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ORIGINAL RESEARCH

Diagnostic Value of Pentraxin-3 in COVID-19 Pediatric Patients

Pentraksin 3'ün COVID-19 Çocuk Hastalarındaki Tanı Değeri

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Abstract

Objective: Many studies have investigated the relationship of hematological, biochemical, immunological, and inflammatory markers with clinical severity during severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection. In this study, we determined the use of Pentraxin-3 as an acute phase marker in infection diagnosis, follow-up, and prognosis.

Method: The study was initiated after ethics committee approval and consent from the patients and their relatives. A total of 167 children, including 103 outpatients and inpatients with SARS-CoV-2 infection confirmed by polymerase chain reaction and a control group consisting of 64 healthy children, were included in the study. The treatments, symptoms, radiological pneumonia findings, leukocyte count, absolute lymphocyte and neutrophil counts, neutrophil/lymphocyte ratio, C-reactive protein (CRP) and Pentraxin-3 values of the patients were recorded and compared with those of the control group.

Results: There was no statistically significant difference between the patient and control groups in terms of age and gender (p>0.05). The mean absolute neutrophil and neutrophil/lymphocyte ratios of the study group were significantly higher than those of the control group. CRP, ferritin averages, and CRP >5 mg/L ratio of the study group were significantly higher than those of the control group. Although Pentraxin-3 values were higher in the study group, no statistically significant difference was found between the control group and the study group. Ferritin levels were found to be significantly higher in inpatients than in the outpatient group.

Conclusion: We found high CRP, absolute neutrophil count, neutrophil/lymphocyte ratio, lymphocyte count, and platelet count in children with SARS-CoV-2 infection. It should be noted that patients with high ferritin values may require inpatient treatment at the time of admission. Although

Öz

Amaç: Şiddetli akut solunum sendromu-koronavirüs-2 (SARS-CoV-2) enfeksiyonunun seyrinde hematolojik, biyokimyasal, immünolojik ve enflamatuvar belirteçlerin klinik şiddet ile ilişkisini araştıran birçok çalışma bulunmaktadır. Bu çalışmada, akut faz belirteci olarak Pentraksin-3'ün enfeksiyon tanı, takip ve prognoz belirlemede kullanımını belirlemeyi amaçladık.

Yöntem: Çalışmaya etik kurul onayı sonrası hasta ve yakınlarından onam alınarak başlanmıştır. Çalışmaya polimeraz zincir reaksiyonu ile doğrulanmış SARS-CoV-2 enfeksiyonu olan ayaktan ve yatan 103 hasta ve 64 sağlıklı çocuktan oluşan kontrol grubu olmak üzere toplam 167 çocuk dahil edildi. Hastaların tedavileri, semptomları, radyolojik pnömoni bulguları, lökosit sayısı, mutlak lenfosit ve nötrofil sayıları, nötrofil/lenfosit oranı, C-reaktif protein (CRP) ve Pentraksin-3 değerleri kaydedildi ve kontrol grubu ile karşılaştırıldı.

Bulgular: Hasta ve kontrol grupları arasında yaş ve cinsiyet açısından istatistiksel olarak anlamlı fark yoktu (p>0,05). Çalışma grubunun ortalama mutlak nötrofil, nötrofil/lenfosit oranları kontrol grubuna göre istatistiksel olarak anlamlı derecede yüksekti. Çalışma grubunun CRP, ferritin ortalamaları ve CRP >5 mg/L oranı kontrol grubuna göre istatistiksel olarak anlamlı yüksekti. Pentraksin-3 değerleri çalışma grubunda daha yüksek olmasına rağmen, kontrol grubu arasında istatistiksel olarak anlamlı bir fark bulunmadı. Ferritin düzeyleri yatan hastalarda ayaktan tedavi grubuna göre istatistiksel olarak anlamlı yüksek bulundu.

Sonuç: SARS-CoV-2 enfeksiyonlu çocuklarda CRP, mutlak nötrofil sayısı, nötrofil/lenfosit oranı yüksek, lenfosit sayısı ve trombosit sayısı düşük bulduk. Ferritin değeri yüksek olan hastaların başvuru anında yatarak tedavi gerektirebileceği akılda tutulmalıdır. Pentraksin-3 değerleri çalışma grubunda daha yüksek olmasına rağmen istatistiksel olarak anlamlı bir

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Abstract

Pentraxin-3 values were higher in the study group, no statistically significant difference was found. Further studies with larger patient groups are needed to use Pentraxin-3 as a prognostic indicator in SARS-CoV-2 infection.

Keywords: Children, COVID-19, C-reactive protein, leukocyte, Pentraxin-3

Öz

fark bulunmadı. Pentraksin-3'ün SARS-CoV-2 enfeksiyonunda prognostik bir gösterge olarak kullanılabilmesi için daha geniş hasta grupları ile ileri çalışmalara ihtiyaç vardır.

Anahtar kelimeler: COVID-19, C-reaktif protein, çocuk, lökosit, Pentraksin-3

Introduction

The disease caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection has been named Coronavirus disease-2019 (COVID-19) by the World Health Organization and has been declared a pandemic as of March 11, 2020 (1). Obtaining meaningful data on biomarkers in SARS-CoV-2 infection and clinical follow-up of the patient at the time of admission, whether inpatient or outpatient; it will help to predict the severity of morbidity and mortality.

Pentraxins are a family of glycoproteins responsible for innate humoral immunity (2). The pentraxin family is divided into short and long pentraxin according to their n-terminal group structure (3). C-reactive protein (CRP) and Serum Amyloid P Component produced in hepatocytes are called short pentraxin (4). Neuronal pentraxin 1, neuronal pentraxin 2, neuronal pentraxin receptor, Pentraxin-3 (PTX-3) and pentraxin-4 are long pentraxins (5).

In our study, we aimed to evaluate the correlation of PTX-3 values with total leukocyte count, neutrophil and lymphocyte counts, neutrophil/lymphocyte ratio, CRP values in children with COVID-19 and to determine the use of PTX-3 as an acute phase marker in diagnosis, follow-up, and prognosis of infection.

Materials and Methods

Our study was approved by the Ethics Committee University of Health Sciences Turkey, İstanbul Haseki Training and Research Hospital with the protocol number 233 on 23.12.2020. Informed consent forms were obtained from all participants in the study and control groups and their families.

A total of 103 symptomatic or asymptomatic SARS-CoV-2 polymerized chain reaction (PCR) positive and 64 healthy children 0-18 years old admitted to our hospital were included in our study. In the study and control groups, individuals with an underlying chronic disease and a history of ongoing drug use and those who did not sign the consent form were excluded from the study.

SARS-CoV-2 oropharyngeal and nasal swab samples were studied in the microbiology laboratory of our hospital using RT-PCR, and the results were recorded (Bioksen ArGe Technical Co. Ltd, Turkey; Biospeedy®).

Venous blood sera for PTX-3 were frozen at 80 °C for study. The total blood count, ferritin, CRP, and D-dimer tests of all participants were studied on the same day in the biochemistry laboratory of our hospital. Ferritin and CRP tests in Roche COBAS 8000 device; D-dimer test was performed on Simens BCS XP device. The total blood count was studied on a Mindray BC 6800 plus device. Frozen sera in the study population were studied using the E-EL-H1574 Elabscience brand ELISA PTX-3 kit and the Biotech ELX800 ELISA reader device on the same day under the same ambient conditions. PTX-3 results were obtained in pg/mL.

The positive value for CRP was >5 mg/L, and the upper limit for D-dimer was 0.55 mg/L. The upper limit for leukocytes was taken as 10000/µL. The hemoglobin value for age was taken as 2SDS below the anemia limit.

The findings of physical examination and complaints of the patients suggesting lung involvement were performed by radiological imaging, and the presence of pneumonia was revealed.

Statistical Analysis

SPSS 15.0 for Windows was used for statistical analysis. Descriptive statistics; numbers and percentages for categorical variables, mean, standard deviation, minimum, maximum, median, and interquartile range for numerical variables. Comparisons of numerical variables in two independent groups were made using the Mann-Whitney U test when the normal distribution condition was not met.

The ratios in the groups were compared using chi-square analysis. The relations between numerical variables were determined using Spearman correlation analysis when the parametric test condition was not met. The statistical alpha significance level was set as $p < 0.05$.

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Results

In the study group, 49 patients were female (47.6%) and 54 patients were male (52.4%). There was no statistically significant difference between the study and control groups in terms of gender distribution (p=0.760). No statistically significant difference was found in the age distribution of the study and control groups (p=0.817) (Table 1).

Of the 103 patients in the study group, 93 (90.3%) were outpatients; ten (9.7%) were inpatients. While 67 (65%) of 103 patients in the study group were symptomatic, 36 (35%) were asymptomatic, and PCR was performed because of contact with an individual with COVID-19. In the study group, 6 patients (5.8%) had pneumonia findings confirmed by computed tomography (CT) (Table 1).

Table 1. Demographic data of the patients and distribution of symptoms, follow-up type, and pneumonia findings

		Study group	Control group	p
Age (year)	Median (min-max)	12 (7-16)	12.5 (7.25-15)	0.817[1]
Gender	Female	49 (47.6)	32 (50.0)	0.760
	Male	54 (52.4)	32 (50.0)	
Follow-up type	Outpatient	93 (90.3)		
	Inpatient	10 (9.7)		
Symptoms	Yes	67 (65.0)		
	No	36 (35.0)		
Pneumonia	Yes	6 (5.8)		
	No	97 (94.2)		

[1]: Mann-Whitney U test

Table 2. Study group symptoms and distribution

Symptoms	n	%
Fever	22	33.8
Cough	16	24.6
Nausea and vomiting	10	15.4
Headache	10	15.4
Weakness	8	12.3
Respiratory distress	7	10.8
Throat ache	5	7.7
Diarrhea	5	7.7
Other symptoms	5	7.7
Anorexia	4	6.2
Muscle pain	4	6.2
Nasal congestion	3	4.6
Loss of taste and smell	2	3.1
Unrest	2	3.1
Palpitation	2	3.1

The most common symptoms in those who were symptomatic from the study group were fever with 33.8% and cough with 24.6% (Table 2).

The mean absolute neutrophil and neutrophil/lymphocyte ratios of the study group were found to be significantly higher than those of the control group (p=0.039, p<0.001). The mean lymphocyte and platelet counts of the study group were significantly lower than those of the control group (p<0.001, p=0.009). There was no statistically significant difference between the study and control groups in terms of hemoglobin, hematocrit, anemia detection percentage, erythrocyte count (RBC), leukocytosis percentage, and mean platelet volume (MPV) (p>0.05) (Table 3).

The mean ferritin level of inpatients treated was statistically significantly higher than that of outpatients (p=0.012). No statistical difference was found in terms of other variables. CRP, ferritin averages, and the ratio of patients with CRP >5 mg/L in the study group were found to be significantly higher than those in the control group (p<0.001 for each). Although the mean PTX-3 value was found to be lower in the control group, no statistically significant elevation was found in the case group (p=0.399) (Table 4).

There was only a statistically significant and weak positive correlation between PTX-3 and the neutrophil/lymphocyte ratio (NLR) of the laboratory parameters (r=0.14, p=0.030). No significant relationship was found between the other variables.

There was no statistically significant difference in the laboratory parameters of patients with and without symptoms (p>0.05).

In our study, we found radiologically confirmed viral pneumonia in thoracic CT scans performed on patients with suspected pneumonia and in 5.8% of the case group. The lymphocyte levels of patients with pneumonia findings were statistically significantly higher than those without pneumonia (p=0.039) (Table 5).

Although PTX-3 values were higher in the study group in our study, no statistically significant difference was found between them and the control group. In childhood, COVID-19 has a milder clinical manifestation, and the prognosis appears to be better than that in adults (6). In a study examining 29 case reports and 17 case series reported up to June 20, 2020, data from 114 pediatric COVID-19 cases were evaluated, and 15% of cases were asymptomatic, while the most common symptoms were fever (64%), cough (35%), rhinorrhea, and mild symptoms (16%) (7). In our study, the most common symptoms were fever and cough, which is consistent with the literature (Table 2).

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In a study of 576 pediatric COVID-19 patients, the hospitalization rate was 8.0 per 100,000 population. The highest rate of hospitalization was found in patients under 2 years of age with 24.8%. Out of 208 (36.1%) hospitalized children whose medical records were thoroughly examined, 69 (33.2%) were admitted to the intensive care unit, 12 (5.8%) required invasive mechanical ventilation, and one died. In this study, the pediatric hospitalization rate was found to be lower than that in adults (8). In our study, 90.3% of the case group was followed up as an outpatient, and 9.7% was hospitalized. Only one of the hospitalized patients was followed up in our pediatric intensive care unit without the need for invasive mechanical ventilation for close follow-up. There were no deaths among the 103 cases we followed (Table 1).

In a review of 7480 cases, chest CT scans were performed in 73.9% of all pediatric cases, and 32.7% of them were normal. In another review, unilateral CT findings were found in 36% of 2914 cases and bilateral CT findings in 64% (9). In our study, we found viral pneumonia in 5.8% of the study group (Table 1).

In a meta-analysis conducted in the adult age group, higher leukocytes, decreased lymphocytes, and decreased platelet counts were found in patients with severe disease and those who lost their lives compared with those who had mild disease and survived (10). In a meta-analysis of 48 studies examining 5829 pediatric patient data, common laboratory findings were defined as normal leukocyte count (69%) and lymphopenia (16%) (11). In a meta-analysis of 624 pediatric patient data from 24 studies on 27 COVID-19 markers, leukocyte count changes were found in 32% of mild pediatric cases (19% decrease, 13% increase). The rates of neutropenia and lymphopenia in mild patients were 52% and 46%, respectively. Leukocytosis has been noted to differ from adult studies. In contrast to adults with severe COVID-19 who show severe lymphopenia, children with severe COVID-19 had increased and decreased lymphocyte counts with almost equal frequency, and the majority were found to have normal numbers. In general, it has been interpreted that leukocyte indices are not reliable indicators of disease severity in children (12). The change in the normal values of childhood leukocyte values according to age is perhaps the factor constituting the main limitation

Table 3. Comparison of complete blood count parameters of the study and control groups

		Study group	Control group	p
Hemoglobin (gr/dL)	Median (IQR)	13.1 (12.5-14.3)	13.3 (12.825-14.475)	0.216[a]
Hematocrit (%)	Median (IQR)	39.4 (37.3-42.5)	39.25 (37.8-42.2)	0.927[a]
Anemia	n (%)	11 (10.7)	4 (6.3)	0.330[b]
RBC[1] (mm^3)	Median (IQR)	4.72 (4.5-5.11)	4.77 (4.52-4.95)	0.643[a]
Leucocyte count (mm^3)	Median (IQR)	6840 (5460-8760)	7155 (6082.5-8337.5)	0.447[a]
Leucocytosis	n (%)	26 (25.2)	15 (23.4)	0.792[b]
Absolute neutrophil	Median (IQR)	3660 (2670-5450)	3275 (2475-4082.5)	**0.039[a]**
Lymphocyte count	Median (IQR)	2030 (1410-2830)	2870 (2267.5-3612.5)	**<0001[a]**
Platelet count (mm^3)	Median (IQR)	259000 (213000-305000)	281000 (253000-339250)	**0.009[a]**
MPV[2] (fL)	Median (IQR)	9.7 (9.1-10.4)	9.5 (9-10.275)	0.354[a]
Neuthrophile/lymphocyte ratio	Median (IQR)	1.77 (1.1-3.67)	1.155 (0.82-1.725)	**<0.001[a]**

[1]: Red blood cell (RBC), [2]: Mean platelet volume (MPV), [a]: Mann-Whitney U test, [b]: Chi-square analysis, IQR: Interquartile range

Table 4. Biochemical parameters in the study and control groups

		Study group	Control group	
CRP (mg/L)	Median (IQR)	2.2 (0.7-5.3)	0.415 (0.24-1.095)	**<0.001[a]**
CRP n (%)	>5 mg/L	23 (25.0)	2 (3.2)	**<0.001[b]**
Ferritin (ng/mL)	Median (IQR)	53.95 (35.05-94.25)	26.9 (19.275-43.2)	**<0.001[a]**
Pentraxin-3 (pg/mL)	Median (IQR)	0.96 (0.37-4.29)	1.36 (0.63-4.6)	0.399[a]
D-dimer (mg/L)	Median (IQR)	0.47 (0.255-0.84)		
D-dimer n (%)	<0.55	19 (57.6)		
	>0.55	14 (42.4)		

[a]: Mann-Whitney U test, [b]: Chi-square analysis, IQR: Interquartile range, CRP: C-reactive protein

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in the analysis of leukocyte and subgroup values of patients with COVID-19 in the literature.

The incidence of thrombocytopenia in COVID-19 is approximately 13% (13). In a meta-analysis, it was noted that the platelet count decreased in severely ill patients. Mechanism of thrombocytopenia; consumption with the effect of viral infection and mechanical ventilation, endothelial damage and thrombosis formation, infection of the bone marrow with virus, decrease in platelet formation from megakaryocytes, and diffuse intravascular coagulation. It has been reported that there is a close relationship between thrombocytopenia and mortality (14). Thrombocytopenia is associated with respiratory failure in the pediatric age group (15). In our study, we did not find a difference in the mean platelet count between the outpatient and inpatient groups, but we found a lower mean platelet count in the patient group (Table 3).

In our study, the absolute neutrophil count in the patient group was significantly higher than that in the control group; we found significantly low lymphocyte and platelet counts, and these data were found to be consistent with those of adult studies (Table 3). In adult patients, the lymphocyte count is normal or low in the early period with non-specific symptoms, whereas cytokine storms show a significant decrease in the second week (16).

The NLR is the ratio obtained by dividing the absolute neutrophil count by the absolute lymphocyte count. In a meta-analysis of 828 patients with COVID-19, 407 of whom were severe, out of 6 studies conducted in China, NLR was found to be significantly higher in the group with severe disease (16). In a retrospective review examining the data of 125 patients with COVID-19, NLR significantly predicted mortality above the threshold value determined on the 2nd and 5th days of hospitalization (17). In general, an increase in neutrophils can be defined as a response to systemic inflammation, and a decrease in lymphocytes can indicate insufficiency of cellular immunity. The relatively low mortality in the pediatric age group and the prevalence of mild and asymptomatic infections compared with adults may limit the use of NLR as a predictor of mortality in the pediatric patient group. In our study, we found higher NLR in the patient group, but we did not find a statistically significant difference in NLR between outpatients and inpatients (Table 3). Although NLR is an easily accessible and inexpensive parameter in the evaluation of inflammatory response and cellular immunity, large case studies including serial measurements to be performed in clinics with high mortality rates are required for its use in clinical practice.

Table 5. Complete blood count and biochemical parameters of patients with and without pneumonia

| | Pneumonia findings | | | | |
| | Yes | | No | | |
	Median	IQR	Median	IQR	p
Hemoglobin	12.85	12.5-15.0	13.1	12.5-14.25	0.949
Hematocrit	40.6	36.8-44.55	39.4	37.25-42.05	0.602
Anemia n (%)	1 (16.7)		10 (10.3)		0.501
RBC[1]	5.015	4.42-5.78	4.71	4.505-5.09	0.371
Leukocyte count	7080	5902.5-9272.5	6840	5440-8775	0.709
Leukocytosis n (%)	1 (16.7)		25 (25.8)		1.000
Absolute neutrophil	3620	1852.5-4650	3660	2720-5555	0.418
Lymphocyte count	2405	2360-5120	1980	1335-2790	**0.039**
Platelet count	285500	252750-347250	258000	212000-303500	0.149
MPV[2]	9.8	9.175-10.35	9.7	9.1	0.888
Neutrophile/lymphocyte ratio	1.07	0.61-1.69	1.9	1.125	0.055
CRP (mg/L)	2.85	1.1-13.375	1.95	0.7	0.580
CRP >5 mg/L n (%)	1 (16.7)		22 (25.6)		1.000
Pentraxin-3 (pg/mL)	2.705	1.575-11.305	0.96	0.36	0.099
Ferritin (ng/mL)	77	52.95-126.35	52.9	28.8	0.189
D-dimer (mg/L)	0.2	0.19	0.47	0.29	0.133
D-dimer >0.55 n (%)	1 (33.3)		13 (43.3)		1.000

[1]: Red blood cell (RBC), [2]: Mean platelet volume (MPV), Mann-Whitney U test and chi-square analysis, IQR: Interquartile range, CRP: C-reactive protein

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In studies conducted to date, no abnormality has been detected in hemoglobin and RBC values in patients with mild and severe COVID-19. In our study, we did not find a significant difference in RBC, hemoglobin, and hematocrit mean and anemia percentages between the patients and healthy groups (Table 3).

In a study conducted in our country in which leukocytes, thrombocytes, MPV, and CRP were evaluated in 55 pediatric patients with COVID-19 and 60 healthy controls, MPV values were found to be significantly higher and lymphocyte levels were found to be significantly lower in the patient group (18). Again, in a retrospective study conducted in our country in which data from 251 confirmed and 65 suspected COVID-19 patients were examined, MPV values were not found to be significant for the severity of COVID-19 disease (19). In our study, no statistically significant difference was found between the MPV values of the patient and control groups (Table 3). As far as we could research, we could not find any publication on MPV changes in COVID-19, except for two studies we found in the literature.

A meta-analysis of 1810 pediatric patients, in which Badal et al. (20) analyzed data from 20 studies, found high D-dimer and LDH levels with a high prevalence of leukopenia and lymphopenia. High levels of procalcitonin (25%), ferritin (26%), and CRP (19%) have been reported as common laboratory markers (20).

In our study, we found the CRP and ferritin averages and the rate of patients with CRP >5 mg/L to be significantly higher in the patient group compared with the control group (p<0.001 for all) (Table 4). We found the mean ferritin level of inpatients to be significantly higher than that of outpatients (p=0.012). We found a high ferritin level was significant as a prognostic indicator of the disease that may lead to hospitalization.

In a study conducted by Genç et al. (21) in adult patients, they revealed that it may be a significant biomarker in predicting mortality in COVID-19 pneumonia. In our study; although we found the mean of PTX-3 in the study group to be higher than that in the control group, we did not find a statistically significant difference between them and the control group (Table 4, p=0.339). We found a statistically significant positive and weak correlation between PTX-3 and NLR (p=0.030). However, we did not detect any correlation between PTX-3 and other parameters.

In 2016, a study was published showing that PTX-3 is a more sensitive marker for LRTI in children than CRP, which is frequently used in the clinic (22). No correlation between CRP levels and the severity of viral disease has been described. CRP values are insufficient to differentiate between viral and bacterial infections. In a study in which 104 children under the age of three with viral lower respiratory tract infections were divided into three groups as those with mild, moderate, and severe disease, CRP, PTX-3, serum amyloid A, and serum amyloid P values were compared and PTX-3 was compared with other biomarkers. When combined, it was found to be significant in showing the severity of the disease (23). There are other studies on PTX-3 and respiratory tract diseases. Licari et al. (24) compared the data of 121 pediatric patients with allergic asthma with those of 63 healthy controls and found that serum PTX-3, D-dimer, and eosinophil counts were higher in the asthmatic group. However, the measured serum PTX-3 value was not correlated with disease severity. In a study conducted by Kim et al. (25) with 140 asthmatic pediatric patients and 120 healthy controls, they showed that high sputum PTX-3 values detected in the patient group were correlated with atopic status and disease severity. In a study by Tekerek et al. (26) in ventilator-associated pneumonia, they found PTX-3, procalcitonin, and surfactant protein D values higher in 50 patients with VAP than in 30 healthy controls, and they found no difference in CRP values. PTX-3 is found not only in blood but also in other body fluids such as pleural fluid (27). Correlation of sputum PTX-3 measurement with asthma severity, studies in which PTX-3 elevation was found to be significant in respiratory tract diseases; the demonstration of increased local PTX-3 synthesis by alveolar macrophages in the lung in serum and sputum samples suggests that it can provide predictions about the severity and prognosis of COVID-19.

Genç et al. (21) grouped 88 patients with confirmed COVID-19 as survivors and non-survivors and found PTX-3 to be statistically significantly higher in the non-survival group (p=0.045) and showed it as a mortality biomarker. In a study conducted in adult patients with confirmed COVID-19, PTX-3 was measured using the ELISA method and it was stated that it provided mortality prediction with 89% sensitivity and 92% specificity. Also PTX-3; it was correlated with CRP, IL-6, procalcitonin, presepsis, and D-dimer (28). Brunetta et al. (29) found increased plasma PTX-3 values in 96 patients with COVID-19. It has been emphasized that PTX-3 is a stronger and independent predictor of mortality, better than traditional markers of inflammation in hospitalized patients.

In our study, we found PTX-3 values higher in the patient group than in the control group, but we did not find a

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statistically significant difference between the two groups (Table 5, p=0.399). This may be related to the milder clinical and better prognosis of COVID-19 in childhood. As far as we can research from the literature, our study is the first study on PTX-3 values in the pediatric population with COVID-19. Further studies on the prognostic significance of PTX-3 in COVID-19 with a larger number of cases may yield more comprehensive information on this subject.

In our study, 65% of the 103 patients included in the study group were symptomatic, and 35% consisted of asymptomatic patients whose PCR samples were taken because they were in contact. There was no significant difference in the laboratory data of symptomatic and asymptomatic patients in terms of studied values (p>0.05).

The lymphocyte levels of patients with pneumonia findings were statistically significantly higher than those without pneumonia (p=0.039). These data contradict the information in the literature regarding the monitoring of lymphopenia in severe disease. This can be attributed to the low rate of pneumonia in our study group (Table 5).

Study Limitations

There are limitations in our study, such as the small number of patients, significantly asymptomatic patients, and 6 (5.8%) patients with pneumonia who had severe infections.

Conclusion

As a result, we found that NLR was higher in the patients than in the control group. Although there was a correlation between PTX-3 and NLR values, we did not find pentraxin values significantly higher in the study group. PTX-3 does not appear to be an appropriate biomarker in the diagnosis and follow-up of COVID-19 patients. Studies with more patients are required on this subject.

Acknowledgment: I would like to thank the pediatric clinic assistants and nurses for their help in the preparation of this study.

Ethics

Ethics Committee Approval: Our study was approved by the Ethics Committee University of Health Sciences Turkey, İstanbul Haseki Training and Research Hospital with the protocol number 233 on 23.12.2020.

Informed Consent: Informed consent forms were obtained from all participants in the study and control groups and their families.

Authorship Contributions

Concept: D.Ö.T., K.Ş., M.E., G.A., Design: D.Ö.T., K.Ş., M.E., G.A., Data Collection or Processing: D.Ö.T., G.A., K.Ş., İ.Y., Analysis or Interpretation: M.E., İ.Y., Literature Search: M.E., D.Ö.T., K.Ş., G.A., İ.Y., Writing: M.E., K.Ş., G.A., Supervision: M.E., G.A., K.Ş.

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

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ORIGINAL RESEARCH

Evaluation of the Quality of Life and Psychiatric Comorbidities of Oral and Injectable Therapy Users with Multiple Sclerosis

Multipl Skleroz Hastalarında Hastalık Modifiye Edici Enjekte Edilebilir ve Oral Tedavi Kullanıcılarının Yaşam Kalitesi ile Psikiyatrik Komorbiditelerinin Değerlendirilmesi

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Abstract

Objective: Considering inconsistent findings and the absence of published longitudinal studies on large-scale community cohorts, this study aimed to assess the relationship between treatment modalities (injectable vs. oral therapy) and psychiatric symptoms and quality of life (QoL) in individuals with multiple sclerosis.

Method: This cross-sectional study involved 42 patients with multiple sclerosis diagnosed according to McDonald's 2017 criterion. Participants were grouped into those receiving injectable disease-modifying therapies (DMTs) (19 patients), oral DMTs (22 patients), and healthy controls (20 patients). The Expanded disability status scale, Hamilton depression rating scale (HAM-D), 36-item short form survey (SF-36), Hamilton anxiety rating scale (HAM-A), and headache impact test were applied.

Results: The healthy control group exhibited statistically higher SF-36 total scores than the oral and injectable therapy groups (p<0.05). The HAM-D and HAM-A scores were significantly lower in the healthy control group than in both the oral and injectable therapy groups (p<0.05). HAM-D and HAM-A scores were negatively correlated with the SF-36 total (p<0.01).

Conclusion: Our study contributes to the field by investigating the QoL and psychiatric symptoms in patients receiving both oral and injectable disease-modifying therapy. Our findings show that the effects of oral and injectable DMT use on QoL and psychiatric symptoms are similar.

Keywords: Anxiety, depression, injectable therapy, multiple sclerosis, oral therapy

Öz

Amaç: Tutarsız bulgular ve büyük topluluk kohortlarında yayımlanmış uzunlamasına çalışmaların olmaması dikkate alındığında, bu çalışma multipl sklerozlu bireylerde tedavi yöntemleri (enjekte edilebilir vs. oral tedavi) ile psikiyatrik belirtiler ve yaşam kalitesi arasındaki ilişkiyi değerlendirmeyi amaçlamaktadır.

Yöntem: Bu kesitsel çalışma, McDonald'ın 2017 kriterlerine göre tanı almış çoklu multipl sklerozlu 42 hastayı içeriyordu. Katılımcılar, enjekte edilebilir hastalık modifiye edici tedavi (DMT) alanlar (19 hasta), oral DMT alanlar (22 hasta) ve sağlıklı kontrol grubu (20 hasta) olarak gruplandırılmıştır. Genişletilmiş özürlülük durum ölçeği, Hamilton depresyon değerlendirme ölçeği (HAM-D), sağlık durumu anketi kısa form-36 (SF-36), Hamilton anksiyete değerlendirme ölçeği (HAM-A) ve baş ağrısı etki testi uygulanmıştır.

Bulgular: Sağlıklı kontrol grubuna kıyasla, oral tedavi grubu ve enjekte edilebilir tedavi grubu arasında SF-36 toplam puanları açısından anlamlı düşük bulunmuştur (p<0,05). HAM-D ve HAM-A puanları, sağlıklı kontrol grubunda hem oral tedavi grubundan hem de enjekte edilebilir tedavi grubundan istatiksel olarak daha düşüktü (p<0,05). HAM-D ve HAM-A puanları, SF-36 toplamı ile negatif olarak korelasyon göstermiştir (p<0,01).

Sonuç: Çalışmamız hem oral hem de enjekte edilebilir hastalık modifiye edici tedavi alan hastalarda yaşam kalitesi ve psikiyatrik belirtileri değerlendirerek literatüre katkıda bulunmaktadır. Bulgularımız, oral ve enjekte edilebilir DMT kullanımının yaşam kalitesi ve psikiyatrik belirtiler üzerinde benzer etkilere sahip olduğunu göstermektedir.

Anahtar kelimeler: Anksiyete, depresyon, enjekte edilebilir tedavi, multipl skleroz, oral tedavi

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Introduction

Multiple sclerosis (MS) is an autoimmune disorder that is a leading cause of disability, particularly among young adults. MS is increasingly recognized as a disease with modifiable lifestyle components that significantly impair the quality of life (QoL), affecting development and progression (1-3). Since the early 1980s, QoL has been a crucial component of health status, initially defined in chronic diseases and later adapted for specific conditions like MS (4,5). QoL is a crucial outcome in MS that should be measured in clinical trials (6), predicting disability progression (7,8), and should be more widely utilized by clinicians (9), potentially as a primary disease management goal (10).

For many patients with MS, QoL decreases as the condition advances and the burden of psychiatric symptoms increases (11). Psychiatric comorbidity's adverse impact on QoL is well established, yet it is often overlooked or inadequately treated (12). Prior research has demonstrated that both psychological and physical aspects of QoL can be affected by disease progression, disability level, lifestyle choices, socio-economic factors, and the use of disease-modifying therapies (DMTs) (13,14).

Although there is no known cure for MS, the primary treatment goals are prevention of relapses, regaining function post-relapse, and impeding disability progression (15). Various DMTs have been effective in achieving these goals (16). In Turkey, seven oral DMTs have legal approval for MS treatment: Teriflunomide, dimethyl fumarate, fingolimod, monomethyl fumarate, cladribine, siponimod, and ozanimod (teriflunomide, dimethyl fumarate, fingolimod, cladribine) (17). Injectable treatments like glatiramer acetate and interferon β were considered primary medications before oral DMT approval (11). Some patients prefer transitioning from injectable to oral DMTs because of inadequate disease control, side effects, or diminished QoL (11).

Limited research has explored patient-reported QoL and psychiatric symptoms during the switch from injectable to oral medications. Existing studies evaluating the QOL among various DMT users have shown varying results (11). Given inconsistent findings and lack of literature, this study aims to assess the relationship between treatment modalities (injectable vs. oral therapy) and psychiatric symptoms and QOL in individuals with multiple sclerosis.

Materials and Methods

This cross-sectional study included patients diagnosed with multiple sclerosis. Patients diagnosed with MS according to McDonald's 2017 criteria (18) who applied to the Neurology clinic outpatient unit at the University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital between March 2023 and August 2023 were included. The study groups were as follows: Patients receiving injectable therapy, patients receiving oral DMTs, and healthy controls. Patients aged between 18 and 65 years, literate, and with no treatment changes for at least 1 year will be included in the study. Patients with a history of another neurological disease, such as head trauma that would prevent the interview, mental retardation, dementia, and other neurological diseases that could lead to organic mental disorders, such as epilepsy, using another immunosuppressive drug, and patients with psychiatric diagnosis or treatment were excluded. Healthy controls consisted of individuals aged 18-65 years that were literate and without neurological and psychiatric disease diagnoses and treatment.

Initially, 90 MS patients were included in the study. However, 22 patients were excluded because of irregular medication use, 12 patients because of treatment changes related to unresponsiveness, and 14 patients because of the addition of steroids to their treatment.

Informed consent was obtained verbally and in writing from all participants. We administered the semi-structured socio-demographic and clinical data form, Hamilton depression rating scale (HAM-D), 36-item short form survey (SF-36), Hamilton anxiety rating scale (HAM-A), and headache impact test (HIT-6) to consenting patients participating in the study. Expanded disability status scale (EDSS) scores were calculated during the neurological examination of the patients by a clinician.

Ethical Approval

The research protocol underwent scrutiny and approval from the Scientific Research Ethics Committee of the University of Health Sciences Turkey, Hamidiye Faculty of Medicine (IRB: 30.12.2022-28/1), strictly adhering to the principles outlined in the Declaration of Helsinki.

Measures

The anxiety scale, developed by Beck et al. (19), evaluates the frequency of anxiety symptoms using a 21-item self-assessment scale with scores ranging from 0 to 3. A higher score signifies a greater level of anxiety experienced. A Turkish validity and reliability study for this scale was conducted by Ulusoy et al. in 1996.

The Beck depression scale (BDI) is a self-report instrument that gages emotional, cognitive, somatic, and motivational

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states using a Likert-type scale with 21 items. Each question is scored between 0 and 3, and a higher score indicates a more pronounced level of depression. The Turkish validity and reliability study for the BDI was carried out by Teğin in 1987 and Hisli (20).

The SF-36 is a generic instrument that assesses health-related QoL over the past four weeks across eight dimensions: Physical functioning (PF), role physical (RP), bodily pain (P), general health (GH), vitality (V), social functioning (SF), role emotional (RE), and mental health (MH). All items related to each dimension (excluding health transition) are aggregated and transformed into a scale ranging from 0 to 100, where a higher score indicates a better state of health or well-being (21,22).

The six-item headache impact test (HIT-6) offers a comprehensive assessment of adverse headache impact and is designed for both clinical practice and research. It evaluates the impact on social functioning, role functioning, vitality, cognitive functioning, psychological distress, and headache pain severity. The HIT-6 score, ranging from 36 to 78, indicates impact severity, with larger scores indicating greater impact. Severity categories are as follows: Little or no impact (49 or less), some impact (50-55), substantial impact (56-59), and severe impact (60-78). HIT-6 exhibits excellent internal consistency, test-retest reliability, construct validity, and responsiveness in general headache patients (23).

Statistical Analysis

Statistical analysis was performed using IBM SPSS. Descriptive statistical methods such as mean, standard deviation, frequency, and percentage were used to analyze the study data. The normality of quantitative data was assessed using the Shapiro-Wilk test. Non-normally distributed quantitative variables were compared between groups using the Kruskal-Wallis test, and post-hoc analysis was conducted using the Mann-Whitney U test. The chi-square (χ^2) test was employed to compare qualitative variables across groups. Correlations between parametric variables were assessed using Pearson's test, with statistical significance set at $p < 0.05$.

