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

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Editorial Correspondence

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REVIEW

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Original Article / Orijinal Araştırma

The Relationship of Blood Parameters with the Severity of Carbon Monoxide Poisoning

Karbon Monoksit Zehirlenme Şiddeti ile Kan Parametrelerinin İlişkisi

Seref Emre Atis, Aysenur Yamac, Tevfik Sarikaya

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Abstract

Introduction: Carbon monoxide (CO) poisoning is one of the most common poisonings worldwide. Many studies have investigated the relationship between predictive parameters and CO poisoning severity. We aimed to investigate the relationship between blood parameter values with poor outcome in CO poisoning, and CO values measured in blood.

Material and Method: This is a retrospective study. Patients who had CO levels ≥10% in their blood gas were included in the study. Patients were divided into 2 groups as those who required hyperbaric oxygen and those who do not. Demographic data such as age, gender of the patients, as well as CO levels in the blood gases of the patients, hemoglobin, leukocyte, neutrophil, platelet counts of the blood count, and MPV and PDW values were recorded. Also, creatinine, troponin, CRP, ALT values were recorded as well.

Results: The study was conducted with 110 patients. The mean age of the patients was 46.80±18.18 years. When the parameters were examined, the median WBC count of patients with patients who required HBO therapy was 8.73 [7.54-11.83], and the median WBC count of patients who did not require HBO therapy was 8.01 [6.96-9.72] (p=0.038). The median lymphocyte count of patients who required HBO therapy was determined as 2.73 [1.85-3.36], and this value was found to be higher than patients who did not require HBO therapy (p=0.026).

Conclusion: WBC and lymphocyte counts are higher in CO poisoning patients who required hyperbaric oxygen therapy. But these two values were not found to be independent risk factors in predicting hyperbaric oxygen therapy.

Keywords: Poisoning, carbon monoxide, oxygen, lymphocyte, leukocytes

Öz

Giriş: Karbon monoksit (CO) zehirlenmesi dünya çapında en yaygın zehirlenmelerden biridir. CO zehirlenmesi ile zehirlenme şiddetini tahmin edecek parametreleri araştırmak için birçok çalışma bulunmaktadır. Bu çalışmada kan parametre değerleri ile kanda ölçülen CO değerleri ve zehirlenmenin sonlanımı arasındaki ilişkiyi araştırmayı amaçladık.

Gereç ve Yöntem: Çalışmamız retrospektif bir çalışmadır. Kan gazında CO düzeyi ≥%10 olan hastalar çalışmaya dahil edildi. Hastalar hiperbarik oksijen ihtiyacı olanlar ve olmayanlar olarak 2 gruba ayrıldı. Hastaların yaş, cinsiyet gibi demografik verileri ile kan gazlarındaki CO düzeyleri, hemoglobin, lökosit, nötrofil, kan sayımı trombosit sayıları, MPV ve PDW değerleri kaydedildi. Ayrıca kreatinin, troponin, CRP, ALT değerleri de kaydedildi.

Bulgular: Çalışmaya 110 hasta dahil edildi Hastaların yaş ortalaması 46,80±18,18 idi. Parametreler incelendiğinde HBO tedavisi gereken hastaların WBC sayımı ortancası 8,73 [7,54-11,83], HBO tedavisi gerektirmeyen hastaların WBC sayısı ortancası 8,01 [6,96-9,72] (p=0,038) idi. Benzer şekilde HBO tedavisi gereken hastaların lenfosit sayısı ortancası 2,73 [1,85-3.36] olarak belirlendi ve bu değer HBO tedavisi gerektirmeyen hastalara göre daha yüksek bulundu (p=0,026).

Sonuç: Hiperbarik oksijen tedavisi gerektiren CO zehirlenmesi olgularında WBC ve lenfosit sayıları daha yüksektir. Ancak bu iki değer hiperbarik oksijen tedavisini öngörmede bağımsız risk faktörleri değillerdir.

Anahtar Kelimeler: Zehirlenme, karbonmonoksit, oksijen, lenfosit, lökosit

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INTRODUCTION

Carbon monoxide (CO) poisoning is one of the most common poisonings worldwide. Intoxication may cause only mild symptoms such as headache or nausea, or it may progress with a severe course that causes mortality.[1] CO binds to hemoglobin with greater affinity than oxygen and caused impaired use and utilization of oxygen by tissues. Also, it causes delayed neurological sequelae with concomitant lipid peroxidation.[2] Clinicians' suspicion is required for diagnosis, especially in mild cases, together with clinical symptoms and signs. The CO level measured in the blood is the most used method in the diagnosis.[3] There are many studies that have investigated the relationship between predictive parameters and CO poisoning severity.[1,4] The relationship between lymphocyte, neutrophil, troponin, and mean platelet volume with the severity of the poisoning has been demonstrated.[5,6] In addition, it has been shown that the neutrophil-lymphocyte ratio may be effective in predicting major cardiac adverse events in severe carbon monoxide poisoning.[7]

In our study, we aimed to investigate the relationship between blood parameter values with poor outcome in CO poisoning, and CO values measured in blood.

MATERIAL AND METHOD

Study Design

Our study was planned as a retrospective study. The study was conducted after the approval of the Karabük University Non-Interventional Clinical Researches Ethics Committee (Decision No:2022/820) and the data obtained using the hospital information system were anonymized and statistical analysis and interpretations were made in a blind manner.

Selection of Participants

Patients who applied to the emergency department with the suspicion of CO poisoning and had CO levels ≥ %10 in their blood gas were included in the study. Patients with CO levels <10, lack of data to be collected in the study, patients who were pregnant or under the age of 18 at the time of application were excluded from the study. Patients were divided into 2 groups as those who required hyperbaric oxygen (HBO) and those who do not. Patients with CO level ≥ %25, patients with ischemic chest pain or ECG changes or troponin positivity at presentation, patients with syncope, loss of consciousness, and abnormal neuropsychiatric disorders at presentation were defined as patients who required HBO.

Data Collection

Demographic data such as age, gender of the patients, as well as CO levels in the blood gases of the patients, hemoglobin (Hb), leukocyte, neutrophil, platelet counts of the blood count, and MPV and PDW values were recorded. Also, creatinine, troponin, CRP, ALT values were recorded as well.

Outcome

To investigate the relationship of platelet count, MPV, and PDW values with the course of the disease and relation of CO levels.

Statical Analysis

Statistical analysis was performed using the IBM SPSS Statistics 22 (IBM SPSS, Turkey) package program. In summarizing the data, descriptive statistics were tabulated for continuous variables as mean ± standard deviation or median and quartile width, depending on the distribution. Categorical variables were summarized as numbers and percentages. The normality test of numerical variables was checked with the Shapiro Wilks test, histogram, and Q-Q plot graphs. Comparison of the quantitative data, if they fit the normal distribution, Student's T-test was evaluated. If it did not fit the normal distribution, the Mann-Whitney U test was used. Correlation analyzes were used to investigate the relationships of continuous data. Logistic regression analysis was used to determine independent parameters affecting hyperbaric oxygen treatment. The chi-square test was used to compare the qualitative data and the significance was determined as $p<0.05$ during the tests.

RESULTS

The study was conducted with 140 patients. 30 patients were excluded from the study due to the lack of laboratory data. In our study, which was investigated on 110 patient data in total, 67 (60.9%) of the patients were women. It was determined that 45 (40.9%) of the patients included in the study received hyperbaric oxygen therapy. The mean age of the patients was 46.80±18.18 years. All demographic data and laboratory parameters of all patients are summarized in **Table 1**.

Table 1. Demographic data and laboratory parameters of the patients

Gender	
Female n (%)	67 (60.9%)
Male n (%)	43 (39.1%)
HBO therapy	
Yes n (%)	45 (40.9%)
No n (%)	65 (59.1%)
Age (year)	46.80±18.18
CO (%)	23.46±11.69
PLT (109/L)	243.40±73.55
PDW	16.23±0.49
Hgb (g/dL)	13.53±1.87
MPV (fL)	9.96±1.27
WBC (109/L)	8.14 [7.18-10.05]
Lymphocyte (109/L)	2.43 [1.68-3.10]
Neutrophil (109/L)	5.23 [4.11-6.88]
Troponin (ng/ml)	0.001 [0.001-0.013]
Creatinine (mg/dl)	0.77±0.28
ALT (u/L)	18.00 [13.00-27.00]
CRP (mg/L)	3.20 [1.30-6.12]

When the demographic data and laboratory parameters of patients who required HBO therapy or were not examined, the median WBC value of patients with patients who required HBO therapy was 8.73 [IQ 25-75, 7.54-11.83], and the median WBC count of patients who did not require HBO therapy was 8.01 [IQ 25-75, 6.96-9.72]. The median WBC count of patients who required HBO therapy was higher than those who did not (p=0.038). Similarly, the median lymphocyte count of patients who required HBO therapy was determined as 2.73 [IQ 25-75, 1.85-3.36], and this value was found to be higher than patients who did not require HBO therapy (p=0.026). PLT, PDW, and MPV values of patients with and without HBO indication were not statistically different from each other (p=0.218, p=0.983, and p=0.592, respectively). Other demographic data and laboratory parameters are summarized in **Table 2**.

Table 2. Comparison of demographic data and laboratory values of patients with and without indication for HBO therapy

Value	HBO indication (+)	HBO indication (-)	p
Gender(female) n (%)	25 (64.6%)	42 (55.6%)	0.338χ
Age (year)	48.53±19.94	48.60±16.90	0.408*
CO (%)	33.75±7.79	16.33±8.05	<0.001
PLT (109/L)	253.82±82.02	236.20±66.77	0.218
PDW	16.23±0.48	16.23±0.50	0.983
Hgb (g/dL)	13.44±1.75	13.61±2.02	0.636
MPV (fL)	9.88±1.35	10.02±1.22	0.592
WBC (109/L)	8.73 [7.54-11.83]	8.01 [6.96-9.72]	0.038¥
Lymphocyte (10^9/L)	2.73 [1.85-3.36]	2.13 [1.40-2.86]	0.026
Neutrophil (10^9/L)	5.23 [4.01-8.73]	5.24 [4.12-6.12]	0.557
Troponin (ng/ml)	0.009 [0.001-0.310]	0.001 [0.001-0.100]	0.001
Creatinine (mg/dl)	0.81±0.26	0.74±0.30	0.183
ALT (u/L)	18.00 [14.00-25.50]	20.00 [12.50-27.00]	0.633
CRP (mg/L)	3.20 [1.44-6.15]	3.40 [1.25-6.05]	0.704

χChi-square test was performed, *Student's T-test was performed, ¥Mann Whitney-U test was performed

In the logistic regression analysis performed to determine the independent parameters for HBO treatment, lymphocyte and WBC counts were not found to be independent risk factors in the logistic regression analysis (**Table 3**).

Tablo 3. Logistic regression analysis for hyperbaric oxygen indication

	Wald	Odds ratio	95% C.I.	
WBC	2.543	1.238	0.952	1.611
Lymphocyte	1.175	0.728	0.410	1.293
Platelet	0.230	1.002	0.993	1.012
CO	23.815*	1.378	1.212	1.568

C.I.= confidence interval, Omnibus χ2 (4) = 87.39 p<0.001 R2 = 0.739 (Negelkerke)

DISCUSSION

In our study, the mean age of the patients presenting with CO poisoning was 46.80±18.18 years, which is similar to other studies in the literature.[8,9] In a study investigating troponin I elevation in CO poisoning, it was found that WBC count was higher in patients with troponin elevation than in patients without troponin elevation, but no difference was found between lymphocyte levels between these two groups.[10] Bagci et al. devided the patients presenting with CO poisoning into 2 groups mild-moderate and severe. According to the analyzes made in the study, there was no difference between the two groups in terms of MPV or platelet values, while the lymphocyte value was found to be higher in cases of severe poisoning.[11] In another study, patients were divided into 2 groups as those with and without severe CO poisoning, and WBC, lymphocyte, troponin, and MPV values were found to be higher in severe poisoning cases.[12] It was found that patients with high CO levels at admission had significantly higher troponin values in studies that examined patients with delayed neuropsychiatric sequelae after carbon monoxide poisoning.[13,14] Similarly, we found that WBC and lymphocyte counts, and troponin values were found to be higher in patients with an indication for HBO therapy than in patients without an indication for HBO therapy. Temrel et al. compared the laboratory values of the control group with a CO level of less than 10% and the patients with a CO level of more than 10% and found that WBC, neutrophil count, and MPV values were higher in the CO poisoning group, lymphocyte value was lower, and platelet value was not different in both groups.[15] Unlike our study, the reason for the higher MPV value and lymphocyte count being lower may be the study was conducted with a control group without CO poisoning cases. Similar to our study, Karaman et al. found that the WBC counts of the patients who required HBO therapy were significantly higher than those who do not require HBO therapy and the lymphocyte count increased with the increase in CO levels.[16]

In our study, when the parameters that could be used to determine the need for HBO therapy were examined, it was found that only the CO level was an independent factor in predicting the treatment. Similarly, Liao et al. determined that the CO value and Modified Poisoning Severity Score were independent factors for HBO therapy.[17]

Limitation

Our study is a single-center study and has relatively few patients. In the study, there was no data on the mortality of the patients. In addition, we did not investigate late neurophysiological sequela.

CONCLUSION

WBC and lymphocyte counts are higher in CO poisoning patients who required hyperbaric oxygen therapy, which we can define as serious. However, these two values were not found to be independent risk factors in predicting hyperbaric oxygen therapy.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was conducted after the approval of the Karabük University Non-Interventional Clinical Researches Ethics Committee (Decision No:2022/820).

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

Predictive Level of Routine Laboratory Parameters in Hospitalized COVID-19 Patients on Severity of Illness

Hastanede Yatan COVID-19 Hastalarında Rutin Laboratuvar Parametrelerinin Hastalığın Şiddeti Üzerindeki Öngörü Değeri

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Abstract

Aim: Early prediction of Coronavirus disease 2019 (COVID-19) disease severity is important to reduce mortality. Therefore, we sought to determine the clinical correlation between these baseline routine laboratory parameters and their effects on mortality by retrospectively investigating the routine laboratory parameters of hospitalized COVID-19 patients on admission day.

Material and Method: This retrospective-observational study population consisted of 415 hospitalized COVID-19 patients. Patients were divided into three groups (mild, moderate, and severe) according to their clinical status on admission day. On admission, fifteen routine biochemical and hematological laboratory parameters of COVID-19 patients were evaluated.

Results: Aspartate aminotransferase (AST), alanine transaminase (ALT), lactate dehydrogenase (LDH), ferritin, International Normalized Ratio (INR), and d-dimer levels were higher in non-survivors than in survivors, regardless of the initial disease severity group classification. No statistically significant difference was found between the groups in terms of uric acid, monocyte, and platelet levels.

Conclusions: There is a need for an urgent scale for detecting COVID-19 severity. AST, ALT, LDH, ferritin, INR, and d-dimer levels may help predict the disease's severity in COVID-19.

Keywords: COVID-19, biochemical parameters, disease severity

Öz

Amaç: Koronavirus hastalığı 2019 (COVID-19) hastalık şiddetinin erken tahmini, mortaliteyi azaltmak için önemlidir. Bu nedenle, hastaneye yatırılan COVID-19 hastalarının rutin laboratuvar parametrelerini kabul gününde geriye dönük olarak araştırarak, bu temel rutin laboratuvar parametreleri ile mortalite üzerindeki etkileri arasındaki klinik ilişkiyi belirlemeye çalıştık.

Gereç ve Yöntem: Bu retrospektif-gözlemsel çalışma popülasyonu, hastaneye yatırılan 415 COVID-19 hastasından oluşmaktadır. Hastalar başvuru günlerindeki klinik durumlarına göre (hafif, orta ve şiddetli) üç gruba ayrıldı. Başvuru sırasında COVID-19 hastalarının on beş rutin biyokimyasal ve hematolojik laboratuvar parametresi değerlendirildi.

Bulgular: Aspartat aminotransferaz (AST), alanin transaminaz (ALT), laktat dehidrojenaz (LDH), ferritin, Uluslararası Normalleştirilmiş Oran (INR) ve d-dimer seviyeleri, başlangıçtaki hastalık şiddeti grup sınıflandırmasına bakılmaksızın, hayatta kalanlarda hayatta kalanlardan daha yüksekti. Ürik asit, monosit ve trombosit sayıları açısından gruplar arasında istatistiksel olarak anlamlı fark bulunmadı.

Sonuç: COVID-19 şiddetini tespit etmek için acil bir ölçeğe ihtiyaç vardır. AST, ALT, LDH, ferritin, INR ve d-dimer seviyeleri, COVID-19'daki hastalık şiddetini tahmin etmeye yardımcı olabilir.

Anahtar Kelimeler: COVID-19, biyokimyasal parametreler, hastalık şiddeti

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) had caused over 5 million deaths globally since the first case was identified.[1] Studies on the diagnosis and treatment of this disease continue globally. Early prediction of the severity of COVID-19 is important to reduce mortality. Biochemical and hematological laboratory parameters are among the tests that can help clinicians in this context.[2-5]

Although there are many studies that examine the clinical characteristics of COVID-19 patients, there are a limited number of studies that predict clinical surveillance and mortality according to the day of admission. Biochemical and hematological parameters can be useful in this context.

Initial laboratory tests with a high neutrophil level (>0.7 10^3/L), lymphopenia (0.8 10^3/L), increased C-reactive protein (CRP; >4.75 mg/dL), and elevated lactate dehydrogenase (LDH; >593 U/L) levels were the most important predictors of mortality in severe acute respiratory syndrome coronavirus (SARS-CoV) patients, according to previous studies.[3-6] Both severe and fatal COVID-19 patients had increased biomarkers of cardiac and muscular damage. At presentation, patients who died had significantly high cardiac troponin levels, indicating the possibility of viral myocarditis, cardiac damage from progression to multiple organ failure (MOF), and secondary cardiac injury from organ-targeted diseases (e.g., renal or liver failure). Even when laboratory parameters measured primarily at admission are combined with significant elevations in liver enzymes (alanine aminotransferase (ALT) and aspartate aminotransferase (AST), renal biomarkers (blood urea nitrogen, creatinine), and coagulation measures, a picture of MOF emerges in patients who develop the severe form of the disease.[7] In addition, the International Federation of Clinical Chemistry Working Group recommended that, the biochemical and hematological tests can be helpful in COVID-19 for the diagnosis of tissue-organ damage, the determining and monitoring the course of the disease.[8]

Therefore, we aimed to determine the clinical correlation between these baseline laboratory parameters on admission day and their effects on mortality, by retrospectively investigating the laboratory parameters of hospitalized COVID-19 patients.

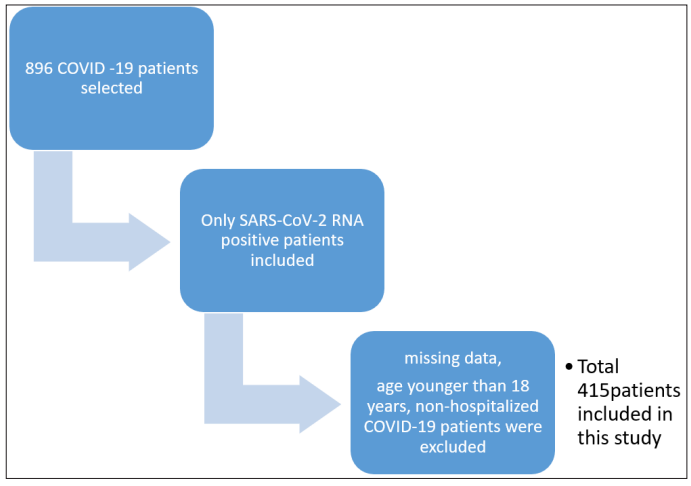
MATERIAL AND METHOD

Study Design and Participants

This retrospective-observational study was conducted at a pandemic hospital (Çanakkale Onsekiz Mart University Hospital) in Turkey. The sample size selection was not made. The patients admitted on the study date according to the exclusion and inclusion criteria were included in the study. The study population consisted of 415 confirmed COVID-19 patients who were hospitalized from March 23 to June 1, 2020. The patients were diagnosed with COVID-19 according to the World Health Organization (WHO) provisional guidelines with positive SARS-CoV-2 RNA detection. 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 on thoracic computed tomography (CT) together with appropriate clinical findings was defined as a possible COVID-19 patient.[9]

The exclusion criteria were missing data, age younger than 18 years, and non-hospitalized COVID-19 patients.

The comparison was made without considering some factors such as the patients' previous medical history (smoking, diabetes, hypertension, etc.). These data could not be evaluated because it was a retrospective study. The groups were selected only according to the severity of the disease at the time of the first admission.



Graph 1. Flowchart of study design.

Definitions

The study population was divided into 3 groups according to their clinical status on admission day, according to the diagnosis and treatment protocol for COVID-19 pneumonia published by the Turkish Ministry of Health's Guideline for COVID-19 Diagnosis and Treatment.

Group 1 (mild COVID-19 patients): Defined as mild clinical symptoms and no sign of pneumonia on imaging or oxygen saturation of 93% or more at rest or more than 50% lesions on thoracic computed tomography (CT).

Group 2 (moderate COVID-19 patients): Defined as fever and respiratory symptoms with radiological findings of pneumonia but without the severe or critical features.

Group 3 (severe COVID-19 patients): Defined as respiratory distress (≥30 breaths per min), oxygen saturation of 93% or less at rest, ratio of arterial partial pressure of oxygen to fractional concentration of oxygen in inspired air of 40 kPa or less, or more than 50% lesion progression over 24–48 hours in thoracic CT.

Procedures

All medical records (demographic, clinical, laboratory tests, and radiological) on admission day and outcomes (discharge or exitus) of hospitalized COVID-19 cases were reviewed retrospectively. The levels of white blood cell (WBC), neutrophil, lymphocyte, monocyte, platelet, hemoglobin (Hgb), hematocrit (HTC), AST, ALT, uric acid, International Normalized Ratio (INR), lactate dehydrogenase (LDH), ferritin, and d-dimer were evaluated. All data was entered into a case form. All laboratory tests were studied at our hospital's biochemistry and microbiology laboratories using standard procedures. The classification of severity for COVID-19 patients was made according to the clinical and radiological findings on the admission day.

Ethical approval: In carrying out the study, accordance to the principles in the Helsinki Declaration revised in 2013 was followed. The study was approved by the COVID-19 Scientific Research Evaluation Commission of the General Directorate of Health Services of the Turkish Ministry of Health on the date of April 5, 2020, and the local ethics commission of our center (date: 03.06.2020, number: 2020-08). Institutional permission was obtained from the Turkish Ministry of Health, the local ethics committee and the hospital administration to conduct the study.

Statistical Analysis

The SPSS Package Program version 20.0 was used to analyze the data (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp; 2011). Number, percentage, median, minimum, and maximum, mean and standard deviations were used in the presentation of descriptive data. Chi-Square test was used to compare categorical data. The compliance of the data to normal distribution was evaluated by Kolmogorov Smirnov test and Shapiro Wilk test. The student T test and one-way ANOVA test were used to compare variables with normal distributions, while the Mann Whitney U test and Kruskal Wallis test were used to compare variables with non-normal distributions. Tamhane's T2 correction was applied for binary comparison of variables that were found to be statistically significant in the normal distribution, and the Dunn-Bonferroni correction was applied for binary comparison of variables that did not fit. A p-value lower than 0.05 (< 0.05) was accepted as statistically significant.

RESULTS

A total of 415 patients (59.5% men) diagnosed as COVID-19 pneumoniae were included in the study (Graphic 1). Demographical characteristics of the patients are given in **Table 1**. The patients were divided into 3 groups according to the severity of the disease. There were 222 patients in Group 1, 165 patients in Group 2, and 28 patients in Group 3.

A statistically significant difference was found between the groups in terms of age (p=0.0001). The median age of Group 1 patients was lower than that of Group 2 and Group 3 patients, and this difference was statistically significant in paired comparisons (p=0.0001, p=0.0001, respectively). The median age of Group 2 patients was lower than that of Group 3 patients, and this difference was significant in paired comparisons (p=0.041). There was no significant difference in gender between the groups (p=0.216).

The evaluation of the examined laboratory parameters based on patients as follows.

a. White Blood Cell (WBC) levels: A statistically significant difference was found between the groups according to WBC levels (p=0.0001). Group 3 patients had a higher WBC median level than the other groups. This difference was statistically significant in the corrected paired comparisons (p=0.0001, p=0.0001, respectively). The median WBC of the Group 2 patients was higher than the median of the Group 1 patients, and this difference was significant in corrected paired comparisons (p=0.023).

b. Neutrophil levels: The median of neutrophils in group 3 patients was higher than the medians of group 1 and group 2 patients, and these differences were statistically significant in the corrected paired comparisons (p=0.0001, p=0.0001, respectively).

c. Lymphocyte levels: There was a statistically significant difference between the groups in terms of lymphocytes (p=0.0001). The median lymphocyte level for Group 1 patients was higher than the medians of Group 2 and Group 3 patients, and these differences were statistically significant in smoothed paired comparisons (p=0.001, p=0.0001, respectively). The median lymphocyte of group 2 patients was higher than the median of group 3 patients, and this difference was significant in corrected paired comparisons (p=0.0001). It was found that the lowest lymphocyte value was in group 3 patients.

Table 1. Age and gender characteristics of the patients.

	Group 1 (n=222)		Group 2 (n=165)		Group 3 (n=28)		p value
	mean±sd	mean (min-max)	mean±sd	mean (min-max)	mean±sd	mean (min-max)	
Age (year)	49.2±17.4	46.0 (19.0-94.0)	62.7±15.9	63.0 (21.0-93.0)	72.0±12.1	70.5 (46.0-93.0)	0.0001
	n (%)		n (%)		n (%)		p
Gender							0.216*
Female	91 (41.0)		70 (42.4)		7 (25.0)		
Male	131 (59.0)		95 (57.6)		21 (75.0)		

*mean±sd: mean±standard deviation, p *: One-Way ANOVA Test, *= p<0.05 statistically significant.

d. Monocyte and thrombocyte levels: No statistically significant difference was found between the groups in terms of the median of monocytes and platelets.

e. Hemoglobin: The median hemoglobin of Group 1 patients was higher than the median of Group 2 and Group 3 patients, and these differences were p=0.003, p=0.0001 in the corrected paired comparisons).

f. Hematocrit: There was a significant difference between the groups (p=0.0001). The hematocrit levels of group 1 patients were higher than the mean of Group 3 patients, and this difference was significant as used in the corrected paired tables (p=0.011).

g. Alanine transaminase (ALT): The median of ALT levels was higher in group 3 patients than the other groups (Group 1 and Group 2) and were istatistically significant in the corrected paired comparisons (p=0.047, p=0.004, respectively).

h. Aspartate aminotransferase (AST): The AST levels were significantly different between groups (p=0.0001). The median level of AST in Group 3 patients was higher than the medians in groups 1 and 2, and these differences were significant in corrected paired comparisons (p=0.0001, p=0.016).

I. Uric acid: There was no significant difference in uric acid medians between the groups (p=0.205).

j. Lactate dehydrogenase (LDH): There was a significantly significant difference in LDH levels between the groups (p=0.0001). The median LDH of the Group 3 patients was higher than the medians of Group 1 and Group 2 patients, and these differences were significant in paired comparison with correction (first order p=0.0001, p=0.030). The median LDH of Group 2 patients was higher than the median of Group 1 patients, and this difference was significant with corrected paired comparison (p=0.0001).

k. International Normalized Ratio (INR): There were variously significant differences in INR between the groups (p=0.0001). The median INR of Group 3 patients was higher than the median of Group 1 and Group 2 patients, and these differences were significantly significant in pairwise comparison with correction (first row p=0.0001, second row p=0.0001). The median INR of Group 2 patients was higher than the median of Group 1 patients, and this difference was significant with corrected paired comparison (p=0.006).

l. Ferritin: There was a statistically significant difference between the groups in terms of ferritin (p=0.0001). The median level of ferritin levels of Group 3 patients was higher than that of Group 1 and Group 2, and this was statistically significant in the smoothed paired comparisons (p=0.0001, p=0.0001, respectively).

m. D-dimer: There was a statistically significant difference between the groups in terms of d-dimer levels (p=0.0001). The median level of d-dimer levels of Group 2 patients was higher than the median of Group 1 patients, and this difference was significant in corrected paired comparisons (p=0.003) (**Table 2**).

Table 2. Comparison of laboratory parameters according to groups.

Laboratory parametres	Group 1 (n=222)		Group 2 (n=165)		Group 3 (n=28)		P value
	Mean ±sd	mean (min-max)	Mean ±sd	mean (min-max)	Mean ±sd	mean (min-max)	
White blood cell level, 10^9 cells per L	7305.5±3120.3	6400.0 (2700.0-19900.0)	8733.9±4794.6	7400.0 (2400.0-33700.0)	18710.7±29238.4	13750.0 (3100.0-164000.0)	0.0001
Neutrophil level, 10^9 cells per L	4587.3±2760.6	3600.0 (1000.0-17700.0)	6331.5±4565.8	4800.0 (1100.0-31800.0)	14296.4±15269.2	12600.0 (2800.0-86800.0)	0.0001
Lymphocyte level, 10^9 cells per L	1931.8±1760.1	1600.0 (100.0-24200.0	1558.2±1019.4	1400.0 (200.0-8500.0)	1735.7±4634.9	600.0 (200.0-23900.0)	0.0001
Monocyte level, 10^9 cells per L	643.6±292.1	600.0 (100.0-1900.0)	712.7±385.4	600.0 (100.0-2400.0)	2417.9±9218.7	550.0 (100.0-49499.0)	0.228
Platelet level, 10^9 cells per L	220572.7±79576.3	209000.0 (87000.0-693000.0)	237181.8±97783.4	221000.0 (36000.0-580000.0)	228857.1±102670.2	253500.0 (47000.0-375000.0)	0.216
Haemoglobin, g/dL	13.6±1.7	14.0 (8.0-17.0)	12.9±2.2	13.0 (5.0-19.0)	11.6±2.4	12.0 (8.0-16.0)	0.0001
Hematocrit g/dL	39.6±4.7	39.8 (24.5-50.7)	38.3±6.2	38.6 (13.3-52.7)	35.1±7.5	35.0 (23.2-49.3)	0.0001*
ALT (U/L)	27.6±42.3	18.9 (4.3-473.5	25.3±27.9	16.8 (4.0-239.2)	62.4±91.4	25.3 (7.8-462.6)	0.004
AST (U/L)	29.1±38.8	21.3 (9.3-425.0)	34.1±30.3	23.0 (9.4-215.9)	129.1±274.6	39.6 (14.6-1275.0)	0.0001
Uric acid (mg/dL)	5.2±2.7	4.7 (1.9-26.8)	5.5±2.2	5.3 (0.4-12.5)	5.1±2.1	5.0 (1.9-10.8)	0.205
Lactate dehydrogenase, units per L	248.2±104.4	219.0 (93.0-831.0)	308.2±142.8	265.0 (127.0-1122.0)	420.6±207.2	306.5 (193.0-921.0)	0.0001
INR	1.0±0.1	1.0 (0.8-1.5)	1.1±0.3	1.0 (0.8-3.8)	1.7±1.9	1.2 (0.9-11.5)	0.0001
Ferritin (ng/mL)	252.9±336.9	159.2 (4.2-2000.0)	343.3±388.9	197.0 (10.5-2000.0)	778.8±676.9	516.8 (54.0-2000.0)	0.0001
D-dimer (µg/mL)	0.228±0.264	0.14 (0.02-1.216)	5.21±7.38	2.78 (0.06-3.57)	1.313±1.11	1.028 (0.05-3.695)	0.0001

*mean ± sd: mean ± standard deviation, Aminotransferase (ALT), Aspartate Aminotransferase (AST), p: Kruskal Wallis Test, p *: One-way ANOVA Test, *= p<0.05 statistically significant.

Examining the relationship between mortality and laboratory parameters

A significant difference was found between patients with and without mortality in terms of WBC, neutrophil, lymphocyte, hemoglobin, hematocrit, ALT, AST, LDH, INR, ferritin, and d-dimer (p=0.0001, 0.0001, 0.004, 0.0001, 0.0001, 0.0001, 0.0001, 0.0001, 0.0001, 0.0001, 0.0001, 0.0001, 0.0001, 0.0001, respectively). However, there was no significant difference in monocyte, thrombocyte, or uric acid levels (p > 0.05) (**Table 3**).

DISCUSSION

It was thought that inflammation and heart/muscle damage biomarkers, liver and kidney function biomarkers, Interleukins 6 (IL-6), Interleukins 10 (IL-10), serum ferritin and coagulation parameters are significantly increased in both severe and fatal COVID-19 patients.[3] COVID-19 is characterized by lymphopenia, increased activation of the inflammatory cascade, and cardiac involvement, all of which have a high prognostic value. The fundamental processes, however, are still poorly understood.[10] However, the literature information on parameters other than these laboratory parameters is changing rapidly, as the global studies conducted by many different researchers, by the days of the first year of the pandemic. Our study provides a comprehensive description of COVID-19 cases using laboratory parameters, and the risk factors for severe COVID-19. In additionally, our study differs from other studies due to the evaluation of a wider range of biochemical and hematological parameters compared to the current literature. Our study is different in that it offers an evaluation with simple routine and non-complex tests that can guide the course of COVID-19.

Screening, clinical care, and the prevention of major consequences might all benefit from effective biomarkers. WBC, lymphocyte, neutrophil, platelet, eosinophil, and hemoglobin levels and neutrophil–lymphocyte ratio (NLR) are hematologic indicators used to stratify COVID-19 patients.[10] Among the main contributions of laboratory tests to the clinician are to assist the staging of COVID-19 patients, predict their prognosis, and therapeutic monitoring. Many laboratories that can help determine the risk of development of acute respiratory distress syndrome (ARDS), disseminated intravascular coagulation (DIC), multi-organ failure (MODS) and hemophagocytic lymphohistiocytosis (HLH) / Macrophage activation syndrome (MAS) / cytokine storm. parameter is available.[5]

According to literature research, there are many studies showing that the levels of WBC,[3] CRP,[5,9,11] erythrocyte sedimentation rate (ESR),[7,12] LDH,[4-9] creatine kinase (CK),[3,4,8] serum ferritin,[3] IL-6,[3,9] d-dimer,[5,8] serum amyloid A,[7] albumin,[5,9] lymphocyte,[3,5,11] platelet,[3] neutrophil,[11] total bilirubin,[3] serum potassium[5] and procalcitonin,[5,9] may have an important place in predicting the course and prognosis of

Table 3. Comparison of of laboratory parameters of survivors and non-survivors.

	Survivors (n=368)		Non-survivors (n=47)		p
	Mean ±sd	Mean (min-max)	Mean ±sd	Mean (min-max)	
White blood cell level, 10^9 cells per L	7857.7±3770.3	7000.0 (2400.0-27600.0)	14814.9±23318.5	9100.0 (3100.0-164000.0)	0.0001
Neutrophil level, 10^9 cells per L	5264.5±3534.2	4100.0 (1000.0-24200.0)	11221.3±12962.2	7700.0 (2500.0-86800.0)	0.0001
Lymphocyte level, 10^9 cells per L	1734.9±968.9	1500.0 (100.0-8500.0)	2036.2±4880.5	800.0 (200.0-24200.0)	0.0001
Monocyte level, 10^9 cells per L	670.8±329.6	600.0 (100.0-2400.0)	1731.9±7118.5	600.0 (100.0-49400.0)	0.986
Platelet level, 10^9 cells per L	239628.4±89381.2	214500.0 (36000.0-693000.0)	205510.6±83832.9	191000.0 (47000.0-375000.0)	0.147
Haemoglobin, g/dL	13.4±1.9	14.0 (8.0-19.0)	11.6±2.5	12 (5.0-17.0)	0.0001
Hematocrit g/dL	39.2±5.2	39.4 (24.5-52.7)	35.1±7.5	34.6 (13.3-49.4)	0.001*
ALT (U/L)	26.7±37.7	18 (4-473.5)	47.2±72.7	23.2 (5.0-462.6)	0.004
AST (U/L)	30.4±35.6	21.6 (9.3-425.0)	95.5±213.5	37.3 (13.3-1275)	0.0001
Uric acid (mg/dL)	5.2±2.4	4.8 (1.9-26.8)	6.1±2.9	5.8 (0.4-12.2)	0.101
Lactate dehydrogenase, units per L	266.6±111.9	233.0 (93.0-831.0)	415.9±222.0	342.0 (149.0-1122.0)	0.0001
INR	1.1±0.6	1.0 (0.8-11.5)	1.3±0.4	1.2 (0.9-3.1)	0.0001
Ferritin (ng/mL)	284.5±344.4	177.9 (4.2-2000.0)	814.9±670.0	496.1 (54.0-2000.0)	0.0001
D-dimer (µg/mL)	0.347±0.498	0.182 (0.03-0.3298)	1.430±1.194	1.024 (0.5-3695.0)	0.0001

*mean ± sd: mean ± standard deviation, Aminotransferase (ALT), Aspartate Aminotransferase (AST), p: Kruskal Wallis Test, p *: One-Way ANOVA Test, *= p<0.05 statistically significant.

COVID-19 patients. Henry et al.[3] evaluated 21 studies in which 3377 patients were included in their meta-analysis study. In this meta-analysis, while 18 studies (n=2984) compared laboratory findings between severe and non-severe COVID-19 patients, 3 studies (n=393) were found to compare survivors and deceased.[3] In our study, we compared the laboratory findings according to both disease severity and mortality development. In this meta-analysis, it was found that those with severe disease and those who died had high WBC levels and decreased lymphocyte and thrombocyte levels. In our study, increased WBC and neutrophil levels and lower lymphocyte levels were detected both in Group 3 and non-survival group. There was no significant difference in platelet levels in both comparisons.

In studies, lymphopenia has been one of the most controversial parameters associated with disease severity in COVID-19. Additionally, liver dysfunction, increasing serum inflammatory markers, serum ferritin and LDH levels related to cytokine storm, abnormal coagulation parameters such as increasing plasma d-dimer levels and troponin levels have been frequently reported in severe disease or non-survivors.[12] In a review study, 189 studies and 57,563 COVID-19 patients were evaluated. In this study, Hgb and Htc levels were found to be lower in patients such as the elderly, those with comorbidities like diabetes and hypertension, and those admitted to ICUs.[13] In our study, the lowest Hgb and Htc levels were found in both Group 3 patients and non-survival patients, and this is consistent with the literature. In addition, Group 3 patients were also found to be statistically older in our study. For these reasons, we think it is difficult to reach a full judgement.

Wendel Garcia et al.[14] have reported significantly increased CRP, creatinine, troponin, d-dimer, lactate, neutrophil, and WBC levels in ICU non survivor COVID-19 patients. Similarly, in the multivariable regression analyzes; baseline higher creatinine, d-dimer, lactate, potassium levels have been found to be significantly associated with mortality.[14]

Clinical biochemistry laboratories contribute greatly to the clinical decision with their test results. The importance of some tests that can be ordered from every patient on a routine basis has increased in this disease. Blood levels of some inflammatory markers increase due to initial or accompanying secondary infection. These markers play a role not only in the management of the disease but also in the severity classification of the disease. Although a great progress has been made in vaccination studies today, targeted treatment and follow-up is important.[14,15] For example, platelet levels has been quickly accepted as a potential biomarker for COVID-19 patients since it is a simple, inexpensive, and readily available biomarker that has been independently related with disease severity and mortality risk in ICU. The number of platelets in COVID-19 patients was reported to be considerably lower, and non-survivor patients had less platelets than survivors.[10] In another study by Sun et al.[16], patients were divided into 4 groups: mild, moderate, severe (20%), and critical (33%) according to the clinical severity of disease, similarly to our study. This study emphasized that the levels of lymphocytes were significantly lower and gamma glutamyl transferase (GGT), LDH, AST, ALT, CRP, ESR, and ferritin levels were significantly higher in severe and critically ill COVID-19 patients. In addition, CRP, lymphocyte levels, and di-dimer levels were significant and were associated with disease severity according to logistic regression analysis.[16] Another meta-analysis study including 660 articles suggested that higher CRP, LDH levels and lymphopenia are associated with disease severity in COVID-19.[17] There was no statistically significant difference between the groups in terms of uric acid, monocyte and platelet levels. In our study, AST, ALT, LDH, ferritin, INR, and d-dimer levels were higher in both Group 3 patients and non-survival patients. This finding was also consistent with the current literature.

Different studies on the relationship of di dimer value with disease severity and mortality; reported that d-dimer levels above 1-2 µg/mL at the time of admission are associated with disease severity and mortality.[18-22] In our study, the d-dimer value was> 1 µg / mL in both patients who were directly hospitalized in ICU on admission day and in patients who developed mortality, and it was found to be statistically significantly higher compared to other groups.

COVID-19 is a disease that still puts humanity in grave danger. New strains are a menace even with the vaccines. We still need an urgent scale for COVID-19 severity. Correlation between severity and AST, ALT, LDH, ferritin, INR, and d-dimer values can help predict the disease's severity.

CONCLUSIONS

There is an urgent need for inexpensive, easily accessible predictors of the disease clinical course in COVID 19. Correlation between severity and AST, ALT, LDH, ferritin, INR, and d-dimer levels can help predict the disease's severity. There is a need for markers to be used in determining the clinical course of outpatients, too.

Limitations of the study: This study has limitations such as being single-center, retrospective, and including only inpatient COVID-19 patients. Furthermore, the sample size may be a factor in the absence of meaningful results. Because of the sample size, the predicted difference between groups in terms of expected outcomes may be affected. The groups were selected only according to the severity of the disease at the time of the first admission.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the COVID-19 Scientific Research Evaluation Commission of the General Directorate of Health Services of the Turkish Ministry of Health on the date of April 5, 2020, and the Çanakkale Onsekiz Mart University Clinical Researches Ethics Committee of our center (date: 03.06.2020, number: 2020-08).

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

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Original Article / Orijinal Araştırma

Experience in a Thoracic Surgery Clinic During the COVID-19 Pandemic

COVID-19 Pandemisi Sırasında Göğüs Cerrahisi Kliniği Deneyimimiz

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Abstract

Aim: During the COVID-19 pandemic, all elective surgeries, except emergency surgeries and surgeries for patients with malignancy, were postponed. In this study, patients who presented to the thoracic surgery clinic of our hospital during and those who presented before the COVID-19 pandemic were compared, and changes in characteristics of the patients presenting to the thoracic surgery clinic during the COVID-19 pandemic were investigated.

Material and Method: Age, gender, and reason for admission to the hospital were documented for all patients who presented to the thoracic surgery clinic of our hospital during March 2019–March 2020 and March 2020–March 2021. Patients presenting to the clinic were categorized into malignancy, trauma, chest pain, pneumothorax, and other disease groups.

Results: In total, 947 patients presented to the clinic in the pre-pandemic period. Conversely, 756 patients presented to the clinic during the pandemic. In the pre-pandemic period, 353 patients presented with trauma; this number decreased to 154 during the pandemic. Additionally, during the pandemic, a decrease was observed in all patient admissions other than those due to malignancies.

Conclusion: During the pandemic, there has been a decrease in patient admissions due to trauma, mostly as a result of curfews and restrictions. However, there has been a significant increase in the number of patients presenting with lung malignancies during the pandemic. This may be due to findings of incidental lung masses in the thoracic computed tomography performed after COVID-19 prediagnosis.

Keywords: COVID-19, thoracic surgery, malignancy

Öz

Amaç: Pandemi döneminde acil cerrahi operasyonlar ve malignitesi olan hastalar dışında elektif operasyonlar ertelenmesine rağmen göğüs cerrahi poliklinik hizmeti devam etti. Çalışmada pandemi öncesi göğüs cerrahisi polikliniğine başvuran hastalar ile pandemi döneminde başvuran hastaların karakteristiğinde bir değişim olup olmadığı değerlendirildi.

Gereç ve Yöntem: Mart 2019- Mart 2020 dönemleri ile Mart 2020-Mart 2021 dönemleri arasındaki göğüs cerrahisi polikliniğine başvuran hastaların yaşları, cinsiyetleri, hastaneye başvuru sebepleri dökümente edildi. Polikliniğe başvuran hastalar malignite, travma, göğüs ağrısı, pnömotoraks ve diğer hastalıklar olarak sınıflandırılmıştır.

Bulgular: Pandemi öncesi dönemde toplamda 947 hasta polikliniğe başvururken pandemic döneminde sayı 756 idi. Travma nedeniyle polikliniğe basvuran hasta sayısı 353 iken pandemi döneminde 154 idi. Pandemi döneminde diğer başvuru sebepleri azalırken malignite nedeniyle basvuru artmış olarak izlendi.

Sonuç: Çok büyük oranda sosyal kısıtlamalara bağlı olarak pandemi döneminde travmalara bağlı başvurularda azalma görülmüştür. Akciğer malignite hastalarında pandemi döneminde hem oransal hem de gözle görülür derecede sayısal artış olmuştur. Covid 19 ön tanısı nedeniyle çekilen toraks tomografilerinde rastlanan insidental akciğer kitleleri bu artıştan sorumlu tutulabilir.

Anahtar Kelimeler: COVID-19, Göğüs Cerrahisi, malignite

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a viral agent that can cause a broad spectrum of clinical symptoms ranging from cold-like symptoms to acute respiratory distress syndrome. COVID-19 originated from Wuhan, China and spread throughout the world in 2019; it was later declared as a pandemic by the World Health Organization. In Turkey, the first case of COVID-19 was detected in March 2020.

All elective surgeries performed in thoracic surgery clinics were postponed during the COVID-19 pandemic, and only emergency surgeries and surgeries for patients with malignancies were performed during this period. In addition, many thoracic complications caused by COVID-19 were treated during the pandemic.

Thoracic surgery clinics continued to operate during this period. In the present study, it was investigated whether the covid 19 pandemic caused a change in the characteristics of patients who applied to the thoracic surgery outpatient clinic.

MATERIAL AND METHOD

Surgeries performed in the thoracic surgery clinic of our hospital were examined, and the number of surgeries performed was compared over 1-year pre-pandemic and pandemic periods. Information such as age, gender, and reason for admission to the hospital were documented for all patients who presented to the thoracic surgery clinic of our hospital during March 2019–March 2020 and March 2020–March 2021. Ethical approval for this study was obtained from the ethics committee of Ankara Bilkent City Hospital (Approval number: E1-21-2165). This study has been conducted in accordance with the principles set forth in the "Helsinki Declaration".

Patients presenting to the outpatient clinic were categorized into malignancy, trauma, chest pain, pneumothorax, and other disease groups.

RESULTS

The number of patients who presented to the outpatient clinic in the pre-pandemic period was 947. In contrast, the number of patients presenting to the clinic during the COVID-19 pandemic was 756. During the pre-pandemic period, the total number of patients presenting to the clinic with a pre or definitive diagnosis of lung cancer and those presenting with the diagnosis of lung or other malignancies was 34 (3.6%).

Patients who received inpatient treatment due to trauma and presented for follow-up after discharge, those who were followed up and treated as outpatients, and patients presenting for the first time comprised the trauma group. A total of 353 (37.3%) patients were present in the trauma group during the pre-pandemic period.

