vaccine in our study, the most common side effects were Arm soreness, Headache, Fatigue and Joint pain. We argue that it is important to use multi-layered and evidence-based strategies to raise the frequency of vaccination and to address the concerns and ownership of the vaccine in relation to the COVID-19 vaccine. In order to minimize widespread information pollution and hostility associated with vaccination, healthcare professionals should lead and strongly support vaccination programs.

Keyword: CoronaVac, COVID-19, vaccination, SARS-CoV-2, side effects

Öz

Amaç: Çeşitli Covidien-19 aşıları arasında Türkiye'deki Sinovac aşılama programı, Çinli firmalar tarafından geliştirilen coronavac aşısı ile yürütülmektedir. Amacımız CoronaVac aşısının Türk sağlık profesyonellerinde erken yan etkilerini belirlemekti.

Gereç ve Yöntem: CoronaVac ile aşılanan gönüllü sağlık personeli, ilk dozdan dört hafta sonra değerlendirildi. Demografik, klinik özellikler ve aşılama sonrası yan etkiler kaydedildi. İstatistiksel analiz SPSS 15.0 yazılımı ile yapıldı.

Bulgular: Çalışma 516 gönüllü ile gerçekleştirilmiştir. Ortalama yaş 34.53±7.80 yıl olup, katılımcıların çoğunluğu (%58.1) kadındır. Çalışmada en büyük meslek grubu hemşirelerdi(%34.8) ve sigara içme oranı %27,1 idi. Katılımcıların yaklaşık üçte biri (%31) daha önce bir COVID-19 enfeksiyonuna ve antikor pozitifliğine (%27.9) sahipti. En sık görülen yan etkilerin kol ağrısı (%55.8) olduğu, ardından baş ağrısı (%24.8), yorgunluk (%18.6) ve eklem ağrısı (%7.8) olduğu belirlendi. Aşılamadan sonraki üçüncü günde bir kişide COVID-19 teşhisi konuldu. Dördü (%0,8) senkop, bir kişi ise COVID-19 nedeniyle günlük işlerine ara verdiklerini belirtti.

Sonuç: Çalışmamızda CoronaVac aşısının erken yan etkileri arasında en sık görülen yan etkiler Kol ağrısı, Baş Ağrısı, Yorgunluk ve Eklem ağrılarıydı. Gönüllülerimizde hayatı tehdit eden herhangi bir yan etki görmedik. Aşılama sıklığını artırmak ve COVID-19 aşısıyla ilgili endişeleri gidermek için çok katmanlı ve kanıta dayalı stratejiler kullanmanın önemli olduğunu düşünüyoruz . Aşılamayla ilgili yaygın bilgi kirliliğini ve düşmanlığı en aza indirmek için sağlık profesyonelleri aşı programlarına liderlik etmeli ve güçlü bir şekilde desteklemelidir.

Anahtar Kelimeler: CoronaVac, COVID-19, aşılanma, SARS-CoV-2, yan etkiler

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INTRODUCTION

The clinical features of Coronavirus-19 (COVID-19) disease, caused by the SARS-CoV-2 virus that wasfirst described in Wuhan, China,have a wide spectrum ranging from simple flu-like symptoms to severe acute respiratory syndrome.[1]

There is an urgent need for an effective vaccine against COVID-19 to control and alleviate the burdenof pandemic on healthcare. Scientists globally started research studies for vaccine development since the beginning of the pandemic.[2]

The CoronaVac (Sinovac, China) vaccine, developed by using an established technique of inactivating the virus chemically, is used for mass inoculation against COVID-19 in Turkey.[3] Some studies have already reported that the CoronaVac has a favorable safety profile and provides immunogenicity. The results of the first phase 1/2 trial showed that the inactivated coronavirus vaccine had a good tolerability and increased the humoral immunity in people aged 18-59 years.[4-6]

Vaccination has been widely accepted as an effective way of lessening the burden of infectious diseases by medical authorities. Nevertheless, the efficiency of vaccination is directly dependent on the acceptance by the public.[7] The public suspicion and anxiety about the safety and efficacy of the vaccines have a negative impact on the vaccination programs and might develop into vaccine opposition in extreme circumstances.[8] Research studies for evaluating the public confidence in COVID-19 vaccinations found a reduction in the rates of intention to be vaccinated by a potential vaccine in general.[9-13]

There is a direct link between the confidence in the safety and efficacy of vaccines and the trust felt for healthcare personnel, the health system, and policymakers of vaccination programs according to public needs.[14]

The first tier of COVID-19 vaccination in Turkey consisted of healthcare personnel. Our purpose was to identify the early-term adverse effects of CoronaVac in Turkish healthcare personnel.

MATERIAL AND METHOD

This study was conducted on volunteered healthcare personnel who were in the first tier of people for COVID-19 vaccination launched on January 14, 2021, in Turkey. The volunteered health personnel administered with the initial dose ofCoronaVac (Sinovac, China) had been evaluated four weeks after vaccination. The signed informed consent of all participants and the study was carried out with the permission of Harran University Clinical Researches Ethics Committee (Date: 15.03.2021, Decision No: HRU/21.06.36) which was in compliance with the principles of the Declaration of Helsinki.

The demographics (age, gender, height, weight, profession) and the clinical properties (the presence of chronic diseases, previous COVID-19 infection, SARS-CoV-2 antibody positivity) were recorded. The post-vaccination adverse effects, either local (swelling/redness at the injection site, soreness/pain in the ipsilateral arm of injection) or systemic (fever, allergic rash, fatigue, nausea, vomiting, headache, syncope, joint/muscle pain, loss of appetite/smell/taste, dyspnea, cough, flu-like symptoms) were noted. Open-ended questions like the development of COVID-19 after the vaccination and the discontinuation of daily routines due to adverse effects were also questioned.

The healthcare personnel who did not volunteer and who had active COVID-19 were excluded from the study.

Statistical Analysis

Statistical analysis was performed using the SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA). Descriptive statistics of continuous variables were shown as mean and standard deviation (SD) values while numbers and percentages were used to show the categorical data.

RESULTS

The study was completed with 516participants with a mean age of 34.53±7.80 years. The majority of the participants were female (58.1%), and nursing(n:180) was the most common (34.8%) healthcare profession in the study. Almost one-third of the participants (27.1%) were smokers, and 2.3% were past smokers. The most common chronic disease was found to be asthma in 12 participants. It was found that 160 people in the study had previous COVID-19, and 27.9% of the participants had antibodies against COVID-19. The demographics and the clinical characteristics of the study participants are shown in **Tables 1** and **2.**

The most commonly reported post-vaccination adverse effect (n:288, 55.8%) was the pain on the vaccination site . The following adverse effects included headache (n:128, 24.8%), fatigue (n:96, 18.6%), and joint/muscle pain (n:40, 7.8%). The development of COVID-19 infection in the post-vaccination 3rd day was reported in only one participant. Five people, one of whom with the COVID-19 and four of whom had syncope, reported the discontinuation to dailyroutines. Thereported adverse effects were summarized in **Table 3**.

Table 1. Demographics of participants

Variables	Mean±SD / n (%)
Age (years)	34.53±7.80
Height (cm)	168.16±8.37
Weight (kg)	71.86±12.76
Gender	
Female	300 (58.1%)
Male	216 (41.9%)
Profession	
Physician	128 (24.8%)
Nurse	180 (34.8%)
Hospital security officer	32 (6.2%)
Medical secretary	72 (14%)
Hospital custodian	44 (8.5%)
Radiology technician	32 (6.2%)
Others	28 (5.4%)

Table 2. Clinical features

Variables	n (%)
Smoking	
Yes	140 (27.1%)
No	364 (70.5%)
Quit	12 (2.3%)
COVID-19disease history	
Yes	160 (31%)
No	356 (69%)
COVID-19 Antibody in serology	
Positive	144 (27.9%)
Negative	240 (6.5%)
Not tested	132 (25.6%)
Chronic Diseases	
Thyroiditis	8 (1.6%)
Rheumatoid disease	8 (1.6%)
Ulcerative colitis	4 (0.8%)
Diabetes mellitus	8 (1.6%)
Asthma	12 (2.3%)
Hypertension	4 (0.8%)
Chronic hepatitis	4 (0.8%)

Table 3. Post-vaccination adverse effects

	n (%)
Arm pain	288 (55.8)
Headache	128 (24.8)
Fatigue	96 (18.6)
Joint pain	40 (7.8)
Swelling at vaccination site	36 (7)
Fever	28 (5.4)
Flu-like symptoms	16 (3.1)
Sore throat	8 (1.6)
Dizziness	8 (1.6)
Allergic rash	8 (1.6)
Impaired taste	8 (1.6)
Vomiting	8 (1.6)
Loss of appetite	4 (0.8)
Dsypnea	4 (0.8)
Syncope	4 (0.8)
Cough	4 (0.8)
Others	5 (3.9)

DISCUSSION

In the first report of the Phase 1/2 trial of CoronaVac, all reported adverse effects were mild to moderate. The most common post-vaccination complaint was the soreness at the injection site in 9% of the study group, followed by fever (3%). Additionally, headache and mucocutaneous rash were more frequently observed in the group administered with a 6 µg dose of vaccine. No statistically significant difference in local and systemic adverse effects was observed between the placebo and the remaining groups. Serious side effects which were considered to be unrelated to the vaccination were reported in 2% of the participants.[2] Similarly in our study, no life-threatening early-term adverse effects to CoronaVac were observed in 526 healthcare personnel evaluated four weeks after the vaccination.

In our study, all adverse effects reported were in the range of mild to moderate. The frequency of arm soreness/ pain in our group was more frequent than reported by Wu et al. Similar to our results, Zhang et al. reported mild to moderate side effects in their study and tenderness at the injection site was the most commonly observed effect in their study. In our study the most commonly reported post-vaccination adverse effect (n:288, 55.8%) was the pain on the vaccination site. Zhang et al. also reported a case of acute allergic reaction, which had a good response to dexamethasone therapy.[15] In other studies on inactivated COVID-19 vaccine, post-vaccination effects were reported mild to moderate similar to ours.[4,5,16]

The mean age in our study was 34.53±7.80 years, but in the study of Zhang et al. it was 42.4±5.8 years.[15] Considerably, the age discrepancy between our study and the study of Zhang was due to the fact that our study group consisted of actively working healthcare personnel.

While the COVID-19 vaccine was presented to the public experiencing the pandemic-related psychological and physical stress, many conspiracy theories on COVID-19 pandemic and vaccines started to appear in the popular and social media.[9,10,17] The factors related to COVID-19 vaccine hesitancy are similar to those for previous vaccines such as the properties of the vaccines, the political factors, and the attitude and beliefs against vaccination.[18] The data from questionnaires revealed the public hesitancy regarding the efficacy of the vaccines and anxiety regarding the uncertainty of protection duration, safety, and side effects.[8,9,12]

In this study, it is noteworthy to report that the healthcare personnel who had previous COVID-19 (31%) and antibody positivity against SARS-CoV-2 (27.9%) were eager to be vaccinated. This kind of attitude is a definite indicator of pioneer roles the healthcare personnel have.

It is well-known since old times that the recommendations and actions of healthcare personnel result in higher vaccination rates in public. Still, the healthcare specialists are considered as the most trustworthy information source by the public.[19-21] Hence, in a recent questionnaire, participants quoted that the possibility of COVID-19 vaccine acceptance would be higher if the recommendation was made by healthcare providers.[13]

We consider the younger mean age and a small number of comorbidities in our study group as well as the unknown long-term adverse effects of the vaccine as the limitations of the current study. Further long-term studies with larger size and older age groups are required. In the current study, we wanted to emphasize the safety of inactivated coronavirus vaccine, CoronaVax.

CONCLUSION

No early-term life-threatening adverse effects after CoronaVac were reported in this study. We suggest that it is critical to use multi-tiered and evidence-based strategies to have the public embrace the idea and overcome the anxiety, and boost the frequency of COVID-19 vaccination. The healthcare personnel should pioneer and firmly support the vaccination programs to minimize the widespread information pollution and opposition to vaccination..

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Harran University Clinical Researches Ethics Committee (Date: 15.03.2021, Decision No: HRU/21.06.36).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article / Orijinal Araştırma

Thoughts and Attitudes of Adults About Medicines Used for COVID-19; A Descriptive Study

Erişkin Bireylerin COVID-19'a Yönelik Kullanılan İlaçlarla İlgili Düşünce ve Tutumları; Tanımlayıcı Bir Çalışma

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Abstract

Aim: With this study; it was aimed to determine the usage status and attitudes towards the drugs currently used/recommended for the treatment of COVID-19 and various medications or nutritional supplements to support immune system, and the factors affecting usage status of them, according to the condition of having COVID-19.