Results

Table 1 compares the socio-demographic and clinical data of the participants in the current study. Grouping of the patients (n=61) according to their current drug regimen indicated that 22 patients were using oral therapy, 19 were using injectable therapy, and 20 were using healthy controls. The average age for oral therapy was 38.95±9.56, injectable therapy was 39.61±10.57, and healthy control was 39.55±11.73. 54.5% of oral therapy, 68.4% of injectable therapy, and 45% of healthy controls were female. No notable statistical distinction was detected across the three groups concerning age and gender (p>0.05). The educational level (measured in years) significantly differed, with higher levels observed in the healthy control group compared with both the oral therapy and injectable therapy groups (p<0.001). No significant differences were found in marital status, smoking habits, duration of disease, and history of psychiatric disorders among the oral therapy, injectable therapy, and healthy control groups (p>0.05). Individuals receiving oral and injectable therapies exhibited a higher frequency of "no/irregular" employment status compared with the healthy control group (p<0.05). The average EDSS score of the oral therapy group was 2.17±1.38 and the injectable therapy group was 2.25±1.35, and no statistically significant variation was noted between the groups.

Both HAM-D and HAM-A scores were significantly lower in the healthy control group than in the oral therapy group and the injectable therapy group (p<0.05). HIT-6 scores did not show statistically significant differences among the three groups (p>0.05). Physical functioning, general health subscales, and SF-36 total scores were significantly higher in the healthy control group than in the oral therapy and injectable therapy group (p<0.05). The pain and social functioning subscale scores were notably lower in the injectable therapy group than in the healthy control group, with statistical significance (p<0.05).

Table 2 presents the correlation values between socio-demographic and clinical data. HAM-A (r=-0.607, p<0.01) and HAM-D (r=-0.560, p<0.01) scores exhibited a negative correlation with SF-36 total scores. Moreover, a negative correlation was noted between the HIT-6 score and the SF-36 total score (r=-0.313, p<0.05). The correlation data for the SF-36 subscales and other variables can be found in Table 2.

Discussion

Evaluating the QoL in patients with MS has become integral to diagnosis, aiming to minimize its negative impact on daily functioning through treatment (24). Our study contributes to the literature by assessing QoL and psychiatric symptoms in patients receiving both oral and injectable disease-modifying therapy (DMT). Our findings show that the effects of oral and injectable DMT use on QoL

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Table 1. Comparative evaluation of socio-demographic and clinical data

All participants (n=61)	Oral therapy (n=22)	Injectable therapy (n=19)	Healthy control (n=20)	df/χ^2	p^1	p^2	p^3	p^4
	Mean ± SD/n (%)	Mean ± SD/n (%)	Mean ± SD/n (%)					
[a]Age	38.95±9.56	39.61±10.57	39.55±11.73	2	0.882			
[a]Education (years)	10.27±4.90	12.11±3.66	16.9±6.52	2	**0.000**			
[b]Gender (female)	12 (54.5)	13 (68.4)	9 (45.0)	2.186	0.335			
[b]Marital status (not married)	8 (36.4)	8 (42.1)	3 (15.0)	3.775	0.151			
[b]Employment (no/irregular)	13 (59.1)	11 (57.9)	1 (5.0)	16.976	**0.002**	OT>HC, IT>HC		
[b]Smoking (yes)	2 (9.1)	6 (31.6)	8 (40.0)	5.581	0.061			
[b]History of psychiatric disorders (yes)	5 (22.7)	4 (21.1)	1 (5.0)	2.839	0.242			
[a]Duration of disease (years)	8.47±3.98	7.31±5.08	-	1	0.211			
[a]EDSS	2.17±1.38	2.25±1.35	-	1	0.727			
[a]HAM-D	15.27±8.04	11.38±7.45	5.20±5.69	2	**0.000**	0.221	**0.000**	**0.010**
[a]HAM-A	14.00±8.34	13.0±9.24	6.05±5.08	66	**0.003**	0.656	**0.001**	**0.014**
[a]HIT-6	53.68±8.13	54.66±10.08	49.45±8.39	2	0.152			
[a]SF-36 total	491.35±134.14	491.78±149.16	593.98±116.53	2	**0.024**	0.937	**0.018**	**0.018**
[a]Physical functioning	76.81±21.90	75.78±24.79	92.00±12.29	2	**0.006**	1.00	**0.001**	**0.030**
[a]Role limitations due to physical health	62.50±38.38	59.21±37.46	80.00±32.03	2	0.142			
[a]Role limitations due to emotional problems	51.51±39.47	68.42±40.78	73.33±36.83	2	0.125			
[a]Energy/fatigue	51.13±19.87	50.26±23.24	57.25±23.47	2	0.358			
[a]Emotional well-being	57.45±18.20	54.94±21.03	65.40±17.47	2	0.209			
[a]Social functioning	68.18±19.94	64.47±18.75	77.50±18.40	2	**0.043**	0.421	0.096	**0.015**
[a]Pain	72.61±23.97	63.15±23.00	79.50±12.23	2	0.078	0.180	0.460	**0.019**
[a]General health	51.13±16.47	55.52±22.16	69.00±14.47	2	**0.003**	0.377	**0.000**	**0.035**

p^1: Oral therapy vs. injectable therapy vs. healthy control, p^2: Oral therapy vs. injectable therapy, p^3: Oral therapy vs. healthy control, p^4: Injectable therapy vs. healthy control, p<0.05 statistically significant (bold values). χ^2: Chi-square, SD: Standard deviation, OT: Oral therapy, IT: Injectable therapy, HC: Healthy control, EDSS: Expanded disability status scale, HAM-D: Hamilton depression rating scale, HAM-A: Hamilton anxiety rating scale, HIT-6: Headache impact test, SF-36: 36-Item short form survey,
[a]: Kruskal-Wallis and Mann-Whitney U tests as post-hoc tests were used, [b]: Chi-square test was used. p^3 p^4 Mann-Whitney tests as post-hoc tests were

Table 2. Correlation analysis of socio-demographic data and clinical characteristics

r	Age	Duration of the illness	EDSS	HAM-D	HAM-A	HIT-6
Physical functioning	-0.414**	-0.229	-0.228	-0.149	-0.239	-0.260
Role limitations due to physical health	-0.480**	-0.238	-0.373*	-0.421**	-0.368*	-0.290
Role limitations due to emotional problems	-0.361*	-0.359*	-0.419**	-0.295	-0.399**	-0.032
Energy/fatigue	-0.217	-0.060	-0.112	-0.544**	-0.501**	-0.309
Emotional well-being	-0.030	0.066	-0.185	-0.500**	-0.415**	-0.173
Social functioning	-0.201	-0.008	-0.057	-0.582**	-0.488**	-0.127
Pain	-0.216	-0.244	-0.092	-0.180	-0.586**	-0.306
General health	-0.342*	-0.060	-0.041	-0.538**	-0.379*	-0.305
SF-36 total	-0.446**	-0.248	-0.343*	-0.560**	-0.607**	-0.313*

r: Pearson correlation coefficient, EDSS: Expanded disability status scale, HAM-D: Hamilton depression rating scale, HAM-A: Hamilton anxiety rating scale, HIT-6: Headache impact test, SF-36: 36-Item short form survey, *: The correlation is significant (two-tailed) at the 0.05 level, **: Correlation is significant at the 0.01 level (two-tailed)

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and psychiatric symptoms are similar. Moreover, although the patients were under treatment, they had poor QoL and more psychiatric symptoms than the healthy control group.

Clinical outcomes in MS result from a complex interplay of immune-mediated inflammation and neurodegeneration (25). Inflammatory demyelinating lesions in the CNS's white matter are the recognized hallmark, leading to symptomatic relapses. While these white matter lesions are well identified, it is increasingly acknowledged that gray matter lesions, though harder to detect with magnetic resonance imaging, may be more extensive (25). Moreover, gray matter plays a pivotal role in enabling normal daily functioning in humans (26). However, current disease-modifying treatments have primarily been assessed on the basis of their impact on white matter lesions and licensed for their effect on relapses (25). In our study, we found that depression and anxiety scores were higher in patients with MS than in healthy controls, regardless of the treatment modality. Perhaps this is because DMTs have more pronounced effects on white matter lesions than on gray matter lesions, regardless of the route of administration.

In our study, no notable differences were found in both QoL and clinician-reported disability status between patients using oral and injectable DMTs. Previous studies comparing QoL among users of injectable and oral DMTs, as well as those switching between them, have shown conflicting results (27-31). In agreement with our findings, Stuchiner et al. (11) observed no significant differences in the impact of transitioning to oral disease-modifying therapies on patient QoL. For instance, the evaluate patient outcomes trial found improved outcomes when patients switched from injectable to oral DMT fingolimod, including enhanced QoL and reduced fatigue and depression (29-31). In contrast, a study on patients switching to teriflunomide found sustained stable QoL. In another study comparing the QoL among relapsing MS patients using different DMTs, no significant differences were noted between users of fingolimod, interferon β-1b, and natalizumab (27).

Major depressive disorder and anxiety disorders are frequently found in individuals with MS and are linked to decreased treatment adherence, poorer functional status, and lower QoL (32). In our study, we found that depression and anxiety scores were higher in patients with MS than in healthy controls, regardless of the treatment modality. Moreover, we observed that the presence of both anxiety and depression symptoms is related to poor QoL in MS patients. While depression in MS has been extensively studied, anxiety disorders have received less attention (32).

Studies using self-report scales indicate a point prevalence of clinically significant anxiety in MS ranging from 25% to 41% (33,34). Anxiety symptoms had a more pronounced negative impact on the QoL subparameters than depression symptoms in our study.

Study Limitations

Our study had several limitations. Although we grouped drugs by the type of use, we did not consider potential effects based on their pharmacological properties and doses. In addition, we did not evaluate MS severity. The cross-sectional design and limited number of participants restrict the generalizability of our study's results.

Conclusion

The approval of new oral drugs for MS offers benefits and more convenient administration routes. However, concerns arise because of the lack of long-term efficacy data and the potential for several adverse events. Oral DMT use may not be superior to injectable DMT use in terms of QoL, disability, and psychiatric symptoms. Moreover, despite effective treatments, psychiatric disorders in MS are under-detected and under-treated. Hence, determining the optimal treatment for each patient requires comprehensive assessments of safety, efficacy, monitoring needs, tolerability, and cost-effectiveness.

Ethics

Authorship Contributions

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Is Adenoid Hypertrophy Associated with Childhood Afebrile Seizure?

Adenoid Hipertrofisi Çocukluk Çağı Afebril Konvüzyonu ile İlişkili Olabilir mi?

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Abstract

Objective: Afebrile seizures may occur during childhood and may recur with different etiologies. The relationship between hypoxia and disease has been frequently emphasized in the literature. Our aim was to determine whether airway stenosis and adenoid tissue volume are effective in the course of afebrile seizures and, if so, to determine how this relationship is correlated.

Method: Adenoid tissue volume and nasopharyngeal distance were measured from brain magnetic resonance imaging images taken for routine cranial imaging of children aged 2-8 years who presented to the Pediatric Emergency Unit of Van Yüzüncü Yıl University Hospital with afebrile seizures. Demographic characteristics, anticonvulsant drug use, adenoid hypertrophy symptoms, and the number of convulsive episodes were recorded. Statistical analysis was performed on the variables determined.

Results: This study examined 156 children who were admitted to the hospital with afebrile seizures between the specified dates, within the specified age range, and who met the inclusion criteria were examined. The mean ages of the 92 boys and 64 girls were 3.94±0.139 years. No statistically significant intergroup difference was found between the sexes regarding age, number of afebrile seizure episodes, or nasopharyngeal distance (p>0.05). Although 145 (92.9%) of the patients were using only one anticonvulsive drug, 11 (7.1%) were using two anticonvulsive drugs. Adenoid tissue volume dimensions were significantly higher in boys (2.17±0.09) than in girls (1.87±0.12) (p=0.023). There was a statistically significant positive correlation between adenoid volume and the number of afebrile seizure episodes (r=0.586, p=0.0001; n=156).

Conclusion: Increased volumetric adenoid tissue size may be an effective factor in recurrent episodes of childhood afebrile seizure.

Keywords: Adenoid hypertrophia, afebrile seizure, childhood

Öz

Amaç: Afebril konvüzyonlar çocukluk çağında farklı etiyolojilerle ortaya çıkabilmekte, farklı etiyolojilerle tekrar edebilmektedir. Literatürde sıklıkla hipoksi ile hastalığın ilişkisi vurgulanmış olup amacımız hava yolu darlığı ve adenoid doku volümünün afebril konvüzyonların seyrinde etkili olup olmadığını, varsa bu ilişkinin nasıl bir ilişki gösterdiğini saptamaktır.

Yöntem: Van Yüzüncü Yıl Üniversitesi Hastanesi Çocuk Acil Ünitesi'ne afebril konvüzyon ile başvuran 2-8 yaş arasındaki çocukların rutin kraniyal görüntülemesi için çekilen beyin manyetik rezonans görüntülerinden adenoid doku volümü ve nazofarengeal mesafesi ölçümleri yapıldı. Hastaların demografik özellikleri, antikonvülzan ilaç kullanımları, adenoid hipertrofisi semptomları ve konvülziv atak sayıları kaydedildi. Belirlenen değişkenler açısından istatistiksel analiz yapıldı.

Bulgular: Çalışmada, belirlenen tarihler arasındaki hastanemiz çocuk acil ünitesine afebril konvüzyon ile başvuran, belirlenen yaş aralığındaki ve dahil edilme kriterlerine uygun 156 çocuk retrospektif olarak incelenmiştir. Doksan iki erkek ve 64 kız çocuğunun ortalama yaşı 3,94±0,139 olup cinsiyetler arasında yaş, afebril konvüzyon atak sayısı ve nazofaringeal mesafe açısından istatistiksel anlamlı farklılık saptanmamıştır (p>0,05). Hastaların 145'i (%92,9) sadece bir antikonvülsif ilaç kullanırken, 11'i (%7,1) iki antikonvülsif ilaç kullanmaktaydı. Adenoid doku volüm boyutları erkek çocuklarında (2,17±0,09) kız çocuklarından (1,87±0,12) istatistiksel olarak anlamlı şekilde yüksekti (p=0,023). Çocukların adenoid volümü ve afebril konvüzyon atak sayıları arasında ise istatistiksel olarak anlamlı şekilde pozitif yönde bir korelasyon mevcuttu (r=0,586, p=0,0001; n=156).

Sonuç: Adenoid doku volümetrik boyutlarında artış çocukluk çağı ateşsiz konvüzyon ataklarında etkili faktörlerden biri olarak düşünülebilir.

Anahtar kelimeler: Adenoid hipertrofi, afebril nöbet, çocukluk çağı

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Introduction

A seizure is a short-term change in regular electrical activity in the brain that leads to changes in perception, awareness, movement, or behavior (1). Seizures, broadly classified as febrile and non-febrile, account for approximately 1% of emergency department admissions (2). Many underlying pathological causes, such as infections, genetics, traumatic or non-traumatic brain injury, metabolic or electrolyte disturbances, and neurodevelopmental conditions, can result in abnormal neuronal activity even in the absence of fever (3). This aspect adds complexity to clinical assessment and raises questions regarding causes and the probability of recurrence (4). Afebrile seizures are neurological conditions characterized by the occurrence of two or more seizures with a gap of at least 24 hours between them, often without a known cause. Childhood epilepsy is linked to various additional health issues, such as social-emotional and cognitive difficulties (5). Longer seizure duration, hyperglycemia, age at onset ≥11 years, and acidosis were predictive of seizure recurrence in children with new-onset afebrile seizures (6). Abnormal electroencephalography (EEG) findings are also considered in the risk of recurrence (7)

Adenoid hypertrophy is usually self-limiting and resolves during puberty when adenoids atrophy and regress (8). Diagnosis of adenoid tissue size with infectious and non-infectious etiologies can be performed with lateral direct radiography or flexible nasopharyngoscopy without the risk of radiation using a reliable and satisfactory method (9,10). It may cause narrowing of the passage in the upper respiratory tract and may lead to undesirable long-term effects if not treated at the appropriate time (11). In the literature, cognitive impairment in patients with adenoid hypertrophy has also been shown to be reversed by adenoidectomy (12), and amygdala/hippocampus volume ratios were higher in children with adenotonsillar hypertrophia-induced obstructive sleep apnea syndrome (OSAS) (13). Because intermittent hypoxemia may cause changes in some brain structures, we aimed to determine whether there is a relationship between unprovoked afebrile seizures and adenoid tissue volume.

Materials and Methods

Subjects

Between 1/9/2018 and 1/5/2021, patients between 2 and 8 years of age admitted to the pediatric emergency unit with afebrile seizure, with no cerebral pathology on routine brain magnetic resonance imaging (MRI) imaging and no biochemical pathology on laboratory tests were included after ethics committee approval (2023/11-12). Patients under 2 years and over 8 years of age, patients with febrile seizure, patients with congenital cerebral anomalies, and patients with intracranial mass, bleeding, demyelinating, and metabolic diseases were not included.

Volumetric Adenoid Measurements

By a radiologist with 10 years of experience, raw images were converted to multiplayer reformation images in an magnetic resonance (Siemens magnetom, Altea, 1.5T, Germany) workplace. The area of the adenoid tissue entering each cross-sectional area from right to left on the sagittal images was measured by manual method, and the areas were combined with the volume generation module in preset settings, and the data obtained were recorded in cubic centimeters.

Statistical Analysis

Descriptive statistics were used to summarize continuous variables, including mean, standard error, median, and interquartile range. Categorical variables were summarized using counts and percentages. The Mann-Whitney U test was employed to compare non-categorical variables with continuous variables. Pearson correlation coefficients were computed to assess the relationships between continuous variables. Statistical significance was set at 5%, and calculations were conducted using the SPSS (IBM; version 26) statistical software package.

This study did not receive financial support, and there are no conflicts of interest among the authors. The Van Yüzüncü Yıl University Non-Interventional Clinical Research Ethics Committee approved the study (no: 2023/11-12).

Results

A total of 156 children in the specified age range who presented to the Pediatric Emergency Unit of Van Yüzüncü Yıl Hospital with afebrile seizure between the specified dates and who met the inclusion criteria were determined.

The mean age of 92 (58.9%) boys and 64 (41.1%) girls was 3.94±0.139 years, and no statistically significant difference was found between the sexes in terms of age, number of afebrile seizure episodes, and nasopharyngeal distance (p>0.05). Although 145 (92.9%) of the patients were using only one anticonvulsive drug, 11 (7.1%) were using two anticonvulsive drugs. All patients were taking their medication regularly. Eighty-five (54.4%) patients

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were being treated with sodium valproate, 28 (17.9%) with phenobarbital, and 36 (23%) with levetiracetam. Seven (4.5%) patients were receiving dual combinations of different antiepileptic drugs. All patients were taking their medications regularly.

Adenoid tissue volume dimensions were significantly higher in boys (2.17±0.09: mean ± stderror) than in girls (1.87±0.12; mean ± stderror) (p=0.023) (Table 1). There was a statistically significant positive correlation between adenoid volume and the number of afebrile seizure episodes (r=0.586, p=0.0001; n=156) (Figure 1).

Discussion

Conditions affecting the central nervous system, which both develop intensively from childhood to adolescence and are most vulnerable to injury in childhood, can lead to problems such as attention deficit, autism spectrum disorder, developmental delay, learning difficulties, cerebral palsy, and seizures (14-16). Seizures were ranked among the prevalent neurological conditions observed in pediatric emergency units. Timely identification of epilepsy onset in children experiencing non-fever-related seizures

Table 1. Age, adenoid volume, and seizure episodes according to gender

	Gender	n	Median (IQR)	Mean rank	p
Age	Male	92	4 (2.75)	80.57	0.483
	Female	64	3 (3)	75.52	
Adenoid volume	Male	92	2 (1.38)	85.37	0.023
	Female	64	1.7 (1.27)	68.63	
Nasopharyngeal distance	Male	92	2.1 (1.68)	74.64	0.201
	Female	64	2.3 (2.5)	84.05	
Seizure recurrence	Male	92	3 (1)	83.63	0.068
	Female	64	3 (1)	71.13	

IQR: Interquartile range

Figure 1. Seizure recurrence and adenoid volume

is of paramount importance (17). When assessing the first occurrence of afebrile seizures in children, according to the recommendations of the American Academy of Neurology, it is advised to include EEG and neuroimaging examinations as part of neurodiagnostic assessments (18,19).

In a study in which the determinants of abnormal electroencephalogram and neuroimaging findings were investigated in children admitted to the emergency department with afebrile seizures, the number of boys and girls was almost equal (4), whereas in our patient group, male patients were more common. In a study published in 2015 from a center in Japan, when the recurrence risks of patients aged between 1 month and 15 years who were followed up for at least 2 years after the first unprovoked seizure were evaluated, partial seizures were found to be statistically significant compared with generalized seizures in terms of recurrence. Children with focal discharges had significantly more recurrences than those with normal EEGs (20). The risks of recurrence of afebrile seizures include lethargy and lactate elevation, duration of the seizure, and age at onset (17). Age at onset ≥11 years, acidosis, longer seizure duration, and hyperglycemia were predictors of seizure recurrence in children who experienced their first afebrile seizure (6). The relationship between seizure susceptibility and chronic hypoxia has also been shown in recent years. Long-term oxygen deprivation does not just initiate the activation and proliferation of microglia and astrocytes due to oxidative stress and neuroinflammation; it also leads to neuronal excitotoxicity by suppressing sodium and potassium ATP activity, elevating blood-brain barrier permeability, altering ion transporter expression, and diminishing cerebral blood flow (16).

Adenoids, lymphoid tissue known as part of the Waldeyer ring, can cause OSAS, chronic sinusitis, otitis, developmental anomalies in the craniofacial region, speech disorders, and articulation errors. It is also known that oxygen saturation is affected, and hypoxic status occurs due to airway obstruction and respiratory difficulties in people with enlarged adenoid tissue associated with different causes (11,13,15). Finger palpation and oral examination of adenoids using a mirror or direct radiography of the lateral nasopharynx are frequently used to detect adenoid tissue (21,22). In recent years, nasal endoscopy has also been widely used for diagnosis (23). Although MRI is not a routine procedure for nasopharyngeal adenoid hypertrophy, it is often used in head and neck imaging studies. When the cranio-caudal, left-right, and anterior-posterior dimensions of nasopharyngeal adenoid tissues in

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approximately 6700 MRIs taken in the same health center between 0-82 ages are measured, it has been shown that adenoid tissue significantly regresses with age in head/neck MRI imaging performed for different reasons in different age groups. The cranio-caudal and left-right sizes of nasopharyngeal adenoid hypertrophy were largest in 0-9 years and decreased with age (24). On the other hand, in a different study, it was declared to disappear completely in adulthood. This study evaluated 189 patients who were referred for brain MRI scan with no history or clinical evidence of adenoid disease to determine the age-specific appearance of normal adenoid tissue, as measured on sagittal T1-weighted midline MRI images (25). In animal model studies, obstructive sleep apnea was found to induce neuronal cell loss in several brain regions, resulting in brain regions leading to changes in mood and cognition functions, particularly in the pediatric age. A review of the available evidence shows that many of the arguments in favor of causality converge and support the notion that OSA can cause both reversible and irreversible neural damage and functional impairments (26). In a study including 10 children with polysomnographically confirmed OSA and 8 healthy controls of similar age and sex with no evidence of sleep-disordered breathing in an overnight sleep study, Kheirandish-Gozal et al. (27) reported that several brain regions in children with obstructive sleep apnea, including the middle and posterior corpus callosum, prefrontal cortex, hippocampus, thalamus, and cerebellar areas, demonstrated decreased entropy values. MRI alterations pointed to acute pathological impacts caused by obstructive sleep apnea (27). In a comparative study of 100 patients with adenotonsillar hypertrophy and OSAS and 100 healthy children in the same age group, children with adenotonsillar hypertrophy and OSAS displayed greater amygdala sizes and ratios of amygdala to hippocampus volumes compared with their healthy counterparts. However, their hippocampal volumes were comparatively lower. Additionally, there was a correlation between the duration of the disease and the presence of hypoxemia conditions with amygdala/hippocampus volume ratios. Apnea-hypopnea index and SaO_2 <90% were significantly positively correlated with amygdala and hippocampus ratios (13). Canessa et al. (28) examined the brain structures of children with OSA and discovered reduced volumes in several brain regions, including the hippocampus, left posterior parietal cortex, and right superior frontal gyrus, compared with the healthy control group. This study of 17 children with OSA demonstrated for the first time the existence of structural brain abnormalities in regions vulnerable to hypoxemia that can be altered by treatment (28). We believe that adenoid tissue, which causes oxygen changes with the narrowing of the airway passage, is associated with childhood afebrile seizures. With these data in the future, there will be advances in research that will make progress on whether individualized therapies exist to deepen the relationship between chronic hypoxia, which we know increases neuronal excitability, and seizure susceptibility.

Study Limitations

The validity of our retrospective study is an important limitation. In the future, follow-up according to seizure type, EEG findings, and sleep disorders in a wider age range and prospective follow-up will help obtain more detailed results.

Conclusion

Since no study on adenoid dimensions, afebrile convulsions, and seizure attacks has been found in the literature to the best of our knowledge, our study showed that adenoid volumetric may be among the factors that cause recurrence in children with seizures, and adenoid size should be kept in mind as a risk factor for seizure recurrence.

Ethics

Ethics Committee Approval: This study did not receive financial support, and there are no conflicts of interest among the authors. The Van Yüzüncü Yıl University Non-Interventional Clinical Research Ethics Committee approved the study (no: 2023/11-12).

Informed Consent: The consent of the patients has been obtained.

Authorship Contributions

Surgical and Medical Practices: N.A., Concept: H.A., Design: N.A., H.A., Data Collection or Processing: H.A., Analysis or Interpretation: N.A., H.A., Literature Search: H.A., Writing: N.A.

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ORIGINAL RESEARCH

Effects of Type D Personality on SARS-CoV-2-Related Fears, Anxiety, and Depression in Patients with Chronic Pain

Kronik Ağrı Hastalarında Tip D Kişilik Özelliklerinin SARS-CoV-2 İlişkili Korkular, Anksiyete ve Depresyon Üzerindeki Etkisi

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Abstract

Objective: Individuals experiencing chronic pain have an elevated risk of psychological distress during a pandemic. This study aimed to examine the correlation between type D personality traits, apprehension regarding diseases and viruses, and anxiety and depression in patients with chronic pain throughout the pandemic period.

Method: The study included 115 patients with chronic pain who presented to the physical therapy outpatient clinic of our hospital. Data were collected from the patients using five instruments: Socio-demographic data form, visual analog scale, type D personality scale, fear of illness and virus evaluation scale (FIVE), Beck depression inventory, and Beck anxiety inventory. Participants were divided into two groups based on their type D personality, and data from the two scales were compared.

Results: Type D personality traits were identified in 36 patients with chronic pain included in the study. Although demographic characteristics showed no disparities between groups, individuals exhibiting type D personality traits displayed elevated scores in FIVE total, illness, and contamination fear, as well as anxiety and depression, compared with those without type D personality (p=0.013, p=0.027, p=0.032, p=0.009, and p=0.032, respectively).

Conclusion: In patients with chronic pain, type D personality traits are associated with increased anxiety and depression along with fear of Coronavirus disease-2019-related illness and virus.

Keywords: Anxiety, chronic pain, COVID-19, depression, fear of illness and virus evaluation scale, SARS-CoV-2, type D personality

Öz

Amaç: Kronik ağrı yaşayan bireyler, bir pandemi sürecinde psikolojik sıkıntıya daha fazla maruz kalabilirler. Bu çalışma, pandemi döneminde kronik ağrı hastalarında tip D kişilik özellikleri, hastalık ve virüs korkusu ile anksiyete ve depresyon arasındaki ilişkiyi incelemeyi amaçlamaktadır.

Yöntem: Çalışmaya hastanemizin fizik tedavi polikliniğine başvuran 115 kronik ağrılı hasta dahil edildi. Veriler, hastalardan beş enstrüman kullanılarak toplandı: Sosyo-demografik veri formu, görsel analog skala, tip D kişilik ölçeği, hastalık ve virüs değerlendirme ölçeği (FIVE), Beck depresyon envanteri ve Beck anksiyete envanteri. Katılımcılar, tip D kişiliklerine göre iki gruba ayrıldı ve ölçeklerden elde edilen veriler karşılaştırıldı.

Bulgular: Çalışmaya dahil edilen kronik ağrılı hastaların 36'sında tip D kişilik özellikleri tespit edildi. Demografik özellikler açısından gruplar arasında farklılık gözlenmezken, tip D kişilik özelliklerine sahip olanlarda, tip D kişilik özellikleri olmayanlara göre daha yüksek FIVE toplam skorları, hastalık ve kontaminasyon korku skorları ile anksiyete ve depresyon skorları saptandı (sırasıyla p=0,013, p=0,027, p=0,032, p=0,009 ve p=0,032).

Sonuç: Kronik ağrılı hastalarda, tip D kişilik özellikleri Koronavirüs hastalığı-2019 ile ilişkili hastalık ve virüs korkusu ile birlikte artmış anksiyete ve depresyon ile ilişkilidir.

Anahtar kelimeler: Anksiyete, COVID-19, depresyon, hastalık ve virüs değerlendirme ölçeği, kronik ağrı, SARS-CoV-2, tip D kişilik

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Introduction

The initial recognition of severe acute respiratory syndrome-coronavirus-2 was the identification of a novel viral respiratory condition in Wuhan, China, in December 2019, and spread rapidly through the respiratory tract, affecting the entire world (1). On March 11, 2020, the World Health Organization officially classified the illness as a worldwide pandemic, marking a critical juncture in the global health landscape (2).

Because the exact course of this first-ever pneumonia was unknown, uncertainty and panic arose around the world. A global quarantine was imposed with significant restrictions on education, social life, and work. The goal was to slow the spread of the virus. Socio-economic problems, social isolation, and feelings of loneliness elevate psychosomatic symptoms such as depression and anxiety, particularly acute stress, in society, besides the fear of illness, death, and loss of loved ones (3). There has also been a significant increase in the diagnosis of sleep disorders and post-traumatic stress disorder (3).

Chronic pain is characterized by the International Association for the Study of Pain (IASP) as enduring or repetitive pain that persists beyond a 3-month duration or persists after the usual tissue recovery period (4). It affects approximately 20% of the general population (5). Chronic pain causes disability, emotional instability, and social isolation, all of which significantly reduce quality of life (5). Pain management is a fundamental human right. However, the Coronavirus disease-2019 (COVID-19) pandemic has forced healthcare systems worldwide to devote resources to intensive care units and other COVID-19-specific facilities. Elective health services, including those for chronic pain, were suspended during this period. This leads to major disruptions in the management of patients with chronic pain (5). In addition, the fear of death from the disease, uncertainty, anxiety about the future, and the sense of being alone due to the inability to access health services have placed patients with chronic pain among the groups at higher risk of psychological distress compared to the broader community (5).

Type D personality may increase susceptibility to psychological distress during the COVID-19 pandemic. It is defined as a chronically stressed personality characterized by negative affect and social inhibition (6). Negative affect is described as an inclination toward adverse emotions such as melancholy, unease, despondency, and restlessness, while social inhibition is defined as an incapacity to convey emotions in social settings due to the apprehension of rebuff (6,7). People with type D personality disorder are more likely to experience psychological distress, anxiety, depression, and physical and mental illness than those who do not have this personality (8,9).

We postulated that individuals exhibiting type D personality traits would demonstrate a correlation with heightened levels of anxiety, depression, and apprehension regarding COVID-related contamination and illness within the cohort of patients with chronic pain in our investigation. Individuals with type D personality traits are at increased risk of psychological distress during the pandemic among chronic pain patients. This study aimed to evaluate the impact of COVID-19 on the psychological aspects of individuals with chronic pain and investigate the influence of type D personality characteristics on these psychological symptoms. Consequently, an early identification of high-risk cohorts becomes feasible, thereby enabling timely referral for psychiatric interventions among susceptible individuals.

Materials and Methods

Sample

Participants included 115 patients who presented to our hospital's physical therapy outpatient clinic during the COVID-19 pandemic, were diagnosed with chronic pain according to the IASP's 2020 chronic pain diagnostic criteria, and were scheduled to receive electrotherapy treatment in our hospital's physical therapy department (4). None of our patients were carrying COVID-19.

Inclusion and Exclusion Criteria

Inclusion criteria for the study; being between the ages of 18-65, having chronic regional pain lasting longer than 3 months, exclusion criteria; no known psychiatric or neurological disease. All participants consented to participate in the study.

Ethical Considerations

The study adhered to the ethical principles stated in the Declaration of Helsinki. This study was approved by the Ethics Committee for Clinical Research at the Medipol University Faculty of Medicine (10840098-772.02-1217). The study was explained to the participants, and written informed consent was obtained.

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Evaluation

Several instruments were used to collect data. All participants completed the socio-demographic data form, visual analog scale (VAS), type D personality scale, Beck anxiety inventory, Beck depression inventory, and fear of illness and virus scale (FIVE).

Socio-demographic data form: This form assesses participants' age, gender, education, occupation, marital status, smoking and alcohol use, history of chronic illness, drug use, psychiatric illness, and psychiatric drug use.

VAS: The VAS is evaluated on a scale of 10 points. 0 indicates no pain and 10 points indicates unbearable pain. One-three indicates mild, 4-7 moderate, 8-10 severe pain (10).

Type D personality scale (DS-14): The DS-14 assesses distressed personality. It contains 14 items characterized by two subscales: Negative affect and social inhibition. Each item has a score ranging from 0 to 4 (11). Individuals who scored 10 or higher on both subscales are classified as having a type D personality.

Beck anxiety inventory: The Beck anxiety scale was used to measure anxiety levels. The test comprises 21 questions with scores ranging from 0 to 3. The scale yields a total score ranging from 0 to 63, with high scores indicating high levels of anxiety (12).

Beck depression inventory: The Beck sepression inventory consists of 21 questions, each with a score ranging from 0 to 3. The total score ranged from 0 to 63, with higher scores indicating severer depression (13).

FIVE scale: This scale was developed by Professor Jill Ehrenreich-May from the University of Miami. There are three versions of FIVE (adult, child and parent). The adult version consists of a total of 35 items and four subscales (1: Fears about contamination and illness, 2: Fears about social distancing, 3: Behaviors related to illness and virus fears, and 4: Impact of illness and virus fears). This is a 4-point Likert-type scale consisting of 35 questions, with scores ranging from 1 to 4 (14). The scale generates a total score ranging from 0 to 140. Total and percentile scores can be calculated for each subscale. The subscale totals are as follows: 36 for the fears of contamination and illness subscale, 40 for fears about social distancing, 56 for behaviors related to illness and virus fears, and 8 for the impact of illness and virus fears. Higher scores on the behaviors related to illness and virus fears subscale indicate that fear-related behaviors were more frequent. Higher scores on the impact of illness and virus fears subscale reflects a higher level of potential deterioration. Permission was obtained for the original and translated forms.

Statistical Analysis

The normality of distribution of continuous variables was tested using the Shaphiro-Wilk test. The Mann-Whitney U test was used to compare non-normal data, and the Kruskal-Wallis and Dunn multiple comparison tests were used to compare non-normal data among the three groups. The chi-square and Bonferroni tests were used to examine relationships between categorical variable pairs. Spearman's correlation test was used for the correlation analysis. Statistical analysis was performed using SPSS for Windows version 24.0. Correlations were evaluated using Spearman's rank correlation coefficient. $P<0.05$ was considered statistically significant.

Results

This study included 115 patients with chronic pain (53 with low back pain, 32 with neck pain, 17 with knee pain, and 13 with shoulder pain) scheduled to receive electrotherapy in the hospital. The mean duration of pain was 9±3.4 months. The average age of the subjects was 44.5±14.1 years. The participants were 65.2% (n=75) female and 34.8% (n=40) male. They were 77.4% (n=89) married and 22.6% (n=26) single. History of concomitant chronic diseases (diabetes, hypertension, hypothyroidism, and asthma) was present in 39.1% (n=45) of the participants. Among the participants, 23.5% were smokers; none had a history of alcohol consumption. The mean VAS score of the patients was 6.4±1.4. The mean total FIVE score in patients with chronic pain was 64.5±19.0 (Table 1). The FIVE total score had a

Table 1. Average clinical parameter values for chronic patients

	Mean ± SD
Age	44.5±14.1
VAS	6.4±1.4
Negative affect	10.9±7.3
Social inhibition	9.3±5.2
Anxiety	10.0±9.4
Depression	10.0±7.6
FIVE total	64.5±19.0
Fear of contamination and illness	16.9±6.9
Behaviors related to illness and virus fear	25.5±8.7
Impact of illness and virus fears	2.8±1.3
Fears of social distancing	18.9±7.4

VAS: Visual analog scale, FIVE: Fear of illness and virus evaluation, SD: Standard deviation

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weak positive correlation with negative affect and social inhibition (p=0,012 and p=0.007 correspondingly).