The number of patients presenting to the clinic due to noncardiac and nontraumatic chest pain during the pre-pandemic period was 61 (6.5%). The total number of patients with pneumothorax who presented to the clinic for the first time, received treatment, and came to the clinic for follow-up during the pre-pandemic period was 28 (2.9%). The total number of patients presenting to the clinic for other reasons during the pre-pandemic period was 471 (49.7%).

In summary, a total of 947 patients presented to only one thoracic surgeon in the thoracic surgery clinic of our hospital during the 1-year period before the pandemic. Between 11 March 2020 and 11 March 2021, a total of 115 (15.2%) patients presented to the outpatient clinic due to malignancy, 154 (20.4%) due to trauma, 129 (17.1%) due to chest pain, 19 (2.5%) due to pneumothorax, and 339 (44.8%) due to other reasons. The total number of patients who presented to the clinic during this period was 756 (**Table 1**).

DISCUSSION

An increase of approximately four-fold was observed in the number of patients with malignancies presenting to the thoracic surgery outpatient clinic during the COVID-19 pandemic. This may be due to the fact that conducting only cancer treatment-related procedures and emergency surgical procedures were permitted during the COVID-19 pandemic. Furthermore, patients were concerned that they would become infected from the hospital, which caused them to postpone their application. The inaccessibility of outpatient clinic appointments, and the incidental detection of a mass in thoracic tomography procedures due to the pre-diagnosis of COVID-19 may have contributed to this increase observed in patients with malignancy. When monthly differences in the number of patients were determined, it was found that while there was no difference during the pre-pandemic period (p=0.276) the number of patients increased month by month as the COVID-19 pandemic progressed. Patients with lung cancer constituted the majority of the malignancy group. In addition to having cancer, the patients were worried about having COVID-19. Most patients believed that having COVID-19 would be lethal for them.

The current conundrum faced by healthcare professionals in treating patients with lung cancer during the COVID-19 pandemic is the need to balance the risk of a potentially life-threatening infection with COVID-19 against the consequences of not treating or delaying a life-threatening malignancy. Previous studies report that the course of COVID-19 is severe in patients with lung cancer, with a hospitalization rate of 62% and a mortality rate of 25%.[1] Although the disease course has severe outcomes, overall only 11% of patients with lung cancer died due to COVID-19 during the pandemic period.

Table 1: Distribution of patient admissions observed during the prepandemic and pandemic periods

Period	Malignancy	Trauma	Chest pain	Pneumothorax	Other pathologies	Total
Prepandemic	34 (3.6%)	353 (37.3%)	61 (6.5%)	28 (2.9%)	471 (49.7%)	947
Pandemic	115 (15.2%)	154 (20.4%)	129 (17.1%)	19 (2.5%)	339 (44.8%)	756

[1] Outpatient clinic admissions due to trauma decreased by approximately 50% during the COVID-19 pandemic ($p<0.001$). The main reason for this decrease was the restrictions and curfews imposed owing to the pandemic. The conscious effort by people to reduce social activities, avoid crowded places, and maintain social distancing may have caused a decrease in trauma cases.

Clinical management strategies have been implemented for trauma patients during the COVID-19 pandemic.[2] As a part of such preventive strategies, the clinics in our hospital have also taken efforts to protect patients from COVID-19. This effort including to follow-up and treat COVID-19 positive trauma patients in different wards, and adopt different strategies for the management of COVID-19 positive patients that requiring surgery. Similar to patients with cancer, COVID-19-related anxiety was also observed in trauma patients. The number of patients presenting to the clinic with nontraumatic chest pain increased as the COVID-19 pandemic progressed, and the number of admissions doubled compared to that in the pre-pandemic period.

In the present study, cardiac causes were excluded in all patients presenting to the clinic with chest pain. Furthermore, 30% of the patients with chest pain had a history of COVID-19. Pain complaints of patients were usually related to the back and parasternal joints.

During the COVID-19 pandemic, curfews were implemented throughout the world and most patients were afraid to visit healthcare institutions. This led to a three-fold increase in online searches for chest pain symptoms on the internet compared to those in the pre-pandemic period.[3] Chest pain is a common symptom of life-threatening medical conditions such as coronary artery disease, aortic dissection, and pulmonary embolism; however, it is not a common symptom of COVID-19.[4] Social restrictions and curfews forced people to remain in their homes and lead an inactive lifestyle. The effect of inactivity on the musculoskeletal system may have caused an increase in chest pain complaints.

The number of patients with pneumothorax presenting to the thoracic surgery clinic decreased during the COVID-19 pandemic. Pneumothorax is one of the rare complications of COVID-19.[5,6] However, the majority of COVID-19-related pneumothorax cases consist of patients under mechanical ventilation support in intensive care units. The development of pneumothorax in patients with COVID-19 under mechanical ventilation support is a poor prognostic factor, and often fatal.[7,8] The patients with a history of pneumothorax who were followed up in the thoracic surgery clinic reported that they did not want to come to the hospital during the pandemic because they were afraid of COVID-19 transmission.

The number of patients presenting with other diseases and conditions treated in the thoracic surgery outpatient clinic also decreased during the COVID-19 pandemic. This can be explained by the concern that these patients may be infected with COVID-19 during their hospital visits.

CONCLUSION

There has been a decrease in patient admissions due to trauma during the COVID-19 pandemic mostly as a result of curfews and restrictions.

However, there has been a significant increase in patients presenting with lung malignancies during the COVID-19 pandemic. The proportional increase in such patients presenting can be explained by the decrease in the number of admissions for other reasons. Furthermore, the increase is likely due to incidental diagnoses during thoracic computed tomography performed for COVID-19 diagnosis and follow-up.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethical approval for this study was obtained from the ethics committee of Ankara Bilkent City Hospital. Approval number is E1-21-2165.

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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Original Article / Orijinal Araştırma

Optic Nerve and Retinal Layer Measurements with Optical Coherence Tomography in PCR Positive and Negative COVID-19 Patients

PCR Pozitif ve Negatif COVID-19 Hastalarında Optik Koherens Tomografisi ile Optik Sinir ve Retinal Katman Ölçümleri

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Abstract

Aim: COVID-19 targets all tissue and organ systems, not just the lungs. The optic nerve and retina with extensive microvascular nutrition are prone to viral involvement. Optical coherence tomography is a technology that provides detailed information about both optic nerve and retinal structure. The study was carried out to investigate possible changes in the optic nerve and retinal structure of patients with COVID-19 infection, dividing PCR positivity or negativity.

Material and Method: Thirty PCR positive COVID-19 patients with different ages and varying admission complaints were included in the study. Twenty-five COVID-19 patients who were PCR negative with similar age and gender were selected as a secondary group for comparison. All patients underwent ophthalmologic examination, including slit-lamp biomicroscopy, funduscopy, and Optical Coherence Tomography (OCT). These examinations were performed four weeks after the diagnosis of COVID-19 for full compliance with the mandatory isolation. In addition, Retinal Nerve Fiber Layer Thickness (RNFL), retinal thickness, and retinal volume measurements were performed.

Results: No statistical significance was observed in any parameter between the PCR positive or negative patients when the comparative analysis for both eyes in RFNL measurements. There was a significant difference in retinal thickness measurements between the PCR positive and negative groups regarding left eye central retinal thickness (p=0.047). In addition, there was no statistical difference in retinal volume measurements.

Conclusion: Retinal imaging with optical coherence tomography is a non-invasive, reproducible, and rapid technique in which subclinical or overt retinal pathologies can be detected during COVID-19. Therefore, management of COVID-19 patients should include retinal assessment with close follow-up, especially in patients with headaches and optic pain.

Keywords: Optical coherence tomography, retinal nerve fiber layer thickness, COVID-19, optic nerve

Öz

Amaç: COVID-19 sadece akciğerleri değil tüm doku ve organ sistemlerini hedef almaktadır. Kapsamlı mikrovasküler beslenmeye sahip optik sinir ve retina viral tutuluma yatkındır. Optik koherens tomografi, hem optik sinir hem de retina yapısı hakkında detaylı bilgi veren bir teknolojidir. Çalışma, COVID-19 enfeksiyonu olan PCR pozitif ve negatif hastaların optik sinir ve retina yapısındaki olası değişiklikleri araştırmak amacıyla gerçekleştirilmiştir.

Gereç ve Yöntem: Çalışmaya farklı yaş ve farklı başvuru şikayetlerine sahip PCR pozitif 30 COVID-19 hastası dahil edildi. Benzer yaş ve cinsiyet grubundaki yirmi beş PCR negatif COVID-19 hastası karşılaştırma yapabilmek adına ikincil bir grup olarak tanımlandı. Tüm hastalara yarık lamba biyomikroskopisi, fundoskopi ve Optik koherens tomografi (OCT) dahil oftalmolojik muayene yapıldı. Bu muayeneler, zorunlu izolasyona tam uyum için COVID-19 tanısından dört hafta sonra yapıldı. Ayrıca Retina Sinir Lif Tabaka Kalınlığı (RNFL), retina kalınlığı ve retina hacmi ölçümleri yapıldı.

Bulgular: RNFL ölçümlerinde her iki göz için karşılaştırmalı analiz yapıldığında PCR pozitif COVID-19 hastaları ile PCR negatif grup arasında herhangi bir parametrede anlamlı fark gözlenmedi. Retina kalınlığı ölçümlerinde sol göz santral retina kalınlığı açısından PCR pozitif ve negatif gruplar arasında anlamlı fark vardı (p=0.047). Bununla birlikte, retina hacim ölçümlerinde istatistiksel bir fark yoktu.

Sonuç: Optik koherens tomografi ile retina görüntüleme, COVID-19 sırasında subklinik veya aşikar retina patolojilerinin tespit edilebildiği, invazif olmayan, tekrarlanabilir ve hızlı bir tekniktir. Bu nedenle COVID-19 hastalarının yönetimi, özellikle baş ağrısı ve oküler ağrısı olan hastalarda yakın takip ile retina değerlendirmesini içermelidir.

Anahtar Kelimeler: Optik koherens tomografi, retina sinir lif tabaka kalınlığı, COVID-19, optik sinir

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INTRODUCTION

COVID-19 is caused by SARS-COV-2, a novel beta coronavirus that has caused a life-threatening infection that has caused millions of deaths worldwide. SARS-COV2 uses a spike protein that binds directly with a strong affinity to human angiotensin-converting enzyme 2 (ACE2) to enter human cells.[1] Although the lungs are the primary site of involvement in COVID-19 infection, problems related to the disease have been detected in various organs. In the COVID-19 infection, which is still not prevented globally, optic surface disorders, mainly conjunctivitis, have been described in approximately 10% of patients.[2] However, little is known about how it affects the retina and the optic nerve as part of the central nervous system (CNS).[3] The human eye has its renin-angiotensin system, located not only on the eye's surface but also in the retina.[4] In addition, several human respiratory viruses (including coronavirus CoV) are neuroinvasive and neurotropic, with potential neuropathological consequences in vulnerable populations. The neurological symptoms seen in patients with viral infections are caused by what is known as a "cytokine storm", which includes pro-inflammatory and anti-inflammatory cytokines as an immune response to viral infection of the CNS. An exaggerated response to infection can lead to meningitis, encephalitis, meningoencephalitis, or death. The COVID-19 pandemic, caused by SARS-CoV 2, is a human respiratory virus that infects the respiratory tract and can cause pneumonia and respiratory failure similar to SARS-CoV, displaying neuroinvasive neurotropic abilities.[5] Optical coherence tomography (OCT) is a promising technology developed to evaluate tissue thickness in vivo, such as the retinal nerve fiber layer (RNFL). This technology was initially designed for fiberoptic use. OCT is a non-invasive imaging technique that obtains detailed retina images using low coherence light. It is a reliable and reproducible method for measuring retinal layers and detecting changes in layer thickness with high resolution.[6] This technique has been used successfully to monitor changes in retinal layers in several ophthalmological and neurological diseases such as glaucoma, multiple sclerosis, and Alzheimer's disease.[7,8] With a prototype instrument, OCT data was reported to correlate with the known topography of human retinas.[9] Reproducibility studies using an OCT prototype have shown standard distributions (SD) of measurement of RNFL and retinal thicknesses of approximately 10 to 20 µm (10%-20%) in normal and glaucomatous eyes.[10,11]

This study evaluated total, superior, and inferior peripapillary retinal nerve fiber layer thickness (RNFL), mean retinal thickness, central retinal thickness, and total retinal volume in COVID-19 patients according to PCR results. Thus, our study is the first in the literature that examines optic nerve and retina measurements according to PCR results in COVID-19 patients.

MATERIAL AND METHOD

Subjects

The study included 30 COVID-19 patients of different ages and admission complaints. The SARS-CoV-2 virus genetic material was detected by reverse transcriptase-polymerase chain reaction (RT-PCR) in the nasal swab sample. Twenty-five COVID-19 patients of similar age and sex who were PCR negative were selected as a secondary comparison group. The PCR positive group was formed by patients with COVID-19 who presented in the hospital's Emergency Department (ED) and successfully recovered from the infection between 23 and 29 March 2020. Inclusion criteria were: 18 to 70 years old; SARS-CoV-2 infection was confirmed by a positive reverse transcriptase-polymerase chain reaction (RT-PCR) test from a nasopharyngeal swab and written informed consent. The PCR negative group consisted of patients diagnosed with COVID-19 by clinical examination and lung tomography but did not have SARS-CoV-2 virus in the swab test. Those who had ongoing symptoms were in quarantine, could not go to the hospital due to their general health condition, and had accompanying psychiatric, neurological, or eye diseases were excluded from the study. The individuals volunteered for the study by signing the informed consent form. After the pre-approval from the study by the Republic of Turkey Ministry of Health, ethical approval was obtained from the Amasya University Ethical Board with 13.09.2021-32307 date and number.

Ophthalmologic Exam and Optic Nerve Imaging

All patients underwent ophthalmologic examination, including slit-lamp biomicroscopy, funduscopy, and OCT. These examinations were performed four weeks after the diagnosis of COVID-19 for full compliance with the mandatory isolation. RNFL, retinal thickness, and retinal volume measurements were performed with the Topcon 3D 2000 (3D OCT 2000, Topcon Corporation, Tokio, Japan) OCT device. All peripapillary RNFLT measurements were made using a circular scan pattern centered on the optic nerve. The eye-tracking system allowed any subsequent OCT scan to be scanned precisely at the exact location as the last scan. The OCT software calculated the average RNFLT for the overall global (360 degrees). RNFL measurements were noted globally and in the three quadrants (superior, inferior, total). A single experienced physician carried out all OCT examinations.

Statistics

Data analysis was performed using SPSS version 24.00 (IBM, New Castle, NY, USA). Continuous variables were used as mean and standard deviation (SD), while numbers and percentages were used for categorical variables. Age and gender differences between the groups were compared using the Chi2 and t-student tests. The normality of the variables was evaluated using the Kolmogorov-Smirnov test. Student t-test was used for group comparisons of OCT measurements. Statistical significance was determined as 0.05.

RESULTS

While 43.3% of the PCR positive were women, the mean age group was 46.6±18.2. While 46.6% of the PCR negative group were women, the mean age was 47.3±15.9 years. There was no difference between the groups regarding age and gender (p=0.648 and p=0.716, respectively). No statistical significance was observed in any parameter between the PCR positive and negative patients when the comparative analysis for both eyes in RFNL measurements (**Table 1**).

Table 1. Peripapillary optical coherence tomography (OCT) results in Polymerase Chain Reaction (PCR) positive and negative COVID-19 patients.

Optic Nerve OCT (µm)	PCR positive (n=30)		PCR negative (n=25)		p value
	Mean	SD	Mean	SD	
Rnfl Total - Right	96.2	10.8	93.1	9.9	0.234
Rnfl Total - Left	99.1	8.0	93.3	8.4	0.116
Rnfl Superior - Right	115.5	13.9	103.5	14.4	0.432
Rnfl Superior - Left	116.8	11.7	101.6	11.9	0.537
Rnfl Inferior - Right	116.8	16.1	106.8	16.5	0.678
Rnfl Inferior - Left	123.6	17.1	107.9	17.8	0.719

SD: standard deviation; Rnfl: retinal nerve fiber layer.

There was a significant difference in retinal thickness measurements between the PCR positive and negative groups regarding left eye central retinal thickness (p=0.047). However, there was no statistical difference in retinal volume measurements (**Table 2**).

Table 2. Retinal thickness and volume measurements of Polymerase Chain Reaction (PCR) positive and negative COVID-19 patients.

Optical Coherence Tomography Measurements	PCR + (n=30)		PCR - (n=25)		p value
	Mean	SD	Mean	SD	
Average Retinal Thickness - Right (µm)	272.0	14.5	273.7	12.3	0.301
Average Retinal Thickness - Left (µm)	272.5	15.1	273.5	11.8	0.128
Central Retinal Thickness - Right (µm)	192.6	25.6	191.7	28.3	0.237
Central Retinal Thickness - Left (µm)	202.7	27.5	189.9	22.8	0.047
Total Retinal Volume - Right (µm3)	7.69	0.41	7.56	0.3	0.431
Total Retinal Volume - Left (µm3)	7.71	0.42	7.56	0.3	0.381

SD: standard deviation. +: positive, -: negative.

DISCUSSION

The retinal manifestations of COVID-19 infection are interesting. For example, one study reported fine cotton wool spots and focal hyperreflective areas on the inner retina in a small number of patients with confirmed COVID-19 infection.[12] On the other hand, another study suggested that hyperreflective areas on OCT scans may represent normal retinal vessels, and cotton wool spots may represent myelinated nerve fiber layer or be associated with other retinal pathologies.[13] Thus, these studies have shown that coronaviruses can induce a variety of retinal pathologies.

Table 3. Statistical data of RNFL and retinal measurements by PCR positive and negative group.

Variable	N	N*	Mean	SE Mean	StDev	Minimum	Q1	Median	Q3	Maximum
C RNFL T R	25	5	93.08	2.02	10.12	62.00	90.00	95.00	100.00	104.00
C RNFL T L	25	5	93.32	1.71	8.56	73.00	87.00	95.00	99.00	112.00
C RNFL S R	25	5	103.48	2.95	14.73	65.00	92.50	105.00	113.50	125.00
C RNFL S L	25	5	101.64	2.44	12.19	70.00	93.00	101.00	110.50	127.00
C RNFL I R	25	5	106.84	3.37	16.84	71.00	96.50	105.00	121.50	136.00
C RNFL I L	25	5	107.88	3.64	18.21	66.00	96.00	107.00	125.00	136.00
C ART R	25	5	273.67	2.51	12.55	246.60	264.15	276.20	281.25	298.50
C ART L	25	5	273.47	2.41	12.06	248.70	264.70	275.00	280.70	294.30
C CRT R	25	5	191.72	5.78	28.89	164.00	175.00	184.00	192.00	282.00
C CRT L	25	5	189.92	4.65	23.24	169.00	176.50	183.00	194.50	282.00
C TRV R	25	5	7.5576	0.0620	0.3102	6.9700	7.3050	7.5400	7.7800	8.2900
C TRV L	25	5	7.5624	0.0562	0.2811	7.0300	7.4000	7.5000	7.7600	8.2800
P RNFL T R	30	0	96.23	2.00	10.95	76.00	89.75	94.00	105.25	119.00
P RNFL T L	30	0	99.10	1.49	8.15	84.00	93.00	98.50	105.25	114.00
P RNFL S R	30	0	115.50	2.58	14.13	85.00	108.75	116.00	123.75	143.00
P RNFL S L	30	0	116.80	2.17	11.87	90.00	108.50	115.50	128.00	137.00
P RNFL I R	30	0	116.77	3.00	16.42	85.00	101.00	121.00	129.25	144.00
P RNFL I L	30	0	123.60	3.17	17.34	83.00	112.75	124.50	134.25	161.00
P ART R	30	0	271.97	2.68	14.70	243.20	258.73	272.20	281.38	298.90
P ART L	30	0	272.46	2.80	15.31	238.40	258.65	275.40	283.73	300.00
P CRT R	30	0	192.60	4.76	26.05	158.00	176.00	186.50	203.75	272.00
P CRT L	30	0	202.73	5.11	27.99	164.00	183.75	192.50	224.75	295.00
P TRV R	30	0	7.6887	0.0758	0.4153	6.8800	7.3125	7.7000	7.9525	8.4500
P TRV L	30	0	7.7090	0.0775	0.4243	6.7400	7.3275	7.7850	8.0225	8.4800

C: PCR negative, P: PCR positive, RNFL: retinal nerve fiber layer, ART: average retinal thickness, CRT: central retinal thickness, TRV: total retinal volume, T: total, S: superior, I: inferior, R: right eye, L: left eye, SE: standard error, StDev: standard deviation.

However, our study did not observe subtle or prominent central or peripheral retinal findings, such as vascular abnormalities or cotton wool spots determined by OCT scans. In addition, many studies have reported that ophthalmologic results and retinal findings are associated with the severity of COVID-19 infection.[14,15] However, retinal manifestations such as hemorrhages, cotton swabs, and vascular changes appear time-dependent.[16,17] One research found macular RNFL thickness in patients recovering from COVID-19 compared to healthy subjects.[18] Another study also showed localized thinning of RNFL in patients with COVID-19.[19] In contrast, our study could not observe a different outcome in COVID-19 patients regarding RNFL. Involvement of the inner retinal layers has been reported using OCT in multiple neurodegenerative diseases. Braak's hypothesis regarding its etiology in Parkinson's is that a neurotropic virus invades the nervous system. Interestingly, the preclinical phase of Parkinson's may present olfactory and gastrointestinal symptoms similar to COVID-19.[20] Peripapillary RNFLT and retinal thickness are thinner due to nerve damage in OCT of Parkinson's patients.[21-23] Also, multiple sclerosis can be triggered by an infectious agent, the most likely cause being a virus. Animal models explain that the best method of inducing neuroinflammation is intracranial grafting, which leads to optic nerve inflammation.[24] However, we could not detect the expected changes in retinal thickness and volume measurements in the light of these studies. The most important thing is that positive or negative PCR results did not differentiate the measures. The clinical diagnosis of COVID-19 may be why OCT results are similar. In addition, the fact that we did not distinguish between patient groups and patients in terms of disease severity, although we conducted clinical studies on mild and healed patients, may explain our results.

CONCLUSIONS

This study did not show convincing evidence that SARS-CoV-2 can cause changes in RNFL measurements, retinal thickness, and volume, contrary to literature data. Nevertheless, retinal imaging with optical coherence tomography is a non-invasive, reproducible, and rapid technique in which subclinical or overt retinal pathologies can be detected during COVID-19. Therefore, management of COVID-19 patients should include retinal assessment with close follow-up, especially in patients with headaches and optic pain. The results of studies like this may highlight the pathophysiology of COVID-19, especially in optic involvement with neurological symptoms. However, for a meaningful assessment of the optic nerve and retinal measurements in COVID-19 patients, it is essential to evaluate the clinical course of both the control groups consisting of healthy individuals and the clinical course. In addition, future studies are needed to assess whether these changes in the retinal layers of COVID-19 have lasting and long-term effects.

Limitations

The clinical features of the patients included in this study, such as the relatively long post-COVID time until OCT images are captured, no need for hospitalization during the COVID period, or somewhat mild to moderate COVID symptoms, may reflect disease severity and less severe COVID-19. Conversely, our cases' infection severity and duration may explain the absence of these retinal findings. In addition, the inability to include the control group in our study limited our ability to compare with healthy individuals.

ETHICAL DECLARATIONS

Ethics Committee Approval: After the pre-approval from the study by the Republic of Turkey Ministry of Health, ethical approval was obtained from the Amasya University Ethical Board with 13.09.2021-32307 date and number.

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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Original Article / Orijinal Araştırma

Investigating the Hepatitis E Seroprevalence Rates Among Hemodialysis Patients in Turkey with Pool Analyses Method

Türkiye'deki Hemodiyaliz Hastalarında Hepatit E Seroprevalans Oranlarının Havuz Analizi Yöntemi ile Araştırılması

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Abstract

Objectives: Hepatitis E virus (HEV) is a worldwide public health problem that affects both poor and developed countries. Hemodialysis (HD) patients have been reported to be at risk for HEV infection due to the likelihood of parenteral and/or nosocomial transmission. The goal of this study was to analyze studies on HEV seroprevalence rates among hemodialysis patients and to highlight differences in disease seroprevalence between geographic regions.

Material and Method: Published literature in English and Turkish language (full text articles or detailed abstracts) on HEV seroprevalence among hemodialysis patients from Turkey were elavuated. Google Scholar, Pubmed, the Scopus, ULAKBIM TR Dizin and the Web of Science databases were scanned by using the keywords " hepatitis E virus " or " HEV " and " hemodialysis patient " or " hemodialysis " and " seroprevalence" or "IG G" and "Turkey"or "Turkish". The publications were assessed based on their general frequency, location, region and year.

Results: The published literature on HEV seroprevalence among Turkish hemodialysis patients in both English and Turkish was reviewed. Only 11 articles were found according to the search criteria. Most of the studies (27.27%) were from the Southeast Anatolia Region. There were no studies from the Marmara and Eastern Anatolia regions. The regional seroprevalence of HEV among hemodialysis patients was highest in the Central Anatolia region (23.43%) and in the Southeastern Anatolia region (21.26%), and lowest in the Aegean region (5.95%). No studies were found in the literature search for the Marmara and Eastern Anatolia regions.

Conclusion: The median of HEV seroprevalence rate was found as 17.62% in this study. The studies were limited, and it is necessary to increase the number of publications on HEV seroprevalence in risky groups from our country.

Keywords: HEV, Hepatitis E virüs, hemodialysis

Öz

Amaç: Hepatit E virüsü (HEV), hem yoksul hem de gelişmiş ülkeleri etkileyen dünya çapında bir halk sağlığı sorunudur. Hemodiyaliz (HD) hastalarının parenteral ve/veya hastane kaynaklı bulaşma olasılığı nedeniyle HEV enfeksiyonu riski altında olduğu bildirilmiştir. Bu çalışmanın amacı, hemodiyaliz hastaları arasındaki HEV seroprevalans oranlarına ilişkin çalışmaları analiz etmek ve coğrafi bölgeler arasındaki hastalık seroprevalansındaki farklılıkları vurgulamaktı.

Gereç ve Yöntem: Türkiye'den hemodiyaliz hastalarında HEV seroprevalansı hakkında İngilizce ve Türkçe yayınlanmış literatür (tam metin makaleler veya ayrıntılı özetler) ele alındı. Google Scholar, Pubmed, the Scopus, ULAKBİM TR Dizin ve Web of Science veri tabanları " hepatit E virüsü " veya " HEV " ve " hemodiyaliz hastası " veya " hemodiyaliz " ve " seroprevalans " veya " IG G " ve "Türkiye" veya "Türk" anahtar kelimeleri kullanılarak tarandı. ". Yayınlar genel sıklık, yer, bölge ve yıl bazında değerlendirildi.

Bulgular: Türk hemodiyaliz hastalarında HEV seroprevalansı hakkında hem İngilizce hem de Türkçe yayınlanmış literatür gözden geçirildi. Arama kriterlerine göre sadece 11 makale bulundu. Araştırmaların çoğu (%27,27) Güneydoğu Anadolu Bölgesi'nden yapılmıştır. Marmara ve Doğu Anadolu bölgelerinden herhangi bir çalışma yapılmamıştı. Hemodiyaliz hastalarında bölgesel HEV seroprevalansı en yüksek İç Anadolu bölgesinde (%23.43) ve Güneydoğu Anadolu bölgesinde (%21.26), en düşük ise Ege bölgesinde (%5.95) bulundu. Marmara ve Doğu Anadolu bölgeleri için yapılan literatür taramasında herhangi bir çalışmaya rastlanmadı.

Sonuç: Bu çalışmada HEV seroprevalans oranı ortancası %17,62 olarak bulundu. Çalışmalar sınırlı olup, ülkemizden riskli gruplarda HEV seroprevalansı ile ilgili yayınların arttırılması gerekmektedir.

Anahtar Kelimeler: HEV, Hepatit E virüs, hemodiyaliz

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INTRODUCTION

Hepatitis E virus (HEV) is a small, non-enveloped virus with a single-stranded ribonucleic acid (RNA) genome. It is classified in the Hepevirus genus and the Hepeviridae family. Among the eight different HEV genotypes, HEV1, HEV2, HEV3, HEV4 and the recently reported HEV7 are mainly responsible for human infection.[1,2] HEV is one of the viruses that can cause liver disease and is spread via the fecal-oral or transplacental routes. However, the data obtained in recent years have revealed that the virus is zoonotic, and that parenteral and vertical transmission may even be possible.[3,4] Although rare in developed countries, HEV infection is common in developing countries.[3] HEV is most often caused by insufficient clean water supply and is seen in developing countries with poor environmental cleanliness.[4] HEV infection is a worldwide public health problem that affects both poor and developed countries. World Health Organization has estimated that 20 million HEV infections occur each year in the world, and the HEV infection had caused 44 000 deaths in the year 2015.[5] It is endemic to Asia, the Middle East, Africa, and Central America. HEV outbreaks involving large numbers of people have been reported in several regions.[4] Despite this HEV is still poorly understood, and clinicians routinely overlook this or misdiagnose this infection.[6] In endemic and nonendemic locations across the globe, clinical manifestation, source of infection, and route of exposure differ depending on HEV genotype and epidemiology. The presentation, diagnosis, prognosis, and natural history of HEV infection might be acute or chronic, further confusing the presentation, prognosis, diagnosis, and natural history of illness. Correct identification and diagnosis of HEV, on the other hand, has significant implications for patient care, disease control, preventative efforts, and the characterisation of transmission pathways and epidemiology.[4,6] The previous studies on anti-HEV seropositivity from Turkey indicate that the frequency of HEV infection is increasing.[4] It has been reported that hemodialysis (HD) patients are at risk for HEV due to the possibility of parenteral and/or nosocomial transmission.[7,8]

The goal of this study was to use the pool analysis approach to analyze studies on HEV seroprevalence rates among hemodialysis patients and to highlight differences in disease seroprevalence between geographic regions.

MATERIAL AND METHOD

Published literature in English and Turkish language (full text articles or detailed abstracts) on HEV seroprevalence among hemodialysis patients from Turkey were elavuated.

Google Scholar, Pubmed, the Scopus, ULAKBIM TR Dizin and the Web of Science databases were scanned by using the keywords " hepatitis E virus " or " HEV " and " hemodialysis patient " or " hemodialysis " and " seroprevalence" or "IG G" and "Turkey"or "Turkish".

The articles were assessed based on their general frequency, location, region and year.

The data obtained were analyzed using Statistical Package for the Social Sciences (SPSS) for Windows Version 23.0 software (SPSS Inc., Chicago, IL, USA). Data were reported as mean ± standard deviation values, number, and percentage. Descriptive statistics were used in the statistical evaluation.

To estimate the seroprevalence of HEV among HD patients, the pooled method was used and the simple mapping method for visualization.

Ethics approval: Ethics committee approval is not necessary since the literature research work was used in the research. The study was carried out in accordance with the principles of the 2013 revised Helsinki Declaration.

RESULTS

The published literature on HEV seroprevalence among Turkish hemodialysis patients in both English and Turkish was reviewed. Only 11 articles were found according to the search criteria. Most of the studies (27.27%) were from the Southeast Anatolia Region. There were no studies from the Marmara and Eastern Anatolia regions (**Table 1**).

Table 1. Studies according to geographical regions in Turkey (n=11) (9-19).

Geographical region	n	%
Aegean	2	18.18
Marmara	0	0
Eastern Anatolia	0	0
Central Anatolia	3	27.27
Mediterranean	2	18.18
Black Sea	1	9.09
Southeast Anatolia Region	3	27.27

The regional seroprevalence of HEV among hemodialysis patients was highest in the Central Anatolia region (23.43%) and in the Southeastern Anatolia region (21.26%), and lowest in the Aegean region (5.95%). No studies were found in the literature search for the Marmara and Eastern Anatolia regions (**Figure 1**). The median of HEV seroprevalence rate was found as 17.62% in this study.

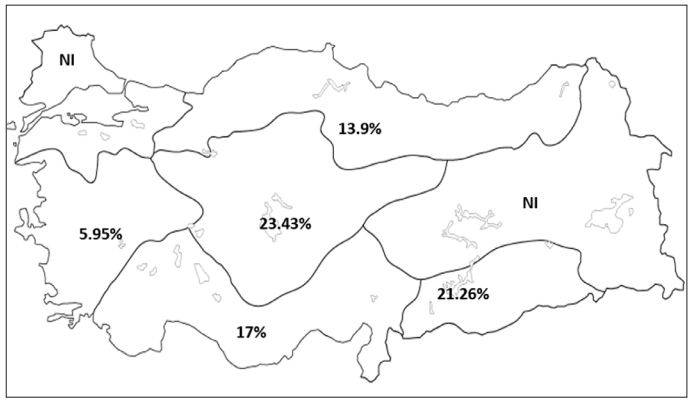

Figure 1. Hepatitis E seroprevalence rates among hemodialysis patients in Turkey.

The most of the publications (63.64%) were published before the 2000s (**Table 2**).

Table 2. Studies according to the publication years (n=11).

Publication year	n	%
1990-2000	7	63.64
2001-2010	2	18.18
After 2011	2	18.18

DISCUSSION

Hepatitis and human immunodeficiency viruses are the most frequent bloodborne viral infections in HD units and the general population, respectively.[7] HEV seroprevelance rates are known to be higher in some risky groups, such as hemodialysis patients. This may be due to many blood changes or invasive procedures. HEV Infection is a growing health concern among these patients. To date, numerous studies have been undertaken around the world to explore the seroprevalence of HEV among hemodialysis patients, however the results are inconsistent.[4,20]

Haffar et al.[21] did a meta-analysis that found a link between HD and HEV seroprevalence. According to their findings, HD patients had a higher seroprevalence of HEV compared to non-HD controls (OR 2.47, 95 percent CI: 1.79-3.40, I2=75.2 percent, P.01). Several risk factors for HEV infection in HD patients have been discovered in another review study by Hosseini-Moghaddam et al.[22] including older age, living in rural vs. urban regions, low education, and HD duration.

Also the limited number of studies were published from Turkey.[4] This study aimed to analyze the HEV seroprevalence rates among hemodialysis patients according to geographic regions.

Although studies have been carried out in different risk groups in various studies, the highest HEV seropositivity rates were found in the Eastern Anatolia Region.[4] But it was found that in this study, most of the studies (27.27%) were from the Southeast Anatolia Region. There were no studies from the Marmara and Eastern Anatolia regions. The regional seroprevalence of HEV among hemodialysis patients was highest in the Central Anatolia region (23.43%) and in the Southeastern Anatolia region (21.26%).

The HEV seroprevalence found in this study is lower (17.62%), than those observed in hemodialysis patients in other countries (68.9 % in Sudan, 39.6 % in Egypt, 36.8 % in England, 30% in Japan; but higher than 10.2 percent in Tunisia (10.2%) and in Italy (6%).[20]

The seroprevalence studies in high-risk populations can assist determine whether the HEV vaccine is needed in our country and, if so, which groups should be immunized. Immunization is an effective and safe method of preventing infectious diseases in general, and HEV infection is no exception. There is presently no the Food and Drug Administration (FDA)-approved HEV vaccine.

CONCLUSION

It is necessary to increase the number of publications on HEV seroprevalence in risky groups from our country.

Limitation: There were limited studies in this study.

ETHICAL DECLARATIONS

Ethics Committee Approval: There is no need as it is a document study.

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

The Clinical Significance of Shock Index and GFR in the Differential Diagnosis of Perforated Appendicitis

Şok İndeksi ve GFR'nin Perfore Apandisit Ayırıcı Tanısındaki Klinik Önemi

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Abstract

Aim: The aim of the study is to investigate whether the shock index (SI) and glomerular filtration rate (GFR) have significance in differentiating acute appendicitis from complicated perforated acute appendicitis.

Material and Method: Patients were searched retrospectively on the hospital database. Age, gender, C-reactive protein (CRP), leukocyte (WBC), total bilirubin (T.BIL), urea, creatinine, pulse , and arterial blood pressure (TA) values of the patients were searched retrospectively on the hospital database and a database was created by using these patient variables. GFR and SI were calculated by using these data. The shock index (SI), calculated by dividing heart rate by systolic blood pressure. The surgical notes about patients were reviewed retrospectively, and they were divided into two groups, namely perforated appendicitis and non-perforated appendicitis. The data were analyzed to investigate whether GFR and SI were effective in predicting perforation.

Results: It was observed that Pulse/TA (shock index) (SI) value had more frequent pathological findings in patients with perforated appendicitis (p<0.001). It was found that age (p=0.001), CRP (p<0.001), WBC (p<0.001), T. BIL (p=0.002), Pulse (p=0.017), and SI (p<0.001) values of the patients in the perforated appendicitis group were higher than those of the patients in the normal appendicitis group, while GFR (p<0.001) and TA (p<0.001) values were lower (p<0.05).

Conclusion: It is thought that SI and GFR may be a prognostic parameter for showing both perforation and the associated increased mortality rate.

Keywords: Shock index, perforated appendicitis, abdominal pain

Öz

Amaç: Çalışmanın amacı akut apandisit ile komplike olmuş perfore akut apandisit ayırımında şok indeksinin (SI) ve glomerüler filtrasyon hızı (GFR)'nin öneminin olup olmadığı araştırılmasıdır.

Gereç ve Yöntem: Hastalar hastane veri tabanı kullanılarak retrospektif olarak taranmıştır. Hastaların yaş, cinsiyet, C-reaktif protein (CRP), lökosit (WBC), total bilirubin (T.BİL), üre, kreatinin, nabız (NBZ), arteryal tansiyon (TA) değerleri hastane kayıt sisteminden geriye dönük taranmış ve veri tabanı oluşturulmuştur. Bu veriler kullanılarak GFR ve SI hesaplanmıştır. Şok İndeksi nabız sayısının sistolik kan basıncına bölünmesiyle bulunmuştur. Hastaların ameliyat notları retrospektif olarak incelenmiş ve hastalar perfore apandisit ve perfore olmayan apandisit olarak iki gruba ayrılmıştır. Veriler analiz edilerek GFR ve SI'nin perforasyonu öngörmede etkili olup olmadığı araştırılmıştır.

Bulgular: Perfore apandisit hastalarında NBZ/TA değerinin daha sık patolojik bulguya sahip olduğu gözlenmiştir (p<0,001). Perfore apandisit grubunda yer alan hastaların Yaş (p=0,001), CRP (p<0,001), WBC (p<0,001), T. BİL (p=0,002), NBZ (p=0,017) ve NBZ/TA (p<0,001) değerlerinin normal apandisit grubunda yer alan hastalara göre daha yüksek; GFR (p<0,001) ve TA (p<0,001) değerlerinin ise normal apandisit grubunda yer alan hastalara göre daha düşük olduğu gözlenmiştir (p<0,05).

Sonuç: SI'nin ve GFR'nin hem perforasyonu hem de buna bağlı artan mortalite oranını göstermede prognostik bir parametre olabileceği düşünülmektedir.

Anahtar Kelimeler: Şok indeksi, perfore apandisit, karın ağrısı

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INTRODUCTION

Acute abdominal pain accounts for about 10% of emergency department admissions. Acute appendicitis (AA) is among the most common causes of these admissions.[1] Although it has well-known symptoms such as right lower quadrant pain and loss of appetite, early diagnosis can be difficult in some cases.[2] Although physical examination (PM), ultrasonography (USG), computed tomography (CT), and diagnostic laparoscopy are methods used in diagnosis, they are known to be costly.[3] Scoring systems, such as Alvarado, RIPASA, Fenyo, Tzakis, and Eskelinen, have been developed to assist diagnosis. Although these scoring systems have been developed to aid diagnosis, their sensitivity and specificity are low.[4,5] Failure to detect AA early has been associated with significant morbidity and mortality. While mortality is 0.1% in non-perforated AA cases, it has been reported as 5% in perforated AA.[6] For this reason, various blood tests and their combinations have been used recently to determine the diagnosis and severity of appendicitis. While leukocyte (WBC), C-reactive protein (CRP), and bilirubin are the most commonly used blood tests, CRP was found to be superior to others in predicting perforation.[7] Inflammation markers, such as platelet/lymphocyte ratio (PLR), neutrophil/lymphocyte ratio (NLR), and delta neutrophil index (DNI), have also been introduced recently, and it has been emphasized that they may be important in the diagnosis and prognosis of AA.[8,9] The shock index (SI), calculated by dividing heart rate by systolic blood pressure, is known as an estimator for hemodynamic stability and is widely used to predict mortality and morbidity in various diseases, especially under shock conditions.[10] Low glomerular filtration rate has been associated with increased complication rates in many cases.[11]

This study was conducted to investigate the significance of shock index and GFR in differentiating acute appendicitis from complicated perforated acute appendicitis.

MATERIAL AND METHOD

The approval of the Balıkesir University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee was obtained for the study (date: January 26, 2022; decision number: 2022/009). In the study, 158 patients who underwent an operation with the diagnosis of acute appendicitis in the Department of General Surgery, Faculty of Medicine, Balıkesir University between the dates of 2019-2021 were examined retrospectively.

Data Collection and Patient Selection

A total of 158 patients who were admitted to the emergency department with abdominal pain and underwent an operation for acute appendicitis were included in the study. Age, gender, CRP, WBC, total bilirubin (T.BIL), urea, creatinine, pulse , and arterial blood pressure (TA) values of patients were retrospectively searched on the hospital database system and a database was created. GFR and SI were calculated using these data. The surgical notes of patients were reviewed retrospectively, and they were divided into two groups, namely perforated appendicitis and non-perforated appendicitis. The data were analyzed to find out whether GFR and SI were effective in predicting perforation.

Statistical Analysis

The SPSS (Statistical Package for the Social Sciences) 25.0 software package was used for statistical analysis of the data. Categorical measurements were summarized as numbers and percentages, and continuous measurements as mean and standard deviation values (median and 95% CI values where appropriate). Shapiro-Wilk test was used to determine whether the parameters in the study showed a normal distribution. Chi-square and Fisher's exact tests were employed to compare categorical expressions. Mann-Whitney U test was used for the parameters that did not show normal distribution. The predictive diagnostic value of the Pulse/TA levels of patients included in the study in terms of normal and perforated appendicitis groups was analyzed by ROC curve analysis. According to the findings, the area under the ROC curve for Pulse/TA was 0.759 (95% confidence interval (CI): 0.685-0.823; p<0.001). The Pulse/TA cut-off (threshold) value of the patients in terms of groups was 0.87 (specificity: 87.23%, 95% CI: 74.3-95.2, sensitivity: 61.26%, 95% CI: 51.5-70.4) (**Table 1**, **Figure 1**). The level of statistical significance was taken as 0.05 in all tests.

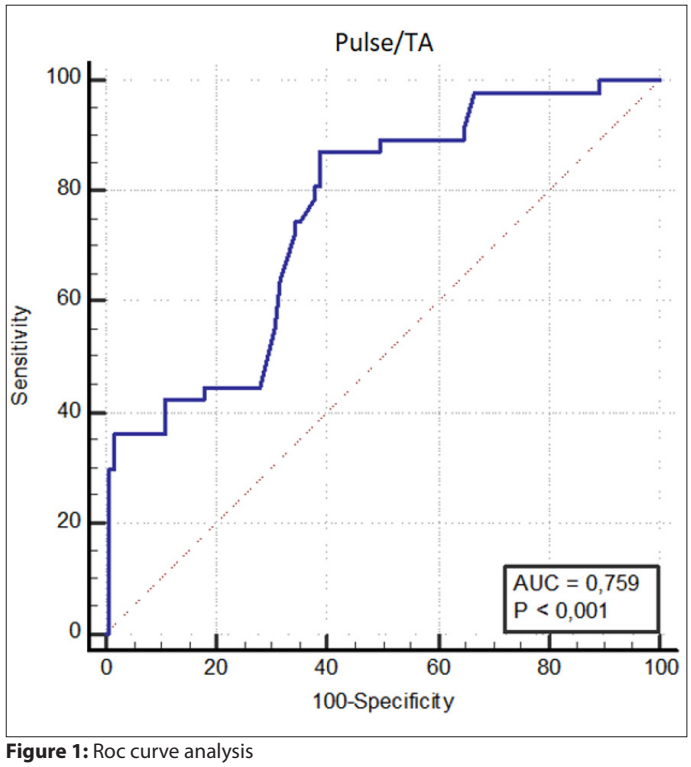

Figure 1: Roc curve analysis

Table 1. Roc curve analysis

	Pulse/TA
AUC (95%-CI (%))	0.759 (0.685-0.823)
Cut-off	>0.87
Sensitivity (%)(95%-CI (%))	87.23 (74.3-95.2)
Specificity (95%-CI (%))	61.26 (51.5-70.4)
PPV (95%-CI (%))	48.8 (42.4-55.2)
NPV (95%-CI (%))	91.9 (84.1-96.0)
P	<0.001

* p<0,05, **p<0,001, Roc curve test

RESULTS

The mean age ± standard deviation (mean±sd) of all patients included in the study was 42.5±17.5 and it was 50.1±19.7 in the perforated appendicitis group, and 39.2±15.5 in the normal appendicitis group. Age was significantly higher in the perforated appendicitis group (p=0.001). There were 23 female (48.9%) and 24 male (51.1%) patients in the perforated appendicitis group, and 43 female (38.7%) and 68 male (61.3%) patients in the normal appendicitis group. There was no gender-based differences between the groups (p=0.235). It was found that the incidence of perforation was higher in patients with a high shock index that was calculated by dividing the pulse rate by systolic blood pressure (p<0.001). Similarly, CRP (p<0.001), WBC (p<0.001), T.BIL (p=0.002), and pulse (p=0.017) values were found to be significantly higher in the perforated appendicitis group in the normal appendicitis group. On the contrary, GFR (p<0.001) and TA (p<0.001) values were observed to be lower in the perforated appendicitis group than in the normal appendicitis group (**Table 2**).

When the factors affecting the Pulse/TA (Shock Index) ratio were examined, it was found that it affected the shock index of only patients with perforated appendicitis by 7.97 times (OR: 7.971, 95% CI: 2.536-25.052), and that other parameters had no effect (p<0.001) (**Table 3**).