Material and Method: The descriptive research was conducted in Family Medicine outpatient clinics. Data were collected with a questionnaire prepared by the researchers through the internet (sites on social media) due to the pandemic. The e-questionnaire form was shared on the internet a total of 10 times at 6-day intervals.

Results: 1484 people participated, 60.8% were female, 51.5% was a healthcare professional. While 23.3% had a known disease; 19.3% of them had COVID-19 infection, 79% of them received outpatient medication. Although not recommended, it was observed that the most used drugs were Vitamin C and antipyretic drugs, followed by vitamin D and antibiotics. 87.5% who have had COVID-19 infection stated that they used the drugs as suggested/written on to them. The reasons of those who did not use drugs: fear of its side effects, not seeing it necessary, using herbal products and observing and using it if necessary. People who living with a person under the age of 18 in the same household (p=0.042), who had a chronical disease (p=0.014) and regular drug users (p=0.003) were reported that they used COVID-19 drugs as suggested/written on them.

Conclusion: New information is emerging day by day about the treatment of COVID-19 disease, infodemic causes the spread of false information about the disease and its treatment both among the public and in scientific circles. The results of our study also support this situation. The healthcare system should be structured in accordance with the pandemic conditions in order to explain the importance of the use of medicines.

Keywords: COVID-19, medicines, nutritional supplements, infodemic

Öz

Amaç: Bu çalışma ile; COVID-19 tedavisinde halen kullanılan/önerilen bağışıklık sistemini destekleyici çeşitli preparatlar, besin takviyeleri ve ilaçlara yönelik erişkinlerin düşünce ve tutumlarının ve kullanım durumlarını etkileyen faktörlerin belirlenmesi amaçlanmıştır.

Gereç ve Yöntem: Tanımlayıcı tipteki araştırma Aile Hekimliği polikliniklerinde yürütülmüştür. Veriler, pandemi nedeniyle internet (sosyal medyadaki siteler) üzerinden araştırmacılar tarafından hazırlanan anket ile toplanmıştır. E-anket formu internette 6 gün arayla toplam 10 kez paylaşılmıştır.

Bulgular: 1484 kişi katıldı, %60,8'i kadın, %51,5'i sağlık çalışanıydı. %23,3'ünün bilinen bir hastalığı varken; bu kişilerin %19,3'ü COVID-19 enfeksiyonu geçirdiğini, %79'u ayakta tedavi gördüğünü belirtti. Önerilmemesine rağmen en çok kullanılan ilaçların C vitamini ve ateş düşürücü ilaçlar olduğu, bunu D vitamini ve antibiyotiklerin takip ettiği görüldü. COVID-19 enfeksiyonu geçirenlerin %87,5'i ilaçları kendilerine önerildiği/üzerlerine yazıldığı şekilde kullandığını belirtmiştir. Önerildiği halde ilaç kullanmayanların nedenleri: yan etkilerinden korkmak, gerekli görmemek, bitkisel ürünleri kullanmak ve gerekirse gözlemlemek ve kullanmak. Aynı hanede 18 yaşından küçük bir kişiyle yaşayanlar (p=0,042), kronik hastalığı olanlar (p=0,014) ve düzenli ilaç kullananlar (p=0,003) COVID-19 ilaçlarını önerildiği/üzerlerinde yazıldığı gibi kullandıklarını bildirdiler.

Sonuç: COVID-19 hastalığının tedavisi hakkında her geçen gün yeni bilgiler ortaya çıkıyorken; infodemi, hem halk arasında hem de bilim çevrelerinde hastalık ve tedavisi hakkında yanlış bilgilerin yayılmasına neden olmaktadır. Çalışmamızın sonuçları da bu durumu desteklemektedir. İlaç kullanımının önemini anlatabilmek için sağlık sistemi pandemi koşullarına uygun olarak yapılandırılmalıdır.

Anahtar Kelimeler: COVID-19, ilaçlar, besin takviyeleri, infodemi

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INTRODUCTION

After originating in China, COVID-19 epidemic which has affected the whole world in a short period of three months, continues to threaten all humanity despite more than one year.[1] According to the data of the World Health Organization; it is seen that the number of cases originating from COVID-19 has reached 144,587,350 and the number of deaths is 3,075,007 worldwide.[2]

In Turkey, the first case of COVID-19 was seen on 11 March 2020 and 4 days after the first death occurred bonded to the COVID-19. During the period until 22/04/2021; total number of cases 4,446,591 and the total number of deaths from COVID-19 is stated as 36,975.[3]

Some drugs are being evaluated or developed for the management of COVID-19 from the first stage of the disease. These drugs; antivirals (eg, Remdesivir, Favipiravir), antibodies (eg Convalescent Plasma, Hyperimmune Immunoglobulins), anti-inflammatory agents (dexamethasone, statins), targeted immunomodulatory therapies (eg, Tocilizumab, Sarilumab, Anakinra, Ruxolitinib) anticoagulants (eg Heparin) and antifibrotics (eg Tyrosine Kinase Inhibitors). Different treatment modalities applied may have different effects on different disease symptoms at other stages of the disease. While viral inhibition is expected to be most effective in the early phase of infection, immunomodulatory agents are useful in hospitalized patients to prevent disease progression, and anticoagulants can be useful to prevent thromboembolic complications. Although there are many treatment modalities, studies show that the drug treatment that is initiated early and taken at the right doses in COVID-19 infection greatly prevents the progression of the disease and reduces the intensive care admission rate.[4-7] In our country, there are treatment recommendations for asymptomatic COVID-19 cases, possible/definite cases of COVID-19 with mild to moderate pneumonia and COVID-19 cases with hospitalization indication. Treatment with Hydroxychloroquine and/or Favipiravir is started in outpatients, this treatment is delivered directly to individuals by institutions affiliated to the Ministry of Health as soon as the person recover from illness.[8] However, there is no mechanism that controls the treatment process and the use of drugs. Drug use is done with the consent of the people. It is observed that drug use of individuals is also affected due to infodemic.[9,10] No study has been found on the use of the medicines recommended for them in case of illness and the factors affecting this.

It is known that some people use various medications or nutritional supplements (multivitamins, minerals) to support immune system in addition to the drugs for COVID-19 infection during the pandemic process.[11] In this process, various situations such as misuse due to information pollution and various factors, drug refusal, irregular use are also encountered. No studies have been found in the literature review about this very common situation in daily practice.

With this study, it was aimed to determine the usage status and attitudes towards the drugs currently used/recommended for the treatment of COVID-19 and various medications or nutritional supplements to support immune system, and the factors affecting usage status of them, according to the condition of having COVID-19.

MATERIAL AND METHOD

The descriptive research was conducted between the dates of 20th January 2021 and 20th March 2021 in Hacettepe University Faculty of Medicine, Department of Family Medicine. The population of the research consists people over the age of 18 in Turkey. After the approval of the ethics committee, those who completely filled out the e-questionnaire form shared by the researchers on the web with "Google forms" for two months were included in the study. Epi Info 7 StatCalc was used to calculate the minimum sample size for universe whose prevalence and number are unknown, and the sample size was estimated as 384 adults, assuming 95% confidence interval and 5% sampling error.

The questionnaire form used in the study was prepared by the researchers by scanning the literature. In addition to 20 questions where sociodemographic data (age, gender, educational status, marital status, number of children, number of people living in the same household, presence of individuals over 65 and under 18 living in the same household, occupation, employment status, working style during the pandemic) and the disease states of the participants and their relatives during the pandemic (presence of known disease, presence of regularly used drugs, presence of an individual with COVID-19 in their vicinity, presence of quarantine due to contact) are questioned, 14 questions asked to those who had COVID-19 infection (treatment process, symptoms, positivity of COVID-19 infection in individuals in the same household, which drugs were started, whether the patient used the treatment in accordance with the treatment and dose, if not, the reasons, the use of vitamin supplements before, during and after the disease, prophylactic attitude towards drug use), 9 questions asked to those who have not had been infected (thoughts about COVID-19, thoughts about drugs and negative, use of vitamin supplements for prevention, attitude towards prophylactic drug use).

Data were collected with a questionnaire prepared by the researchers through the internet (Whats up, Facebook) due to the pandemic. The e-questionnaire form was shared on the internet a total of 10 times at 6-day intervals. Individuals who filled out the voluntary consent form, which was attached to the beginning of the questionnaire form, were able to access the questionnaire questions. People over the age of 18 who responded to all data were included in the study.

Transferring the data obtained in the study to electronic media (data entry) and statistical analysis of the data were performed using IBM SPSS Statistics Premium 23 V statistical computer package program licensed by Hacettepe University. Descriptive statistics were specified as distributions, as percentage, mean, median, quartiles, minimum-maximum values, and standard deviation. If necessary, the compliance

of variables to normal distribution was checked with Kolmogorov Smirnov and Shapiro Wilk tests. For the comparison of independent two-group continuous variables conforming to normal distribution, the t-test in independent groups, the Mann Whitney U test for the comparison of continuous variables with independent two groups that did not comply with the normal distribution, for categorical variables, the Pearson Chi-square test was used to evaluate whether there was a difference between the groups, and when necessary, the Fisher test in 2x2 order, ANOVA test was used to compare the means of more than two independent groups. When parametric conditions could not be provided, Kruskal Wallis variance analysis was used. It was planned to conduct correlation analysis to evaluate the linear relationship between variables, and multivariate analysis to examine the cause-effect relationship between variables. Alpha 0.05 was taken.

Permissions

Ethics committee approval of the research was obtained from Hacettepe University Non-Interventional Clinical Research Ethics Committee (Date: 19/01/2021, Decision No: GO21/123). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

RESULTS

Sociodemographic Features

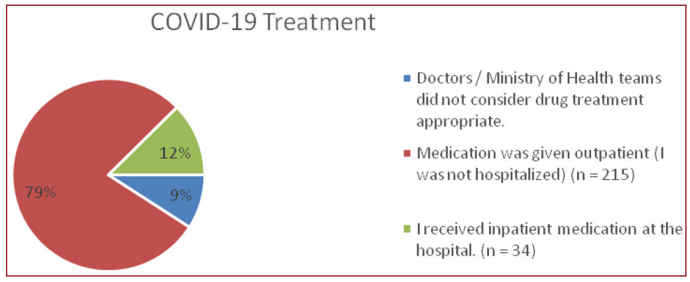
The average age of the participants in our study, in which 1484 people participated, was 35.94 + 12.42 (min=18; max=81). Of the participants, 60.8% (n=902) were female, 84.2% (n=1246) were between 18-50 years old, 1.6% were above 65 years old, 67.9% (n=1008) were university graduates, 59% (n=876) were married, 66.2% (n=982) of them live with 3 or more people in the same household, 8.1% (n=120) live with someone over 65 years old in the same household, and 45.1% (n=669) live with children under 18 in the same household and 51.5% (n=764) was a healthcare professional, 13.3% (n=198) were not working, 70.1% (n=1041) were working full time. While 23.3% (n=346) had a known disease; 25% (n=371) of them regularly used medication.

Features Related to COVID-19 Infection

Of the participants, 19.3% (n=286) of themselves and 65.2% (n=967) of their relatives had COVID-19 infection, 23.5% (n=349) of them remained in quarantine due to contact with someone with COVID-19 infection.

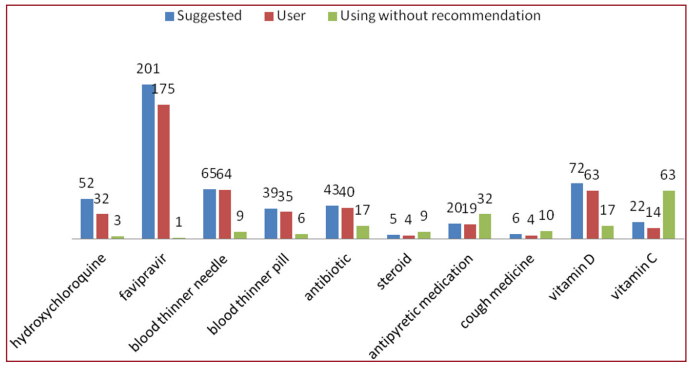
Disease and drug use characteristics of those who had COVID-19 infection

Of the participants who have had COVID-19 infection, 49.6% (n=107) of them had COVID-19 infection in the person (s) with whom they lived in the same household during the period when they had COVID-19 infection and 79% (n=215) of them received outpatient medication. Treatment modalities are presented in the **Graphic 1**.