The prevalence of type D personality disorder among individuals with chronic pain was 31.3% (n=36). No disparities in socio-demographic characteristics were observed between patients with chronic pain and those with type D personality (Table 2). Patients exhibiting type D personality in the chronic pain group displayed markedly elevated scores for anxiety and depression compared with those without (p=0.009 and p=0.032, correspondingly). In patients with chronic pain and type D personality, the mean FIVE total score was 70.0±17.9. The FIVE total score and the FIVE fear of contamination and illness subscale score were significantly higher in chronic patients with type D personalities than in chronic patients without type D personalities (p=0.013 and p=0.027, correspondingly) (Table 3). When the patients with chronic pain were evaluated according to sex, there were more female patients, with a rate of 65.2% (n=75). Depression, anxiety, effect of concerns about illness and viruses, and negative affect were found to exhibit a notable increase in female individuals suffering from chronic pain compared with

male patients (p=0.002 and p=0.001, correspondingly) (Table 4). Nevertheless, gender-based demographic data did not reveal any noteworthy distinctions.

Correlational analysis indicated that negative affect, a component of type D personality, exhibited a mild positive correlation with anxiety, the total FIVE score, and the impact of illness and virus fears and moderate positive correlation with depression among patients with chronic pain. The social inhibition subscale of type D personality demonstrated a weak positive correlation with depression, total FIVE score, fear of contamination and illness, and concerns about social distancing (Table 5).

Discussion

Being the first study to examine illness and infection-related anxiety and psychological status in patients with chronic pain during the COVID-19 pandemic, our findings revealed that depression and anxiety levels, the impact of illness and virus fears, and negative affectivity were significantly higher in female patients than in male patients. When the effect of type D personality on patients with chronic pain

Table 2. Comparison of the socio-demographic characteristics of the groups				
Type D		No	Yes	p
Gender	Female	49 (62.0%)	26 (72.2%)	0.393
	Male	30 (38.0%)	10 (27.8%)	
Marital status	Married	60 (75.9%)	29 (80.6%)	0.759
	Single	19 (24.1%)	7 (19.4%)	
Smoking	Yes	17 (21.5%)	10 (27.8%)	0.619
	No	62 (78.5%)	26 (72.2%)	
Comorbid disease	No	52 (65.8%)	18 (50.0%)	0.16
	Yes	27 (34.2%)	18 (50.0%)	

Table 3. Comparison of clinical parameters between patients with chronic pain with and without type D personality			
Type D	No (79)	Yes (36)	p-value
Age	43.6±14.3	46.3±13.8	0.372
VAS	6.1±0.3	6.5±1.7	0.926
Negative affect	7.6±5.4	18.61±5.14	**<0.001**
Social inhibition	6.8±3.5	15.06±4.1	**<0.001**
BAI	8.5±9.0	13.39±9.6	**0.009**
BDI	7.8±5.3	15.34±9.5	**<0.001**
FIVE total	62.0±19.1	70.0±17.9	**0.013**
Fear of contamination and illness	15.9±6.3	19.4±7.7	**0.027**
Behaviors related to illness and virus fear	24.8±8.18	27.0±9.7	0.351
Impact of illness and virus fears	2.8±1.4	2.9±1.2	0.387
Fears of social distancing	18.3±7.6	20.1±7.0	0.177

VAS: Visual analog scale, BAI: Beck anxiety inventory, BDI: Beck depression inventory, FIVE: Fear of illness and virus evaluation

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was evaluated, anxiety and depression scores, FIVE total score, and behaviors associated with illness and virus fears were notably higher in those exhibiting type D personality than in those without. Our study also found that illness and virus fears were associated with negative affect, anxiety, depression, and the FIVE total score, indicating the negative psychological impact of the pandemic on patients with chronic pain. These results support our hypothesis that type D personality is associated with depression, anxiety, and illness-virus fear in individuals with chronic pain. As far as we know, our study is the first to explore the connection between type D personality and fear of viruses in patients with chronic pain.

Earlier studies have associated possessing a type D personality, also referred to as a "stressed personality" or "distressed personality", with heightened levels of anxiety, depression, diminished quality of life, and an unfavorable self-assessment of health conditions (15). Individuals with type D personalities tend to experience increased worry,

heightened nervousness, and self-blame. They maintain a pessimistic outlook on life and possess low self-confidence and life satisfaction (8,9). Furthermore, individuals with type D personalities harbor negative perceptions of social relationships, experience reduced social support, and exhibit weak connections with others (16). Considering these factors, the presence of a type D personality in individuals with chronic pain who are already vulnerable to psychological impacts due to the heightened stress and anxiety associated with the pandemic exacerbates their situation.

Research has examined that examine individuals characterized by type D personality in terms of how this personality affected them during the COVID-19 epidemic. Gębska et al. (17) identified that stomatognathic system disorders were most frequently associated with symptoms such as headaches, pain in the neck and shoulder girdle, and teeth clenching among physiotherapy students with type D personality, surpassing those without type

Table 4. Evaluation of clinical parameters according to sex

Gender	Female (75)	Male (40)	p-value
Age	45.5±11.1	48.1±18.1	0.592
VAS	6.5±1.1	6.3±2.1	0.38
BAI	12.1±10.0	5.9±6.4	**0.001**
BDI	11.3±7.3	7.3±7.7	**0.002**
Negative affect	12.0±7.3	8.6±6.9	**0.017**
Social inhibition	9.4±4.9	9.1±5.9	0.594
FIVE total	62.7±19.2	67.5±18.1	0.093
Fear of contamination and illness	17.0±6.7	16.9±7.2	0.841
Behaviors related to illness and virus fear	24.1±7.7	28.0±9.7	**0.033**
Impact of illness and virus fears	2.8±1.3	2.8±1.5	0.381
Fears of social distancing	18.5±7.5	19.5±7.4	0.37

VAS: Visual analog scale, BAI: Beck anxiety inventory, BDI: Beck depression inventory, FIVE: Fear of illness and virus evaluation

Table 5. Correlation analysis

Parameter	Negative affect		Social inhibition	
	r	p	r	p
BAI	0.38	**<0.001**	0.119	0.225
BDI	0.618	**<0.001**	0.296	**0.002**
VAS	0.013	0.931	0.034	0.822
FIVE total	0.244	**0.012**	0.263	**0.007**
Fear of contamination and illness	0.187	0.054	0.305	**0.001**
Behaviors related to illness and virus fear	0.15	0.126	0.087	0.376
Impact of illness and virus fears	0.202	**0.039**	0.114	0.247
Fears of social distancing	0.145	0.138	0.21	**0.031**
Note: Spearman's Correlation test				

VAS: Visual analog scale, BAI: Beck anxiety inventory, BDI: Beck depression inventory, FIVE: Fear of illness and virus evaluation
Negative emotional social inhibition is a component of type D personality

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D personality in their study exploring the correlation of SSD with type D personality during the pandemic. In a separate investigation conducted by Gębska et al. (18), individuals with symptoms of type D personality were significantly more prone to temporomandibular joint issues. Moreover, the incidence of depression was notably higher among students who exhibited type D personality traits. Tuman (19) identified a correlation between type D personality and heightened levels of anxiety, depression, and fear of illness and virus among healthcare workers during the pandemic. Condén et al. (20) found that psychosomatic symptoms were strongly associated with type D personality and musculoskeletal pain. We observed that individuals with chronic pain exhibiting type D personality traits demonstrated elevated levels of anxiety, depression, and apprehension regarding illness and viruses compared with those without type D personality traits.

Depression and chronic pain are two conditions that affect each other. Studies have shown that both are related to brain regions and the nervous system, and that depression can worsen pain perception (21-23). There is also evidence that chronic pain can lead to depression (22). In patients with chronic pain and depression, higher levels of pain intensity and functional limitations are observed. Pain management is also more difficult in patients with depression (22). The relationship between pain and depression can be better explained by neurobiological factors. The same neurotransmitters are known to affect both pain and mood (23). Individuals with type D personality traits are more susceptible to depression (15). This is even more significant in patients with chronic pain and type D personality. In infectious disease outbreaks, anxiety, depression, and general fear increase (24). Studies on SARS survivors have shown that the most common long-term psychiatric problems are post-traumatic stress disorder and depression (24). Similarly, increases in post-traumatic stress disorder, depression, panic disorder, and obsessive-compulsive disorder have been observed in patients with COVID-19 (25,26). The coexistence of chronic pain and type D personality disorder can negatively impact mental well-being and reduce quality of life. Therefore, an early diagnosis of type D personality disorder and effective pain management are important.

In our study, 31.3% of patients with chronic pain had a type D personality. This personality type is associated with various diseases, particularly cardiovascular conditions (27). Evidence suggests that type D personality traits

increase the risk of heart attack and are more common in individuals with heart disease, establishing a link between these personality traits and cardiovascular conditions (27). Several studies have found the prevalence of type D personality to be 31.9% in patients with myofascial pain syndrome, 33% in those with fibromyalgia syndrome, 38.7% in those with psoriasis, and 44.5% in those with multiple sclerosis patients (15,28-30). Our study's findings are similar to other research on the prevalence of type D personality. However, it is important to note that the prevalence of type D personality may vary across countries due to genetic and cultural factors (31). Our study also found that female patients with chronic pain had higher levels of depression, anxiety, illness, virus fear impact, and negative affect than male patients. This may be due to women's increased susceptibility to psychological stress, different stress-coping behaviors between genders, and the female gender being a risk factor for various psychiatric disorders (32). Additionally, the prevalence of chronic pain is higher in women than in men (33). Similarly, our study found that 65.2% of patients experienced chronic pain.

This study used the newly developed FIVE scale to assess illness and virus fear in patients with chronic pain following the COVID-19 pandemic. In a larger study involving 560 individuals, including healthcare workers, primary immunodeficiency patients, and those with severe asthma and additional comorbidities (cancer, cardiovascular disease, hypertension, and diabetes), healthcare workers' scores were significantly higher than those of other risk groups. Notably, hypertensive patients had the lowest scores on all scales. In our study of 115 patients with chronic pain, the FIVE total score was found to be 64.5±19.0. In the Çölkesen et al. (34) study, FIVE total scores showed a positive correlation with depression and anxiety scores. Although our study did not show a correlation between FIVE total scores and anxiety or depression, a positive correlation was found between negative affectivity and social inhibition scores.

Intervening type D personality traits can provide numerous benefits, both individually and socially. These interventions can help reduce the risk of chronic health conditions, enhance quality of life, diminish negative emotions such as anxiety and depression, improve social functioning, and lower healthcare costs. Investing in interventions to improve type D personality traits is a significant investment for both individuals and society.

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Study Limitations

There are certain limitations to our study: First, our study is a cross-sectional study. Second, patients were assessed using self-report scales without undergoing a psychiatric diagnostic interview. Third, given that the research was conducted on individuals with chronic pain scheduled for treatment in the physical therapy department of our hospital during the pandemic, it was not feasible to perform comparisons with a control group from the general population lacking comorbidities. In addition, type D personality is a relatively new concept that has not yet been fully accepted in the literature. Some researchers argue that there are not enough evidence to consider type D personality as a separate personality type and that its stigmatizing nature warrants ethical scrutiny. More research is needed in the future to better understand type D personality, including its causality, diagnostic criteria, and treatment.

Conclusion

This study investigated the psychological impact of the COVID-19 pandemic on patients with chronic pain. To our knowledge, this study represents the first exploration of the connection between type D personality traits and fears of illness and viruses in patients with chronic pain during the pandemic. Anxiety, depression, and fears of illness and viruses were discerned to be more prevalent in patients with chronic pain exhibiting type D personality traits. In addition, female patients and those exhibiting type D personality traits experienced higher levels of depression, anxiety, illness and virus fear, and negative affect. These results highlight the vulnerability of patients with chronic pain during public health crises and underscore the importance of considering personality traits when evaluating psychological well-being. Our study also identified a positive correlation between illness and virus fears and negative affectivity, anxiety, and depression in patients with chronic pain. This suggests that the pandemic has exacerbated negative emotions and psychological distress in this population. Further research is needed to explore the long-term psychological effects of the pandemic on patients with chronic pain and to develop targeted interventions to improve their mental health and quality of life.

Ethics

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Association Between Ultrasonographically Detected Fatty Liver and Maternal Lipid Levels and Adverse Obstetric Outcomes

Ultrasonografi ile Saptanan Yağlı Karaciğerin Maternal Lipid Düzeyleri ve Olumsuz Obstetrik Sonuçlarla İlişkisi

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Abstract

Objective: Fatty liver, which is increasingly common in pregnancy, is associated with maternal health risks. This study aimed to explore the association between ultrasound-detected fatty liver, maternal lipid levels, and adverse obstetric outcomes

Method: This prospective cohort study included pregnant women who attended the Gynecology Department of University of Health Sciences Turkey, Prof. Dr. Cemil Taşçıoğlu City Hospital between 24 and 42 weeks of gestation for their antenatal visit. The study period was from February 1, 2020, to December 31, 2020.

Results: The 232 participants were divided into two groups based on ultrasound findings: Group 1 (n=121) with grade 0-1 fatty liver, and Group 2 (n=111) with grade 2-3 fatty liver. Statistically significant increases in maternal age, pregestational body mass index (BMI), and fetal weight were observed among women diagnosed with fatty liver on ultrasound. Regarding BMI, a cut-off value of ≥27.2 kg/m² exhibited a sensitivity of 58.6%, specificity of 66.12%, positive predictive value (PPV) of 61.30%, negative predictive value (NPV) of 63.50%, and LR(+) of 1.73%. Similarly, for triglycerides, a cut-off value of ≥240 mg/dL showed sensitivity of 62.16%, specificity of 87.60%, PPV of 82.10%, NPV of 71.60%, and LR(+) of 5.01%. Multivariate logistic regression analysis revealed a decreased risk of small for gestational age [0.98 (0.96-1.00) odds ratio (OR) 95%

Öz

Amaç: Gebelikte giderek yaygınlaşan yağlı karaciğer, maternal sağlık riskleriyle ilişkilidir. Bu çalışma, ultrasonografi ile tespit edilen yağlı karaciğerin, maternal lipid düzeyleri ve olumsuz obstetrik sonuçlarla olan bağlantısını araştırmayı amaçlamaktadır.

Yöntem: Bu prospektif kohort çalışması, 1 Şubat 2020-31 Aralık 2020 tarihleri arasında Sağlık Bilimleri Üniversitesi, Prof. Dr. Cemil Taşçıoğlu Şehir Hastanesi, Kadın Hastalıkları ve Doğum Kliniği'ne 24-42 haftalık gebelik döneminde antenatal ziyaret için başvuran hamile kadınları içermektedir.

Bulgular: Ultrasonografi bulgularına dayanarak 232 katılımcı iki gruba ayrılmıştır: Grup 1 (n=121) derece 0-1 yağlı karaciğer, ve Grup 2 (n=111) derece 2-3 yağlı karaciğer olanlar. Ultrasonografi ile yağlı karaciğer tanısı konulan kadınlarda maternal yaş, gebelik öncesi vücut kitle indeksi (VKİ) ve fetal ağırlıkta istatistiksel olarak anlamlı artışlar gözlemlenmiştir. VKİ için, ≥27,2 kg/m² eşik değeri %58,6 duyarlılık, %66,12 özgüllük, %61,30 pozitif öngörü değeri (PPV), %63,50 negatif öngörü değeri (NPV) ve 1,73 pozitif olasılık oranı LR(+) bulunmuştur. Benzer şekilde, trigliseritler için, ≥240 mg/dL eşik değeri %62,16 duyarlılık, %87,60 özgüllük, %82,10 PPV, %71,60 NPV ve 5,01 LR(+) göstermiştir. Çok değişkenli lojistik regresyon analizi, gestasyonel diyabet riskinde artış [0,98 (0,96-0,99) olasılık oranı (OO) %95 güven aralığı (GA); p=0,045)] ve gestasyonel yaşa göre düşük

Abstract

confidence interval (CI); p=0.016)] and an increased risk of gestational diabetes mellitus [0.98 (0.96-0.99) OR 95% CI; p=0.045)].

Conclusion: Fatty liver in pregnancy is associated with an increased risk of gestational diabetes mellitus (GDM), but not with other adverse obstetric outcomes.

Keywords: Adverse obstetric outcome, fatty liver, pregnancy, maternal lipid levels

Öz

doğum ağırlığı riskinde azalma [0,98 (0,96-1,00) OO %95 GA; p=0,016)] ortaya koymuştur.

Sonuç: Gebelikte yağlı karaciğer, gestasyonel diyabet riskinde artış ile ilişkilidir, ancak diğer olumsuz obstetrik sonuçlarla ilişkili değildir.

Anahtar kelimeler: Gebelik, maternal lipid düzeyleri, olumsuz obstetrik sonuçlar, yağlı karaciğer

Introduction

Pregnancy is associated with certain physiological changes that aim to provide adequate energy stores for both the mother and the fetus. These adaptations affect maternal blood lipid concentrations, and the levels of high-density lipoprotein (HDL), total cholesterol (TC), low-density lipoprotein (LDL), and triglycerides (TG) increase significantly as the pregnancy progresses (1). In later weeks of pregnancy, insulin resistance increases ketogenesis, gluconeogenesis, and lipolysis in fasting pregnant women. Placental lipoprotein lipase hydrolyzes TG to reach the fetus. TG must be hydrolyzed to free fatty acids and transported across the placenta (2). HDL-C has vasodilatory, antioxidant, antithrombotic, and anti-inflammatory effects, and its levels increase after 12 weeks of pregnancy as a result of elevated blood estrogen concentrations, whereas TC and LDL-C levels increase in the second and third trimesters (3,4).

Non-alcoholic fatty liver disease (NAFLD) encompasses a significant number of diffuse liver diseases. NAFLD is defined as the presence of hepatic steatosis, either by radiological methods or histological analysis, in the absence of alcohol consumption and other secondary causes of fatty liver. Obesity, diabetes, and metabolic syndrome are the risk factors for NAFLD. Maternal NAFLD has been found to be associated with abnormal fetal growth and obstetric complications (5,6). B-mode ultrasound allows the assessment of the grades of fatty liver. The total area of steatotic hepatocytes exceeding 20% exhibited higher sensitivity and specificity for the diagnosis of fatty liver. Although ultrasound testing has a higher diagnostic specificity in lower grades of fatty liver, its diagnostic sensitivity decreases because of high rates of false negative results (7,8).

Preeclampsia, gestational diabetes mellitus (GDM), preterm birth, and macrosomia have been reported in women with dyslipidemia and high cholesterol, low-density lipoprotein, TG, and low HDL levels (9,10). Fat infiltration in the liver parenchyma affects blood lipid levels. A limited number of studies on fatty liver during pregnancy have also found a relationship between NAFLD and adverse obstetric outcomes (11,12). The aim of this study was to examine the association between fatty liver detected on ultrasound and maternal lipid levels mitigate and to investigate its relationship with adverse obstetric outcomes.

Materials and Methods

This prospective cohort study included pregnant women who attended the Gynecology Department of University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital between 24 and 42 weeks of gestation for their antenatal visits. The study period was from February 1, 2020, to December 31, 2020. Gestational age was calculated according to the date of the last menstrual period or ultrasound findings at <20 weeks of gestation. The exclusion criteria were as follows: multiple pregnancies, smoking, alcohol use, maternal age of <18 years, chromosomal anomalies, maternal chronic liver, kidney, thyroid, or heart disease, asthma, chronic hypertension, autoimmune disorders, pregestational diabetes, metabolic storage disease, inflammatory bowel disease, polycystic ovary syndrome, chronic drug use, positive hepatic markers, and previously diagnosed dyslipidemia. Participation in the study was voluntary. Written informed consent was obtained from all participants. Fasting blood samples were obtained from all mothers at ≥24 weeks of gestation. Lipid profile tests, including low-density lipoprotein (LDL-C), high-density lipoprotein (HDL-C), TG, and TC, were performed as part of the routine pregnancy follow-up during the antenatal visits. Obstetric ultrasound was performed to monitor fetal development, and hepatic ultrasound was used to determine the grade of fatty liver infiltration. All obstetric examinations were conducted by a single obstetrician (S.G), while hepatic assessments were performed by a lone radiologist (S.O), using the Esaote My Lab Seven machine equipped with a 1-8-MHz convex-array abdominal probe. The intraclass correlation coefficient

(ICC) was used to evaluate the consistency of the results. Specifically regarding ultrasound assessments for fatty liver disease, the level of agreement between observers was determined by conducting two separate examinations, spaced 1 h apart, involving a cohort of 20 pregnant women. The resulting ICC was 0.83 [with a 95% confidence interval (CI) of 0.68-0.90].

The US grading criteria for fatty infiltration of the liver were follows (13): Grade 0 (Normal) - normal liver echotexture; Grade 1 (Mild) - diffuse and slight increase in fine echoes in the hepatic parenchyma, with normal visualization of the portal vein borders and diaphragm; Grade 2 (Moderate), moderate and diffuse increase in fine echoes, with slightly impaired visualization of the portal vein borders and diaphragm; and Grade 3 (Severe), marked increase in fine echoes, with poor or no visualization of the diaphragm, portal vein borders, and posterior portion of the right lobe.

The patients were followed up until delivery. Out of the 244 pregnant women initially selected, 232 were included in the study because the birth records of 12 patients were not available. Fetal weight, gestational age at delivery, mode of delivery, indications for cesarean delivery, neonatal gender, and maternal and obstetric outcomes were recorded. The following reference ranges were established: serum TG <150 mg/dL, TC <200 mg/dL, LDL <130 mg/dL, and HDL >50 mg/dL.

The diagnosis of GDM was made in 1 step, as recommended by the International Association of Diabetes and Pregnancy Study Groups (14). The diagnosis of preeclampsia was made according to the criteria of the International Society for the Study of Hypertension in Pregnancy (15).

Ethical Approval

This study was conducted in accordance with the Declaration of Helsinki. The Ethics Committee of University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital, approved the study (date: 27/01/2020/no: 48670771-514.10./15).

Statistical Analysis

Statistical analyses were performed using number cruncher statistical system 2007 Statistical Software (Utah, USA).

Apart from descriptive methods (mean, standard deviation, median, interquartile range), the Shapiro-Wilk normality test was used to check whether the variables followed a normal distribution, the independent t-test was used for pairwise comparisons of groups with normally distributed variables, and the Mann-Whitney U test was used for variables with non-normal distribution. Chi-square and Fisher's Exact tests were used to compare qualitative data. The areas under the receiver operating characteristic curve were calculated for differential diagnosis in the presence of grade 2-3 fatty liver, sensitivity, specificity, positive and negative predictive values, LR(+) and the cut-off values of the variables were determined. A p-value of <0.05 was considered statistically significant.

Results

The 232 participants were subdivided into Group 1 (n=121), consisting of pregnant women with ultrasound findings of steatosis grade 0-1, and Group 2 (n=111), consisting of pregnant women with ultrasound findings of steatosis grade 2-3. It should be noted that patients with grade 0-1 steatosis according to ultrasound findings were not diagnosed with NAFLD.

Maternal demographic characteristics and lipid levels are presented in Table 1. Maternal age and body mass index (BMI) were significantly higher in Group 2 than in Group 1 (p=0.011, and p=0.0001, respectively). There were no significant differences between the groups with respect to gravidity, parity, miscarriage rate, mode of delivery, and indications for cesarean delivery.

Mean fetal weight was significantly higher in Group 2 (3336.94±435.01 g) than in Group 1 (3196.98±438.4 g) (p=0.016). Patients in group 2 had significantly higher TG levels and lower HDL-C levels (p=0.0001 and p=0.008 respectively) compared with those in group 1. However, there were no statistically significant differences in TC and LDL-C levels between the two groups.

The pregnancy outcomes are presented in Table 2. There were no significant differences between the groups with respect to the development of adverse outcomes, including large for gestational age (LGA) infants, preeclampsia, abruptio placentae, fetal demise, GDM, oligohydramnios, polyhydramnios, preterm premature rupture of membrane (PPROM), low birth weight (LBW), premature rupture of membrane (PROM), macrosomia, preterm birth, and postterm birth. However, the incidence of small for gestational age (SGA) was significantly lower in Group 2 than in Group 1 (p=0.024).

Receiver operator characteristic curves were created and in predicting the presence of fatty liver, the area under the curves (AUCs) for HDL, LDL, and cholesterol were as follows: HDL: 0.604 (95% CI: 0.538-0.668); LDL: 0.529 (95% CI: 0.463-0.595), and cholesterol: 0.532 (95% CI: 0.466-0.598).

Table 1. Demographic characteristics and maternal lipid levels		Group 1 n=121 (Grade 0-1)		Group 2 n=111 (Grade 2-3)		p
Age	Mean (SD)	28.47±6.07		30.45±5.68		**0.011ᵃ**
Delivery	Vaginal	51	42.15%	52	46.85%	0.472ᵇ
	Cesarean	70	57.85%	59	53.15%	
Indications for cesarean sections	Previous cesarean	42	58.34%	31	52.54%	0.471ᵇ
Fetal distress		12	16.67%	11	18.64%	
Progress failure		5	6.94%	10	16.95%	
Cephalopelvic disproportion		7	9.72%	2	3.39%	
Macrosomia		2	2.78%	2	3.39%	
Malpresantation		3	4.17%	2	3.39%	
Placenta previa		1	1.39%	1	1.69%	
Gravida	Mean (SD)	2.44±1.34		2.72±1.54		0.163ᶜ
	Median (IQR)	2 (1-3)		2 (2-4)		
Parity	Mean (SD)	1.09±1.09		1.34±1.16		0.085ᶜ
	Median (IQR)	1 (0-2)		1 (1-2)		
Abortus	Mean (SD)	0.36±0.72		0.38±0.83		0.804ᶜ
	Median (IQR)	0 (0-1)		0 (0-0)		
Test weeks	Mean (SD)	31.43±4.1		34.01±3.08		**0.0001ᵃ**
Maternal weight	Mean (SD)	65.69±11.22		71.18±12.65		**0.001ᵃ**
Maternal height	Mean (SD)	160.56±5.5		159.75±4.93		0.238ᵃ
BMI	Mean (SD)	25.43±4.31		27.87±5.01		**0.0001ᵃ**
HDL-C	Mean (SD)	69.07±14.06		64.23±13.31		**0.008ᵃ**
LDL-C	Mean (SD)	140.93±40.11		140.05±57.28		0.893ᵃ
Cholesterol	Mean (SD)	245.75±49.44		251.12±53.45		0.428ᵃ
Trygliseride	Mean (SD)	180.36±47.36		264.55±79.57		**0.0001ᵃ**
Fetal weight	Mean (SD)	3196.98±438.4		3336.94±435.01		**0.016ᵃ**
Gestational age	Mean (SD)	38.64±1.59		38.76±1.69		0.582ᵃ
Gender	Female	52	42.98%	55	49.55%	0.337ᵇ
	Male	69	57.02%	56	50.45%	
Assisted reproductive technology		1	0.83%	0	0.00%	0.316ᵈ

ᵃ: Independent t-test, ᵇ: Chi-square test, ᶜ: Mann-Whitney U test, ᵈ: Fisher's Exact test, BMI: Body mass index (kg/m²), SD: Standard deviation, IQR: Interquartile range, HDL-C: High-density lipoprotein, LDL-C: Low-density lipoprotein

The AUC values for BMI (0.645, 95% CI: 0.579-0.706) and TG (0.828, 95% CI: 0.773-0.874) exceeded the threshold values, indicating significant predictive capability. Subsequently, cut-off values were calculated, as illustrated in Figure 1.

BMI, at a cut-off value of ≥27.2 kg/m², had a sensitivity of 58.6%, specificity of 66.12%, positive predictive value (PPV) of 61.30%, negative predictive value (NPV) of 63.50%, and LR(+) of 1.73% in predicting grade 2-3 fatty liver. Meanwhile, TG at a cut-off value of ≥240 mg/dL had a sensitivity of 62.16%, specificity of 87.60%, PPV of 82.10%, NPV of 71.60%, and LR(+) of 5.01% in predicting grade 2-3 fatty liver.

Regarding the distribution of adverse obstetric outcomes, no statistically significant differences were observed between the <240 mg/dL TG and ≥240 mg/dL TG groups or between the <27 kg/m² BMI and ≥27 kg/m² BMI groups (Table 3).

Multivariate logistic regression analysis for fatty liver in predicting obstetric outcomes was performed after adjusting for maternal age and BMI (Table 4). NAFLD was found to be an independent predictor of lower risk for SGA [0.98 (0.96-1.00) odds ratio (OR) 95% CI; p=0.016)], and elevated risk for GDM [0.98 (0.96-0.99) OR 95% CI; p=0.045)].

Table 2. Obstetric outcomes

	Group 1 n=121 (Grade 0-1)		Group 2 n=111 (Grade 2-3)		p
LGA	11	9.09%	17	15.32%	0.143[a]
Preeclampsia	7	5.79%	9	8.11%	0.485[a]
Abruptio placentae	1	0.83%	2	1.80%	0.511[b]
SGA	8	6.61%	1	0.90%	**0.024[b]**
Fetal demise	1	0.83%	0	0.00%	0.337[b]
GDM	6	4.96%	8	7.21%	0.472[a]
Oligohydramnios	7	5.79%	3	2,70%	0.248[a]
Polyhidramnios	2	1.65%	0	0.00%	0.174[b]
PROM	7	5.79%	4	360%	0.435[a]
PPROM	1	0.83%	1	0.90%	0.951[b]
LBW	9	7.44%	3	2.70%	0.104[a]
Macrosomia	5	4.13%	6	5.41%	0.649[a]
Preterm birth	14	11.57%	10	9.01%	0.522[a]
Postterm birth	1	0.83%	2	1.80%	0.511[b]

[a]: Chi-square test, [b]: Fisher's Exact test, LGA: Large for gestational age, SGA: Small for gestational age, GDM: Gestational diabetes mellitus, PROM: Premature rupture of membrane, PPROM: Preterm premature rupture of membrane, LBW: Low birth weight
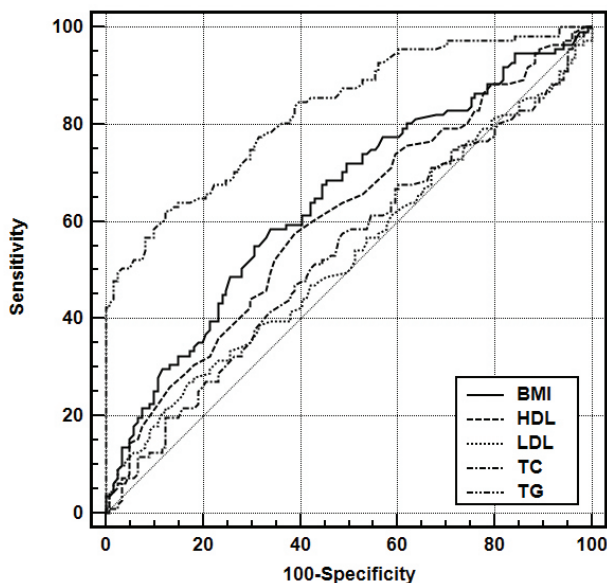
Figure 1. Receiver operating characteristic curve of maternal serum triglycerid (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol (TC) and body mass index (BMI) in the prediction of Grade 2-3 fatty liver in pregnancy

Discussion

Fatty liver during pregnancy, particularly in the context of NAFLD, has been correlated with a high incidence of adverse obstetric outcomes. Patients with NAFLD during gestation exhibit a notable increase in the incidence of several complications compared with those without the condition. Specifically, they are more frequently diagnosed with gestational diabetes (7-8% vs. 23%), hypertensive complications (4% vs. 16%), postpartum hemorrhage (3-5% vs. 6%), and preterm birth (5-7% vs. 9%). These findings underscore the importance of recognizing and managing NAFLD during pregnancy to mitigate maternal and fetal health risks.In this study, maternal age, pregestational BMI, and fetal weight were significantly higher in women with fatty liver on ultrasound. In addition, higher maternal serum TG and lower HDL levels were observed in that group. Lower risk for SGA but elevated risk of GDM were observed after adjusting for maternal age and BMI.

In a meta-analysis, liver ultrasound was found to be a reliable tool, with 84.8% sensitivity and 93.6% specificity, for detecting moderate to severe fatty liver (16). The prevalence of NAFLD in pregnant women was found to be 18.4% in Korean and 17.6% in Canadian populations (17,18). In our study, the rate of fatty liver in pregnancy detected on ultrasound was 47.8%, which is extremely high as compared with other studies. The difference might have resulted from the fact that our study population was >24 gestational weeks, whereas other studies were conducted in the first trimester, and maternal lipid levels are known to increase in late pregnancy. In one study, an increase in serum TG levels and a decrease in HDL-C levels were found in patients with moderate and severe steatosis (19). In our study, TG levels were found to be significantly higher and HDL levels were lower in the fatty liver group, which is consistent with the literature. When the cut-off value of

Table 3. Adverse obstetric outcomes of the triglyceride and BMI groups

	<240 mg/dLTG		≥240 mg/dLTG		p	<27 kg/m² BMI		≥27 kg/m² BMI		p
LGA	14	9.52%	14	16.47%	0.118[a]	13	10.57%	15	13.76%	0.456[a]
Preeclampsia	8	5.44%	8	9.41%	0.250[a]	7	5.69%	9	8.26%	0.441[a]
Abruptio placentae	2	1.36%	1	1.18%	0.905[b]	1	0.81%	2	1.83%	0.492[b]
SGA	7	4.76%	2	2.35%	0.360[a]	7	5.69%	2	1.83%	0.129[a]
Fetal demise	1	0.68%	0	0.00%	0.446[b]	1	0.81%	0	0.00%	0.345[b]
GDM	9	6.12%	5	5.88%	0.941[a]	7	5.69%	7	6.42%	0.815[a]
Oligohydramnios	8	5.44%	2	2.35%	0.264[a]	4	3.25%	6	5.50%	0.399[a]
Polyhydramnios	2	1.36%	0	0.00%	0.280[b]	1	0.81%	1	0.92%	0.932[b]
PROM	9	6.12%	2	2.35%	0.193[a]	8	6.50%		2.75%	0.180[a]
PPROM	1	0.68%	1	1.18%	0.694[b]	1	0.81%	1	0.92%	0.932[b]
LBW	10	6.80%	2	2.35%	0.140[a]	7	5.69%	5	4.59%	0.705[a]
Macrosomia	7	4.76%	4	4.71%	0.985[a]	5	4.07%	6	5.50%	0.607[a]
Preterm birth	13	8.84%	11	12.94%	0.323[a]	13	10.57%	11	10.09%	0.905[a]
Postterm birth	2	1.36%	1	1.18%	0.905[b]	2	1.63%	1	0.92%	0.634[b]

[a]: Chi-square test, [b]: Fisher's Exact test, LGA: Large for gestational age, SGA: Small for gestational age, GDM: Gestational diabetes mellitus, PROM: Premature rupture of membrane, PPROM: Preterm premature rupture of membrane, LBW: Low birth weight

TG was set as ≥240 mg/dL, no increase in adverse obstetric outcomes was detected.

Weight gain and obesity are important risk factors for developing fatty liver, and 80% of NAFLD cases are associated with obesity and BMI >30 kg/m² (20,21). Insulin resistance plays an important role in hepatic steatosis. Higher maternal BMI was found to be associated with higher TC levels in early pregnancy and elevated TG levels in both early and late pregnancy (22). In another study, elevated levels of total cholesterol, LDL-C, and TG but decreased levels of HDL-C were observed in patients with high BMI (22,23). In our study, the cut-off value for BMI was ≥27.2 kg/m², and BMI was found to be significantly higher in patients with grade 2-3 steatosis, which is consistent with other reports. Interestingly, no increase in poor obstetric outcome rate was observed in the high-BMI group versus the low-BMI group.

Maternal TG levels are important predictors of fetal size in late pregnancy. Low HDL-C levels and hypertriglyceridemia are predictive of macrosomia (24). In one study, fasting TG levels in the 95th centile were found to be associated with LGA (25). However, in our study, no increase in the risk of LGA and fetal macrosomia was detected in patients with hypertriglyceridemia.

Unlike other trials, our study was conducted in patients in late pregnancy. Although there was no increase in LGA and macrosomia rates, fetal birth weight was significantly higher and the rate of SGA infants was significantly lower in the group with Grade 2-3 steatosis. However, some studies were not able to find a relationship between NAFLD and SGA infants (12), although Hagström et al. (26) found an increased risk of LBW in mothers with fatty liver in their study, and an elevated risk of gestational diabetes in pregnant women with NAFLD was reported. De Souza et al. (18) stated that fatty liver detected on ultrasound between 11-14 weeks of gestation was a reliable predictor of mid-pregnancy dysglycemia. In a multicenter study, a higher risk for GDM in NAFLD and its correlation with the severity of steatosis were reported (17). Herath et al. (12) found a relationship between NAFLD and hyperglycemia, but the correlation was not significant after adjusting for BMI and age. In our study, a higher risk for GDM in women with Grade 2-3 fatty liver was confirmed after adjusting for maternal age and BMI.