Table 3. Factors affecting the Shock Index

	p	Effect size (OR)	95% Confidence Interval	
			Lowest	Highest
Age	0.489	0.991	0.965	1.017
Gender (1)	0.702	1.187	0.493	2.860
Normal appendicitis		1.000		
Perforated appendicitis	<0.001	7.971	2.536	25.052
CRP	0.562	0.997	0.987	1.007
WBC	0.344	1.064	0.936	1.208
T.BIL/100	0.688	0.809	0.287	2.282
CREATININE /100	0.501	3.829	0.077	190.246
UREA	0.455	1.019	0.969	1.072
GFR	0.981	1.000	0.969	1.032
Constant	0.691	0.273		

Variable(s) entered on step : Age, Gender, Normal appendicitis, Perforated appendicitis, CRP, WBC, T.BIL/100, CREATININ/100, UREA, GFR
CRP:C reactive protein, WBC:Leukocytes, T.BIL:Total Bilirubin, GFR: Glomerularfiltration rate, TA: Arterial Blood Pressure,

Table 2. Evaluation of clinical and demographic data

	Normal appendicitis (n=111)	Perforated appendicitis (n=47)	Total (n=158)	p
	n(%)	n(%)	n(%)	
Gender				
Male	68 (61.3)	24 (51.1)	92 (58.2)	0.235[c]
Female	43 (38.7)	23 (48.9)	66 (41.8)	
Pulse/TA (Shock Index) (SI)				
<0.87 normal	69 (62.2)	9 (19.1)	78 (49.4)	<0.001**.[c]
≥0.87 pathological	42 (37.8)	38 (80.9)	80 (50.6)	
	Normal appendicitis (n=111)	**Perforated appendicitis (n=47)**	**Total (n=158)**	**p**
	Mean±sd Med (%95 CI)	**Mean±sd Med (%95 CI)**	**Mean±sd Med (%95 CI)**	
Age	39.2±15.5 35.5 (32-41)	50.1±19.7 54 (42-60)	42.5±17.5 40 (35-44.95)	0.001**.[b]
CRP	20.9±23.6 12 (8-14)	88.3±63.4 80 (45-109)	41.1±50.3 18 (12-23)	<0.001**.[b]
WBC	11.3±2.7 11 (11-11.3)	13.8±3.5 13 (12-14.5)	12.1±3.2 0.63 (0.59-0.7)	<0.001**.[b]
T. BIL	0.65±0.33 0.6 (0.54-0.64)	0.84±0.39 0.8 (0.66-0.9)	0.71±0.36 0.86 (0.85-0.88)	0.002**.[b]
CREATININE	0.86±0.13 0.86 (0.85-0.87)	0.93±0.25 0.88 (0.78-1.0)	0.88±0.17 25 (23-26)	0.354[b]
UREA	25.5±6.9 25 (23-26)	31.1±17.2 27 (24-31)	27.2±11.2 102 (99-104)	0.077[b]
GFR	105.7±15.6 105 (102.5-107.5)	87.1±22.1 90 (82-96)	100.2±19.7 102 (99-104)	<0.001**.[b]
TA	106.4±9.6 105 (105-110)	93.8±9.6 94 (90-96)	102.6±11.2 100 (100-105)	<0.001**.[b]
Pulse	88.9±8.4 90 (88-90)	93.0±6.7 90 (90-94)	90.2±8.1 90 (90-90)	0.017*.[b]
Shock Index (SI)	0.84±0.14 0.84 (0.78-0.87)	1.0±0.16 0.93 (0.91-1.06)	0.89±0.16 0.90 (0.87-0.91)	<0.001**.[b]

* p<0,05, **p<0,001, [b]: Mann-Whitney-U test, [c]: chi-square and Fisher Exact test, sd: standard deviation, Med: median, %95 CI: %95 confidence interval. CRP: C reactive protein, WBC: Leukocyte, T.BIL: Total Bilirubin, GFR: Glomerularfiltration rate, TA: Arterial Blood Pressure,

DISCUSSION

Early detection of acute appendicitis can prevent negative consequences such as perforation, which can be associated with significant morbidity and even mortality. Studies on biomarkers used in addition to clinical findings and imaging methods are used to help diagnose patients with suspected appendicitis, especially in children, women with pregnancy, and elderly patients.[12,13] Recently, there has been an increasing trend in non-surgical treatment methods in patients whose AA cannot be diagnosed clearly or in selected patient groups.[14] Antibiotic treatment or endoscopic retrograde appendicitis therapy (ERAT) are some of these treatments.[15] Non-surgical treatment modalities are considered especially in uncomplicated AA cases. Therefore, it has become important to distinguish perforated appendicitis cases from normal appendicitis cases. It is known that WBC values mostly increase in cases of acute appendicitis, but it has been emphasized that they do not have a predictive significance in differentiating normal appendicitis from complicated appendicitis. Similarly, the serum bilirubin value has also been shown to be a potential biomarker for perforated appendicitis, but it has been stated that it does not have enough sensitivity and specificity. CRP, on the other hand, was found to be superior to bilirubin.[7,16,17] In our study, WBC, CRP and blood bilirubin levels were found to be significantly higher in perforated appendicitis, which is consistent with previous studies. The SI calculated by dividing heart rate by systolic blood pressure has been used to predict adverse outcomes in hemorrhagic shock and cardiovascular, pulmonary, and neurological diseases.[10,18] In the pulmonary embolism study, in which the cut-off value was taken as 1.0 for SI, a SI value of greater than 1.0 was associated with an increase in mortality.[19] In a study conducted by Chung et al. in geriatric patients with influenza, a SI value that was greater than the determined cut-off value was found to be associated with high mortality. Of these patients, those who had a high shock index were shown to have a seven times higher risk of mortality than those who did not. In addition, it was stated that SI had a high specificity and negative predictive value for showing 30-day mortality.[20] In their study on patients with septic shock, Jouffroy et al. determined the SI cut-off value as 0.9 and found that there was an increase in mortality in patients above this value.[21] Similarly, in patients with COVID-19, the rate of mortality was found to be 21% in those with an SI below the determined value, while it was found to be 70% in patients above the determined value.[22] In our study, the SI cut-off value was determined as 0.87 (specificity: 87.23%, 95% CI: 74.3-95.2, sensitivity: 61.26%, 95% CI: 51.5-70.4) (**Table 1**, **Figure 1**). The high rate of perforated appendicitis in patients with a high SI was found to be statistically significant.

GFR is a parameter that has been used for a long time and is accepted as the gold standard in the evaluation of kidney function.[23] Yoshioka et al. stated that low GFR after gastric endoscopic submucosal dissection (ESD) in patients diagnosed with chronic kidney disease (CKD) was directly related to postoperative bleeding.[24] In a case-control study conducted on patients with appendicitis, GFR was found to be low in the perforated appendicitis group.[25] In our study, GFR rates were found to be low in the perforated appendicitis group, which was consistent with the literature.

CONCLUSION

It is known that perforation increases mortality. In addition to previous studies to predict mortality, SI and GFR are thought to be prognostic parameters for showing both perforation and the associated increased mortality rate. The limitation of the study is that it is retrospective, but it is thought to be significant since it is the first study in which SI and GFR were evaluated together to predict the diagnosis of perforated appendicitis.

ETHICAL DECLARATIONS

Ethics Committee Approval: The approval of the Balıkesir University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee was obtained for the study (date: January 26, 2022; decision number: 2022/009).

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

Relation of Anxiety and Hopelessness Levels of Healthcare Workers with Personality Traits During COVID-19 Period

COVID-19 Sürecinde Sağlık Çalışanlarının Anksiyete ve Umutsuzluk Düzeylerinin Kişilik Özellikleri ile İlişkisi

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Abstract

Aim: Corona Virus Disease-2019 (COVID-19) is an acute respiratory infection that began in Wuhan province in China, and spread to many countries around the world. Many studies were conducted in the literature to evaluate the mental health of healthcare employees during the COVID-19 period. The purpose was to evaluate the relation of the anxiety and hopelessness levels caused by COVID-19 pandemia period with personality traits of healthcare workers.

Material and Method: A total of 451 people participated in our study; including 221 healthcare workers and 230 non-medical community sampling. All participants filled the Coronavirus Anxiety Scale (CAS), Beck Hopelessness Scale (BHS), Revised Eysenck Personality Survey-Shortened Form (EPS-RCF).

Results: All the subscale scores of CAS and BHS were found to be high in healthcare employ healthcare workers ($p<0.05$). The EPS-RCF neurotism subscale was also found to be high in healthcare workers ($p<0.05$). During the COVID-19 period, the anxiety and hopelessness levels of healthcare workers were found to be higher than non-medical community sampling. It was also found that the personality trait of neurotism was dominant in healthcare workers, and that personality traits were associated with both anxiety and hopelessness levels.

Conclusion: Our findings are very important for healthcare workers all over the world to reduce their anxiety, to increase future expectations, motivations and hopes for the future, and to be spiritually good during this pandemia period.

Keywords: COVID-19, healthcare workers, anxiety, hopelessness, personality traits.

Öz

Amaç: Korona virüs hastalığı-2019 (COVID-19); Çin Wuhan eyaletinden başlayıp dünya üzerinde pek çok ülkeye yayılan bir akut solunum yolu enfeksiyonudur. Literatürde COVID-19 sürecinde sağlık çalışanlarının ruh sağlıklarını değerlendirmek için çok sayıda çalışma yapılmıştır. Bu çalışmanın amacı; COVID-19 pandemi döneminin neden olduğu kaygı ve umutsuzluk düzeylerinin sağlık çalışanlarının kişilik özellikleri ile ilişkisini değerlendirmektir.

Gereç ve Yöntem: Çalışmamıza toplam 451 kişi katıldı; 221 sağlık çalışanı ve 230 tıbbi olmayan sağlık çalışanı olamayan kişi dahil edildi. Tüm katılımcılara; sosyodemografik veri formu, Koronavirus Anksiyete Ölçeği (KAÖ), Beck Umutsuzluk Ölçeği (BUÖ), Gözden Geçirilmiş Eysenck Kişilik Anketi-Kısaltılmış Formu (EKA-GGK) uygulandı.

Bulgular: Sağlık çalışanlarının KAÖ ve BUÖ tüm alt ölçek puanları yüksek bulundu ($p<0.05$). EKA-GGK nörotizm alt boyutu sağlık çalışanlarında yüksek olarak bulunmuştur ($p<0.05$). COVID-19 döneminde sağlık çalışanlarının kaygı ve umutsuzluk düzeylerinin sağlık çalışanı olmayan gruptan fazla olduğu görülmüştür. Ayrıca sağlık çalışanlarında nevrotik kişilik özelliğinin baskın olduğu ve kişilik özelliklerinin hem kaygı hem de umutsuzluk düzeyleri ile ilişkili olduğu bulunmuştur.

Sonuç: Bulgularımız; tüm dünyada yaşanan bu salgın döneminde sağlık çalışanlarının anksiyetelerinin azaltılması, gelecek beklentilerinin, motivasyonlarının ve gelecek ile ilgili umutlarının arttırılması, ruhsal olarak iyi olmaları açısından oldukça önemlidir.

Anahtar Kelimeler: COVID-19, sağlık çalışanları, anksiyete, umutsuzluk, kişilik özellikleri.

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INTRODUCTION

Corona Virus Disease-2019 (COVID-19) is an acute respiratory infection that began in Wuhan province in China, and spread to many countries around the world. COVID-19 was declared a global pandemia causing severe respiratory disease by the World Health Organization (WHO).[1] With the current data, it was been reported that 15.666.671 people were infected, and 636.787 people died worldwide.[2] The disease causes fever, radiological evidence of pneumonia, serious shortness of breath, and physical symptoms, as well as serious damage to the mental health of societies.[3] It was found that there were increases in in negative emotions of people like anxiety, depression, irritability, and decreases in positive emotions like being satisfied with life.[4] A study conducted with the participation of more than 50.000 people in China found that 35% of the participants were psychologically distressed.[5] In addition to the stress and anxiety experienced by societies all over the world, it is possible to argue that healthcare workers who struggle with the disease in the first line, who are busy, working for longer durations to meet the health needs of patients, and who are at risk of being infected every day, are exposed to a source of distress that can override their coping skills. After the stress and distress experienced, it is argued that the mental health of healthcare workers is at risk.[6]

Many studies were conducted in the literature to evaluate the mental health of healthcare employees during the COVID-19 period.[6-10] In a study evaluating 134 healthcare workers, it was found that 12.7% of the participants showed depressive symptoms, and 20.1% showed anxiety symptoms.[7] In another study conducted with hospital anxiety depression scale, it was calculated that 11.7% of the participants exceeded the cut-off score of depression subscale, and 24.7% of the anxiety subscale.[8] In studies included in the literature, it was reported that there might be anxiety and depressive symptoms in healthcare workers,[6-8] and in addition, different psychiatric effects like irritability, stress, loneliness, hopelessness, insomnia, fatigue and hopelessness a with different psychiatric effects.[9] The increased workload, lack of protective equipment, high risk of transmission and working under severe pressure with the epidemic period were shown to have a negative effect on the physical and mental health of healthcare workers.[11] In the light of all these data, the first purpose of the present study was to examine the levels of anxiety and hopelessness of healthcare workers by comparing them with non- healthcare workers community sampling. As the second purpose, it was also aimed to evaluate the relation of anxiety and hopelessness levels with personality traits.

MATERIAL AND METHODS

Ethical Statement

This cross-sectional, descriptive study research was carried out online. The approval of the Local Ethics Board of Clinical Studies of Fırat University Faculty of Medicine was received with number 97132852/050.01.04 to conduct the study. The study was conducted in line with the Helsinki Declaration.

Study Design and Participants

The study was conducted online. People between the ages of 25 and 55 volunteering to participate in the study, who filled out and approved the electronic forms, were included in our study. Those who had chronic diseases that required medical treatment, who reported that they were receiving psychiatric treatments, and those who did not want to participate in the study were excluded from the study. Aside from the group that included healthcare workers, people who were not healthcare workers were also included in the study as the Control Group. All participants filled in the Sociodemographic Data Form, Coronavirus Anxiety Scale (CAS), Beck Hopelessness Scale (BHS), Revised Eysenck Personality Survey-Shortened Form (EPS-RCF).

Data Collection Tools

Sociodemographic Data Form: Considering the purposes of the study, it was prepared by the researchers in line with the literature review. It contains demographic data like age, marital status, place of education, level of education, working status, job position, and economic level. In addition to demographic data, it also has questions on whether the patient required treatment, medical and psychiatric disease, as well as clinical evaluation.

Coronavirus Anxiety Scale (CAS): It was developed by Lee.[12] The scale is in 5-Point Likert style and has one dimension. Each item is rated between 0 and 4. "0" refers to "never", "1" refers to "rarely/less than one or two days", "2" refers to "a few days", "3" refers to "more than seven days", and "4" refers to "almost every day in the last two weeks". The reliability study of the scale was conducted for Turkish by Evren et al.[13]

B**eck Hopelessness Scale (BHS):** It was developed by Beck et al.[14] The scale is a 20-point self-notification scale. Feelings about the future, loss of motivation, total hopelessness scores are calculated. The higher the scores, the higher the person's level of hopelessness. Seber et al. conducted the Turkish validity and reliability study.[15]

Revised Eysenck Personality Survey-Shortened Form (EPS-RCF): It has 24 items, each question is answered as "yes" or "no" with 3 subscales, which are "Extroversion", "Narcissism" and "Psychoticism". In addition to these subscales, the purpose with the "Lie" subscale is to prevent and control bias in the implementation of the scale.[16,17]

Statistical Analysis

Statistical Package for Community Sciences (SPSS Inc., Chicago, IL) version 20 program was used to evaluate the data obtained from the participants. The distributions of the data were analyzed with the Kolmogorov-Smirnov Test. Categorical data were shown as number and percentage, and numerical data were shown as mean and standard deviation. Mann-Whitney U-test was used in the comparisons on numerical data. In the evaluation of the categorical data, the Chi-Square Test or Fisher's Exact Test were used. The relations between the scales scores with each other was examined with the Pearson Correlation Analysis. Statistical significance was taken as $p<0.05$ in all analyses.

RESULTS

Online forms were sent to a total of 300 healthcare workers for the study; however, 50 people refused to participate in the study, 16 people could not be included in the study because they did not fill the forms sent online. As the Control Group, online forms were sent to 280 people who were not healthcare workers; however, 35 people refused to participate in the study, and 8 people could not be included in the study because they did not fill the forms. A total of 221 healthcare workers and 230 non-healthcare workers who met the inclusion criteria were included in our study as the community sampling (i.e. the Control Group). No statistically significant differences were detected between the mean age of the participants, the marital status, and the education levels. However, the gender, professions and economic status were statistically different between groups (**Table 1**).

Table 1. Distribution of demographic data of the participants

	Healthcare workers group (n= 221)	Non-healthcare community sampling; control group (n=230)	P
Age (Mean±SD)	33.78±12.16	34.86±12.01	>0.05
Gender (Female/Male)	160/61 (72.4/27.6%)	130/100 (56.52/43.29%)	<0.05
Marital Status			
Married	142 (64.3%)	158 (68.7%)	
Single	69 (31.2%)	64 (27.8%)	>0.05
Separated	10 (4.5%)	8 (3.5%)	
Educational Status			
High School Graduate	8 (3.61%)	31 (13.5%)	
University Graduate	199 (90%)	176 (76.5%)	
Still Studying	14 (6.3%)	23 (10%)	
Occupation			
Academician	15 (6.8%)	-	
Specialist Doctor	70 (31.7%)	-	
Practicing Physician	37 (16.7%)	-	
Dentist	10 (4.5%)	-	
Pharmacist	4 (1.8%)	-	
Nurse/Healthcare Officer	70 (31.7%)	-	
Medical Secretary	15 (6.8%)	-	
Employee	-	67 (29.13%)	
Civil Servant	-	99 (43%)	
Military personnel	-	16 (7%)	
Housewife	-	48 (20.9%)	
Income Status			
Below ₺2.000	-	29 (12.6%)	
₺2-5.000	62 (28.1%)	74 (32.7%)	<0.05
₺5-10.000	71 (32.1%)	73 (31.7%)	
Above ₺10.000	88 (39.8%)	54 (23.5%)	
Smoking Status	50/162/9	66/146/18	
Yes/No/Quit	22.6/73.3/4.1%	28.7/63.5/7.8%	
Alcohol Use	16/201/4	25/198/7	
Yes/No/Quit	7.2/91/1.8%	10.9/86.1/3%	

No participants had medical or psychiatric disease requiring treatment. The Chi-Square Test and the Fisher-exact Test was used in the calculations. The values given in the "Age" line are presented as Mean±Standard Deviation, while other values are given as n (%).

The number of people who were actively working in their own businesses during the pandemic period were 164 people (74.2%) in healthcare workers, and 66 (28.7%) in non-healthcare sampling. Detailed data on working status and location of healthcare workers during the pandemic period is given in the **Figure 1**.

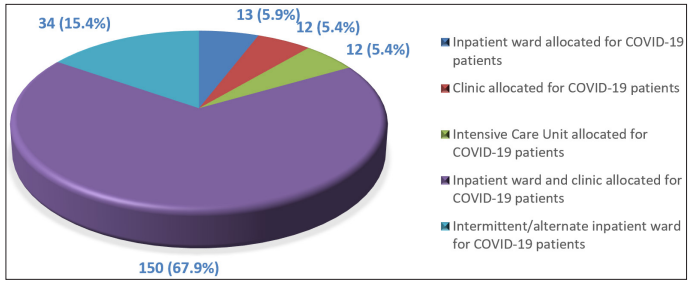

Figure 1. Workplace during pandemia period healthcare workers group

When the distribution of the quantitative variables of the participants was examined, it was determined that the healthcare worker group received a higher score ($p<0.05$). For Beck Hopelessness Scale, the scores of healthcare workers from all subscales were calculated to be higher than the other group (**Figure 2**). For Eysenck Personality Inventory, the scores received from the subscale of Neurotism was determined to be high in healthcare workers (**Figure 3**). When the relations between some demographic characteristics of healthcare workers and quantitative variables were examined, it was found that women's CAS scores were higher than those of men ($p=0.000$). Similarly, the scores of women in the subscale of EPS-RCF "Neurotism" and the subscale of "Hope" were higher (the p values were 0.001, 0.003, respectively). No relations were detected between marital status and age. When healthcare workers were divided into professions like specialist doctors, general practitioners, and nurses, no differences were found between the scale scores of the groups. Only the BHS Feelings about the Future subscale was higher in specialist doctors than in other professions. In this subscale, the ranking of the scores was listed as specialist doctors, general practitioners, dentists, pharmacists and nurses. The scores of healthcare workers who worked actively in pandemia period were much higher in all the scales applied. This result was independent of the unit worked. In other words, the scores of the healthcare workers who worked actively in pandemia period in pandemia ward, pandemia emergency department, pandemia intensive care unit were much higher in all scales. The scores of smokers were much higher in all subscales of BHS. Similarly, the scores of healthcare workers who used alcohol in all subscales of the BHS were higher than the group that did not drink alcohol. No relations were detected between smoking and alcohol and the CAS and EPS-RCF. The correlation analysis results of healthcare workers are presented in **Table 2**.

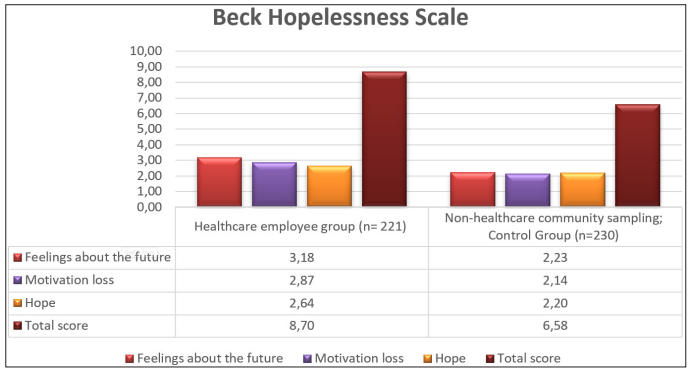

Figure 2. Distribution of quantitative variables of the participants-1

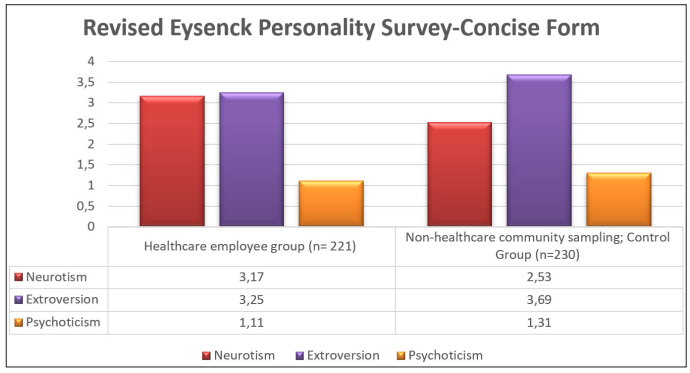

Figure 3. Distribution of quantitative variables of the participants-2

Table 2. Pearson Correlation Analysis results of healthcare workers

		Beck Hopelessness Scale			
	CAS	Feelings about the future	Motivation loss	Hope	Total score
Beck Hopelessness Scale					
Feelings about the future	.321*	-	.748*	.742*	.921*
Motivation loss	.383*	.748*	-	.683*	.946*
Hope	.381*	.742*	.683*	-	.869*
Total score	.392*	.921*	.946*	.869*	-
EPS-RCF					
Neurotism	.330*	.538*	.517*	.563*	.592*
Extroversion	-.020	-.222*	-.196*	-.241*	-.239*
Lie	.028	-.004	.023	.029	.017
Psychoticism	.068	-.077	.043	-.113	-.043

Abbreviation given in the table: CAS: Coronavirus Anxiety Scale, EPS-RCF: Revised Eysenck Personality Survey-Concise Form. The values given in the table are the "r" values. Pearson Correlation Analysis was used in the calculations.

DISCUSSION

In our study, we examined the anxiety and hopelessness levels experienced by healthcare workers during the COVID-19 period by comparing them to community sampling that consisted of non- healthcare workers. We also evaluated the relation of anxiety and hopelessness levels with personality traits.

Emergency plans were put into practice in our country and around the world during the COVID-19 pandemia period. Measures like protecting social distance, wearing masks, the concept of flexible working hours for employees, and less out-of-the-house and postponing non-urgent healthcare applications were taken.[18] These measures, together with new living and working conditions, increased the stress and pressure on all communities and healthcare workers. People being under psychiatric pressure during epidemic periods, feeling intense stress and some psychiatric symptoms are considered as expected conditions.[19] Studies were conducted to examine the effect of the pandemic period on the psychiatric health of healthcare workers. Studies in which only healthcare workers were evaluated were intense.[7-9,18] Comparative studies, like our study, were limited.[6,20] In a study that was conducted with 59 doctors and nurses, some healthcare workers were found to show severe depressive symptoms.[21] In a broader study conducted with healthcare workers working in twenty different hospitals, the employees had depressed symptoms with a rate of 50.4%, anxiety symptoms with 44.6%, insomnia at 34%, and stress with a 71.5%.[22] In a study conducted with 442 healthcare workers in our country, 41.2% of the participants were under intense stress, 64.7% had depressive symptoms, and 51.6% showed anxiety symptoms. It was reported that participants with female gender, being single, and low work experience had higher depression, anxiety and stress scores.[18] In a study that anxiety and hopelessness levels were found to be high in healthcare workers. State anxiety is usually associated with stressful events. Anxiety in the face of ongoing events with uncertainty like the pandemia can be described as state anxiety. In this study, the state anxiety levels of healthcare workers were found to be as high as expected.[20] Similarly, in our study, healthcare workers were compared with non-medical community sampling. Corona virus anxiety scale is a state anxiety measuring tool that evaluates the extent of the corona virus-related anxiety. The scores of this scale were found to be high in healthcare workers when compared with non-medical community sampling. Also, the hopelessness levels of healthcare workers were found to be high. It was reported in the literature that the anxiety and hopelessness levels were associated with increased anxiety levels, which means that hopelessness has increased.[23] Similarly, the anxiety levels of participants increased, and their hopelessness levels increased.

Our study is the first one in the literature that examines the relation of anxiety and hopelessness levels of healthcare workers with personality traits during the COVID-19 period. When the general personality characteristics of groups were compared, it was found that the Neurotism scores of healthcare workers were higher than non-medical community sampling. EPS-RCF, other subscales, psychoticism and extroversion were found to be higher in non-medicine community. In a study that examined the personality characteristics of healthcare workers with Eysenck Personality Survey, the dominant personality trait of the healthcare group was found to be Neurotism, which is similar to our results.[24] In another study, it was found that extroversion and psychoticism were higher

among clinical psychologists, and Neurotism was dominant in general medical doctors.[25] In addition to the fact that Neurotism was dominant in healthcare workers, which is similar to the literature, it was also found that Neurotism scores showed a positive correlation with all subscales of corona virus anxiety and hopelessness scale. The extroversion personality trait was found to be negatively related with all subscales of the BHS. This result was similar to the literature data. In many studies conducted on different groups in the literature, the sub- dimension of Eysenck Personality Scale was positively associated with the anxiety and hopelessness scale scores; however, the extroversion and hopelessness scales were determined to be negatively associated with all subscales.[26,27]

Women's anxiety scores were calculated as more than men in many studies conducted during the COVID-19 pandemic period.[11,20,28] In our results, similarly, the CAS scores of women were higher than men. However, some studies found that women had higher hopelessness levels similar to anxiety. [20] In our study, no relations were detected between the marital status of the participants and the scales applied. The data obtained about the marital status in the literature were contradictory. Some studies reported high anxiety levels in married people,[20] and no relation with marital status, which is similar to our results.[18] Although a study in the literature found that the anxiety levels of nurse and specialist doctor were similar,[20] another study found that the anxiety levels of nurses were higher than other healthcare workers.[29] Our results did not differ in anxiety or hopelessness levels between the nurse/medical officer and doctors.

Limitation

Our results should be evaluated by considering some limitations. The first of these limitations is that the study was of a cross-sectional nature. Other limitations were the relatively inadequate number of sampling and people's being evaluated with self-notification scales. These limit the generalization and interpretation of the results obtained here. Further studies are needed with larger sample groups in order for our findings to become important.

CONCLUSION

As a result, it was found in our study that the anxiety and hopelessness levels of healthcare workers during the COVID-19 period were higher than non-medical community sampling. It was also found that the personality trait of Neurotism was dominant in healthcare workers. Finally, personality traits were found to be associated with anxiety and hopelessness levels. In the light of our findings, it is very important to reduce the anxiety of healthcare workers during the unexpected and unpredictable pandemia period to increase future expectations, motivations and hopes for the future, to be spiritually healthy, and indirectly, for the healthcare workers to become beneficial to patients.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by Fırat University Non-Invasive Local Ethical Board and Provincial Health Management, and was implemented in accordance with Helsinki Declaration (Ethical approval number: 97132852/050.01.04).

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

Risk Factors for Venous Thromboembolism in Patients with Spinal Cord Injury: A Single-Center Turkish Study

Spinal Kord Yaralanmalı Hastalarda Venöz Tromboembolizm için Risk Faktörlerinin Ortaya Konması: Tek Merkezli Türkiye Verileri

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Abstract

Objective: Spinal cord injury (SCI) occurs due to trauma or non-traumatic conditions may be associated with comorbidities related to cardiovascular system and higher risk for venous thromboembolism (VTE). This study aimed to identify risk factors for VTE in patients with SCI who participated the inpatient rehabilitation program.

Material and Method: The study included 326 patients diagnosed as SCI that were admitted to the inpatient tertiary research hospital rehabilitation clinic and enrolled in a conventional rehabilitation program. The data were collected retrospectively. Risk factors for developing VTE were identified.

Results: There were no significant differences in age, comorbidities or SCI etiology between the patients with and without VTE. The groups differed significantly in gender, level of injury and duration of SCI. Risk factor for VTE were only level of injury.

Conclusions: The present findings show that paraplegic injury level may be considered risk factor for developing VTE in SCI patients. It should be considered when approaching the possibility of VTE in SCI patients.

Keywords: Spinal cord injury, venous thromboembolism, deep venous thromboembolism, pulmonary embolism

Öz

Amaç: Spinal kord yaralanması travmatik veya travmatik olmayan nedenlerle oluşur ve kardiyovasküler sistem hastalıkları ve yüksek venöz tromboembolizm (VT) riski ile ilişkilidir. Bu çalışmanın amacı yatarak rehabilitasyon programına dahil edilmiş spinal kord yaralanmalı hastalarda VT gelişimi için risk faktörlerini ortaya koymaktır.

Gereç ve Yöntem: Çalışma spinal kord yaralanması tanısı olan ve 3. Basamak araştırma hastanesi rehabilitasyon kliniğine başvurup konvansiyonel rehabilitasyon programına dahil edilen 326 hastadan oluşmaktadır. Veriler retrospektif olarak toplanmıştır. Venöz tromboembolizm için risk faktörleri ortaya konmuştur.

Bulgular: Yaş, ek sistemik hastalıklar veya spinal kord yaralanması etiyolojisi açısından VT olan ve olmayan gruplar arasında fark yoktur. Gruplar cinsiyet, yaralanma seviyesi ve yaralanma süresi açısından farklılık göstermektedir. Tek risk faktörü yaralanma seviyesidir.

Sonuç: Bu çalışmada spinal kord yaralanmalı hastalarda yaralanma seviyesi risk faktörü olarak bulunmuştur. Spinal kord yaralanmalı hastalara VT açısından yaklaşımda akılda bulundurulmalıdır.

Anahtar Kelimeler: Spinal kord yaralanması, venöz tromboembolizm, derin venöz tromboembolizm, pulmoner emboli

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INTRODUCTION

Spinal cord injury (SCI) occurs due to trauma or disease, resulting in impairment, including motor-sensory deficits, bladder and bowel dysfunction, and pulmonary complications. Disability varies with injury level and whether or not the injury is complete or incomplete.[1] SCI is also associated with comorbidities related to the cardiovascular system. Irregularities of cardiac rhythm, orthostatic hypotension, or absence of cardiac pain can occur. Additionally, the risk of venous thromboembolism (VTE) is higher in SCI patients than in general population. [2] VTE includes deep venous thromboembolism (DVT) and pulmonary embolism (PE). Hypercoagulability and stasis are the most common factors that lead to deep vein thrombosis in SCI patients.[3]

DVT and PE are associated with multiple factors during all phases of SCI. It was reported that patient age and the presence of another injury are independent risk factors for VTE during the acute phase of SCI,[4] whereas some studies reported that patient age, gender, race, completeness of injury, and neurosurgery were not associated with VTE.[5] One study on the factors related to VTE in acute SCI patients in Australia observed that weight, male gender, duration of hospitalization, and lower limb fractures are risk factors for VTE;[6] however, it was noted that the risk of VTE is higher during the acute phase of SCI[7] and a systematic review reported that risk of VTE is higher even during the subacute phase (3-6 months).[8] The present study aimed to identify the risk factors for VTE in SCI patients during all phases of SCI.

MATERIAL AND METHOD

Patients

This retrospective study included SCI patients that were hospitalized in the inpatient rehabilitation clinic of Başkent University Medical School, Ankara Hospital, Ankara, Turkey, between January 2005 and January 2021. The data were collected from the records of the patients kept by the health care professionals. Patients with paralysis due to rheumatologic diseases, those with SCI accompanying traumatic brain injury and those were using anticoagulant agents due to atrial fibrillation and valve replacement were excluded. In all, data for 358 SCI patients were retrospectively analyzed, but due to incomplete data, 32 patients were excluded from the study, leaving 326 patients. Only the first time hospitalizations of the patients were taken into consideration and only complications during hospitalizations and venous thromboembolism histories were recorded.

Patient age, co-morbidity, etiology of SCI (traumatic or non-traumatic), duration of SCI, completeness of injury, injury level, functional and ambulation level, complications of SCI, including spasticity, bladder-bowel incontinence and urinary tract infections, and the presence of other trauma or fracture, were recorded. Spinal cord injuries occurred by spinal cord compression, vascular disease, neoplasms, hemorrhage, syringomyelia and myelitis were classified as non-traumatic spinal cord injuries. Completeness of injury was based on the Asia Impairment Scale (AIS), as follows: AIS A: complete injury; AIS B, C, and D: incomplete injury. Participants with a paraplegia showed a lesion below Th1 and participants with a tetraplegia a lesion level between C1-7. Functional assessment and level of ambulation were determined according to the Functional Independence Measure (FIM) and the Functional Ambulation Classification (FAC), respectively.

FIM is an 18-item scale used to assess physical, cognitive, and social functioning, with a focus on disability.[9] The FIM motor subscale includes self-care, sphincter control, locomotion, and transfer information. The FIM cognitive subscale collects information about communication and social functioning. Additionally, FIM is used to objectively assess development. FAC is a 6-point Likert-type (0-5) scale used to evaluate walking ability and the need for human support during ambulation. In this study FAC ambulation was categorized as dependent (non-ambulatory or ambulatory with physical assistance) (FAC score: 0-2) and independent (FAC score: 3-5).[10]

Duration of SCI was defined as acute SCI (<3 months), subacute SCI (3-6 months), and chronic SCI (>6 months). The level of spasticity was determined according to the Modified Ashworth Scale (MAS). Patients were classified whether they had spasticity or not.[11] VTE was diagnosed according to establishment of the clinical probability of DVT or PE (pain, swelling, and/or dyspnea) based on an elevated D-dimer value, venous doppler ultrasonographic findings, and pulmonary imaging findings. If the venous doppler ultrasound finding was positive with clinical suspicion, the patients were diagnosed as deep vein thrombosis. If the venous Doppler ultrasound finding was negative, when the D-dimer result was found to be high, the patients were planned to have an ultrasound 6-8 days later. Despite clinical suspicion, deep vein thrombosis was excluded in patients with venous Doppler ultrasound findings negative and normal D-dimer level. For the diagnosis of PE, high-risk suspicion (patients with shock or/with hypotension) with positive immediate Computed tomography pulmonary angiography is diagnosed as pulmonary embolism. For the patients with non-high risk; elevated D-dimer and positive multi-detected spiral computed tomography is diagnosed also as pulmonary embolism.[12] All patients included in the study received thromboprophylaxis during their stay in our inpatient rehabilitation clinic (40 mg enoxaparin).[13] The study was performed in accordance with the Declaration of Helsinki. Ethics committee approval was received from Başkent University School of Medicine (Date: 24.05.2022, Decision No: KA22/203)

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows v.24.0 (IBM Corp., Armonk, NY, US). Continuous variables are shown as mean±SD, and categorical data

are shown as number and percentage. The Kolmogorov-Smirnov test was used to determine the normality of the distribution of continuous variables. Normally distributed data were compared with chi-square test, non-normally distributed data were compared using the Mann Whitney U test. For multivariate analysis estimating the risk of DVT/PE independent predictors of developing DVT/PE were tested using binary logistic regression analysis. The Hosmer-Lemeshow test was used for model concordance. The level of statistical significance was set at $p<0.05$.

RESULTS

Of the 326 SCI patients (mean age of 50.76 years) included in the study, 209 were male and 117 were female. In total, 238 of the patients were paraplegic and 88 were tetraplegic. Injuries were motor complete in 119 patients and incomplete in 207 patients. In all, 28 of the patients developed VTE, of which 7 had both DVT and PE.

Demographic and clinical characteristics of the patients are given in **Table 1**. There weren't any significant differences in age, co-morbidities (hypertension (HT), diabetes mellitus (DM), coronary artery disease (CAD), and malignancy) (p=0.574, p=0.858, p=0.477, p=0.096, respectively) or etiology between the SCI patients with and without VTE (p=0.695). There were significant difference between gender and level of injury (p=0.014). There weren't any significant differences in FIM, FAC, completeness of paralysis, urinary tract infection, presence of spasticity, presence of heterotopic ossification, bladder and bowel continence, decubitus ulcer or another injury or fracture between the patients with and without VTE.

Table 1. Demographic and clinical characteristics in the patients with and without VT

	Without VT (n=298)	With VT (n=28)	Total (n=326)	p
Age (Mean±SD)	50.65±19.47	51.85±19.79	50.76±19.47	0.748*
Gender (n, %)				
Female	101 (33.9%)	16 (57.1%)	117 (35.9%)	0.014**
Male	197 (66.1%)	12 (42.9%)	209 (64.1%)	
Etiology (n, %)				
Traumatic	192 (64.4%)	17 (60.7%)	209 (64.1%)	0.695**
Non-traumatic	106 (35.6%)	11 (39.3%)	117 (35.9%)	
Injury level (n, %)				
Tetraplegia	85 (28.5%)	3 (10.7%)	88 (27.0%)	0.045**
Paraplegia	213 (71.5%)	25 (89.3%)	238 (73.0%)	
DM (n, %)				
No	259 (86.9%)	24 (85.7%)	283 (86.8%)	0.858**
Yes	39 (13.1%)	4 (14.3%)	43 (13.2%)	
HT (n, %)				
No	217 (72.8%)	19 (67.9%)	236 (72.4%)	0.574**
Yes	81 (27.2%)	9 (32.1%)	90 (27.6%)	
Malignancy (n, %)				
No	280 (94.0%)	24 (85.7%)	283 (86.8%)	0.096**
Yes	18 (6.0%)	4 (14.3%)	22 (6.7%)	
CAD (n, %)				
No	277 (93.0%)	25 (89.3%)	302 (92.6%)	0.477**
Yes	21 (7.0%)	3 (10.7%)	24 (7.4%)	

* Chi-square testi, ** Mann Whitney U test

The SCI patients with and without VTE showed significant difference in duration of SCI (p=0.020) (**Tables 2** and **3**).

Based on the multivariate logistic regression analysis model, the higher odds of VTE were associated with level of injury (paraplegia/tetraplegia) (p=0.024). Accordingly, regarding the risk of developing VTE paraplegic patients had a 60-fold higher risk than tetraplegic patients (p=0.024, 95% CI: 1.7-2094.7) (**Table 4**).

Table 2. Clinical characteristics in the patients with and without VT

	Without VT (n=298)	With VT (n=28)	Total (n=326)	p
AIS (n,%)				
A	106 (35.6)	13 (46.4)	119 (36.5)	0.213**
B	39 (13.1)	6 (21.4)	45 (13.8)	
C	73 (24.5)	3 (10.7)	76 (23.3)	
D	80 (26.8)	6 (21.4)	86 (26.4)	
Duration of disease (n,%)				
Acute (<3 months)	149 (50.0)	19 (67.9)	168 (51.5)	0.020**
Subacute (3-6 months)	52 (17.4)	7 (25.0)	59 (18.1)	
Chronic (>6 months)	97 (32.6)	2 (7.1)	99 (30.4)	
Presence of another injury (n,%)				
Yes	27 (9.1)	24 (85.7)	295 (90.5)	0.323**
No	271 (90.9)	4 (14.3)	31 (9.5)	
FIM scores median (median±SD)				
FIM	60 (13-126)	52 (19-101)	59 (13-126)	0.061*
FAC level (n,%)				
FAC				
0-2	278 (93.3)	27 (96.4)	305 (93.6)	0.518**
3-5	20 (6.7)	1 (3.6)	21 (6.4)	

* Chi-square test ** Mann Whitney U test; FIM: Functional Indepence Measurement, FAC: Functional Ambulation Classification

Table 3. Comparison of the clinical characteristics in the patients with and without VT

	Without VT (n=298)	With VT (n=28)	Total (n=326)	p
Heterotopic ossification (n,%)				
Yes	10 (3.4)	1 (3.6)	11 (3.4)	0.777**
No	288 (90.9)	27 (96.4)	315 (96.6)	
Urinary tract infection (n,%)				
Yes	174 (58.4)	21 (75.0)	195 (59.8)	0.087**
No	124 (41.6)	7 (25.0)	131 (40.2)	
Bladder continence (n,%)				
Yes	129 (43.3)	8 (28.6)	137 (42.0)	0.131**
No	169 (56.7)	20 (71.4)	189 (58.0)	
Bowel continence (n,%)				
Yes	136 (58.4)	10 (35.7)	146 (44.8)	0.313**
No	162 (54.4)	18 (64.3)	180 (55.2)	
Spasticity (n,%)				
Yes	121 (40.6)	8 (28.6)	129 (39.6)	0.213**
No	177 (59.4)	20 (71.4)	197 (60.4)	
Decubitus ulcer (n,%)				
Yes	75 (25.1)	11 (39.2)	86 (26.4)	0.106**
No	223 (74.9)	17 (50.8)	240 (73.6)	

** Mann Whitney U test

Table 4. Determining estimated relative risks for developing VT with logistic regression analysis in patients with SCI

	Odds Ratio	95% Confidence interval (Lower-Upper)	p
Injury Level	60.0	1.7-2094.7	0.024

* The model included gender, injury level and duration of disease .

DISCUSSION

The present study aimed to identify risk factors for VTE in SCI patients. Since, one-third of our patients were related to the non-traumatic etiology, the mean age was 50.76. The findings show that only level of injury (paraplegia/ tetraplegia) is an independent risk factor for developing VTE in SCI patients. Additionally, there was a significant difference in gender, level of injury and duration of SCI between the patients with and without VTE. Among the 16 female patients in the present study with VTE, 4 had both PE and DVT. Although, previously, male gender was identified as an independent risk factor for developing VTE in SCI patients, in the general population there isn't a significant difference between genders in incidence of VTE and that female gender is associated with recurrent VTE.[1,6,14-16]

Among the present study's 28 SCI patients with VTE, 16 did not have any co morbidities, but 2 patients had HT, 2 had DM, 2 had DM and HT, 1 had HT and CAD, 4 had HT and an undefined malignancy, and 1 had neurofibromatosis. According to the literature, both in the general population and SCI patients, such conditions as malignancy, congestive heart failure, obesity, and lower extremity fracture are risk factors for VTE; however, in the present study there wasn't a significant difference in these conditions or comorbidities between the patients with and without VTE.[6,14,17] It should be noted that the present study did not take into consideration patient body mass index. Maung et al.[1] reported that SCI patients with high-level thoracic injury had the highest risk for VTE, whereas those with high-level cervical injury had the lowest risk. Furthermore, earlier studies reported that SCI patients with thoracic-level injury have a higher risk for developing VTE.[7] Similarly, in the present study injury level was determined as an independent risk factor for developing VTE and a higher risk of thromboembolism was found in paraplegic patients compared to tetraplegic patients. The reason for this has not been determined in previous studies.[18]

Spasticity is known to protect against the development of VTE in SCI patients;[19] however, in the present study there wasn't an association between developing VTE and spasticity. Similarly, Green et al.[20] observed that SCI patients with flaccid paralysis had a higher risk of VTE than those with spasticity. In SCI patients immobilization can lead to VTE;[21,22] however, there wasn't a significant difference in FIM or FAC scores between the present study's SCI patients with and without VTE. In addition, both patient groups were similar in terms of independence and ambulation. It is well-known that immobilization is a risk factor for VTE due to stasis in immobilized extremities or paralyzed muscles, according to the Virchow triad.[21,22] In the present study low FIM and FAC scores were not observed to be risk factors for developing VTE, which was unexpected, but might have been due to the fact that all the SCI patients included study were inpatients undergoing conventional rehabilitation and were not considered fully immobile. Due to the same reason, completeness of injury was not observed to be a risk factor for developing VTE as well.[6,12,23,24]

In the present study there was a significant correlation between duration of SCI. It was reported earlier that VTE occurs most commonly in SCI patients within 3 months of injury,[7] the risk of VTE remains high in subacute SCI patients,[8] and that risk differs in acute- and subacute-phase SCI patients; however, according to the present study's multivariate analysis duration of SCI was not a risk factor.

CONCLUSION

The present study has some limitations, including lack of analysis of patient body mass index. In addition, only symptomatic VTE was considered, and lower extremity venous Doppler ultrasonography was not performed in all of the SCI patients. Based on the present findings, we conclude that the risk of developing VTE is high in paraplegic patients. Although, gender and duration of SCI differed significantly in patients with and without VTE, they were not found as risk factors for developing VTE in SCI patients. Clinician awareness of the risk factor might help yield optimal treatment outcomes in SCI patients undergoing rehabilitation.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethics committee approval was received from Başkent University School of Medicine (Date: 24.05.2022, Decision No: KA22/203)

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 author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Original Article / Orijinal Araştırma

Comparison of Patients with Chronic Obstructive Pulmonary Disease that Hospitalized in University Hospital and State Hospital

Üniversite Hastanesi ve Devlet Hastanesi'nde İzlenen Kronik Obtrüktif Akciğer Hastalığı Olan Hastaların Karşılaştırılması

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Abstract

Aim: Chronic obstructive pulmonary disease (COPD) is an important mortality and morbidity reason and brings serious burdens to the economies of countries. We analyzed differences in examination, treatment and approach that may affect the economic burden of COPD in hospitalized patients with a diagnosis of COPD exacerbation in state and university hospitals

Material and Method:104 patients who were being treated in university hospital (UH) and 102 patients in State Hospital (SH) because of COPD were included. The difference in approach of physicians and cost analysis between two hospitals were compared.

Results: The average age was higher in SH (p=0.010). Comorbities were higher in UH (p<0.001). The number of patients who received nebulizer treatment (p=0.020) in UH and total number of nebulizer medication used was higher in SH (p<0.001). The number of patients for whom intravenous (IV) medication was used and the number of total IV medication used was higher in SH (p<0.001). The total number of IM medication used was higher in UH (p<0.001). The number oral antibiotics used was higher in UH (p<0.001). The penicillins, macrolids, penicillin-macrolids were used more in patients in UH. The cephalosporins and quinolons were used more in SH (p<0.001). Inhaler corticosteroid (ICS) (p<0.001), salbutamol+ipratropiumbromur combination in nebulizer form (p<0.001) and IV teophilin was used in more patients in SH (p=0.013). The use of salbutamol in nebulizer form was more in UH (p<0.001). Spirometry, arterial blood gas analysis (respectively p<0.001, p<0.001), chest radiography was applied more in UH (p=0.024). Total cost (p<0.001), total and daily medication costs was more in SH (p<0.001). Costs other than medication was more in UH (p=0.021).