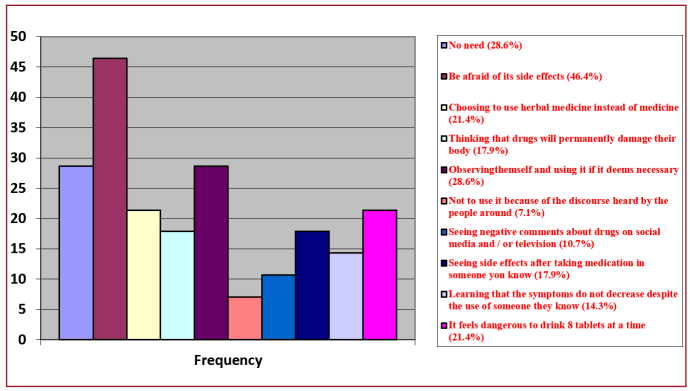
Graphic 1. Distribution of treatment modalities of participants who have had COVID-19 infection

The drugs recommended and the rates of drugs used by the participants who have had COVID-19 infection are given in the **Graphic 2**. Although not recommended, it was observed that the most used drugs were Vitamin C and antipyretic drugs, followed by vitamin D and antibiotics.



Graphic 2. The drugs recommended and the rates of drugs used by the participants who have had

Of the participants, 87.5% (n=188) who have had COVID-19 infection stated that they used the drugs as suggested/written on to them. The reasons of those who did not use drugs as suggested/written on are in the **Graphic 3**. The most common reason: fear of its side effects, not seeing it necessary, using herbal products and observing and using it if necessary.



Graphic 3. The reasons of those who did not use drugs as suggested/written on

Factors affecting the participant's use of drugs as suggested/written on them are presented in the **Table 1**. People who had live a person under the age of 18 living in the same household (p=0.042), who had a chronical disease (p=0.014) and who were regularly drug users (p=0.003) were reported that they used drugs as suggested/written on them.

While 38.4% (n=75) of those who had COVID-19 infection were taking additional vitamin supplements to protect against COVID-19 in the pre-illness period; 75% (n=149) stated that they received additional vitamin supplements during the period of illness, and 45.4% (n=98) stated that they received additional vitamin support in the post-illness period. Of the participants who have had COVID-19 infection, 23.6% (n=46) stated that they believed in using prophylactic drugs to protect against COVID-19.

The thoughts of those who have not had COVID-19 infection on the disease and drug use

Of the participants who did not have COVID-19 infection, 58.9% (n=712) of those stated that it was a seriously fatal disease for everyone, 67.4% (n=820) stated that they would use the drugs given by the Ministry of Health/doctors in case of having COVID-19 infection, and 23.1% were undecided about using. 40.3% stated that the drugs cannot prevent the progression of the disease, 72% stated that the drugs cannot reduce the infectiousness or were unstable, and 37.7% stated that the drugs cannot reduce your complaints/symptoms.

Factors affecting the use of drugs to be given in case of COVID-19 infection of the participants are presented

Table 1. Factors affecting the participant's use of drugs as suggested/written on

	Regular use of medicines as suggested/written on				p
	Yes		No		
	%	n	%	n	
Gender *					
Female	63.3	119	59.3	16	0.685
Male	36.7	69	40.7	11	
Marital Status *					
Married	63.3	119	59.3	16	0.685
Single/widow/divorced	36.7	69	40.7	11	
Education Status *					
Graduated high school and lower than high school	6.9	13	11.1	3	
Graduated from a university	64.9	122	59.3	16	0.707
Postgraduate/Doctorate graduate	28.2	53	29.6	8	
Having Children *					
Yes	54.8	103	59.3	16	0,662
No	45.2	85	40.7	11	
Number of people in the same household *					
1	12.8	24	0	24	
2	19.7	37	14,8	41	0.080
3	21.8	41	18,5	46	
4	30.9	58	55,6	73	
Having a person over the age of 65 living in the same household *					
Yes	5.3	10	74	2	0.658
No	94.7	178	92.6	25	
Having a person under the age of 18 living in the same household *					
Yes	54.3	102	33.3	9	0.042
No	45.7	86	66.7	18	
Profession *					
Healthcare professional	8	15	14.8	4	
Non-health profession member	67.6	127	70.4	19	0.329
Has no profession	24.5	46	14.8	4	
Working status *					
Not working	16.5	31	18.5	5	
Full time working	80.9	152	74.1	20	0.401
Part-time/seasonal work	2.7	5	7.4	2	
Having illness *					
Yes	29.8	56	7.4	2	0.014
No	70.2	132	92.6	25	
Drug use *					
Yes	30.9	58	3.7	1	0.003
No	69.1	130	96.3	26	
Someone who has had COVID-19 infection nearby *					
Yes	88.8	167	100	27	0.068
No	11.2	21	0	0	
Quarantine due to contact with someone with COVID-19 infection *					
Yes	58	109	63	17	0.623
No	42	79	37	10	
	Median (interquartile range)		Median (interquartile range)		p
Age **	31.00 (19)		29.00 (12)		0.307
Scale score **	4.00 (1.0)		4.00 (3.0)		0.531

Data were given as n (%) and d median (interquartile range).; *Chi-square test; **Mann Whitney-U test

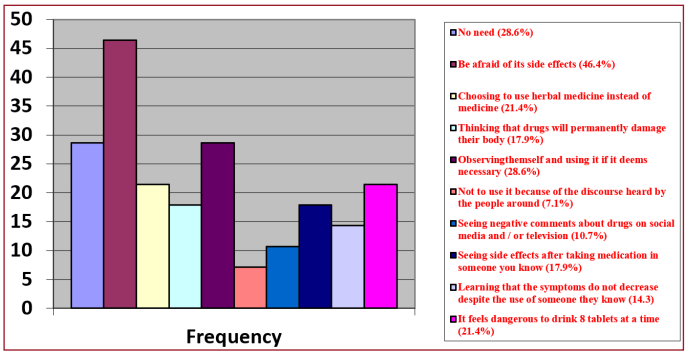
in the **Table 2**. People who were regularly drug users (p=0.022), who not stated that the drugs cannot prevent the progression of the disease (p<0.001), who not stated that the drugs cannot reduce the infectiousness or were unstable (p<0.001), and who not stated that the drugs cannot reduce your complaints/symptoms (p<0.001) were reported that they would use drugs given in case of having COVID-19 infection.

Table 2. Factors affecting the use of drugs to be given in case of COVID-19 infection of the participants

	Using medicines to be given in case of having COVID-19 infection						p
	Yes		No		Undecided		
	%	n	%	n	%	n	
Gender *							
Female	62.3	503	60	69	59.6	167	0.702
Male	37.7	305	40	46	40.4	113	
Marital Status *							
Married	56.8	459	61.7	71	62.9	176	0.163
Single/widow / divorced	43.2	349	38.3	44	37.1	104	
Education Status *							
Graduated high school and lower than high school	9.7	78	17.4	20	9.6	27	
Graduated from a university	67	541	62.6	72	70	196	0.097
Postgraduate / Doctorate graduate	23.4	189	20	23	20.4	57	
Having Children *							
Yes	51.9	419	55.7	64	53.9	151	0.670
No	48.1	389	44.3	51	46.1	129	
Number of people in the same household *							
1	10.4	12	12.4	100	10	28	
2	19.1	22	21.8	176	21.1	59	0.798
3	23.5	27	21.4	173	25.7	72	
4	27.8	32	29.2	236	28.9	81	
Having a person over the age of 65 living in the same household *							
Yes	8.2	66	8.7	10	8.6	24	0.966
No	91.8	742	91.3	105	91.4	256	
Having a person under the age of 18 living in the same household*							
Yes	42.9	347	53.0	61	48.2	135	0.063
No	57.1	461	47.0	54	51.8	145	
Profession *							
Healthcare professional	14.2	115	17.4	20	12.5	35	
Non-health profession member	51.9	419	46.1	53	49.3	138	0.499
Has no profession	33.9	274	36.5	42	38.2	107	
Working status *							
Not working	24.1	195	27	31	23.6	66	
Full time working	68.8	556	67	77	70	196	0.947
Part-time / seasonal work	7.1	57	6.1	7	6.4	18	
Having illness *							
Yes	23.5	190	27	31	20.4	57	0.329
No	76.5	618	73	84	79.6	223	
Drug use *							
Yes	24.8	200	33	38	20	56	0.022
No	75.2	608	67	77	80	224	
Someone who has had COVID-19 infection nearby *							
Yes	65.1	526	60	69	61.8	173	0.406
No	34.9	282	40	46	38.2	107	
Quarantine due to contact with someone with COVID-19 infection *							
Yes	23.6	191	27.8	32	18.2	51	0.070
No	76.4	617	72.2	83	81.8	229	
Thinking that drugs for COVID-19 infection prevent disease progression *							
Yes	78.2	632	17.4	20	23.2	65	
No	4.2	34	47	54	16.8	47	<0.001
Undecided	17.6	142	35.7	41	60.0	168	
Thinking that drugs for COVID-19 infection reduce infectiousness *							
Yes	36.3	296	6.1	7	11.8	33	
No	36.9	298	65.2	75	56.4	158	<0.001
Undecided	26.5	214	28.7	33	31.8	89	
Thinking that COVID-19 infection medications will reduce complaints / symptoms *							
Yes	80.4	650	13.9	16	30.7	86	
No	3.6	29	48.7	56	11.4	32	<0.001
Undecided	16.0	129	37.4	43	57.9	162	
	Median (interquartile range)		**Median (interquartile range)**		**Median (interquartile range)**		**p**
Age **	32.00 (19)		33.00 (15)		31.00 (16)		0.992
Scale score **	4.00 (1.00)		4.00 (1.00)		4.00 (1.00)		0.140

Data were given as n (%) and d median (interquartile range).; *Chi-square test; **Kruskal Wallis test

Considering the reasons for those who were reported that they would not use drugs given in case of having COVID-19 infection were: fear of side effects, thinking of to take 8 tablets at a time is dangerous, observing and thinking of using it myself, or fear that the drug will cause permanent damage. The reasons for those who do not intend to use drugs are in the **Graphic 4**.



Graphic 4. The reasons for those who do not intend to use drugs

While 51.2% of those who did not have COVID-19 infection took vitamin supplements, 56.2% stated that they did not believe in using prophylactic drugs (to avoid the disease).

DISCUSSION

In our study, which evaluated the use of drugs and nutritional supplements used in the treatment of COVID-19 by people with COVID-19 infection, the reasons for not using them, and the opinions of those who did not have an infection about these drugs; those who had COVID-19 infection mostly used the drugs recommended for treatment (87.5%); although not recommended, the drugs mostly used were Vitamin C, antipyretic drugs and vitamin D; it was observed that 67.4% of those who did not have COVID-19 infection stated that they would use the drugs to be given in case of having COVID-19 infection and approximately half of them received vitamin supplements. These results show that there is a prejudice in the society regarding drugs for COVID-19 disease, which is a newly described disease in our lives, but the use of drugs in case of disease is not bad in contrast to the prejudices of people in the disease-free group. It was observed that half of the participants were taking medicines and vitamins for prevention and the use of vitamins increased significantly in case of illness.

In our study, it was observed that 65.2% of the participants' relatives had a COVID-19 infection, and 19.3% themselves. As of 21/04/2021, there are a total of 4,384,624 cases and 36,613 patients in our country, that is, 0.05% of the society has had COVID-19 infection. In our study, according to community data, the frequency of people with COVID-19 infection was higher, the reason is related to our sample, but reaching more people with COVID-19 infection than the number of the population was a positive situation for our study to evaluate the drug use of these people. In our study, it was observed that 79% of the participants who had COVID-19 infection received outpatient medication. In accordance with our study, a large cohort that included more than 44,000 people with COVID-19 from China, showed that 81% of the people with COVID-19 have mild symptoms and not hospitalized.[12]

Currently, in our country, it is recommended to use Hydroxychloroquine 200 mg tablet and/or Favipiravir 200 mg tablet for 5 days in asymptomatic definite COVID-19 cases where COVID-19 infection will be monitored on an outpatient basis, and in possible/definite COVID-19 treatment with uncomplicated or mild-moderate pneumonia.[8] Prophylactic anticoagulation therapy is recommended to prevent coagulation in some COVID-19 patients.[7] Apart from this, antipyretic drugs, antibiotics and in some cases, vitamins can be recommended. In our study, it was observed that Favipiravir, one of the routinely recommended drugs, was the most administered drug, followed by subcutaneous anticoagulation drugs and Hydroxychloroquine. 87.5% of the participants who had COVID-19 infection stated that they used the drugs recommended for COVID-19 treatment as described/written on them. It is noteworthy that 87% of the participants were used regularly/as recommended Favipiravir, which is one of the routinely recommended drugs, and 61.5% of the Hydroxychloroquine are used regularly/as recommended, and the frequency of use of other recommended drugs is higher than these drugs. Among the reasons for not using the drugs among the participants in our study, the most common reasons were being afraid of its side effects, not seeing it necessary, using herbal products instead of medicines and observing oneself and using it if it deems necessary. It is thought that infodemic may be effective in both the frequency of drug use and the reasons why people do not use it regularly. It is known that there is anxiety against the disease and anxiety in the society for the treatment of COVID-19 infection and its treatment, which is a new disease and new information is added every day.[13,14] In particular, we think that the information obtained from inaccurate sources about the side effects of drugs and the anxiety felt against the disease are effective in the results of our study.