Numerous studies have investigated the relationships between variations in maternal lipid levels and poor obstetric outcomes, without resorting to ultrasound testing in pregnant women with fatty liver. A higher risk of GDM was found to be correlated with elevated TG levels (27). In a meta-analysis comparing groups with and without GDM, TC and LDL-C levels remained unchanged, whereas HDL-C levels significantly decreased in the GDM group in the second and third trimesters of pregnancy. In addition, TG levels in GDM were found to be higher in the third trimesters (28).

Dyslipidemia detected during pregnancy may cause preeclampsia and endothelial dysfunction. In the Chinese population, increased maternal serum TG levels in late pregnancy were independently associated with an elevated risk of preeclampsia, GDM, macrosomia, and LGA but a decreased risk of SGA. A statistically significant relationship was found between decreased HDL-C levels and elevated risk of GDM and fetal macrosomia (29). Hagström et al. (26) observed an increased risk for PE in women with NAFLD, but the statistical significance disappeared after adjusting for maternal BMI. In our study, no increased risk for developing preeclampsia was found in women with fatty liver.

Apart from studies that linked decreased TG levels and preterm birth, the literature offers reports about the relationship between high maternal lipid levels and elevated risk for preterm birth (1,30). Some studies among pregnant women with NAFLD found a higher risk for preterm birth in the fatty liver group (26). While others detected no such relationship (12). In our study, an increased risk of preterm birth was not detected, either in women with high-grade fatty liver or those with elevated TG levels.

Regarding the mode of delivery, in addition to publications confirming higher rates of cesarean section in women with NAFLD, some reports found that delivery mode was not affected (12,26). In our study, no differences were found between the groups in terms of cesarean section rates or indications for cesarean delivery.

Study Limitations

The study has several limitations. Data on socio-economic status, race, nutritional status, and maternal education were not analyzed. In addition, it is possible for the NAFLD grading to change during pregnancy due to differences in dietary habits, emesis gravidarum, and weight gain. The main limitation of this study was that longitudinal follow-ups for fatty liver in the first trimester and postpartum period could not be performed.

Conclusion

Fatty liver in pregnancy is associated with increased rates of adverse obstetric outcomes. It is necessary to distinguish between hyperlipidemia detected during pregnancy and physiological processes. However, there is no consensus on determining the cut-off values of lipid levels. In our study, Grade 2-3 steatosis was associated with more advanced maternal age, significantly higher BMI, and higher fetal weight. Increased maternal TG levels and decreased HDL levels were detected in that group. Although we found no relationship between obstetric outcomes such as preeclampsia, abruptio placenta, fetal loss, LBW, LGA, preterm birth, PROM, PPROM, and fatty liver, multivariate logistic regression analysis revealed an elevated risk for GDM and a decreased risk for SGA. It may be necessary to classify these pregnant women as "high-risk" patients and examine their long-term health outcomes because they may face cardiovascular risks later in life. Ultrasound testing is an important imaging modality in the diagnosis of fatty liver during pregnancy, especially because of its low cost and lack of exposure to radiation.

Ethics

Authorship Contributions

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ORIGINAL RESEARCH

Clinical Characteristics, Risk Factors, and Angiographic Profile of Syrian Refugees Admitted with Acute Coronary Syndrome in a Tertiary Center in Turkey

Türkiye'de Üçüncü Basamak Bir Merkeze Akut Koroner Sendromla Başvuran Suriyeli Mültecilerin Klinik Özellikleri, Risk Faktörleri ve Anjiyografik Profilinin İncelenmesi

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Abstract

Objective: To investigate the impact of refugee life on cardiovascular events has not been adequately studied. We examined the angiographic profile and risk factors of Syrian refugees who migrated to Turkey and presented to our clinic with acute coronary syndrome.

Method: In this retrospective descriptive study, 201 Syrian refugees who underwent coronary angiography for acute coronary syndrome were included. Demographic data, laboratory values, risk factors, and in-hospital outcomes were recorded. To assess the burden of coronary atherosclerosis, the SYNTAX 1 score, number of diseased vessels, TIMI thrombus burden, and flow grade were determined. Data not conforming to normal distribution were presented as median values.

Results: Most of the population was male (70.6%), with a mean age of 56 (49.5-61). The rates were 41.8%, 37.8%, and 20.4%, respectively. The prevalence of risk factors was as follows: hypertension (59.2%), diabetes (36.8%), hyperlipidemia (86%), smoking (65.6%), and previous coronary artery disease (21.3%). In 83% of the patients, the SYNTAX 1 score was >22; 50.4% had a high thrombus burden, 95% had multivessel disease, 74.1% underwent stent implantation, and 17.9% required coronary artery bypass grafting. The in-hospital mortality rate was 5% (10).

Öz

Amaç: Mülteci yaşamının kardiyovasküler olaylar üzerindeki etkisi yeterince incelenmemiştir. Türkiye'ye göç eden Suriyeli mültecilerden akut koroner sendrom ile kliniğimize başvuranlarda anjiyografik profil ve risk faktörlerini incelemeyi amaçladık.

Yöntem: Retrospektif tanımlayıcı çalışmamızda, akut koroner sendrom tanısıyla koroner anjiyografi yapılan 201 Suriyeli mülteci dahil edildi. Hastaların demografik verileri, laboratuvar değerleri, risk faktörleri ve hastane içi sonuçları kaydedildi. Koroner ateroskleroz yükünü değerlendirmek için SYNTAX 1 skoru, hasta damar sayısı, TIMI trombüs yükü ve akım derecesi belirlendi. Normal dağılıma uymayan veriler ortanca değer olarak sunuldu.

Bulgular: Popülasyonun çoğunluğu erkeklerden (%70,6) oluşuyordu ve yaş ortalaması 56 (49,5-61) idi. ST yükselmesiz miyokard enfarktüsü %41,8, ST yükselmeli miyokard enfarktüsü %37,8, kararsız anjina pektoris %20,4 oranındaydı. Risk faktörleri sıklığı; hipertansiyon %59,2, diyabet %36,8, hiperlipidemi %86, sigara kullanımı %65,6, önceki koroner arter hastalığı öyküsü %21,3 idi. Hastaların %83'ünde SYNTAX 1 skoru >22, %50,4'ünde yüksek trombüs yükü, çok damar hastalığı %95, stent implantasyon oranı %74,1, koroner arter baypas greftleme ihtiyacı %17,9 idi. Hastane içi ölüm oranı %5 (10) idi.

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Abstract

Conclusion: Our study revealed that Syrian refugees have a significant burden of coronary artery disease. These findings demonstrate the importance of cardiovascular care strategies for refugees.

Keywords: Acute coronary syndrome, immigrant health, Syrian refugees

Öz

Sonuç: Çalışmamız, Suriyeli mültecilerin ciddi koroner arter hastalığı yüküne sahip olduklarını ortaya koymuştur. Bu sonuçlar, mültecilerde kardiyovasküler bakım stratejilerinin önemini kanıtlamaktadır.

Anahtar kelimeler: Akut koroner sendrom, göçmen sağlığı, Suriyeli mülteciler

Introduction

Cardiovascular diseases (CVD) account for 31% of all deaths worldwide. Approximately three-quarters of these deaths occur in low-and middle-income countries. However, most clinical research data are from developed countries (1). Effective management of CVD-related health expenditures is possible by examining underdeveloped countries and special groups such as refugees (2). If the prevalence of modifiable risk factors in the mentioned groups can be determined through clinical studies, mortality and economic benefits can be achieved (3).

Social differences impact CVD. Modifiable risk factors for CVD are influenced by the development levels of countries. However, the development level is not the only determinant. Extraordinary situations, such as wars and natural disasters, also have an impact. Additionally, ethnic factors also play a role as well (4).

The epidemiological consequences of war impact societies. Long-term conflicts lead to economic problems, inadequate healthcare services, psychological stress, malnutrition, and unhealthy living conditions. Conflict environments lead to refugee migration, and refugees encounter issues such as increased smoking, unhealthy diets, and lifestyles (5). Turkey hosts more than 3.5 million Syrians because of the conflict in Syria. Syrian refugees living in Turkey have access to the same healthcare services as Turkish citizens, free of charge. However, there are no adequate clinical studies on CVD among refugees (6).

Syrian refugees have many conventional risk factors and a high risk of atherosclerosis. However, the number of studies in this field has been remarkably low. We believe that the prevalence of risk factors, clinical outcomes, stent implantation and coronary artery bypass grafting (CABG) rates, coronary artery structure, atherosclerosis burden, and in-hospital mortality in acute coronary syndrome (ACS) patients among refugees should be investigated. The effects of ethnic differences and geographical changes on CVD can also be examined through studies in this field. In this study, we analyzed the clinical and angiographic profiles and in-hospital results of Syrian refugees living in Turkey who were admitted to our clinic with a diagnosis of ACS.

Materials and Methods

Study Protocol

In this retrospective study, the angiographic, clinical, and laboratory features of 201 consecutive Syrian refugee patients who were admitted to the cardiology clinic of University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital with a diagnosis of ACS between January 1, 2017, and December 31, 2020, were analyzed. There was no financial support or interest in this study. Necessary patient consent was obtained. Patients who had previously undergone CABG were excluded from the study. Those of Syrian ethnicity who immigrated to Turkey as postwar refugees were included in this study. The diagnosis of ACS is based on evidence-based European guidelines. Patients were recorded as having ST-elevated MI (STEMI), non-ST-elevated MI (NSTEMI), and unstable angina pectoris (USAP) (7). By scanning our hospital's database, we obtained laboratory values, in-hospital mortality rates, and the number of patients who underwent CABG. Angiography images were monitored to create the angiographic profile. Using universal TIMI thrombus and flow gradings, the thrombus and flow grades in the infarct-related artery were determined. These gradings were recorded both before and after the procedure (8,9). Patients were classified into low (grades 1, 2, and 3) and high thrombus burden (grades 4 and 5). In the presence of >50% stenosis in non-infarct-related arteries, the vessel was considered a diseased coronary vessel. The number of diseased vessels was calculated. If there were two or three main vessel diseases, multivessel disease was considered. Infarct-related arteries were recorded as the left main coronary artery (LMCA), left anterior descending artery (LAD), circumflex artery (CX), right coronary artery (RCA), and their subbranches. A web-based score calculator (http://www.syntaxscore.com) was used to calculate the SYNTAX 1 score. Because the SYNTAX 1 score was not normally distributed, the median mean score was determined, and the scores were grouped as ≤22, 22-33, ≥33.

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The presence of hypertension (HT), hyperlipidemia (HL), and diabetes mellitus (DM) was determined according to the definitions of the European guidelines (10). History of previous coronary artery disease (CAD) was recorded. Only the presence of stent implantation was considered evidence of CAD. The smoking rate was recorded. Contrast-induced nephropathy (CIN) was determined and recorded according to universal definitions (11). Increases in creatinine levels within the first 72 hours were defined as non-CIN.

Ethical Approval

Ethics committee approval for this retrospective study was obtained from the Clinical Research Ethics Committee of the University of Health Sciences Turkey, İstanbul Training and Research Hospital (date: 25.02.2022, decision no: 85). This study was conducted in accordance with the Declaration of Helsinki.

Statistical Analysis

The SPSS 16.0 statistical package was used in the evaluation. In cases where the data were not normally distributed, median values were calculated and minimum-maximum values were given. Means and standard deviations were calculated for normally distributed values. Because there was no comparison group, the p-value was not calculated.

Results

The aim of this retrospective descriptive study was to evaluate the demographic and angiographic characteristics of Syrian refugees who presented to our clinic with ACS. Additionally, it aimed to determine in-hospital outcomes and the prevalence of CVD risk factors. Of the 201 patients included in the study, men comprised the majority (70.6%). The overall average age was 56 (49.5-61). The average age of women (60) was higher than men (54). The average length of hospital stay was 4 (2-5) days. 59.2% of the patients had HT, and 36.8% had DM. Both risk factors were more common in women (HT in men: 58.4%, DM: 30.9%; in women: HT 61.01%, DM 50.8%). The HL rate was 86%, and the rate was similar in both gender groups. The smoking rate was 65.6%, and the history of previous CAD was 21.3% (43), both of which were more common in men (34). The most common form of presentation was NSTEMI (41.8%). In angiography, 76.1% of the patients underwent stent implantation, and 17.9% had a CABG decision. Medical treatment was applied without revascularization in 10 patients, and there was no critical stenosis in 6 patients. The in-hospital mortality rate was 5%, CIN was 6.5%, and non-CIN was 4%. Clopidogrel was used in 68.7% of the patients, Ticagrelor in 17.4%, and

Prasugrel in 0.5%. Basic demographic data, risk factors, laboratory values, and ACS subtypes are presented in Table 1.

Aneurysmal vascular structures were found in 4.5% (9) of patients. In the distribution of infarct-related arteries, the LAD had the highest rate at 48.3% (97); others were the RCA at 31.9% (64), CX at 25.9% (52), and LMCA at 1% (2). Vessels with more than 50% critical stenosis unrelated to infarction are presented in Table 2. In 30 of the 153 patients who received stents, a second intervention was planned. Multivessel disease was common; 137 patients having critical stenosis in 3 vessels, 54 patients in 2 vessels, and 2 patients in 1 vessel, unrelated to infarction. There were no additional critical stenosis in 8 patients.

The median SYNTAX 1 score was 29.5 (0-113.5). Only 17% of the patients had a SYNTAX 1 score ≤22. Of the 24 patients

Table 1. Basic demographic data, risk factors, laboratory values, and ACS subgroup analysis

Variables	Values
Age (year)	56 (49.5-61)
Gender n,%	
Male	142, 70.6
Female	59, 29.4
ACS subgroup n (%)	
NSTEMI	84, 41.8
STEMI	76, 37.8
-Anterior	36, 17.9
-Inferior	36, 17.9
-Lateral	3, 1.5
-Posterior	1, 0.5
USAP	41, 20.4
Risk factors (n)	
HT	119, 59.2
DM	74, 36.8
HL	173, 86.0
Complete blood count (n=200), 10³	
WBC (10³/µL)	10 (8-13)
LYMPH (10³/µL)	2.4 (1.9-3.3)
HB (g/dL)	13 (12-14.1)
MCV (10³/µL)	85 (81-89)
PLT (10³/µL)	264 (216-314)
Kidney function values (n=200)	
Creatine (mg/dL)	0.8 (0.7-0.9)
BUN (mg/dL)	32.5 (25-40)
eGFR (mL/min/1.73 m²)	97.5 (82.5-108)
Lipid profile (mg/dL)	
LDL-C (n=101)	136 (110-159)
HDL-C (n=95)	36 (31-44)
TG (n=92)	186.5 (126-255)
Glycemic profile	
HbA1c (%) (n=68)	7.45 (5.8-10.9)
Glucose (mg/dL) (n=200)	143 (108-228)

ACS: Acute coronary syndrome, BUN: Blood urea nitrogen DM: Diabetes mellitus, e-GFR: Estimated glomerular filtration rate, HB: Hemoglobin, HDL-C: High-density lipoprotein cholesterol, HL: Hyperlipidemia, HT: Hypertension, LDL-C: Low-density lipoprotein cholesterol, LYMPH: Lymphocyte, MCV: Mean corpuscular volume, NSTEMI: Non-ST Elevation myocardial infarction, PLT: Platelet, STEMI: ST elevation myocardial infarction, TG: Triglyceride, USAP: Unstable angina pectoris, WBC: White blood cell

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with a SYNTAX 1 score ≥33, 12% underwent CABG (Table 3). In 71% of the patients, the SYNTAX 1 score ranged from 22 to 33. High thrombus burden (grades 4-5) was observed in 50.4% of the patients (Table 4). Six of 10 patients who died in the hospital had a TIMI thrombus grade of 5, and this high thrombus grade was more common in the STEMI group.

Although the TIMI flow grade was initially 0/1 in 110 patients, it was determined as 3 in 160 patients after the procedure (Table 5). Of 34 patients with TIMI 0/1 flow after the procedure, 8 underwent STEMI, 16 underwent NSTEMI, and 10 underwent USAP. In 16 patients, CABG was decided without percutaneous revascularization or because flow could not be established. Five of the other 18 patients were hemodynamically unstable during the procedure and died.

Discussion

In this study, we found that Syrian refugees with ACS have complex coronary arteries and a high prevalence of risk factors. The high SYNTAX 1 score confirms this. The next step is to address this condition. The lifestyle of the country where refugee migrate affects CVD. High CVD risk should be identified early and poor outcomes should be reduced. Poor living conditions are associated with poor prognosis in patients with ACS (12). Cardiovascular risk factors are quite high among refugees. Depression is also associated with increased CVD mortality (13). Countries like Turkey that accept refugees have specific responsibilities. Cardiovascular risk factors among refugees should be identified early and treated. Factors leading to poor outcomes should be eliminated by evaluating living conditions. According to the WHO STEPS study, 58.7% of Syrian refugees in Turkey have at least three CVD risk factors

(14). Despite the presence of many risk factors among Syrian refugees, studies in this field are few. Conducting our study on patients with ACS will increase awareness of the importance of addressing modifiable risk factors. This, in turn, will contribute to better patient management. Ultimately, this approach will improve long-term patient outcomes.

Multivessel disease and a high SYNTAX 1 score indicate the prevalence of atherosclerotic disease. The SYNTAX 1 score is directly proportional to coronary TIMI thrombus burden and inversely proportional to flow grade. These parameters are interrelated and can predict mortality risk (15,16). Therefore, in our study, all these parameters were examined when assessing CVD severity.

According to the INTERHEART study, the highest rates of HT and DM were found in Southeast Asia at 59.2% and DM at 38.8% (17). However, in our study, the rates were even higher. In a study comparing 67 Syrians and 427 Turks who underwent CABG, HT was found to be 35.8% and DM 32.8% among Syrian refugees. The SYNTAX 1 score was also higher in the refugee group (6). In the TURKMI study examining Turkish AKS cases in Turkey , HT and DM were 49.5% and 37.9%, respectively. Compared with our study, the DM rates were similar (18). However, the HT rate in our study was higher than that of Turks in the TURKMI study.

Study Limitations

The major limitation of our study is its retrospective nature. The failure to evaluate family history and obesity as risk factors is a limitation. The single-center study design limits the study population and makes it insufficient. This was a descriptive study without a control group. Prospective studies with a control group are recommended.

Table 2. Vessels not related to infarction causing ≥50% stenosis

Coronary arteries	Number of patients with critical stenosis
LMCA	7
LAD	147
LAD side branch	38
CX	90
CX side branch	54
RCA	110
RCA side branch	13

CX: Circumflex artery, LAD: Left anterior descending artery, LMCA: Left main coronary artery, RCA: Right coronary artery

Table 3. SYNTAX 1 score distribution of patients

Score value	n, %
≤22	34, 17
22-33	143, 71
≥33	24, 12

Table 4. Distribution of pre-procedure TIMI thrombus grades

TIMI grade	Number of patients
TIMI 0	37
TIMI 1	47
TIMI 2	3
TIMI 3	12
TIMI 4	20
TIMI 5	82

Table 5. Preprocedure and postprocedure TIMI flow grade of the patients

TIMI flow grade	Pre-procedure	Post-procedure
0	97	17
1	13	17
2	8	7
3	83	160

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Conclusion

The Syrian civil war is a public health issue with serious health implications for refugees. We believe that this increases the risk factors for CVD. Lack of research in this area may lead to insufficient health services for refugees. Our study examining the angiographic profiles and in-hospital outcomes of patients with ACS can contribute to refugee health. Prospective studies on refugees will help develop prevention and treatment strategies.

Ethics

Ethics Committee Approval: Ethics committee approval for this retrospective study was obtained from the Clinical Research Ethics Committee of the University of Health Sciences Turkey, İstanbul Training and Research Hospital (date: 25.02.2022, decision no: 85). This study was conducted in accordance with the Declaration of Helsinki.

Informed Consent: The study was designed retrospectively.

Authorship Contributions

Surgical and Medical Practices: E.M.F., S.G., İ.Y., M.E.A., M.Z., S.Ö., E.D., E.O., Concept: E.M.F., S.G., İ.Y., M.E.A., M.Z., S.Ö., E.D., E.O., Design: E.M.F., S.G., İ.Y., M.E.A., M.Z., S.Ö., E.D., E.O., Data Collection or Processing: E.M.F., S.G., İ.Y., M.E.A., M.Z., S.Ö., E.D., E.O., Analysis or Interpretation: E.M.F., S.G., İ.Y., M.E.A., M.Z., S.Ö., E.D., E.O., Literature Search: E.M.F., S.G., İ.Y., M.E.A., M.Z., S.Ö., E.D., E.O., Writing: E.M.F., S.G., İ.Y., M.E.A., M.Z., S.Ö., E.D., E.O.

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ORIGINAL RESEARCH

Inducible Nitric Oxide Synthase (iNOS) is a Potential Marker of Myocardial Infarction with Non-obstructive Coronary Artery Disease (MINOCA)

İndüklenebilir Nitrik Oksit Sentaz (iNOS), Obstrüktif Olmayan Koroner Arter Hastalığı ile Birlikte Miyokard Enfarktüsü (MINOCA) için Potansiyel Bir Belirteçtir

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Abstract

Objective: The currently available cardiac biomarkers are not sufficient to differentiate between myocardial infarction with non-obstructive coronary arteries (MINOCA) and acute coronary syndrome (ACS) without the use of coronary angiography. In this context, this study aimed to evaluate inducible nitric oxide synthase (iNOS) activity as a potential marker for the differential diagnosis of MINOCA and ACS.

Method: The study population comprised 734 consecutive patients who presented to our hospital with chest pain between July 2022 and January 2023. Leftover plasma samples collected in EDTA vials were sent for troponin T estimation within 24 hours of the onset of chest pain. Patients' blood samples were collected into tubes for malondialdehyde (MDA), iNOS, and total sialic acid (TSA) measurements and centrifuged at 4000 g, 4 °C for 10 min, and the sera obtained as a result were kept at -25 °C until the analyses were performed.

Results: The mean age of the study population, which consisted of 648 patients [421 (65.6%) males, was 62±12] years. There were no significant difference between the MINOCA and ACS patients in MDA and homocysteine levels. Univariate logistic regression analysis revealed significant correlations between gender, age, diabetes mellitus (DM), glucose, urea, iNOS, smoking, hemoglobin, platelets, lymphocytes, monocytes, neutrophils, triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, creatine, and TSA as significant predictors of MINOCA. Further analysis of these variables using

Öz

Amaç: Mevcut kardiyak biyobelirteçler, koroner anjiyografi kullanılmadan, obstrüktif olmayan koroner arterlerin eşlik ettiği miyokard enfarktüsü (MINOCA) ile akut koroner sendrom (AKS) arasında ayrım yapmak için yeterli değildir. Bu bağlamda bu çalışma, MINOCA ve AKS ayırıcı tanısında potansiyel bir belirteç olarak indüklenebilir nitrik oksit sentaz (iNOS) aktivitesinin değerlendirilmesi amacıyla yapılmıştır.

Yöntem: Çalışma evrenini Temmuz 2022 ile Ocak 2023 tarihleri arasında hastanemize göğüs ağrısı şikayetiyle başvuran 734 hasta oluşturdu. EDTA şişelerinde toplanan kalan plazma örnekleri göğüs ağrısının başlamasından sonraki 24 saat içinde troponin T çalışılması için gönderildi. Hastalardan malondialdehit (MDA), iNOS ve total sialik asit (TSA) ölçümleri için kan örnekleri tüplere alınarak 4000 g, 4 °C'de 10 dakika santrifüj edildi ve elde edilen serumlar -25 °C'de analizler yapılana kadar saklandı.

Bulgular: Dört yüz yirmi biri (%65,6) erkek olmak üzere 648 hastadan oluşan çalışma örnekleminin yaş ortalaması 62±12 idi. MINOCA ve AKS hastaları arasında malondialdehit (MDA) ve homosistein düzeyleri arasında anlamlı fark yoktu. Tek değişkenli lojistik regresyon analizi cinsiyet, yaş, diabetes mellitus (DM), glikoz, üre, iNOS, sigara içme durumu, hemoglobin, trombosit, lenfosit, monosit, nötrofil, trigliserit, düşük yoğunluklu lipoprotein kolesterol, yüksek yoğunluklu lipoprotein kolesterol, kreatin ve toplam sialik asit (TSA) için MINOCA'nın önemli belirleyicileri olarak anlamlı ilişkiler ortaya çıkardı. Bu değişkenlerin çok

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multivariate logistic regression revealed that sex, age, presence of DM, glucose and urea levels, and iNOS were independent predictors of MINOCA. The iNOS level was significantly higher in patients with MINOCA than in those with ACS. The optimal iNOS cut-off value of >1372.9 pg/mL predicted MINOCA with 99.4% sensitivity and 93.7% specificity (area under the curve: 0.99, 95% confidence interval: 0.979-0.996, p<0.001).

Conclusion: iNOS activity may help distinguish between ACS and MINOCA without the need for coronary angiography.

Keywords: Acute coronary syndrome (ACS), inducible nitric oxide synthase (iNOS), myocardial infarction with non-obstructive coronary arteries (MINOCA)

Öz

değişkenli lojistik regresyon analizi ile; cinsiyet, yaş, DM varlığı, glikoz, üre seviyeleri ve iNOS'nin MINOCA için bağımsız belirleyiciler olduğunu ortaya çıkardı. MINOCA hastalarında iNOS düzeyi AKS hastalarına göre anlamlı derecede yüksekti. Optimum iNOS cut-off değeri >1372,9 pg/mL, MINOCA'yı %99,4 duyarlılık ve %93,7 özgüllükle öngördü (eğri altında kalan alan: 0,99, %95 güven aralığı: 0,979-0,996, p<0,001).

Sonuç: iNOS aktivitesinin ölçülmesinin koroner anjiyografiye gerek kalmadan AKS ile MINOCA ayrımında yardımcı olabileceğini düşünüyoruz.

Anahtar kelimeler: Akut koroner sendrom (AKS), indüklenebilir nitrik oksit sentaz (iNOS), obstrüktif olmayan koroner arterlerle birlikte miyokard enfarktüsü (MINOCA)

Introduction

Ischemic heart disease is the leading cause of death worldwide, accounting for 12.7% of all deaths. Acute coronary syndrome (ACS) encompasses a wide spectrum of clinical conditions, ranging from unstable angina to non-ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI). Most patients with anginal symptoms have no obstructive coronary artery disease (CAD) (1). Myocardial infarction with non-obstructive coronary arteries, that is, ≤50% stenosis in a major epicardial artery, is termed MINOCA. MINOCA is characterized by a heterogeneous group of conditions, including causes of epicardial and microvascular myocardial ischemia, such as plaque disruption, epicardial coronary spasm, spontaneous coronary dissection, microvascular spasm, and coronary distal embolization (2,3). Takotsubo cardiomyopathy and myocarditis, which were initially included in MINOCA, were later excluded. The prevalence of MINOCA among all type 1 myocardial infarctions (MI) is approximately 10%. It is more common in female patients with NSTEMI (4). Up to 50-60% of patients undergoing elective coronary angiography for suspected CAD actually have non-obstructive CAD. Various biochemical parameters have been investigated in the differential diagnosis of ACS and MINOCA without the need for coronary angiography. Coronary angiography performed to rule out epicardial stenosis is an invasive procedure with the risk of various complications.

A family of enzymes known as NO synthases (NOSs) generates NO. NOSs have three distinct isoforms: neuronal NOS (nNOS, NOS1), inducible NOS (iNOS, NOS2), and endothelial NOS [endothelial NOS (eNOS), NOS3]. In humans, these isoforms have ~55% homology; they differ in their intracellular location, regulation, and enzymatic properties, including their activity and susceptibility to various inhibitors (5). In ACS, platelets, which are bound to the subendothelium, are activated following plaque rupture and further stimulate thrombus formation by producing thromboxane A2 (TxA2) and increasing thrombin formation. Endothelial products such as prostacyclins and nitric oxide (NO) play an important role in the regulation of platelet activation and aggregation (6). NO impairment is common in patients with MINOCA via microvascular dysfunction and in those with ACS (7-9). In ACS, excess nitric oxide is generated in excess during ischemic attack because of marked activation of the inducible nitric oxide synthase (iNOS) enzyme by different cytokines, resulting in serious adverse effects. However, there are no studies on iNOS activity in patients with MINOCA.

The currently available cardiac biomarkers are not sufficient to differentiate between MINOCA and ACS without the use of coronary angiography. In this context, this study aimed to evaluate iNOS activity as a potential marker in the differential diagnosis of MINOCA and ACS.

Materials and Methods

Population and Sample

The study population consisted of 734 consecutive patients admitted to our hospital between July 2022 and January 2023 with chest pain, as indicated by changes in electrocardiogram or elevated cardiac troponin T levels (>0.03 ng/mL).

A total of 86 patients with 1) recent hospitalization for myocardial infarction, unstable angina, acutely decompensated heart failure (HF), deep vein thrombosis or pulmonary embolism or conduction of any cardiac revascularization procedure; 2) any history of surgery in the

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preceding few months; 3) evidence of hepatic dysfunction; 4) presence of concomitant illness(es) including infectious and connective tissue diseases and neoplasm; and, 5) intake of immunosuppressant agents were excluded from the study. Therefore, 86 patients were excluded from the study. In conclusion, the study sample consisted of 648 patients. Leftover plasma samples collected in EDTA vials were sent for troponin T estimation within 24 hours of the onset of chest pain.

Patients' blood samples were collected into tubes for malondialdehyde (MDA), iNOS, and total sialic acid (TSA) measurements and centrifuged at 4000 g, 4 °C for 10 min, and the sera obtained as a result were kept at -25 °C until the analyses were carried out. MDA, an end-product of lipid peroxidation, was measured using the method described by Yoshioka et al. (10) based on the reaction between thiobarbituric acid and MDA. The optical density of the end products was measured at 535 nm. iNOS activity was evaluated using the method described by Miranda et al. (11). Accordingly, nitrate was reduced to nitrite by $VaCl_3$ and then reacted with sulfanilamide in an acidic environment to produce a colored diazonium compound, the optical density of which was measured at 540 nm. TSA was measured colorimetrically based on the method described by Sydow (12) using a spectrophotometer (UV-1201, Shimadzu, Japan). Accordingly, all bound sialic acid was separated using perchloric acid in serum, and the supernatants were boiled by Ehrlich's reagent. The optical density of the product was measured at 525 nm (12). Among the cardiac markers, human cardiac troponin-I (cTn-I) and iNOS were measured using commercial enzyme-linked immunoassay (ELISA) kits (Elabscience Biotechnology, Beijing, China), and homocysteine was measured using a spectrophotometer (Epoch, Biotech, USA) and another commercial ELISA kit (ELK Biotechnology, Wuhan, China).

Data Collection

Complete blood counts and biochemical test results were retrospectively obtained from intravenous blood samples before coronary angiography. Blood samples were collected from patients after 12 hours of fasting in the morning. Standard methods were used for routine biochemical tests, including lipid profile, glucose, urea, and creatinine measurements. Sialic acid was estimated spectrophotometrically using thiobarbituric acid, as described by Aminoff (13). Plasma samples of 10 µL were reacted with a strong acid, i.e., periodate reagent (25 mM periodate in 0.125 N H_2SO_4), to release sialic acid. Excess periodate reagent was reduced using sodium arsenite

solution (2% sodium arsenite in 0.5 N HCl). 2 mL of thiobarturic acid solution (0.1 M thiobarturic acid in 1 N NaOH) was added to the resulting mixture, incubated for 8 min. in boiling water bath, and then cooled in ice. The resulting colored complex was extracted by acid butanol (butanol in 5% HCl), and its optical density was measured at 549 nm.

Angiographic Analysis

Coronary angiography was performed using the standard Judkins technique without nitroglycerin (Siemens Medical Solutions, Erlangen, Germany). Two experienced physicians who were blinded to the study evaluated the angiograms, and the visually smooth contours with no wall irregularities were considered normal.

All patients underwent coronary angiography for ACS via the femoral artery within 90 minutes of hospital admission. Patients with STEMI were administered 300 mg of acetylsalicylic acid and 180 mg of oral loading ticagrelor at admission. Patients who could not be administered ticagrelor were given a 300-600 mg oral clopidogrel loading dose according to the myocardial revascularization guidelines of the European Society of Cardiology instead of ticagrelor (14,15). Standard intravenous bolus unfractionated heparin (70-100 U/kg) and additional doses were administered as needed to achieve an activating clotting time of >250 s before coronary intervention. Stenting of the infarct-related artery with drug-eluting stent was successfully completed immediately after coronary angiography in suitable patients.

The study protocol was approved by the Local Ethics Committee (Ethics Committee of the Deanery of the Faculty of Medicine of Kafkas University; approval no. 80576354-050-99/83, approval date: 08/06/2023).

Statistical Analysis

The SPSS 22.0 (Statistical Product and Service Solutions for Windows, Version 22.0, IBM Corp., Armonk, NY, U.S., 2013) software package was used for statistical analyses. The descriptive statistics obtained from the collected data were expressed as mean ± standard deviation for continuous variables determined to conform to the normal distribution, as median with 0.25 and 0.75 quantiles for continuous variables determined not to conform to the normal distribution, and as percentage values for categorical variables. The t-test or Mann-Whitney U test was used to compare continuous variables between the groups, whereas Fisher's exact test or the chi-square test was used to compare categorical variables between the

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groups. Univariate Cox proportional hazards analyses were conducted for all clinically relevant variables that could potentially predict MINOCA. Multivariate Cox regression analysis of variables found to be significant in univariate analyses was performed with stepwise backward conditional elimination to determine independent predictors of MINOCA (p<0.05). The receiver operating characteristic curve analysis was used to determine the optimal iNOS cut-off value for predicting MINOCA.

Results

The baseline demographic and laboratory characteristics of patients are presented in Table 1. The study sample consisted of 648 patients, including 477 with ACS and 171 with MINOCA. The mean age of the study population, of which 421 (65.6%) were male, was 62±12 years. There were no significant differences between the ACS and MINOCA groups in terms of hypertension, lymphocyte and eosinophil counts, total cholesterol, C-reactive protein, homocysteine, and MDA levels. Platelet and lymphocyte counts were significantly higher in patients with MINOCA, whereas hemoglobin levels and neutrophil and monocyte counts were significantly higher in patients with ACS. High-density lipoprotein cholesterol (HDL-c) and triglyceride levels were significantly lower and low-density lipoprotein cholesterol (LDL-c) was significantly higher in patients with ACS than in those with MINOCA. Among the renal parameters investigated within the scope of the study, urea and creatine levels were significantly higher in patients with ACS than in those with MINOCA. Troponin levels were also significantly higher in patients with ACS than in those with MINOCA. On the other hand, iNOS activity and TSA levels were significantly higher in patients with MINOCA than in those with ACS.