Conslusion: We believe that adherence to the guidelines has a very important effect on cost in patients hospitalized with COPD exacerbation

Keywords: COPD, drug, economic burden, state hospital, university hospital

Öz

Amaç: Kronik obstrüktif akciğer hastalığı (KOAH) önemli bir mortalite ve morbidite nedenidir ve ülke ekonomilerine ciddi yükler getirmektedir. Devlet ve üniversite hastanelerinde, KOAH alevlenmesi tanısı ile yatırılan hastalarda KOAH'ın getirdiği ekonomik yükü etkileyebilecek olan muayene, tedavi ve yaklaşım farklılıklarını incelemeyi amaçladık.

Gereç ve Yöntem: Üniversite hastanesinde (ÜH) tedavi gören 104 hasta ile Devlet Hastanesinde (DH) KOAH nedeniyle tedavi gören 102 hasta çalışmaya dahil edildi.İki hastane arasındaki hekimlerin yaklaşım ve maliyet analizleri karşılaştırıldı.

Bulgular: SH'de yaş ortalaması daha yüksekti (p=0,010). UH'de komorbiditeler daha yüksekti (p<0,001). UH'de nebulizer tedavisi alan hasta sayısı (p=0,020) ve toplam sayı kullanılan nebulizatör ilaç miktarı DH'de daha yüksekti (p<0,001). İntravenöz (IV) ilaç kullanılan hasta sayısı ve kullanılan toplam IV ilaç sayısı DH'de daha yüksekti (p<0,001). Toplam İM sayısı UH'de daha fazlaydı (p<0,001). UH'de kullanılan oral antibiyotik sayısı daha fazlaydı (p<0,001). UH'li hastalarda penisilinler, makrolidler, penisilin-makrolitler daha fazla kullanıldı.Sefalosporinler ve kinolonlar SH'de daha fazla kullanıldı (p<0,001). DH'de inhaler kortikosteroid (ICS) (p<0,001), nebulizer formda salbutamol+ipratropiumbromur kombinasyonu (p<0,001) ve daha fazla hastada IV teofilin kullanıldı (p=0,013). UH'de nebulizer formda salbutamol kullanımı daha fazlaydı (p<0,001).Spirometri, arter kan gazı analizi (sırasıyla p<0,001, p<0,001), akciğer grafisi UH'de daha fazla yapıldı (p=0,024). Toplam maliyet (p<0,001), toplam ve günlük ilaç maliyetleri DH'de daha fazlaydı (p<0,001). UH'de ilaç dışı maliyetler daha fazlaydı (p=0,021).

Sonuç: KOAH alevlenmesi ile hastaneye yatırılan hastalarda maliyet üzerine kılavuzlara uyumun çok önemli bir etkisi olduğuna inanıyoruz.

Anahtar Kelimeler: KOAH, devlet hastanesi, ekonomik yük, ilaç, üniversite hastanesi

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INTRODUCTION

COPD is a significant burden on the economies of many countries. Economic burden occurs due to both direct and indirect costs. While direct cost includes expenditures for diagnosis, treatment, prevention and rehabilitation, indirect cost includes expenses due to loss of workforce, disability, premature death.[1] According to the United States (USA) 2010 data, the total cost regarding COPD was 50 billion dollars, of which 30 billion US dollars were spent for direct.[2]

Hospitalization constitutes the most important part of the direct cost. The majority of hospitalizations are due to COPD exacerbations (50-75%). Advanced age and stage COPD, longer hospitalization and comorbidities are among the factors that increase the cost.[3] Our aim in this study is to analyze the cost of patients hospitalized with the diagnosis of COPD in two different hospitals and to compare the treatment approach to patients with COPD.

MATERIAL AND METHOD

This retrospective observational study was carried out by retrospectively reviewing the medical records of patients hospitalized with the diagnosis of COPD attack between January 2008 and December 2013 at the chest diseases clinic of Kahramanmaraş Sütçü İmam University Medical Faculty Hospital (UH) and Necip Fazıl Kısakürek State Hospital (SH) in Kahramanmaraş and followed up by a pulmonologist. Patients who were followed up in the intensive care unit or were taken to the intensive care unit later were excluded from the study. In addition, patients who underwent dialysis, interventional procedures (gastroscopy-colonoscopy, bronchoscopy, and pulmonary CT angiography) were not included in the study. A total of 206 patients were included in the study, of which 104 patients from in the UH and 102 patients from SH. The drug therapy given to patients, performed imaging tests, pulmonary function tests, total costs, drug and non-drug costs, daily costs, and daily drug costs were calculated from the registry system of the hospitals.

The drugs and the number of drugs used in the patients were examined according to the method of administration(IV, IM, nebulizer form, and subcutaneous). Among the bronchodilators in the nebulizer form, SABA (salbutamol), and SAMA+SABA (salbutamol + ipratropium bromide) combination was assessed. As steroids, only nebulizer form of ICS (fluticasone or budesonide) were included in the study. Penicillin,cephalosporin, quinolone, and macrolide group antibiotics were counted and recorded as oral antibiotics. While calculating the antibiotics given as IV, carbapenem group antibiotics were also recorded in addition to this group of antibiotics. As subcutaneous, only enoxaparin was taken into account. As IV drugs, antibiotics,proton pump inhibitors (PPI), antiemetics, systemic steroids, non-steroidal anti-inflammatory drugs (NSAIDs), acetylcysteine, and theophylline were evaluated. As IM, analgesics were evaluated.

Demographic data, comorbidities, arterial blood gas (ABG) count, pulmonary function test (PFT) count, and length of hospitalization of the patients were reviewed from the records. Direct chest radiography and thorax CT number were recorded by reviewing epicrises and invoices.

All data between the two hospitals were compared. The mean hospitalization time was calculated. In addition, patients with a hospital stay of 11 days or more were recorded.

The ethics committee approval from the local ethics committee of Kahramanmaraş Sütçü İmam University and the necessary approval from the officials of Necip Fazıl Kısakürek State Hospital were obtained (Approvel number:2013-15-08).

Statistical Analysis

Independent student's t-test was used for the evaluation of the means, and the Chi-square test for the evaluation of the percentages. The Mann Whitney-U test was used for parameters that not normally distributed. A value of $p < 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS 19.0 statistical package program.

RESULTS

Of the 104 patients hospitalized in UH with a diagnosis of COPD, 79 (76%) were male. Of the 102 patients hospitalized in SH with a diagnosis of COPD, 79±11 (77.7%) were male. The mean age of the patients was 66.6±11.5 years in UH and 70.6±11.3 years in SH (p=0.010). In terms of comorbidities, those with atherosclerotic heart disease and heart failure were recorded as heart diseases. Cardiac comorbidity was present in 31 (29.8%) patients in UH and 10 (9%) patients in SH, it was higher in UH (p <0.001). While the number of patients with hypertension was 34 (32.6%) in UH, it was 13 (12.7%) in SH (p<0.001). The number of patients with diabetes mellitus (DM) was 4 (3%) in UH, 6 (5%) in SH and found to be similar (p=0.491) (**Table 1**).

Table 1. Comparison of groups' demographic data and comorbidities

	University hospital	State hospital	p value
Age (years)	66.6±11.5	70.6±11.3	0.010*
Gender (male/female) n(%)	79/25 (75.9/24.1)	79/23 (77.4/23.6)	0.80
Heart disease	31 (29.8%)	10 (9%)	<0.001*
Hypertension	34 (32.6%)	13 (12.7%)	<0.001*
Diabetes mellitus	4 (3%)	6 (5%)	0.49

The number of patients who received nebulizer treatment in UH was 99 (95%), and 102 (100%) in SH (p=0.02). Considering the total number of nebulizer drugs used 4,838 were used in SH and 3,460 in UH that significantly higher were used in SH (p<0.001). The number of patients who received IV drugs was 99 (95%) in UH and 102 (100%) in SH. The total number

of IV drugs used was 2,795 in UH and 5,936 in SH. Significantly more IV drug use was present in SH (p<0.001). The number of patients who received IM drug was 5 (4%) in UH and 3 (2%) in SH (p=0.486). The total number of IM drugs used was 22 in UH and 10 in SH (p=0.026). Enoxaparin was used in 80 (76%) patients in UH and 57 (55.8%) patients in SH. Enoxaparin was used more in UH (p<0.001) (**Table 2**).

Table 2. Comparison of the groups by the administration method of the drugs

	University hospital	State hospital	p value
Number of patients using nebulizer medication	99 (95%)	102 (100%)	0.020
Total number of nebulizer drugs	3460	4838	<0.001
Number of patients using IV drugs	99 (95%)	102 (100%)	0.02
Total number of IV drugs	2795	5936	<0.001
Number of patients using IM medication	5 (4%)	3 (2%)	0.48
Total number of IM drugs	22	10	0.02
Number of patients using subcutaneous drugs	80 (76%)	57 (55.8%)	<0.001
Total number of subcutaneous drugs	509	427	<0.001
ICS	72 (69.2%)	94 (92.1%)	<0.001
Salbutamol	57 (54.8%)	25 (24.5%)	<0.001
Salbutamol+ipratropium bromide	48 (46.1%)	85 (83.3%)	<0.001
Theophylline	67 (64.4%)	81 (79.4%)	0.013

IM:intramuscular, IV:intravenous

Considering the antibiotics used, the number of patients who used oral antibiotics in UH was 56 (53%), while this number was 13(12.7%) in SH (p<0.001). The number of patients receiving IV antibiotics was 58 (55.7%) in UH and 90 (88%) in SH (p<0.001). The total number of oral antibiotics used was 795 in UH and 127 in SH. The total number of IV antibiotics used was 1,216 in UH and 1,696 in SH. The number of oral antibiotics used was significantly higher in UH (p<0.001), and the total number of IV antibiotics was less in UH, however, this difference was not statistically significant (p=0.063). The number of patients who received penicillin group antibiotics was 53 (50.9%) in UH and 22 (21.5%) in SH, and more in UH (p<0.001). Cephalosporin antibiotics were used in 19 patients (18.2%) in UH and in 44 patients (43.1%) in SH and were used more in SH (p<0.001). While macrolide group antibiotics were used in 25 (24%) patients in UH, they were used in 6 (5%) patients in SH and the difference was significant (p<0.001). Penicillin and macrolide groups were used together in 14 (13.4%) patients in UH and 2 (1.9%) patients in SH(p=0.002). Cephalosporin and macrolide group antibiotics were used together in 8 (7.6%) patients in UH and 2 (1.9%) patients in SH (p=0.540). The number of patients who received quinolone group antibiotics was 5 (4.8%) in UH and 35 (34.3%) in SH, and it was used significantly more in SH (p<0.001). The number of patients who received carbapenem group antibiotics was 3 (2.8%) in UH and 2 (1.9%) in SH (p=0.669) (**Table 3**).

Table 3. Comparison of antibiotics used in university and state hospitals

	University hospital	State hospital	p value
Number of patients using oral antibiotics	56 (53%)	13 (12.7%)	<0.001
Total number of oral antibiotics	795	127	<0.001
Number of patients using IV antibiotics	58 (55.7%)	90 (88%)	<0.001
Total number of IV antibiotics	1216	1696	0.06
Penicillin	53 (50.9%)	22 (21.5%)	<0.001
Cephalosporin	19 (18.2%)	44 (43.1%)	<0.001
Macrolide	25 (24%)	6 (5%)	<0.001
Penicillin+Macrolide	14 (13.4%)	2 (1.9%)	0.002
Cephalosporin+ Macrolide	8 (7.6%)	2 (1.9%)	0.54
Quinolone	5 (4.8%)	35 (34.3%)	<0.001
Carbapenem	3 (2.8%)	2 (1.9%)	0.66

IV:intravenous

ICS was used in 72 (69.2%) patients in UH and 94 (92.1%) patients in SH. It was used more in SH (p<0.001). The number of patients receiving SABA in nebulizer form was 57 (54.8%) in UH, 25 (24.5%) in SH, and it was higher in UH(p<0.001). SABA+SAMA was used in 48 (46.1%) patients in UH and in 85 (83.3%) patients in SH(p<0.001). SABA was used significantly more in UH, and SABA+SAMA was used significantly more in SH. IV theophylline was used in 67 (64.4%) patients in UH and 81 (79.4%) patients in SH. Theophylline was used more in SH(p=0.013)(**Table 2**).

PFT was performed in 64 (61.5%) patients in UH and in 18 (17.6%) patients in SH, and more PFT was performed in UH (p<0.001). ABG analysis was performed in 79 (75.6%) patients in UH and in 17 (16.6%) patients in SH, and it was more in UH (p<0.001).

Chest radiography was performed in 89 (85.5%) patients in UH and 74 (72.5%) patients in SH, and the difference was significant (p=0.024). Lung tomography was performed in 32 (30.7%) patients in UH and 26 (25.4%) patients in SH and it was similar (p=0.411).

While the number of patients hospitalized for 11 days or more in UH was 12 (11.5%), the number of patients hospitalized for 11 days or more in SH was 16 (15.6%)(p=0.437). The mean hospitalization time was 6.6 days in UH and 7.2 days in SH (p=0.260).

In cost analysis, total cost, daily cost, drug cost, non-drug cost, and daily drug cost were examined. The mean total cost was 740 TL (352.3 USD) per person in UH and 938 TL (446.6 USD) in SH. The mean cost per person was found to be higher in SH (p<0.001).

The mean daily cost was found to be 115.5 TL (55 USD) per person in UH and 126.6 TL in SH, and there was no statistical difference (p=0.071). The non-pharmaceutical mean cost was 524 TL (60.2 USD) per person in UH and 453 TL (215.7 USD) in SH. Non-drug cost was significantly higher in UH (p=0.026). Total drug cost was 247 TL (117.6 USD) in UH and 484 TL (230.4 USD) in SH (p<0.001). The mean daily drug cost per person in UH was 38.7 TL (18.4 USD), while it was found to be 60.2 TL (26.6 USD) in SH (p<0.001). Total drug cost and daily drug cost were significantly higher in SH (**Table 4**).

Table 4. Comparison of the two groups in terms of cost analysis.

	University hospital (min-max)	State hospital (min-max)	p value
Total cost	58.66-3453.53 TL	174.71-6589.45 TL	<0.001
Daily cost	17.53-251.99 TL	43.6-366.08 TL	0.07
Non-drug cost	42.22-1914 TL	73.3-1695.14 TL	0.021
Drug cost	6.28-2197.03 TL	10.40-5609.69 TL	<0.001
Daily drug cost	3.06-549.26TL	5.20-311.65TL	<0.001

Min: minimum, max: maximum

When compared in terms of mortality rates, no patient was lost during hospitalization in UH. In SH, one patient has died during the follow-up.

DISCUSSION

Besides being an important cause of morbidity and mortality, the high cost of COPD puts a serious burden on the economies of the country. According to US data, the total cost used for COPD was 24 billion US dollars in 1993, and 50 billion US dollars in 2010. Of this, USD 30 billion is consisted of direct costs. According to US data, there was a more than 2-time increase in the total cost used for COPD in 17 years. Direct cost constitutes approximately 2/3 of the total cost according to 2010 data.[3]

The expenses regarding the hospitalization constitutes the most important part of the direct cost. In a study involving Canada, France, Italy, Spain, the Netherlands, USA, and UK, hospitalization costs constitute 52-84% of the direct cost.[4] Of direct costs, 54% are constituted by hospitalizations in the UK.[5] In a study conducted in Italy, the direct cost varies between 1500-3900 Euros per year, depending on the severity of COPD.[6] In the Netherlands, it has been stated that the direct cost due to COPD is three times the expenditures for asthma.[7] In a study conducted with 85 patients in Romania, the direct cost per patient in a year has been found to be 1456 Euros, and it has been stated that 82.5% of this cost was hospitalizations.[8] According to 2008 data in Canada, 1000 Canadian dollars were spent for each day of hospitalization in patients with COPD and the total annual cost of hospitalization has been stated as 1.5 billion Canadian dollars.[9]

In a study published in 2011 and conducted by Özkaya et al in a chest diseases hospital in Turkey, the cost of hospitalization per patient in a total of 7832 patients hospitalized in 5 years has been found to be 718 USD.[10] In another study of Varol et al. with 376 patients (SH) published in 2013, it has been stated that this cost was 1833 TL (872.8USD) on average.[11] In our study, this cost was found to be 740 TL (352.3USD) for UH and 938 TL (446.6USD) for SH. While the mean hospitalization time was 14.5 days in Özkaya et al's study[10] it was 6.6 days in UH and 7.2 days in SH in our study. The cost per patient was found to be lower in both centers in our study than in the mentioned study. This difference may be due to the fact that patients who were followed up in the intensive care unit and underwent interventional procedures were not included in our study and the hospitalization period was short. In the study of Deniz et al. covering state hospitals in 2014, the total cost was 808.5 dollars per patient and the drug cost was 223.1 dollars, while the total cost was similar to our study, the drug cost was much higher in SH in our study.[12]

In the 3-year cost analysis of patients with COPD hospitalized in a university hospital in Iran by Torabipour et al., it has been seen that the most important part of the expenses were hospitalization time and drugs.[13] In the study of Varol et al., the mean cost of drugs per patient was 526.5 TL (250.7USD), which was 28.7% of the total cost.[11] In the study conducted by Özkaya et al., it has been stated that the drug cost constituted 53.5% of the total cost.[10] In our study, the mean drug cost was 247 TL (117.7 USD) in UH and 33.6% of the total cost. In SH, the mean cost of drugs was found to be 484 TL (230.7 USD), which was 51.3% of the total cost. The drug cost was found to be significantly higher in SH. We think that the reason for this is the use of more nebulizing corticosteroids and more expensive antibiotics in SH.

In the study of Varol et al., considering the hospitalization time of the patients, patients who were hospitalized in the intensive care unit have been also included in the study and it has been stated that a total of 35.6% of the patients were hospitalized for 11 days or more.[11] In our study, patients hospitalized in intensive care were not included in the study, and patients who were hospitalized for 11 days or more were 11.5% of patients in UH and 15.6% in SH. The fact that we did not include patients in the intensive care unit may be a factor in the short hospitalization time.

COPD is more common in the elderly population and hospitalization rates of elderly COPD patients are increasing. According to US national data published in 2005, 65% of hospitalized COPD patients have been stated to be over 65 years old.[14] In another study involving 390 patients in Spain, the mean age of hospitalized COPD patients has been found to be 72.[15] In our study, the mean age of patients hospitalized in UH was found to be 66.6 years, and 70.6 years in SH and were consistent with other studies.

In the BREATHE study, which included Central Mediterranean and Northern Europe, hospitalization rates have been found to be significantly higher in patients with COPD with comorbidities.[16] Comorbidities detected in COPD, especially cardiac causes are factors that increase hospitalizations . In a study involving approximately 21,000 people at risk of atherosclerosis, cardiac comorbidity has been observed at 22% in patients with COPD and 9% in patients without COPD.[17] In a study examining patients with COPD, hypertension has been found in 40% to 60% of patients.[18] In two studies, DM has been found to be 1.5-1.8 times higher in COPD patients compared to the normal population.[17,19] In our study, cardiac comorbidity was found as 29.8% and hypertension was found as 32.6% in patients hospitalized in UH, cardiac comorbidity was found as 9% and hypertension was found as 12.7% in SH. These rates we found were similar to the rates in other

studies. DM was found as 3% in patients hospitalized in UH and 5% in patients hospitalized in SH. The DM rates we found in the two groups in our study were detected to be lower than the studies in the world. Cardiac comorbidity and HT were found at a higher rate in UH than SH, and the difference was statistically significant. We think that the reason for this may be due to the more complexity of the patients who apply or are referred to UH.

Antibiotic treatment has been shown to reduce short-term mortality to 77%, treatment failure to 53%, and sputum purulence to 44%.[14,20] Antibiotic option should be determined according to local antibiotic resistance. In a study conducted in China, 87.91% of patients hospitalized with a diagnosis of COPD have used antibiotics. However, they have not provided information about the oral-IV, and antibiotic groups. The empirical therapy recommended, according to the GOLD 2020 update, is amoxicillin clavulanic acid, second-generation cephalosporins, and new fluoroquinolones. Whether the antibiotic administration method is IV or oral may vary depending on the patient's well oral intake or the pharmacokinetics of the drug. However, oral administration of antibiotics should be preferred.[14] In our study, the number of patients receiving oral antibiotics in UH was 56 (53%), while this number was 13 (12.7%) in SH ($p<0.001$). The number of patients receiving IV antibiotics was 58 (55.7%) in UH and 90 (88%) in SH. Penicillin group was used most frequently and followed by macrolide group antibiotics in UH. In SH, on the other hand, the cephalosporin group was used most frequently, and the quinolone group antibiotics were used the second. This situation shows us that the guidelines are followed better in the treatment of COPD patients in UH.

In patients hospitalized with a diagnosis of COPD attack, SABA can be used alone or together with SAMA.[1] There are studies showing that ICS, when added to the treatment, reduces the risk of acute exacerbation.[21,22] However, no studies showing that it reduces hospitalization were encountered, and there are no results showing a negative effect.[23] ICS treatment is recommended for patients with COPD who have two or more attacks per year and whose FEV1 is below 50%.[14] Because COPD is a neutrophil-dominated inflammatory process. ICSs are not recommended to be used alone in COPD. In randomized-controlled, prospective studies involving a large number of patients for three years, it has been shown that ICS treatment alone does not change the natural history of COPD.[24,25] Theophylline is not preferred as the first choice in the treatment of COPD due to its potential side effects. Theophylline is recommended if patients with severe and very severe COPD are symptomatic despite the use of inhaler long-acting β2 agonists, ICS, and anticholinergics.[14]

In our study, the number of patients receiving theophylline in UH and SH was found to be 67 (64.4%), 81 (79.4%), respectively. According to these results, theophylline is still a widely used drug in this region. In this study, it was observed that nebulizer form ICS, SABA+SAMA, theophylline and number of nebulizer drugs used in SH were significantly higher than UH. Bronchodilator treatments in both groups, except the frequent use of theophylline, were found to be acceptable and in accordance with the guidelines.

CONCLUSION

In our study, it was found that pulmonary function test, arterial blood gas analyses, and chest radiography were performed significantly more in UH. More tests in UH may be due to the fact that patients in this hospital have more comorbidities. This situation may explain that non-drug costs in UH are higher than in SH.

There were some deficiencies in this study. As it is a retrospective study and the hospital records are incomplete, our data may be limited. The patients included in our study could not be classified according to GOLD staging.

Our aim in this study was to examine the cost of patients hospitalized with a diagnosis of COPD and the treatment approach to patients with COPD in two separate hospitals. As far as we know, there is no study comparing university hospitals and state hospitals on this subject.

There are many recommendations in the literature to reduce the costs regarding COPD. These recommendations are methods such as telemedicine, patient education, some pharmacological recommendations, and pulmonary rehabilitation. In addition, in order to reduce the cost of inpatients with COPD, rational use of antibiotics and corticosteroids during hospitalization in accordance with the guideline will contribute to reducing costs. We think that performing outpatient treatment with appropriate drugs, correct drug administration of patients, pulmonary rehabilitation, and vaccination will reduce hospitalizations, thus reducing direct and indirect costs..

ETHICAL DECLARATIONS

Ethics Committee Approval: The ethics committee approval from the local ethics committee of Kahramanmaraş Sütçü İmam University and the necessary approval from the officials of Necip Fazıl Kısakürek State Hospital were obtained (Approvel number:2013-15-08).

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

A New Biomarker in The Distinction Between Stable Coronary Artery Disease and Acute Coronary Syndrome: Thiols

Stabil Koroner Arter Hastalığı ile Akut Koroner Sendrom Arasındaki Ayrımda Yeni Bir Biyobelirteç: Tiyoller

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Abstract

Aims: Thiols are important elements for oxidation reactions and under oxidative stress. The aim of this study was to determine thiole levels, an antioxidative marker in coronary artery disease patients with stable and acute coronary syndrome.

Material and Method: 210 of the patients included in the study were diagnosed with acute coronary syndrome (ACS), 205 consisted of patients with stable angina pectoris (SAP). Thiol groups levels and thiol/disulphide homeostasis was measured by spectrophotometrically.

Results: Native thiol (332.03±59.84 to 404.71±67.64, p<0001 and total thiol levels (367.07±64.62 to 454.28±78.49, p<0001), disulfide (17.52±8.56 to 24.79±11.17, p<0001, native thiol/disulfide (5.3±2.6 to 6.1±2.5, p<005) and total thiol /disulfide (4.77±2.08 to 5.36±2, p<003) ratios were decreased in the ACS groups compared to the SAP groups

Conclusions: Thiol levels and thiol / disulfide ratios can be used as markers to evaluate ACS.

Keywords: Thiol, acute coronary syndrome, stable angina pectoris

Öz

Amaç: Tiyoller, oksidasyon reaksiyonları ve oksidatif stres durumlarında önemli elementlerdendir. Bu çalışmanın amacı, stabil koroner arter hastalığı hastalarında ve akut koroner sendromlu (AKS) hastalarda bir antioksidan belirteç olan tiyol düzeylerini belirlemektir.

Gereç ve Yöntem: Çalışmaya 210'u AKS, 205'i ise stabil angina pektoris (SAP) tanısı alan hasta dahil edildi. Tiyol gruplarının seviyeleri ve tiyol/disülfid homeostazı spektrofotometrik olarak ölçüldü.

Bulgular: SAP gruplarına kıyasla AKS gruplarında nativ tiyol düzeyleri (332,03±59,84' e karşı 404,71±67,64, p<0001, toplam tiyol düzeyleri (367,07±64,62' e karşı 454,28±78,49, p<0001), disulfid (17,52±8,56' e karşı 24,79±11,17, p<0001, nativ tiyol/disulfid (5,3±2,6' e karşı 6,1±2,5, p<005) ve toplam tiyol/disulfid (4,77±2,08' e karşı 5,36±2, p<003) oranları azalmış olarak tespit edildi.

Sonuç: Tiyol düzeyleri ve tiyol/disülfid oranları AKS' yi değerlendirmede belirteç olarak kullanılabilir.

Anahtar Kelimeler: Akut koroner sendrom, tiyol, stabil angina pectoris

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INTRODUCTION

Despite all the developments in diagnosis and treatment, atherosclerotic heart diseases still account for more than 1/3 of the total deaths worldwide.[1] Several of the pathological mechanisms of atherosclerosis, in order of occurrence, such as endothelial dysfunction, lipid penetration and accumulation into the vascular intima, exaggerated adaptive immune responses, vascular smooth muscle cell proliferation, and extracellular matrix remodeling.[2] On the other hand, some studies have shown that oxidative stress plays a role in atherosclerosis.[3-6] When the oxidant stress occurs, it causes endothelial dysfunction; activates an inflammatory response, immune reaction and thrombus formation, oxidized lipids are formed; and initiates sequential vascular events.[7,8]

Thiol groups are an antioxidant cascade that plays a vital role in the elimination of reactive oxygen species.[9,10] The components of antioxidants that provide homeostasis in this group are total thiol, natural thiol, disulfide and derived from them, disulfide / natural thiol, natural thiol/total thiol and disulfide/total thiol ratios. Thiols are an organic compound containing a sulfhydryl (-SH) group, which reacts with reactive oxidant molecules and neutralizes them. Their primary function is to prevent the formation of any oxidative stress state in cells and organisms.[10,11] When thiols cause an antioxidation reaction, it causes the formation of reversible disulfide bonds. When the oxidation reaction is compensated, the disulfide bonds formed can be reduced back to thiol groups. In other words, the thiol/disulfide balance is dynamic and can be maintained through this cycle. The evaluation of this balance gives information about oxidation-antioxidation structure in plasma. Adverse changes in the thiol- disulfide balance can cause disruptions in the normal function and structure of organs and eventually cause diseases such as diabetes, malignancy and atherosclerotic heart diseases.[12,14]

Few studies have observed the relationship between coronary artery disease (CAD) and thiol levels. The present study aimed to determine thiol levels, an antioxidative marker in CAD patients with stable angina pectoris (SAP) and acute coronary syndrome (ACS), and to compare these parameters between these groups.

MATERIAL AND METHOD

A total of 415 patients were included in this study. While 210 of these patients had been diagnosed with ACS, 205 had been diagnosed with SAP. In the ACS group, 75 were ST-segment elevation myocardial infarction (STEMI), 87 were non-STEMI, and 48 were unstable angina pectoris (UAP). Medical history, including cardiovascular risk factors and medications, was recorded on all participants. Routine physical examinations of all patients were performed.

During hospitalization, SAP and the occurrence of ACS (STEMI), non-STEMI, UAP), and SAP are recognized by standard criteria.[15,16] Patients admitted with ACS performed coronary angiography for invasive emergency strategy and continued with a percutaneous coronary intervention (PCI) where necessary. In the other patient group, it was generally accepted for coronary angiography to be performed, and PCI continued when necessary with the intervention and treatment strategy determined by clinicians. Selective coronary angiography (CAG) was performed using the Judkins technique with 6 or 7 French (F) catheters with a right or left femoral approach. Iopromide (Ultravist-370®) or Iohexol (Omnipaque® 350 mg / mL) was used as an opaque agent. In all patients, coronary arteries were visualized with cranial and caudal tilt in the left and right oblique planes. The patients with a PCI procedure were continued with a 6 or 7 F guiding catheter. The stent was implanted, and the length of the lesion calculated by at least two invasive cardiologists.

On admission to the hospital (coronary intensive care or coronary angiography service), venous blood samples were obtained, which measure baseline blood variables (such as comprehensive metabolic panel and complete blood count) and thiol levels. The samples for thiols were centrifuged at 1500g for 10 min. The plasma was stored at -80°C and all samples were processed simultaneously. Thiol group levels and thiol/disulfide homeostasis was measured as defined by Erel et al (17). Serum natural thiol and total thiol levels were determined spectrophotometrically. First, serum natural thiol levels were measured after the reaction without any treatment with 5, 5'-dithiobis-2-nitrobenzoic acid (DTNB). Second, to measure total thiol levels, dynamic disulfide bonds in serum samples were reduced using sodium borohydride (NaBH4) to form free functional thiol groups. Then, formaldehyde was used to remove unused NaBH4 completely, and total thiol groups, including both reduced and natural ones, were measured following the reaction with DTNB. Since the reduction of a disulfide bond produces two separate thiol groups, the number of dynamic disulfide bonds was calculated by determining half of the difference between total thiol and natural thiol.

During hospitalization, medical treatment regimens were applied to all patients according to the current guidelines of the European Society of Cardiology.[16,18,19]

Exclusion criteria were evaluated as follows: age<18 years, continuing infection, inflammatory disorders, congenital heart disease, severe valvular heart disease, untreated cancer, pregnancy, organ failures and the taking of supplemental vitamins.

Before study inclusion, all patients gave their written informed consent. The research protocol of the present investigation was approved by the local research ethics committee and complies with the Declaration of Helsinki (Kayseri City Hospital, Clinical research ethics committee; 03/2020-20)

Statistical Analyses

All analyses were performed using SPSS V 21.0 for Windows (version 21.0; SPSS, Chicago, Illinois). All data are presented as mean±standard deviation unless otherwise stated. The Kolmogorov-Smirnov test was used to analyze the distribution pattern. A comparison of parametric values between the two groups was performed employing independent samples t-test. A comparison of nonparametric values between the two groups was performed by the Mann-Whitney U test. Continuous variable distribution among the groups was done by One Way Anova. Variability between groups was performed by the LSD test. Categorical variables were compared with the chi-square test. Receiver operating characteristic curve (ROC) analysis was used to determine native thiol, total thiol, disulfide and diagnostic value of ACS. P-value<0.05 was accepted as significant.

RESULTS

A total of 415 patients were included in the study (mean age 62.7±10.61). While 210 of the patients included in the study created ACS (STEMI, non-STEMI, UAP), 205 of them constituted stable CAD. Baseline characteristics between ACS and stable CAD are given in **Table 1**. Also, the presence of hypertension, diabetes mellitus, dyslipidemia, and smoking were similar in all groups (**Table 1**).

Table 1: Basal characteristic, biochemical and hematological parameters between groups.

Variables	Acute Coronary Syndrome (n=210)	Stable Angina Pectoris (n= 205)	P value
Age	63.5±10.9	62 ±10.8	.172
Hypertension, n (%)	87	82	.754
Diabetes mellitus, n	58	50	.824
Hyperlipidemia, n	79	81	.814
Smoking, n	105	102	.911
Left ventricular ejection fraction	47.1±9.6	50±10.24	.0001*
Glucose	160.4±88.6	128.8±55.7	.0001*
Blood urea nitrogen	19.4±8.38	16.3±6.53	.0001*
Glomerular filtration rate	89±23.79	91.8±25.7	.320
Creatine	1.8±8,9	1.4±6.6	.588
Aspartate aminotransferase	36.3±29.6	24.3±19.2	.0001*
Alanine aminotransferase	27.6±12.3	20.3±14.1	.001*
Total cholesterol	182.1±41.2	200.3±46.6	.0001*
Triglyceride	158.9±81.8	161.2±73.2	.165
High-density lipoprotein-cholesterol	41.4±11.8	40.4±16.4	.443
low density lipoprotein- cholesterol	111.2±35	116.4±40.2	.183
Sodium	138.4±6.34	137.6±10.8	.315
Potassium	4.5±2.4	5.6±10.5	.131
Hemoglobin A1c	8.8±2.7	7.7±1.7	.018*
Uric acid	6,6±5.7	5.4±1.5	.408
White blood counts	12.5±3.6	8.6 ±3.8	.0001*
Hemoglobin	14.3±1.8	14.5±1.8	.254
Platelets	252.4±78.6	263.2±76.6	.165

Data are expressed as mean ± standard deviation for normally distributed data. *statistically significant (p<0.05)

Laboratory analyses revealed no significant difference between the groups in terms of biochemical parameters such as LDL cholesterol, HDL cholesterol, triglyceride levels, urea and creatinine levels (p>0.05) (**Table 1**). However, since one of the groups ACS, AST, ALT, and glucose values were significantly different in the ACS group (p<0.001, p=0.001 and p<0.001, respectively) (**Table 1**).

When the hematological parameters are examined between the two groups, there is no significant difference between hemoglobin and platelet values (p>0.05). In contrast, a significant difference was found in the white blood cell count (p<0.001) (**Table 1**). Because the patient groups had ACS, a significant difference was detected in the left ventricular ejection fraction.

When the native thiol and total thiol droplets were examined between the two groups, a statistically significant difference was found (p<0.001) (**Table 2**). The disulfide /native thiol and disulfide /total thiol ratios decreased in the ACS group compared with SAP. In subgroup analysis, both native thiol, total thiol, disulfide value and their rates were low in all ACS groups. Interestingly, this change was not significant in the subgroup analysis. However, there was no difference between the STEMI groups and non-STEMI groups or between the STEMI groups and the UAP groups or between the non-STEMI groups and UAP. Still, a significant difference was observed between all subgroups and SAP group. (**Table 3**) (**Figure 1**).

Table 2: Relationship between thiol and disulfide between groups

Variables	Acute Coronary Syndrome (n=210)	Stable Angina Pectoris (n= 205)	P value
Native thiol	332.03±59.84	404.71±67.64	.0001*
Total thiol	367.07±64,62	454.28±78.49	.0001*
Disulfide	17.52±8.56	24.79±11.17	.0001*
Native thiol / disulfide	5.3±2.6	6.1±2.5	.005*
Total thiol / disulfide	4.77±2.08	5.36±2	.003*

Data are expressed as mean ± standard deviation for normally distributed data. *statistically significant (p<0.05)

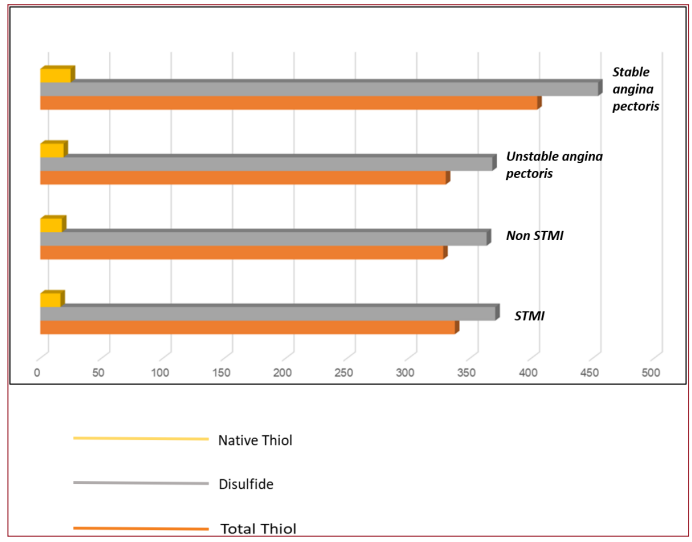

Figure 1: Analysis of thiol and disulfide levels relation of all subgroups

Table 3: Anova test data of thiol and disulfide relation of all subgroups

Variables	STEMI (n=75)	NonSTEMI (n=96)	Unstable angina pectoris (n=48)	Stable Angina pectoris (n=246)	Control (n=72)	P value
Native thiol	260.86±37.49	330.66±11.65	360.31±5.14	413.52±30.62	514.46±33.26	>0001*
Total thiol	289.19±40.60	366.91±13.92	400.09±5.51	461.06±34.25	584.64±41.43	>0001*
Disulfide	16.64±7.49	20.74±2.5	20.25±9.53	22.01±11.79	33.16±11.51	>0001*
Native thiol / disulfide	0.058±0.027	0.055±0.07	0.0505±0.023	0.046±0.023	0.057±0.02	,024*
Total thiol / disulfide	0.065±0.03	0.061±0.78	0.056±0.26	0.051±0.026	0.065±0.022	,022*

Data are expressed as mean ± standard deviation for normally distributed data. STEMI: ST elevated myocardial infarctions, *statistically significant (p<0.05)

Other interesting data of the study are the receiver operating characteristic curve (ROC) analysis results. In the ROC analysis, it was determined that native thiol, total thiol, and disulfide ratios were quite sensitive and specific in finding stable CAD. This analysis is stable CAD with 63% sensitivity and 66% specificity for disulfide 17.5 shear value with 73% sensitivity and 70% specificity for 361.3 shear value of natural thiol, with 71% sensitivity and 70% specificity, showed that he predicted arterial disease (p<0.001 in three values) (**Figure 2**).

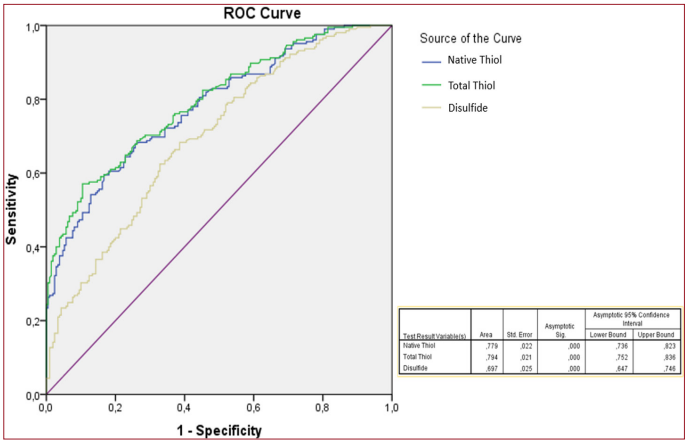

Figure 2: Receiver–operating characteristic analysis and curve for predicting stable coronary disease.

DISCUSSION

Our study is the first to investigate the relationship between thiol levels and disulfide/thiol ratio among all subgroups of ACS patients. We found that native and total thiol levels were significantly decreased in patients with the STEMI, non-STEMI, and UAP patients than the SAP groups. We did not find any significant difference between the ACS subgroups. Also, another interesting finding was shown in the ROC analysis: thiol and disulfide values predict an average of 70% sensitive and 70% specificity in detecting patients with SAP.

Oxidative stress can be described as the disruption of the balance between oxidants and antioxidants in favor of oxidants and causes harmful effects.[20] Oxidants (reactive oxygen species (ROS), which are the products of aerobic cellular metabolism, can occur in the intracellular or extracellular environment.[21-23] Physiologically, to maintain the oxidant-antioxidant balance, it is adapted to the body's antioxidant defense system composed of enzymes such as superoxide dismutase, glutathione peroxidase and catalase, enzyme-free molecules such as albumin, bilirubin and glutathione.[24,25] When oxidants are produced in large quantities or cannot be eliminated by antioxidants, cells cause active ROS to attack and changes occur.[24,26-28] Oxidative stress and inflammation are closely interrelated, and both cause injury to many cells in which they are involved in the endothelium and endothelial dysfunction is the first stage of atherosclerosis.[29-31] In our study, thiol and disulfide values and rates, which are the pre-emptive markers of the antioxidant system, were significantly lower than the stable CAD.

Thiols are sulfur analogs of alcohols and disulfides are structures containing adjacent double sulfur atoms.[13,32] The role of thiol/disulfide balance is vital in antioxidant reactions. Also, thiols, which are among the main components of intracellular and extracellular damage protection mechanisms, are non-enzymatic antioxidants. Plasma thiol groups reduce oxidative damage in diseases in the pathophysiology of inflammatory processes such as CAD, rheumatoid arthritis and diabetes mellitus.[33,34] In our study, low levels of thiol and disulfide in high ACS, especially in patients with stable CAD, may be evidence of the effect of the inflammatory and antioxidant system.

The relationship between atherothrombotic cardiovascular disease and oxidant stress has been demonstrated in several studies. These studies have shown that increased oxidant stress markers predict coronary heart disease and predict patients with coronary artery risk factors such as diabetes, hypertension, smoking, hyperlipidemia and obesity.[7] In the study of Schwedhelm et al., isoprostanes, which are considered as a marker of oxidant stress and are formed by peroxidation of arachidonic acid and are found to be high in patients with CAD and and showed that the risk of this disease increased by 30.8 times in those with the highest level of tertile isoprostane.[35] Shishehbor et al. found that plasma isoprostane levels were significantly higher in CAD with significant coronary artery stenosis.[36] Moreover, in the studies by Shishehbor et al and Guzik and et al., it was found that nitrotyrosine levels and expression of the NAD(P)H oxidase were significantly higher in patients with CAD than in controls.[37,38] Walter et al. found that serum lipid hydroperoxides levels during admission are also an independent indicator of the development of major adverse cardiovascular events.[39] In our study, low levels of thiol and disulfide may have triggered ACS. In other words, it should not be forgotten that it may be the cause, not the result.

The importance of antioxidants for atherothrombotic vascular disease occurs when there is a decrease in the catalytic activity of antioxidant enzymes. Decreased enzyme expression, genetic polymorphism, change in the functional properties of the enzyme, all result in reduced antioxidant capacity.[7] In the Espinola-Klein et al study, in the long-term follow-up of patients with documented atherosclerotic vascular disease, the lowest GPx-1 activity and the highest experience of cardiovascular events were determined. [40] Chen et al. and Dick et al. have shown that less heme oxygenase expression was associated with an increased risk of restenosis in peripheral arterial disease following an intervention. At the same time, successful coronary artery stenting procedures revealed that they were associated with an increased risk of restenosis as well as major adverse coronary and cerebrovascular events.[41,42] Elcik et al suggested that the thiol disulphide volume on admission was independently associated with the development of contrast-induced nephropathy after PCI in patients with ACS. [43] In our study, following these data, it was low in a severe event such as ACS.

In the literature, studies revealing the relationship between plasma thiol levels and thiol/ disulfide ratio and CAD are limited. Altiparmak et al demonstrated that the disulfide/ thiol ratio did not change significantly, but decreased native thiol levels were associated with the presence and severity of CAD.[9] Kundi et al showed that native thiol, total thiol and disulfide levels were lower in acute myocardial infarction (AMI) patients when compared to the controls and mean disulfide/native thiol and mean disulfide/total thiol ratios were higher in patients with AMI patients.[44] In our study, it has been shown that these values are high in patients with stable CAD, in addition to ACS patients. As a result, an antioxidant deficiency is thought to trigger ACS: it can indicate a significant difference between the stable patient and the unstable patient.

In the study published by Morrow et al., oxidant stress marker, myeloperoxidase concentration in patients with myocardial infarction was higher than those with UAP and associated with adverse complications such as non-fatal myocardial infarction or recurrent ACS events within the first 30 days.[45] Kundi et al study showed that the comparison of STEMI and non-STEMI patients did not reveal any differences for thiol, total thiol and disulfide levels or disulfide/ native thiol and disulfide/ total thiol ratio.[44] In our study, similar to Kundi et al. and the opposite of Morrow et al, plasma thiol levels and thiol/disulfide ratio decreased in the STEMI patients. However, there was no difference between the STEMI patients and the non-STEMI patients or any other subgroup of the ACS. Besides, in our study, in contrast previous studies, it was also found that thiol levels and thiol/ disulfide ratio were lower in the UAP patients compared to the stable CAD group. On the other hand, we found that there was no statistically significant difference between the ACS subgroups in thiol levels and thiol/disulfide ratios. It can be assumed that the decrease in serum thiol and disulfide levels is due to the use of reactive free radical and non-radical species to limit their harmful effects and pathophysiological sequences. These results suggest that thiol levels and thiol/ disulfide ratios can be used as markers to evaluate ACS.

Our work had some limitations. Firstly, this was a single-center retrospective study and there was a comparatively small number of patients. Thus, the selected population may not represent the whole aimed cohort. The second limiting factor was the evaluation of thiol levels with only one measurement. We did not evaluate the follow-up period. This is the first study to show these results: new studies with a more significant number of patients are needed to confirm the results obtained.

CONCLUSION

We think that ACS, which is quite difficult to distinguish, may be a new marker in distinguishing UAP from stable CAD. Besides, we have once again demonstrated the antioxidant system effect in ACS pathology in this study.

This is the first study to show these results: new studies with a more significant number of patients are needed to confirm the results obtained.

ETHICAL DECLARATIONS

Ethics Committee Approval: Kayseri City Hospital, Clinical research ethics committee; 03/2020-20

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

Frequency of Asymptomatic Human Immunodeficiency Virus, Syphilis, Hepatitis B and Hepatitis C in Circumcised Male Patients Diagnosed with Urethritis

Korunmasız Cinsel İlişki Sonucu Üretrit Tanısı Alan Sünnetli Hastalarda Asemptomatik HIV, Hepatit B, Hepatit C ve Sifiliz Görülme Sıklığı

Ender Siyez

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Abstract

Aim: In this study, it was aimed to determine the frequency of asymptomatic Human Immunodeficiency Virus (HIV), Hepatitis B, Hepatitis C, and syphilis in circumcised patients diagnosed with urethritis transmitted by sexual intercourse because of unprotected sexual contact.