Although not recommended by the physician for those with COVID-19 infection, it has been observed that the most used drugs are Vitamin C and antipyretic drugs, followed by vitamin D and antibiotics. As a result, for antipyretic and antibiotics, people could not go to the health center due to the need to be isolated at home after being diagnosed with infection, and they may have taken medication according to their own knowledge of their symptoms. For antipyretics, it was recommended to patients with COVID-19 to use antipyretics in case of fever by health professions.[15] A healthy immune system is very important in preventing viral infections, and vitamins such as A, C, D and E and minerals such as zinc, copper, selenium, and iron are known to play an important role in maintaining a healthy immune response.[16] In addition, since there is no currently approved drug for the treatment of COVID-19, any potential therapeutic that can reduce the severity of the disease

becomes important for both the prescribing physicians and the public.[17] In our study, it is an expected result that people with COVID-19 infection used vitamins by their own decisions to improve the course of the disease. Vitamin usage rates of participants with COVID-19 infection and the comparison of these rates according to pre-illness (38.4%), illness period (75%) and post-illness (45.4%) and the usage rates of those who did not have COVID-19 infection (51.2%), the effects of this situation can be seen. According to the distribution, it is noteworthy that the most frequent vitamin supplements were taken during the illness period, and the frequency of use increased after the illness compared to the pre-ill period.

In the study, when the factors affecting the participants' use of drugs as suggested was seen that those have children under 18 years of age, those have chronic diseases and regular drug users used much more regularly and frequently. Chronic diseases are in the first place among the risk factors that increase mortality rates in the COVID-19 epidemic all over the world[18,19] it is thought that this risk may be one of the most important reasons for those with chronic diseases and regular drug users to use the drugs recommended for COVID-19 infection more regularly and frequently than others. It was thought that those with children under the age of 18 may have acted more sensitive on this issue due to the unclear course of this disease in children,[21,22] and the lack of a drug administered to children yet.

In our study, the opinions of those who did not have COVID-19 infection about the drugs to be given by the Ministry of Health/doctors were also evaluated. 32.6% of these people stated that they would not use the medications given in case of having COVID-19 infection. When these people were asked the reasons, they most frequently stated that they were afraid of the side effects of the drug, drinking 8 tablets at a time was dangerous, observing and thinking about using it myself or fear that the drug would cause permanent damage. It is noteworthy that these people who think that the COVID-19 infection drugs do not prevent the progression of the disease, do not reduce the contagiousness, and reduce the complaints/symptoms. Again, these results are thought to have negative effects of infodemic.[22]

In addition to many reviews or publications about the effects of drugs related to COVID-19 infection in the literature,[15] no study has been found that affects the perceptions and usage of these drugs in the society. In this context, we think that our study will make a significant contribution to the literature. Providing more accurate information on this subject and directing the society to correct information sources should be the first step to be taken in this regard.

Conducting our study online due to the decrease in outpatient applications due to the pandemic and the sociodemographic diversity of the applicants (especially age) is the most important limitation of the study. It cannot be expected that the segment reached in online surveys can be generalized to the whole society.

CONCLUSION

New information is emerging day by day about the treatment of COVID-19 disease, and this infodemic situation causes the spread of false information about the disease and its treatment both among the public and in scientific circles. The results of our study also support this situation. The healthcare system should be structured in accordance with the pandemic conditions in order to explain the importance of the use of medicines by healthcare workers to the infected people more clearly, to reach the treatment (antipyretic, antibiotic, painkiller, etc.) for their symptoms under the supervision of the doctor, should be avoided. In addition, primary health care workers have a lot of work in order to prevent the prejudices of people who have not had an infection and to improve the perception of drugs in the whole society.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethics committee approval of the research was obtained from Hacettepe University Non-Interventional Clinical Research Ethics Committee (Date: 19/01/2021, Decision No: GO21/123).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Orjinal Araştırma / Original Article

Investigating the Relationship Between Insulin Perceptions and Diabetes Self-Management of Intensive Care Patients with Type 2 Diabetes

Yoğun Bakıma Yatan Tip 2 Diyabetli Hastaların İnsüline Karşı Algıları ile Diyabet Öz Yönetimleri Arasındaki İlişkinin İncelenmesi

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Abstract

Aim: This study aimed to determine the level of perception of insulin and diabetes symptom management of patients with Type 2 diabetes who received inpatient treatment in intensive care.

Material and Method: This descriptive study was conducted in the Internal Medicine and Anesthesia Intensive Care units of a state hospital during the period of December 01, 2020 and March 31, 2021. The sample of the study was composed of 100 voluntary patients who used insulin. Research data were collected via the Patient Introduction Form, Diabetes Self-Management Questionnaire and the Insulin Treatment Appraisal Scale. Written permission was obtained from ethics committee and patients. The data analysis consisted of arithmetic mean, number, percentage, Spearman's Correlation, Mann Whitney U and Kruskal Wallis tests.

Results: The average age of the patients was 44.57±14.8, 52% were female, 72% were single. The mean duration of insulin use was 2.8±1.17 years. Patients' Insulin Treatment Appraisal positive and negative item subscale mean scores were 12.56±3.43 and 48.18±12.09, respectively. Patients' mean Diabetes Self-Management Questionnaire total score was 4.07±1.74 (range: 0.62-8.75). There was a significant difference between the marital status, education level, existence of chronic disease and complications, regular use of insulin and Diabetes Self-Management Questionnaire and Insulin Treatment Appraisal Scale scores.

Conclusion: Patients have a high negative perception towards insulin use and their diabetes self-management is below the average. There was a high level of negative correlation between patients' negative insulin perception and glucose management and diet control sub-dimensions of their diabetes self-management. Accordingly, it is recommended to plan individual or group trainings in order to raise awareness about diabetes self management and patients' insulin treatment.

Keywords: Insulin Perceptions, Self-Management, Type 2 Diabetes Mellitus

Öz

Amaç: Bu çalışma ile yoğun bakımda yatarak tedavi gören Tip 2 diyabet hastalarının insüline karşı algıları ve diyabet semptom yönetim düzeyinin belirlenmesi sağlanacaktır.

Gereç ve Yöntem: Tanımlayıcı olan bu çalışma 1 Aralık 2020 ve 31 Mart 2021 tarihleri arasında bir devlet hastanesinin Dahiliye ve Anestezi Yoğun Bakım ünitelerinde gerçekleştirilmiştir. Çalışmanın örneklemini insülin kullanan 100 gönüllü hasta oluşturmuştur. Araştırma verileri Hasta Tanıtım Formu, İnsülin Tedavisi Değerlendirme Ölçeği ve Diyabet Öz Yönetim Skalası ile toplandı. Araştırmanın etik kurul izni ve hastalardan yazılı izin alındı. Verilerin analizi, aritmetik ortalama, sayı, yüzde, korelasyon, Mann Whitney U ve Kruskal- Wallis testleri kullanılarak yapıldı.

Bulgular: Hastaların yaş ortalaması 44,57±14,8 olup, %52'si kadındır. Hastaların insülin kullanma yıl ortalaması 2.8±1.17 yıldır. Hastaların Diyabet Öz Yönetim Skalasından aldıkları toplam puan ortalamaları 4.07±1.74'tür (0,62-8,75). Hastaların İnsülin Tedavisi Değerlendirme Ölçeği pozitif ve negatif madde alt boyutu puan ortalamaları sırasıyla 12.56±3.43; 48.18±12.09'dur. Hastaların medeni durumu, eğitim düzeyi, kronik hastalık ve komplikasyon varlığı, düzenli insülin kullanımı ile Diyabet Öz Yönetim Skalası ve İnsülin Tedavisi Değerlendirme Ölçeği puan ortalamaları arasında anlamlı bir fark olduğu saptandı.

Sonuç: İnsülin kullanan Tip 2 diyabetli hastaların insülin kullanımına karşı negatif algısının fazla olduğu ve diyabet öz yönetimlerinin ortalamanın altında olduğu bulunmuştur. Hastaların negatif insülin algısı ile diyabet öz yönetiminin glikoz yönetimi ve diyet kontrolü alt boyutları arasında yüksek düzeyde negatif ilişki bulunmuştur. Hastaların diyabet öz yönetimi ve insülin tedavisine yönelik farkındalık oluşturulması amacıyla bireysel veya grup eğitimlerinin planlanması önerilmektedir.

Anahtar Kelimeler: İnsülin Algısı, Öz Yönetim, Tip 2 Diyabet

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INTRODUCTION

Type 2 Diabetes Mellitus (T2DM), which accounts for approximately 90% of all diabetics, is a metabolic syndrome characterized by hyperglycemia as a result of insulin resistance and impaired insulin secretion.[1-3] The incidence of T2DM is gradually increasing due to obesity and sedentary life. According to the International Diabetes Federation Diabetes Atlas 2019 data; the estimated number of diabetic patients in the world is approximately 463 million and this number will reach 700 million by 2045. Based on these data, Turkey is expected to be among the top 10 countries with the highest number of people with diabetes in the year 2045.[1,4]

When diabetes is not controlled, it causes complications in many parts of the body, leading to frequent hospitalizations and premature death. According to IDF (International Diabetes Federation) data, approximately 4.2 million adults between the ages of 20-79 died due to diabetes and its complications in 2019.[1] The worldwide increase in diabetes mellitus and the related complications such as hypoglycemia, diabetic ketoacidosis, retinopathy, nephropathy, neuropathy and diabetic foot show the importance of diabetes self-management. Self management in diabetes includes the self-care behaviors that ensure compliance with the use of medication, medical nutrition therapy, and physical activity. Individuals with diabetes should have knowledge and acquire self-care skills to ensure self-management.[5] It is imperative to transform self-management skills into a lifestyle to keep uncontrollable blood glucose, which is the main problem in individuals with diabetes, within normal limits and to prevent father complications.[6] Learning self-care skills will facilitate their adaptation to treatment by providing them with the skills to cope with the disease and getting more satisfaction from life.[6,7]

Insulin is reported as the most effective treatment method in the treatment of hyperglycemia.[8] Studies have shown that insulin therapy is effective in slowing down the development and progression of chronic complications of diabetes.[9,10] More than half of patients with type 2 diabetes need insulin therapy after 5 years. Despite the importance of insulin therapy, many patients with type 2 diabetes are unwilling or afraid of insulin therapy. This negative perception of insulin therapy is called "psychological insulin resistance".[11,12] Studies have reported that approximately 40-70% of patients with type 2 diabetes refuse insulin therapy.[12,13] Patients may be resistant to insulin use due to reasons such as pain, hypoglycemia, accelerated weight gain, feelings of inadequacy and ineffectiveness in individuals as a result of decreased independence, and feelings of embarrassment in the community related to using insülin.[14-16]

The sooner diabetes management training is initiated, the lower will be the rate of complications and associated mortality. It has been observed that diabetic patients spend their lives more comfortably, acquire self-efficacy and enjoy a higher quality of life with successful symptom management.[17-19] Also, the literature reports that it is necessary to evaluate the negative and positive perceptions of individuals with T2DM about insulin treatment before or after starting treatment.[5,20] Evaluating the perceptions of diabetic patients will facilitate the planning of effective interventions for symptom management and behavioral change. This study aimed to determine the level of diabetes symptom management of patients with T2DM who received inpatient treatment in intensive care. In addition, the study explored the relationship between patients' insulin perceptions and their diabetes self-management.

MATERIAL AND METHOD

This study was conducted in the Internal Medicine and Anesthesia Intensive Care units of a state hospital during the period of December 01, 2020 and March 31, 2021. The study universe consisted of the patients hospitalized with the diagnosis of T2DM in the mentioned clinics of the hospital (N=150). The sample of the study was composed of 100 voluntary patients who had sufficient awareness to answer questionnaire and scale questions and who used insulin.

Data Collection

Written consent was obtained from the patients who volunteered to participate in the study by having them sign the informed consent form. The patients who gave written consent were asked to fill out the Patient Introduction Form, Diabetes Self-Management Questionnaire (DSMQ) and Insulin Treatment Appraisal Scale (ITAS).