Table 1. Distribution of patients' baseline characteristics and laboratory test results among the study groups							
	ACS group (n=477)		MINOCA group (n=171)		Overall study group (n=648)		p-value
Age (years)	63	±12	60	±11	62	±12	**0.017**
Sex, n (%) (male) (mean)	352	74.7	69	40.4	421	65.6	**<0.001**
Smoking status, n (%), (mean)	213	46.6	51	29.8	264	42	**<0.001**
Presence of DM, n (%) (mean)	176	38	40	23.4	216	34.1	**0.001**
Presence of HT, n (%) (mean)	285	61.4	90	53.3	375	59.2	0.065
EF (%) (mean)	56	±10	61	±7	58	±9	**<0.001**
Hemoglobin level (g/dL) (mean)	14.11	±1.94	13.3	±2.1	13.91	±1.98	**<0.001**
Platelet count (10³/mL) (mean)	229	±62	243	±67	233	±64	**0.007**
Neutrophil count (10³/mL) (median)	6.7	(5.02-8.89)	4.60	(3.6-6)	6.1	(4.4-8.3)	**<0.001**
Lymphocyte count (10³/mL) (median)	1.87	(1.3-2.59)	2.17	(1.5-2.9)	1.91	(1.4-2.7)	0.005
Eosinophil count (10³/mL) (median)	0.12	(0.1-0.2)	0.14	(0.1-0.2)	0.12	(0.1-0.2)	0.134
Monocyte count (10³/mL) (median)	0.56	(0.4-0.7)	0.48	(0.37-0.63)	0.5	(0.4-0.7)	**0.001**
Glucose level (mg/dL) (median)	132	(107-169)	103	(95-128)	121.5	(101.5-158)	**<0.001**
Total cholesterol level (mg/dL) (mean)	178.02	±47.68	179.39	±50.98	178.38	±48.54	0.407
LDLC level (mg/dL) (mean)	115.7	±40.5	107.5	±38.3	113.5	±40	**0.033**
HDLC level (mg/dL) (mean)	42	±10	49	±12	43	±11	**<0.001**
Triglyceride level (mg/dL) (median)	92	(59-139)	107	(75-163)	95	(63-147)	**0.002**
Troponin level (ng/dL) (median)	712.9	(109.4-3657.8)	90.1	(26.4-492.9)	401	(58.7-2345)	**<0.001**
Urea level (mg/dL) (median)	37	(39-40)	34	(28-44)	36	(29-47)	**0.008**
Creatine level (mg/dL) (median)	0.94	(0.82-1.12)	0.85	(0-73-1.07)	0.93	(0.78-1.12)	**<0.001**
CRP level (mg/dL) (median)	5.5	(2.71-12.3)	5.51	(2.8-13.3)	5.51	(2.72-12.17)	0.661
Homocysteine level (µmol/L) (mean)	13.65	±2.47	13.37	±6	13.58	±3.73	0.329
iNOS level (pg/mL) (median)	792.6	(692.7-928.6)	2036.8	(1756.8-2394.3)	893.4	(723.9-1637.05)	**<0.001**
TSA level (mg/dL) (median)	84.2	(76.2-96.4)	93.7	(81.9-136.4)	86.7	(77.2-98.95)	**<0.001**
MDA level (µmol/L) (mean)	26.8	5.9	27.5	5.9	27	5.9	0.191

ACS: Acute coronary syndrome, MINOCA: Myocardial infarction with non-obstructive coronary artery disease, DM: Diabetes mellitus, HT: Hypertension, EF: Ejection fraction, LDLC: Low-density lipoprotein-cholesterol, HDLC: High-density lipoprotein-cholesterol, CRP: C-reactive protein, iNOS: Inducible nitric oxide synthase, TSA: Total sialic acid, MDA: Malondialdehyde

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Univariate logistic regression analysis revealed significant correlations between sex, age, diabetes mellitus (DM), glucose, urea, iNOS, smoking, hemoglobin, platelets, lymphocytes, monocytes, neutrophils, triglycerides, LDL-c, HDL-c, creatine, and total sialic acid (TSA) as significant predictors of MINOCA (Table 2). Further analysis of these variables with the multivariate logistic regression analysis revealed gender [odds ratio (OR): 0.107, 95% confidence interval (CI): 0.030-0.388; p=0.001], age (OR: 0.940, 95% CI: 0.893-0.990; p=0.002), presence of DM (OR: 0.183, 95% CI: 0.049-0.681; p=0.011), glucose (OR: 0.988, 95% CI: 0.977-1.000; p=0.045), urea (OR: 1.028, 95% CI: 1.000-1.057; p=0.049) levels, and iNOS (OR: 1.010, 95% CI: 1.007-1.013; p<0.001) as independent predictors of MINOCA (Table 2).

The optimal iNOS cut-off value of >1372.9 pg/mL predicted MINOCA with 99.4% sensitivity and 93.7% specificity [AUC: 0.99 (95% CI: 0.979-0.996, p<0.001)] (Figure 1).

Discussion

Several studies have investigated the role of nitric oxide in ACS, with a particular focus on its impact on vascular function, plaque stability, and thrombosis. This study examined the use of iNOS activity in the differential diagnosis of ACS and MINOCA for the first time in the literature. Accordingly, the primary outcome of this study was that iNOS levels were significantly higher in patients

with MINOCA than in those with ACS, whereas the secondary outcome was that an optimal iNOS cut-off value of >1372.9 predicted MINOCA with 99.4% sensitivity and 93.7% specificity.
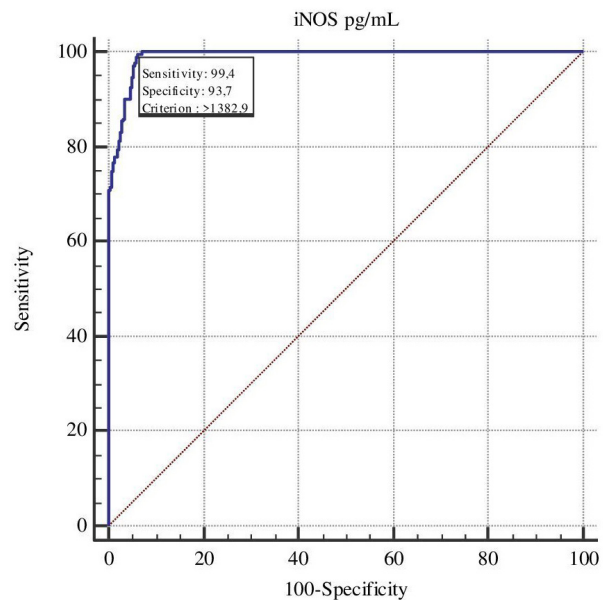
Figure 1. Receiver operating characteristic curve analysis of the efficacy of using iNOS activity to predict MINOCA

iNOS: Inducible nitric oxide synthase, MINOCA: Myocardial infarction with non-obstructive coronary arteries

Table 2. Results of univariate and multivariate models for predicting MINOCA in patients with ACS					
	Univariate			**Multivariate**	
	Univariate OR, 95% CI		**p**	**Multivariate OR, 95% CI**		**p**
Gender	0.224	(0.155-0.324)	**<0.001**	0.107	(0.030-0.388)	**0.001**
Age	0.981	(0.966-0.996)	**0.014**	0.940	(0.893-0.990)	**0.020**
Diabetes mellitus	0.498	(0.334-0.743)	**0.001**	0.183	(0.049-0.681)	**0.011**
Glucose	0.987	(0.982-0.992)	**<0.001**	0.988	(0.977-1.000)	**0.045**
Urea	0.993	(0.984-1.003)	0.166	1.028	(1.000-1.057)	**0.049**
iNOS	1.008	(1.006-1.010)	**<0.001**	1.010	(1.007-1.013)	**<0.001**
Smoking	0.558	(0.152-0.046)	0.378	-	-	-
Hemoglobin	1.000	(0.995-1.004)	0.959	-	-	-
Platelet	0.994	(0.984-1.004)	0.230	-	-	-
Lymphocyte	0.940	(0.534-1.652)	0.829	-	-	-
Monocyte	1.440	(0.263-7.897)	0.674	-	-	-
Neutrophil	0.972	(0.825-1.144)	0.732	-	-	-
Triglyceride	1.003	(0.995-1.011)	0.472	-	-	-
LDL-c	1.000	(1.000-1.000)	0.851	-	-	-
HDL-c	1.018	(0.963-1.075)	0.530	-	-	-
Creatine	1.447	(0.565-3.707)	0.441	-	-	-
TSA	0.996	(0.991-1.002)	0.184	-	-	-

ACS: Acute coronary syndrome, MINOCA: Myocardial infarction with non-obstructive coronary artery disease, iNOS: Inducible nitric oxide synthase, OR: Odds ratio, CI: Confidence interval, LDL-c: Low-density lipoprotein cholesterol, HDL-c: High-density lipoprotein-cholesterol, TSA: Total sialic acid

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NO levels can be relevant in ACS as nitric oxide plays a crucial role in regulating blood vessel function and blood flow. NO helps dilate blood vessels, thereby improving blood flow and reducing heart workload. However, the production and availability of NO may be impaired in ACS (16). Additionally, oxidative stress and inflammation, which are prevalent in ACS, may also negatively affect NO levels. Oxidative stress can decrease the availability of NO by promoting its reaction with reactive oxygen species, leading to the formation of peroxynitrite, a potent oxidant that further damages the endothelium (17). Decreases in NO levels during ACS may contribute to vasoconstriction, platelet aggregation, and inflammation, all of which are factors associated with disease progression. Given the complex nature of the relationship between NO and ACS, variations may occur in individual cases. Consultation with medical professionals is essential for the accurate diagnosis, treatment, and management of ACS (16-19).

In an animal model, it was demonstrated that the cytokine-mediated overexpression of iNOS was followed by massive NO production, which caused toxic effects on cardiomyocytes, including necrosis and reduced adenosine triphosphate (ATP) content (20). This can be achieved by direct action on the myocardium during ischemia-reperfusion (21). Yang et al. (22) demonstrated another effect of iNOS expression in patients with myocardial infarction. iNOS is not expressed in the healthy heart, and its formation is induced by pro-inflammatory factors (23). Expression of constitutive isoform eNOS decreased in ACS patients' neutrophils compared to healthy control subjects. In contrast, iNOS enzyme expression was markedly induced in acute myocardial infarction (24). This finding can be attributed to the possible action of cytokines released during ACS, stimulating iNOS expression and downregulating eNOS (19). El-Baheie et al. (25) reported that iNOS mRNA concentrations were significantly higher in patients with ACS than in healthy controls, and iNOS mRNA concentrations predicted ACS with 100% sensitivity and specificity. In parallel, this study emphasizes the estimation of iNOS mRNA expression as a highly sensitive and specific assay for ACS diagnosis compared with cardiac troponin. High iNOS expression in peripheral blood leukocytes of children affected by acute Kawasaki disease has been reported in the cardiovascular system (26), especially when associated with progressive coronary artery lesions (27). Comparable results have been reported in cases of dilated cardiomyopathy, ischemic and valvular disease, and ischemic disease-related HF (28).

Coronary microvascular dysfunction, which is expressed by coronary microvascular spasm, accounts for approximately 20% of MINOCA patients (29). Oxidative stress, endothelial dysfunction, and low-grade chronic inflammation contribute to the pathogenesis of coronary artery spasm. Yamada et al. suggested that thiol oxidation-induced oxidative stress causes coronary artery spasm, resulting in impaired endothelium-dependent vasodilation. The underlying mechanism of coronary vasomotor dysfunction may be endothelium-dependent or endothelium-independent. Endothelium-dependent dysfunction originates from an imbalance between endothelium-derived relaxing factors, such as NO, and endothelium-derived constrictors, such as endothelin. Endothelium-independent function is based on myocyte tone. Oxidative stress can cause vasoconstriction and endothelial damage, resulting in coronary microvascular dysfunction and vasospasm, leading to the pathogenesis of MINOCA. Although animal and human studies have provided evidence of the role of oxidative stress in cardiovascular disorders, antioxidant applications are ineffective in preventing cardiovascular mortality.

Studies have shown that serum total sialic acid levels are elevated in cardiovascular diseases due to an increase in acute-phase reactants in these patients. Elevated sialic acid levels may be attributed to scattering or secretion from damaged cells following acute myocardial infarction. Although the role of sialic acid in the pathogenesis of atherosclerosis has been investigated in many studies, its role as a prognostic marker has not been investigated yet (30). A large-scale prospective study reported that high serum sialic acid content was a strong predictor of cardiovascular mortality (31). Serum total sialic acid levels were significantly higher in patients with ACS than in healthy controls. Serdar et al. (32) found that total sialic acid levels progressively increased significantly in patients with unstable angina, NSTEMI, and STEMI. Interestingly, in our study, TSA levels were significantly higher in patients with MINOCA than in those with ACS, as in iNOS. The fact that TSA and iNOS levels have not been compared to date in patients with ACS and MINOCA in the literature makes this finding even more valuable. However, further studies with larger populations are needed to confirm the findings of this study.

In line with the literature data (33), the ACS patients included in this study mostly consisted of female and older patients. Factors such as smoking status, presence of DM, and dyslipidemia, which were reported to increase the risk

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of ACS in the literature (33), were also more common in the ACS patients included in this study.

The criteria for an ideal biomarker include its role in diagnosis and screening, as well as its ability to influence therapy and improve patient outcomes. In clinical practice, physicians rely on available biomarkers to support the diagnosis of ACS, including creatine phosphokinase and creatine kinase myoglobin binding tests. However, the positivity of both MINOCA and ACS patients for these markers renders differential diagnosis impossible without coronary angiography. To the best of our knowledge, no previous study has evaluated the efficacy of iNOS activity in the differential diagnosis of MINOCA and ACS. The findings of this study indicate that iNOS activity can be effectively used as a biomarker to differentiate between patients with ACS and those with MINOCA indistinguishable from cardiac biomarkers. Evaluation of iNOS activity can be routinely performed in daily clinical practice because it is feasible, cost-effective, and easy to perform. The results of the iNOS activity evaluation can be made available within 3-4 hours after the collection of blood samples. Moreover, the clinical efficacy of iNOS as a cardiac marker may be further enhanced if it is associated with a therapeutic target, as it can help tailor the therapeutic strategy, allowing the treatment to be personalized.

Study Limitations

There are several limitations to this study. First, this was a single-center, retrospective study with a relatively small sample size. Second, the fact that both ACS and MINOCA feature dynamic and rapidly evolving clinical situations may potentially hinder the generalizability of our findings. As a reason, this study was designed to evaluate iNOS activity as a biomarker in the differential diagnosis of ACS and MINOCA; however, iNOS activity is likely to change during the course of both ACS and MINOCA and due to therapeutic interventions, and the collected research data feature measurements performed in each individual at a single time point. Therefore, although it was possible to examine the correlations that exist between these parameters in this study, our findings did not provide much evidence on the dynamics of the system and how ACS, MINOCA, and therapeutic interventions might have affected these correlations.

Conclusion

In conclusion, iNOS activity may help distinguish between ACS and MINOCA without the need for coronary angiography. However, the mean iNOS levels of patients with ACS may vary depending on the study and patient populations investigated in these studies as well as the measurement techniques used. Therefore, further large-scale studies are needed to corroborate the findings of this study in general and to elucidate the role of oxidative stress in ACS and MINOCA.

Ethics

Ethics Committee Approval: The study protocol was approved by the Local Ethics Committee (Ethics Committee of the Deanery of the Faculty of Medicine of Kafkas University; approval no. 80576354-050-99/83, approval date: 08/06/2023).

Informed Consent: Informed consent was obtained from all patients.

Authorship Contributions

Concept: M.K., M.Ö., İ.R., M.A., Design: M.K., M.Ö., İ.R., M.A., Data Collection or Processing: İ.A., T.O., A.A., Z.Ç., Analysis or Interpretation: Y.K., D.İ., Drafting Manuscript: M.Ö., İ.A., T.O., A.A., Z.Ç., M.K., Critical Revision of Manuscript: İ.R., M.K., D.İ., M.A., Y.K., Final Approval and Accountability: M.K., M.Ö., İ.A., T.O., D.İ., A.A., Z.Ç., M.A., Y.K., İ.R., Writing: M.K., M.Ö., İ.A., T.O., D.İ., A.A., Z.Ç., M.A., Y.K., İ.R.

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ORIGINAL RESEARCH

The Effect of Digital Parenting Awareness on Problemic Media Use by Primary School Children

Dijital Ebeveynlik Farkındalığının İlkokul Çocuklarında Problemli Medya Kullanımına Etkisi

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Abstract

Objective: To examine the impact of digital parenting awareness (DPA) levels on problematic media use (PMU) among children.

Method: This cross-sectional study was conducted with children between the ages of 7-11 who admitted to the family medicine outpatient clinic of a tertiary hospital between 09.06.2022 and 08.12.2022, and met the inclusion criteria for themselves and their parents. Data were obtained through the Patient Information Form, Digital Parenting Awareness Scale (DPAS), and Problematic Media Use Measure-Short Form (PMUM-SF) administered to the parents.

Results: A total of 301 children, with an average age of 8.21±1.13 years and 174 (57.8%) girls, were included in the study. Most children had access to televisions (80.1%), mobile phones (67.4%), and tablets (34.6%) during the day. The percentage of those who spent ≥5 hours in front of the screen was 3.7% on weekdays and 14.6% on weekends. The mean PMUM-SF score was 17.37±7.40. The mean scores were 7.25±2.41 for Being Negative Model (NM), 9.05±3.34 for Digital Negligence (DN), 15.96±3.29 for Efficient Use (EU) and 15.09±3.61 for Protection From Risks (PR). There was a positive relationship between PMU, NM, and DN, but a negative relationship between EU and PR (p<0.001 for all). There were significant differences in gender, academic performance, weekday and weekend screen time, and PMUM-SF score (p=0.006; p<0.001; p<0.001; p<0.01, respectively). There was a significant relationship between the duration of weekday and weekend screen time and all subdimensions of DPAS (p<0.05 for all).

Conclusion: Although the DPA was moderate to good in parents, the PMU level was low in children. The PMU increased as the DPA decreased. PMU was higher among male students, those with low academic performance, and those who spent more time in front of screens. Children of parents with low DPA duration had increased screen time.

Keywords: Awareness, digital parenting, problematic media use, screen time

Öz

Amaç: Bu çalışmada; dijital ebeveynlik farkındalığı (DEF) düzeyinin çocuklarda problemli medya kullanımı (PMK) üzerine etkisinin incelenmesi amaçlandı.

Yöntem: Bu kesitsel çalışma, üçüncü basamak bir hastanenin aile hekimliği polikliniğine 09.06.2022-08.12.2022 tarihleri arasında başvuran, kendileri ve ebeveynleri çalışmaya dahil etme kriterlerini karşılayan 7-11 yaş arası çocuklar ile gerçekleştirildi. Veriler; hasta bilgi formu, Dijital Ebevenlik Farkındalık Ölçeği (DEFÖ) ve Problemli Medya Kullanım Ölçeği-Kısa Formu'nun (PMKÖ-KF) ebeveynlere uygulanması ile elde edildi.

Bulgular: Çalışmaya yaş ortalaması 8,21±1,13 yıl olan ve 174'ü (%57,8) kız olan toplam 301 çocuk dahil edildi. Çocukların gün içerisinde en çok televizyona (%80,1), cep telefonuna (%67,4) ve tablete (%34,6) erişimi vardı. Ekran başında ≥5 saat zaman geçirenlerin oranı hafta içi %3,7 iken hafta sonu %14,6 idi. PMKÖ-KF puanı ortalama 17,37±7,40 idi. DEFÖ alt boyut puan ortalamaları Olumsuz Model Olma (OMO) için 7,25±2,41, Dijital İhmal (Dİ) için 9,05±3,34, Verimli Kullanım (VK) için 15,96±3,29 ve Risklerden Korunma (RK) için 15,09±3,61 idi. PMK ile OMO ve Dİ arasında pozitif yönlü; VK ve RK arasında negatif yönlü anlamlı korelasyon vardı (hepsi için p=0,001). Cinsiyet, okul başarısı, çocuğun hafta içi ve hafta sonu ekran karşısında geçirdiği süre ile PMKÖ-KF puanı açısından anlamlı farklılık bulundu (p=0,006; p=0,001; p=0,001; p=0,01 sırasıyla). Çocuğun ekran karşısında geçirdiği süreler ile DEFÖ'nün tüm alt boyutları arasında anlamlı ilişki vardı (hepsi için p<0,05).

Sonuç: Ebeveynlerde DEF orta-iyi düzeyde iken çocuklarda PMK düzeyi düşük bulundu. DEF azaldıkça PMK artmakta idi. Erkeklerde, okul başarısı düşüklerde ve ekran karşısında uzun süre geçirenlerde PMK daha fazla idi. DEF düzeyi düşük olanların çocuklarında ekran süresi artmaktaydı.

Anahtar kelimeler: Dijital ebeveynlik, ekran süresi, farkındalık, problemli medya kullanımı

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Introduction

The internet, smartphones, tablets, television, radio, newspapers, and magazines are the most widely used media tools in mass communication (1). With the digitalization and easy accessibility of media tools, especially smartphones and tablets, their use by children is increasing (2,3).

When used consciously and appropriately, media tools are beneficial for child mental development and education (4-6). However, misuse of media tools can lead to many negative consequences. Problematic media use (PMU) is defined as excessive or improper use of media that causes problems in functionality (7). PMU paves the way for internet, television, smartphone, and digital game addiction (8). As exposure to digital media tools increases, physical problems, such as obesity and musculoskeletal disorders, as well as neuropsychiatric problems, such as sleep disorders, anxiety disorders, depression, attention deficit, and hyperactivity, may occur in children (9-11). Studies have also demonstrated that as PMU increases, academic achievement decreases in children (11-13). Therefore, for individuals aged 6 years and older, the American Academy of Pediatrics recommends reducing screen exposure as much as possible and having a strategy for managing electronic media to maximize its benefits (14).

To prevent PMU and its negative effects on children, parents must increase their awareness and ensure the efficient and safe use of media tools (15). "Digital parenting" is defined as parents being aware of the risks as well as the benefits of digital technologies, ensuring controlled use, and being a positive role model (16). High awareness of digital parenting contributes to children's development and academic success in relation to cognitive, mathematical, and thinking skills and protects children from negative consequences (17).

In this study, we aimed to examine the effect of digital parenting awareness (DPA) on PMU by children aged between 7 and 11.

Materials and Methods

Study Design

This study was planned as a single-center and, cross-sectional research. This study was conducted on children aged 7-11 years who were admitted to the family medicine outpatient clinic of a tertiary hospital between June 9 and December 12, 2022, and met the inclusion criteria for themselves and their parents.

The children and their parents who were included in the study did not have any severe psychiatric illness or communication barriers, such as hearing and speech disorders or cognitive dysfunction. Their parents consented to their participation in the study. Participants' parents were informed in detail, and verbal and written consent was obtained. All procedures were carried out in accordance with the Declaration of Helsinki. The study was approved by the Local Ethics Committee of University of Health Sciences Turkey, Gaziosmanpaşa Training and Research Hospital (date: June 8, 2022, no: 90).

Data Collection Tools

Data were collected from the parents through the administration of the patient information form, Digital Parenting Awareness Scale (DPAS), and Problematic Media Use Measure-Short Form (PMUM-SF).

Patient Information Form

The form, which was prepared by us and expected to be answered by the parents, included items that question the socio-demographic characteristics of the child (age, gender, number of siblings, school achievement), socio-demographic characteristics of the parents (age, education, and income status), and characteristics related to screen exposure (media tools used by the child and parents and frequency, etc.).

PMUM-SF

The scale, developed by Domoff et al. (7) in 2019 to investigate PMU in children aged 4-11 years, has a 27-item long form and a 9-item short form. The Turkish validity and reliability study of the long and short forms of the scales was conducted by Furuncu and Öztürk (8) in 2019. PMUM-SF has a single-factor structure and is scored on a 5-point Likert type (1= Never, 5= Always). The total PMUM-SF score was obtained by averaging the scores for all items. High scores on the scale indicate high PMU. Cronbach's alpha value for the short form of the scale is 0.93 (8).

DPAS

The DPAS, developed by Manap and Durmuş (16) in 2020, comprises a total of 16 items and four sub-dimensions. The subdimensions are as follows; protection from risks (PR), efficient use (EU), negative model (NM), and digital negligence (DN). Parents were asked to rate how often they encountered each statement (1=Never, 5=Always). The subdimensions of the DPAS were evaluated independently of each other, and the scores obtained varied between 4 and 20. Higher scores in the PR and EU subdimensions indicate

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higher DPA levels, whereas higher scores in the NM and DN subdimensions indicate lower DPA levels. The Cronbach's alpha internal consistency coefficients of the DPAS ranged from 0.634 to 0.799 (16).

Statistical Analysis

The SPSS v.22.0 package was used for data analysis in this study. Descriptive data on the socio-demographic information of the participants were presented in the form of frequency tables. Kolmogorov-Smirnov and Shapiro-Wilk tests showed that the parameters did not conform to a normal distribution. In the comparison of quantitative data, the Kruskal-Wallis test was used for intergroup comparisons of the parameters, and Dunn's test was used to determine the group causing the difference. The Mann-Whitney U test was used to compare parameters between the two groups. Spearman's rho correlation analysis was used to examine the relationships among the parameters. Significant differences were evaluated at the p<0.05 level.

Results

This study included 301 children aged 7-11 years with a mean age of 8.21±1.13 years. One hundred and seventy-four of the children (57.8%) were female. Two hundred sixty (86.4%) of the data collection forms were completed by mothers and 41 (13.6%) by fathers. Table 1 shows the distribution of the socio-demographic characteristics of children and their parents.

Table 2 shows the characteristics of children's and their parents' screen exposure based on the parent's statement. Accordingly, children most frequently accessed televisions (80.1%), mobile phones (67.4%), and tablets (34.6%) during the day. The value seen in the table regarding children's mobile phone use only represents access during the day and does not indicate mobile phone ownership. It is likely that children have easier access to their parents' phones. A total of 39.2% of parents (n=118) stated that they had previously received information about screen exposure in their children (Table 2).

Table 1. Socio-demographic characteristics of children and their parents			
		Min-max	Mean ± SD (median)
Child's age		7-11	8.21±1.13 (8)
Maternal age (n=300)		24-51	37.01±4.93
Paternal age (n=297)		29-57	40.76±5.55
Number of siblings		1-8	1.64±1.02 (1)
		n	%
Child's gender	Female	174	57.8
	Male	127	42.2
School success	Weak	2	0.7
	Middle	34	11.3
	Good	139	46.2
	Very good	126	41.9
Maternal educational status	Literate	14	4.7
	Primary school	56	18.7
	Middle school	57	19.0
	High school	78	26.0
	University	95	31.7
Paternal educational status	Literate	6	2.0
	Primary school	56	18.9
	Middle school	54	18.2
	High school	99	33.3
	University	82	27.6
Income status	Low	62	20.6
	Moderate	186	61.8
	High	53	17.6

SD: Standard deviation

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Table 2. Characteristics of children and their parents' screen exposures

		n	%
Media tools that children can access during the day	Computer	49	16.3
	Television	241	80.1
	Tablet	104	34.6
	Mobile phone	203	67.4
	Game console	15	5
Media tools that the mothers could access during the day (n=300)	Computer	44	14.7
	Television	192	64
	Tablet	19	6.3
	Mobile phone	269	89.7
	Game console	3	1
Media tools that fathers can access during the day (n=297)	Computer	75	25.3
	Television	169	56.9
	Tablet	11	3.7
	Mobile phone	279	93.9
	Game console	4	1.3
Total screen exposure time on weekdays (hours)	None	6	2
	0-60 minutes	54	17.9
	1-2 hours	156	51.8
	3-4 hours	74	24.6
	5 hours or more	11	3.7
Mothers' total screen exposure time on weekdays (n=300)	None	9	3
	0-60 minutes	62	20.7
	1-2 hours	122	40.7
	3-4 hours	89	29.7
	5 hours or more	18	6
Fathers' total screen exposure time on weekdays (n=297)	None	16	5.4
	0-60 minutes	39	13.1
	1-2 hours	103	34.7
	3-4 hours	93	31.3
	5 hours or more	46	15.5
Total screen exposure time of children on weekends	None	7	2.3
	0-60 minutes	19	6.3
	1-2 hours	108	35.9
	3-4 hours	123	40.9
	5 hours or more	44	14.6
Mothers' total screen exposure time on weekend (n=300)	None	12	4
	0-60 minutes	37	12.3
	1-2 hours	109	36.3
	3-4 hours	107	35.7
	5 hours or more	35	11.7

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Table 2. continued

		n	%
Fathers' total screen exposure time on weekdays (n=297)	None	11	3.7
	0-60 minutes	33	11.1
	1-2 hours	71	23.9
	3-4 hours	127	42.8
	5 hours or more	55	18.5
Parental prior knowledge of screen exposure in children	Yes	118	39.2
	No	183	60.8
Sources of information (n=118)	Doctor/healthcare worker	34	28.8
	Media	49	41.5
	Social media	57	48.3
	Medical resources	31	26.3
	Other	24	20.3

Table 3. Descriptive information about the total and subdimension scores obtained from each scale

	Min-max	Mean ± SD	Median	Cronbach's alpha
DPAS				
Negative model	4-14	7.25±2.41	7	0.654
Digital negligence	4-20	9.05±3.34	9	0.818
Efficient use	5-20	15.96±3.29	16	0.792
Protection from risks	5-20	15.09±3.61	15	0.647
PMUM-SF	1-4.56	1.93±0.82	1.8	0.897

SD: Standard deviation, DPAS: Digital parenting awareness scale, PMUM-SF: Problematic media use measure-short form

Table 4. Correlations of the total and subdimension scores of the scales with various children's variables

		DPAS-NM	DPAS-DN	DPAS-EU	DPAS-PR	PMUM-SF
Age	r	-0.001	-0.033	0.023	-0.028	0.009
	p	0.984	0.565	0.697	0.624	0.872
Number of siblings	r	-0.044	0.042	-0.086	-0.095	0.120
	p	0.482	0.504	0.166	0.126	0.054
Maternal age	r	-0.033	0.152	-0.160	-0.134	0.097
	p	0.570	**0.008***	**0.005***	**0.020***	0.093
Paternal age	r	-0.090	0.141	-0.094	-0.094	0.089
	p	0.122	**0.015***	0.104	0.104	0.126

*: Spearman's rho correlation, DPAS: Digital parenting awareness scale, PMUM-SF: Problematic media use measure-short form, EU: Efficient use, NM: Negative model, DN: Digital negligence, PR: Protection from risks

Table 3 presents descriptive information about the total and subdimension scores of the DPAS and PMUM-SF. The mean PMUM-SF score was 17.37±7.40. The mean scores of the DPAS subscales were 7.25±2.41 for NM, 9.05±3.34 for DN, 15.96±3.29 for EU, and 15.09±3.61 for PR (Table 3).

There was a statistically significant correlation between the PMUM-SF score and the DPAS subscales of NM (r=0.304; p=0.001), DN (r=0.476; p=0.001), EU (r=-0,202; p=0.001) and PR (r=-0.344; p=0.001).

Tables 4 and 5 present the relationships between various variables and the total and subscale scores of the scales. There were significant differences in gender, academic performance, weekday and weekend screen time, and PMUM-SF score (p=0.006; p<0.001; p<0.001; p<0.01, respectively). There was a significant relationship between the duration of weekday and weekend screen exposure time and all subdimensions of DPAS (p<0.05 for all) (Table 5).

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Table 5. Correlations of the total and subdimension scores of the scales with variables of children and parents

		DPAS-NM	DPAS-DN	DPAS-EU	DPAS-PR	PMUM-SF
		Mean ± SD (median)	Mean ± SD (median)	Mean ± SD (median)	Mean ± SD (median)	Mean ± SD (median)
Child's gender	Female	7.16±2.27 (7)	8.9±3.27 (9)	15.95±3.3 (17)	15.31±3.48 (16)	1.82±0.78 (1.6)
	Male	7.36±2.59 (7)	9.25±3.43 (9)	15.98±3.3 (16)	14.79±3.78 (15)	2.08±0.85 (1.9)
	[1]p	0.771	0.467	0.923	0.273	**0.006***
School success	Middle	7.12±2.33 (7)	10.24±3.54 (11)	15.79±3.75 (16)	15.29±4.07 (16)	2.27±0.92 (2.4)
	Good	7.49±2.56 (7)	9.34±3.1 (9)	15.56±3.34 (16)	14.66±3.64 (15)	1.98±0.75 (1.9)
	Very good	7.01±2.25 (7)	8.37±3.38 (8)	16.48±3.09 (17)	15.56±3.42 (16)	1.76±0.82 (1.5)
	[2]p	0.337	**0.001***	0.074	0.099	**0.001***
Maternal educational status	Literate	7.14±2.63 (7)	8.29±2.16 (8)	16.14±3.61 (18)	15.36±4.27 (16)	1.87±0.64 (1.8)
	Primary sch.	6.73±2.49 (6)	8.66±3.72 (9)	16.61±3.52 (18)	16.09±3.57 (17)	1.89±0.84 (1.7)
	Middle sch.	7±2.29 (7)	9.21±2.86 (9)	15.6±3.57 (17)	14.96±3.58 (15)	1.82±0.68 (1.7)
	High school	7.5±2.5 (7)	9.14±3.91 (9)	15.62±3.45 (16)	14.81±4.02 (15)	2.05±0.98 (1.8)
	University	7.49±2.32 (7)	9.24±3.01 (9)	16.08±2.79 (16)	14.73±3.13 (15)	1.93±0.78 (1.8)
	[2]p	0.188	0.524	0.312	0.121	0.934
Paternal educational status	Literate	6.17±2.14 (6)	7.5±1.05 (8)	14.33±3.56 (14)	13.83±4.22 (14)	1.83±0.61 (1.8)
	Primary sch.	6.82±2.46 (6)	9.04±3.47 (9)	15.93±3.43 (17)	15.23±3.73 (16)	1.99±0.89 (1.8)
	Middle sch.	6.94±2.46 (7)	8.81±3.17 (9)	16.72±3.3 (18)	15.76±3.54 (16)	1.85±0.65 (1.7)
	High school	7.23±2.17 (7)	8.9±3.26 (8)	15.97±3.32 (16)	15.09±3.74 (16)	1.88±0.81 (1.7)
	University	7.87±2.59 (7)	9.45±3.6 (9)	15.59±3.09 (16)	14.71±3.39 (15)	1.95±0.86 (1.7)
	[2]p	0.059	0.651	0.119	0.422	0.970
Total screen exposure time on weekdays (hours)	None	5.5±1.64 (5)	5.67±1.51 (5)	18±3.16 (20)	17±3.95 (18)	1.35±0.41 (1.2)
	0-60 min.	6.94±2.37 (6)	8.11±2.88 (7)	16.76±2.97 (18)	15.76±3.58 (17)	1.59±0.54 (1.5)
	1-2 hours	7.02±2.3 (7)	8.74±2.89 (9)	16.08±3.16 (17)	15.29±3.41 (16)	1.88±0.77 (1.7)
	3-4 hours	8.14±2.46 (8)	10.5±4.02 (10)	15.18±3.59 (16)	14.15±3.88 (14)	2.24±0.86 (2.1)
	≥5 hours	6.91±2.74 (6)	10.09±3.36 (10)	14.55±3.39 (14)	14.18±3.46 (15)	2.54±1.39 (2)
	[2]p	**0.003***	**0.001***	**0.017***	**0.047***	**0.001***
Children's total screen exposure time on weekends	None	6.29±1.98 (5)	7.43±2.94 (7)	18.29±3.15 (20)	16.57±4.39 (19)	1.46±0.64 (1.2)
	0-60 min.	6.32±2.03 (6)	7.68±2.58 (8)	15.53±3.82 (17)	15.16±3.76 (16)	1.31±0.37 (1.1)
	1-2 hours	6.98±2.47 (7)	8.27±2.96 (8)	16.79±2.74 (18)	15.96±3.15 (16)	1.8±0.72 (1.7)
	3-4 hours	7.45±2.35 (7)	9.4±3.2 (9)	15.37±3.42 (16)	14.6±3.73 (15)	1.98±0.79 (1.8)
	≥5 hours	7.89±2.46 (8)	10.84±4.04 (10)	15.41±3.52 (16)	14.05±3.74 (15)	2.45±1 (2.2)
	[2]p	**0.042***	**0.001***	**0.004***	**0.013***	**0.001***
Knowledge of screen exposure in children	Yes	6.89±2.28 (6)	8.42±3.11 (8)	16.51±3.09 (17)	15.61±3.42 (16)	1.87±0.82 (1.7)
	No	7.48±2.47 (7)	9.46±3.42 (9)	15.61±3.38 (16)	14.75±3.7 (15)	1.97±0.83 (1.8)
	[1]p	**0.043***	**0.008***	**0.022***	0.053	0.231

[1]: Mann-Whitney U test, [2]: Kruskal-Wallis test, *: p<0.05, note: Two children with poor school achievement were excluded from the comparison. DPAS: Digital parenting awareness scale, PMUM-SF: Problematic media use measure-short form, EU: Efficient use, NM: Negative model, DN: Digital negligence, PR: Protection from risks

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Discussion

In this study, which aimed to investigate digital awareness in parents and examine its effect on PMU in children aged 7-11 years, it was found that parents' digital awareness was at a medium-good level and PMU in their children was at a low level. As DPA decreased among parents, PMU increased among children.

DPA can be examined in four subdimensions: "Being negative model", "digital neglicence", "efficient use" and "protection from risks" with the measurement tool developed by Manap and Durmuş (16). Parents with more NM and DN behaviors had lower DPA levels, whereas parents with more EU and PR behaviors had higher DPA levels (16). They also showed that parents with healthy family roles had fewer NM and DN behaviors but more EU and PR behaviors. Parents whose children had internet addiction reported more NM and DN behaviors and less EU and PR behaviors (18). In this thesis study, Arslan (19) showed that the higher the NM and DN behaviors in parents, the higher the level of PMU in children aged 4-11 years. PMU was found to be lower in children of parents with high RK behaviors (19). Similarly, in Coşkunalp's (20) study, it was shown that as the digital efficacy of parents decreased, the level of PMU increased in children aged 7-10 years.