Material and Method: We retrospectively investigated the serological results of HIV, Hepatitis B, Hepatitis C, and Syphilis diseases in 364 male patients diagnosed with urethritis, all of them were circumcised during childhood. The study included patients who applied to the urology outpatient clinic of secondary state hospital between January 2017 and December 2019 with symptoms or signs of urethritis. In the examination, only urethral discharge could be seen without symptoms. After the patients were examined, first void urine samples were taken. Also at the first examination, peripheral blood samples were tested for HIV, Hepatitis B, Hepatitis C, and syphilis antibodies.

Results: As a result of retrospective screening of the serological results of 364 male patients diagnosed with urethritis, Hepatitis B positivity was 1.09% with 4 cases, Hepatitis C positivity was found as 0.27% in 1 case and the Syphilis positivity rate was 1.92% with 7 cases in 364 patients. None of the patients had HIV positivity.

Conclusions: The fact that HIV-positive patients were not encountered in patients diagnosed with urethritis due to unprotected sexual contact has led to the thought that circumcision might have a protective contribution in these patients with urethritis who were all circumcised. Also, screening tests, especially syphilis, should be performed on all patients diagnosed with STI infection.

Keywords: Sexually transmitted disease, circumcision, HIV, syphilis, hepatitis B and hepatitis C

Öz

Amaç: Bu çalışmanın amacı korunmasız cinsel ilişki sonucu üretrit tanısı alan sünnetli hastalarda asemptomatik HIV, Hepatit B, Hepatit C ve sifiliz görülme sıklığının incelenmesidir.

Gereç ve Yöntem: Çocukluk döneminde sünnet olan ve üretrit tanısı almış olan 364 hastada HIV, Hepatit B, Hepatit C ve sifiliz için seroloji sonuçları retrospektif olarak incelenmiştir. Çalışma grubu Ocak 2017-Aralık 2019 yılları arasında ikinci basamak devlet hastanesine üretrit semptomları ile başvuran hastalardan oluşmaktadır. Hastaların bir kısmında sadece muayene bulgusu olarak üretral akıntıları vardı. Muayene sonrasında idrar örnekleri ve bunu takiben de HIV, Hepatit B, Hepatit C ve sifiliz için periferik kan örnekleri alındı.

Bulgular: Üretrit tanısı alan 364 hastanın seroloji sonuçları retrospektif olarak incelendiğinde 4 hastada (%1,09) Hepatit B pozitif, 1 hastada (%0,27) Hepatit C pozitif ve 7 hastada (%1,92) Sifiliz pozitif olarak bulundu. Hiçbir hastada HIV pozitifliği bulunmadı.

Sonuç: Korunmasız cinsel ilişki sonrası üretrit tanısı alan hiçbir hastada HIV-pozitif olmamasında sünnetin koruyucu etkisinin olabileceği düşünülmektedir. Bununla birlikte cinsel temasla bulaşan enfeksiyon tanısı alan hastalarda başta sifiliz olmak üzere diğer cinsel temasla geçen hastalıkların da taraması yapılması önerilmektedir.

Anahtar kelimeler: Cinsel yolla bulaşan hastalıklar, sünnet, HIV, sifiliz, hepatit B ve hepatit C

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INTRODUCTION

A sexually transmitted infection (STI) is defined as an infection that results from the transmission of a pathogenic organism by sexual contact with any genital or anal contact with another person's genitals, anus, or mouth.[1] STI are a major public health problem and the key marker of unprotected sexual contact. STIs can be seen at all ages, while often affecting adolescents and young people. STIs cause pelvic inflammatory disease, infertility, genital malignancies and increase the risk of Human Immunodeficiency Virus (HIV) acquisition and transmission while having negative effects on sexual life and maternal-child health. Asymptomatic or symptomatic STIs enhance HIV shedding at genital mucosal sites and increase infectiousness from HIV-positive individuals. Therefore, timely recognition of STIs, their treatment, and prevention are of great importance in preventing HIV transmission. According to Joint United Nations Programme on HIV/AIDS (UNAIDS) 2020 data, while 38 million HIV-positive people lived in the world, 1.7 million new HIV-positive cases were detected in 2019, while 690 thousand people died from AIDS-related illnesses.[2]

In many countries, the most common STI syndrome seen in men is urethritis.[3] Since STIs can be asymptomatic, their screening is important for early detection of infection and prevention of its spread. Testing is the only way to screen and diagnose these infections. The epidemiological data on syphilis, Hepatitis B (HBV), Hepatitis C (HCV), and HIV in our country consist of blood bank data, since the largest series of blood donors belong to the selected, healthy population that does not give a history of risky sexual contact. According to Izmir Ataturk Training and Research Hospital Blood Center data, 80454 Blood donors applied to the center between 2004 - 2010, were investigated by VDRL, HBsAg, anti-HVC, anti-HIV. There were 39 VDRL positive donors (0.04%), 1,054 HBsAg positive donors (1.31%), 312 anti-HCV positive donors (0.38%), and 2 anti-HIV positive donors (0.002%).[4]

Male circumcision is one of the oldest surgical procedures, and almost all Muslim and Jewish men are circumcised. [5] 99% of the male population of almost all ages in our country is circumcised for religious and social reasons.[6] The relationship between STI and male circumcision was first reported by Hutchinson in 1855 in the study that 61% of non-Jews and 19% of Jewish patients had syphilis.[7] Subsequent studies support this finding by reporting higher than expected cases of uncircumcised men compared to be circumcised in case series of genital herpes, syphilis, chancroid, and gonorrhea.[8-10] Three randomized controlled trials demonstrating the effectiveness of circumcision in HIV prevention in young men in Africa have been very promising. [11-13]

In this study, we aimed to investigate the frequency of asymptomatic HIV, HBV, HCV, and Syphilis in patients who developed urethritis after unprotected sexual intercourse in a country where almost all the population is circumcised.

MATERIAL AND METHOD

Between 2017 January to December 2019, 1100 patients diagnosed with urethritis applied to the secondary state hospital urology outpatient clinic. 8 urologists work in our outpatient clinic. During this period, it was seen that only 364 patients were screened for HIV, HBV, HCV and syphilis disease, depending on doctors' preferences. All these 364 patients are primary and circumcised during childhood were retrospectively investigated. Since female patients with the same complaints and symptoms apply to the gynecology department, female patients are not seen in the urology outpatient clinic. Patients had complaints of dysuria, urethral discharge, and urethral pruritus. In the examination, only urethral discharge could be seen without symptoms. An anogenital examination includes inspection of the penis, scrotum, perianal area, and palpation of the penoscrotal contents. Clinicians also asked each patient if they used condoms for sexual contact. After the examination, the first void urine was examined. For the diagnosis of urethritis positive leukocyte esterase test on first-void urine or greater than or equal to 10 leukocytes per high-power microscopic field of the first-void urine sediment were used. Differential diagnosis of Neisseria gonorrhoeae and Chlamydia trachomatis could not have been made. Also at the first examination, peripheral blood samples were tested for HIV, HCV, HBV, and syphilis antibodies.

For syphilis screening, firstly the nontreponemal test was applied, Venereal Disease Research Laboratory (VDRL) test method (MedNet Gmbh Germany, Acro Biotech Inc USA). If VDRL was reactive, a treponemal test was applied, Treponema pallidum hemagglutination assay (TPHA) (MonlabTest Barcelona, Spain). HBsAg, anti-HCV, and anti-HIV screening tests were performed by enzyme-linked immunosorbent assay (ELISA) (Architect System, Model i 2000sr Abbott Diagnostics, USA). Anti-HIV positive cases were studied again and in cases of repetitive anti-HIV positivity, serum samples were sent to Refik Saydam Hygiene Center for Western Blot confirmation. Samples with positive HBV and HCV results were re-tested and when they were positive again, the patients were referred to the infectious diseases department for confirmation tests and follow-up.

Syndromic urethritis treatment was applied after the laboratory results of the patients were obtained. For partner treatment, all patients were informed that those with whom the patients had sexual contact should also use medication. All patients with urethritis were informed for serologic analysis again in the 6th and 12th months after serological analysis was performed at the time of admission.

The study protocol was approved by Izmir Demokrasi University Buca Seyfi Demirsoy Training and Research Hospital Non-interventional Clinical Researches Ethics Committee (Date: 31.03.2021, Decision No: 2021/3-24).

Statistical Analysis

Patients' age was defined as mean ± SD. All statistical analyses were performed by using the Statistical Package for the Social Sciences (SPSS) Version 24.0.

RESULTS

The electronic medical records were analyzed. There were 364 men enrolled in the study, all circumcised during childhood. The age of the patients varied between 16 and 59 and the average age was 27,65 (M=27.65, sd=8.7). When the age distribution of the patients is observed, the majority is between the ages of 20-29 with 63.2%, and especially between 20-24, it comes first with 37.3%. We learned from the anamnesis of all the patients that they had heterosexual intercourse and they did not use condoms regularly. 275 of 364 patients were single (75.54%) 89 were married (24.45%). Anogenital examinations of all patients were evaluated as normal.

When the serological test results were evaluated, there were not any anti-HIV positive patients. We identified 7 (1.92%) people after screening them with VDRL and TPHA for syphilis. When the patients with syphilis are examined by age groups, it is the most intense group with 3 patients (42%) over the age of 35. The treatment of these 7 patients was initiated and their follow-up continued. While anti-HCV positivity was detected in only one patient (0.27%) in the HBC screening, HbsAg positivity was found in 4 patients (1.09%) for HBV. No HIV was found in patients with urethritis, and the distribution of Hepatitis B, Hepatitis C and Syphilis cases according to age groups is given in **Table 1**.

Table 1: Age distribution of the study population (n= 364)

	n (%)	Hepatitis B HBsAg		Hepatitis C Anti-HCV		Syphilis VDRL		Total	
		f	%	f	%	f	%	f	%
Age < 19	29 (8.0)	-	-	-	-	-	-	-	-
Age 20-24	136 (37.3)	1	25.0	-	-	1	14.3	2	16.7
Age 25-29	94 (25.9)	-	-	-	-	2	28.6	2	16.7
Age 30-34	46 (12.6)	1	25.0	1	100	1	14.3	4	33.3
Age 35	59 (16.2)	2	50.0	-	-	3	42.8	4	33.3
Total	364 (100)	4	100	1	100	7	100	12	100

HBsAg: Hepatitis B surface antigen, HCV: Hepatitis C, VDRL: Veneral Disease Research Laboratory test method.

DISCUSSION

Urethritis is the most common STI and we encounter it frequently in our daily practice. Circumcision not has effect on preventing urethritis.[14] Again, no mention has been made of the relation between hepatitis transmission and circumcision. The HbsAg and anti-HCV rates that were found as a result of the study are close to the blood bank results in our country. In the study group, HbsAg positivity was 1.09% in 364 patients with 4 cases. In our country, according to Izmir Ataturk Training and Research Hospital Blood Center data, 80454 Blood donors HBsAg was positive in 1.054 donors (1.31%). Since we live in the same geography, if European Centre for Disease Prevention and Control (ECDC) data is looked at, in Europe HBV prevalence is estimated to be 0.9% corresponding to almost 4.7 million HBsAg-positive cases.[15] In the study group, anti-HCV positivity was found as 0.27% in 1 case in 364 cases. While anti HCV positivity was 0.38% according to the data of our country's blood bank when we looked at the patients in our study group, it was found 0.27%. Studies have shown that adults in a stable heterosexual relationship with HCV-infected partners were not associated with an increase in virus transmission risk.[16] In recent years, however, outbreaks of HCV have been reported in men who have sex with men, probably due to the sexual practices involving anorectal mucosal trauma and presence of genital ulcerative disease, especially those co-infected with HIV. It is important to investigate the prevalence of sexual transmission of HCV in risky sexual behavior.[17] According to ECDC, prevalence for HCV is 1.1%, corresponding to around 5.6 million anti-HCV-positive cases.[18]

In the study group, syphilis was the highest in asymptomatic patients with urethritis due to unprotected sexual contact, and the rate was 1.92% with 7 cases in 364. Syphilis is closely related to public health because of its sexual transmission, latent course, and can be transmitted through transfused blood. Our country's blood bank syphilis screening results are 40/100000 and ECDC data syphilis prevalence result is 7/100000.[18] It was mentioned that previous studies that circumcision reduces the transmission of syphilis disease. The rate of asymptomatic syphilis in patients diagnosed with urethritis as a result of risky sexual behaviors, whether circumcised or not, is 1.92%, which is a high rate. This high rate indicates the need for public health interventions, and the implementation of risk reduction strategies that focus on those with unprotected sexual contact. It has been reported that this rate reaches up to 15% in people who engage in risky sexual behavior around the world.[19-21]

As it is mentioned before, circumcision reduces the transmission of ulcerative diseases such as HIV and syphilis in many studies. There was not anti-HIV positivity in any of 364 patients who had unprotected sexual contact and were diagnosed with urethritis accordingly. The first AIDS case in Türkiye was diagnosed in 1985, and the total official number was reported as 6188 at the end of December 2012.[22] Türkiye is one of the lowest countries in Europe with HIV-1/AIDS prevalence. Our country's blood bank HIV screening results are 2/100000. HIV positivity continues to be at a lower level compared to the European countries in which Türkiye is in the same geography. According to ECDC HIV prevalence was 6.3/100,000 population.[23]

While 80% of HIV-positive cases are through sexual contact, 70% of them are through vaginal intercourse, the rest are through anal sex. As it turns out, the penis plays an important role in contamination. After three RCTs showed that circumcision reduces the spread of HIV infection in young men in Africa, there have been many studies on how circumcision prevents this. However, the mechanism of how circumcision reduces the transmission is still not fully understood. The uncircumcised penis is more susceptible to minor trauma and ulcerative disease, and the

preputial sac acts as a reservoir for pathogenic organisms that accumulate under the prepuce.[24] Depending on the infection, immune system cells consisting of CD4 + T cells, Langerhans cells, and macrophages are collected in the mucosal epithelium. While these immune system cells protect from infectious microorganisms, when they encounter HIV, CD4 receptors form portals for HIV uptake and are transported to Langerhans cells. Langerhans cells bind with HIV and migrate rapidly, forming conjugates with T cells and transferring HIV to T cells. Thus, T cells can initiate the spread of the infection. The removal of the preputium during circumcision results in the removal of portal cells for HIV entry, which is densely located in the inner part of the foreskin.[25-27] During intercourse in the uncircumcised penis, the foreskin retracts and exposes a large surface area of high-density superficial Langerhans and other HIV target cells to HIV-infected secretions. After circumcision, a significant reduction in anaerobic bacteria was observed due to the removal of subpreputial anoxic microenvironments. The reduction in anaerobic bacteria reduces the number of Langerhans cells activated, thus eliminating the gate to HIV.[28,29]

When the age distribution of the patients with urethritis is looked at, it is seen that they are in the adolescent group with a rate of 8.5%. It is thought that this figure is high and remarkable. Despite the contribution of circumcision in reducing the rates of some sexually transmitted diseases, it is necessary to see that it is not enough by itself and is ineffective at preventing every STI. Sexual health education at schools and counseling people with risky sexual behaviors on ways to avoid STIs are being done. When used correctly and consistently, male latex condoms are the most effective method to reduce the risk of STI.[30] Pre-exposure vaccination of people at risk could be effective for vaccine-preventable STIs. Identification of asymptomatically infected people and people with symptoms associated with STIs; effective diagnosis, treatment, counseling, and follow-up them. Postexposure prophylaxis should be kept in mind in appropriate cases. It is necessary to also evaluate the partners of the people infected with STI, to treat them if they are ill, and inform them about the STIs.

This study was subject to several limitations. Firstly, the cases included in our study consisted of male patients with a history of risky sexual behavior and, according to them, suffering from urethritis. However, due to the conditions of our country, the urology outpatient clinics of the hospitals mainly serve male patients in the young and adult age groups. The fact that female patients prefer gynecology outpatient clinics prevents a healthy interpretation in terms of gender distribution, which can be considered as a limitation of our study. Another limitation is that the study was retrospective, a nonrandomized small number of patients, and single centered. Large multicenter studies are necessary for more detailed results.

CONCLUSION

We examined men who were circumcised due to social and cultural reasons of 99% of the men in the society and who were diagnosed with urethritis because of sexual intercourse without using a condom. Although HIV positive rates in terms of our geographical location are still low, there has not been any encounter of HIV positivity in patients with STI because of risky behaviors. It is thought that circumcision may contribute to this. In addition, as a result of the study, the rate of asymptomatic syphilis to be 1.92% is considered as a high rate. This result indicates the need for public health interventions, and the implementation of risk reduction strategies that focus on those with unprotected sexual contact. It was found that only 364 out of 1100 patients who applied to the urology outpatient clinic with urethritis were screened. Due to the 1.92% detection rate of syphilis, it is thought that more willingness and determination should be made in screening for asymptomatic STI diseases in STI cases.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study protocol was approved by Izmir Demokrasi University Buca Seyfi Demirsoy Training and Research Hospital Non-interventional Clinical Researches Ethics Committee (Date: 31.03.2021, Decision No: 2021/3-24).

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

The Changes in The Anti-HBs Values Following COVID-19 Pneumonia

COVID-19 Pnömonisi Sonrası Anti-HBs Değerlerindeki Değişiklikler

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Abstract

Aim: We aimed to determine if there is a decrease in Anti-HBs titer below the protective value during Coronavirus-19 disease (COVID-19).

Material and Method: A prospective study was made of 67 patients who had positive Anti-HBs values checked in the last 1 year. Demographic data and the previous Anti-HBs values were collected from the patient files and the laboratory findings of new Anti-HBs titers checked after one months later following COVID-19 infection were compared with the previous ones.

Results: In the postcovid evaluation, a statistically significant decrease in the Anti-HBs levels of COVID-19 patients was determined with respect to previous values before COVID-19 infection ($p<0.001$).

Conclusion: In our study, we found that there was a statistically significant decrease in Anti-HBs levels after COVID-19 infection, but none of them were below protective Anti-HBs levels. As a result,we can say that despite the COVID-19 infection,protection against Hepatitis B continues in people with positive Hepatitis B antibodies.

Keywords: COVID-19, Anti-HBs , antibody level

Öz

Amaç: Coronavirus-19 hastalığı (COVID-19) sırasında Anti-HBs titresinin koruyucu değerin altına düşüp düşmediğini belirlemeyi amaçladık.

Gereç ve Yöntem: Son 1 yıl içinde pozitif Anti-HBs değerleri kontrol edilen 67 hasta ile prospektif bir çalışma yapıldı. Demografik veriler ve önceki Anti-HBs değerleri hasta dosyalarından toplandı ve COVID-19 enfeksiyonundan bir ay sonra kontrol edilen yeni Anti-HBs titrelerinin laboratuvar bulguları öncekilerle karşılaştırıldı.

Bulgular: COVID-19 sonrası yapılan değerlendirmede COVID-19 hastalarının Anti-HBs düzeylerinde COVID-19 enfeksiyonu öncesi önceki değerlere göre istatistiksel olarak anlamlı düşüş saptandı ($p<0.001$).

Sonuç: Çalışmamızda COVID-19 enfeksiyonu sonrası Anti-HBs düzeylerinde istatistiksel olarak anlamlı bir düşüş olduğunu ancak bunun koruyucu Anti-HBs düzeyinin altında olmadığını gördük. Sonuç olarak Hepatit B antikoru pozitif kişilerde COVID-19 enfeksiyonuna rağmen Hepatit B'ye karşı koruyuculuğun devam ettiğini söyleyebiliriz.

Anahtar Kelimeler: COVID-19, Anti-HBs, antikor düzeyi

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INTRODUCTION

Coronavirus-19 disease (COVID-19) is an infectious disease caused by a newly discovered. Coronavirus which was first seen in Wuhan. This new virus was identified in 2019, SARS-CoV-2, has caused a pandemic of respiratory illness and called COVID-19 pandemia. It spreads from person to person mainly by respiratory droplets produced when an infected person breaths, talks, laughs, sings, coughs or sneezes. This virus unfortunately can spread also by asymptomatic people. Larger droplets may fall to the ground in a few seconds, but tiny infectious particles can hang in the air and accumulate in closed places. COVID-19 is associated with diffuse lung damage. Most of the hospitalizations were due to Pneumonia. Glucocorticoids may modulate inflammation-mediated lung injury and thereby reduce progression to respiratory failure and death.[1] Steroids may be required in patients who do not respond to antiviral therapy. Sometimes this treatment can be given in high doses. It is obvious that there is a possibility of activation of diseases that may exacerbate in immunosuppression in the body due to immunosuppression that may develop due to both the disease andthe drugs to be used. One of them is hepatitis B virus (HBV) infection. HBV infection remains a major global healthcare challenge.[2] Approximately 95% of individuals acutely infected in adulthood will spontaneouslyseroconvert and lose hepatitis b surface antigen (HBsAg).[2] It is well known that immunosuppression can stimulate replication of hepatitis B virus and precipitate severe flares of HBV infection. Fortunately, it can be largely prevented by prophylactic therapy with oral AntiHBV nucleosid/nucleotide analogues.[3] HBV is a heterotropic virus that has been shown in previous publications to be exacerbated under immunosuppression. An increasing number of therapeutic agents used are likely to interfere with the natural course of HBV infection. The risk of HBV reactivation is much lower in patients negative for HBsAg and positive for Hepatitis B Core antibody (Anti-HBc).[4] Anti-HBs is an antibody produced by the body against the surface antigen of the hepatitis B virus. Clinical interpretation of (+) Anti-HBs is recovery from acute or chronic infection and immunity following vaccination. HBsAg negative, AntiHBc positive serology usually indicative of past exposure to virus. Testing for HBV serology before initiating immunosuppressive medication is recommended by international societies.[2] Activation after exacerbation can lead to severe liver failure and can be mortal. Risk can be minimised through appropriate screening, monitoring and antiviral prophylaxis.

Therefore, the risk of hepatitis B activation should be estimated and precautions should be taken in necessary patients. The aim of our study is to investigate if there will be a decrease in Anti-HBs values and if so, will we need or not a booster vaccination following COVID-19 infection.

MATERIAL AND METHOD

Data collection

The research was designed as a prospective study and included 100 patients diagnosed and hospitalized with COVID-19 pneumonia in University of Health Sciences, Prof. Dr. Cemil Tascioglu City Hospital between July 2021 and October 2021. Sixty seven of these 100 patients met the study criterias. The study inclusion criteria were as follows: 1-) Having given consent to participate in the study, 2-) Anti-HBs positive and HbsAg negative patients hospitalized with COVID-19 pneumonia, 3-) Not to be diagnosed with malignancy. 4-) To be over 18 years old.

Data were retrieved from the each patient with the diagnosis of COVID-19 pneumonia, in respect of medical history, age and sex; the laboratory data including Anti-HBs and Anti-HBc IgG values checked for nonspecific reasons in the last 1 year before internationalization of these patients were taken from medical records. It means Anti-HBs titers were checked at least once before and after COVID-19 infection. During the hospitalizations,we also recorded the laboratory findings like fibrinogen, ferritin, d-dimer, complete blood count including lymphocyte count, C-reactive protein (CRP), procalcitonin,internalised normalised ratio (INR), glucose, urea, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumine, total bilirubine (T.bil), direct bilirubine (D.bil) and the duration of hospitalization time, given treatments and their duration, if any, cases of referral to the intensive care unit and discharge information.

When the patients who were discharged after hospitalization with covid -19 pneumonia came to the outpatient clinic control one month later, blood was taken from each patient in a biochemistry tube and centrifuged, and their blood serum was placed in 2 ml eppendorfs and stored in the refrigerator at -80 degrees in the laboratory of our hospital until the end of the study. When sufficient number of patients was reached, blood serums were taken out of the refrigerator which was at -80 degrees and Anti-HBs measurements were made. Anti-HBs levels were examined by using the Roche Hitachi Cobas 8000 modular analyzer system (Roche Diagnostics, Germany).

To conduct this study, ethical approval was granted by the Local Ethics Committee (reg: E- 48670771- 514.10). Prior to the study, informed consent was obtained from all patients.

Statistical Analysis

Normality control of continuous variables was evaluated with the Shapiro Wilk test. Non-parametric methods were chosen in the relevant analyzes since Anti-HBs values did not conform to the normal distribution. The Wilcoxon test was used to compare the 1st and 2nd Anti-HBs values, the Mann Whitney U test was used to compare the two independent groups, and the Spearman Rho correlation coefficient was calculated while examining the linear relationship with continuous variables. Data analysis was done in SPSS 21 program and $p<0.05$ was considered statistically significant.

RESULTS

One hundred patients who had previous Anti-HBs positivity in the last one year, with the diagnosis of COVID-19 pneumonia have been evaluated. A total of 67 adult patients who met the study criteria were included in the study. The patients comprimised 41 males (61.2%) and 26 females (38.8%) with a mean age of 58.3±18.4 years. Summary of the demographic and laboratory findings of the patients are shown in **Table 1**. Total AntiHBc was positive in 43 (64.2%) of the patients. 24 (35.8%) patients have not received immunosuppressive treatment. 43 (64.2%) Patients have received immunosuppressive treatment. The decrease in Anti-HBs titers after COVID-19 infection was statistically significant (p<0.001). Anti-HBs titers before and after the COVID-19 infection are shown in **Table 2** and **Figure 1**.

The decrease in Anti-HBs values was higher in men compared to women (p=0.002). The difference in Anti-HBs levels between male and female genders is shown in **Table 3**. When compared with other laboratory parameters and length of stay, it was observed that the albümin level had a significant effect on the difference in Anti-HBs values before and after COVID-19 infection. As albumin values decrease, an increase in Anti-HBs difference is observed (r:-0.273 p=0.025). The findings are shown in **Table 4**. In addition, when the difference of Anti-HBs values before and after COVID-19 infection was evaluated according to the treatment applied, no significant relationship was found. Anti-HBs difference according to treatment is shown with **Table 5**. Among our 67 patients, 4 (6%) patients have postcovid Anti-HBs levels of less than 20 miu/mL. These values were near to the lower protective limit of Anti-HBs level. The 9 patients who had Anti-HBs levels of 1000 miu/mL before COVID-19 infection, have also postCOVID Anti-HBs levels of 1000 except one patient whose Anti-HBs level has decreased 57.5%. Of these 9 patients only one has antiHBc IgG (+) an the other 8 have Anti-HBc IgG (-). There were not a statistically significant difference between the Anti-HBc IgG positive and negative groups with respect to the amount of decreasement in Anti-HBs levels.

Table 2: Anti-HBs values before and after COVID-19 infection

	Mean±SD	Median [IQR]	Min-Max	P value
1.Anti-HBs	304.1±329.2	149 [61-427.8]	13.7-1000	<0.001*
2.Anti-HBs	263.2±312.2	118 [43.7-394]	10.9-1000	
Anti-HBs difference	40.9±104.7	13.3 [0-53]	-275-700	

p: Wilcoxon test, *: refers to significant values, 1.Anti-HBs : Anti-HBs level before COVID-19 infection, 2. Anti-HBs : Anti-HBs level after COVID-19 infection.

Table 3: Anti-HBs difference between male and female genders

Anti-HBs difference	Mean±SD	Median [IQR]	Min-Max	P Value
Female	-2.7±84	4.38 [-15.3-21]	-275-202	0.002*
Male	68.5±107.9	27 [6.3-114]	-90.3-425	

p: Mann Whitney U test, *: refers to significant values

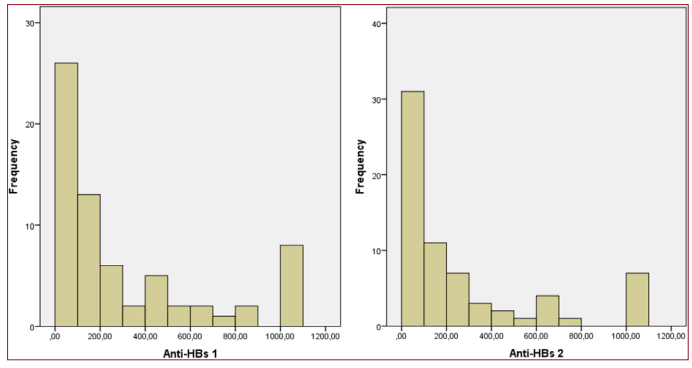

Figure 1: Anti-HBs values before and after COVID-19 infection.

Table 1: Summary of the demographic and laboratory findings of the patients

	Mean±SD	Median [IQR]	Min-Max
Age (year)	58.3±18.4	58 [44-74]	21-92
Albumin (g/dL)	3.4±0.5	3.2 [3-3.8]	2.2-4.2
Total bilirubin (mg/dL)	0.6±0.4	0.6 [0.3-0.9]	0-2.1
GGT (U/L)	69.5±56.7	53 [36.5-87.5]	14-419
WBC (µl/mL)	7573.6±4058.2	7000 [4700-9400]	1200-21900
Hb (g/dL)	12.5±2.6	13 [11.2-13.9]	7.7-17
Trombosit (/mm³)	217761.2±98937.1	201000 [144000-289000]	25000-486000
CRP (mg/L)	100.7±73.1	94 [26.5-155.8]	0.7-271
Procalcitonin (ng/mL)	0.5±1.4	0.08 [0-0.3]	0.01-7.6
D-Dimer (ng/mL)	1147.7±1178	800 [320-1500]	60-5800
Ferritin (ml/ng)	835.8±758.1	670 [231-1203]	34-3243
Fibrinogen (mg/dL)	563.5±189.1	583 [462-694]	170-1012
INR	1±0.3	1 [0.9-1.1]	0.2-3
Glucose (mg/dL)	133.1±65.6	111 [88-155]	71-355
ALT (U/L)	39.6±37.9	24 [16-52]	3-187
Creatinin (mg/dL)	1.3±1.6	0.8 [0.7-1.1]	0.2-8.3
Lymphocyte count (10^9/L)	849.1±520.2	800 [500-1060]	100-3000
Hospitalization (day)	12.8±9.1	11 [7-17]	3-57

GGT: Gamma-glutamyl transferase, WBC: White Blood Cell. Hb:hemoglobin, CRP: C-reactive protein, INR: International normalized ratio, ALT: Alanine aminotransferase

Table 4: The effect of laboratory parameters and length of stay on Anti-HBs difference

Anti-HBs difference	r	p
Age	0.24	0.05
Anti HBc IgG (s/co)	-0.203	0.1
Albumin (g/dL)	-0.273*	0.025*
Total bilirubin (mg/dL)	0.087	0.486
GGT (U/L)	0.171	0.171
WBC (µl/mL)	-0.006	0.962
Hb (g/dL)	0.028	0.823
Thrombocyte	-0.01	0.935
CRP(mg/L)	-0.027	0.831
Procalcitonin (ng/mL)	-0.091	0.466
D-Dimer (ng/mL)	0.219	0.074
Ferritin (ml/ng)	-0.011	0.931
Fibrinogen (mg/dL)	0.115	0.36
INR	0.035	0.78
Glucose (mg/dL)	-0.047	0.708
ALT (U/L)	0.081	0.514
Creatinin (mg/dL)	0.015	0.903
Lymphocyte count(10^9/L)	-0.048	0.702
Hospitalization (day)	0.239	0.051

p: Spearman Rho Correlation, *: refers to significant values, GGT: Gamma-glutamyl transferase, WBC: White Blood Cell, Hb: hemoglobin, CRP: C-reactive protein, INR: International normalized ratio, ALT: Alanine aminotransferase

Table 5: The effect of the treatment applied in COVID-19 patients on the level of Anti-HBs difference

	Anti-HBs difference			
	Mean±SD	Median [IQR]	Min-Max	P Value
Anti-HBc IgG				
Present	43.9±95.2	21.3 [4.5-90]	-275-267.42	0.099
Absent	35.5±121.8	6.6 [0-35.2]	-157-425	
Immunoplasma				
Present	34.6±49.2	19.7 [1.82-6]	-6.3-129	0.822
Absent	41.5±108.8	13.3 [0-60.5]	-275-425	
Methylprednisolone				
Present	33.6±91.1	12.3 [0-32.5]	-157-267.42	0.425
Absent	45.5±113.3	21.3 [0-71.5]	-275-425	
Pulse steroid				
Present	33.7±61.9	12.1 [0-65.5]	-65-189	0.79
Absent	43.3±116.1	16.4 [0-56.7]	-275-425	
Tocilizumab				
Present	79.1±95.9	36 [12.4-]	12.4-189	0.296
Absent	39.1±105.4	12.9 [0-51.5]	-275-425	
Macrolide				
Present	40±91.3	18 [0-67.9]	-157-364	0.661
Absent	42.5±127.3	7.4 [0-32.4]	-275-425	
Ceftriaxone				
Present	43.2±115.8	13.7 [3.18-69.5]	-275-425	0.616
Absent	35±71.4	13.3 [0-44]	-50.4-266	
Piperacillin tazobactam				
Present	16.9±127.9	12.6 [0-41]	-275-266	0.647
Absent	45.6±100.2	16.4 [0-64.2]	-157-425	
Dexamethasone				
Present	62.8±108.5	33.2 [5.05-108]	-90.3-364	0.184
Absent	32.2±103	12.5 [0-34.8]	-275-425	
Meropenem				
Present	13±0.5	13 [12.6-]	12.6-13.3	0.985
Absent	41.8±106.2	14.7 [0-60.5]	-275-425	

p: Mann Whitney U test

DISCUSSION

In the current medical literature there was not any information about the effect of COVID-19 infection itself on Anti-HBs levels. In our research the Anti-HBs levels of the patients with COVID-19 infection were decreased significantly (p<0.001). No significant difference was found between immunosuppressive treatment or the use of any drug and the significant decrease in Anti-HBs values. We thought that the decrease in Anti-HBs values was secondary to the COVID-19 infection itself. In the prospective study of Sergio Rodriguez et al they analysed the risk of HBV reactivation in patients with severe COVID-19 undergoing immunosuppressive therapy. By supporting our findings, they showed that the risk of HBV reactivation in patients with severe COVID-19 undergoing immunosuppressive treatment is low.[5]

Perillo et al. said that steroids decrease specific T-cell response and increases the virus replication and the risk of infection is directly proportional to the duration and dose of the steroid.[6] In our research we have not seen any effect of duration or amount of steroids given on Anti-HBs levels. Demet Yalcın Kehribar et al. studied the impact of tumor necrosis factor alpha antagonist treatment on antibody titer of hepatitis B surface antigen and they showed that there was a statistically significant decrease in the Anti-HBs levels after immunosuppressive treatment also they observed that in a small number of patients the level of Anti-HBs decreased to a risky level.[7] Therefore they suggested booster vaccination against hepatitis B virus in these patients. In our study also similar to their research there was not any reactivation of hepatitis B virus. The study of Yuri Cho et al. was named as the titer of Anti-HBs prevent rituximab-related viral reactivation in resolved hepatitis B patients with non-Hodgkin's lymphoma.[8] They showed that 8 cases of 108 resolved hepatitis B patients had HBV reactivation with Anti-HBs titers less than 100 mıu/mL. They said that high baseline Anti-HBs titers prevented HBV reactivation and suggested antiviral prophylaxis should be considered according to Anti-HBs titer. In another study of Tamori et al. they also showed that there was a significantly decrease in Anti-HBs levels after anti-TNF alpha treatment.[9] Vassilopoulos et al. had similar results with Tamori et al.[10] Cam et al. showed that protective AntiHBs levels remarkably altered after chemotherapy in the pediatric oncology cases.[11] Francois-Xaiver et al.said that monitoring the AntiHBs level remains necessary as it has been reported that only 42% of HIV infected responders kept their protective titers 13-18 months after their last dose of vaccine.[12,13] Marinaki et al. emphasized that immunosuppression is intimately associated with increased viral replication.[14-20] In our study,the decrease in Anti-HBs values was higher in men compared to women. Although there is no information in the literatüre on this subject,it was thought that this situation may be due to hormonal differences between 2 genders because sex hormones may have an affect on immunity; in women, estrogen reduces pro-inflammatory signals.[21] Kim S et al.

emphasized that although the effect of gender on immunity is well known,more studies are needed on this subject.[22] Irelli et al. said that androgens suppress the activity of immune cells and estradiol improves immune responses; estrogens stimulate plasma cells to produce immunoglobulins.[23] Also there is a greater oxidative stress in men due to reduced activity of antioxidants.[24] The strength of immune responses differ between women and men; women are in general able to mount a more vigorous immune response to infections and vaccinations.Common biological pathways leading to immune activation are regulated by sex linked factors.[25] Guglielmo et al. expressed that hepatitis B virus represents a leading cause of acute or chronic liver disease so the goal is to assure individual protection, also providing booster doses when needed after many years following the primary vaccination but we suggest that after viral infections maybe we should not wait untill late years and we may need early booster vaccinations.[26]

CONCLUSION

To sum up; in our research we observed that the Anti-HBs levels of the patients with COVID-19 infection decreased significantly; we haven't seen any reactivation. At beginning of our research we had wondered which Anti-HBs levels were more likely to decrease after COVID-19 infection but we could not see a cut off value for Anti-HBs level. In non of the patients, despite the decrease in Anti-HBs levels, we have not seen a decrease of Anti-HBs levels to a risky level below the protective value. For this reason, we thought that intermittent booster doses of HBV vaccination were not necessary in our patients. On the other hand, in some of the patients there were Anti-HBs decrease near to the lower limit of protective Anti-HBs values, therefore, if we can search more patients maybe we would find more decreasements below the protective Anti-HBs levels. Therefore further research is needed to validate this with more patients.

ETHICAL DECLARATIONS

Ethics Committee Approval: Approval for this study was granted from University of Health Sciences, Prof. Dr. Cemil Tascioglu City Hospital Ethics Committee for Clinical Studies in July 2021 (reg: E- 48670771- 514.10).

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

The State-Trait and Death Anxiety of Turkish Society During The COVID-19 Pandemic

COVID-19 Pandemisi Sırasında Türk Toplumunun Durumluk-Süreklilik ve Ölüm Kaygısı

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Abstract

Introduction: The novel coronavirus disease (COVID-19) quickly spread all over the world and caused many deaths in Türkiye as in the whole world. COVID-19 is potentially lethal and effects the mental health of people. It is important to detect the potential psychological changes in a timely manner during pandemic. We aimed to determine the anxiety levels and associated risk factors of the society during COVID-19 in Türkiye.

Material and Method: This was a cross-sectional study conducted throughout Türkiye during the pandemic. The questionnaires were delivered to the participants via Google Forms which contain three main parts: 1) Demographics, 2) State-Trait Anxiety Inventory (STAI), and 3) Thorson–Powell's Revised Death Anxiety Scale (RDAS). The questionnaire was first published on April 15, 2020, and data were collected for a period of 30 days.

Results: 8,917 questionnaire forms filled out by Turkish society were included in the study. The anxiety level and fear of death were higher in olders, females, parents, smokers, people who have comorbidities, social media users, and people who have higher education levels.

Conclusion: In our study, It was determined that COVID-19 has negatively affected the mental health of the population by increasing the anxiety levels and fear of death in Türkiye. People who have higher anxiety levels and fear of death should be identified, and psychological support should be provided to these people.

Keywords: COVID-19, mental health, Turkish society, state-trait anxiety inventory, Thorson–Powell's revised death anxiety scale

Öz

Giriş: Yeni koronavirüs hastalığı (COVID-19) tüm dünyaya hızla yayılarak tüm dünyada olduğu gibi Türkiye'de de çok sayıda ölüme neden olmuştur. COVID-19 potansiyel olarak öldürücüdür ve insanların ruh sağlığını etkiler. Potansiyel psikolojik sorunları tespit etmek önemlidir. Türkiye'de COVID-19 sürecinde toplumun kaygı düzeylerini ve ilişkili risk faktörlerini belirlemeyi amaçladık.

Gereç ve Yöntem: Bu, pandemi döneminde Türkiye genelinde yapılmış kesitsel bir çalışmadır. Anketler katılımcılara üç ana bölümden oluşan Google Formlar aracılığıyla iletildi: 1) Demografi, 2) Durumluk-Sürekli Kaygı Envanteri (STAI) ve 3) Thorson-Powell'ın Gözden Geçirilmiş Ölüm Kaygısı Ölçeği (RDAS). Anket ilk olarak 15 Nisan 2020 tarihinde yayınlanmış ve 30 günlük bir süre boyunca veriler toplanmıştır.

Bulgular: Türk toplumu tarafından doldurulan 8.917 anket formu çalışmaya dahil edildi. Yaşlılarda, kadınlarda, anne-babalarda, sigara içenlerde, ek hastalığı olanlarda, sosyal medya kullananlarda ve eğitim düzeyi yüksek olanlarda kaygı düzeyi ve ölüm korkusu daha yüksekti.

Sonuç: Çalışmamızda, COVID-19'un Türkiye'de kaygı düzeylerini ve ölüm korkusunu artırarak nüfusun ruh sağlığını olumsuz yönde etkilediği belirlendi. Kaygı düzeyi ve ölüm korkusu yüksek olan kişiler belirlenmeli ve bu kişilere psikolojik destek sağlanmalıdır.

Anahtar Kelimeler: COVID-19, akıl sağlığı, Türk toplumu, durumluk-sürekli kaygı envanteri, Thorson-Powell'ın gözden geçirilmiş ölüm kaygısı ölçeği

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INTRODUCTION

SARS-CoV-2 is a disease that is primarily transmitted via droplets and direct contact with contaminated surfaces has high morbidity and is potentially lethal.[1-3] After The World Health Organization declared COVID-19 a pandemic, this declaration has caused universal concern and affected the mental health of people.[4] Faced with a potential threat of illness, people tend to develop self-protective behaviors.[5] According to the behavioral immune system theory, people are likely to develop negative mental assessments and emotions to protect themselves.[6,7] Furthermore, epidemics trigger these negative mental assessments and emotions.[8,9]

Negative emotions can lead to a decline in the immune function of people and disrupt normal physiological mechanisms.[10] People can overreact to any disease in cases where they do not receive adequate psychological support.[5,9] Therefore, it is important to detect the potential psychological changes caused by COVID-19 in a timely manner. Determination of the anxiety level in the society can play an important role in ensuring a preventive approach and providing appropriate treatments for people under risk.

This study aimed to determine the anxiety levels and associated risk factors of the society during COVID-19 in Türkiye.

MATERIAL AND METHOD

This was a cross-sectional study conducted throughout Türkiye during the pandemic. The study was conducted in compliance with the Declaration of Helsinki and approved by Aksaray University School of Medicine, Aksaray Education and Research Hospital Scientific Research Evaluation Committee with decision no: 2020/03-48.

A self-report questionnaire designed via Google forms which is written in Turkish and contains three main parts: 1) Demographics (age, gender, marital status, having children or not, education level, social media use, smoking habit, and comorbid diseases), 2) State-Trait Anxiety Inventory (STAI), 3) Thorson–Powell's Revised Death Anxiety Scale (RDAS). Data collection began on April 15, 2020, and continued for one month. The questionnaire did not include personal information such as name, phone number, or e-mail. Participants under the age of 18 years and those who had known psychiatric diseases prior to the pandemic were excluded from the study.

Scales Used

STAI consists of two parts, each of which comprises 20 questions: the state anxiety subscale (STAI-S) measures anxiety at a given time, while the trait anxiety subscale (STAI-T) measures long-term anxiety levels. All items are scored using the 4-point Likert-type scale. There are ten reverse-scored statements on STAI-S and seven on STAI-T. During the evaluation process, each statement is scored between 1 and 4 points depending on the selected option such that the score is either negative (thereby reducing the total anxiety score) or positive (thereby increasing the total anxiety score) according to the selected option. To calculate the final score, 50 points as a fixed value are added to the obtained STAI-S score and 35 points to the continuous anxiety subscale score. The resulting value indicates the individual's anxiety score. Accordingly, the highest value was 80 and the lowest value was 20. Thus, a score of 20–35 points indicates a low level of anxiety, 36–41 points a moderate level of anxiety, and 42–80 points a high level of anxiety.[11,12]

RDAS was developed by Thorson and Powell.[13] It includes 25 items: 17 are statements such as "Coffins distress me" and 8 are negative statements such as "I don't worry about being in a state of insolvency forever." These items are rated on a 5-point Likert-type scale from 0 to 4. In negative statements, the Likert scale is reversed from 4 to 0. The total score can be a minimum of 0 and maximum of 100. Higher points indicate higher death anxiety. This scale was translated into Turkish, and its validity and reliability study was conducted by Karaca and Yıldız.[14]

Statistical Analysis

Data were analyzed using SPSS version 22.0. Visual (histogram and probability graphs) and analytical methods (Kolmogorov–Smirnov test) were used to determine if the variables showed normal distribution. Descriptive analyses were expressed as means±standard deviation for variables showing normal distribution and as median and interquartile range (IQR) for non-normally distributed variables. Student's t-test for continuous variables was used in comparisons between the two groups.

The STAI-S, STAI-T, and RDAS values were normally distributed. The student's t-test was used to compare groups with two categories and the one-way analysis of variance to compare groups consisting of three or more categories (age and education level). P-values of <0.05 indicated statistical significance. Binary post hoc comparisons were performed using the Tukey test.

RESULTS

After 30 days, 9,860 questionnaire forms were completed online. Of these, 835 participants who were aged <18 years and 108 participants who had a known psychiatric disease were excluded from the study. Thus, 8,917 questionnaire forms were included in the study. Of the participants, 52.6% (n=4,694) were female and 47.4% (n=4,223) were male. The median age was 35 (IQR: 13, range: 18–72) years. The majority of the participants (n=8,058, 90.4%) used social media, and 1,523 (17.1%) had comorbid diseases. The participants' demographic data are summarized in **Table 1**.

The STAI-S, STAI-T, and RDAS scores of the participants were 45.75±4.6, 41.08±4.7, and 53.78±15.9, respectively. State anxiety and fear of death (STAI-S=46.64±4.4,

RDAS=54.34±14.5) were significantly higher in women than in men ($p < 0.001$). There was no significant difference between men and women in terms of STAI-T scores (p=0.09). The level of anxiety and fear of death in parents were significantly higher than those who had no children (STAI-S, p=0.029; STAI-T, $p < 0.001$; RDAS, $p < 0.001$). The relationship between the sociodemographic characteristics and the scores is shown in **Table 2**.

Table 1. Socio-demograhic characteristics of study participants

Number of participants	**8917 (100)**
Age, median (IQR)	35 (13)
Age group	
18-30	2978 (33.4)
31-50	5169 (58)
51-64	674 (7.6)
≥65	96 (1.1)
Gender	
Female	4694 (52.6)
Male	4223 (47.4)
Education level	
Primary school	791 (8.9)
High school	3318 (37.2)
University	4808 (53.9)
Marital status	
Married	5515 (61.8)
Single	3402 (38.2)
Do you have a child?	
Yes	5061 (56.8)
No	3856 (43.2)
Smoking status	
Smoker	3344 (37.5)
Non-smoker	5573 (62.5)
Chronic medical condition	
Yes	1523 (17.1)
No	7394 (82.9)
Use of social media	
Yes	8058 (90.4)
No	859 (9.6)

Data were presented as n (%) except age.