Patient Introduction Form: In form has a total of 13 questions about patient's age, gender, education level, socioeconomic level, height, weight, the duration of insulin use, who implemented the insulin treatment, whether the insulin treatment was regular, the existence of any chronic complications, existence of any other chronic diseases and how the patient felt when diagnosed with diabetes. This form was prepared by the researcher in line with the literature.[5,8,17,21]

Insulin Treatment Appraisal Scale: ITAS was developed by Snoek et al.[22] and its validity and reliability study was carried out by Surucu et al.[5] in Turkey. ITAS is a 5-item Likert-type scale with 20 items. The rating scale was designed as a Likert type scale with the options ranging from "strongly disagree" (1 point) to "strongly agree" (5 points). The scale consists of 2 sub-dimensions with 4 positive items (3,8,17,19) and 16 negative items. When the scale is scored, positive items are scored in reverse. The sum of the four positively expressed items (4-20) provides the positive evaluation sub-dimension while the sum of 16 negatively expressed items (16-80) provides the negative evaluation sub-dimension. Total scale score is obtained by adding the 16 items with negative expressions and the four items with positive expressions after they are reversed. The total of all the items (20 items) provides the total score (20–100). The scale has no cut-off point. A high positive evaluation score indicates a high positive appraisal towards insulin, while a high negative evaluation score indicates a negative perception of insulin use.[5,22] The internal consistency analysis of the scale

(Cronbach's Alpha) was found to be 0.905 in our study and 0.80 in Surucu et al.[5]

Diabetes Self-Management Questionnaire (DSMQ): DSMQ was developed by Schmitt et al.[23] in 2013 and the validity and reliability study of the scale was carried out by Eroğlu and Sabuncu[17] in Turkey. The scale is a 4-point Likert type scale with 16 items. The rating scale was designed as a Likert type scale with the options ranging from "does not apply to me all" (0 points) to "applies to me very much" (3 points). The scale consists of 4 sub-dimensions: Glucose Management (GM), Dietary Control (DC), Physical Activity (PA) and Healthcare Use (HU). In DSMQ, 7 items are calculated as they are and 9 items are calculated in reverse (Item total score obtained from the total scale or sub-dimension) /(Maximum item total score that can be obtained from the total scale or sub-dimension) x10) For unanswered questions, 3 points are subtracted from the maximum item total score that can be obtained from the total scale or sub-dimension. A minimum of 0 and a maximum of 10 points can be obtained from the scale. If an item is omitted, it is evaluated as -3 points. As the score gets closer to 10, diabetes self-management increases.[17,23] Internal consistency analysis of the scale (Cronbach's Alpha) was found 0.899 in our study and 0.85 in Eroğlu and Sabuncu.[17]

Ethical Declarations: To ensure compliance with ethical principles, written permission for non-interventional clinical research was obtained from the ethics committee (12/10/2020-90/72) and the institution (Number=E-44021967-605.01) where the study was conducted. The patients who were included in the study were informed about the study and their written permission to participate in the study was obtained. Written permission was obtained from authors, who conducted the Turkish validity and reliability study to use the scale in the study.

Data Analysis: The study data were analyzed with the SPSS 20.0 statistical program. Mean, standard deviation, number-percentage distributions were used to evaluate the descriptive characteristics of the patients. The Kolmogorov-Smirnov test was used to analyze whether the data were suitable for normal distribution. Spearman's Correlation Analysis was performed for correlation analysis. Mann Whitney U test and Kruskal Wallis test were used to evaluate the difference between ITAS and DSMQ mean scores according to independent variables. P values <0.05 were considered significant.

RESULTS

The mean age of the patients included in the study was 44.57±14.8. 52% were women, 72% were single, 47% were primary school graduates, 52% had a chronic disease other than T2DM, and 51% had a chronic complication related to T2DM. The mean body mass index (BMI) of the patients was 23.31±3.04 kg/m2. The mean duration of insulin use was 2.8±1.17 years (range 1-4). It was found that 71% of the patients administered insulin on their own and 68% did not apply insulin regularly (**Table 1**).

Table 1. Distribution of the participants according to their sociodemographic and insulin usage characteristics (n=100)

	n	%
Age (M±SD)	44.57±14.84 (20-78)	
BMI (kg/m2) (M±SD)	23.31±3.04 (17-34)	
Gender		
Female	52	52
Male	48	48
Marital status		
Single	28	28
Married	72	72
Education level		
Primary school	47	47
High school	36	36
University	17	17
Complication		
Yes	51	51
No	49	49
Chronic disease		
Yes	52	52
No	48	48
Administering insulin		
Itself	71	71
Family	14	14
Other	15	15
Regular use of insülin		
Yes	32	32
No	68	68
Insulin duration (years) (M±SD)	2.8 ± 1.17 (1-4)	

Note. M=Mean, SD=standard deviation, BMI= Body mass index

Patients' mean DSMQ total score was 4.07±1.74 (range 0.62-8.75). Table 2 presents the mean scores of the sub-dimensions. Patients' ITAS positive and negative item subscale mean scores were 12.56±3.43 and 48.18±12.09, respectively (**Table 2**).

Table 2. Patients' DSMQ and ITAS total and sub-dimension mean scores (n=100)

	M	SD	Min	Max
DSMQ				
GM	3.62	2.63	0	10
DC	4.21	2.44	0	10
FA	4.42	2.52	0	8.89
HU	4.41	1.42	1.11	7.78
Total	4.07	1.74	0.62	8.75
ITAS				
Positive	12.56	3.43	4	19
Negative	48.18	12.09	24	65

Note. DSMQ= Diabetes Self-Management Questionnaire, GM=Glucose Management, DC=Dietary Control, PA=Physical Activity and HU=Healthcare Use, ITAS=Insulin Treatment Appraisal Scale, M=Mean, SD=standard deviation

There was no significant difference between DSMQ and ITAS total and subscale scores according to age and gender (p>0.05). University graduate patients had higher DSMQ total and subscale scores compared to the primary and high school graduates (p<0.001). It was found that total DSMQ total and all

subscale mean scores of the married patients were higher and lower ITAS negative item mean score compared to the scores of the single patients (p<0.001). DSMQ total and all subscale mean scores and ITAS positive item subscale scores of the patients with complications were statistically significantly higher compared to those without complications (p<0.05). Patients with chronic disease had higher DSMQ total and all subscale and ITAS positive item scores compared to the patients without chronic disease (p<0.001). ITAS positive item sub-dimension mean scores were found to be high while ITAS negative item sub-dimension was found to be lower in patients who regularly used insulin compared to those who did not use it regularly (p<0.001). It was found that DSMQ total and GM, DC, HU subscale scores of patients who used insulin regularly were higher than those who did not have regular use (p<0.001) (**Table 3**).

Table 3. DSMQ and ITAS Total and Sub-Dimensional Scores by Independent Variables

	DSMQ									
	GM		DM		FA		HU		Total scale	
	Median	M±Sd	Median	X̄±Ss	Median	Median	X̄±Ss	X̄±Ss	Median	X̄±Ss
Education level										
Primary school	63.16	4.5±2.42	63.86	5.23±2.05	38.09	3.33±1.75	63.26	5.01±1.24	61.24	4.56±1.48
High school	47.07	3.43±2.72	46.57	3.98±2.43	62.76	5.49±2.27	45.51	4.2±1.38	50.21	4.13±1.85
University	22.76	1.61±1.8	21.88	1.86±1.68	58.85	5.16±3.53	25.79	3.2±1.03	21.41	2.56±1.33
	x2=25.364 p<0.001		x2=27.831, p<0.001		x2=18.407, p<0.001		x2=24.167, p<0.001		x2=23.631, p<0.001	
Marital status										
Married	60.9	4.44±2.62	61.98	5.14±2.14	61.25	5.4±3.25	60.17	4.88±1.3	60.98	4.63±1.63
Single	23.77	1.52±1.02	20.98	1.82±1.24	46.32	4.04±2.07	25.62	3.21±0.92	23.55	2.63±1.02
	Z=-5.789, p<0.001		Z=-6.421, p<0.001		Z=-2.444, p<0.001		Z=-5.544, p<0.001		Z=-5.803, p<0.001	
Complication										
Yes	56.71	3.8±1.98	58.69	4.75±1.95	66.36	5.83±2.6	63.15	4.97±1.16	55.52	4.13±1.17
No	44.04	3.43±3.18	41.98	3.64±2.78	35.26	3.07±1.52	37.34	3.83±1.44	45.28	4±2.19
	Z=-2.199, P=0.028		Z=-2.913, P=0.004		Z=-5.667, p<0.001		Z=-4.612, p<0.001		Z=-1.769, p=0.077	
Chronic disease										
Yes	59.8	4.21±2.4	60.88	4.98±2.08	63.03	5.53±2.69	64.1	5.02±1.74	59.3	4.41±1.46
No	40.43	2.99±2.74	39.26	3.37±2.54	38.93	3.4±1.85	35.77	3.75±1.37	40.97	3.7±1.95
	Z=-3.361, p=0.001		Z=-3.767, p=0.004		Z=-4.390, p<0.001		Z=-5.258, p<0.001		Z=-3.163, p=0.002	
Regular use of insülin										
Yes	82.89	6.60±2.22	82.48	6.93±1.46	53.4	4.66±2.58	66.39	5.21±1.37	80.11	5.85±1.53
No	35.26	2.22±1.3	35.45	2.93±1.63	44.33	3.92±2.33	43.02	4.04±1.29	36.57	3.23±1.06
	Z=-7.716, p<0.001		Z=-7.654, p<0.001		Z=-1.544, p=0.123		Z=-3.896, p<0.001		Z=-7.015, p=<0.001	

	ITAS					
	Positive		Negative		Total	
	Median	X̄±Ss	Median	X̄±Ss	Median	X̄±Ss
Education level						
Primary school	57.72	13.43±3.65	43.29	44.21±12.94	47.6	57.64±15.92
High school	43.67	11.72±3.65	55.4	50.72±11.43	52.4	62.44±14.52
University	45	11.94±0.97	60.06	53.76±6.56	54.5	65.71±7.24
	x2=5.619, p=0.06		x2=5.797, p=0.055		x2=0.95, p=0.622	
Marital status						
Married	51.51	12.69±3.95	43.83	45.19±12.83	46.28	57.89±15.96
Single	47.89	12.21±1.37	67.66	55.86±4.27	61.34	68.07±5.05
	Z=-0.565, p=.572		Z=-3.695, p<0.001		Z=-2.332, p=0.02	
Complication						
Yes	66.82	14.53±3.02	50.29	47.31±12.27	55.63	61.84±14.87
No	33.51	10.51±2.51	50.71	49.08±11.96	45.16	59.59±14.2
	Z=-5.79, p<0.001		Z=-0.073, p=0.942		Z=-1.804, p=0.071	
Chronic disease						
Yes	60.74	13.81±3.69	47.47	45.92±12.96	51.8	59.73±16.09
No	39.41	11.21±2.53	53.78	50.63±10.67	49.09	61.83±12.67
	Z=-3.706, p<0.001		Z=-1.088, p=0.276		Z=-0.466, p=0.641	
Regular use of insülin						
Yes	30.22	9.88±2.93	16.5	31.69±3.86	16.5	41.56±5.98
No	60.04	13.82±2.89	66.5	55.94±4.25	66.5	69.76±6.04
	Z=-4.838, p=<0.001		Z=-8.052, p=<0.001		Z=-8.046, p=<0.001	

Note. DSMQ= Diabetes Self-Management Questionnaire, GM=Glucose Management, DC=Dietary Control, PA=Physical Activity and HU=Healthcare Use, ITAS=Insulin Treatment Appraisal Scale,, M=Mean, SD=standard deviation, Z=Mann-Whitney U Testi, x2= Kruskal-Wallis

The relationship between patients' DSMQ sub-dimensions and ITAS positive and negative item sub-dimensions was evaluated with Spearman's Correlation Analysis. A weak positive significant relationship was found between the GM, DC, FA sub-dimensions and the ITAS positive item sub-dimension ($p<0.005$). A strong negative significant correlation was found between the GM, DC sub-dimension and the ITAS positive item sub-dimension ($p<0.005$) (**Table 4**).

Table 4. Correlation between DSMQ and ITAS

DSMQ	ITAS			
	Positive		Negative	
	r	p	r	p
GM	0.394**	p<0.001	-0.709**	p<0.001
DC	0.322**	.001	-0.723**	p<0.001
FA	0.29**	.003	-0.17	.866
HU	0.051	.616	-0.23	.021

Note. DSMQ= Diabetes Self-Management Questionnaire, GM=Glucose Management, DC=Dietary Control, PA=Physical Activity and HU=Healthcare Use, ITAS=Insulin Treatment Appraisal Scale, ** Correlation is significant at the 0.01 level

DISCUSSION

Type 2 Diabetes Mellitus, one of the most common types of diabetes in society, usually occurs after the age of 40 and its incidence increases with aging. The disease is reported to be more common among women in developing countries while there is no difference in the rate of incidence in terms of gender in developed countries.[2,24] In this study, the mean age of the patients was 44.57±14.8 and 52% of them were women. National and international studies in the field report the mean age of the patients as over 50 with varying ratios for men and women.[5,8,20,21,23,25-28] In this study, the mean age was found to somewhat younger compared to the literature. T2DM is more prevalent when accompanied by obesity. Prevalence of diabetes in obese people is at least twice as high compared to non-obese people.[24,28] The patients in this study were in the normal weight category with an average BMI of 23. Previous studies demonstrated that diabetic patients are generally in the category of slightly overweight and obese.[5,17,20,22,26] The mean BMI may be lower in this study compared to other studies in the literature due to the young age of the patients.