In our study, PMU levels were higher in children of parents with more NM and DN behaviors, and PMU levels decreased as PR and EU behaviors increased. Our study is similar to the literature in this respect and emphasizes the importance of increasing the DPA and ensuring that they guide their children in the correct use of media tools.

The use of media tools can be influenced by various factors. It has been shown that children of different genders may prefer to use different media tools and that PMU behaviors are particularly high in boys (13,19,20). In another study, during the pandemic, no significant relationship was found between gender and PMU. Considering that the use of media tools increased in all segments of society during the pandemic period, this could have been an expected result (21). However, no significant difference was observed between gender variables and parents' digital awareness and competencies (19,20).

In our study, similar to the literature, no significant difference was found in DPA according to sex; however, the PMU was higher in boys. This may be because, in traditional families in our society, girls' use of media tools is more controlled. There is a need to raise DPA, regardless of gender, from PMU and to address its possible negative consequences.

The age of the child is another factor associated with the use of media tools (17,22). The duration of the use of media tools increases with an increase in the ability to use devices, especially in early childhood, and the use of social media and access to harmful content online increases in adolescence (23). However, Magis-Weinberg et al. (21) did not find a relationship between child age and PMU during the pandemic period. Studies explaining the relationship between child age and DPA are limited. Coşkunalp (20) observed that parents of older children had lower levels of digital efficacy.

In our study, no correlation was found between age and DPA and PMU. The age range of the children included in our study falls outside of early childhood and adolescence, which are examined in detail in terms of the use of media tools as mentioned above. Further research on different age groups should be conducted to contribute to the literature.

As parents get older, their restrictive behavior toward their children in terms of time and content in the use of media tools may decrease, and the tendency of screen addiction in children may increase (18,19,24). In contrast, a study showed that restrictive attitudes were more common in parents over the age of 40 (25). However, studies have not reported a significant relationship between parental age and PMU (19,20).

In our study, a relationship was found between parental age and DPA; PR behaviors increased, and DN levels decreased with increasing maternal age. This may be due to the difficulty in adapting to digital devices with advancing age and a low level of knowledge about possible risks. However, parents who are introduced to digital tools at a younger age may be more aware of the disadvantages of these tools.

Parents' digital awareness also differs according to socio-economic status. As parents' education and income levels increase, their digital parenting scores also increase (26). In Manap and Durmuş's (18) study, which was conducted in 2021, it was observed that parents with university degrees were more likely to exhibit NM behavior. In a study conducted by Akkaya et al. (27), it was observed that EU behavior increased with parental education level, but no significant relationship was found with income level. The level of PMU may also be affected by parental education level and income level (28).

In this study, no significant relationship was found between parental education level, income level, and PMU. However, low-income parents were less likely to engage in NM. This

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may be because access to digital media tools becomes more difficult as income declines.

With the increase in the duration of parents' media tool usage, there has been a corresponding rise in media tool usage among children, potentially leading to various physical and psychological issues (21,29,30). As parental smartphone use duration increased, NM and DN behaviors also increased (18). The levels of DPA and PR behaviors decreased as the parents' screen-use time increased, whereas NM and aggressive behaviors increased (27). In our study, PMU increased as the duration of using media tools increased among children. However, similar to the literature, it was observed that the parent's DPA subscales were negatively affected. PMU will become less common if parents impose acceptable limits on their own media use as well as their children's.

Study Limitations

This study has some limitations. First, due to the single-center and cross-sectional design of the study, the findings may not be generalized to the general population. Second, parents may have avoided giving correct answers to some of the questions because they fear being exposed to negative criticism. Contributions to the literature should continue with more comprehensive and multicenter studies.

Conclusion

In this study; PMU levels were found to be low in children aged 7-11 years, and their parents were observed to have moderate to good levels of DPA. As DPA decreases, PMU increases in children. Parents' digital awareness should be further increased and possible negative consequences should be prevented through timely intervention, especially for children at high risk of PMU.

Ethics

Ethics Committee Approval: The study was approved by the Local Ethics Committee of University of Health Sciences Turkey, Gaziosmanpaşa Training and Research Hospital (date: June 8, 2022, no: 90).

Informed Consent: Participants' parents were informed in detail, and verbal and written consent was obtained.

Authorship Contributions

Concept: E.E., S.T.K., O.B., Design: E.E., S.T.K., O.B., Data Collection or Processing: E.E., S.T.K., Analysis or Interpretation: E.E., S.T.K., Drafting Manuscript: S.T.K.,

Critical Revision of Manuscript: E.E., S.T.K., O.B., Final Approval and Accountability: E.E., S.T.K., O.B., Supervision: S.T.K., Writing: E.E., S.T.K., O.B.

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ORIGINAL RESEARCH

YouTube for Information on Childhood Constipation: Is It Reliable?

YouTube'da Çocukluk Çağı Kabızlığı Hakkındaki Bilgiler Güvenilir mi?

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Abstract

Objective: To determine the quality and reliability of videos obtained by searching the keywords "constipation in children" on YouTube.

Method: We obtained 73 videos by searching the keyword "constipation in children" on YouTube, which were evaluated and scored independently by two pediatricians using the scoring systems; "Global Quality Scale" and "quality criteria for consumer health information".

Results: When the mean scores of the viewers were evaluated, 54.8% of the videos were interpreted as poor, 13.7% as medium, and 31.5% as good quality according to "quality criteria for consumer health information" scoring, while 52.1% were interpreted as low, 19.2% as medium, and 28.7% as high quality according to "global quality scale" scoring. When video score ratings were compared with the duration, number of views, and likes of the videos, no significant relationship was found between the views of the videos and "quality criteria for consumer health information" and "global quality scale" scores of the first and second viewers (p=0.369, p=0.316, p=0.632, p=0.815 respectively). Similarly, no significant relationship was found between the number of likes and the "quality criteria for consumer health information" and "global quality scale" scores of the first and second viewers (p=0.367, p=0.407, p=0.645, p=0.931, respectively).

Conclusion: Most YouTube videos on childhood constipation are of very low quality, and the high number of views and likes does not correlate with high quality.

Keywords: Constipation, DISCERN, GQS, pediatrics, YouTube

Öz

Amaç: YouTube'da "çocuklarda konstipasyon" anahtar kelimeleri ile arama yapılarak elde edilen videoların kalite ve güvenilirliğini belirlemektir.

Yöntem: YouTube'da "çocuklarda kabızlık" anahtar kelimeleri ile arama yapılarak elde edilen 73 video, 2 bağımsız çocuk doktoru tarafından eş zamanlı olarak izlendi ve "küresel kalite ölçeği" ve "tüketici sağlık bilgileri için kalite kriterleri" puanlama sistemleri ile değerlendirildi.

Bulgular: İzleyicilerin ortalama puanları değerlendirildiğinde, videoların %54,8'i "tüketici sağlık bilgileri için kalite kriterleri" puanlamasına göre kötü, %13,7'si orta ve %31,5'i iyi kalite olarak yorumlanırken, "küresel kalite ölçeği" puanlamasına göre %52,1'i düşük, %19,2'si orta ve %28,7'si yüksek kalite olarak yorumlandı. Video puanları videoların süresi, izlenme sayısı ve beğenilme oranları ile karşılaştırıldığında, videoların izlenme oranları ile birinci ve ikinci izleyicilerin "tüketici sağlığı bilgileri için kalite kriterleri" ve "küresel kalite ölçeği" puanlamaları arasında anlamlı bir ilişki bulunmamıştır (sırasıyla p=0,369, p=0,316, p=0,632, p=0,815). Benzer şekilde, beğeni sayısı ile birinci ve ikinci izleyicilerin "tüketici sağlığı bilgileri için kalite kriterleri" ve "küresel kalite ölçeği" puanlamaları arasında anlamlı bir ilişki bulunmamıştır (sırasıyla p=0,367, p=0,407, p=0,645, p=0,931).

Sonuç: Çocukluk çağı kabızlığı ile ilgili YouTube videolarının çoğu çok düşük kalitededir ve yüksek görüntüleme ve beğeni sayısı yüksek kalite ile ilişkili değildir.

Anahtar kelimeler: DISCERN, GQS, kabızlık, pediyatri, YouTube

Introduction

Constipation is defined by the North American Society of Pediatric Gastroenterology (NASPGHAN) as uncomfortable difficulty or delay in defecation lasting ≥2 weeks and is one of the most common problems of childhood (1). Studies have shown that this condition affects 8.9% of the global pediatric population (2). Although factors such as metabolic and hormonal irregularities, cows' milk allergy, muscle tone, nervous system disorders, and medication use also play a role among the causes, the most common cause in children is functional constipation, and the Rome IV criteria are used for diagnosis (3). Because treatments generally include long-term approaches and lifestyle changes, parents are looking for alternative, fast-acting treatments, and with the increasing use of the internet, families frequently turn to the web for help.

According to a report investigating internet usage in the United States, 91.8% of the American public used the internet in 2023, and 23% of individuals between the ages of 25 and 34 using the internet in the United Kingdom are seeking health-related information (4,5). YouTube, a popular online video sharing and social media platform, has 118 million subscribers according to data shared in 2023, and approximately 65,000 new video clips are being added to the website daily by users, and nearly 100 million video clips are being watched (6,7).

There are numerous videos on YouTube about constipation, which is a common health problem in childhood. However, there are no previous studies regarding the reliability of these videos. Therefore, we aimed to evaluate the content of constipation videos on this widely used platform with objective and evidence-based information in terms of actuality and accuracy.

Materials and Methods

On a designated date, after clearing the search history, 73 videos on the YouTube platform, which were obtained by typing "constipation in children" in the search tab, were included in the study by calculating the simple random sample size among the videos with a view count of 10,000 or more and made in the last 5 years (with 95% reliability and 80% incidence rate). The videos were viewed by two independent pediatricians in separate locations within a week, and they were evaluated using two assessment tools. The evaluations were based on the latest ESPGHAN and NASPGHAN recommendations on functional constipation in childhood.

The duration of the selected videos, the number of views, comments, and likes, and whether the unloaders were health professionals or not were recorded. Videos containing advertisements, repetitive videos, videos that were irrelevant to the topic, and videos that were not in English were excluded from the study.

Open access modified DISCERN (quality criteria for consumer health information) and global quality scale (GQS) scores were used to determine the reliability of the videos.

Modified DISCERN Assessment Tool

The modified DISCERN assessment tool was used as a quality criterion measurement tool for measuring consumer health information. Based on 5 main items, the video is evaluated based on the clarity and comprehensibility of explanations, accessibility of references, balanced and unbiased information, indication of additional sources of information, and whether the video evaluates controversial or uncertain areas. It is stated that videos with a score below 3 should be ignored by patients (Table 1) (8).

GQS Assessment Tool

The GQS assessment tool is a GQS that rates videos with a minimum score of 1 and a maximum score of 5. Videos that are not useful for patients, are of low quality, and contain incomplete information receive 1 point; videos that are of limited benefit, low quality, and contain limited information receive 2 points; videos that are of moderate benefit and discuss only some important information receive 3 points; videos that are useful, have high-quality content and video flow, contain relevant information but do not cover some topics receive 4 points; very useful videos, of first-class quality, and cover all information receive 5 points; videos that score 1-2 points are considered low quality, 3 points are considered moderate quality, and 4-5 points are considered high quality (Table 2) (9).

No patients were included in the study. All of the scoring tools used in this study is freely accessible and do not require permission to use. The study was approved by

Table 1. Modified DISCERN assesment tool
Reliability of information (1 point for each yes, 0 points for each no)
The explanations given in the video are clear and understandable
Accessible and useful reference sources (publications, studies, etc.)
The information provided in the video is balanced and unbiased
Additional sources of information are mentioned
The video evaluates controversial or unclear information
≤2 points: Poor 3 points: Fair ≥4 points: Good

Medipol University Non-Invasive Clinical Research Ethics Committee of Medipol University (document number: E-43037191-604.01.01-12352).

Statistical Analysis

For normally distributed parameters, the independent samples t-test was used for comparisons between two groups, and the One-Way Analysis of Variance (ANOVA) test was used for comparisons between more than two groups. For non-normally distributed parameters, the Mann-Whitney U test was used for comparisons between two groups, and the Kruskal-Wallis test was used for comparisons of more than two groups. Pearson's chi-square test and Fisher's Exact chi-square test was used to compare categorical variables. The correlation between numerical variables was analyzed using Spearman's correlation coefficient. All analyses were performed in two-way and $p<0.05$ was considered statistically significant.

Results

We analyzed a total of 73 videos about constipation in children, which were released on the YouTube platform and in English.

When the contents of the videos were analyzed, 47.9% of the videos provided general information about constipation, 49.3% only mentioned treatment, and only 2.7% mentioned patient experiences (Figure 1). Forty-two videos (57.5%) were uploaded by health professionals, and 31 videos (42.5%) were uploaded by the community (Figure 2).

The average duration was 5.6±6.4 minutes, the average number of views was 182,505±433,060, and the average number of likes was 1.299±3.700. Since 14 videos were closed to comments, the average number of comments on the remaining 59 videos was 55.36±101.09, and the number of comments on the most commented videos was 513 (Table 3).

When the mean scores of the first and second viewers were evaluated, 54.8% of the videos were interpreted as
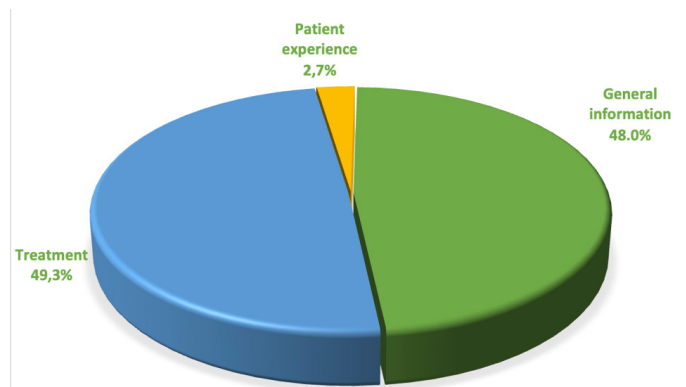
Figure 1. Video content
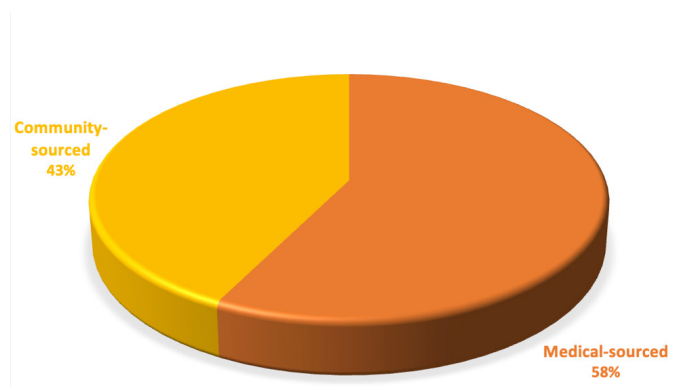
Figure 2. Evaluation of videos by source

Table 2. GQS assesment tool	
GQS	**Explanation**
1	Inadequate Poor and weak information flow.
2	Overall poor quality. Some information was verified but many important issues were omitted. Insufficient and limited information for the audience.
3	Average quality. Inadequate flow. Some important information was covered but many important issues and points were not adequately addressed.
4	Good quality overall. Covered a lot of important information but some topics and points were not covered. Useful for the audience.
5	High quality and streaming. Very useful by the audience.
Evaluation	**≤2 points: Low quality 3 points: Moderate quality ≥4 points: High quality**

GQS: Global quality scale

Table 3. Statistics on the number of views, duration, likes and comments of videos		
Video statistics	**Mean ± SD**	**Median (min-max)**
Number of views	182.505±433.060	68.000 (7.600-3.100.000)
Video duration, seconds	336.70±381.82	245 (42-3.056)
Number of likes	1.299±3.700	301 (0-27.000)
Number of comments	55.36±101.09	23 (0-513)

SD: Standard deviation

poor quality, 13.7% as medium quality, and 31.5% as good quality according to the DISCERN scoring, while 52.1% were interpreted as low quality, 19.2% as medium quality, and 28.7% as high quality according to the GQS scoring (Table 4).

The average DISCERN and GQS scores were significantly higher for videos uploaded by health professionals than those uploaded by the community (p<0.001). Of the videos from the community sources, 71.4% received the lowest score on the DISCERN scale and 71.5% received the lowest score on the GQS scale, and none of the videos were classified as good or high quality. In contrast, 54.9% of videos uploaded by healthcare professionals received a score of 4 or 5 on the DISCERN scale and 47.6% received a score of 4 or 5 on the GQS scale (Table 5).

Videos containing general information about constipation, such as definition and symptoms, had higher DISCERN and GQS scores. Videos that did not contain general information

and focused only on treatment or patient experiences had low DISCERN and GQS scores (Table 6).

When the relationship between the number of views of the videos and the score ratings was analyzed, no significant relationship was found between the average DISCERN score and the number of views (p=0.352), whereas videos with an average GQS score of 4 had the highest number of views (p=0.028).

Inter-rater reliability was assessed by comparing the ratings of two viewers, and Cohen's kappa coefficient was calculated for evaluation. It was found to be Κ=0.709 for DISCERN scoring and Κ=0.690 for GQS scoring, and it was considered sufficiently reliable.

When video score ratings were compared with the duration, number of views, and likes of the videos, a significant positive correlation was found between the DISCERN evaluation score of the first and second viewers and the duration of the video (r=0.261, r=0.242/p=0.026, p=0.039,

Table 4. Average score of two viewers for DISCERN and GQS

DISCERN	Number (n)	Frequency (%)	GQS	Number (n)	Frequency (%)
Poor	**40**	**54.8%**	**Low**	**38**	**52.1%**
1	28	38.4%	1	28	38.4%
2	12	16.4%	2	10	13.7%
Fair	**10**	**13.7%**	**Medium**	**14**	**19.2%**
3	10	13.7%	3	14	19.2%
Good	**23**	**31.5%**	**High**	**21**	**28.7%**
4	20	27.4%	4	16	21.9%
5	3	4.1%	5	5	6.8%
Total	**73**	**100.0%**	**Total**	**73**	**100.0%**

GQS: Global quality scale

Table 5. Comparison of mean DISCERN and GQS assessment scores by video source

	Medical sourced	Community sourced	p-value
Mean DISCERN **1**	3 (7.1%)	25 (71.4%)	**<0.001****
2	8 (19.0%)	4 (13.0%)	
3	8 (19.0%)	2 (6.6%)	
4	20 (47.8%)	0 (0%)	
5	3 (7.1%)	0 (0%)	
Mean GQS **1**	3 (7.1%)	25 (71.5%)	**<0.001****
2	7 (16.6%)	3 (9.7%)	
3	12 (28.6%)	2 (6.5%)	
4	15 (35.7%)	1 (3.3%)	
5	5 (11.9%)	0 (0%)	

GQS: Global quality scale, Pearson's chi-square test was used in the comparisons and significant p-values are indicated with ** sign

Table 6. Relationship between video content and average score points

		Video content			
		General information	Treatment	Patient experience	p-value
DISCERN-mean	1	1 (2.9%)	26 (72.2%)	1 (50%)	<0.001**
	2	7 (20%)	4 (11.1%)	1 (50%)	
	3	9 (25.7%)	1 (2.8%)	0 (0%)	
	4	16 (45.7%)	4 (11.1%)	0 (0%)	
	5	2 (5.7%)	1 (2.8%)	0 (0%)	
GQS-mean	1	1 (2.9%)	26 (72.2%)	1 (50%)	<0.001**
	2	6 (17.1%)	3 (8.3%)	1 (50%)	
	3	12 (34.3%)	2 (5.6%)	0 (0%)	
	4	12 (34.3%)	4 (11.1%)	0 (0%)	
	5	4 (11.4%)	1 (2.8%)	0 (0%)	

GQS: Global quality scale, percentages in parentheses indicate row percentages. Pearson's chi-square test was used in the comparisons and significant p-values are indicated by **

respectively). Furthermore, there was a significant positive correlation between the GQS rating score of the first viewer and the duration of the video (r=0.264, p=0.024), whereas there was no correlation between the GQS rating score of the second viewer.

No significant relationship was found between the views of the videos and DISCERN and GQS scores of the first and second viewers (p=0.369, p=0.316, p=0.632, p=0.815 respectively). Similarly, no significant relationship was found between the number of likes and DISCERN and GQS by the first and second viewers (p=0.367, p=0.407, p=0.645, p=0.931, respectively) (Table 7).

Discussion

With growing internet access, the frequency of patients and their caregivers using YouTube platforms to obtain information about health conditions and to seek remedies has increased (4,5). However, despite the rapid increase in access, no supervision is possible regarding the content of videos on YouTube and the accuracy and objectivity of the information provided. In our study, we aimed to evaluate the videos on YouTube about one of the common problems of childhood, constipation, using objective and evidence-based scales in terms of accurate information. As a result of this evaluation, the reliability of the videos was found to be quite low.

According to the DISCERN scale, 23 of the videos analyzed in our study were of high quality, 10 of medium quality, and 40 of low quality. According to the GQS scale, 21 of the samples were found to be high quality, 14 were found to be medium quality, and 38 were found to be low quality. In a previous study examining videos about enuresis nocturna

using GQS, it was shown that 58% of the videos were of low quality, 16% were of medium quality, and 26% were of high quality (10). In a study published by Pamukcu and Izci Duran (11), videos demonstrating anakinra self-injection were examined, and 43.1% of these videos were of high quality, 35.3% were of medium quality, and the mean DISCERN score was 49 and the GQS score was 3. This difference between studies may be due to the fact that the majority of the videos were published by medical personnel or doctors in the studies with higher quality videos. Differences in the quality of community-based videos may be interpreted as different degrees of knowledge of the community about different diseases.

In various studies investigating videos about the administration of Botox, fibromyalgia, spondyloarthritis, psoriatic arthritis, food poisoning, and anakinra injection, it was reported that the majority of videos were shared by health care professionals (11-19). In our study, it was determined that 42 videos (57.5%) were of medical origin, whereas 31 videos (42.5%) were of community origin, which is consistent with previous data.

Although videos uploaded by medical professionals are generally found to be of higher quality, it is possible that these videos are not of sufficient standard. Although most videos were uploaded by medical professionals, some studies have shown that the outcomes were inadequate (20). In the study by Toprak and Tokat (10), even though most of the videos were uploaded by healthcare professionals, the quality level was generally low. In our study, 71.4% of the videos that scored 1 point in DISCERN scoring were community-originated, whereas this rate was quite low in medical-originated videos (7.1%). Similarly,

Table 7. Correlation between the number of views, duration, likes, comments and video scores

		Number of views	Video duration (sec)	Number of likes	Number of comments	DISCERN 1st viewer	GQS 1st viewer	DISCERN 2nd viewer	GQS 2nd viewer
Number of views	r	1	-0.088	0.963**	0.757**	-0.107	-0.119	-0.057	-0.028
	p		0.457	<0.001	<0.001	0.369	0.316	0.632	0.815
	n	73	73	73	59	73	73	73	73
Video duration (sec)	r	-0.088	1	-0.052	0.063	0.261*	0.264*	0.242*	0.185
	p	0.457		0.659	0.638	0.026	0.024	0.039	0.118
	n	73	73	73	59	73	73	73	73
Number of likes	r	0.963**	-0.052	1	0.758**	-0.107	-0.098	-0.055	-0.01
	p	<0.001	0.659		<0.001	0.367	0.407	0.645	0.931
	n	73	73	73	59	73	73	73	73
Number of comments	r	0.757**	0.063	0.758**	1	-0.22	-0.216	-0.228	-0.184
	p	<0.001	0.638	<0.001		0.095	0.1	0.083	0.163
	n	59	59	59	59	59	59	59	59
DISCERN-1st viewer	r	-0.107	0.261*	-0.107	-0.22	1	0.970**	0.935**	0.885**
	p	0.369	0.026	0.367	0.095		<0.001	<0.001	<0.001
	n	73	73	73	59	73	73	73	73
GQS-1st viewer	r	-0.119	0.264*	-0.098	-0.216	0.970**	1	0.924**	0.885**
	p	0.316	0.024	0.407	0.1	<0.001		<0.001	<0.001
	n	73	73	73	59	73	73	73	73
DISCERN-2nd viewer	r	-0.057	0.242*	-0.055	-0.228	0.935**	0.924**	1	0.913**
	p	0.632	0.039	0.645	0.083	<0.001	<0.001		<0.001
	n	73	73	73	59	73	73	73	73
GQS-2nd viewer	r	-0.028	0.185	-0.01	-0.184	0.885**	0.885**	0.913**	1
	p	0.815	0.118	0.931	0.163	<0.001	<0.001	<0.001	
	n	73	73	73	59	73	73	73	73

r: Pearson correlation coefficient, p: Two-way significance value, n: Number of videos evaluated, DISCERN-1st viewer: DISCERN score according to 1st viewer, GQS-1st viewer: GQS score according to 1st viewer, DISCERN-2nd viewer: DISCERN score according to 2nd viewer, GQS-2nd viewer: GQS score according to 2nd viewer, GQS: Global quality scale

71.5% of the videos with a score of one in the GQS scoring were community-originated, whereas this rate was 7.1% in medically-originated videos. It was determined that the scores of the videos sourced from healthcare professionals were significantly higher. We found that 47.8% of the medically sourced videos were at a high level in the DISCERN scoring, and 35.7% were at a high level in the GQS scoring. Although medical-sourced videos scored significantly higher than community-sourced videos, the number of videos that received a full score in terms of quality was only 7.1% according to DISCERN and 11.9% according to GQS.

In a review investigating the consequences of obtaining health information over the internet on the doctor-patient relationship, Luo et al. (21) showed that poor quality internet information, especially when shorter doctor-patient times were included, decreases confidence in the doctor, suggesting that improving the quality of information on the internet may increase this trust. In such cases, improving the quality of videos may not only provide families with reliable information but also strengthen the doctor-patient relationship.

The videos included in our study were categorized into three groups according to content: General information,

treatment, and patient experience. Of the videos, 49.3% contained information on treatment, 48% on general information, and 2.7% on patient experience. Videos containing general information were significantly more likely to be categorized as good, whereas videos focusing on treatment or patient experiences had significantly lower DISCERN and GQS scores.

The evaluation of videos on YouTube within the community is determined by the number of likes, comments, and views. In this study, the mean number of views, likes, and comments of the videos was 182.505, 1299, and 55.36, respectively, and no significant correlation was found between the number of views, likes, and comments of the videos and the DISCERN and GQS scores of the first and second viewers. Similar results were reported in another study that evaluated YouTube videos on food poisoning. In a study by Li et al. (18), the number of likes and views was not found to be associated with video quality. Toprak and Tokat (10) also found that the number of video likes, views, and comments did not reflect video quality. The fact that the most liked, viewed, and commented videos did not receive high scores suggests that society may not be able to evaluate the quality of videos accurately enough, which is concerning.

In their study, Toprak and Tokat (10) found a positive correlation between video duration and GQS and DISCERN scores. This may be explained by the fact that as the video length increases, the amount of information contained tends to increase. In our study, a positive, moderately significant relationship was found between the DISCERN score and the duration of the video, and a positive, moderately significant relationship was found between the DISCERN score and the duration of the video in the evaluation of the second viewer; however, no difference was observed between the GQS score of the second viewer and the duration of the video.

In our study, in videos evaluated by two different physicians, inter-rater reliability was calculated using Cohen's kappa coefficient, and the agreement rates were 70.9% for DISCERN and 69% for GQS. There are conflicting reports on the results of reliability calculations. Landis and Koch (22) defined 0-20 as low, 0.21-0.40 as fair, 0.41-0.60 as moderate, 0.61-0.80 as adequate and 0.81-1.0 as excellent, but these interpretations could not be supported by sufficient scientific evidence. Fleiss (23) defined values above 0.75 as excellent, 0.40-0.75 as excellent, 0.40-0.75 as average, and below 0.40 as poor. Although our study was evaluated as adequate according to Landis and Koch (22) and average

according to Fleiss (23) these evaluations have a low level of scientific evidence, and similar rates have been found in other studies.

Our study is the first to evaluate videos about constipation, which is one of the most common problems in childhood, despite the increasing use of the internet for health information and the high number of viewings of health-related videos. Independent evaluation of the videos by two viewers at separate locations and the use of two scales increases the objectivity of our study.

Study Limitations

Our study has some limitations. First, since only English videos were included in our study, some social and geographical differences may not have been incorporated. In addition, since our study was conducted on videos from the last five years, we may have fallen behind in following the information on YouTube, which contains constantly changing data and has a high number of daily video uploads; thus, the results obtained may be evaluated in terms of a limited period.

Conclusion

This study showed that most YouTube videos on childhood constipation were of very low quality according to both DISCERN and GQS assessment tools. Furthermore, the high number of views and likes did not correlate with high quality, and the use of these videos for medical information is not recommended.

Ethics

Ethics Committee Approval: The study was approved by Medipol University Non-Invasive Clinical Research Ethics Committee of Medipol University (document number: E-43037191-604.01.01-12352).

Informed Consent: No patients were involved in the study.

Authorship Contributions

Surgical and Medical Practices: Y.E.Ö., R.T., A.Ö., Concept: Ö.B., Y.E.Ö., Ö.B.G., Design: Ö.B., Y.E.Ö., A.Ö., Data Collection or Processing: Ö.B., Y.E.Ö., Ö.B.G., A.Ö., Analysis or Interpretation: Y.E.Ö., Ö.B.G., R.T., Literature Search: Ö.B., Y.E.Ö., R.T., Writing: Ö.B., Y.E.Ö.

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

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ORIGINAL RESEARCH

Periprosthetic Fracture Literature Since 1990: A Bibliometric Analysis

1990'dan Beri Periprostetik Kırık Literatürü: Bibliyometrik Analiz

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Abstract

Objective: This study presents a comprehensive bibliometric analysis of the literature on periprosthetic fracture since 1990. The goal is to uncover prevalent themes, key authors, and geographical trends. Periprosthetic fractures are significant complications in patients undergoing geriatric arthroplasty. Although traditional literature reviews on this subject exist, bibliometric methods may uncover previously unseen trends and nuances that may have been overlooked.

Method: The Web of Science database was searched from January 1990 to December 2022, retrieved 2445 articles and reviews. Data were imported into CiteSpace and VOSviewer for keyword, authorship, citation burst analysis, and co-citation clustering.

Results: An exponential growth in periprosthetic fracture literature since the late 1990s was noted. The United States led in research output, followed by the United Kingdom and Germany. Prominent authors experiencing citation bursts included Lewallen, Berry, Duncan, Masri, and Abdel. Co-citation analysis revealed ten prominent clusters, with high silhouette values indicating strong thematic cohesion.

Conclusion: This study provides a holistic view of the evolution and current state of periprosthetic fracture research. The study highlights the United States of America, the United Kingdom, and Germany as leaders but notes increasing contributions from other countries. This study reveals the changing landscape as well as influential authors and thematic clusters in this field.

Keywords: Bibliometric analysis, cluster analysis, periprosthetic fractures

Öz

Amaç: Bu çalışma, 1990'dan bu yana periprostetik kırık literatürüne dair kapsamlı bir bibliyometrik analiz yapmaktadır. Amacı, yaygın temaları, ana yazarları ve coğrafi eğilimleri ortaya çıkarmaktır. Periprostetik kırıklar, geriatrik artroplasti popülasyonunda önemli bir komplikasyondur. Bu konuda geleneksel literatür incelemeleri mevcut olsa da, bibliyometrik yöntemler daha önce görülmemiş eğilimleri ve nüansları ortaya çıkarabilir.

Yöntem: Web of Science veritabanı, Ocak 1990'dan Aralık 2022'ye kadar taranmış, 2445 makale ve inceleme elde edilmiştir. Veriler, anahtar kelime, yazarlık ve alıntı patlaması analizi ile birlikte ko-sitasyon kümelemesi için CiteSpace ve VOSviewer'a aktarılmıştır.

Bulgular: 1990'ların sonlarından bu yana periprostetik kırık literatüründe üssel bir artış gözlemlenmiştir. Araştırma sonucunda Amerika Birleşik Devletleri önde gelmekte olup, ardından İngiltere ve Almanya gelmektedir. Alıntı patlaması yaşayan öne çıkan yazarlar arasında Lewallen, Berry, Duncan, Masri ve Abdel bulunmaktadır. Ko-sitasyon analizi, yüksek siluet değerleriyle güçlü tematik uyum gösteren on önemli küme ortaya çıkarmıştır.

Sonuç: Bu çalışma, periprostetik kırık araştırmalarının evrimini ve mevcut durumunu bütünsel bir bakış açısıyla sunmaktadır. Amerika Birleşik Devletleri, İngiltere ve Almanya'nın lider olduğu görülmekle beraber, diğer ülkelerden artan katkılar da son yıllarda dikkat çekmektedir. Bu çalışma, bu alandaki değişen literatürü, etkili yazarları ve tematik kümeleri ortaya koymuştur.

Anahtar kelimeler: Bibliyometrik analiz, küme analizi, periprostetik kırıklar

Introduction

Osteoarthritis (OA) is an important cause of disability in the elderly population (1). The number of joint replacements for OA performed annually has been increasing worldwide (2). Although hip and knee replacements have been the dominant surgical approach, shoulder arthroplasty has been associated with an even greater rate of growth (3). They are performed both in the elective and emergency settings, depending on the patient's presentation (4,5). With the ever-increasing number of surgeries, the number of reported complications has also increased. A major complication of joint replacement surgery is periprosthetic fracture. Periprosthetic fractures can occur intra- or postoperatively and can cause significant morbidity and mortality (6-8).

As the body of literature expands, it is often easier to identify the main issues of controversy, whereas minor trends or areas of interest, and geographical trends might go unnoticed. Bibliometric analysis is an approach that aids in recognizing patterns within a vast array of publications and in comprehending inherent data. This could involve pinpointing prevalent themes or keywords and creating visual representations of the citation network, relevant journals, and other significant data.

This study aimed to conduct a comprehensive bibliometric analysis of the literature on periprosthetic fractures published since 1990, with the objective of revealing prevalent themes, influential authors, and geographical trends in research output. The analysis aims to provide valuable insights into the evolution of this field and to identify key research contributions and potential directions for future research.

Materials and Methods

The Web of Science (WoS) database by Clarivate Analytics was searched in June 2023, covering the period from January 1990 to December 2022, using the following query in the title, abstract, or keywords: [TS=("periprosthetic fracture" OR "periprosthetic fracture*")] OR [TI=("periprosthetic fracture" OR "periprosthetic fracture*")] OR [AB=("periprosthetic fracture" OR "periprosthetic fracture*")]. The document type was an article or review article in English. Only the Science Citation Index Expanded and Emerging Sources Citation Index results were included. Overall, 2445 results were obtained. Titles, authors, abstracts, institutions, countries, journals, references, and citation information were recorded.

Statistical Analysis

The obtained data were imported into CiteSpace 6.1. R6, 64-Bit (Drexel University, Philadelphia, PA, USA) (9) and VOSviewer 1.6.15 (10). Keywords, authorship, and citation burst analysis were also performed. The network of keywords and organizations was analyzed and visualized using VOSviewer. Co-citation analysis and clustering were performed using CiteSpace. Clusters were analyzed using silhouette and centrality metrics and labeled using different algorithmic methods [latent semantic indexing (LSI), log-likelihood ratio (LLR), and mutual information (MI)]. A p-value of less than 0.05 was considered statistically significant.

Results

The literature regarding periprosthetic fractures has been published since the late 1990s (Figure 1). In the first decade, 50 publications were identified, of which the total number of citations was 69. In 2022 alone, there were 252 publications and 6591 citations on the topic, underlining the exponential growth of the subject area.