The STAI-S, STAI-T, and RDAS scores were significantly different between the age groups ($p < 0.001$). According to the Tukey post hoc subgroup analysis, this difference was found to be attributable to the difference between the ≥65 years age group and other groups ($p < 0.001$; **Table 3**).

Table 3. Comparison of STAI-S, STAI-T and RDAS scores between age groups

	18-30	**31-50**	**51-64**	**≥65**	**P value**
STAI-S	45.94±5.2	45.57±4.2	45.6±3.1	50.98±5.4	<0.001
STAI-T	41.45±5.1	40.9±4.5	40.04±4	46.75±4.9	<0.001
RDAS	50.82±16.6	54.9±15.4	56.48±14.3	63.86±15.8	<0.001

Data were presented as mean±SD. STAI-S: State-Trait Anxiety Inventory-State, STAI-T: State-Trait Anxiety Inventory- Trait, RDAS: Thorson–Powell's Revised Death Anxiety Scale

There were statistically significant differences among the STAI-S, STAI-T, and RDAS scores in terms of their education levels. The Tukey post hoc subgroup analysis showed that all groups were statistically different in all three scores ($p < 0.05$). The post hoc analysis results were also consistent with error bar graphs (**Figure 1**).

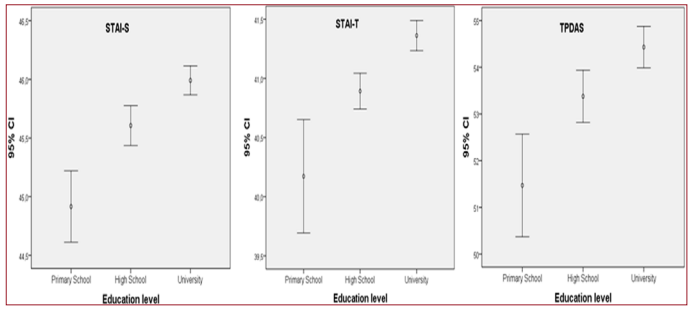

Figure 1. The post hoc analysis results were also consistent with error bar graphs

Table 2. Comparison of STAI-S, STAI-T and RDAS scores between demographic groups

	STAI-S			**STAI-T**			**RDAS**		
	mean±SD	**P value**	**t**	**mean±SD**	**P value**	**t**	**mean±SD**	**P value**	**t**
Gender									
Female	46.64±4.4	<0.001	-19.445	41±4.7	0.09	1.697	54.34±14.5	<0.001	-3.548
Male	44.77±4.5			41.17±4.74			53.14±17.3		
Marital status									
Married	45.68±4.1	0.073	1.885	41.13±4.7	0.263	-1.12	54.03±15.6	0.061	-1.893
Single	45.87±5.2			41.01±4.7			53.37±16.4		
Do you have a child?									
Yes	45.85±3.9	0.029	-2.28	41.24±4.5	<0.001	-3.625	54.31±15.7	<0.001	-3.629
No	45.62±5.3			40.87±5			53.07±16.2		
Smoking habit									
Smoker	45.86±5.1	0.109	1.672	40.79±4.7	<0.001	-4.474	54.26±16.9	0.029	2.241
Non-smoker	45.69±4.2			41.26±4.7			53.48±15.3		
Comorbid disease									
Yes	47.23±4.1	<0.001	-13.89	41.28±4.5	0.071	-1.807	55.76±16.7	<0.001	-5.337
No	45.45±4.6			41.04±4.8			53.37±15.7		
Social media use									
Yes	45.82±4.5	<0.001	-4.009	41.12±4.6	0.072	-2.198	53.91±15.5	0.04	-2.477
No	45.15±5.2			40.74±5.9			52.49±19.5		

STAI-S: State-Trait Anxiety Inventory-State, STAI-T: State-Trait Anxiety Inventory- Trait, RDAS: Thorson–Powell's Revised Death Anxiety Scale

DISCUSSION

This study was designed to examine the state-trait and death anxiety levels among the Türkiye community. The results of this study have confirmed that COVID-19 affected mental health by increasing state-trait and death anxiety in Türkiye as in the whole world. The anxiety level and fear of death were higher in olders, females, parents, smokers, people who have comorbidities, social media users, and people who have higher education levels.

It is known that the anxiety level of the community increases during epidemics.[8,15] A study conducted one year after the SARS epidemic reported that stress levels increased rather than decreased over time, and worryingly high levels of depression, anxiety, and post-traumatic stress disorder were observed.[16] The COVID-19 pandemic has caused psychological problems across the world.[17-19] Qiu et al. reported that 35% of the Chinese population had psychological problems.[20] A study conducted in the United States reported that more than half of the participants exhibited depressive symptoms and more than 25% exhibited signs of moderate and severe anxiety.[18] Moreover, the implementation of unprecedented strict quarantine measures has led to a gradual alienation of and lack of communication among people, and indirectly, to depression.[20,21] The high infection risk of COVID-19 and its high mortality rate within a short duration suggests that the level of anxiety increased more than that during previous epidemics. The high STAI-S, STAI-T, and RDAS scores obtained in the present study also support this notion.

Previous studies indicated differences between men and women in terms of risk perception during epidemics.[22,23] This was further corroborated by studies conducted during the COVID-19 pandemic, and women who had higher anxiety and stress levels were shown to be more prone to depression than men.[24-26] Similar to the findings in the literature, the present study found that the anxiety levels and fear of death were significantly higher in women than in men. These results confirm the fact that women perceive the disease to be more contagious and deadly.

It is known that people have increased anxiety levels during epidemics because of the possibility of them transmitting the disease to their families and loved ones.[22,23,27] A study conducted in our country demonstrated that people who lived with their family had a higher level of depression and anxiety than those who lived alone.[25] A Germany-based study reported that having a child is a factor that plays a role in the increased anxiety and depression experienced during the pandemic.[28] In the present study, the anxiety level and fear of death of parents were significantly higher than those without children. However, there was no such relationship between being married or unmarried. This may be due to that the married participants did not have any children yet.

Health awareness increases with the education level. Awareness of the transmission risk as well as the seriousness of the measures taken ensures a better understanding of the possible consequences. A study in Türkiye showed that university graduates had the highest levels of anxiety and depression.[25] Roberts et al. reported that people with a high education level had higher health awareness and were prone to experience higher levels of anxiety and stress during the pandemic.[29] In the present study, all three scores increased in parallel with the level of education, and participants who were university graduates experienced serious anxiety and fear of death.

Studies conducted during the pandemic reported that younger people had a higher level of anxiety and stress.[24,25,29,30] This may be due to the fact that young participants who used social media more actively were affected by negative news that could provoke depression. In the present study, we did not observe higher levels of anxiety and fear of death in social media users. However, in contrast with the literature, anxiety levels and fear of death were significantly higher in elderly people than in young. The main reason for this may be the fact that COVID-19 has a poorer prognosis in the elderly and in people with comorbid diseases while it is mostly asymptomatic in young people. In addition, the curfew that was implemented for more than 3 months for people older than 65 years in Türkiye may be contributed to this outcome.

Limitations

Our study has some limitations. i) This questionnaire was conducted online to prevent the transmission of COVID-19 and to reach a higher number of participants. Therefore, the number of older people in this study was limited compared to the number of older people in the population. Considering that the anxiety level and fear of death were higher in older people, the small number of older people included may have affected our results. ii) The participants may have given inaccurate answers to complete the questionnaire in a shorter period of time, and this may have affected the outcomes of the present study. iii) Due to the cross-sectional nature of the study and the use of a self-report scale, the entire society could not be represented homogeneously.

CONCLUSION

The present study is the most comprehensive study conducted in Türkiye in terms of the number of participants and sheds light on the anxiety levels of Turkish society during the pandemic. It was determined that COVID-19 has negatively affected the mental health of the population by increasing the anxiety levels and fear of death in Türkiye. People who have higher anxiety levels and fear of death should be identified, and psychological support should be provided to these people.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by Aksaray University School of Medicine, Aksaray Education and Research Hospital Scientific Research Evaluation Committee with decision no: 2020/03-48.

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

Does Preoperative Nutritional Assessment Affect Clinical Outcomes in Children with Acute Appendicitis?

Pediatrik Akut Apandisitlerde Preoperatif Beslenme Değerlendirilmesi Klinik Sonuçları Etkiler Mi?

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Abstract

Background: Malnutrition increases postoperative complications in pediatric surgery patients.

Objective: The present study aims to examine whether the preoperative nutritional status has any effects on postoperative outcomes in patients with pediatric acute appendicitis who require urgent surgery.

Material and Method: This retrospective clinical study was conducted in the Department of Pediatric Surgery. Seventy-four patients were included in this study, and the data were analyzed retrospectively. After preoperative determination of malnutrition status by the Gomez classification system, BMI calculation results were compared with clinical outcomes.

Results: Seventy-four children who underwent appendectomy procedures were included in this study. The mean age was 11.5±3.7 years. Of the included patients in this study, 64.9% were male, while 35.1% were female. The length of hospital stay was 1.77±1.34 days. A BMI cut-off value of fewer than 16.74 was statistically significant ($p<0.001$), with 100.0% percent sensitivity and 68.66% specificity. Wound infection was more common in patients whose BMI value was lower than 16.74 ($p=0.010$). The findings showed that the mean age ($p<0.001$) of the patients with a BMI value below 16.74 was lower, and their hospital stay was longer ($p=0.011$).

Conclusion: Nutritional status assessment is an essential part to care children undergoing surgery. In the present study, we discovered that mild-to-moderate malnutrition and low BMI before surgery increase the postoperative morbidity, hospital stay, and wound infection frequency in children. Our findings suggest that this evaluation system can lead to positive changes in postoperative management.

Keywords: Nutritional status assessment, acute appendicitis, postoperative complications

Öz

Arka plan: Malnutrisyon, pediatrik cerrahi hastalarda postoperatif komplikasyonların artmasına sebep olur.

Amaç: Bu çalışma, acil cerrahi gerektiren akut apandisitli çocuk hastaların preoperatif beslenme durumunun postoperatif sonuçlara etkisini belirlemeyi amaçladı.

Gereç ve Yöntem: Bu retrospektif kesitsel çalışma, Çocuk Cerrahisi Kliniğinde yürütülmüştür. Toplam 74 hasta çalışmaya alınmış ve verileri geriye dönük olarak incelenmiştir. Hastaların preoperatif Gomez malnutrisyon sınıflandırmaları, beden kitle indeksleri (BMI) belirlenerek klinik sonuçlarla karşılaştırılmıştır.

Sonuçlar: Apandisit nedeni ile ameliyatları yapılan 74 çocuk hasta bu çalışmaya dahil edildi. Yaş ortalaması 11,5±3,7 yıldı. Çalışmaya alınan hastaların %64.9'u erkek, %35.1'i kadındı. Hastanede yatış süresi 2,96±2,1 gündü. Hastaneye başvuru süresi 1,77±1,34 gündü. BMI cut-off değerinin 16,74'ün altında olması, %100.0 sensitivite, %68.66 spesifite ile istatistiksel olarak anlamlı bulunmuştur. BMI değeri 16,74'ün altında olan hastalarda yara yeri enfeksiyonu görülme sıklığı daha yüksek idi ($p=0,010$). BMI değeri 16,74'ün altında olan hastaların yaş ($p<0,001$) ortalamalarının daha düşük olduğu ve hastanede kalış sürelerinin daha uzun olduğu saptandı ($p=0,011$).

Sonuç: Beslenme değerlendirmesi, akut apandisit nedeni ile ameliyat edilen hastalarda hastaların yönetiminin çok önemli bir parçasıdır. Bu çalışmada, preoperatif hafif-orta malnutrisyonun ve zayıf BKİ çocuklarda postoperatif morbiditeyi, hastanede kalış süresini, yara yeri enfeksiyon sıklığını artırdığını gördük. Bu değerlendirme sistemlerinin postoperatif yönetiminde olumlu değişikliklere zemin hazırlayacağını düşünmekteyiz.

Anahtar Kelimeler: Beslenme değerlendirmesi, akut apandisit, ameliyat sonrası komplikasyonlar

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INTRODUCTION

The patient's nutritional status before the operation influences the complications after the operation. Pre-operative nutritional status assessment in pediatric patients undergoing surgery may be useful in preventing post-operative wound infections, delays in wound healing, and prolonged hospital stay.

Many studies have shown the importance of proper nutrition in the post-surgery recovery of pediatric patients. In the absence of adequate nutrition, the surgical stress on the child can place significant demands on the metabolism, potentially leading to organ and system dysfunction.[1,2]

Malnutrition is a risk factor for postoperative complications in patients undergoing abdominal surgery, according to many studies published in recent years.[3,4] The link between poor preoperative nutrition and poor surgical outcomes, on the other hand, is unclear. The scarcity of high-quality, randomized and controlled studies that found a statistically significant association makes evaluating the effects of malnutrition on surgical outcomes in pediatric patients challenging.

Despite the well-known negative effects of poor nutritional status, to our knowledge, the effects of preoperative nutritional status on postoperative outcomes in pediatric patients undergoing surgery have not been thoroughly investigated. Drawing on this, we sought to investigate the effects of preoperative nutritional status on wound healing in 74 patients aged 0 to 18 years who underwent appendectomy for acute appendicitis in our hospital in 2020.

MATERIAL AND METHOD

The study was carried out with the permission of Adana City Training and Research Hospital Clinical Researches Ethics Committee (Date: 02.12.2021, Decision No: 1660). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The present retrospective study included 74 patients with acute appendicitis who underwent an appendectomy in the Department of Pediatric Surgery, City Training and Research Hospital, Health Sciences University, between January 1, 2020, and December 31, 2020. After the determination of the patient's nutritional status and body mass index using the Gomez classification, the relationship between preoperative nutritional status and clinical outcome was evaluated (**Table 1**). Patients between 0-18 years who were operated on due to acute appendicitis were included in this study. The patients' demographic data, Gomez malnutrition classification, body mass index (BMI), hospital stay, wound infections, and laboratory data were all examined. It was assessed as prolonged hospitalization 48 hours following the surgery. Patients who were discharged by oral feeding within 48 hours of appendectomy were classified as non-complicated, while those who were discharged after 48 hours were classified as complicated.

Table 1. Gomez Classification-Body Mass Index (BMI)

Gomez Classification

The Gomez classification is determined by comparing the child's body weight to the body weight of a healthy, normally growing child of the same age group.

Weight for age (%)=(Child weight/Height of healthy child at the same age) x100

Percentage of Weight by Age	Comment
90-110%	Healthy Child
75-89%	1: Mild Malnutrition
60-74%	2: Moderate Malnutrition
<60%	3: Severe Malnutrition

Body Mass Index (BMI)

BMI = weight (kg) divided by height (in meters squared).

- Less than 18.5 kg/m: Weak.
- Between 18.5 and 24.9 kg/m: Normal weight.
- Between 25 and 29.9 kg/m: Overweight.
- Between 30 and 39.9 kg/m: Obese.
- Over 40 kg/m: Severely obese (morbidly obese)

Statistical Analysis

The data were statistically analyzed using the SPSS 23.0 package program. Continuous measurements were summarized as mean, deviation, and minimum-maximum values, while categorical measurements were summarized as numbers and percentages. The Shapiro-Wilk test was used to assess conformity to the normal distribution. To compare categorical variables, the chi-square and Fischer tests were used. In groups with a normal distribution, the independent Student's t-test was used, while in groups that did not fit normally, the Mann-Whitney U test was used. The sensitivity and specificity values to the BMI value were calculated based on the Gomez score variable of the patients included in the present study. The cut-off value was determined by examining the area under the ROC curve. In all tests, the statistical significance level was set to 0.05.

RESULTS

The present study included 74 children who had appendectomy surgery. The mean age was 11.5±3.7 years. Appendectomy was performed on 50% of patients aged seven to 13. 64.9% of the patients in this study were male, while 35.1% were female. According to the preoperative Gomez malnutrition classification, 58.1 percent of the patients were healthy, 32.4 percent had mild malnutrition, and 9.5 percent had moderate malnutrition. There was no evidence of severe malnutrition in any of the patients. The total length of stay in the hospital was 2.96±2.1 days. The duration of admission to the hospital was 1.77±1.34 days. The diameter of the appendix was measured to be 10.1±3.33 mm. The average C-reactive protein in laboratory parameters was 41.4±72.1 mg (Normal value 0-5 mg) (**Table 2**).

Table 2. Examination of demographic data

	Frequency (n)	Percentage (%)
Gomez		
Normal	43	58.1
Mild	24	32.4
Middle	7	9.5
Wound infection		
with wound infection	11	14.9
without wound infection	63	85.1
Sex		
Male	48	64.9
Female	26	35.1
Distribution of Age		
0-6 years	8	10.8
7-13 years	37	50.0
14-18 years	29	39.2
	Mean+SS	**Med (min-max)**
Weight	44.2±17.6	46.3 (9-80)
BMI	19.5±4.8	18.74 (10.74-34.24)
Age (year)	11.5±3.7	12 (0-16)
Length of hospitalization	2.96±2.1	2 (1-15)
The duration of admission to the hospital	1.77±1.34	1 (1-10)
Appendix diameter (mm)	10.1±3.3	10 (4-20)
WBC	15.5±4.9	15.9 (4.5-26.6)
NE%	75.3±14.7	79.9 (9.8-91.5)
LY%	15.2±10.8	10.6 (4-45.5)
PLT	307.9±82.6	295 (168-650)
CRP	41.4±72.1	8.65 (0.1-303)

WBC: White blood cell (5.14-13.3 10^), NE: neutrophil percentage (22.4-69%), LY: Lymphocyte percentage (18.4-66.6%), PLT: Platelet count (150-400 10^)

The mean preoperative BMI of the patients was 19.5±4.8. The BMI value of the patients was subjected to ROC analysis based on their Gomez score (**Figure 1, Table 3**). The values for sensitivity and specificity were calculated. As a result of the examination, the calculated cut-off value for the BMI value was fewer than 16.74, with 100.0 percent sensitivity and 68.66 percent specificity, which was statistically significant (p<0.001). The patients were divided into two groups based on their BMI (below and above 16.74). The differences between the parameters were statistically determined. Wound infection was more common in patients with a BMI greater than 16.74 (p=0.010). Low BMI patients were more common in the 0-6 age group and the 7-13 age group (p<0.001). While the mean age of patients with low BMI was lower (p<0.001), the length of hospital stay (p=0.011), appendix diameter (p=0.026), NE percent (p=0.041) and PLT (p=0.002) values were all higher (p<0.05) (see **Table 4**).

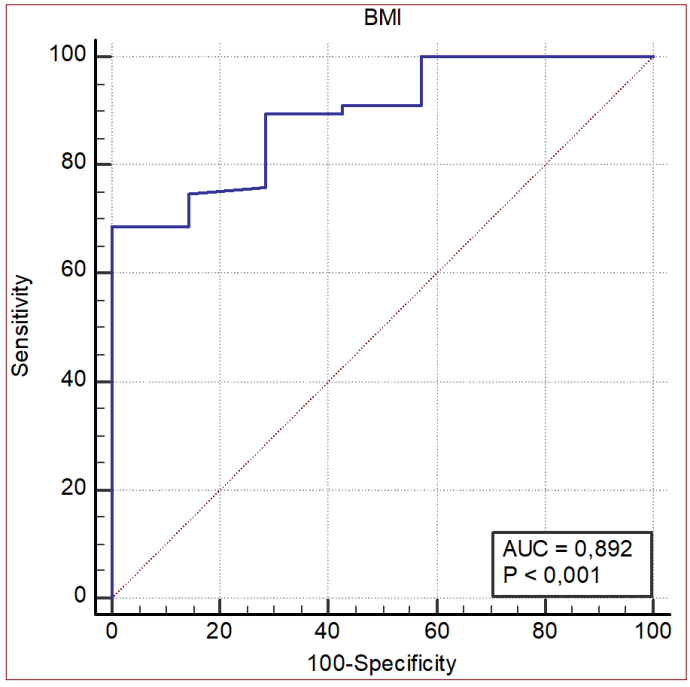

Figure 1.

Table 3. Examination of the value between Gomez score and BMI through the ROC curve

	BMI
Threshold (cut-off)	<16.74
AUC (95% CI)	0.892 (0.799-0.952)
Sensitivity (95% CI)	100 (59-100)
Specificity (95% CI)	68.66 (56.2-79.4)
PPV (95% CI)	100 (100-100)
NPV (95% CI)	25 (19-32.2)
P	<0.001**

* p<0,05, ROC curve test

Table 4. Differences in relevant parameters between groups with BMIs fewer than and greater than 16.74

	BMI Low (n=28) n(%)	BMI High (n=46) n(%)	
Wound infection			
with wound infection	8 (28.6)	3 (6.5)	0.010**.[c]
without wound infection	20 (71.4)	43 (93.5)	
Sex			
Male	21 (75)	27 (58.7)	0.154[c]
Female	1(25)	19 (41.3)	
Distribution of Age			
0-6 years	5 (17.9)	3 (6.5)	
7-13 years	20 (71.4)	17 (37)	<0.001**.[c]
14-18 years	3 (10.7)	26 (56.5)	
	Low (n=28)	**High (n=46)**	
Age (year) [b]	9 (2-15)	14 (0-16)	<0.001**
Length of stay in hospital [b]	3 (1-15)	2 (1-7)	0.011*
The duration of admission to the hospital [b]	1.5 (1-5)	1 (1-10)	0.500
Appendix diameter (mm)[b]	10 (5-19)	10 (4-20)	0.026*
WBC[a]	16.3±4.7	15.0±5.0	0.287
NE%[b]	83.8 (54.5-91.5)	78 (9.8-91.3)	0.041*
LY%[b]	8.9 (4.7-37.4)	11.8 (4-45.5)	0.075
PLT[a]	346.0±84.6	284.7±72.9	0.002**
CRP[b]	16.2 (0.2-297.3)	6.77 (0.1-303)	0.099

*p<0.05, **p<0.001, a: Independent Student t-test, b: Mann-Whitney U test, c: Chi-square and Fisher's exact test

DISCUSSION

Nutritional assessment is essential in the care of surgical patients. The Gomez malnutrition classification is a screening tool used in pediatric patients to detect preoperative malnutrition. We employed the Gomez score and BMI preoperatively to assess preoperative malnutrition in patients in this study, and we discovered that more than half of our patients were not malnourished. However, we discovered that 14.9 percent of patients with mild to moderate Gomez and BMI fewer than 16.74 had infectious processes after surgery, and their hospital stay was significantly prolonged ($p<0.05$). In the present study, we discovered that the risk of wound infection was statistically significantly higher in patients whose BMI was fewer than the cut-off value we established. As a result, identifying patients with nutritional deficiencies before surgery is critical for avoiding sub-optimal outcomes. Many parameters, such as weight, length, mid-arm circumference, and triceps skinfold thickness, have been used in the literature to assess nutritional status. Some methods were used to try to determine nutritional status.[5-8]

We aimed to investigate if there was a postoperative correlation between Gomez classification and BMI. We discovered a statistically significant association between preoperative weight and postoperative wound infection. 9 Koofy et al. discovered the highest prevalence of malnutrition in patients undergoing gastrointestinal surgery in the screening developed according to STRONGKIDS newly published ESPEN (European Society for Clinical Nutrition and Metabolism) guidelines used in his study and discovered a significant correlation between preoperative age and postoperative complications.[9-13]

The findings obtained in the study conducted by Roberson et al. suggest that preoperative malnutrition may be a modifiable risk factor for preventing surgical complications and is associated with increased morbidity in surgery.[13-15]

Previous research identified malnutrition predictors, such as hypoalbuminemia, weakness, and the need for nutritional support, as potential indicators of poor postoperative outcomes.[16-17]

Secker et al. observed and evaluated patients for nutrition-related complications for 30 days after surgery. These complications were divided into four categories: length of hospital stay, emergency reoperations, hospital readmission, infection complications, and non-infectious complications.[18]

According to Wessner, consensus would be ideal for evaluating standard nutrition in pediatric surgery patients and would guide further studies.[19] Toole et al. revealed that children with mild malnutrition required a longer hospital stay in a retrospective study to determine the preoperative nutritional status in children with congenital heart disease.[20] Based on anthropometric data, a cross-sectional cohort study of 125 patients found that 12% of the patients were malnourished and 40% had a high BMI, with no relationship found between complications.[21]

Because of age differences, it has been challenging to develop a standard malnutrition analysis in children. As a result, many studies have a direct impact on postoperative outcomes, which is especially important in pediatric surgery patients to best predict nutritional status with various combinations and due to the high metabolic rates and energy requirements after surgery.

CONCLUSION

Nutritional assessment is a critical component of the care of children undergoing surgery. In the present study, we revealed that mild-to-moderate malnutrition before surgery increased postoperative morbidity, hospital stay, and wound infection frequency in children with low BMI. The findings suggest that routinely implementing these evaluation systems into clinical practice can pave the way for positive changes in postoperative management strategies.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Adana City Training and Research Hospital Clinical Researches Ethics Committee (Date: 02.12.2021, Decision No: 1660).

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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Original Article / Orijinal Araştırma

Short-Term Effect of Sodium Glucose Co–Transporter 2 Inhibitors on Routine Laboratory Examinations

SGLT-2 İnhibitörleri'nin Kısa Vadede Bazı Laboratuvar Testleri Üzerine Etkisi

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Abstract

Background: In this study, we aimed to examine the effect of Sodium Glucose Cotransporter 2 inhibitors (SGLT-2i) on routine laboratory test results at 12 weeks of follow-up among type 2 diabetes mellitus (T2DM) patients using empagliflozin and dapagliflozin.

Material and Method: Three hundred ten patients with a diagnosis of T2DM (over 18 years of age) with SGLT-2i added to stable triple combination therapy were included in this study. Patients who received either empagliflozin (10 mg once daily) (n:170) or dapagliflozin (10 mg once daily) (n:140) in addition to their current treatment regimen were divided into two groups. Laboratory findings of all patients were recorded before treatment and during follow-up in the 12 weeks.

Results: Both empagliflozin and dapagliflozin had similar profiles of improvement of mean fasting blood glucose, and HbA1c. High improvement in lipid profiles and spot urinary parameters were detected in dapagliflozin group compared to empagliflozin group. At 12-week follow-up, change in other laboratory parameters did not differ significantly between the groups. In terms of total side effects, no difference was observed between treatment groups.

Conclusions: Empagliflozin and dapagliflozin had similar effects on fasting blood glucose and HbA1C at 12-week follow-up. It can be considered that dapagliflozin may be preferred due to its positive effect on the lipid profile, especially in the population with cardiovascular disease.

Keywords: Sodium glucose cotransporter 2 inhibitors, diabetes mellitus, empagliflozin, dapagliflozin, lipid panel

Öz

Amaç: Bu çalışmada, Tip-2 Diabetes Mellitus (T2DM) ile takipli ve empagliflozin veya dapagliflozin kullanan hastalarda 12 haftalık süreçte Sodyum Glukoz Kotransporter 2 inhibitörlerinin (SGLT-2i) günlük rutinde kullanılan bazı laboratuvar test sonuçları üzerindeki etkisini incelemeyi amaçladık .

Gereç ve Yöntem: T2DM (18 yaş üstü) ile takipli ve üçlü kombinasyon tedavisine SGLT-2i eklenen üç yüz on hasta bu çalışmaya dahil edildi. Mevcut tedavi rejimlerine ek olarak empagliflozin (günde bir kez 10 mg) (n : 170) veya dapagliflozin (günde bir kez 10 mg) (n: 140) alan hastalar iki gruba ayrıldı. Tüm hastaların laboratuvar bulguları tedavi öncesi ve 12 haftalık takip sonrasında kaydedildi .

Bulgular: Hem empagliflozin hem de dapagliflozin grupları , ortalama açlık kan şekeri ve HbA1c'de benzer iyileşme oranlarına sahipti. Empagliflozin grubuna kıyasla dapagliflozin grubunda lipid profillerinde ve spot idrar parametrelerinde yüksek düzeyde iyileşme saptandı . 12 haftalık takipte diğer laboratuvar parametrelerindeki değişiklik gruplar arasında anlamlı farklılık göstermedi. Toplam yan etkiler açısından tedavi grupları arasında fark gözlenmedi .

Sonuç: Empagliflozin ve dapagliflozin , 12 haftalık takipte açlık kan şekeri ve HbA1C üzerinde benzer etkilere sahipti. Özellikle kardiyovasküler hastalığı olan popülasyonda dapagliflozinin lipid profiline olan olumlu etkisi sebebiyle tercih sebebi olabileceği düşünülebilir.

Anahtar Kelimeler: Sodyum glukoz kotransporter 2 inhibitörleri , diabetes mellitus, empagliflozin , dapagliflozin , lipid paneli

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INTRODUCTION

Diabetes mellitus (DM) is a metabolic disease characterized by hyperglycemia and it occurs due to disturbances in the secretion of insulin or the effect of insulin on peripheral cells.[1] With the increasing prevalence of type 2 DM (T2DM), adequate glycemic control cannot be achieved in a significant percentage of patients, and the disease causes many comorbidities and life-threatening conditions, especially with the addition of renal and cardiac complications.[2,3] The change of lifestyle and oral anti-hyperglycemic drugs (OADs), which are generally used in first-line treatments, have prognostic importance in the management of T2DM. OADs, including Sodium Glucose Cotransporter 2 inhibitors (SGLT-2i), demonstrate anti-hyperglycemic effects with several different mechanisms.[4] SGLT-2i have high efficacy, safety, and tolerability profiles without significant risk of hypoglycemia and are generally considered as second or third-line anti-hyperglycemic drugs.[5] They can also be used in monotherapy when metformin is contraindicated.[6]

SGLT-2i (empagliflozin, dapagliflozin, etc.), which are frequently preferred in the treatment of T2DM, show cardio-protective and reno-protective effects.[7-9] This is associated with anti-hyperglycemic effects via the inhibition of sodium glucose reabsorption in the renal tubules independent of insulin. Thus, they are able to exert osmotic diuretic, natriuretic, and glycosuric effects.[10] Due to these effects, SGLT-2i increase sodium delivery to the macula densa and cause vasoconstriction in the afferent arteriole, contributing reno-protective effects by reducing the load on the glomeruli. They also show cardio-protective effects by reducing cardiac afterload.[11] Increasing evidence indicates that empagliflozin, which is a highly effective agent for secondary prevention, is a safer option in terms of both renoprotective and cardio-protective attributes.[12,13] However, there are limited studies evaluating the effects of empagliflozin and dapagliflozin on routine laboratory test results in the short term.

Therefore, in this study, we aimed to examine the effect of empagliflozin and dapagliflozin on some routine laboratory test results at 12 weeks of follow-up among T2DM patients using SGLT-2i.

MATERIAL AND METHOD

This study was planned as a single-center retrospective study between June 2019 and June 2020 in Ankara City Hospital. Sample size was calculated based on changes in HbA1c levels in the T2DM cohort at 12 weeks of follow-up in groups using empagliflozin and dapagliflozin. Accordingly, it was determined that at least 90 patients were required in both treatment groups to detect a difference of 0.4% with power of 90% and a significance level of 0.05 (assuming standard deviation of 1.2% and a correlation coefficient of 0.7). The study was approved by the Ankara City Hospital Ethics Committee (Date: 11.2021, Decision No: E2-21-99). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study population

Adults aged between 18 and 80 years with a diagnosis of T2DM who were treated with a stable triple combination therapy including the administration of metformin (2000 mg/day or maximum tolerated dose), glimepiride (8 mg/day or maximum tolerated dose), and dipeptidyl peptidase 4 inhibitors (100 mg/day sitagliptin/vildagliptin or maximum dose according to the local label) for 12 weeks before administration of an SGLT2i as well as lifestyle changes but who did not achieve glycemic control (hemoglobin A1c (HbA1c) of >7%) were evaluated. Three hundred ten T2DM patients using only triple oral antidiabetics with SGLT-2i added to their treatments were included in this study.

The following individuals were excluded from the study: female patients who were pregnant or lactating, and those who had experienced gestational diabetes; patients with type 1 diabetes; patients with a history of cancer or currently undergoing anticancer treatment; those with chronic pancreatitis, steroid-induced diabetes mellitus, Cushing's syndrome, acromegaly, abnormal serum creatinine levels (>1.5 mg/dL in men and >1.4 mg/dL in women), serum aspartate transaminase (AST) or alanine transaminase (ALT) levels 3 times the upper limit of the normal range, previous history of SGLT2i treatment, glomerular filtration rate of <45, history of diabetic ketoacidosis, genitourinary system infection, or acute renal failure; and individuals using, angiotensin converting enzyme inhibitor (ACEI), angiotensinogen receptor blocker (ARB) and diuretic drugs.

Study Protocol

Clinical, demographic, and laboratory findings were recorded from the hospital's automation system and patient files. Patients who received either empagliflozin (10 mg once daily) or dapagliflozin (10 mg once daily) in addition to their current treatment regimen were divided into two groups. Laboratory findings of all patients were recorded before treatment and at the end of 12 weeks of follow-up.

Laboratory parameters

In the morning, fasting blood samples were drawn for biochemical parameters and other laboratory parameters. After the blood samples were centrifuged at 2500×g for 10 minutes, plasma and serum samples were separated. All parameters were evaluated from the same laboratory. Serum glucose, serum electrolytes, ALT, AST, GGT, ALP was measured on a Beckman Coulter AU 5800 autoanalyzer (Beckman Coulter Inc., Brea, CA, USA) using the enzymatic ultraviolet hexokinase method. HbA1c was measured by cation-exchange high-performance liquid chromatography method using the ARKRAY ADAMS A1c HA8180 automated glycohemoglobin analyzer (ARKRAY Global Business

Inc., Kyoto, Japan). Urine albumin levels were evaluated with Novatrend TM Fluorescence Immunoassay Analyzer. Albumin was measured using the bromocresol green method. Total cholesterol was measured by enzymatic colorimetric method and high-density lipoprotein cholesterol (HDL-C) was measured by enzymatic colorimetric method with a Hitachi modular autoanalyzer (Roche Diagnostic Corp., Indianapolis, IN, USA). Low-density lipoprotein cholesterol (LDL-C) level was calculated with the Friedewald formula for patients with triglyceride concentrations of <400 mg/dL.[14] Patients with triglyceride concentrations of >400 mg/dL were evaluated by enzymatic colorimetric method with the second-generation LDL-C Plus Kit and the Hitachi Modular P800 (Roche Diagnostic Corp., Indianapolis, IN, USA).

Endpoints and assessments

The primary and secondary endpoints in this study were calculated by subtracting 12-week values from baseline values for the empagliflozin and dapagliflozin groups. The primary endpoint was assessed as changes in HbA1c, fasting plasma glucose (FPG) levels, lipid profiles and other laboratory parameters. Secondary endpoints were evaluated adverse events like dysuria, dyspepsia, urinary tract infection.

Statistical analysis

The STATA program (StataCorp LLC, College Station, TX, USA) was used for data analysis. Normality testing was performed with the Shapiro–Wilk test. Normal distributions were shown as mean±standard deviation and non-normal distributions as median (interquartile range: 25^{th}-75^{th} percentile). Categorical variables were expressed as numbers and percentages. Student's T test or the Mann–Whitney U test was used to compare numerical variables between the AR and RR groups. Chi-square, Yates correction, and Fisher's exact chi-square tests were used for comparisons of categorical data. Changes of laboratory parameters at the 12 weeks compared to baseline were evaluated by repeated measures for ANOVA analysis. The effect of potential risk factors contributing to the change in CMR parameters were examined by multivariate linear regression analysis. Values of p<0.05 (*) were considered significant in statistical analysis.

RESULTS

The mean age of study population was 51.9±8.7 years and consisted mostly of males (65.8%) with a representative risk profile for T2DM. SGLT-2i distributions were 54.8% (n:170) empagliflozin and 45.2% (n:140) dapagliflozin. Demographic characteristics were no significant difference in empagliflozin and dapagliflozin groups (**Table 1**).

Table 1. Demographic characteristics of patients with Type 2 diabetes mellitus

Variables	All population n=310	Empagliflozin n=170	Dapagliflozin n=140	P
Age, years	51.9±8.7	50.9±9.7	52.8±7.8	0.278
Gender, n(%)				
Male	204 (65.8)	111 (65.3)	93 (66.4)	0.834
Female	106 (34.2)	59 (34.7)	47 (33.6)	
BMI, kg/m2	28.6±3.0	28.9±3.6	28.3±2.5	0.299
Smoking, n(%)	83 (26.8)	42 (24.7)	41 (29.3))	0.365
Alcohol use, n(%)	16 (5.2)	8 (4.7)	8 (5.7)	0.798
Comorbidity, n(%)				
CHD	31 (10.0)	20 (11.8)	11 (7.9)	0.342
Lung disease	23 (7.4)	12 (7.1)	11 (7.9)	0.830
Thyroid disease	30 (9.7)	14 (8.2)	16 (11.4)	0.441
Hyperlipidemia	167 (53.9)	89 (52.4)	78 (55.7)	0.555
Anemia	18 (5.8)	9 (5.3)	9 (6.4)	0.808
Drugs, n(%)				
Metformin	292 (94.2)	159 (93.5)	133 (95.0)	0.633
Sulfonylurea	49 (15.8)	23 (13.5)	26 (18.6)	0.274
DPI	74 (23.9)	43 (25.3)	31 (22.1)	0.517
Glitazone	4 (1.3)	4 (2.4)	-	0.186
Glinide	4 (1.3)	-	4 (2.9)	0.087
Insulin	49 (15.8)	25 (14.7)	24 (17.1)	0.639
Non-steroid	36 (11.6)	16 (9.4)	20 (14.3)	0.214
PPIs	75 (24.2)	45 (26.5)	30 (21.4)	0.302
Statin	86 (27.7)	45 (26.5)	41 (29.3)	0.582

Data are mean±standard deviation, median (IQR), or number (%). *, considered statistically significant (p<0.05). Abbreviations: CHD, coronary heart disease; DPI, dry powder inhaler; PPI, proton pump inhibitors

Mean total cholesterol (191.3±27.3 vs 214.0±39.6; P=0.001), median LDL–C (106.3±22.9 vs 130.0±30.3; P<0.001), median triglyceride (153.5 vs 204.5; P=0.029), median urine protein (69 vs 161; P<0.001), median microalbumin (10.8 vs 27.7; P=0.033) baseline levels were lower in empagliflozin group compared to dapagliflozin group. Other laboratory findings were no significant difference in empagliflozin and dapagliflozin groups (**Table 2**).

At 12 weeks follow-up, changes in short-term laboratory findings in patients with SGLT-2i treatment are shown in detail in **Table 2**. In both SGLT-2i treatment groups, mean hemoglobin levels, mean UREA levels, mean phosphorus levels, and mean calcium levels were higher on 12 weeks compared to baseline, and FPG, HbA1C, gamma glutamyl transferase, and urine microalbumin to creatinine ratios were lower (P<0.05) and these changes were similar between the two groups (ΔP>0.05).

In dapagliflozin groups, mean total cholesterol levels (214.0±39.6 vs 190.0±34.4; P<0.001), median LDL (130.0±30.3 vs 98.1±20.7; P=0.002), median triglyceride levels (204.5 vs 154; P<0.001), median urine protein levels (161 vs 110.7; P<0.001), and median urine protein to creatinine ratio levels (108 vs 80; p=0.048) were lower on 12 weeks compared to baseline, while mean HDL – C levels was higher (45.8±9.5 vs 48.7±8.0; P=0.013). These parameters did not change in empagliflozin group (**Table 2**).

Table 2. Changes in short-term laboratory findings in patients added to SGLT-2i treatment

Variables	Empagliflozin n=170			Dapagliflozin n=140			P1	P2
	Baseline	12 weeks	P	Baseline	12 weeks	P		
Hemoglobin, g/dL	14.4±1.2	14.9±1.3	<0.001*	14.6±1.4	15.2±1.4	<0.001*	0.303	0.601
WBC, x10^3 /mL	7.8±2.2	7.7±1.6	0.826	7.9±1.9	7.8±1.6	0.662	0.819	0.931
Neutrophil, x10^3 /mL	4 (3.3-5.4)	4.2 (3.4-5.2)	0.273	4.2 (3.4-5.2)	4.1 (3.4-5.3)	0.907	0.731	0.339
Lymphocyte, x10^3 /mL	2.6±0.7	2.4±0.6	0.067	2.7±0.6	2.7±0.8	0.824	0.451	0.120
Platelet, x10^3 /mL	276.5±62.1	271.6±65.0	0.299	267.8±68.7	270.6±73.1	0.540	0.515	0.241
FPG, mg/dL	160.5 (125-204)	129.5 (102-151)	<0.001*	172 (135-209)	133 (116-156)	<0.001*	0.326	0.747
HbA1c, %	9.1±1.9	7.6±1.1	<0.001*	9.3±1.4	7.6±0.7	<0.001*	0.388	0.355
Urea, mg/dL	32.0±9.2	35.6±7.1	0.044*	31.2±7.3	35.5±9.0	<0.001*	0.341	0.395
Creatinine, mg/dL	0.8±0.1	0.8±0.2	0.611	0.8±0.1	0.8±0.1	0.690	0.705	0.126
eGFR, mL/dk/1.73 m²	99.3±10.0	97.6±13.6	0.241	97.1±10	96.5±13.5	0.811	0.289	0.350
Sodium, mmol/L	139.2±2.5	139.4±1.7	0.690	139.7±2.5	139.7±1.8	0.953	0.407	0.850
Potassium, mmol/L	4.5±0.4	4.4±0.3	0.089	4.5±0.4	4.4±0.4	0.121	0.841	0.870
Phosphorus, mg/dL	3.7±0.5	4.0±0.7	0.010*	3.5±0.5	3.8±0.5	<0.001*	0.165	0.533
Magnesium, mg/dL	1.8±0.4	1.9±0.2	0.134	1.9±0.2	1.9±0.2	0.146	0.418	0.729
Calcium, mg/dL	9.6±0.4	9.8±0.5	0.033*	9.6±0.4	9.8±0.5	0.005*	0.286	0.709
Total protein, mg/dL	7.1±0.3	7.1±0.5	0.845	7.0±0.5	7.1±0.4	0.103	0.373	0.716
Uric acid, mg/dL	4.7 (3.7-5.7)	4.7 (3.7-5.1)	0.863	4.4 (3.8-5.0)	4.3 (3.8-5.6)	0.891	0.117	0.747
Albumin, g/dL	4.7±0.3	4.7±0.3	0.103	4.7±0.3	4.7±0.3	0.101	0.150	0.875
Total cholesterol, mg/dL	191.3±27.3	186.4±41.8	0.344	214.0±39.6	190.0±34.4	<0.001*	0.001*	0.040*
HDL, mg/dL	44.8±9.8	45.8±10.5	0.198	45.8±9.5	48.7±8.0	0.013*	0.615	0.046*
LDL, mg/dL	106.3±22.9	103.4±32.0	0.469	130.0±30.3	98.1±20.7	<0.001*	<0.001*	<0.001*
Triglyceride, mg/dL	153.5 (117-270.5)	152 (97-197)	0.145	204.5 (137-321)	154 (119-185)	<0.001*	0.029*	0.023*
ALT, U/L	30 (20-44)	28 (21-36)	0.507	27 (20-42)	25 (21-35)	0.118	0.843	0.264
AST, U/L	21 (16-30)	18 (13-24)	0.105	20 (15-25)	17 (13-22)	0.101	0.311	0.636
GGT, U/L	34 (21-48)	28.5 (20-47)	0.046*	36 (24-58)	28 (19-49)	0.001*	0.543	0.691
ALP, U/L	84 (72-102)	80 (68-89)	0.122	84 (66-105)	79 (62-89)	0.105	0.878	0.775
Urine protein, mg/L	69 (58.3-112.8)	80.2 (59.1-111.3)	0.768	161 (80.3-200.1)	110.7 (79.6-143)	0.002*	<0.001*	0.042*
Urine creatinine, mg/dL	82.9 (36.2-141.2)	83.6 (64.4-103.1)	0.739	93.7 (37.8-178)	92.0 (78.2-118)	0.271	0.236	0.747
Urine mA, mg/L	10.8 (5-29.7)	7.3 (3.4-14.2)	0.011*	27.7 (9.6-38.6)	4.7 (2.9-15)	<0.001*	0.033*	0.028*
Urine PCR, mg/g cr	98 (69-123)	97.5 (68-129)	0.655	108 (79-132)	80 (66-112)	0.048*	0.212	0.035*
Urine mACR, mg/g cr	14.1 (4.4-27.7)	7.6 (3.9-12.8)	0.025*	10.2 (6.8-20.5)	4.8 (3-9.9)	0.038*	0.779	0.292

Data are mean±standard deviation, median (IQR), or number (%). *, considered statistically significant (p<0.05). P1, baseline laboratory findings in Empagliflozin vs Dapagliflozin; P2, change of laboratory findings in Empagliflozin vs Dapagliflozin. Abbreviations: WBC, white blood count, FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; eGFR, estimated glomerular filtration rate; HDL, high density lipoprotein; LDL, low density lipoprotein; ALT, alanin aminotransferaz; AST, aspartate aminotransferase; GGT; gamma glutamyl transferase, ALP, alkalen fosfataz

The incidence of adverse events was 31.7% (n:97), and the most common were dysuria (15.2%), dyspepsia (11.3%), and urinary tract infection (7.1%). Adverse event and its subtypes did not differ significantly in the SGLT-2i treatment groups (**Table 3**).

Table 3. Advers Events

Adverse Effects	All population n=310	Empagliflozin n=170	Dapagliflozin n=140	P
Dysuria, n(%)	47(15.2)	26(15.3)	21(15.0)	0.999
Dyspepsia, n(%)	35(11.3)	20(11.8)	15(10.7)	0.858
Urinary tract infection, n(%)	22(7.1)	13(7.6)	9(6.4)	0.825
Vaginitis, n(%)	3(1.0)	1(0.6)	2(1.4)	0.866
Back/Hip pain, n(%)	3(1.0)	0	3(2.1)	0.182
Documented hypoglycemia, n(%)	2(0.6)	0	2(1.4)	0.395
Weight gain, n(%)	2(0.3)	2(1.2)	0	0.503
Total adverse effects, n(%)	97(31.7)	54(31.8)	43(30.7)	0.843

Data are number (%).

DISCUSSION

In this study, the short-term effects of empagliflozin and dapagliflozin as adjunctive therapy for patients with lifestyle changes and T2DM who experienced inadequate glycemic control with traditional first-line OADs were evaluated. Both empagliflozin and dapagliflozin had similar profiles of improvement of mean FPG, and HbA1c. However, dapagliflozin was associated with a more significant improvement in lipid profiles and spot urinary parameters compared to empagliflozin. In terms of total side effects, no difference was observed between treatment groups.