Diabetes management is based on the patient's self-assessment of diabetes care outcomes. Diabetes management includes nutritional therapy, regular exercise, blood glucose control, medication and education management and compliance with these parameters.[3,17,24] In this study, patients' mean DSMQ score was found to be 4.07±1.74. Accordingly, these patients' diabetes self- efficacy was below the average. dabetes self-management was found to be below the intermediate level. When the literature is reviewed, it is seen that there are studies supporting our study results.[26,29] Another important point in diabetes management is the compliance of the patients with the treatment plan that includes diet, exercise and medical applications.[30,31] In this study, patients' self-management in regards to glucose management, diet control, physical activity and the use of health services was also found to be low. Previous studies in the field determined that 50%, 71.7%, and 37% of the patients complied with their treatment.[30,32] Other national studies reported that patients had a low rate of exercise, did not pay attention to their diet, had a low rate for visiting the doctor and had high rates of experiencing hyperglycemia or hypoglycemia.[25,31]

In type 2 diabetes, insulin treatment starts in cases where acute and chronic complications occur, glycemic control is impaired due to various reasons, and glycosuria accompanies hyperglycemia.[33] Insulin treatment is initiated in approximately half of the patients with type 2 diabetes in approximately 5 years after the diagnosis.[8] In this study, the mean duration of insulin use was found to be approximately 3 years. In Holmes eat al.[26] and Snoek et al.[22], the mean duration for starting insulin treatment was found to be 4.1 and 5.3 years, respectively. Although it is known that approximately half of the diabetes patients in the world need insulin treatment, it is argued that the patients do not take insulin in sufficient amounts.[5,9] In this study, patients' positive perception towards insulin treatment was moderate. While there are other studies in literature that identified lower positive perception scores than this study,[5,8] there are also other studies with similar or higher positive perception scores.[20,26,27] In addition, as a result of our study, it can be argued that patients' negative perception towards insulin treatment was high. Negative insulin assessment is common among T2DM adults.[26] It is seen that there are studies in the literature that support our study results. However, unlike our study, Ozden et al (2019) found lower negative perception scores (17.4) towards insulin.[34]

Self-efficacy is a significant predictor of negative insulin treatment perception in patients with type 2 diabetes.[8] This study also found a highly significant negative correlation between the GM and DC sub-dimensions of the diabetes self-management scale and negative insulin perception. Accordingly, it is concluded that the negative insulin perception is high in patients with high GM and DC management in diabetes. Similarly, Holmes et al.[26] and Sürücü and Samancıoğlu[8] also determined that those with more negative insulin appraisals had a decrease in diabetes self-efficacy.

Acute or long-term complications can be observed in diabetes as a result of uncontrolled blood glucose levels. Half of the patients (51%) in this study reported having a chronic complication. In other studies, it is seen that the rates of complications related to diabetes are similar.[5,8,17,26] Preventing possible diabetes complications is crucial to reduce the burden on the people and the community.[1,3] Hence, individuals with diabetes need to acquire self-management skills.[24] In our study, it was determined that patients with complications had better self-efficacy and positive perception towards insulin. It is known that the incidence of complications is high in people with poor diabetes self-management and insulin

perception.[17,26,29] However, this result of our study shows that individuals with complications may have gained more self-efficacy and created a better perception for the management of complications. Unlike our study, in the study of Yanık and Erol,[29] no statistical significance was found between the presence of chronic complications and the level of self-efficacy for diabetes. In our study, it was also found that those with different chronic diseases have better self-management and perception of insulin. A chronic disease other than diabetes increases the risk of complications.[24] These individuals may have gained better self-management to reduce the risk of complications.

As the level of education raises awareness, patients focus more on the symptoms of their illness. In addition, their belief that they can cope with their diseases with appropriate treatment and disease control is increasing. [35] Therefore, patients with a higher education level can be expected to have a higher self-efficacy. In the literature, there are studies reporting that diabetes self-efficacy increases as the education level of individuals increases.[29,36] The finding in our study, unlike the literature, is that patients with higher education levels have lower diabetes self-efficacy. This finding shows that, contrary to expectations, people's belief that they can manage their illness well is not related to education level. In addition, it is thought that some sociodemographic and clinical characteristics such as diabetes duration and education about diabetes also affect this relationship.

The primary helpers of people with diabetes in diabetes management are their families and relatives.[39,40] In our study, it was found that married patients have higher self-management and lower negative perception towards insulin. This finding shows the importance of family support on diabetes management and insulin perception, which is also mentioned in the literature.[38,39] However, unlike our study, Sürücü and Samancıoğlu (2018) determined that living alone reduces negative perception towards insulin therapy.[8] Also, there are studies reporting that marital status is not effective in terms of diabetes management and insulin perception.[25,26,29,36]

It has been reported that patients who use insulin regularly have high positive perceptions of insulin treatment and have low negative perceptions as well as high levels of diabetes self-management. Effective diabetes management requires behavioral adaptation. Individuals' level of compliance to treatment and their attitudes towards diabetes are two factors that affect each other positively.[36] This study determined that patients using insulin regularly, that is, adapting to insulin treatment, increased their positive evaluation of insulin, decreased their negative evaluation and that attitude positively affected their self-care. Therefore, awareness should be raised about the regular use of insulin in individuals with diabetes through education, etc., and patients should be encouraged to use insulin regularly.

CONCLUSION

Our study results show that patients' diabetes self-management or perception of insülin is low. Nurses can contribute to the participation of patients using insulin in diabetes management and to create a positive insulin perception. For this, it can be suggested that the continuity of patient and nurse interaction and that nurses use their trainer and consultancy roles effectively. In addition, our study revealed that patients with diabetes-related complications and another chronic disease have poor self-management and insulin perception. Therefore, planned and regular training on disease management is needed especially for these patient groups. It may be suggested that the education be continued with home visits after discharge. It is recommended to conduct long-term follow-up studies with larger samples in order to determine the effect of planned training on self-management. In addition, it is recommended to replicate the study in diabetic individuals receiving treatment in services and outpatient clinics. Also, different studies can be conducted with samples comprised of Type 1 diabetes patients.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by Izmir Bakircay University Non-interventional Clinical Research Ethics committee (Date: 12/10/2020, Decision No: 90/72).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Orjinal Araştırma / Original Article

Hypermobility in Turkish Schoolchildren: Musculoskeletal Pain, Physical Activity, Balance, and Quality of Life

Türk Okul Çocuklarında Hipermobilite: Kasiskelet Ağrısı, Fiziksel Aktivite, Denge ve Yaşam Kalitesi

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Abstract

Aim: Joint hypermobility is a term used to describe an excessive range of joint motion. Joint hypermobility can be symptomatic or not. The present study aimed primarily to define the prevalence of joint hypermobility in healthy schoolchildren, and secondly, to determine the relationship between hypermobility and pain, physical activity, joint injury, quality of life, and balance.

Material and Method: In this cross-sectional study, the joints of 737 schoolchildren, aged 8 to 15 years, were examined according to the Beighton score (BS). Generalized joint hypermobility was defined by using a cut-off point of ≥6 joints. The participants with a BS between 1 and 5 were accepted as localized hypermobile. If the Beighton score was 0, the participants were accepted as non-hypermobile. Participants were evaluated using questionnaires or tests for pain, balance, physical activity, and quality of life.

Results: The 350 (47.5%) males and 387 (52.5%) females had a mean age of 11.47 ± 1.3 (8-15) years. The prevalence of generalized hypermobility was 13.4%, and we observed localized hypermobility in 65.9% of children and non-hypermobility in 20.6% of children. The most common pain localizations in children were neck (15.9%), lower back (13.7%), upper back (10.6%), shoulders (10.2%), and knees (7.9%). There was no association between pain and hypermobility in children aged 8 to 15 years.

Conclusion: The generalized joint hypermobility group was younger, shorter, and thinner than other groups. Additionally, we observed that hypermobility did not make a difference in terms of pain, quality of life, physical capacity, and balance in school-age Turkish children.

Keywords: Balance, injury, joint hypermobility, pain, quality of life, physical activity

Öz

Amaç: Eklem hipermobilitesi, aşırı eklem hareket aralığını tanımlamak için kullanılan bir terimdir ve semptomatik olabilir. Bu çalışma öncelikle sağlıklı okul çocuklarında eklem hipermobilitesinin prevalansını belirlemeyi ve ikinci olarak hipermobilite ile ağrı, fiziksel aktivite, eklem yaralanması, yaşam kalitesi ve denge arasındaki ilişkiyi belirlemeyi amaçlamıştır.

Gereç ve Yöntem: Bu kesitsel çalışmada, 8-15 yaşları arasındaki 737 okul çocuğunun eklemleri hipermibilite açısından Beighton skoruna göre incelendi. Beighton skoru 6 eklem ve üzeri ise jeneralize eklem hipermobilitesi, 1 ile 5 arasında ise lokalize eklem hipermobilitesi, puan 0 ise hipermobil olmayan olarak kabul edildi. Katılımcılar ağrı, denge, fiziksel aktivite ve yaşam kalitesi için anketler veya testler kullanılarak değerlendirildi.

Bulgular: Katılımcıların 350'si (%47,5) erkek, 387'si (%52,5) kadın ve ortalama yaşları 11,47 ± 1,3 (8-15) yıldı. Jeneralize eklem hipermobilite prevalansı %13,4 idi. Çocukların %65,9'unda lokalize hipermobilite ve %20,6'sında hipermobilite olmadığını gözlemledik. Çocuklarda en sık ağrı lokalizasyonları boyun (%15,9), bel (%13,7), üst sırt (%10,6), omuzlar (%10,2) ve dizler (%7,9) idi. 8-15 yaş arası çocuklarda ağrı ve hipermobilite arasında anlamlı bir ilişki yoktu.

Sonuç: Jeneralize eklem hipermobilitesi olan çocuklar diğer gruplara göre daha genç, daha kısa ve daha inceydi. Ayrıca okul çağındaki Türk çocuklarında hipermobilite varlığının ağrı, yaşam kalitesi, fiziksel kapasite ve denge açısından fark yaratmadığını gözlemledik.

Anahtar Kelimeler: Denge, yaralanma, eklem hipermobilitesi, ağrı, yaşam kalitesi, fiziksel aktivite

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INTRODUCTION

Joint hypermobility (JH) is used to describe an excessive range of joint motion. JH across multiple joints is termed generalized joint hypermobility (GJH). Although GJH is usually isolated and asymptomatic, it can be a part of syndromic diseases (heritable disorders of connective tissue such as Ehlers-Danlos syndromes (EDS), Marfan syndrome, and Osteogenesis imperfecta), and can be symptomatic with pain. Before 2017, the recommended terminologies for symptomatic and/or syndromic GJH were similar and there was a lack of globally accepted description or nomenclature for joint hypermobility.[1] In 2017, the International Consortium on EDS recommended using "hypermobility spectrum disorder" (HSD) for symptomatic, non-syndromic JH.[2,3] The symptomatic JH included single, localized or generalized subtypes. Joint hypermobility without musculoskeletal symptoms was termed asymptomatic GJH.

The Beighton score (BS) is a valid scale to identify JH in children and is calculated through 5 movements and 9 points.

In recent studies, the prevalence of GJH in children was reported between 7% and 36%. The discrepancy of outcomes might be a result of differences in study design; such as the threshold of BS, age of study groups, characteristics of study populations (healthy children, athletes, dancers, or symptomatic cases), and ethnicities. Therefore, the rates of GJH in children are seen as highly variable.[4]

In addition, patients with HSD may present with chronic musculoskeletal pain (MSP), soft tissue injuries, fatigue, decrease in physical capacity, balance, proprioception, and problems with motor development.[4] On the other hand, these hypermobile people may have an advantage in some activities like dancing, gymnastics.[5]

In the present study, we aim primarily to define the prevalence of JH in Turkish schoolchildren, and to classify the children as non-hypermobile (BS=0), localize hypermobile (BS=1-5), and generalized hypermobile (BS=6-9). A second aim is to evaluate these three groups in terms of hypermobility-related conditions such as MSP, physical activity, joint injury, quality of life, and balance in healthy schoolchildren.