Country Analysis

Table 1 summarizes the top 10 countries with the highest number of publications. The United States of America (USA) leads with 873 articles and a centrality of 0.27. The United Kingdom (UK) and Germany also obtained centrality scores, indicating the influence of publications from these countries. The burst analysis results are presented in Figure 2. Figure 3 presents the co-authorship map of the countries. Thicker lines indicate stronger links, larger nodes indicate higher co-authorship counts, and lighter colors indicate more recent co-authorship.
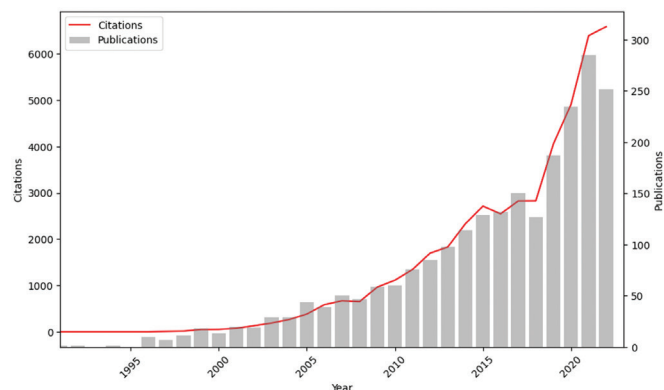
Figure 1. Number of publications and citations generated per year. The red line represents the number of citations

Author and Cited Author Burst Analysis

Figures 4 and 5 show the results of the burst analysis of the top 10 authors and cited authors in the dataset, respectively. The analysis of author bursts between 1990 and 2023 shows that certain authors experienced periods of significant productivity, as evidenced by a surge in the appearance of their works. Lewallen, DG, had a citation burst between 1996 and 2004, with a strength of 4.47. Berry, DJ, exhibited a similar burst between 1997 and 2003, with

a strength of 4.57. Duncan and Masri had citation bursts from 1999 to 2005 with a strength of 4.4. In the mid-2000s, Parvizi emerged as a prominent figure, with citation bursts occurring from 2006 to 2011, reaching a strength of 4.91. Wagner, Eric R. and Abdel, Matthew P. experienced bursts more recently, between 2015 and 2018 and 2017 and 2021, respectively, with strengths of 4.19 and 5.65.

Figure 5 presents the top 10 cited authors in the field who experienced the strongest citation bursts between 1990 and 2023. The three authors with the most recent and ongoing citation bursts are Abdel (2017-2023, strength 54.85),

Table 1. Top 10 most publishing countries between 1990-2022

Ranks	Country	No. of articles	Centrality
1	USA	873	0.27
2	United Kingdom	262	0.18
3	Germany	200	0.08
4	China	120	0.01
5	Canada	114	0.02
6	South Korea	77	0.00
7	Italy	64	0.06
8	Australia	53	0.02
9	France	52	0.02
10	Japan	41	0.01

USA: United States of America

Countries	Year	Strength	Begin	End	1990 - 2023
USA	1996	27.54	1996	2001	
ENGLAND	2002	8.47	2005	2010	
GERMANY	2003	5.74	2009	2012	
SWEDEN	2012	7.43	2012	2014	
SOUTH KOREA	2011	11.45	2014	2019	
FRANCE	2009	6.09	2017	2020	
AUSTRALIA	2011	5.8	2019	2020	
ITALY	2013	11.91	2020	2023	
PEOPLES R CHINA	2014	8.43	2020	2023	
JAPAN	2013	5.86	2020	2023	
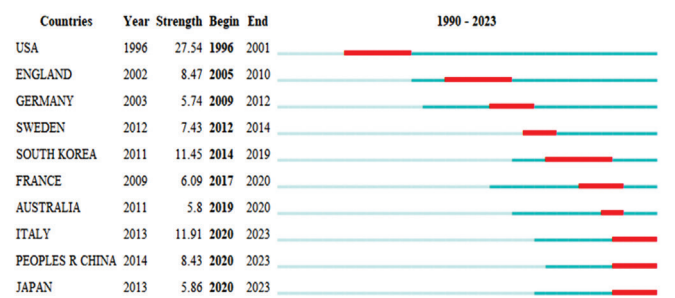
Figure 2. Top 10 countries with the strongest citation bursts

USA: United States of America
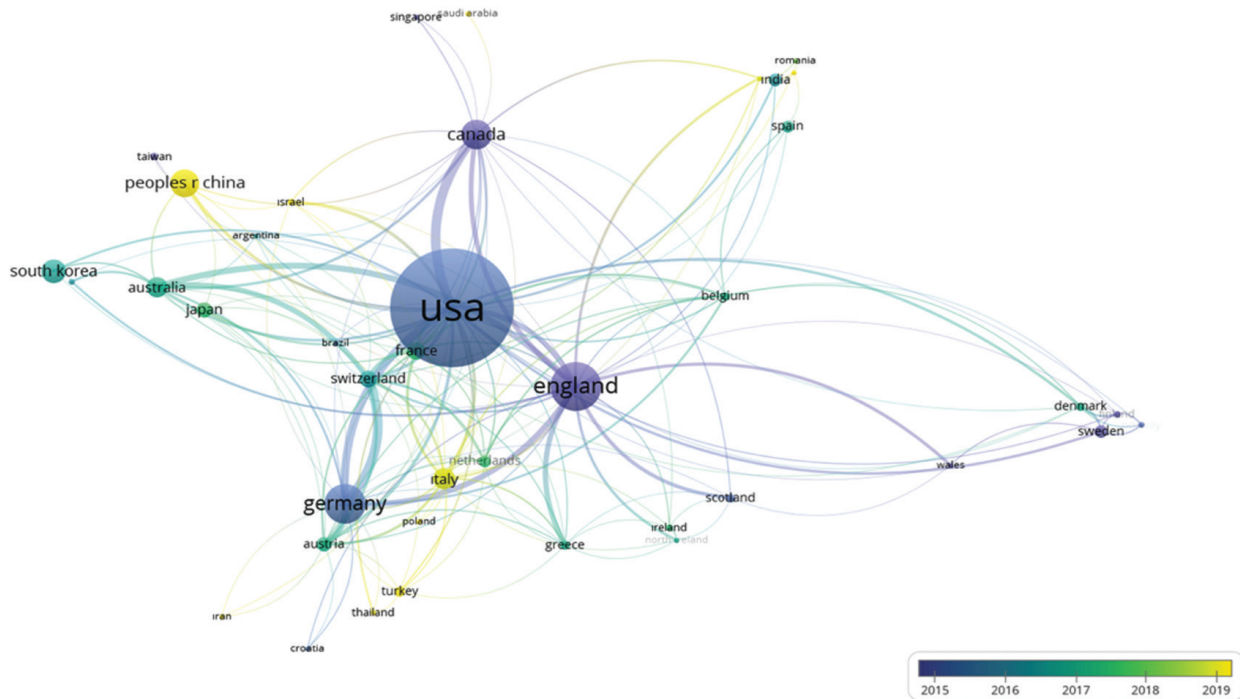
Figure 3. Network representation of country co-authorship. Thicker lines indicate stronger links between countries, while lighter colors indicate newer coauthorships

USA: United States of America

Authors	Year	Strength	Begin	End	1990 - 2023
Lewallen, DG	1996	4.47	1996	2004	
Berry, DJ	1997	4.57	1997	2003	
Duncan, CP	1999	4.4	1999	2005	
Masri, BA	1999	4.4	1999	2005	
Parvizi, Javad	2006	4.91	2006	2011	
Wagner, Eric R	2015	4.19	2015	2018	
Abdel, Matthew P	2015	5.65	2017	2021	
Sculco, Peter K	2019	6.16	2020	2023	
Gu, Alex	2020	3.94	2020	2023	
Springer, Bryan D	2009	4.1	2021	2023	
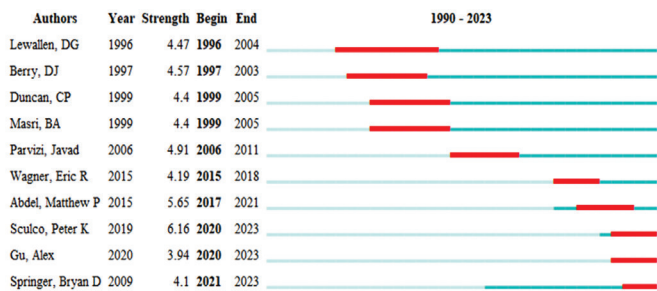
Figure 4. Top 10 authors with the strongest citation bursts

Cited Authors	Year	Strength	Begin	End	1990 - 2023
BEALS R	1997	16.98	1999	2010	
MONT MA	1996	17.23	2002	2012	
KREGOR PJ	2001	17.67	2005	2014	
FULKERSON E	2008	22.12	2009	2017	
HOU ZY	2013	16.32	2013	2017	
THIEN TM	2016	18.97	2016	2023	
ABDEL MP	2017	54.85	2017	2023	
KHANUJA HS	2016	16.76	2018	2023	
HAILER NP	2018	16.65	2018	2023	
KREMERS HM	2019	16.28	2019	2023	
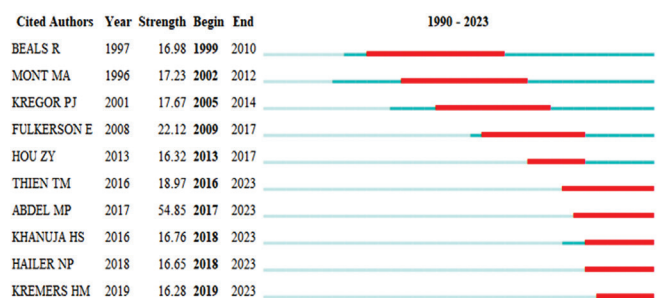
Figure 5. Top 10 cited authors with the strongest citation bursts

Khanuja (2018-2023, strength 16.76), Hailer (2018-2023, strength 16.65), and Kremers (2019-2023, strength 16.28). Abdel's citation burst is particularly notable for its strength, which is 54.85 and is significantly greater than that of the other authors, indicating the significant impact of this author in the field.

Co-citation Analysis and Clustering

Co-citation network analysis was performed on the dataset. In total, 3237 distinct references were identified. These were graphed on a network with 4354 nodes and 17500 links. The ten largest connected clusters are visualized in Figure 6. Table 2 summarizes the 10 largest automatically labeled clusters identified using different algorithms. The most substantial cluster (cluster 0) contained 416 articles and had a silhouette value of 0.865, indicating a high level of internal consistency. The primary theme was periprosthetic fracture, which was identified using both LSI and MI methods, with interprosthetic femoral fracture emerging as a specific subtheme using the LLR method. This theme was also prominently manifested in clusters 1, 3, 5, and 8. Cluster 1 included 279 articles and had a high silhouette value of 0.909; additionally, the direct anterior approach
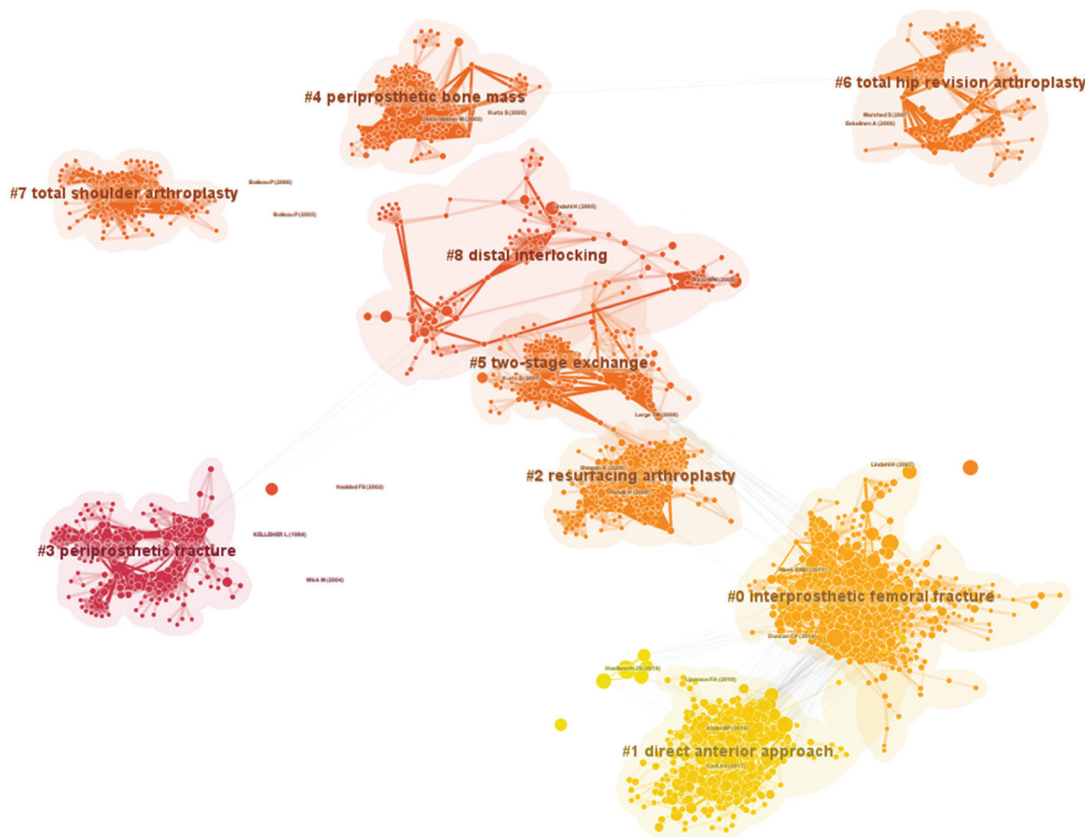
Figure 6. Clustered network map of located references for periprosthetic fractures

was also highlighted as a significant subtheme. Cluster 3 comprised 169 articles, again focusing on periprosthetic fractures, dating back to earlier research in 1995.

Table 3 presents the top-cited publications for each of the 10 largest clusters identified in the cogitation network. These papers represent influential contributions that have shaped the understanding and methodology of each cluster.

Discussion

This bibliometric study presents a comprehensive analysis of orthopedic research output from 1990 to 2022. The literature on periprosthetic fractures has been expanding rapidly, and given the increase in the number of arthroplasty procedures performed, it is safe to assume that this trend will continue in the near future.

Table 2. Summary of the largest 10 clusters in the co-citation network						
Cluster	Size	Silhouette	Label (LSI)	Label (LLR, p-value)	Label (MI score)	Average year
0	416	0.865	Periprosthetic fracture	Interprosthetic femoral fracture (855.44, <0.001)	Infected interprosthetic femoral shaft fracture (3.75)	2011
1	279	0.909	Periprosthetic fracture	Direct anterior approach (871.64, <0.001)	Infected interprosthetic femoral shaft fracture (4.54)	2016
2	189	0.99	Resurfacing arthroplasty	Resurfacing arthroplasty (170.41, <0.001)	Periprosthetic fracture (0.06)	2008
3	169	0.978	Periprosthetic fracture	Periprosthetic fracture (272.89, <0.001)	Periprosthetic fracture (0.05)	1995
4	168	0.991	Periprosthetic bone mass	Periprosthetic bone mass (81.17, <0.001)	Periprosthetic fracture (0.07)	2003
5	143	0.977	Periprosthetic fracture	Two-stage exchange (109.78, <0.001)	Periprosthetic fracture (0.06)	2005
6	125	0.991	Total hip arthroplasty	Total hip revision arthroplasty (57.12, <0.001)	Periprosthetic fracture (0.06)	2005
7	122	1	Total shoulder arthroplasty	Total shoulder arthroplasty (44.73, <0.001)	Periprosthetic fracture (0.07)	2004
8	122	0.991	Periprosthetic femoral fracture	Distal interlocking (167.61, <0.001)	Periprosthetic fracture (0.05)	2001
9	121	0.981	Systematic review	Distal femoral replacement (1082.97, <0.001)	Double-locked plating (0.65)	2018

LSI: Latent semantic indexing, LLR: Log-likelihood ratio, MI: Mutual information

| Table 3. Top cited publication of each cluster		
Cluster	Cluster label	Authors, year, title
0	Interprosthetic femoral fracture	Meek et al., 2011, "The risk of peri-prosthetic fracture after primary and revision total hip and knee replacement"
1	Direct anterior approach	Abdel et al., 2016, "Epidemiology of periprosthetic fracture of the femur in 32 644 primary total hip arthroplasties: a 40-year experience"
2	Resurfacing arthroplasty	Shimmin et al., 2008, "Metal-on-metal hip resurfacing arthroplasty"
3	Periprosthetic fracture	Wick et al., 2004, "Periprosthetic supracondylar femoral fractures: LISS or retrograde intramedullary nailing? Problems with the use of minimally invasive technique"
4	Periprosthetic bone mass	Kurtz et al., 2005, "Prevalence of Primary and Revision Total Hip and Knee Arthroplasty in the United States From 1990 Through 2002"
5	Two-stage exchange	Kurtz et al., 2007, "Projections of Primary and Revision Hip and Knee Arthroplasty in the United States from 2005 to 2030"
6	Total hip revision arthroplasty	Morshed et al, 2007, "Comparison of cemented and uncemented fixation in total hip replacement"
7	Total shoulder arthroplasty	Boileau et al., 2006, "The Grammont reverse shoulder prosthesis: Results in cuff tear arthritis, fracture sequelae, and revision arthroplasty"
8	Distal interlocking	Lindahl et al., 2005, "Periprosthetic Femoral Fractures: Classification and Demographics of 1049 Periprosthetic Femoral Fractures from the Swedish National Hip Arthroplasty Register"
9	Distal femoral replacement	Hoellwarth et al., 2018, "Equivalent mortality and complication rates following periprosthetic distal femur fractures managed with either lateral locked plating or a distal femoral replacement"

Traditional citation analysis mainly relies on citation count, which measures the number of times a particular work or author is cited (11). While this is a good indicator of general influence, it does not necessarily reflect the content or context of the citations nor how works relate to each other.

Co-citation analysis is a bibliometric method that helps researchers discover influential publications and authors, offering a more detailed view than standard literature research (12). Specifically, if two documents are frequently cited together by other papers, they are likely to share a thematic relationship and contribute significantly to their field of research. This approach can highlight key publications or authors that may not necessarily have the highest citation count but are important in shaping the discourse in a given field. This approach is different from bibliographic coupling, which links papers sharing common references. Instead, it links papers that are cited together even though they may not share a common reference (13).

Burst analysis identifies any statistically significant variations in the appearance of a country, author, or title over a given time interval. This technique is essential for determining if and when the citation count for a specific reference has notably increased and offers a different view than traditional citation count lists, which may have a negative bias toward highly influential but recent titles (14). Burst analysis was performed for this study using CiteSpace, an algorithm developed by Kleinberg (15).

The silhouette metric, introduced in 1987 by Rousseeuw (16), is beneficial for estimating the uncertainty in defining a cluster's characteristics. The silhouette value for a cluster ranging from 1 to 1 indicates the level of uncertainty to be considered when examining the nature of the cluster. A value of 1 denotes an ideal distinction from other clusters.

Centrality measures the importance of a node (article, author or country) in a network based on its connections to other nodes. Articles with higher centrality values indicate that they are more central and influential within their clusters (17).

This bibliometric analysis provides insight into the landscape of the literature on periprosthetic fracture and hints at several geographical trends. Notably, the United States has emerged as the most productive country, publishing a staggering 873 articles with a centrality of 0.27. The UK and Germany had 262 and 200 articles, respectively. However, despite the small number of articles, these countries maintained notable centrality, indicating their significant influence on orthopedic research.

When examining the citation burst data, the United States, England, and Germany stood out, suggesting that they had important influence on the literature during certain periods. The USA's citation burst peaked between 1996 and 2001, reflecting the high impact of their research during that time. UK and Germany exhibited significant citation bursts, peaking between 2002 and 2010 and between 2003 and 2012, respectively. Interestingly, countries with fewer overall publications, such as South Korea, Sweden, and Italy, also showed robust citation bursts, indicating a significant contribution to the global body of orthopedic knowledge during their peak periods. In recent years, Italy, the People's Republic of China, and Japan have demonstrated a surge in citation strength from 2020 to 2023. Despite their relatively lower number of publications, their research in the field of orthopedics was highly impactful during this period. These data suggest a growing diversification in influential orthopedic research, with countries beyond the traditionally dominant USA and the UK making significant contributions. It is also worth noting that, although not among the top 10 countries, Turkey is also a prominent newcomer in the field (Figure 3) in co-authorship, with relatively strong links to the United States and Italy.

In co-citation analysis, a cluster signifies a common theme among the references. The characteristics of a group of located references can be determined through cluster label-generated labels of the cluster (18). CiteSpace provides three selection methods based on LSI, the LLR, and MI. Each selection method may highlight different aspects of a cluster (9).

High silhouette values in the clusters (Table 2), ranging from 0.865 to 0.991, illustrate strong intracluster similarity and clear differentiation from other themes, bolstering the robustness of the clustering approach. The exploration of topics such as resurfacing arthroplasty, total hip and shoulder arthroplasty, and systematic reviews further enriches the diversity of research areas covered in the cogitation network.

These results are further contextualized by examining the top-cited publications of each cluster (Table 3). For instance, Meek et al.'s study on the risk of periprosthetic fracture associated with the cluster labeled "interprosthetic femoral fracture" showcases the significance of this research within the field. Similarly, Abdel et al.'s work on the epidemiology of periprosthetic fractures of the femur aligns

with the cluster labeled "direct anterior approach". These top-cited publications encapsulate the core themes of their respective clusters and guide researchers toward influential works on these topics. Because they are strongly linked to other studies in the cluster, understanding or analyzing these studies may provide insights into the entire cluster. These top-cited works may serve as important references for researchers, providing insight into key discussions, debates, and methodologies in the respective fields.

Study Limitations

A key limitation of this study was our reliance on the WoS database, which, although comprehensive, may not include all relevant literature on periprosthetic fractures and may not include significant studies indexed in other databases. Furthermore, bibliometric analysis primarily focuses on quantitative metrics such as citation counts and coauthorship networks. These may not fully capture the quality and impact of the studies, potentially leading to overestimation or underestimation. Lastly, this study may not have accounted for the most recent trends in the field, especially those that have not yet had time to be cited enough times to be picked by the bibliometric method.

Conclusion

This study provides a holistic view of the literature on periprosthetic fracture, tracking its evolution over the past few decades and outlining influential themes, authors, and geographical trends. The United States, the UK, and Germany have been instrumental in leading research output, with increasing contributions from countries such as South Korea, Sweden, Italy, China, Japan, and Turkey. Recognized authors such as Lewallen, Berry, Duncan, Masri, Parvizi, Wagner, and Abdel left significant imprints on the field with their citation bursts. The insights from this study can assist researchers and clinicians in understanding the landscape of periprosthetic fracture research, identifying influential contributors, and identifying future research directions in this rapidly evolving field.

Ethics

Ethics Committee Approval: Not necessary for this manuscript.

Informed Consent: Not necessary for this manuscript.

Authorship Contributions

Concept: E.Ö., S.Y., O.B., Design: E.Ö., S.Y., O.B., Data Collection or Processing: A.B., E.Ç., Analysis or Interpretation: E.Ç., Drafting Manuscript: E.Ö., A.B., E.Ç.,

Critical Revision of Manuscript: S.Y., O.B., Final Approval and Accountability: E.Ö., A.B., E.Ç., S.Y., O.B., Technical or Material Support: A.B., E.Ç., Supervision: S.Y., O.B., Writing: E.Ö., A.B., E.Ç., S.Y., O.B.

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Evaluation of *Bartonella henselae* IFA Seropositivity in Adult Patients Presenting with Various Symptoms at a Tertiary Education and Research Hospital

Üçüncü Basamak bir Eğitim ve Araştırma Hastanesine Çeşitli Semptomlarla Başvuran Erişkin Hastalarda *Bartonella henselae* IFA Seropozitifliğinin Değerlendirilmesi

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Abstract

Objective: *Bartonella henselae, indirect* , is the etiologic agent of cat scratch disease (CSD). Due to the difficulty of isolation and culture of *Bartonella henselae*, indirect fluorescent antibody (IFA) test is commonly used in diagnosis. In this study, we aimed to investigate the role of serology in the diagnosis of classical and atypical CSD by examining different serological titer values of patients with suspected CSD.

Method: Patients were divided into 2 main groups as negative and positive according to the IFA test result. Patients with positive IFA titer were divided into 2 groups as suspected positive IFA (1:64-1:128) and positive IFA (≥1:256) and subgroup analysis was performed.

Results: A total of 197 patients were included in the study and IFA tests were obtained from the laboratory database. The number of IFA immunoglobulin G seropositive patients was 57 (28.9%). The mean age of the patients was 37 (18-87) years, with 104 (52.8%) being female. While 49.7% of all patients had a history of cat contact, 61.4% of the patients in IFA test positive group had a history of cat contact (p=0.037). The most common symptom was lymphadenopathy (77.7%). Axillary lymphadenopathy was more common in the IFA positive group with a rate of 70.2% (p<0.001). The mean duration of LAP was 1 month in the IFA positive group and 2 months in the IFA negative group with a statistically significant difference (p<0.001). Unilateral LAP was significantly more common in the possible positive IFA group with a rate of 79.1% (p=0.043).

Öz

Amaç: *Bartonella henselae*, kedi tırmığı hastalığının (KTH) etiyolojik etkenidir. *Bartonella henselae*'nin izolasyonu ve kültürünün zorluğu nedeniyle, tanıda dolaylı floresan antikor (İFA) testi yaygın olarak kullanılır. Bu çalışmada, KTH'den şüphelenilen hastaların farklı serolojik titre değerleri incelenerek, klasik ve atipik KTH'nin teşhisinde serolojinin rolü incelendi.

Yöntem: Çalışmaya 01 Ocak 2018-01 Ocak 2024 tarihleri arasında KTH semptomları ile başvuran, 18 yaş üstü hastalar dahil edildi. *Bartonella henselae* İFA test sonucuna göre negatif ve pozitif olarak 2 gruba ayrıldı. İFA titresi pozitif hastalar, şüpheli İFA pozitif (1:64 ve 1:128) ve İFA pozitif (≥1:256) olarak 2 gruba ayrılıp alt grup analizi yapıldı.

Bulgular: Laboratuvar veri tabanından toplam 197 hastada *Bartonella henselae* İFA testleri çalışıldığı saptandı. İFA immünoglobulin G seropozitif hasta sayısı 57 (%28,9) idi. Hastaların yaş ortalaması 37 (18-87) yıl ve 104 (%52,8) hasta kadındı. Tüm hastaların içinde kedi teması öyküsü %49,7'sinde mevcuttu. İFA test sonucu pozitif grubun %61,4'ünde kedi teması saptandı (p=0,037). En yaygın semptom lenfadenopatiydi (%77,7). İFA pozitif grupta aksiller lenfadenopati %70,2 ile daha fazlaydı (p<0,001). İFA pozitif grubun LAP ortalama süresi 1 ay, İFA negatif grubun ise 2 ay olup istatistiksel anlamlı farklılık saptandı (p<0,001). Pozitif İFA grubunda tek taraflı LAP %79,1 oranla anlamlı düzeyde daha fazlaydı (p=0,043).

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Evaluation of *Bartonella henselae* IFA Results

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Abstract

Conclusion: CSD should be considered in the differential diagnosis of patients with cat contact who present with unilateral lymphadenopathy, especially in the axillary region, as *Bartonella henselae* infection is not uncommon in the population receiving service from our hospital. Although an IFA titer of ≥1/256 supports the diagnosis, it should be kept in mind that a negative IFA result does not exclude the CSD diagnosis.

Keywords: *Bartonella henselae*, cat scratch disease, lymphadenopathy

Öz

Sonuç: *Bartonella henselae* enfeksiyonunun hastanemize başvuran hastalarda nadir olmadığı, kedi teması olan, tek taraflı, özellikle aksiller bölgede lenfadenopati ile başvuran hastaların ayırıcı tanısında KTH akılda tutulmalıdır. İFA titresi ≥1/256 olması tanıyı kuvvetlendirmekle birlikte negatif İFA sonucunun tanıyı dışlamayacağı unutulmamalıdır.

Anahtar kelimeler: *Bartonella henselae*, kedi tırmığı hastalığı, lenfadenopati

Introduction

Bartonella henselae, a Gram-negative bacillus, is the causative agent of cat scratch disease (CSD), which mostly causes self-limiting lymphadenitis but can also lead to more serious clinical manifestations, such as neuroretinitis, encephalitis, visceral organ involvement, and fever of unknown origin (1). In individuals with HIV, *Bartonella henselae* can cause angiomatosis, peliosis hepatis, and splenitis (2).

Epidemiologic studies from different countries have indicated that CSD is distributed worldwide. Although CSD is mostly observed in young individuals, the disease can affect individuals of all ages (3,4).

Cats are natural reservoirs of *Bartonella henselae*, which causes intraerythrocyte bacteremia that can persist for a year or more. Transmission to humans can occur by scratching or biting an infected cat or by exposure to fleas (5).

The isolation and culture of *Bartonella henselae* is difficult; therefore, it is not commonly used for diagnosis. The diagnosis is based on a recent history of contact with cats or fleas in patients with characteristic clinical features. Serological testing for the presence of antibodies against *Bartonella henselae* using indirect fluorescent antibody (IFA) staining is a widely accepted diagnostic procedure for the laboratory diagnosis of cat-scratch disease. The ability of a serologic test to identify patients with a disease (sensitivity) and those without a disease (specificity) is related to the threshold for a positive result. IFA immunoglobulin (Ig) G titers of <1:64 suggest that the patient does not have an active Bartonella infection, titers of 1:64 or 1:128 suggest possible Bartonella infection, and titers of ≥1:256 strongly suggest active or recent infection. However, serologic tests have some limitations, and a negative serologic test does not exclude CSD in patients with characteristic epidemiologic and clinical features (6-8). In addition, cross-reaction between *Bartonella henselae* and *B. quintana*, *Chlamydia trachomatis*, *Coxiella burnettii*, *Rickettsia rickettsii*, *Ehrlichia chaffeensis*, *Treponema pallidum*, *Francisella tularensis*, and *Mycoplasma pneumoniae leads* to false-positive test results especially in IgG assays (8,9).

There are not enough studies on the epidemiology, clinical features, and serological testing of CSD in Turkey. In this study, we aimed to retrospectively review the clinical data of patients with suspected CSD, determine the current epidemiological features, and examine the role of serology in the diagnosis of classical and atypical CSD in adults with different serological titers.

Materials and Methods

This study was conducted with the approval of the University of Health Sciences Turkey Hamidiye Ethics Committee for Clinical Research (01.08.2024, 22.08.2024-24/477).

In this study, we retrospectively examined the data of all patients who were admitted to our hospital's infectious diseases outpatient clinic between January 01, 2018 and January 01, 2024, were over 18 years of age, had diagnostic codes A44.8, A44.9, and A28.1 for bartonellosis and CSD according to the International Classification of Diseases (ICD-10), and underwent the *Bartonella henselae* IFA test. During the relevant period, *B. henselae* IgM testing was not performed in our hospital.

We excluded patients with immunosuppressive conditions or those receiving immunosuppressive therapy.

We obtained demographic data, clinical features, cat contact history, biochemical, microbiological, and radiological test results of the patients from the hospital database. We reviewed clinical data to determine whether the presenting symptoms were related to CSD and laboratory tests for differential diagnoses. We determined whether patients had an alternative diagnosis based on confirmatory laboratory results or a clinician's diagnosis.

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Serologic Testing

The presence of *Bartonella henselae* IgG antibodies in serum samples was determined by an IFA assay using a commercial kit (Euroimmun, Germany). After the samples were diluted to 1:64, 1:128, 1:256, 1:512, 1:1024, and 1:2048 in phosphate-buffered saline PBS-Tween buffer (provided in the test kit), the IFA assay was conducted following the manufacturer's protocol. Positive and negative controls were also used. Immunofluorescence was observed using a fluorescence microscope at magnifications of 40X and 200X. A titer of ≥1:256 was considered positive for *Bartonella henselae* IgG. A titer of 1:64 and 1:128 were considered indicative of *Bartonella henselae* IgG (8,10).

Patients were divided into 2 main groups: negative and positive according to the *Bartonella henselae* IFA test result. Patients with positive IFA titers were divided into 2 groups as suspected positive IFA (1:64 and 1:128) and positive IFA (≥1:256) and subgroup analysis was performed.

Statistical Analysis

Patient data were analyzed using the IBM Statistical Package for the Social Sciences (SPSS) for Macos 29.0 (IBM Corp., Armonk, NY) software. Frequency and percentage for categorical variables, median, minimum, and maximum for continuous variables are descriptive values. The normality of the variables was evaluated using the Kolmogorov-Smirnov test. In intergroup comparisons, "Mann-Whitney U test" was used for comparison of continuous variables two groups and "chi-square or Fisher's Exact test" was used for comparison of categorical variables. Results were considered statistically significant at p-value was less than 0.05.

Results

A total of 197 patients who underwent *Bartonella henselae* IFA testing were identified from the laboratory database. The number of IFA IgG seropositive patients was 57 (28.9%). Of the 57 seropositive patients, 12.3% (7/57), 45.6% (26/57), 12.3% (7/57), 14% (8/57), 14% (8/57), and 1.8% (1/57) had titers of 1:64, 1:128, 1:256, 1:512, 1:1024, and 1:2048, respectively.

The mean age of the patients was 37 (18-87) years, with 104 (52.8%) being female. There were no significant differences between age and gender distribution and IFA IgG test results.

History of cat contact was present in 49.7% of the patients. Although 61.4% of the IFA-positive group had cat contact, 45% of the IFA-negative group had cat contact, and this difference was statistically significant (p=0.037).

The most common symptom was lymphadenitis/lymphadenopathy (LAP) (n=153, 77.7%). Axillary lymphadenopathy was significantly more common in the IFA-positive group [70.2% (p<0.001)], whereas cervical lymphadenopathy was significantly more common in the IFA-negative group [54.3% (p=0.026)].

The mean LAP duration was 1 month in the IFA positive group was 1 month and in the IFA negative group was 2 months, and this difference was statistically significant (p<0.001) (Table 1). Lymphadenopathy lasting less than 2 months was significantly more frequent in the IFA-positive group, with a rate of 80.7% (p=0.002). Lymphadenopathy lasting more than 3 months was significantly more frequent in the IFA-negative group (p<0.001).

Of the 25 patients with possible bartonella infection, 24 had a positive IFA test result, which was statistically significant (p=0.001). The demographic, clinical, and laboratory findings of the patients according to the IFA results are presented in Table 1.

Of the 57 IFA-positive patients, 24 patients with IFA titer ≥1:256 were included in the possible-positive IFA group and 33 were included in the suspected-positive IFA group. A subgroup analysis was conducted. Unilateral LAP was significantly more common in the true-positive group. The rate of multiple LAPs was 90.9% and statistically more frequent in the suspected IFA-positive group (p=0.01) (Table 2).

Discussion

Polymerase chain reaction (PCR) analysis of biopsy samples collected from lymph nodes or other infected tissues and isolation of the causative agent in culture is definitive for the diagnosis of bartonellosis. Practical use of these methods is difficult because of the requirement for invasive procedures and limited access to molecular testing. For this reason, serological tests are the first step in the diagnosis of CSD (4,6,11). Clinical interpretation of *Bartonella henselae* serology is challenging due to both low sensitivity and specificity. In this study, we aimed to examine the use of IFA titer value in the diagnosis of CSD in clinical practice by examining clinical findings and other laboratory tests.