The progressive nature of diabetes necessitates changes in treatment regimens over time and combination therapy is needed due to the fact that it is usually difficult to achieve the desired glycemic control with monotherapy.[15] It has been reported in previous clinical studies that SGLT-2i are effective in controlling blood glucose levels, reducing body weight, and achieving glycemic control without serious side effects.[16-19] Failure to achieve glycemic control in cases

of T2DM, particularly in terms of high HbA1c levels, may cause an increased risk of cardiovascular and renal disease complications.[20,21] Therefore, HbA1c levels are of prognostic importance in T2DM.[22]

Our results show that empagliflozin and dapagliflozin have similar efficacy in significantly reducing HbA1c in the short term. This efficacy differs from the findings of previous studies. In the studies conducted by Ku et al.[12] and Hussain et al.[13] it was reported that empagliflozin reduced body weight, blood glucose levels, and HbA1c more than dapagliflozin while improving cardio-metabolic risk factors more and reducing the incidence of genitourinary infections. The difference in our study suggests that the two treatment groups with similar mechanisms may have similar efficacy in the short term. Urinary tract infections are a common side effect of SGLT-2i treatment. The difference in our study suggests that the two treatment groups with similar mechanisms may have similar efficacy in the short term. The basis of the proposed pathophysiological mechanism is that glycosuria caused by SGLT2i provides a positive environment for bacterial growth in the urinary tract.[23] In a meta-analysis, only the relationship between dapagliflozin, among all considered SGLT2i, and urinary tract infections was dose-dependent.[24] The dapagliflozin group in our study may explain the low observed frequency of urinary tract infections. However, we think that dyspepsia, which is the most common secondary side effect, is more generally related to metformin.[25,26]

Impaired lipid metabolism in T2DM patients is associated with an increased risk of cardiovascular disease, including atherosclerosis.[27] SGLT2i may affect lipid metabolism, which plays an important role in linking insulin resistance to cardiac injury and even in the development of cardiovascular diseases.[28] In a study conducted with T2DM patients using DPP-4 inhibitors and dapagliflozin, it was reported that dapagliflozin was associated with a significant increase in HDL-C levels.[29] In an experimental study, it was determined that empagliflozin was associated with an increase in LDL-C levels.[30] This effect of empagliflozin was explained by the induction of the transition from carbohydrate to lipid usage for energy in the fasting state.[31] Our findings have shown that patients who received dapagliflozin had worse lipid profiles at baseline but greater improvement in lipid profiles at the 12-week follow-up, whereas those who received empagliflozin did not show a difference in improvement. A possible explanation for this might be differences in pharmacokinetic properties and SGLT2/SGLT1 receptor selectivity. Sodium excretion and osmotic diuresis effects of dapagliflozin are longer-lasting.[31] However, the SGLT2:SGLT1 receptor selectivity ratio of dapagliflozin is approximately half that of empagliflozin.[32] SGLT1 receptors are mostly located in the bowel, and higher selectivity may reduce postprandial blood sugar variations, which may play a helpful role in lowering the risk of heart failure.[33]

SGLT-2i reduce cardiovascular events and may delay the progression of renal disease in patients with T2DM and cardiovascular comorbidities.[34,35] SGLT-2i significantly reduces albuminuria, decreasing the extent of its toxic effects on the renal tubules. This is largely due to the reduction in intraglomerular pressure.[36] Although higher urinary microalbuminuria was initially observed in those receiving dapagliflozin, a greater reduction was found in follow-up. It is thought that this decrease in urinary microalbuminuria was due to a decrease in high levels of advanced glycation end productsdue to blood sugar regulation, decreased oxidative stress, and decreased blood pressure in the afferent arterioles in the proximal renal tubules. This is consistent with the mechanism of dapagliflozin described above. In addition, an increase in Hgb was observed with a possible increase in erythropoietin in patients using SGLT-2i.[37] In our study, there was a moderate increase in serum phosphate and calcium levels, probably due to increased renal tubular phosphate reabsorption.[38] As a result of the weight loss effects of SGLT-2i., a decrease in ggt levels was detected. It can also be said that ggt, which increases in case of inflammation, regresses due to the anti-inflammatory effect of sglt2.[39]

The important limitations of this study are that it was retrospective and was conducted with a limited number of patients. Another limitation of ours is that the effect of SGLT-2i on laboratory findings was examined in a short period of 12 weeks.

CONCLUSIONS

According to the results of our study, we can say that both SGLT-2i have positive effects on blood sugar and lipid panel, while they have neutral effects on other laboratory parameters. However, a much larger sample and a much longer observation period are required to examine such results more effectively.

List of Abbreviations

ACEI: Angiotensin converting enzyme inhibitor, **ALT:** Alanine transaminase, **ARB:** Angiotensinogen receptor blocker, **AST:** Aspartate transaminase, **DM:** Diabetes mellitus , **FPG:** Fasting plasma glucose, **HbA1c:** Hemoglobin A1c, **HDL-C:** High-density lipoprotein cholesterol, **LDL-C:** Low-density lipoprotein cholesterol, **OADs:** Oral anti-hyperglycemic drugs, **SGLT-2i:** Sodium glucose cotransporter 2 inhibitor, **T2DM:** Type 2 diabetes mellitus

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the Ankara City Hospital Ethics Committee (Date: 11.2021, Decision No: E2-21-99).

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

Precipitating Factors and Clinico-Endoscopic Study of Patients with Hepatic Encephalopathy Type C

Hepatik Ensefalopati Tip C Hastalarında Tetikleyici Faktörler ve Kliniko-Endoskopik Çalışma

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Abstract

Introduction: Hepatic encephalopathy (HE) is a decline in brain function as a result of severe liver disease and its inadequacy to remove toxins from the body. It is characterized by personality changes, intellectual impairment, and loss of consciousness. This study was conducted to determine the precipitating factors and endoscopic features of hepatic encephalopathy in patients with liver cirrhosis and evaluate the associated clinical features admitted in a tertiary hospital in Central India.

Material and Method: This hospital-based descriptive cross-sectional study was conducted from November 2016 to October 2018 on 102 patients with hepatic encephalopathy type C, aged above 18. All patients were carefully examined, relevant investigations performed, and data collected through pre-designed proforma. They were sent for statistical analysis where categorical outcomes were compared between study groups using the Chi-square test /Fisher's Exact test.

Results: The prevalence of HE was 19.6% in our study. In this study, we observed that constipation (26.5%), electrolyte imbalance (21.6%), renal failure (18.6%), and upper GI bleeding (18.6%) be among the leading precipitants for HE. Besides liver failure, the associated abnormalities in various factors like coagulation abnormalities, renal derangement, and changes in serum sodium levels can lead to the progression of HE to higher grades.

Conclusion: It is essential to identify the different factors like constipation, electrolyte imbalance, renal failure, and upper GI bleeding early in the course of cirrhosis to help prevent the development of HE.

Keywords: Brain, cirrhosis, hepatic encephalopathy, liver, precipitating factors

Öz

Giriş: Hepatik ensefalopati (HE), ağır karaciğer hastalığı ve vücuttan toksinleri atmakta yetersiz kalması sonucu beyin fonksiyonlarında azalmadır. Kişilik değişiklikleri, zihinsel bozulma ve bilinç kaybı ile karakterizedir. Bu çalışma, karaciğer sirozu olan hastalarda hepatik ensefalopatinin tetikleyici faktörlerini ve endoskopik özelliklerini belirlemek ve Orta Hindistan'da üçüncü basamak bir hastaneye kabul edilen ilişkili klinik özellikleri değerlendirmek için yapılmıştır.

Gereç ve Yöntem: Bu hastane bazlı tanımlayıcı kesitsel çalışma, Kasım 2016 ile Ekim 2018 tarihleri arasında, 18 yaş üstü hepatik ensefalopati tip C'li 102 hasta üzerinde yürütülmüştür. tasarlanmış proforma Kategorik sonuçların çalışma grupları arasında Ki kare testi/Fisher's Exact testi kullanılarak karşılaştırıldığı istatistiksel analiz için gönderildiler.

Bulgular: Çalışmamızda HE prevalansı %19,6 idi. Bu çalışmada HE için önde gelen presipitanlar arasında kabızlık (%26,5), elektrolit dengesizliği (%21,6), böbrek yetmezliği (%18,6) ve üst gastrointestinal kanama (%18,6) olduğunu gözlemledik. Karaciğer yetmezliğinin yanı sıra, pıhtılaşma anormallikleri, böbrek düzensizliği ve serum sodyum seviyelerindeki değişiklikler gibi çeşitli faktörlerdeki ilişkili anormallikler, HE'nin daha yüksek derecelere ilerlemesine neden olabilir.

Sonuç: Siroz seyrinde kabızlık, elektrolit dengesizliği, böbrek yetmezliği ve üst GİS kanaması gibi farklı faktörlerin HE gelişimini önlemeye yardımcı olması için erken dönemde belirlenmesi önemlidir.

Anahtar Kelimeler: Beyin, siroz, hepatik ensefalopati, karaciğer, çöktürücü faktörler

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INTRODUCTION

Hepatic encephalopathy is a challenging complication of advanced liver disease. It is a syndrome and is defined as a spectrum of neuropsychiatric abnormalities in patients with liver dysfunction after excluding brain disease. It is characterized by personality changes, intellectual impairment, and a depressed level of consciousness.[1] Three types of HE are traditionally differentiated according to the underlying cause: Type A as an essential component of acute liver failure, type B as a consequence of portosystemic shunts in the absence of liver dysfunction, and type C in patients with liver cirrhosis and portosystemic bypass.[2] The current discussion concerns whether HE in patients with acute-on-chronic liver failure should be considered separately (type D). It is clinically, pathophysiologically, and prognostically distinct from types A–C. Hepatic encephalopathy occurs in approximately 30–45% of patients with cirrhosis and 10–50% of patients with trans jugular intrahepatic portosystemic shunt, while minimal hepatic encephalopathy affects approximately 20–60% of patients with liver disease.[3]

More than 40% of people with cirrhosis develop hepatic encephalopathy, classified under Type C.[4] More than half of those with cirrhosis and significant HE live less than a year. In those who can get a liver transplant, the risk of death is less than 30% over the subsequent five years.[5] A significant impairment is seen in social interaction, alertness, emotional behavior, sleep, home management, recreation, and past times. Hence it is said that hepatic encephalopathy affects health-related quality of life in cirrhosis patients. So, it is necessary to screen people with cirrhosis for minimal encephalopathy so that treatment can be started early to prevent the development of overt encephalopathy and further complications such as spontaneous bacterial peritonitis or esophageal varices. Further improvement of prognosis would be achieved by early recognition and management of precipitating factors.[6]

There is a lack of studies in India on the precipitating factors of hepatic encephalopathy. Hence, this study was carried out with the primary objective of estimating the prevalence and ascertaining the most common precipitating factor and their frequency in patients with hepatic encephalopathy Type C. They were previously diagnosed with liver cirrhosis and admitted to a tertiary care hospital in central India. The secondary objective was to evaluate the associated clinical features in such cases.

MATERIAL AND METHOD

Study populations

A cross-sectional, single-center, hospital-based, observational study was conducted on 521 consecutive cirrhotic patients who were admitted in the medicine inpatient and intensive care unit (ICU) setting of a tertiary care hospital in central India over two years between Nov 2016 and Oct 2018. Convenient sampling was followed, and the entire sampling frame was included in the study. Institutional Ethics Committee approval was obtained before commencement of the study and written informed consents were collected from the patients.

Patients above 18 years of age diagnosed with liver cirrhosis and hepatic encephalopathy were included in the study. Patients with acute fulminant hepatitis, extrahepatic portal hypertension, other metabolic encephalopathies, intracranial lesions, and those under antipsychotic medication were excluded from the study.

Demographic and clinical data: Patients who fulfilled the inclusion and exclusion criteria were enrolled in the study. All patient demographic data like age, sex, and clinical data like presenting symptoms, signs, blood pressure (BP), along with anthropometric data like height (cm), weight (kg), was obtained. Body mass index (kg/m²) was calculated using the standard formula.

Laboratory investigations: All the patients were investigated using complete hemogram, liver, and kidney function tests, coagulation markers like prothrombin time (PT), international normalized ratio (INR), chest X-ray, and ultrasonography of abdomen. Blood collection was done following all aseptic precautions, and all tests were done on standard laboratory instruments available at the hospital.

Ascitic fluid examination: Ascitic fluid tapping was done in all aseptic conditions as per standard procedure and was examined to rule out the presence of spontaneous bacterial peritonitis.

Endoscopy: All patients were subjected to the upper gastrointestinal (GI) endoscopy to identify the presence of varices. A single, experienced gastroenterologist performed all the endoscopic procedures in study patients.

Classification of HE: Patients with HE were classified as per West-Haven criteria as given below.

Grade 1: Trivial lack of awareness, euphoria or anxiety, shortened attention span and impaired performance of addition; Grade 2: Lethargy or apathy, minimal disorientation for time or place, subtle personality change, inappropriate behavior, and impaired performance of subtraction; Grade 3: Somnolence to semi-stupor, but responsive to verbal stimuli, confusion and gross disorientation and Grade 4: Coma (unresponsive to verbal or noxious stimuli).

Assessment of severity of cirrhosis: The severity of cirrhosis was assessed using the Child Turcotte-Pugh classification criteria.[7] The patients were divided into three groups depending on the severity:

Class A: 5 to 6 points (least severe liver disease)

Class B: 7 to 9 points (moderately severe liver disease)

Class C: 10 to 15 points (most severe liver disease)

Identification of precipitating factors for HE:

Operational definitions

The definitions adopted for confirming different risk factors in patients with cirrhosis were as below:[8]

Constipation: It was defined as straining, lumpy or hard stools, the sensation of incomplete evacuation, the sensation of anorectal blockage/obstruction during at least 25% of defecation with fewer than three defecations per week.

Upper GI bleeding: It was defined as the presence of hematemesis or melena secondary to oesophageal, gastric varices, peptic ulcer, Mallory Weiss tear, gastric erosions, esophagitis. Any bleeding source above ligament of Treitz.

Electrolyte abnormalities: These were defined as evidenced by hyponatremia (<135 mEq/L) or hypokalemia (<3 mEq/L).

Hepatorenal syndrome: It was defined in the presence of cirrhosis with ascites if serum creatinine level ≥ 1.5 mg/dL (133 µmol/L), no or insufficient improvement in serum creatinine level (remains≥ 1.5 mg/dL) 48 hours after diuretic withdrawal and adequate volume expansion with IV albumin, absence of shock, absence of intrinsic renal disease.

Dehydration: It was said to be present when a patient has loss of skin turgor, dry tongue, sunken eyeballs, and evidence of tachycardia and hypotension on clinical examination.

Superimposed liver injury: In the presence of alcoholic hepatitis, hepatitis A, E, or pre-existing hepatitis B or C with deranged liver enzymes.

Infection – SBP: It was defined as an infection of ascitic fluid in the absence of any intra-abdominal, surgically treatable source of infection.

Infection – UTI: It was defined as infections of the lower urinary tract (i.e., the urethra (urethritis) or the bladder (cystitis) with evidence of clinical features and/or presence of at least five pus cells or bacteria identified in urine on microscopy.

Infection – Pneumonia: It was defined as an acute infection of the lung parenchyma by one or co-infecting pathogens with clinical symptoms of cough and fever and/or evidence of consolidation on chest X-ray.

Ethics Statement: The study was approved by the Institutional Review Board and the Ethics Committee of the NKP Salve Institute of Medical Sciences and Research Centre (Date: 2016, Decision No: 17/2016). All participants agreed to and signed the informed consent before the study. Thus, the research has been conducted in compliance with the 1964 Declaration of Helsinki's ethical standards and subsequent amendments.

Statistical Methods

C-P Classification, MELD Score, CBC parameters and renal function parameters, and INR levels were considered as primary outcome variables. Demographic variables, clinical features, and clinical signs and complications were considered as secondary outcome variables. Hepatic encephalopathy (covert vs. overt) was considered as a primary explanatory variable. Descriptive analysis was carried out by mean and standard deviation for quantitative variables, frequency, and proportion for categorical variables. Univariate binary logistic regression analysis was performed to test the association between the explanatory variables and outcome variables. An unadjusted Odds ratio along with 95% CI is presented. P-value <0.05 was considered statistically significant. coGuide version V.1.0 was used for statistical analysis.[9]

RESULTS

A total of 102 subjects were included in the final analysis.

The mean age of the participants was 45.18±7.97 years, and the majority of the study participants were males 101(99.02%) Summary of habits, laboratory parameters (liver function test, creatinine, prothrombin time) of the participants were given (**Table 1**).

Table 1: Summary of personal habits and laboratory parameters (N=102)

Parameters	Summary
Personal habits	
Alcoholism	92 (90.20%)
Tobacco chewing	55 (53.90%)
Smoking	49 (48.0%)
HR	85.97±13.47
SBP	99.39±9.92
DBP	60.88±6.91
Hemoglobin (%)	8.86±1.23
Platelet	1.37±0.31
Serum Creatinine (Mg/Dl)	1.49±0.53
Serum Sodium (130 Meq/L),	133.43±5.34
Serum Potassium (Meq/L)	3.65±0.63
Total Bilirubin (Mg/Dl),	4.1±2.4
Serum Albumin (Mg/Dl),	2.34±0.3
Serum Globulin (Mg/Dl),	3.52±0.4
SGOT (IU)	83.02±24.84
SGPT (IU)	57.89±34.57
Prothrombin Time (Sec)	16.74±2.19
INR	1.66±0.23

UGI-Endoscopy was found to be normal for 30 subjects (29.41%). Out of the 72 (70.59%), subjects showed an abnormality, 25 (24.51%) had small oesophagal varices, 13 (12.75%) had large oesophagal varices, and 11 (10.78%) had oesophagal and gastric varices (**Table 2**). In the present study, the most common precipitating factor detected was constipation (26.5%), followed by electrolyte imbalance (21.6%) and renal failure (18.6%) (**Table 2**). In C P classification 22 (21.57%) subjects comes under class A, 62 (60.78%) comes under class B and 18 (17.65%) comes under class C. MELD score was < 20 for 18 (17.65%), score 21 to 25 for 45 (44.12%), score 26 to 30 for 29 (28.43%), score >30 for 10 (9.80%). 3 (2.94%) subjects comes under grade 0, 11 (10.78%) comes under grade 1, 45 (44.12%) comes under grade 2, 37 (36.27%) comes under grade 3, 6 (5.88%) comes under grade 4 West Haven Grade.

Table 2: Summary of baseline characteristics parameters (N=102 subjects)

Baseline characteristics	Frequency
Clinical features	
Yellow discoloration of eyes	71 (69.61%)
Abdominal distention	68 (66.67%)
Altered sleep	44 (43.14%)
Signs	
Pallor	98 (96.08%)
Icterus	79 (77.45%)
Ascites	71 (69.61%)
UGI-Endoscopy	
Normal	30 (29.41%)
Abnormal	72 (70.59%)
• Small esophageal varices	25 (24.51%)
• Large esophageal varices	13 (12.75%)
• Esophageal and gastric varices	11 (10.78%)
Number connection test (NCT) A and B	14 (13.7%)
Hepatic Encephalopathy	
Covert	14 (13.73%)
Overt	88 (86.27%)
Factors	
Constipation	27 (26.5%)
Electrolyte abnormalities	22 (21.6%)
Renal failure	19 (18.6%)
Upper GI bleeding	19 (18.6%)

Univariate logistic regression to assess the factors affecting Hepatic Encephalopathy (Overt) showed significant relation with C-P classification B (P value=0.004, OR= 6.54), C (P value=0.04, OR=9.71) taking Base line as classification A. Taking MELD score >= 30 as baseline, 21 to 25 (P value=0.01, OR=9.33), 26 to 30 (P value=0.04, OR= 5.78) showed significant relation with Hepatic Encephalopathy (Overt) (**Table 3**).

DISCUSSION

In this cross-sectional observational study, the patients with liver cirrhosis were screened, and the prevalence of hepatic encephalopathy was observed, which was found to be 19.6%. It has been reported that the prevalence of overt HE at the time of diagnosis of cirrhosis is 10–14% in general and 16–21% in those with decompensated cirrhosis. The cumulated numbers indicate that overt HE will occur in 30–40% of those with cirrhosis at some time during their clinical course.[10] A study by Romero-Gomez et al. reported the prevalence of overt HE to be 30% in patients with cirrhosis.[11] A study by Saunders et al. reported that HE was present in 12% of patients with decompensated cirrhosis.[12] Jepsen et al. reported that 11% of patients with cirrhosis developed HE over long-term follow-up.[13] Thus, our estimates are similar to the reported prevalence of HE. This suggests that at least 1 out of 5 patients with cirrhosis would develop HE during the clinical course.

There was a male preponderance with only a single female patient. Tariq et al., in their study, had reported that 53% of patients were males and 47% were females.[14] This contrasts with our observation. The gender difference is probably because most patients included in our study were alcoholics. Alcoholism was the most frequent etiology found in this study, followed by hepatitis B and hepatitis C. In India, alcoholism is more prevalent in males and less frequently seen in females. Heavy drinking has also been reported more in men than women.

Most of the patients had a classical presentation in the form of distension of the abdomen. At end-stage cirrhosis, ascites causes symptoms including abdominal distention, nausea and vomiting, early satiety, dyspnea, lower-extremity edema, and reduced mobility.[15]

Table 3: Univariate logistic regression analysis of factors associated with hepatic encephalopathy (overt) in study population (N=102)

Parameter	Hepatic Encephalopathy		Un adjusted odds ratio 95% CI	P value
	Covert(N=14)	Overt(N=88)		
Age	40.64± 6.23	45.90±8.01	1.095 (1.011-0.1.186)	0.026
Gender (Base line=Female)				
Male	13 (92.86%)	88 (100%)	0 (0-0)	1.000
Female	1 (7.14%)	0 (0%)		
C-P Classification (Baseline =A)				
A	8 (57.14%)	14 (15.91%)		
B	5 (35.71%)	57 (64.77%)	6.514 (1.846-22.990)	0.004
C	1 (7.14%)	17 (19.32%)	9.714 (1.081-87.313)	0.042
MELD Score (Base line = >30)				
≤20	4 (28.57%)	14 (15.91%)	2.333 (0.433-12.568)	0.324
21 To 25	3 (21.43%)	42 (47.73%)	9.333 (1.664-52.337)	0.011
26 To 30	3 (21.43%)	26 (29.55%)	5.778 (1.014-32.930)	0.048
>30	4 (28.57%)	6 (6.82%)		
Complications (Base line = No)				
Upper GI Bleeding	2 (14.29%)	17 (19.32%)	1.437 (0.294-7.029)	0.655
Coagulopathy (Base line = >1.5)				
(INR >1.5)	13 (92.86%)	74 (84.09%)	2.459 (0.297-20.340)	0.404
<1.49	1 (7.14%)	14 (15.91%)		

Most of the patients had a classical presentation in the form of distension of the abdomen. The distention of the abdomen is due to the development of the ascites in patients with cirrhosis. The presence of ascites is the hallmark of decompensated cirrhosis. Patients with cirrhosis are at risk of infections like spontaneous bacterial peritonitis. It has been observed that bacterial infections are common and account for major morbidity and mortality in cirrhosis. Patients with cirrhosis are immunocompromised and increased susceptibility to develop spontaneous bacterial infections, hospital-acquired infections, and a variety of infections from uncommon pathogens.[16] Thus, by assessing the symptomatology, it is possible to determine the severity of patients with cirrhosis.

We found that the percentage of patients in grades 1,2,3 and 4 of HE increased gradually from 9.7% to 83.3% in C-P class C, suggesting a significant association between severity of liver disease and progression of HE grades. This suggests that the severity of HE increases with an increase in severity of the cirrhosis as assessed by CP score. However, the MELD score varied between different grades of HE. Scores of 26 to 30 were seen in 50% of cases with grade 4 HE and were seen in a lower percentage of patients in lower grades of HE. A study by Sharma et al.[10] evaluated the patients with cirrhosis, of which 37%, 36%, and 27% were in C-P class A, B, and C, respectively. They observed that both CP score ($p=0.02$) and MELD score ($p<0.001$) were significantly greater in patients developing minimal HE than non-HE patients.[16] Gupta et al. also reported CP class (52.3%, 67.7%, and 92.3% in class A, B, and C, respectively), MELD score, and venous ammonia levels as predictors of minimal HE in cirrhosis patients.[17] When considering mortality outcomes in HE cases, a study from Udayakumar et al. observed no significant difference in the proportion of patients in CP class B and C or of MELD score in survivors and non-survivors.[18] Similarly, Sasidharan et al. reported patients in CP class C with a MELD score of >15 and serum bilirubin of 7.3 mg/dL were predictors of mortality in severe grades of HE.[19]

Constipation (26.5%) was the most common precipitating factor of HE, followed by electrolyte abnormalities (21.6%), renal failure (19.6%), and upper GI bleed (18.5%). Infection, which is one of the important precipitating factors, SBP and UTI were observed in 8.8% and 5.9% of patients. Most patients had two (57.8%) and three (24.5%) precipitating factors for HE. Thus, the evidence from various studies demonstrates that constipation, infections, electrolyte abnormalities, upper GI bleeding, renal failure, and dehydration as the most frequently encountered factors for the precipitation of HE. Therefore, every attempt should be made to prevent or reduce the occurrence of these complications in patients with cirrhosis.

In this study, INR levels between 1.5 to 2 were seen in 83.3% of patients in grade 4 HE, and level >2 was evident in 66.7% cases in grade 0. The overall distribution of the proportion of patients thus showed a statistically significant difference ($p<0.001$). Raised INR is suggestive of progressed liver disease, and this coagulation abnormality can be seen even in the absence of HE. Our finding is important in that patients in lower grades of HE, i.e., covert HE can also have coagulation abnormalities which should be identified and treated early. A study from Dhanunjaya et al. reported increasing levels of INR with increasing severity of liver disease, which suggests increased coagulation abnormalities. They observed a significant difference in D-dimer levels in increasing severity of the disease assessed by CP class. Thus, apart from coagulation defects, increased fibrinolytic activity could be one of the important factors responsible for the bleeding tendency in liver disease.[20] However, it is important to note that although traditionally, liver cirrhosis has been considered a disease with hypercoagulability state and increased bleeding tendency due to severe homeostatic disruption in liver disease, until recently, there is increasing awareness and evidence that cirrhotic patients are not completely protected from thrombotic events although they have an elevated international normalized ratio and auto anticoagulation.[21]

Though we did not observe any significant association of different grades of HE with factors like platelet count, sodium levels, bilirubin levels, creatinine levels, and serum albumin, these can contribute in various ways to the development and progression of HE. Nearly 25% of patients had small, and 12.8% of patients had large oesophageal varices. Most patients belonged to class B of the CTP classification. The varices are potential sources of upper GI bleeding. Upper GI bleeding is another important precipitating factor, and thus all the patients should be subjected to endoscopy to diagnose varices early and thus prevent HE. Upper GI bleeding is an established risk factor for the precipitation of HE.

We found that the distribution of GI bleeding did not vary significantly ($p=0.655$) in different grades of HE. Similarly, complications like SBP ($p=0.222$), HRS ($p=0.266$), and coagulopathy ($p=0.740$) did not differ significantly in grades of HE. Though the association was observed to be non-significant, the presence of these complications has been identified as precipitants for HE. A study from Romero-Gomez et al. observed that among 63 patients, 34 (53%) exhibited subclinical HE. 30% of them developed overt HE during follow-up.[11] Thus, the presence of complications like oesophageal varices should be looked after in patients with covert HE as it can predict progression to overt HE. This suggests that there is a complex association of different complications with each other, and more complications can result in adverse outcomes.

The limitations of our study were that it involved only a single-center and small sample size. The absence of data on etiology, lack of follow-up data like mortality rate and ICU admission were not assessed, which adds to the limitations. Data was not collected on specific infections except for SBP, UTI, and pulmonary infections. Further, large-scale, multicenter trials should be evaluated using robust clinical outcomes to validate our study.

CONCLUSION

Liver cirrhosis is an important sequela of chronic alcoholism, which is highly prevalent in India. Hepatic encephalopathy is one of the important complications of decompensated cirrhosis. The prevalence of HE was 19.6% in our study, which suggests that one out of five cirrhotic patients can develop HE. It has a very adverse effect on health-related quality of life. The majority of times, one or more precipitating factors are responsible for HE. In our study, we observed that constipation, electrolyte imbalance, renal failure, and upper GI bleeding be among the leading precipitants for HE. Thus, it is important to identify these factors early in the course of cirrhosis to help prevent the development of HE.

Abbreviations: CP-Child-Pugh, GI- Gastrointestinal, HE- Hepatic Encephalopathy, MELD- Model For End-Stage Liver Disease SBP- Systolic Blood Pressure, UTI- Urinary Tract Infection

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the Institutional Review Board and the Ethics Committee of the NKP Salve Institute of Medical Sciences and Research Centre (Date: 2016, Decision No: 17/2016).

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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Original Article / Orijinal Araştırma

Can Inflammation-Based Indices Describe The Poor Prognosis in Palliative Care Patients?

İnflamasyon İlişkili İndeksler, Palyatif Bakım Hastalarında Kötü Prognozu Tanımlayabilir Mi?

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Abstract

Aim: Palliative medicine provides holistic care to increase the quality of life. Predicting prognosis is critical for personalized treatment plan. We aimed to investigate the survival prediction properties of routine biochemistry tests, complete blood count (CBC) and neutrophil/lymphocyte ratios, in addition to biomarker-based indices (the mGPS, PI, and PNI).

Material and Method: The laboratory parameter values, prognostic factor scores, diagnoses and survival time of 139 palliative care patients in the last five weeks of their life were evaluated retrospectively. Cross tables and chi-square tests were used to evaluate whether there was a relationship between qualitative variables, and Pearson's correlation coefficient was used to assess the relationship between quantitative variables.

Results: Ninety-one (65.5%) patients were male and the mean age was 65.9 years (28–91). Results of all three prognostic indices (the mGPS, PI, and PNI) investigated in this study were found to have a statistically significant relationship with the survival time of our patients. In addition, NLR, neutrophil percent, hemoglobin, serum albumin and CRP values were seen to have a statistically significant relationship with the scores of all three prognostic indices. Moreover, it is detected that WBC, NLR, albumin, and CRP values were associated with overall survival.

Conclusion: Our study showed that the PNI, PI, mGPS, and NLR, which are prognostic tools obtained from CBC and biochemistry tests and, which are frequently used, inexpensive, and accessible tests, can predict prognosis in palliative care.

Keywords: Palliative care, prognosis, inflammation

Öz

Amaç: Palyatif tıp, hastaların yaşam kalitesini artırmak için bütünsel bakım sağlar. Kişiselleştirilmiş bir tedavi planı için prognozu tahmin etmek çok önemlidir. Bu nedenle, biyobelirteç bazlı indekslere (mGPS, PI ve PNI) ek olarak rutin biyokimya testleri, tam kan sayımı (CBC) ve nötrofil/lenfosit oranlarının sağkalım tahmin özelliklerini araştırmayı amaçladık.

Gereç ve Yöntem: 139 palyatif bakım hastasının yaşamlarının son beş haftasındaki laboratuvar parametre değerleri, prognostik faktör skorları, tanıları ve sağkalım süreleri geriye dönük olarak değerlendirildi. Nitel değişkenler arasında ilişki olup olmadığını değerlendirmek için çapraz tablolar ve ki-kare testleri, nicel değişkenler arasındaki ilişkiyi değerlendirmek için Pearson korelasyon katsayısı kullanıldı.

Bulgular: Doksan bir (%65.5) hasta erkekti ve yaş ortalaması 65.9 yıl (28-91) idi. Bu çalışmada incelenen her üç prognostik indeksin (mGPS, PI ve PNI) sonuçlarının hastalarımızın sağkalım süreleri ile istatistiksel olarak anlamlı bir ilişkisi olduğu bulundu. Ayrıca NLR, nötrofil yüzdesi, hemoglobin, serum albümin ve CRP değerlerinin her üç prognostik indeksin skorları ile istatistiksel olarak anlamlı bir ilişkisi olduğu görüldü. Ayrıca WBC, NLR, albümin ve CRP değerlerinin genel sağ kalım ile ilişkili olduğu saptandı.

Sonuç: Çalışmamız CBC ve biyokimya testlerinden elde edilen prognostik araçlar olan ve sıklıkla kullanılan, ucuz ve ulaşılabilir testler olan PNI, PI, mGPS ve NLR'nin palyatif bakımda prognozu öngörebildiğini göstermiştir.

Anahtar Kelimeler: Palyatif bakım, prognoz, ınflamasyon

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INTRODUCTION

Palliative care practice, which is the basic principle of holistic patient care, provides symptom control to increase the quality of life of patients with advanced cancer and prevent unnecessary examinations and treatments. Many symptoms, particularly malnutrition and dyspnea are exacerbated in the last period of life. Describing the negative clinical prognosis using the prognostic information of patients with advanced cancer may provide a personalized treatment approach, especially for patients who cannot tolerate aggressive therapy. These predictions are critical for clinicians in recommending and planning medical support interventions such as nutrition and physiotherapy.[1]

Describing the poor prognosis enables the achievement of a dignified death which is the ultimate goal of palliative care. Numerous studies show that the prognostic predictive properties of many biomarkers in various cancers have been studied to contribute to planning the most efficient and patient-centered treatment protocols.[2,3] Instruments frequently used in palliative care for this purpose include the Palliative Prognosis Score (PaP score), Palliative Prognostic Index (PPI), Palliative Performance Scale (PPS) and the Glasgow Prognostic Score (GPS). These tools yield results by evaluating clinical and biomarker data.[4]

Many researchers have indicated that nutritional and immune status have a high relationship with the nascency, progression, and treatment of cancer. The inflammation parameters are appropriate tools to predict the prognosis of cancer. The poor prognosis of patients with malignant tumors is often associated with immune-related systemic inflammatory response.[5] Based on the relationship between inflammation and cancer progression, various inflammation-based indices have been developed as prognostic. Demirelli developed other different inflammatory based prognostic prediction instruments which are used in oncology clinics, are the Modified Glasgow Prognostic Score (mGPS), Prognostic Index (PI), Prognostic Nutritional Index (PNI), and Neutrophil-Lymphocyte Ratio (NLR). However, these tools are not used frequently for palliative care patients, especially in the last weeks of life.[6]

We think that it is important for patients with advanced cancer with a poor prognosis to spend quality time with their loved ones instead of spending their valuable time with unnecessary tests and treatments at the end of their lives. At the same time, this approach may enable cost-effective symptom treatment for terminal stage palliative care patients. In our study, we aimed to investigate the prognostic prediction properties of routine biochemistry tests, complete blood count (CBC), and NLR and biomarker-based indices (the mGPS, PI, and PNI), which are relatively less used in palliative care, in patients with advanced cancer in the last weeks of their life.

MATERIAL AND METHOD

The study was carried out with the permission of Tokat Gaziosmanpaşa University Faculty of Medicine Clinical Researches Ethics Committee (Date: 03.12.2020, Decision No: 20-KAEK-298). The universe of our study was constituted by the adult patients who were treated in our palliative care center and who died between July 1, 2018, and June 30, 2020. Patient records were scanned retrospectively and patient files with missing data were excluded from the study. Parameter values, prognostic factor scores, diagnoses and survival times (days) obtained from the examination results of their clinical controls in the last five weeks of their lives were compared.

Parameters

CBC and biochemistry test results were evaluated for patients with various symptoms treated in our palliative care clinic. Within the scope of biochemistry tests, electrolytes (Na, K, Cl, and Ca), kidney function tests, liver function tests, serum albumin, C-reactive protein (CRP) and procalcitonin values were screened. Neutrophil, lymphocyte, monocyte, platelet, and red blood cell count values were examined using CBC. NLR values obtained from CBC were examined.

Prognostic indexes

The mGPS is based on serum albumin and CRP values. It is scored as 2 if CRP is >10 mg/L and serum albumin is <3.5 g/dL, 1 if only CRP is >10 mg/L, and 0 if these parameters were normal.[2]

PI is based on CRP and leucocyte count. It is calculated as 2 if the CRP value is above 10 mg/L and the leukocyte count is above 10×10^9, 1 if one of the two values is higher, and 0 if both values are normal.[7]

PNI is scored using serum albumin level and lymphocyte count. It is calculated using the formula of 10×serum albumin value (g/dl) +0.005×lymphocyte count (per mm^3). It is scored as 0 if the result is 45 or above, and 1if the value is below 45.[6,8]

Statistical analysis

Descriptive analyses were conducted to provide information about the characteristics of the study groups. The data of continuous variables were in the form of mean ± standard deviation, and data of categorical variables were given as n (%). While comparing the means of quantitative variables between groups, the significance test of the difference between two means and the one-way analysis of variance were used for normally distributed data, and the Mann–Whitney U test and Kruskal–Wallis test were used for non-normally distributed data. Cross tables and chi-square tests were used to evaluate whether there was a relationship between qualitative variables, and Pearson's correlation coefficient was used to assess the relationship between quantitative variables. A p value of less than 0.05, was considered statistically significant, and a ready-made statistics software was used in calculations (SPSS 22.0 Chicago, IL, USA).

RESULTS

Ninety-one (65.5%) patients were male and the mean age of was 65.9 years (28–91). The three most common diagnoses in the patient files screened were lung (29.5%), stomach (12.2%), and colorectal (8.6%) cancers and the mean survival time of patients after their last palliative care visit was 16.5±7.9 days. Results of the three prognostic indices which investigated were found to be statistically significant concerning the survival time of our patients ($p<0.05$). On the other hand, there was no statistical relationship between gender and survival time statistically ($p>0.05$). Gender and prognostic index data are given in **Table 1**.

Table 1: Survival time data regarding gender and prognostic indexes

Variables		Survival time (day)*	p
Gender	Male	16 [10-21]	0.428
	Female	15.5 [10.5-24]	
mGPS	0	29 [16-30]	0.014
	1	18 [11.5-23]	
	2	15 [10-20]	
PNI	0	29 [15-31]	0.003
	1	15 [10-20]	
PI	0	29 [16-30]	0.027
	1	15.5 [10-20]	
	2	15 [10.5-20.5]	

*Median [Q1-Q3] mGPS: modified Glasgow prognostic index, PNI: prognostic nutritional index, PI: prognostic index

We analyzed laboratory data according to the index scores. NLR, neutrophil percent, hemoglobin, serum albumin and CRP values were seen to have a statistically significant relationship with the scores of all three prognostic indices ($p<0.05$). Laboratory parameters found to be statistically significant with prognostic index scores are given in **Table 2**.

The relationship between the parameters and overall survival was investigated using Pearson's correlation test. It is detected that white blood cell (WBC), NLR, albumin, and CRP values have a relationship with survival time, but it was determined to be weak or very weak. (**Table 3**)

Table 3: Statistical parameters correlated with overall survival

Parameters	r	p
NLR	-0.171	0.044
WBC	-0.207	0.015
Albumin	0.332	<0.001
CRP	0.171	0.044

WBC: white blood cell, NLR: neutrophil/lymphocyte ratio

DISCUSSION

Personalized treatment approaches are crucial in palliative medicine, whose primary goal is to increase the quality of life of palliative care patients. At the end of life, in addition to the priorities and expectations of the patients, treatment protocols are shaped by many factors such as the decrease in the benefit–harm ratio of aggressive treatments that have severe side effects. Predicting overall survival is central to planning treatment options, including invasive interventions such as palliative resection, total parenteral nutrition or permanent catheters, for various reasons.[1] In our study, the laboratory parameters (CBC, biochemistry tests) and, NLR, mGPS, PI, and PNI scale scores obtained using the data of patients treated in our palliative care clinic were compared with the life-spans of our patients. All three prognostic scale scores examined were found to have a statistically significant relationship with survival time. WBC, NLR, albumin, and CRP values were also found to be statistically significant with survival, but the correlations were weak.

Table 2: Comparing patients' age and laboratory data according to index scores

Parameters	mGPS				PI				PNI		
	0	1	2	p	0	1	2	p	0	1	p
Age	72.7±5.5*	63.7±13.2*	65.7±12*	0.188	72.6±5.5*	65.7±11.1*	65.3±13.2*	0.214	74.5±10*	65.1±11.7*	0.006
WBC	5.9 [4.3-6]**	8.2 [5.6-9.1]**	9.8 [6.6-13.2]**	0.002	5.9 [4.3-6]**	6.7 [5.1-8.2]**	13.2 [11.3-18]**	<0.001	7.3 [5.9-8.6]**	9 [6.3-13.1]**	0.095
NEU (%)	53.3±30.7*	77.4±13.1*	77.9±15.2*	<0.001	68.2 [12.8-78.8]**	78.8 [68.1-85.8]**	85.1 [76.6-90.1]**	<0.001	68.2 [50-76.4]**	82 [73.6-88.8]**	<0.001
NLR	4.7±1.4*	21.1±30.6*	12.3±11.6*	0.026	4 [3.5-6.6]**	6.5 [4.3-12.1]**	11.5 [6.9-20.3]**	<0.001	3.5 [1.3-5.9]**	9.5 [5.1-17.3]**	<0.001
LYM	13.2 [2.9-19.1]**	7.1 [3.9-13.1]**	9.2 [5.5-14]**	0.614	13.2 [2.9-19.1]**	11.8 [6.8-17.2]**	7.4 [4.3-11.2]**	0.013	26.7±18.5*	10.2±7.3*	<0.001
HGB	11.8±1.4*	11.6±1.6*	9.9±1.9*	0.001	12.6 [9.9-12.9]**	10.1 [9.04-11.3]**	9.7 [8.5-11.1]**	0.02	11.5±2.1*	10.1±1.8*	0.008
Serum Albumin	4 [3.6-4.3]**	3.7 [3.6-4]**	2.7 [2.3-3.1]**	<0.001	4±0.3*	2.8±0.6*	2.7±0.4*	<0.001	3.75±0.59*	2.74±0.58*	<0.001
CRP	5.5 [3.6-8.6]**	73.94 [40.6-138.3]**	106.9 [71.7-168.9]**	<0.001	5.2 [3.6-8.6]**	100.5 [62-149.6]**	124.8 [71.7-177.4]**	<0.001	29.3 [8.7-77.4]**	103.6 [64.6-166.3]**	0.002
Total Protein	6.2 [6-6.7]**	6.6 [6.2-7]**	5.9 [5.4-6.6]**	0.008	6.2 [6-6.7]**	5.8 [5.4-6.6]**	6.1 [5.6-6.7]**	0.135	6.7 [6.2-6.7]**	5.9 [5.5-6.6]**	0.013

*Mean ± SD, **Median [Q1-Q3], WBC: white blood cell, NEU: neutrophil, LYM: lymphocyte, HGB: hemoglobin, NLR: neutrophil/lymphocyte ratio, CRP: C-reactive protein, mGPS: modified Glasgow prognostic index, PNI: prognostic nutritional index, PI: prognostic index, *** Pearson chi-square test was used.

Studies in the literature show that systemic inflammation could play a crucial role in promoting cancer progression and metastasis, because, for example, inflammatory mediators increase vascular permeability and promote cancer cell infiltration through the lymphatic and blood vessels.[9] Hence, CRP, which increases due to tumor growth and tissue inflammation, has been used to determine cancer prognosis.[10] Amano et al., in their study with 1,511 palliative care patients in Japan, showed that high CRP level is associated with poor prognosis and high mortality.[11] In agreement with the literature, our study showed that CRP and overall survival were found to be statistically significantly inversely related; however, due to a low correlation, CRP was not accepted as an independent prognostic factor. This difference among results may be related to the small number of patients in our study.

Inflammation is the main factor in tumor initiation and progression, as it affects various stages of oncogenesis. Indeed, inflammatory cells orchestrate the neoplastic process, promoting tumor proliferation and migration.[12] Tumor-related leukocytosis has been reported in lung, breast, and cervical cancers in the literature.[13] In their study which was conducted with 103 patients, Schernberg et al showed that leukocytosis and neutrophilia are strong prognostic factors for overall survival, progression, and locoregional and distant-free survival in anal cancer treated with chemoradiation.[14] Our study shows that leukocytosis and overall survival have a statistically significant relationship (p=0.015); however, we think that WBC was not an independent prognostic factor due to a low correlation (r=0.207). Another parameter found to be statistically significantly associated with overall survival in our study was NLR. Similar to CRP and leukocytosis, NLR had a weak correlation due to a low regression value. Elevated NLR, another marker of a systemic inflammatory response, has been shown to be significantly associated with poor prognosis in various malignancies.[15] Ahn et al. in their study with 205 patients demonstrated that elevated NLR predicted worse survival in patients with terminal cancer.[16] Many studies have reported that NLR was a prognostic indicator in patients with early or advanced solid tumors in the literature.[15] Weak correlations according to regression analysis of CRP, WBC, and NLR, found to be statistically significantly associated with survival in our study, may be explained by the diversity of cancer diagnoses. The patients we studied were not a homogeneous group, consisting of patients with various cancer diagnoses. The PI which is calculated via CRP serum concentration and WBC, was studied first by Kasymjanova et al.in 2010. In the study, conducted with 134 advanced non-small-cell lung cancer patients, Kasymjanova et al. showed that the PI was a significant prognostic factor for survival.[7] Recently, Gruber et al. reported that the PI independently predicts survival in patients with pancreatic ductal adenocarcinoma undergoing resection.[17] Meanwhile, our study showed that the PI predicts survival in palliative care patients. This result is a strong aspect of our study as to our knowledge, the relationship between the PI and survival in palliative care patients with various cancers has not been studied before.

Inflammation which effects on various stages of cancer causes decreased serum albumin, a negative acute-phase protein.[18] The correlation between serum albumin value and prognosis has been studied by many researchers. Hypoalbuminemia is often detected in advanced cancer patients, and it usually indicates malnutrition and cachexia.[19] In their study with 604 patients, Danan et al. showed that a lower preoperative serum albumin value is associated with an increased rate of wound infection and poorer overall survival in patients with head and neck cancer.[20] It was seen that hypoalbuminemia and overall survival are associated in our study, which agrees with the literature.

The mGPS is a scoring system that works using serum albumin and CRP values to verify systemic inflammation and nutritional status.[21] Researchers posit that the mGPS has prediction value in pancreatic, esophagus, and lung cancers, and its prognostic ability in cancer was indicated by various studies.[22] Tsujino et al. reported that a preoperative measurement using the mGPS predicts survival in non-metastatic renal cell carcinoma prior to nephrectomy.[23] Further, the mGPS was emphasized as an independent prognostic marker in metastatic gastric cancer by Demirelli et al.[6] In our study, the mGPS was an independent prognostic marker in palliative care patients.

The PNI, which was initially identified to evaluate preoperative nutritional conditions and surgical complications in patients with gastrointestinal cancers, reveals nutritional and immunological status via albumin and lymphocyte values.[8] The efficiency of the PNI as a prognostic marker in colorectal, hepatocellular, and pancreatic cancers and renal cell carcinoma has been explained by many studies.[24,25] Okadome et al. found that a low PNI value was associated with poor prognosis in esophageal cancer in their study, which was conducted with 337 patients.[26] Meanwhile, our study showed that the PNI has a prognostic marker feature. In the literature, the PNI and mGPS prognostic tools have been studied with certain cancer types, and their survival prediction properties have been revealed. We believe the fact that the universe of our study includes patients diagnosed with various cancers renders our study effective and powerful. Regarding limitations, this single -center study was conducted in a tertiary palliative care center, so results may not be generalizable.