MATERIAL AND METHOD

Study Group and Design

This cross-sectional study took place in Denizli, a city westward of Turkey. Initially, the document describing the study was shared with directors of schools and the Ministry of Education for permission. After approving the study, a written consent form and a letter that included information about JH, and the study design were sent to parents or legal guardians of 1100 students. Participation in this study was optional, and children with chronic diseases or without signed consent forms were excluded. The study included 737 school children, aged 8 to 15 years, from four different schools. The clinical research ethics committee of Pamukkale University, Faculty of Medicine (decision date, 03/05/2016) approved this study and all procedures were conducted according to the Declaration of Helsinki.

Clinic features and screening tests

1. Demographic and anthropometric parameters

   Age, gender, weight, and height of participants were collected and the body mass index (BMI) was calculated. Children were categorized according to BMI, as underweight, normal weight, overweight and obese.

2. The screening of generalized joint hypermobility

   Joint hypermobility was evaluated using the BS.[5] The BS includes 5 movements and ranges from 0 to 9 points. Four movements are calculated for the left and right sides separately (**Figure 1**). The BS has a high inter-researcher reproducibility in adults and children. It is a well-known, commonly used, valuable, and reliable scale of JH in children.[5-8] Ten pairs of qualified physiotherapists measured the joint angles with a goniometer. There is no fully accepted cut-off value of BS in children; we calculated the prevalence of GJH according to threshold 4, 5, and 6. However, GJH was defined using a cut-off point of ≥6 joints in this study. The participants with a BS between 1 and 5 were accepted as localized hypermobile (LJH). If the BS was 0, the participants were accepted as non-hypermobile (NH).

3. The screening of musculoskeletal pain and injury during daily life and physical activity

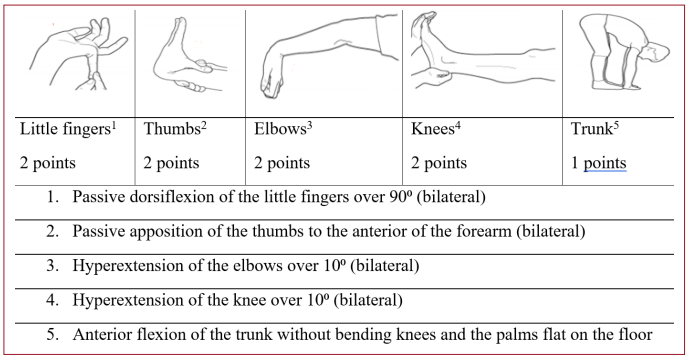

Figure 1. The 9-point maneuvers of Beighton score for diagnosis joint hypermobility

A questionnaire was designed to investigate MSP in schoolchildren. A visual analogue scale (VAS) and a diagram of body parts were used to define the intensity and location of the pain. Five physiotherapists asked the following questions to the participants one by one.

- Have you ever suffered from musculoskeletal pain during your daily life (MSP-DL) in the last month?
  - If yes, show the painful areas on the body diagram.
  - Give a number for your pain severity in daily life between 0-10. (VAS-DL)
- Have you ever suffered from musculoskeletal pain during or after physical activity (MSP-PA) in the last month without injury and trauma?

- If yes, show the painful areas on the body diagram.
- Give a number for your pain severity after physical activity between 0-10. (VAS-PA)

• Have you ever suffered from musculoskeletal injuries?

- If yes, show the injury areas on the body diagram.

4. The screening of hypermobility related conditions

The NH, LJH, and GJH groups were evaluated for physical activity, quality of life, and balance using the physical activity questionnaire for older children (PAQ-C), Paediatric Quality of Life Inventory 4.0 (PedsQL 4.0), Flamingo Balance Test (FBT). The experienced physiotherapists ensured the correct filling of the questionnaires and evaluated FBT carefully. The validity and reliability of PAQ-C and PedsQL 4.0 tests were shown in Turkish children.[9,10]

- PAQ-C is a set of questions that focus on physical activities (sport, dance, game) and their frequency in a week.[11] The replies to questions are evaluated according to a 5-point score (1 point = no activity, 5 points = 7 times or more) and higher points indicate a greater rate of physical activity.
- PedsQL 4.0 is a self-reported questionnaire that includes 4 parts, and 23 items. It determines the physical, emotional, social, and school life of children.[12] The range of scores is between 0 and 100 where higher scores indicate better quality of life.
- FBT is a static balance test used in children.[13] The children were asked to stand barefoot on a balance board with one leg for 60 seconds. The dimensions of the board were 50 cm in length, 4 cm in height, and 3 cm in width. The test score was the number of floor touches with a free foot for 60 seconds. A higher score indicated poor static balance.

Statistical Analysis

Data of the present study were assessed using SPSS (Version 22.0). In this study, 850 participants must provide 90% power and 95% confidence level even in a weak correlation between the parameters (r=0.1).

The quantitative variables were evaluated using the Kolmogorov-Smirnov test, detrended Normal Q-Q Plot, and histogram to define whether they were normally distributed. Normally distributed data were expressed as mean, standard deviation (SD). Non-normally distributed data were presented median, minimum, and maximum. The categorical data were expressed in count and percentage.

Parametric tests (Student -t, ANOVA tests) were used to compare normally distributed independent quantitative variables. If a parametric test was not provided for quantitative parameters, the Mann-Whitney U test or Kruskal Wallis Variance Analysis were used to compare the independent groups. Differences between categorical data were analysed using the Chi-square test. In addition, relationships between variables were evaluated by Spearman or Pearson correlation tests. P values <.05 with a 95% confidence interval were considered significant.

RESULTS

The Demographic Parameters, Hypermobility, and Hypermobility Related Conditions

1. Demographic Parameters

The 350 (47.5%) males and 387 (52.5%) females had a mean age of 11.47 ± 1.3 (8-15) years. The median values of all participants in weight, height, and BMI were 43 (23-109) kg, 151 (126-185) cm, (11.89-36) kg/m2, respectively. According to BMI, the participants were 46.7% underweight, 45.6% normal weight, 6.5% overweight, and 1.2% obese.

There was no significant difference between girls and boys in parameters of age, weight, height, and BMI (**Table 1**).

2. The Beighton Score and Generalized Joint Hypermobility

Out of 737 children, 20.6% had a BS of 0 (no hypermobile joint) and 0.9% of children had a BS of 9. The mean BS was 2.74±2.19 (0-9). The frequency and distribution of BS in girls and boys are shown in **Figure 2**. There was a significant difference between girls and boys (p=0.0001) (**Table 1**).

The prevalence of GJH in different thresholds was defined as 34.1% according to a cut-off of ≥4, 19.7% according to a cut-off of ≥5, and 13.4% according to a cut-off of ≥6. There was no significant sex difference in the three groups (**Table 1**).

By using the new terminology of the 2017 International Consortium on EDS, we observed GJH in 13.4% of children (BS: 6-9), LJH in 65.9% of children (BS: 1-5), and NH in 20.6% of children. In the NH group, the prevalence of boys was significantly higher than girls (p=0.004) (**Table 1**). However, there was no significant difference in the gender parameter between LJH and GJH (**Table 1**).

3. Musculoskeletal Pain and İnjury

Out of 737 participants, 33.4% had MSP-DL and 39.9% had MSP-PA. The mean severity score of MSP was 1.11±1.89 during DL and 1.29±2.02 after PA.

The most common localizations of MSP were neck (15.9%), lower back (13.7%), upper back (10.6%), shoulders (10.2%), and knees (7.9%). In the present study, the prevalence of MSP in the upper back and shoulders were significantly higher in girls (p=0.008, p= 0.019) (**Table 1**).

Over half of children (N=395, 53.6%) reported joint injury. The distribution of joint injury was ankle (N= 346, 46.9%), finger (N= 24, 3.3%), wrist (N= 23, 3.1%), and knee (N=2, 0.3%). However, only 14.8% of children needed medical care due to injury.

There was no significant difference between girls and boys in parameters of MSP-DL, MSP-PA, medical care, and joint injury (**Table 1**). We did not observe a significant difference between boys and girls in the parameter of severity scores of MSP (VAS-DL and VAS-PA) (**Table 1**).

Table 1. Comparison of the demographic characteristics, pain, joint injury, medical care necessity, pain intensity, physical activity, life quality and balance between girls and boys

	Boys	Girls	p value
Mean age (year) ±SD	11.37±1.3	11.56±1.3	**p=0.037***
Mean height (cm) ±SD	151±10.48	151.2±10.11	p=0.344*
Mean weight (kg) ±SD	45.61±12.9	44.45±11.53	p=0.486*
Mean BMI (kg/m^2)±SD	19.72±3.8	19.21±3.57	p=0.069*
Mean BS ± SD	2.47±2.19	2.98±2.16	**p=0.0001***
GJH N (%)			
Cut off≥ 4	108(14.7%)	143(19.4%)	p=0.081**
Cut off≥ 5	60(8.2%)	85(11.5%)	p=0.1**
Cut off≥ 6	39(5.3%)	60(8.1%)	p=0.083**
HSD N (%)			
NH (BS=0)	88(25.1%)	64(16.5%)	**p=0.004****
LJH (BS=1-5)	223(63.7%)	263(68%)	p=0.225**
GJH (BS=6-9)	39(11.1%)	60(15.5%)	p=0.083**
MSP-DL N (%)	107(30.6%)	139(35.9%)	p=0.124**
MSP-PA N (%)	131(37.4%)	163(42.1%)	p=0.194**
Mean VAS of MSP ±SD during daily life	1±1.86	1.21±1.92	p=0.089*
Mean VAS of MSP ±SD after physical activity	1.23±2.1	1.34±2	p=0.209*
Pain location			
Neck N (%)	48(13.7%)	69(17.8%)	p=0.127**
Upper back N (%)	26(7.4%)	52(13.4%)	**p=0.008****
Lower back N (%)	47(13.4%)	54(14%)	p=0.621**
Shoulders N (%)	26(7.4%)	49(12.7%)	**p=0.019****
Knees N (%)	23(6.6%)	35(9.0%)	p=0.213**
Joint injury N (%)	192(54.9%)	203(52.5%)	p=0.514**
Medical care N (%)	56(16%)	53(13.7%)	p=0.379**
Mean PAQ-C score ±SD	27.72±7.1	25.14±7.3	**p=0.0001***
PedsQL4.0			
Mean physical ±SD	84.96±13.45	81.2±14.96	**p=0.0001***
Mean emotional ±SD	77.13±18.65	74.83±19.72	p=0.142*
Mean social ±SD	88.97±15.08	90.42±13.94	p=0.162*
Mean school ±SD	80.29±16.04	81.58±15.31	p=0.332*
Mean FBT ±SD	30.19±8.99	29.12±9.85	p=0.118*

BMI- Body mass index, GJH-Generalized joint hypermobility, SD- Standard Deviation, HSD-Hypermobility spectrum disorders, NH-Not hypermobile, LJH-Localized joint hypermobility, VAS-Visual analogue scale, MSP-Musculoskeletal pain, DL- Daily life, PA- Physical activity, PAQC-Physical activity questionnaire for older children, PedsQL- Pediatric Quality of Life Inventory 4.0, FBT-Flamingo Balance Test, SD-Standard Deviation, *Mann Whitney U Test ** Chi-square test

Comparing Non-hypermobile, Localized Hypermobile, And Generalized Hypermobile Groups

1. Demographic parameters of groups

   We observed significant differences in the demographic features of groups in the present study.

   - There were significant differences in parameters of age, height, and weight between the groups (p=0.001, p=0.004, p=0.001, respectively) (**Table 2**).
   - There was a significant difference in BMI between the three groups (p=0.006) (**Table 2**).
   - The male/female proportions of groups were significantly different (p=0.008) (**Table 3**).

2. Musculoskeletal pain and injury

   There were significant differences in MSP-DL and VAS-DL parameters between the groups.

   - The rate of MSP-DL in the GJH group was significantly lower than the NH and LJH groups (p=0.039) (**Table 3**).
   - The VAS-DL in the GJH group was significantly lower than that of the LJH group (p=0.03) (**Table 2**).
   - There was no difference between the groups in the presence of MSP-PA, joint injury, and necessity of medical care (**Table 3**).

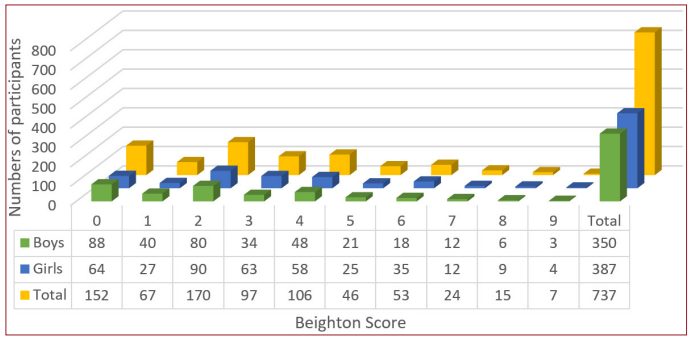

Figure 2. The distribution of Beighton score in boys, girls and all participants

Table 2: Comparison of the demographic characteristics, pain intensity, physical activity, life quality and balance between non-hypermobile, localized hypermobile and generalized hypermobile groups

Characteristics	NH (N=152, 20.6%)	LJH (N=486, 65.9%)	GJH (N=99, 13.4%)	p Value	p Value NH-LJH	p Value NH-GJH	p Value LJH-GJH
Mean age (year) ±SD	11.57±1.21	11.54±1.3	10.98±1.35	**0.001***	0.568	**0.001**	**0.001**
Mean height (cm) ±SD	152.74±11.01	151.24±9.76	147.88±11.04	**0.004***	0.887	**0.004**	**0.011**
Mean weight (kg) ±SD	47.24±11.69	44.89±12.11	42.09±12.86	**0.001***	0.053	**0.000**	**0.041**
Mean BMI (kg/m^2)±SD	20.02±3.36	19.38±3.75	18.89±3.77	**0.006***	**0.026**	**0.008**	0.568
Mean VAS-DL±SD	1.02±1.66	1.22±2.01	0.72±1.6	**0.037***	0.582	0.216	**0.030**
Mean VAS-PA±SD	1.41±2.06	1.28±2.03	1.16±1.93	0.661*	NP	NP	NP
Mean PAQ-C score ±SD	26.15±6.5	26.26±7.6	27.25±7.02	0.360*	NP	NP	NP
PedsQL 4.0							
Mean physical ±SD	84.11±12.77	82.28±15.07	84.69±13	0.276*	NP	NP	NP
Mean emotional ±SD	75.89±18.08	75.76±19.85	76.77±18.02	0.914*	NP	NP	NP
Mean social ±SD	88.0.5±15.94	90.04±14.02	90.82±14.47	0.236*	NP	NP	NP
Mean school ±SD	80.3±14.74	80.78±16.15	82.88±14.55	0.366*	NP	NP	NP
Mean FBT±SD	31.84±10.28	29.2±9.03	28.37±9.76	**0.020***	**0.033**	0.052	0.523

NH-Not hypermobile, LJH-Localized joint hypermobility, GJH-Generalize joint hypermobility, VAS-Visual analogue scale, DL- Daily life, PA- Physical activity, PAQC-Physical activity questionnaire for older children, PedsQL- Pediatric Quality of Life Inventory 4.0, FBT-Flamingo Balance Test, NP-Not performed, SD-Standard Deviation, *Kruskal Wallis Test, p< 0.05 statistically significant

Table 3: Comparison of the gender, MSP, joint injury and medical care necessity between non-hypermobile, localized hypermobile and generalized hypermobile groups

Characteristics	NH (N=152, 20.6%)	LJH (N=486, 65.9%)	GJH (N=99, 13.4%)	p Value
Sex				
Boys N (%)	**88a (57.9%)**	223b (45.9%)	39b (39.4%)	**p=0.008***
Girls N (%)	**64a (42.1%)**	263b (54.1%)	60b (60.6%)	**p=0.008***
MSP-DL N (%)	52a (34.2%)	172a (35.4%)	**22b (22.2%)**	**p=0.039***
MSP-PA N (%)	63a (41.4%)	194a (39.9%)	37a (37.4%)	p=0.812*
Pain location				
Neck N (%)	30 (19.7%)	81 (16.7%)	**6 (6.1%)**	**p=0.011***
Upper back N (%)	19 (12.5%)	52 (10.7%)	7 (7.1%)	p=0.389*
Lower back N (%)	27 (17.8%)	65 (13.4%)	9 (9.1%)	p=0.348*
Shoulders N (%)	13 (8.6%)	56 (11.5%)	6 (6.1%)	p=0.198*
Knees N (%)	11 (7.2%)	39 (8%)	8 (8.1%)	p=0.948*
Joint injury N (%)	88a (57.9%)	254a (52.3%)	53a (53.5%)	p=0.478*
Medical care N (%)	21a (13.8%)	70a (14.4%)	18a (18.2%)	p=0.584*

NH-Not hypermobile, LJH-Localized joint hypermobility, GJH-Generalize joint hypermobility, MSP-Musculoskeletal pain, DL- Daily life, PA- Physical activity, *Pearson Chi-Square, p< 0.05 statistically significant

- There was no significant difference in the location rate of MSP between the NH, LJH, and GJH groups (**Table 3**).

3. Physical activity, quality of life, and balance

   The NH, LJH, and GJH groups were compared to each other for physical activity, quality of life, and balance.

   - In the present study, no significant difference was observed in the capacity of physical activity, quality of physical, emotional, social, and school life between the groups (**Table 2**).
   - There was a significant difference in the balance parameter between the groups. The NH group had a significantly higher score in FBT (p=0.033) (**Table 2**).

Comparing Symptomatic and Non-symptomatic Generalized Hypermobile Groups

The generalized hypermobile group was subdivided, according to whether the children had MSP during DL and after PA in last month, into symptomatic and non-symptomatic. We found out no significant differences in demographic features such as age, weight, height, BMI, and gender between the subgroups in the present study.

DISCUSSION

The present study evaluated hypermobility in Turkish children and defined the frequency of joint hypermobility according to the 2017 new nomenclature of the International Consortium on EDS. It supplemented the information about the relationship between GJH and MSP, physical capacity, balance, and quality of life in healthy schoolchildren.

In this study, the GJH group was significantly younger, shorter, and thinner than the NH and LJH groups. The mean BS was significantly higher in girls than boys. However, in the GJH group, there was no significant difference between the proportion of girls and boys. The rates of MSP-DL and VAS-DL in the GJH group were significantly lower than in the NH and LJH groups. There was no significant difference between boys and girls in the VAS-DL and VAS-PA parameters but the rate of MSP in the upper back and shoulders was significantly higher in girls.

Mainly, we determined no higher MSP rate, poorer quality of life, limited physical capacity, and decreased balance ability in the GJH group than the NH and LJH groups in healthy schoolchildren between 8-15 years.

The prevalence of GJH in the present study was 13.4% in healthy schoolchildren (Cut-off≥6, Age between 8-15 years). The prevalence of GJH in other Turkish studies was between 11.7% and 18.4%. These studies evaluated hypermobility with different cut-offs in different age groups.[14-16] In Asian countries[17-20], the prevalence range was 10-65%, in Europe[21-25] the range was 7-30%, and in other countries (Australia, Egypt, Brazil) the prevalence range was 14.4-64.6%.[6,26,27] The prevalence of GJH has a broad range in children and adolescents in these studies. It seems that race, geographical location, age, study group (dancer, athletes, swimmer, rheumatology outpatient, and healthy schoolchildren or adolescents), and study design (cut-off point for BS) influence the prevalence of GJH.

The BS is a well-known, practical procedure for determining joint hypermobility. In the present study, the mean BS was 2.74±2.19. The mean BS was 2.47±2.19 in boys and 2.98±2.16 in girls, and the difference in the BS between girls and boys was significant. In an Italian study, the difference in the BS was significant between girls (median 3) and boys (median 2).[21] The mean BS in another Turkish study was 2.5.[15]

The female dominance was commonly observed in the JH studies.[6,17,20-22,25,27,28] Others reported no gender difference.[18,19,24,26,29] In our study, the difference in the BS between girls and boys was significant and the prevalence of GJH in girls was higher than boys, but this difference was not significant. Two Turkish studies showed significant female dominance and another one reported no gender difference.[14-16]

The other controversial issue in JH is the threshold of the BS for determining GJH. The cut-off point of the BS was highly variable for the diagnosis of GJH in children and adolescents. It ranged between 4 and 7 in other studies.[4] In this study, 6 was selected as the main cut-off point to define GJH according to recommendations of the International Consortium on EDS.[2]

In recent studies, GJH was defined in the same population according to different thresholds of the BS and these subgroups were compared to each other. In the present study, the prevalence of GJH was determined by 34.1% (cut-off≥4), 19.7% (cut-off≥5), and 13.4% (cut-off≥6). The results of an Italian study were 35.4% (cut-off≥4), 22.2% (cut-off≥5), and 15.1% (cut-off≥6).[21] A Danish study had higher hypermobility rates and the results were 43.2% (cut-off≥4), 27.9% (cut-off≥5), and 21.3% (cut-off≥6).[28] A study from Saudi Arabia reported the prevalence of GJH 15.2% (cut-off≥4) and 7.6% (cut-off≥6).[29] An Indian study reported 58.8% (cut-off≥4) and 44.4% (cut-off≥6)[30] An Australian study reported 48% (cut-off≥4) and 18.6 % (cut-off≥6).[6] The results of GJH in the United Kingdom were 19.2% (cut-off≥4) and 4.2% (cut-off≥6).[22] There was a great similarity between the Italian study and the present study. Both studies evaluated GJH in the same age group, and the geographical area of both studies was close.

Chronic MSP is another prominent issue that is commonly investigated in hypermobile children. The relationship was highly variable.[6,21,28,30,31] The studies that reported the association between MSP and GJH were usually cross-sectional hence the reason for MSP in hypermobility was not clear. Therefore, we still do not know why some hypermobile children were in pain or symptomatic while others were not. In addition, the studies used different methods to show a relationship between JH and MSP, such as odds ratio or comparing group tests. In the present study, hypermobile and non-hypermobile groups were compared to show an association between MSP and GJH. The participants defined the severity and locations of pain during daily life and physical activity using VAS and a body diagram. We observed no significant difference in the rate and severity of MSP between both groups. A previous study from Turkey showed a relation between GJH and MSP and another did not.[14,15] The Italian study that was similar to our study showed no association.[21-23] Some recent studies reported GJH as a risk factor for MSP.[6,28,30,31] Sohrbeck-Nohr et al.[28] stated that GJH contributed to MSP after 14 years of age. Similarly, according to prospective follow-up results of the ALSPAC cohort, the GJH group who had no significant MSP at 13.4 years showed significant association with MSP at 17.8 years.[22,31] The ages of children in our study were between 8-15 years and at these ages, the GJH group was as symptomatic as the LJH and NH groups. However, if JH continued in older ages, it would be frequently symptomatic and cause MSP.

Tobias et al.[31] reported the pain sites: the spine (lower back 16.1%, upper back 8.9%, and neck 8.6%), shoulder (9.5%), knee (8.8%), and ankle/foot (6.8%) in 17.8 years. In the present study, the locations of pain were neck (15.9%), lower back (13.7%), upper back (10.6%), shoulders (10.2%), knees (7.9%), and ankle (6.5%) in 11.5 years. The distribution of pain location in both studies was parallel, but the mean age of the study population and the relation between GJH and MSP was not identical. At an older age, we also observe the painful effect of GJH on our participants.

In this study, the overall self-reported joint injury rate was 53.6% and the distribution of joint injury was ankle (46.9%), finger (3.3%), wrist (3.1%), and knee (0.3%). There was no significant difference in joint injury between boys and girls, and HSD subgroups. Seckin et al.[14] reported the joint sprain (7.4%) as the most common injury in a Turkish study group, and there was a significant difference between boys and girls. Two studies in university students (aged between 17-26 years) from the USA reported no difference in the parameter of joint injury between hypermobile and non-hypermobile groups.[32,33]

In the present study, we observed no difference in physical activity, life quality, and static balance between the NH, LJH, and GJH groups. There was no negative impact of GJH on balance, physical capacity and, quality of physical, emotional, social, and school life. The other studies reported that there was no significant difference in physical function and capacity in the NH, LJH, and GJH groups.[21,28,34] Two studies reported poorer life quality in the hypermobile group due to stress incontinence and gastrointestinal dysfunction.[35,36]

In our study, the NH group had a higher score in FBT and poorer static balance. The LJH and GJH groups had no difference in balance. The other studies reported that the GJH group had no significant difference in dynamic balance, but had significantly better static balance.[23,37]

The main limitation of the present study was being cross-sectional in healthy schoolchildren, and it would have been informative about the follow-up of this GJH group over a longer duration, in terms of developing joint pain and other hypermobility-associated problems.

CONCLUSION

In the present study, we observed no association between MSP and GJH, and no negative influence of GJH on physical activity, life quality, and balance. However, the study population was young (mean age 11.47) and the study was cross-sectional. Prospective long-term studies are necessary to understand better the association of GJH with physical activity, life quality, joint injury, and balance. The follow-up of children with GJH in further studies may help to define the age of becoming symptomatic.

Key point

Joint hypermobility tends to be non-symptomatic at early ages because it is physiological. The well-known association between joint hypermobility and musculoskeletal pain appears in older ages, and long-standing prospective studies are necessary to define the occurring time of symptomatic hypermobility..

ETHICAL DECLARATIONS

Ethics Committee Approval: The clinical research ethics committee of Pamukkale University, Faculty of Medicine (decision date, 03/05/2016) approved this study.

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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

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