CONCLUSIONS

Predicting prognosis in advanced cancer, especially in palliative care, is of key importance in establishing a care plan and using available resources efficiently. We have shown that the PNI, PI, mGPS, and NLR, which are prognostic tools obtained from CBC and biochemistry tests and, which are frequently used, inexpensive, and accessible tests, can predict prognosis in palliative care. Finally, we would like to emphasize the importance using prognostic tools for survival prediction in palliative care about developing personalized treatment plans for patients.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Tokat Gaziosmanpaşa University Faculty of Medicine Clinical Researches Ethics Committee (Date: 03.12.2020, Decision No: 20-KAEK-298).

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

The Effect of Intermittent Fasting on the Growth Hormone and Ghrelin in Rats Feeding on A Standard Diet

Standart Diyet ile Beslenen Ratlarda Aralıklı Beslenmenin Büyüme Hormonu ve Ghrelin Üzerine Etkisi

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Abstract

Aim: In this study, the effect of intermittent fasting on growth hormone (GH) and ghrelin in rats that fed on a standard diet was investigated.

Material and Method: Twelve Wistar albino rats were randomly divided into two groups (n=6 per group). Control group (C): a standard nutrition programme was applied. Intermittent fasting group (IF): a 24-hour break from the non-consecutive diet for 2 days a week (all food restricted except water) was applied together with a standard diet.

Results: As a result of the analysis, it was found that the GH in the intermittent fasting together with the standard diet group tended to increase compared to the control group, and while this value difference was not statistically significant, the ghrelin level was found to be statistically lower than the control group.

Conclusion: As a result, it was found that intermittent nutrition tends to increase the level of GH, and it has a statistically significant lowering effect on ghrelin.

Keywords: Growth Hormone, ghrelin, intermittent fasting, standard diet

Öz

Amaç: Bu çalışmada aralıklı beslenmenin standart diyet ile beslenen ratlarda büyüme hormonu (GH) ve ghrelin üzerine olan etkisi incelendi.

Gereç ve Yöntem: On iki Wistar albino sıçan rastgele kontrol ve aralıklı beslenme olmak üzere iki gruba ayrıldı (n = 6). Kontrol grubu (C): Bu gruba standart beslenme programı uygulandı. Aralıklı beslenme grubu: bu gruba haftada sadece 2 gün (ardışık olmayan) diyet verilmesine 24 saat ara verildi (su hariç tüm besin kısıtlaması)

Bulgular: Yapılan analizler sonucunda standart diyet ile birlikte aralıklı beslenme uygulanan gruptaki büyüme hormonu kontrol grubuna göre artma eğiliminde olup bu değer farkı istatistiki önemde bulunmazken, ghrelin seviyesinin ise kontrol grubuna göre istatistiki önemde düşük olduğu bulundu.

Sonuç: Aralıklı beslenme uygulamasının büyüme hormonu seviyesini arttırma eğiliminde, ghrelin seviyesi üzerinde ise düşürücü yönde etkisinin olduğu görülmüş olup, obezitenin tedavisinde ve oluşumunu önlemede kullanılacak yöntemler arasında değerlendirilebileceği kanısına varılmıştır.

Anahtar Kelimeler: Büyüme hormonu, ghrelin, aralıklı beslenme, standart diyet

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INTRODUCTION

Intermittent fasting has a significant effect on reducing the rate of occurrence of complications that may be associated with weight loss and obesity. In addition to weight loss, intermittent fasting prolongs life with regards to blood sugar levels, heart and brain functions by reducing the incidence of chronic non-communicable diseases associated with aging, such as cancer, kidney disease and diabetes mellitus.[1]

Obesity has become a major social health problem worldwide as a result of the consumption of many unhealthy nutrients and limited physical exercise. By restricting daily food intake with intermittent fasting, triglycerides, total cholesterol, low-density lipoprotein cholesterol, blood pressure, glucose, insulin and C-reactive protein levels are ensured to be within normal ranges due to weight loss.[2]

Intermittent fasting (IF) or time-restricted eating is a form of diet that is practiced by restricting food and energy intake for a certain period of time. By restricting the total calorie intake with this diet, circadian rhythms of nutrition are supported and metabolic homeostasis is created.[3,4]

Ghrelin is a 28-amino acid hunger-stimulating peptide hormone that is mainly formed by P/D1 in the fundus of the stomach and epsilon cells in the pancreas. Ghrelin levels, which increase before meals, decrease after meals. It has an opposite task to the leptin hormone which is released from the adipose tissue and creates a feeling of satiety when it is in sufficient amount.[5] Ghrelin has an important role in the body's energy homeostasis and is an important gastrointestinal hormone that stimulates food intake and adiposity.[6] The ghrelin hormone, whose receptors are located in the hypothalamus, pituitary and vagal afferent nerve endings and trunks located throughout the gastrointestinal tract, strongly stimulates the release of GH from the anterior pituitary.[5] It has been reported that circulating ghrelin levels decrease after food intake.[7]

GH, also known as somatotropin, is produced by somatotropic cells in the anterior pituitary and has a single-chain polypeptide structure with 191 amino acids.[8] GH production is regulated through stress, exercise, nutrition, sleep, and feedback mechanisms. Among the factors regulating the release of GH are growth hormone releasing hormone (GHRH) produced in the hypothalamus, somatostatin produced in various tissues, and ghrelin hormone produced in the gastrointestinal tract. GH levels increase in childhood, reach their highest levels in adolescence, and decrease with advancing age.[9] GH is extremely important in regulating growth during adolescence. For this reason, irregularities in the levels of GH in the organism cause significant health problems. GH deficiency and hypopituitarism in adults are closely related to diseases such as vascular endothelial dysfunction, dyslipidemia and insulin resistance, which are important risk factors for cardiovascular diseases.[10]

MATERIAL AND METHOD

The study was approved by the Van Yüzüncü Yıl University Animal Experiments Local Ethics Committee (Dater: 25.06.2015, Decision No: 192616). This study was conducted according to the Declaration of Helsinki, as revised in 2000. The study was performed on 12 Wistar albino male rats aged 3-4 months and weighing 200-250 g. All other conditions, except for the experimental diet, are provided for in such a way that within the standards of laboratory animal care there are 6 rats in each cage. Rats were classified as the 1st group as the control group (CG) with 6 rats in each group, and a standard diet program was applied to this group (2.8% crude fat, 23.1% crude protein, 5% crude fiber, 7.1% crude ash, and 12.8% moisture). Our 2nd group, on the other hand, was determined as the intermittent fasting together with the standard diet group (with a 24-hour break from the non-consecutive diet for 2 days a week and all food restricted except water). The study was continued for a total of 8 weeks. at the end of the study, blood samples were taken from the hearts of rats euthanized with intraperitoneally administered ketamine (50mg/kg) and serum growth hormone and ghrelin levels were measured by ELISA method.[11]

Taking Blood Samples

At the end of the experiment period, the abdominal region of the rats (control and experimental groups) to which general anesthesia was performed with ketamine (50 mg/kg) was excised in the form of an inverted V letter from the anal (pubis) area to the chest cavity, the abdominal cavity was opened, and the required amount of blood was taken by entering the heart with an injector. The blood taken was transferred to yellow-capped biochemistry tubes and centrifuged at 4000 RPM (RCF=1240xg) for 15 minutes and serums were removed. Serums removed were placed in Eppendorf tubes and stored at -80°C until the study time.

Determination of Ghrelin and Growth Hormone

Serum ghrelin and growth hormone levels were determined using the commercial enzyme-linked immunosorbent analysis (ELISA) rat ghrelin (Cusabio in Biology Research, Houston, USA) and growth hormone (MyBioSource, Inc, San Diego, USA) kits with the method of Quantitative Sandwich.[12]

Statistical Analysis

Descriptive statistics of the groups were given as mean and standard deviation. The Shapiro-Wilk test was used to determine whether the data were distributed normally or not. For the same parameter, whether the differences were significant between the groups or not was evaluated by Kruskal-Wallis Test. In order to determine which group the differences were caused by, post hoc analysis (Tukey HSD) was performed and results with a p value of ($p<0.05$) or less were considered significant. For calculations, SPSS (ver.22) statistical package program was used.

RESULTS

While the serum GH value tended to increase in the group on which intermittent fasting was applied compared to the control group, this difference in value was not found to be statistically significant. The ghrelin value was found to be low in statistical significance compared to the control group (**Table 1**).

Table 1. Mean and standard deviation values of growth hormone and ghrelin in serum samples.

Parameter	Control	Intermittant Fasting	P value
Growth hormone (ng/mL)	10.00±0.585[c]	10.83±1.022[c]	0.584
Ghrelin (pg/mL)	233.64±6.16[a]	201.86±4.95[b]	<0.001

"a,b,c: Shows the difference between groups (Tukey HSD)" bp: It is significant compared to the control group (p<0.05)

While the increase in serum growth hormone was insignificant in the group on which intermittent fasting was applied compared to the control group, the decrease in the ghrelin value was significant (p<0.05) (**Figure 1**).

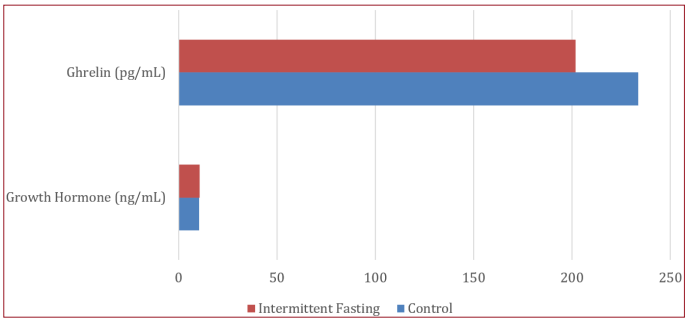

Figure 1. The mean values of serum Growth hormone and Ghrelin between the groups (ng/ml ,mg/dl).

DISCUSSION

It has been reported that decreased circulating ghrelin levels in obesity[13] is caused by disturbances in the ghrelin system, such as, central ghrelin resistance,[14] and ghrelin's inability to induce cessation of food intake.[15] In a study, it was reported that there was a significant decrease in ghrelin levels in six healthy volunteers who fasted for 33 hours.[16] Also, in a study conducted during Ramadan, it was reported that there was a significant decrease in circulating ghrelin levels at the end of Ramadan.[17] In another study, Alzoghaibi et al (2014) indicated that there was no change in ghrelin levels due to fasting during Ramadan.[18] In our current study, it was observed that the level of ghrelin in the group on which intermittent fasting was applied decreased significantly compared to the control group, which is considered compatible with the above studies. It has been reported that gastric nutrient chemosensors have significant contributions to the regulation of ghrelin secretion, which is important for the regulation of food intake and energy homeostasis.[19] In our study, it is thought that the low ghrelin level in the group on which intermittent fasting was applied is caused by the inhibitory effect of intermittent fasting on gastric nutrient chemosensors.

In a study, it was reported that there was an increase in GH levels after fasting for 24 hours.[20] GH has an important role in metabolic adaptations during fasting,[21,22] but there are discrepancies regarding the absolute and relative increase in GH levels during the fasting period. In a study conducted by Alken et al (2008) they again showed that GH levels increased 7 times after a 24-hour fasting.[23] In another study Beer et al (1989) showed that there was an approximately 10 times increase in GH levels after 24-hour fasting, in 6 healthy young men, but this increase was not observed in the group of 8 healthy young women.[24] An increase in GH levels was noted in a 24-hour fasting study in 14 healthy adults.[25] GH levels have been shown to rise after 24 hours in healthy adults who fast for 12 to 36 hours.[26] In another study, it was reported that fasting for less than 3 days significantly increased GH secretion compared to long-term fasting.[27] In another study, conducted by Bouhlel et al. they reported that there was no change in GH levels at the end of fasting held during the month of Ramadan.[28] While the above-mentioned studies of intermittent feeding for a few days showed that the level of GH hormone increased, Bouhlel et al. showed that there was no change in GH levels at the end of Ramadan. In our study, it was observed that GH levels tended to increase in the group on which intermittent fasting was applied compared to the control group, but this increase was not at a significant level. It is reported that ghrelin hormone strongly stimulates the release of GH from the anterior pituitary.[5] It is thought that the GH increase that is not significant in our study is caused the duration of intermittent feeding with the significantly low (**Table 1**) ghrelin level in our intermittent fasting group.

CONCLUSION

In this study we carried out, we are of the opinion that 8-week intermittent fasting practice, 2 days a week, which we applied to the group that fed on a standard diet will have an important contribution to preventing the development of obesity by preventing excessive food consumption by providing a significant decrease in the level of ghrelin hormone, which provides the feeling of hunger, and also in the level of GH hormone, which has many metabolic effects, it will have an important contribution to the regulation of metabolic activities, since it has an effect that tends to increase, although not at a significant level.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the Van Yüzüncü Yıl University Animal Experiments Local Ethics Committee (Dater: 25.06.2015, Decision No: 192616).

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

Clinical Importance of Serum Prolidase and Carbonic Anhydrase III Levels In Patients with Stable Chronic Obstructive Pulmonary Disease

Stabil Kronik Obtrüktif Akciğer Hastalığı Hastalarında Serum Prolidaz ve Karbonik Anhidraz III Düzeylerinin Klinik Önemi

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Abstract

Aim: Chronic obstructive pulmonary disease (COPD) is a disease characterized by irreversible airway flow limitation and chronic airway inflammation. We aimed to investigate the clinical importance of serum prolidase enzyme, which is an indicator of collagen degradation, and Carbonic anhydrase (CA) III enzyme, which has an important function in acid-base regulation, in patients with COPD

Material and Method: In this study, 56 stable COPD patients and 32 healthy subjects without smoking history and comorbidities were included. Serum CA III and prolidase enzyme levels were compared between the two groups.

Results: The statistical difference was not found between the two **groups** in terms of prolidase enzyme levels (p=0.831). There was a statistically significant increase in CA III levels in the COPD group (p=0.001). There were moderate positively correlation between CAIII with partial pressure of carbon dioxide in blood (pCO_2) and negatively correlation between CA III with partial pressure of oxygen in blood (pO_2) in COPD patients (r:0.302, p<0.025; r:-0.314, p:0.02).

Conclusions: We think that there is an important clinical relationship between CA III and COPD, and therefore, CA III may be a candidate biomarker in the follow-up of COPD.

Keywords: COPD, prolidase, carbonic anhydrase III, arterial blood gase

Öz

Giriş: Kronik obstrüktif akciğer hastalığı (KOAH), geri dönüşümsüz hava yolu akış kısıtlaması ve kronik hava yolu iltihabı ile karakterize bir hastalıktır. Kollajen yıkımının bir göstergesi olan serum prolidaz enzimi ile asit-baz regülasyonunda önemli işlevi olan karbonik anhidraz (CA) III enziminin KOAH'lı hastalarda klinik önemini araştırmayı amaçladık.

Gereç ve Yöntem: Bu çalışmaya 56 stabil KOAH'lı hasta ile sigara öyküsü ve ek hastalığı olmayan 32 sağlıklı olgu dahil edildi. Her iki grup arasında serum CA III ve prolidaz enzim düzeyleri karşılaştırıldı.

Bulgular: Prolidaz enzim düzeyleri açısından iki grup arasında istatistiksel fark bulunmadı (p=0,831). KOAH grubunda CA III düzeylerinde istatistiksel olarak anlamlı bir artış vardı (p=0,001). KOAH hastalarında CA III enzimi düzeyi ile kanda kısmi karbondioksit basıcı (pCO_2) arasında orta derecede pozitif, kanda kısmi oksijen basıncı (pO_2) arasında ise negatif korelasyon vardı (r:0,302, p<0,025; r:-0,314, p:0,02).

Sonuçlar: CA III ile KOAH arasında önemli bir klinik ilişki olduğunu ve bu nedenle CA III'ün KOAH takibinde aday bir biyobelirteç olabileceğini düşünüyoruz.

Anahtar Kelimeler: KOAH, prolidaz, karbonik anhidraz III, arter kan gazı

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INTRODUCTION

The prolidase enzyme is involved in the destruction of proline and hydroxyproline, those of the most important amino acids in the collagen structure.[1] Prolidase located in many tissues such as the kidneys, liver, lungs and heart is considered an indicator for collagen turnover.[2] In many studies, plasma prolidase activity was found to be high in clinical pathologies associated with chronic inflammation and collagen deposition in the tissue.[3-5]

Carbonic anhydrase (CA) is a family of zinc metalloenzymes with at least 14 different isoenzymes.[6] CA III is a cytosolic enzyme and it is found especially in the uterus, testis, skeletal muscle, lungs, red blood cells, colon, and kidneys.[7] CA III enzyme participates in the reversible hydration-dehydration reaction of carbon dioxide: $CO_2+H_2O \leftrightarrow HCO_3^- + H^+$. This enzyme plays a role in many physiological processes such as pH regulation and maintenance of ionic balance.[8,9] In many studies, the relationship of CA III enzyme with different diseases has been investigated. Vanaah et al. found that only serum myoglobin increased in patients with infarction, while both serum myoglobin and CA III were significantly increased in patients with neuromuscular disease.[10,11] In the study of Kharbanda et al., it was found that hepatocellular damage due to alcoholism causes low CA III levels in the blood.[12] Therefore, they emphasized that the association of myoglobin and CA III in blood can be used to show skeletal muscle damage.

Chronic obstructive pulmonary disease (COPD) is a disease characterized by irreversible airway flow limitation as a result of exposure to harmful particles and chronic airway inflammation.[13] Due to protease-antiprotease imbalance caused by chronic inflammation, serious effects may occur in the production and destruction cycle of collagen, which is a structural element of the alveolar wall. In addition, airflow limitation and chronic inflammation, gas diffusion (CO_2, O_2) abnormalities in the ongoing process may develop.[14]

COPD is a systemic disease that affects many organs and tissues due to chronic inflammation. Therefore, we aimed to investigate the clinical importance of serum prolidase enzyme, which is an indicator of collagen cycle, and CA III enzyme, which has an important function in acid-base regulation, in patients with COPD. Our study is the first to investigate the relationship between COPD and CA III enzyme levels in the light of literature data.

MATERIAL AND METHOD

This single-center, prospective study was conducted at Harran University, Faculty of Medicine, Department of Chest Diseases between Januray 2019 and June 2019. The study included 56 stable COPD patients newly diagnosed in the outpatient clinic and 32 healthy cases no smoking history and without any comorbidities. This study supported by Harran University Scientific Research Projects (Project No:19302, Approval Date:02/12/2019). A written informed consent was obtained from each participant. The study protocol was approved by the local Harran University Faculty of Medicine Ethics Committee (Date: 13.06.2019, Decision No: HRU/19.06.04). The study was conducted in accordance with the principles of the Declaration of Helsinki. Patients over the age of 18, newly diagnosed with COPD and without any additional systemic disease were included in the study. Patients under the age of 18, with additional systemic disease, previously diagnosed with COPD and receiving treatment, and who presented to the outpatient clinic or emergency service due to an attack of COPD were excluded from the study. Smoking history (in packs/year) and demographic data of all cases were recorded. All patients were diagnosed with COPD based on their medical history, physical examination findings, and pulmonary function test results. Pulmonary function tests of the patients were performed with a spirometer in sitting position. The threshold value of FEV1/FVC <0.7 after bronchodilator was used for the diagnosis of COPD.[13] Venous blood for routine biochemistry and hemogram examinations and arterial blood (brachial/radial artery) for blood gas evaluation were taken from all patients and healthy subjects. Arterial blood gas was obtained from all cases in room air. Biochemical analyses for prolidase and CA III were performed according to the Fine test Sandwich ELISA kit protocol. Human carbonic anhydrase 3 muscle specific ELISA kit and human Xaa-pro dipeptidase/prolidase ELISA kit were used and the sensitivity was determined as 0.252 ng/mL and 0.23 ng/mL, respectively. After adding 100 µL serum samples to 96-plate in the kit, they were incubated at 37°C for 90 minutes. After the incubation, the plate was emptied and washed twice with washing solution and dried. 100 µL Biotin-labeled Antibody was added on it and incubated for 42 minutes at 37°C for 60 minutes. After the incubation, the plate was emptied and washed 3 times with washing solution and dried. 100 µL HRP-Streptavidin Conjugate was added and incubated at 37°C for 30 minutes. After the incubation, the plate was emptied and washed 5 times with washing solution and dried. 90 µL of TMB Substrate was incubated at 37°C in dark for 20 minutes. After the color formation was observed, 50 µL of Stop Solution was added. The data were obtained by reading the plates at 450 nm absorbance in a microplate reader (Biotec-Cytation-1).

Statistical Analysis

SPSS for Windows version 22.0 (SPSS Inc., IL, USA) was used for statistical analyses. Kolmogorov-Smirnov test was used for evaluating if the continuous data were distributed normally. Continuous data were expressed as mean±SD or median (25-75 IQR). They were compared using the Student t or Mann-Whitney U tests according to the distribution. Receiver operating characteristics (ROC) curve analysis was performed in order to determine the optimal cut-off value of CA III for predicting COPD. Correlation between

CA III enzyme and parametres of blood gas variables were demonstrated using Spearman's test. A p value of < 0.05 was considered as statistically significant.

RESULTS

A total of 88 cases, five females (5.6%) and 83 males (94.3%), were included in the study. Demographic and laboratory data of both groups are shown in **Table 1**. While smoking was significantly higher in the patient group, FEV1 and FEV1/FVC values were found to be significantly lower (p<0.001, p<0.001, p<0.001, respectively). Albumin and lymphocyte values were significantly lower in the patient group compared to the control group; C-reactive protein (CRP), white blood cell (WBC), neutrophil, and monocyte ratios were high.

Table 1. Comparison of the demographic and laboratory data of the patient and control groups.

	Patient Group (n=56)	Control Group (n=32)	P
Age, years	62 (55.5-70.0)	58 (54.0-63.0)	0.094
Gender, f/m	4/52	1/31	0.466
Cigarette, package/year	40 (30-55)	0	**<0.001**
FEV1,l	38 (26.0-53.5)	92 (86.0-97.0)	**<0.001**
FEV1/FVC, %	62 (54-68)	85 (79-91)	**<0.001**
Glucose, mg/dL	99 (90-135)	94 (90-100)	**0.026**
Urea, mg/dL	29 (23.5-37.5)	28.0 (25.0-35.0)	0.746
Creatine, mg/dL	0.8 (0.7-0.8)	0.9 (0.7-1.0)	**0.010**
AST, U/L	14 (10.0-19.5)	15.0 (13.0-22.0)	0.090
ALT, U/L	19 (13-26)	20.0 (15.0-23.0)	0.678
Albumin, g/dL	4.1 (3.6-4.6)	4.4 (4.1-4.5)	0.219
LDH, U/L	208.0 (182.5-268.5)	165.0 (135-210.0)	**0.001**
Potassium, mE/dL	6.8 ±17.8	4.2 ±0.7	0.416
CRP, mg/dL	3.2 ±5.2	0.21 ±0.15	**0.002**
WBC, 10^3/mL	9.3 (7.4-11.3)	7.4 (6.5-8.6)	**0.001**
Lymphocyte, 10^3/mL	1.7 (1.1-2.3)	2.3 (2.0-2.9)	**0.001**
Neutrophil, 10^3/mL	5.8 (4.3-8.1)	4.9 (3.8-5.1)	**0.001**
Monocyte, 10^3/mL	0.7 (0.5-0.9)	0.3 (0.2-0.5)	**<0.001**
Eosinophil, 10^3/mL	0.1 (0.0-0.3)	0.1 (0.1-0.2)	0.749
MPV, f/L	7.3 (6.6-8.0)	8.6 (7.5-9.4)	**<0.001**
Platelet, 10^3/mL	282 (242-308.5)	245.0 (223.0-3337.0)	0.526
RDW, %	12.5 (11.2-14.1)	13.0 (11.2-13.8)	0.986

FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactat dehydrogenase; CRP, C-reactive protein; WBC, white blood cell; MPV, mean platelet volume; RDW, red cell distribution width; CA 3, carbonic anhidrase 3.

When arterial blood gas parameters were compared between the two groups, while partial pressure of oxygen in blood (pO_2) and oxygen saturation in the blood (SO_2) values were found to be significantly lower in the patient group, partial pressure of carbon dioxide in blood (pCO_2) and bicarbonat ions in the blood (HCO_3) were significantly higher, there was no significant difference between pH levels (**Table 2**).

Table 2. Comparison of the arterial blood gas of the patient and control groups

	Patient Group (n=56)	Control Group (n=32)	p
pH	7.38 (7.36-7.41)	7.40 (7.38-7.41)	0.232
pO_2, mmHg	59.1 (51.3-69.1)	86 (84.6-88.1)	**<0.001**
pCO_2, mmHg	49.9 (45.14-57.4)	36.2 (35-38)	**<0.001**
HCO_3, mEq/L	27.2 (25.3-30.1)	24 (23.4-25)	**<0.001**
SO_2, %	90.6 (85.2-94.9)	97 (96-99)	**<0.001**
Lactate, mmol/L	1.8 (1.2-2.1)	1.1 (1.0-1.2)	**<0.001**

pO_2 = partial pressure of oxygen in blood; pCO_2 = partial pressure of carbon dioxide in blood; HCO_3= bicorbonat ions in the blood; SO_2 = oxygen saturation in the blood.

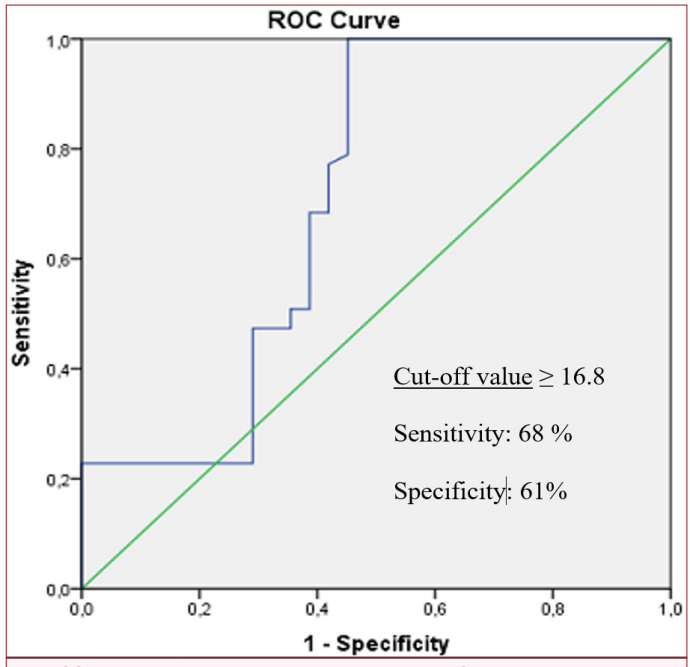
CA III and Prolidase enzyme levels were compared between the two groups. While no statistical difference was found between the two groups in terms of prolidase enzyme levels, there was a statistically significant increase in CA III enzyme levels in the patient group (respectively, p=0.831, p=0.001) (**Table 3**).

Table 3. Comparison of CA III and Prolidase enzyme levels between patient and control groups

	Patient Group (n=56)	Control Group (n=32)	P
Prolidase, U/L	13.9 (2.8-40.7)	11.8 (2.6-53.3)	0.831
CA3, units	20 (14.9-39.2)	7.4 (3.8-44.7)	0.001

Correlation between variables was demonstrated using Spearman's test. The serum CA III value was negatively correlated with pO_2 value and positively correlated with pCO_2 value (r:-0.314, p:0.02; r:0.302, p<0.025).

ROC curve analysis was performed to determine the cut-off value of the CA III enzyme in predicting COPD. With 69% sensitivity and 62% specificity, the cut-off value of CA III enzyme was ≥16.8 (AUC:0.709, P=0.001) (**Figure 1**).



Variable	AUC	95 % CI	P
CA III	0.709	0.579-0.838	0.001

Figure 1. ROC curve of CA3 enzyme level for predicting COPD

DISCUSSION

The main finding of our study is that there is a positive correlation between COPD and serum CA III level due to physiopathologies such as gas diffusion disorder, but contrary to the current literature, no significant result was obtained between serum prolidase and COPD.

COPD is a disease characterized by airflow limitation and chronic inflammation. Currently the most important risk factor is known as smoking. The pathological changes observed in COPD include chronic inflammation with increased numbers of specific inflammatory cell types (macrophage, neutrophils) in different parts of the lung and structural changes resulting from repeated injury and repair. In addition, the increase in circulating cytokines such as CRP, IL-8, TNF, IL-6 and neutrophils are important laboratory parameters observed.[15] In our study, all patients were active smokers and the neutrophil ratio and CRP level of the patient group was statistically significantly higher compared to the control group.

Chronic inflammation in the airways contributes to COPD pathogenesis by disrupting the protease/antiprotease and oxidant/antioxidant balance. Increased levels of proteases, derived from inflammatory cells and epithelial cells, have been observed in COPD patients. Disruption in the protease-antiprotease mechanism increases the destruction of connective tissue components such as collagen.[16] Significant results have been determined with serum prolidase activity in many different pathologies such as cardiac, gynecological, collagen tissue diseases and it has been emphasized to be an important biomarker in these pathologies.[17-19] Therefore, recently, there are different studies investigating the relation of prolidase enzyme, which has a great role in collagen synthesis, with COPD.[20-23] In our study, there was no statistically significant difference between the COPD group and the healthy group in terms of prolidase levels. This result may be due to the low number of COPD patients and the fact that all COPD patients are in a stable period.

Carbonic anhydrase in the red blood cell and in the pulmonary endothelium facilitates the elimination of CO_2 in the lungs. In general, gas transfer for oxygen and carbon dioxide worsens as the disease progresses in the COPD. Reduced ventilation may be also be due to reduced ventilatory drive or increased dead space ventilation. This may lead to CO_2 retention and hypoxemia.[24] Mondrup et al. found that the content of CA isoenzyme B in erythrocytes in chronic obstructive pulmonary disease was significantly higher in hypercapnic patients than in normocapnic patients.[25] According to the literature data, there are no clinical studies conducted between CA III and COPD. For the first time, the relationship between CA III enzyme and COPD was compared in our study. In our study, CA III activity was significantly higher in the COPD group than in the control group. Also, by ROC curve analysis, CA III ≥ 16.8 value predicted COPD with 69% sensitivity and 62% specificity. In addition, we found that the CA III enzyme showed a correlation negative with pO_2 and a correlation positive with pCO_2. The high level of CA III enzyme activity in the COPD group is an indication of the deterioration of acid-base balance in this pathological process and hypoxia-CO_2 retention in erythrocytes. The presence of statistically significant low O_2 and high CO_2 values in arterial blood gases of COPD patients in our study supports this hypothesis.

The main limitations of this study can be listed as follows; 1- low number of patients, 2- being a single center 3- all patients in stable phase, no patients with COPD attack, 4- They are not long-term follow-up.

CONCLUSION

Although the relationship between COPD and serum prolidase level is not consistent with the literature in this study, we can say that CA III enzyme is associated with gas exchange abnormality in COPD. CA III may be a candidate biomarker to be used in COPD patient follow-up and to provide information about the patient's clinic. We believe that it can lead to studies to be conducted in a larger population.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study protocol was approved by the Harran University Faculty of Medicine Local Ethics Committee (Date: 13.06.2019, Decision No: HRU/19.06.04).

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

Referee Evaluation Process: Externally peer-reviewed.

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Review / Derleme

Bell's Palsy's Viral Pathogenicity and The Use of Botulinum Toxin Type A As Treatment

Bell Felcinin Viral Patojenitesi ve Tedavi Olarak Botulinum Toksin Tip A Kullanımı

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Abstract

Bell's palsy is the common name for the inflammation of the cranial nerve VII. The peculiar geniculate ganglion inflammation is idiopathic and causes hemifacial paralysis. Patients who suffer from this paralysis may have their symptoms dissipate between 3 weeks and 3 months. For certain patients whose facial paralysis persist, botulinum toxin type- A might be an efficient treatment. Depending on the severity of the muscular palsy, different treatments can be offered including surgery, steroid, and anti-viral treatment as well as Botox. This review article's purpose is to dive into the possible correlation of viral pathogens with the activation of the facial nerve inflammation, and how patients with Bell's palsy can benefit from Botox type-A as treatment.

Keywords: Bell's palsy, botulinum toxin type A, Botox, facial nerve, muscular paralysis

Öz

Bell'in felci, kraniyal sinir VII'nin iltihaplanmasının ortak adıdır. Kendine özgü genikulat ganglion iltihabı idiyopatiktir ve hemifasiyal felce neden olur. Bu felçten muzdarip olan hastaların semptomları 3 hafta ile 3 ay arasında kaybolabilir. Yüz felci devam eden bazı hastalar için botulinum toksin tip A etkili bir tedavi olabilir. Kas felcinin şiddetine göre botoksun yanı sıra ameliyat, steroid ve antiviral tedavi gibi farklı tedaviler sunulabilir. Bu derleme makalesinin amacı, viral patojenlerin fasiyal sinir iltihabının aktivasyonu ile olası ilişkisine ve Bell felçli hastaların tedavi olarak botoks tip-A'dan nasıl yararlanabileceğine dalmaktır.

Anahtar Kelimeler: Bell paralizi, botulinum toksin tip A, botoks, fasiyal sinir, kas felci

INTRODUCTION

Bell's palsy is a disturbance of the unilateral peripheral facial nerve, also called cranial nerve number VII. Bell's palsy is commonly interchanged with the term "peripheral facial paralysis." It is one of the most typical malfunctions of the facial nerve. About 60 – 75% of the cases are considered idiopathic.[1] Bell's palsy affects approximately 11.5 – 53.3 per 100,000 people across several populations,[2-5] and it usually presents as a subtle unilateral frailty of the facial muscles, significantly reducing the quality of life. Fortunately, the paralysis experienced by patients suffering from this disease is mostly temporary. Seventy percent of patients report the facial weakness going away within 6 months, with only a few cases requiring antiviral treatment, steroid treatment, or surgery. Even when Bell's palsy goes untreated, eighty five percent of the patients will at least experience mild to moderate recovery within three weeks of its onset presentation.

Bell's palsy is well known as an inflammation of the geniculate ganglion of the facial nerve, which causes muscular paralysis via demyelination and possible ischemia. The symptoms experienced by patients who suffer unilateral facial paralysis usually peak in a about a week and slowly resolve between three weeks and three months. Bell's Palsy is most seen in diabetic patients and has been reported in patients of a broad range of ages, however incidence is higher after forty years of age

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regardless of gender. The cranial nerve seven, responsible for the locomotion of the facial muscles, lies in the facial canal in between the tympanic segments where it takes a turn down the stylomastoid foramen. The inflammation of this nerve is proven to cause facial paralysis however, several types of viral infections like human immunodeficiency virus, herpes zoster virus, Hepatitis B, and Epstein Barr virus have been associated with the occurrence of Bell's palsy.[4] Studies have failed to isolate viral DNA causative role. Therefore, whether viruses are the underlying cause of the inflammation reaction in Bell's palsy remains uncertain.

This article serves to provide a comprehensive analysis on the efficacy of botulinum toxin type-A as a treatment for Bell's palsy on multiple evidence-based clinical cases. The main mechanism for BtA treatment of peripheral facial paralysis is through the intramuscular injection of toxins that cause cholinergic inhibition. Although Bell's palsy is considered an idiopathic disease, this article focuses on the correlations of viruses as potential activators of the initial appearance of the inflamed geniculate ganglion and secondary symptoms. This research aims to bring awareness of the pathogenicity of Bell's palsy and its serological, anatomical, and psychological counterparts. Therefore, the purpose of this review is insight into the possible correlation of viral pathogens with the activation of the facial nerve inflammation, and how patients with Bell's palsy can benefit from early detection of Bell's palsy. Early detection is crucial for better treatment of the disease and to greatly ameliorate the uncomfortable weakness of the facial muscle. As hypothesized by the studies of the authors in this review, the research also aims to find an improvement in the muscle paralysis created by the cranial nerve seven and an overall improvement of the disfigurement of the patients faces after being managed with botulinum toxin type A.

Diagnostic Criteria Utilized for Identification of Bell's Palsy Symptoms

The primary indicator of peripheral facial paralysis is the temporary loss of unilateral motor function on the face causing asymmetry. The unilateral muscle weakness presented is usually detected by the patient when looking into a reflector or by a relative. Secondary indicators of Bell's palsy are a lopsided smile, drooping mouth corner, flattening of lip fold, and widening of the eyelid opening.[6,7] These are all common symptoms shown in patients with facial paralysis. Recent research suggests that eyelid closure is an important criterion to identify the degree of severity. It is widely believed that the symptoms of Bell's palsy are triggered by the inflammation of muscles originally caused by viruses. In addition to the previous list of viruses associated with peripheral facial paralysis, studies have been also testing for mononucleosis, shingles, and cold sores in patients that suffer Bell's palsy, as they can all trigger the swelling around the cranial nerve seven.[8]

Several different scales are used to identify and diagnose the severity of Bell's palsy, including the Stennert Index, the Sunnybrook scale, TETRAS, and the six-point House and Brackman scale (Grades I – VI).[9] The House-Brackmann is the most common for clinical use in America; however, the other scales are still used in Europe and for specific types of clinical measures. The House-Brackmann scale identifies grade I as regular nervous function and grade VI as complete facial paresis. Grades II and III are mild to moderate with reduced to barely possible forehead innervation and lid closure being still barely possible with reduced mouth innervation. Grades IV and V are moderately severe to severe asymmetry and incomplete lid closure. Grade VI is complete paralysis and total loss of tone; with no mouth, eyelid, or forehead innervation.[1]

Correlation Between Viruses and Peripheral Facial Paralysis

The root cause of facial palsy is not yet understood in its entirety, and the methods of treatment are complicated. The muscle weakness present in Bell's palsy seems to be reaction to a viral infection causing inflammation and swelling around the nerve that controls the muscles of one side of the face. Bell's palsy has been reported on several studies between ages of 15 and 60 and scarcely ever reoccurs. The Guideline Development Group has been able to identify the acute nature of facial paralysis arrives at is maximum intensity within 72 hours of onset paresis[6], which is key in identifying the best treatment plan. Numerous studies done have provided significant data to correlate viruses and Bell's palsy. A recent study used polymerase chain reaction to sample viral factors in bodily fluids of patients with Bell's palsy. During the study, the research team was able to detect that 71% of the 42 patients tested positive for HHV-6 (Human Herpes Virus). The team concluded that there is a possible correlation in viral material causing the paralysis.[10,11]

Another study in the emergency department of the Charité, Universitätsmedizin Berlin, correlates the inflammation of the geniculate ganglion with viruses. Data was collected and analyzed from 2010 to 2017 where cold viruses triggered the unilateral facial paralysis.[12] After identifying the main ICD-10 hospital diagnosis, the patients were sent to neurology to exclude other symptomatic problems like headache, cranial neuropathies, and severe ear pain. Isolating Bell's palsy specific cases was done so that no other neurological factor would taint the experiment's data. The results concluded that seasonal acute respiratory infections may be a strong candidate for the pathogenicity of facial palsy due to its ability to reactivate the herpes zoster virus (latent).

Botulinum Type A as Treatment for Bell's Palsy

Botulinum toxin was discovered to have a purpose for treating hyperactive motor nerve filaments since 1954 in Brooks VB publication,[13] and theorized since as early as

1822, when Justinus Wurst Kerner,[14] extracted the microbial toxin from a spoiled sausage and observed an interference with muscle nerve transmission. It has been approximately twenty years since the FDA approved the management of botulinum toxin type A for treatment of many neurological diseases. Botulinum toxin works on the muscle by inhibiting its motor cholinergic neurons. A cholinergic neuron is essentially a nerve cell whose function is to release the neurotransmitter acetylcholine, which causes the muscular contraction.[15] In essence, botulinum toxin inhibits the muscles by occluding the exocytosis of acetylcholine that is contained in the vesicles at the neuromuscular junction. This same neuromuscular mechanism is applied when using BTX-A on paralysis of nasolabial fold, buccinator, frontalis, orbicularis oculi, and other muscles innervated by cranial nerve VII.

The results of BTX-A treatment for peripheral facial paralysis have shown to be favorable. Much research suggests the use of the specific Botox "BTX-A" has had better outcomes in treating peripheral facial paralysis.[16] According to the research data collected by Zhang and Pendolino, the treatment of BTX-A on Bell's palsy is efficient, and patients who underwent this treatment reported an improved quality of life. A study by Dr. Kim et. al, measured the menton deviation and volume of the masseter muscles in 16 patients suffering from peripheral nerve paralysis before and after treatment of the BtA injection and found significant improvement in the bulkiness and height of the injected site of the asymmetry. Some patients with menton deviation who had over 3 mm deviations had reductions, but patients without menton deviations had greater and more significant reduction in volume and bulk height in their facial muscle (masseter m.). Depending on the case, one or more active treatments could be necessary to treat the specific bilateral or hemi facial paralysis. For the most part, botulinum toxin type A, has proven to be extremely effective and has shown to improve the mobility of the facial muscles, as well as the overall lifestyle of many patients.[17] Dr. A. Sahan, who treats unilateral facial nerve paralysis even when prior blepharoplasties or other cosmetic surgeries have been done, had similar success rates with BTX-A. 6.5 units of botulinum toxin A, intramuscularly seems to be the typical dosage as correction to minor asymmetries on the face.[18] The study done by Dr. G. Duarte also supports the improvement of blepharospasms by treatment with botulinum toxin type A. BtA showed moderate to large improvement with a reduced 0.93 in the Jankovic Scale.[19] Yet another study of BtA treatment in 92 patients showed a good response in 96% of them showing the common trend that prolonged treatment of BtA is safe and effective.[20]

The Different Derivatives of Botulinum Toxin Proteins

C. botulinum is an anaerobic, gram-positive, and rod-shaped bacteria. There are many different types of proteins derived from the bacteria *Clostridium botulinum*, botulinum toxin type-A being a derived protein, commonly known as "Botox". Some of the other derived proteins have limited effectiveness. There are eight distinguishable toxins at the antigen level: botulinum toxins A, B, Ci, Cii, D, E, F, and G. Excluding Botulinum toxin A. Even though they all block the acetylcholine release, they are not as common and are not heavily utilized in clinical neurology because of their lower efficacy.[21] Because botulinum toxins serotypes do not have the same receptor, they act differently within the cell—hence the difference in potency and duration. The most recommended for patients with bell's palsy, focal dystonia or synkinesis is botulinum toxin type A which has lasting effects of three months. Its use has gained such success that it is considered a concomitant treatment for peripheral facial paralysis.[22]

Research is ongoing as to how and if the rest of the serological specimens of botulinum have other useful purposes besides inhibiting the exocytosis of acetylcholine. An interesting finding in a study published in The international journal of food and microbiology, found that nitrogen seems to inhibit the growth of clostridium bacteria. The nitrogenous agent did not only hamper the bacterial growth of all clostridium bacteria, but it stunted the toxicity of botulinum toxin type B.[23] However, botulinum toxin type A is preferred over its seemingly homologous antigenic counterparts when treating Bell's palsy because of its stability even after being purified. When these toxins are purified, they become unstable and decrease their biological ability to inhibit muscle contraction.

Evaluation of Risks of Treating Peripheral Facial Paralysis with Botulinum Toxins

Treatment risks from BtA injections are low to moderate when it comes to its intermuscular injections on facial muscles. Risks and complications are higher in surgical intervention in treatment of Bell's palsy. Invasive surgical procedures tend to be naturally of greater risk and longer recovery times. As a general precaution it is recommended for patients that receive botulinum toxins treatment to rest for a few days before exercising, getting facials or facial massages, going to laser treatment or IPLs. This recommendation is made to try and avoid the toxins from dislodging and getting absorbed at the wrong areas in the face. From a general point of view, regardless of the etiology or the length of treatment of BtA, it is considered effective and safe to use in facial nerve disorders specifically in hemifacial spasms.[20]

Follow up treatment is usually required for most chronic cases of peripheral facial paralysis. The administration of botulinum toxin A usually requires injections with intervals of 3 months for its desirable effect. However, the intervals and the dosage vary highly depending on the assessment and severity of the disease. The response to the injections should be assessed by the patient and healthcare provider to resolve the paralysis and of course for pain management

reasons. Patients who receive multiple injections within the three-month periods over the years risk the development of toxin tolerance, specifically the patients who received higher than normal dosage. The way the patient does this is by making antibodies for the toxins, often requiring switching to the other serological versions, for example botulinum type B, F and C. For this reason, it is ultimately recommended to take the lowest effective dosage and as less frequently as possible.[21]

Improvement of Quality of Life After Botulinum Toxin Treatment

Bell's palsy can cause physiological problems for many patients depending on how severe the paralysis is, but Bell's palsy can also cause severe psychological stress in patients, hindering their social interactions and causing social withdrawal. A Pearson correlation analysis demonstrated that psychological factors such as tension, vigilance, openness to change and warmth were different in patients suffering from Bell's palsy compared to healthy patients.[24] There was another study where a positive correlation was found between moderate depression and the length of on-set peripheral facial palsy.[25] Furthermore, another clinical experiment made by Dr. Mehta was done in efforts to measure the improvement in patients with facial paralysis after the administration of BtA injections. The study was held at an outpatient clinic that treats facial nerve paralysis and suggested that the general use of botulinum toxin type A has a stable benefit in controlling facial nerve palsies and has a statistically significant improvements in the quality of life.[26]

Peripheral facial paralysis can be pernicious to patients who suffer the condition. A psychological study performed by S. Pouwels et. al. involved 59 patients, 62% of whom were female patients and 38% of whom were male. The aim of the study was to gain understanding on how age and the severity of Bell's palsy would affect the psychological factors on the different patients. The overall population that was above 55 years of age was associated with moderate depression, linking depression with the severity of the disease by applying the Hospital Anxiety and Depression Scale (HADS).[25] 50.8% of the patients reported scoring between 11 and 15 on the HADS scale who had paralysis for less than 5 years. In a more comprehensive study, 6 studies were scrutinized in a reviewed by Dr. J. Fuzi, and ultimately found that there is a positive trend in the improvement of facial paresis through the administration of botulinum toxin type A.[27]

Concluding Remarks

As hypothesized, the administration of botulinum toxin type A proved to be efficient and showed major improvements in the mobility of facial muscles of patients suffering from Bell's palsy. In cases of toxin resistance to BtA, botulinum toxin types B, C, and F can also be administered to treat peripheral nerve palsies. Defining the correlation of the reactivation of certain viral diseases or cell mediated inflammatory responses and facial palsy seems to be necessary to further understand how and why it sparks an inflammation on the facial nerve and consequently cause the popular paralysis. However, there is highly suggestive evidence that viral infections could be contributing to the inflammation of the geniculate ganglion. More research is required on the concomitant treatment of onset peripheral facial paralysis with steroids, antivirals, laser treatment, and physical therapy with botulinum toxin injections. Patients who were experiencing depression as a consequence of Bell's palsy, reported regaining confidence in their social interactions and having big improvements in their quality of life. Botulinum toxin type A has the longest effect on muscle tissue compared to its serological types and it is the most well-regulated serotype for treatment of Bell's Palsy.

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