In a study conducted in Turkey, the seropositivity rate was found to be 9.9% and no statistical difference was observed between men and women (7). In another recent study conducted in our country, Ergin et al. (9) found that 33.3%

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Table 1. Distribution of demographic and clinical findings of patients according to positive and negative test results

Variables		Total (n=197)	IFA negative (n=140)	IFA positive (n=57)	p-value
		n (%) or median (min-max)	n (%) or median (min-max)	n (%) or median (min-max)	
Age (years)		37 (18-87)	37.5 (18-87)	33 (18-72)	0.304
Sex	Male	93 (47.2)	64 (45.7)	29 (50.9)	0.510
	Female	104 (52.8)	76 (54.3)	28 (49.1)	
Cat contact		98 (49.7)	63 (45)	35 (61.4)	**0.037**
Night sweats		27 (13.7)	16 (11.4)	11 (19.3)	0.219
Prior antibiotic use		66 (33.5)	43 (30.7)	23 (40.4)	0.257
Fever		21 (10.7)	13 (9.3)	8 (14)	0.468
Lymphadenopathy	Localized	153 (77.7)	111 (79.3)	42 (73.7)	0.505
	Generalized	44 (22.3)	29 (20.7)	15 (26.3)	
	Unilateral	90 (45.7)	61 (43.6)	29 (50.9)	0.351
	Bilateral	107 (54.3)	79 (56.4)	28 (49.1)	
	Single	42 (21.3)	29 (20.7)	13 (22.8)	0.894
	Multiple	155 (78.7)	111 (79.3)	44 (77.2)	
Region of lymphadenopathy	Cervical	97 (49.2)	76 (54.3)	21 (36.8)	**0.026**
	Axillary	100 (50.8)	60 (42.9)	40 (70.2)	**<0.001**
	Inguinal	52 (26.4)	38 (27.1)	14 (24.6)	0.846
	Supraclavicular	7 (3.6)	4 (2.9)	3 (5.3)	0.415
Duration of lymphadenopathy		1 (1-48)	2 (1-48)	1 (1-24)	**<0.001**
<2 month		125 (63.5)	79 (56.4)	46 (80.7)	**0.002**
>2 month		72 (36.5)	61 (43.6)	11 (19.3)	
<1 month		105 (53.3)	63 (45)	42 (73.7)	**<0.001**
1-3 month		32 (16.2)	23 (16.4)	9 (15.8)	
>1 year		20 (10.2)	18 (12.9)	2 (3.5)	
Size of lymphadenopathy (mm)		24 (5-50)	23 (7-50)	25 (5-50)	0.732
≤20 mm		70 (35.5)	55 (39.3)	15 (26.3)	0.119
>20 mm		127 (64.5)	85 (60.7)	42 (73.7)	
≤40 mm		182 (92.4)	130 (92.9)	52 (91.2)	0.768
>40 mm		15 (7.6)	10 (7.1)	5 (8.8)	
Splenomegaly		10 (5.1)	7 (5)	3 (5.3)	1.000
Hepatomegaly		12 (6.1)	9 (6.4)	3 (5.3)	1.000
WBC (x10^3)		7 (3-20)	7 (3-20)	7 (3.3-13)	0.954
Leukocytosis		22 (11.2)	17 (12.1)	5 (8.8)	0.666
Hemoglobin		13 (5-17)	13 (6-17)	13 (5-16)	0.357
Anemia		36 (18.3)	28 (20)	8 (14)	0.436
PLT (x10^3)		254 (13.2-489)	248 (14.5-489)	264 (13.2-461)	0.267
Thrombocytopenia		5 (2.5)	3 (2.1)	2 (3.5)	0.628
CRP		3 (0-102)	3 (0-102)	4 (0-96)	0.502
CRP > upper limit		70 (35.5)	45 (32.1)	25 (43.9)	0.163
Sedimentation rate		11 (1-120)	11 (1-107)	14 (1-120)	0.547
Sedimentation rate > upper limit		66 (33.5)	49 (35)	17 (29.8)	0.595
Lymph node biopsy histopathology		69 (35)	52 (37.1)	17 (29.8)	0.417
Malignant-atypical		4 (5.8)	4 (7.7)	0 (0)	0.565
Acute inflammation/suppurative/abscess		3 (4.3)	3 (5.8)	0 (0)	0.570
Necrotizing/granulomatous/caseification		36 (52.2)	25 (48.1)	11 (64.7)	0.362
LAP nature in ultrasound					0.439
Benign		150 (76.1)	104 (74.3)	46 (80.7)	
Malign		47 (23.9)	36 (25.7)	11 (19.3)	
Possible Bartonella		25 (12.7)	1 (0.7)	24 (42.1)	**<0.001**

N: Number of patients, IFA: Indirect fluorescent antibody test, CRP: C-reactive protein, WBC: White blood cell, LAP: Lymphadenopathy, PLT: Platelet

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Table 2. Distribution of demographic and clinical findings in titer (+) patients according to suspected and positive IFA				
Variables		Suspected IFA (n=33)	True positive IFA (n=24)	p-value
		n (%) or median (min-max)	n (%) or median (min-max)	
Age (years)		32 (18-62)	38 (19-72)	0.815
Sex	Male	17 (51.5)	12 (50)	1.000
	Female	16 (48.5)	12 (50)	
Cat contact		21 (63.6)	14 (58.3)	0.896
Night sweats		4 (12.1)	7 (29.2)	0.173
Prior antibiotic use		13 (39.4)	10 (41.7)	1.000
Fever		2 (6.1)	6 (25)	0.059
Lymphadenopathy	Localized	21 (63.6)	21 (87.5)	0.086
	Generalized	12 (36.4)	3 (12.5)	
	Unilateral	11 (33.3)	19 (79.1)	0.043
	Bilateral	22 (66.7)	5 (20.9)	
	Single	3 (9.1)	10 (41.7)	**0.010**
	Multiple	30 (90.9)	14 (58.3)	
Region of lymphadenopathy	Cervical	14 (42.4)	7 (29.2)	0.455
	Axillary	26 (78.8)	14 (58.3)	0.170
	Inguinal	9 (27.3)	5 (20.8)	0.806
	Supraclavicular	1 (3)	2 (8.3)	0.567
Duration of lymphadenopathy		1 (1-24)	1 (1-8)	0.770
<2 month		27 (81.8)	19 (79.2)	1.000
>2 month		6 (18.2)	5 (20.8)	
<1 month		25 (75.8)	17 (70.8)	0.518
1-3 month		4 (12.1)	5 (20.8)	
>1 year		2 (6.1)	0 (0)	
Size of lymphadenopathy (mm)		24 (10-45)	25 (5-50)	0.871
≤20 mm		7 (21.2)	8 (33.3)	0.471
>20 mm		26 (78.8)	16 (66.7)	
≤40 mm		32 (97)	20 (83.3)	0.151
>40 mm		1 (3)	4 (16.7)	
Splenomegaly		2 (6.1)	1 (4.2)	1.000
Hepatomegaly		1 (3)	2 (8.3)	0.567
WBC (x10³)		7 (4-12)	7.4 (3.3-13)	0.554
Leukocytosis		2 (6.1)	3 (12.5)	0.640
Hemoglobin		14 (9-16)	13 (5-16)	0.203
Anemia		3 (9.1)	5 (20.8)	0.261
PLT (x10³)		264 (163-361)	282.5 (13.2-461)	0.518
Thrombocytopenia		0 (0)	2 (8.3)	0.173
CRP		3 (0-96)	4 (0-40)	0.708
CRP > upper limit		15 (45.5)	10 (41.7)	0.989
Sedimentation rate		15 (1-93)	10 (2-120)	0.846
Sedimentation rate > upper limit		9 (27.3)	8 (33.3)	0.841
Lymph node biopsy histopathology		9 (27.3)	8 (33.3)	0.841
Necrotizing/granulomatous/caseification		4 (44.4)	7 (87.5)	0.131
LAP nature in ultrasound				0.326
Benign		25 (75.8)	21 (87.5)	
Malign		8 (24.2)	3 (12.5)	

N: Number of patients, IFA: Indirect fluorescent antibody test, CRP: C-reactive protein, WBC: White blood cell, LAP: Lymphadenopathy, PLT: Platelet

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of the samples were positive in antigen evaluation using IFA. Yanagihara et al. (12) reported that 21.3% of 80 patients with suspected CSD were serologically positive for IFA. In a study by Grippi et al. (13), it was reported that seropositivity rates were affected by seasonality (14). In our study, the seropositivity rate was 28.9%. Differences in seropositivity between studies, rates of patients under 18 years of age, seasonality, Bartonella species, and cross-reactivity with *Chlamydia trachomatis*, *Coxiella burnettii*, *Rickettsia rickettsii*, *Ehrlichia chaffeensis*, *Treponema pallidum*, *Francisella tularensis*, and *Mycoplasma pneumoniae* make it difficult to compare IFA results between populations. In our study, gender and age distribution did not significantly affect the diagnosis of CSD, similar to other studies.

Arıcı et al. (7) reported that 73.9% of seropositive patients had a history of cat contact. Tsuneoka and Tsukahara (15) emphasized that 29 of 30 seropositive patients had cat contact. Another study showed that 40-95% of CSD case series had cat contact (8). In our study, 61.4% of the IFA-positive group and 45% of the IFA-negative group had cat contact, and this difference was statistically significant (p=0.037). In other studies, cat contact was investigated in all CSD suspects. We showed that having a history of cat contact strongly suggested the diagnosis of CSD and that IFA titers were significantly more positive in this patient group. However, it should be considered that the disease can also be transmitted by fleas, and CSD can be diagnosed in patients without a history of cat contact.

A study by Tsuneoka and Tsukahara (15)found that of the 186 seropositive patients, 156 (83.9%) had regional lymphadenopathy. The most common finding in Arıcı et al. (7) study was lymphadenitis (63%). In another study by Tay et al. (10), 74% of patients had unilateral and multiple lymphadenopathies. The most common lymph nodes involved were the cervical and submandibular lymph nodes (10). In our study, the rate of lymphadenopathy was 77.7%. The most common region of lymphadenopathy in the IFA-positive group was axillary lymphadenopathy (70.2% and it was statistically significant). The most common site of lymphadenopathy was the axillary region, consistent with the literature. The differences in the sites of lymphadenopathy involvement between the studies were probably related to the site of bacterial inoculation. However, we could not verify this because of a lack of information about the scratching area in the studies.

Although there was no significant difference in terms of lymphadenopathy size, the duration of LAP was statistically significant at 1 month in the IFA-positive group and 2 months in the IFA-negative group. Among patients with Possible CSD, 80.7% had a LAP duration shorter than 2 months. Similarly, previous studies have shown that the duration of LAP in patients with CSD lasts less than 1 month and mostly resolves spontaneously (11). We believe that it is useful to consider differential diagnoses when the duration of LAP is prolonged.

In our study, 24 patients with IFA titer ≥1:256 were included in the possible positive IFA group. In this group, unilateral LAP was significantly more frequent 79.1%. These findings are consistent with the literature and suggest that lymphadenopathy is located on the side of the inoculated area.

Study Limitations

The limitations of our study include the fact that there were no patients aged under 18 years, PCR was not used in diagnostic samples, and seasonality and inoculation site could not be determined. Patients who were requested for *Bartonella henselae* IgG but whose ICD-10 diagnostic criteria were not recorded may not have been reached. Due to the retrospective nature of the study, conditions that could cause false-positive results for *Bartonella henselae* IFA were excluded.

Conclusion

Our findings show that *Bartonella henselae* infection is not rare in Turkey. The initial symptoms of CSD vary and may cause difficulties for clinicians in making a definitive diagnosis. CSD should always be considered in the differential diagnosis of patients with cat contact and unilateral lymphadenopathy, particularly in the axillary and cervical regions. Although an IFA titer ≥1/256 supports the diagnosis, it must be considered that a negative IFA result does not rule out the possibility of CSD. This study provides important epidemiologic and serologic information about CSD in adult patients in our country; however, further studies using different diagnostic methods are necessary to determine the precise incidence.

Ethics

Ethics Committee Approval: This study was conducted with the approval of the University of Health Sciences Turkey Hamidiye Ethics Committee for Clinical Research (01.08.2024, 22.08.2024-24/477).

Informed Consent: Retrospective study.

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Authorship Contributions

Concept: B.S., A.A., Design: B.S., A.A., Data Collection or Processing: B.S., A.A., Analysis or Interpretation: B.S., Literature Search: B.S., A.A., Writing: B.S., A.A.

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CASE REPORT

Management of Multiple Mediastinal Lymph Node Metastasis in Synchronic Colorectal and Lung Carcinomas

Senkron Kolorektal Karsinomunda ve Akciğer Karsinomunda Multiple Mediastinal Lenf Nodu Metastazının Yönetimi

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Abstract

Metastasis of colorectal carcinomas to mediastinal lymph nodes is extremely rare. In this study, it is aimed to share our approach to mediastinal lymph nodes for treating colorectal carcinoma and lung carcinoma detected synchronously. Extended right hemicolectomy was performed when ileus was detected in the patient who presented to the emergency department with the complaint of abdominal pain. The pathological result was reported as signet ring cell carcinoma. The mass in the lung covered >80% of the right lower lobe. Right lower lobectomy and mediastinal lymph node dissection were performed. The pathological result was reported as large cell lung carcinoma. Colorectal carcinoma metastases were detected in subpleural tumor-like foci and mediastinal lymph nodes. There is no consensus on the treatment strategies for such cases. We believe that performing routine mediastinal lymph node dissection is important for determining prognosis and postoperative treatment strategies.

Keywords: Colon cancer, lung cancer, mediastinal lymph node metastasis, thoracic surgery

Öz

Kolorektal karsinomların mediastinal lenf nodlarına metastazı oldukça nadirdir. Bu olgu ile senkron olarak saptanan kolorektal karsinom ve akciğer karsinomunun tedavisinde mediastinal lenf nodlarına yaklaşımımızı paylaşmak istedik. Karın ağrısı şikayetiyle acil servise başvuran hastada ileus saptanması üzerine genişletilmiş sağ hemikolektomi gerçekleştirildi. Patoloji sonucu taşlı yüzük hücreli karsinom olarak raporlandı. Akciğerdeki kitle sağ alt lobun %80'inden fazlasını kaplamaktaydı. Hastaya sağ alt lobektomi ve mediastinal lenf nodu diseksiyonu gerçekleştirildi. Patoloji sonucu büyük hücreli akciğer karsinomu olarak raporlandı. Subplevral tümör benzeri odaklarda ve mediastinal lenf nodlarında ise kolorektal karsinom metastazı saptandı. Bu olguların tedavi stratejileri hakkında genel bir görüş birliği sağlanamamıştır. Prognoz tayininde ve postoperatif tedavi stratejilerinin belirlenmesinde rutin mediastinal lenf nodu diseksiyonun gerçekleştirilmesinin önemli olduğunu düşünüyoruz.

Anahtar kelimeler: Akciğer kanseri, kolon kanseri, mediastinal lenf nodu metastazı, torasik cerrahi

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Introduction

Colorectal cancers (CRC) are one of the most common malignancies seen in developed countries (1). CRC most commonly metastasizes to the regional lymph nodes, liver, bone, lung, and brain. Metastasis of CRC in isolated mediastinal lymph nodes are very rare. When the literature is reviewed, it is seen that there are only a few case reports (2). In this study, it is aimed to report the management of a patient with colon carcinoma with isolated multiple mediastinal lymph node metastases by thoracic surgeons.

Case Report

A 61-year-old male patient presented to the emergency department with abdominal pain. Abdominal computed tomography (CT) revealed dilatation (ileus) in the small bowel loops (Figure 1A, B). General surgeons performed extended right hemicolectomy. On abdominal CT, a diameter of approximately 8x5.5 cm was also observed in the lower lobe of the right lung in the upper sections (Figure 1C). Postoperative positron emission tomography/CT was performed. In the lower lobe of the right lung,

there was a mass of approximately 80x55x85 mm. The maximum uptake (SUV_{max}) of the mass, standardized with 18-fluorodeoxyglucose (18-FDG), was 16.8 (Figure 1D-F). Low levels of relatively increased 18-FDG uptake were observed in the right lower paratracheal, subcarinal, and right hilar lymph nodes in the mediastinum (SUV_{max}: 2). Transthoracic biopsy was performed for the mass in the lower lobe of the right lung. In the pathology report, it was not possible to distinguish whether the lung mass was primary lung cancer or colon carcinoma metastasis. The colon surgery pathology result was reported as signet ring cell carcinoma (Figure 2A-C).
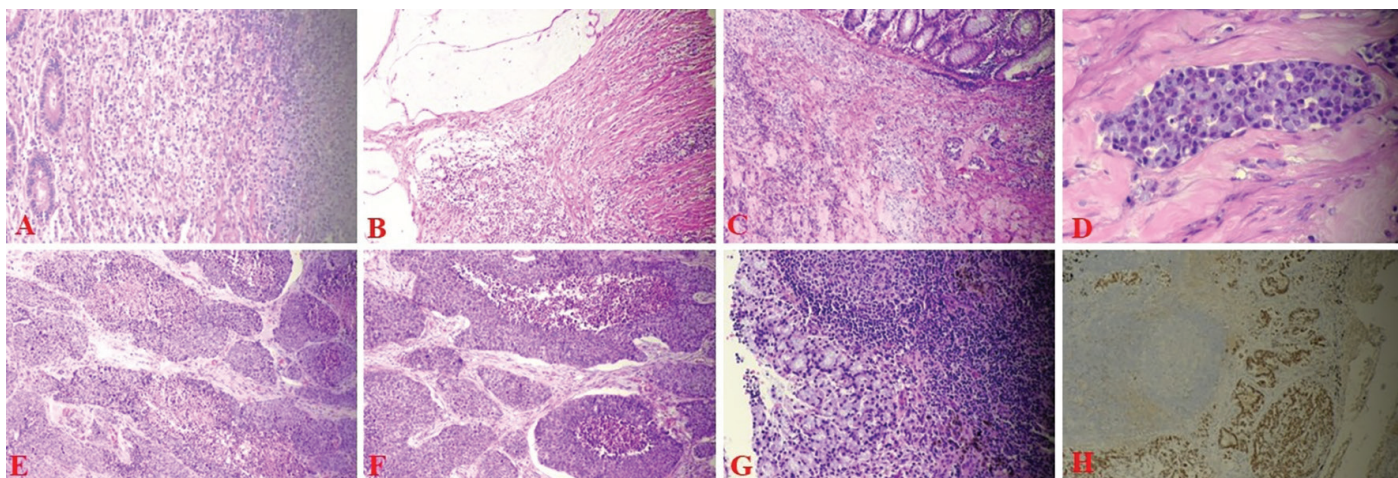
In the intraoperative evaluation, it was observed that the mass occupied more than 80% of the lower lobe of the right lung. Therefore, we preferred right lower lobectomy rather than wedge resection for metastasectomy. Because the diagnosis of metastasis was not certain, we performed mediastinal lymph node dissection. The postoperative pathology was reported as large cell lung carcinoma (Figure 2D, E, Figure 3). Signet ring cells and poorly differentiated adenocarcinoma metastases in the colon were detected in
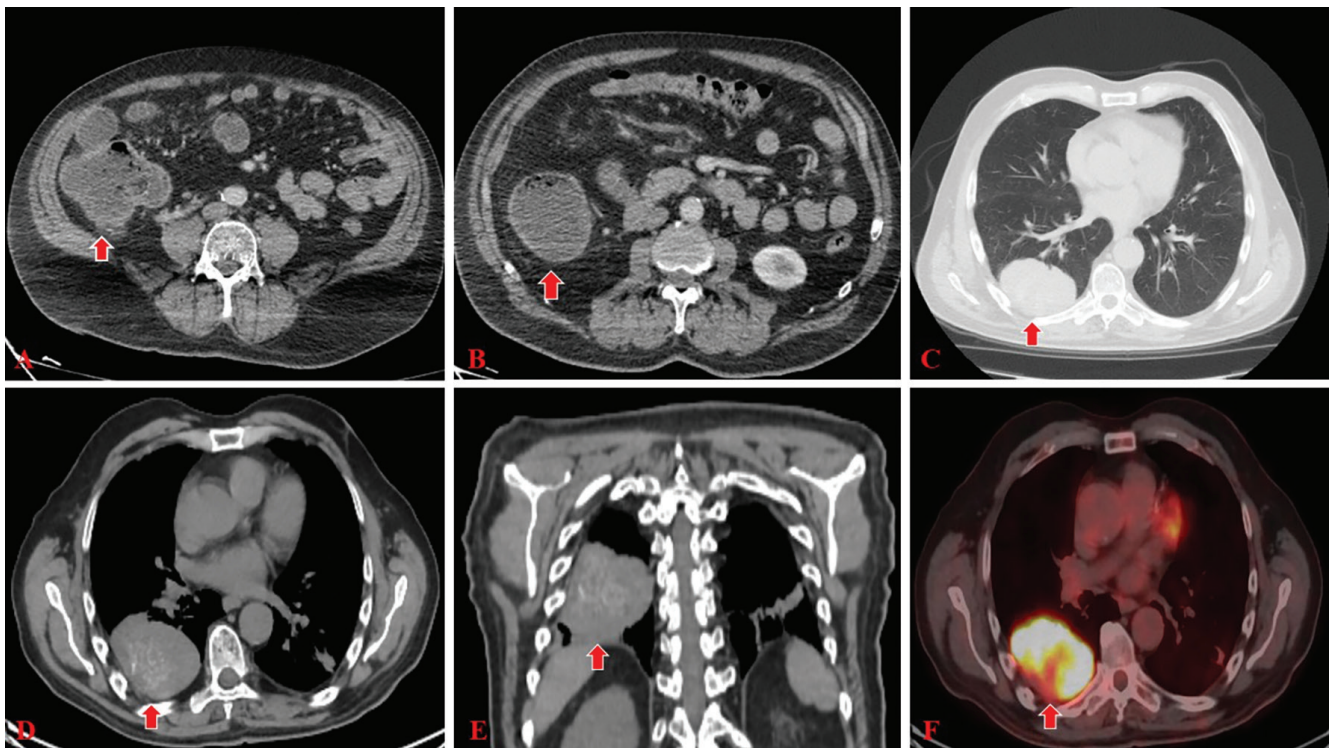
Figure 1. A, B) A 10-cm-long, 4.5-cm-thick mass lesion consistent with a malignant process starting from the 2nd stanza of the duodenum and extending proximally to the 3rd part, significantly narrowing the lumen, **C)** 8x5.5 cm mass located in the lower lobe of the right lung on the upper sections of the abdominal CT, **D, E)** On PET/CT showed a mass lesion in the posterior lower lobe of the right lung approximately 80x55x85 mm in size with soft tissue density, pleural-based lobule contour, containing calcifications accompanied by ground glass densities around it, F) SUV_{max} uptake of lung mass on PET/CT (16.8)

PET/CT: Positron emission tomography/computed tomography

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Figure 2. A) Right hemicolectomy material, signet ring cell carcinoma, tumor size 4.5 cm (HE x200), **B)** Extracellular mucin areas accompanying the tumor (HE x100), **C)** Signet ring cells observed beneath the villi (HE x100), **D)** Vascular invasion of a tumor in the colon (HE x400), **E, F)** Tumor in the lung with necrotic tumor islands in the center (9x8.5x4 cm) (HE x100), **G)** Mediastinal lymph node with signet ring cells (HE x200), H) Mediastinal lymph node, positive immune reaction with CDx2 (x100)
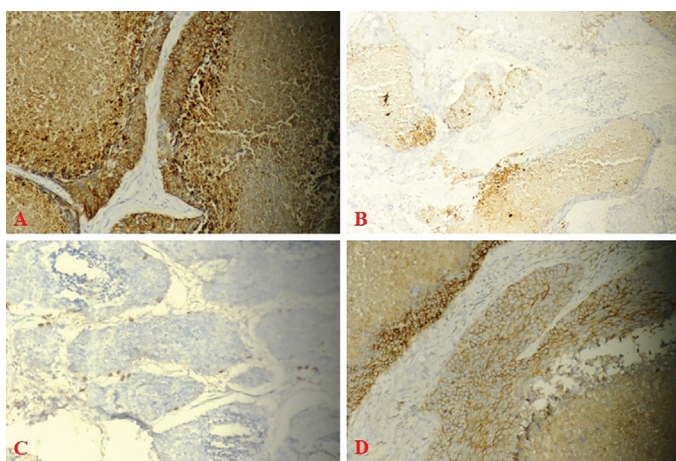
Figure 3. A) Positive immune reaction with Cam5.2 (x200), **B)** Positive immune reaction with Ck7 (x100), **C)** Positive immune reaction with Ck7 (x200), **D)** Positive immune reaction with CD56 (x200)

subpleural tumor-like foci in the lower lobe. It was reported as poorly differentiated colon adenocarcinoma metastases in the mediastinal lymph nodes (Figure 2F, G). Metastasis of lung malignancy was not observed in the mediastinal lymph nodes.

The mass in the lung was accepted as T4N0M0. The mass in the colon was accepted as T4N2M1. The patient was scheduled for chemotherapy every 2 weeks for 8 months and 3 weeks of radiotherapy at the end of chemotherapy. The patient had an acute pancreatitis attack after the fifth radiotherapy session. He was followed up in the intensive care unit. He died on the third day of hospitalization in the intensive care unit because of sepsis.

Discussion

Metastases of CRC usually spread via the portal venous system to local or regional lymph nodes or the liver. Metastases may initially occur as pulmonary metastases (3). Metastasis from CRC to the mediastinal lymph nodes are very rare. It has been reported in the literature only as a case report. Metastases of CRC to the mediastinal lymph nodes are thought to spread via the lymphatic drainage pathways of the liver in patients with liver metastases and via the paravertebral/paraaortic lymphatic plexus in patients with abdominal or pelvic extension (2). Our patient did not have liver metastases, but there was colon carcinoma metastasis in tumor-like foci in the subpleural region of the right lower lobe. We believe that the spread in the mediastinal lymph nodes may have originated in similar ways without intra-abdominal spread or from pulmonary metastases.

In a study investigating survival after resection of lung metastases in patients with CRC, 25 studies involving at least 40 patients were evaluated. A total of 2.925 patients were analyzed. Poor prognostic factors included short disease-free survival, multiple lung metastases, positive hilar or mediastinal lymph nodes, and a high pre-thoracotomy carcinoembryonic antibody level (4). Because our patient had both hilar and mediastinal lymph node metastases, we predicted poor survival.

The approach to mediastinal lymph node metastases in patients with lung metastases in CRC remains uncertain. The necessity of mediastinal lymph node dissection remains controversial. The general approach is that

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systematic hilar and mediastinal lymph node dissection should not be routinely performed in metastasis surgery (5). In our case, it was preferred to perform mediastinal lymph node dissection even though SUV_{max} values were below 2.5 because it was not possible to distinguish whether the lung mass was primary lung cancer or colon carcinoma metastasis. Thanks to the lymph node dissection performed, the TNM stage of the mass in the colon and lung changed. The change in the staging of the masses supports our prediction that the prognosis will be poor because of the involvement of hilar and mediastinal lymph nodes.

Conclusion

Metastasis of CRC in mediastinal lymph nodes are extremely rare. There is no consensus on the treatment strategies. We believe that it is important to perform routine mediastinal lymph node dissection in the resection of lung masses that cannot be differentiated from primary lung cancer and metastases, if there is a diagnosed cancer in the body, in determining the prognosis and determining postoperative treatment strategies.

Ethics

Informed Consent: Written informed consent was obtained from the patient for their anonymized information to be published in this article.

Authorship Contributions

Concept: B.Ö.Ç., K.A., Design: B.Ö.Ç., K.A., Data Collection or Processing: B.Ö.Ç., F.S., S.S.E., Analysis or Interpretation: B.Ö.Ç., N.K., O.K., Drafting Manuscript: B.Ö.Ç., K.A., N.K., Critical Revision of Manuscript: B.Ö.Ç., K.A., F.S., S.S.E., Final Approval and Accountability: B.Ö.Ç., K.A., N.K., F.S., S.S.E., O.K., Technical or Material Support: B.Ö.Ç., K.A., N.K., F.S., S.S.E., O.K., Supervision: K.A., Writing: B.Ö.Ç., K.A., N.K., F.S., S.S.E.

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CASE REPORT

Reconstruction of a Misleading Sebaceous Gland Lesion of an Eyelid: A Case Report

Göz Kapağında Yer Alan Yanıltıcı Bir Sebase Gland Lezyonunun Rekonstrüksiyonu: Olgu Sunumu

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Abstract

Sebaceous carcinoma is a highly malignant eyelid tumor with a notable morbidity and mortality rate. Delay in the diagnosis occurs usually; due to benign formations that are confused in the differential diagnosis. We report the case of sebaceous gland carcinoma in a 61-year-old male patient who presented with a long-standing nodule on the right upper eyelid and had right parotid lymph nodes metastases. After wide excision, reconstruction of the oncologic defect was performed considering the functional and aesthetic results. No residual disease was found in the 4-year follow-up. Successful management of sebaceous gland carcinoma consists of early diagnosis, complete removal of the tumor, and a satisfactory reconstruction method. Treatment should be designed on the basis of the tumor and the patient's needs.

Keywords: Eyelid, reconstruction, sebaceous carcinoma, wide local excision

Öz

Sebase karsinom, önemli bir morbidite ve mortalite oranına sahip oldukça malign bir göz kapağı tümörüdür. Ayırıcı tanıda benign lezyonlar ile karışmasından dolayı tanıda gecikme sık yaşanır. Sağ üst göz kapağında uzun süredir var olan nodül ve sağ parotis lenf nodu metastazı ile başvuran 61 yaşında erkek hastada tanı konan sebase bez karsinomu sunulmaktadır. Geniş eksizyon sonrası fonksiyonel ve estetik sonuçlar göz önünde bulundurularak onkolojik defekt rekonstrüksiyonu yapılmıştır. Dört yıllık takibinde rezidüel hastalık saptanmamıştır. Sebase gland karsinomunun başarılı tedavisi, erken teşhis, tümörün tamamen çıkarılması ve tatmin edici bir rekonstrüksiyon yönteminden oluşmaktadır. Tedavi, tümöre ve hastanın ihtiyaçlarına göre tasarlanmalıdır.

Anahtar kelimeler: Geniş lokal eksizyon, göz kapağı, rekonstrüksiyon, sebase karsinom

Introduction

The eyelids are an anatomical region where roughly 5-10% of all skin cancers occur (1). The most frequent skin tumors in this region are basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) (2). Sebaceous gland carcinoma (SGC) is a rare tumor with morbidities, such as up to orbital exenteration and mortality. This tumor can develop in Meibomian, Zeis, and other sebaceous glands of the eyelid (3). In 1891, Allaire described SGC for the first time (4). A rare cancer that primarily affects the head and neck region. It can behave aggressively and can be either ocular or

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extraocular (5). The ocular region is seen more commonly (34.5-59%) (6), and according to a study by Orr et al. (5), the eyelids are involved in 39% of SGCs. Tumors in the ocular region are seen mainly in the Meibomian, caruncle, and Zeiss glands and eyebrows. Upper eyelids are more frequently affected than lower eyelids because they contain more sebaceous glands. The average age at diagnosis was 67 years. Tumors are more common in women (7). Demographically, Asian people are affected more than other ethnic groups by these tumors (8).

SGC can mimic benign lesions. Therefore, delayed diagnosis is frequently observed. Initially, a preliminary diagnosis can be made of chalazion, chronic conjunctivitis, posterior blepharitis, or Meibomian cyst. In the advanced stages, when the lesion resists local treatment or surgical drainage, the preliminary diagnosis is SCC, BCC, or even lymphoma (9).

The clinical manifestations of madarosis include destruction of the eyelid edge, generalized thickening of the eyelid, and facial shrinkage (10). In the present case, the telangiectatic appearance in the anterior part of the lesion suggests BCC; the fleshy, degradable lower part of the lesion suggested SCC.

Pathogenesis is unknown. Predisposing factors include Muir-Torre syndrome (MTS), periocular radiation, hereditary retinoblastoma, and immunosuppression (10). MTS is an inherited autosomal dominant syndrome linked to sebaceous adenoma or carcinoma, as well as gastrointestinal, endometrial, and urological malignancies. Therefore, patients with SGC should be aware of long-term internal malignancies. Although the patient did not have any radiation exposure or other comorbidities in his/her history, SGC was diagnosed.

SGC has three histological growth patterns: Lobular, comedocarcinoma, and papillary carcinoma. The presented patient's histological type is lobular carcinoma, the most common type (11). The different morphological patterns in the lesion may overlap. Some immunohistochemical staining and proteins can be used for the diagnosis of SGC. Of these, EMA, Ber-Ep4, androgen receptor, and adipophilin were found to be significant (11). EMA, Ber-Ep4, and adipophilin protein were positive in the present case. In lobular patterns, poorly differentiated cells are peripheral between normal sebaceous glands; well-differentiated lipid-producing cells are located in the center. The papillary pattern typically presents as a small conjunctival tumor with fleshy papillary projections. The Comedocarcinoma

subtype is characterized by a large central necrotic core and living cells around it (12).

Poor prognostic factors include longer than six months, vascular-lymphatic infiltration, poor differentiation, extension to the orbit, pagetoid spread, intraepithelial carcinomatous alteration, and upper eyelid involvement. In the present case, a nodular mass was observed on the upper eyelid for 5 years, suggesting poor prognosis. Recurrence occurs in 9-36% of cases. Local metastasis occurs in the parotid, submandibular, and cervical lymph nodes. At the same time, distant metastases occur in the lung, liver, skull, and brain (13), according to a study by Sa et al. SGC with a diameter >20 mm was correlated with an increased risk of local recurrence, lymph node metastasis, distant metastasis, and death from the disease (7). When a tumor involves the entire eyelid, the risk of lymph node and distant metastases increases, even if the tumor diameter exceeds 10 mm. In the study, local recurrence was 6%, lymph node metastasis was 21%, distant metastasis was 7%, and the mortality rate from the disease was 6%. After definitive treatment, metastasis and local recurrence are usually observed within the first 2 years. Metastasis after 5 years is extremely rare (7).

In such an important facial esthetic unit, surgery is the mainstay of treatment. Total parotidectomy, radical neck dissection, and radiation therapy are recommended for patients with regional lymph node metastases. Cryotherapy or radiotherapy may be beneficial for patients who are not candidates for surgery (10). Chemotherapy is used for recurrent, metastatic lesions, but there is no high-level of evidence (13).

This report aimed to present the excision and reconstruction of a lesion that mimics a benign lesion that has been present for a long-time in an esthetically and functionally significant facial unit.

Case Report

A 61-year-old male patient was admitted to the plastic surgery outpatient clinic with the complaint of a mass on the right upper eyelid that had developed in 5 years. Initially, the patient was misdiagnosed because the palpebral mass was negligible and confused with infection. On clinical examination, a firm, painless nodule-like mass was observed covering more than 80% of the right upper eyelid (Figure 1A). Except for hypertension and long-term smoking, the patient had no additional disease and no characteristics-feature in his family history.

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The patient underwent magnetic resonance imaging (MRI), ultrasonography, and positron emission tomography for tumor characterization. Orbital MRI did not reveal any expansion into the orbit. In addition, no pathological lymph nodes were detected on neck ultrasonography. Positron emission tomography revealed 11-mm hypermetabolic metastatic lymphadenopathy in the right preauricular region and a 2-cm hypermetabolic area in the right parotid gland.

Tru-cut biopsy was performed on the parotid gland. The presence of carcinoma infiltration was confirmed. According to the American Joint Committee, the patient had regional cancer of grade T(3c)N(Ia)M(0) that had spread only to the nearby right preauricular lymph nodes and right parotid gland. The ophthalmology department did not recommend orbital excision. Two-stage treatment was administered in March 2018. In the first operation, the tumor was completely excised, with a full-thickness upper eyelid and a 5-mm margin of intact skin (Figure 1B). After resection, a 3.5 cm x2 cm full-thickness tissue defect affecting 80% of the upper eyelid was formed (Figure 1C). The posterior lamella of this defect was reconstructed with a transconjunctival interpolation flap, similar to the Cutle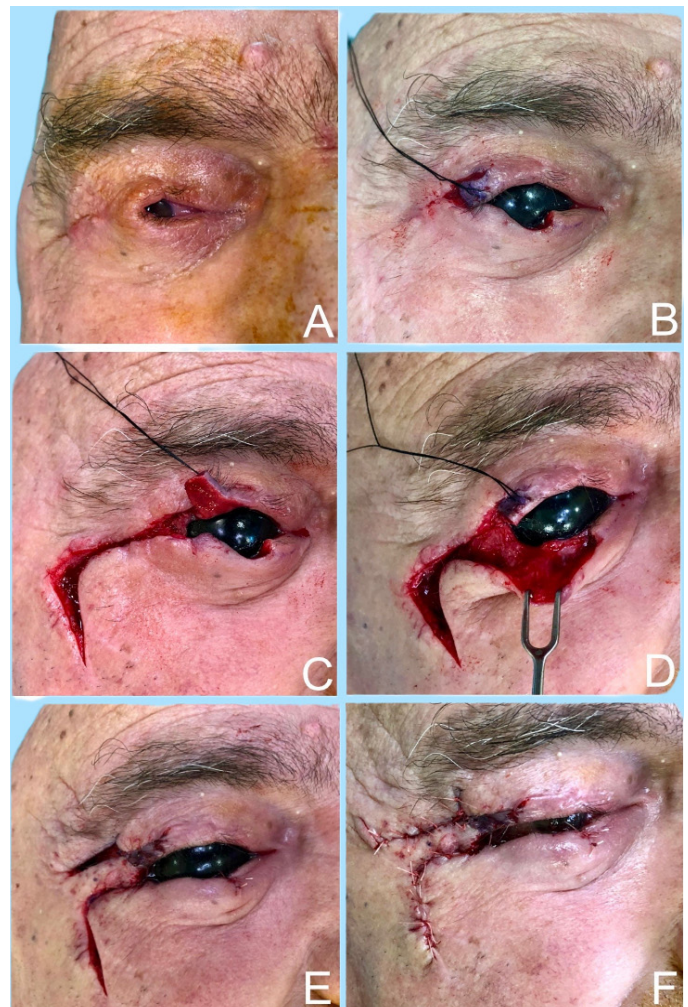r beard flap. The anterior lamella was reconstructed using a lower eyelid-based fasciocutaneous transposition flap. The right lower eyelid donor site was reconstructed using a right cheek advancement flap (Figure 1D). Simultaneously, superficial parotidectomy was performed. The pathology department diagnosed the patient with SGC. After the patient's first surgery, six sessions of adjuvant chemotherapy were administered to the oncology clinic.

In the second operation, after waiting for revascularization, the interpolation flap was separated (Figure 2). Later, the right upper eyelid was revised due to lateral canthal narrowing. The right cheek advancement flap was removed for attachment to the lateral canthus. A conjunctival flap is applied to complete the periorbital reconstruction.

After discharge, follow-up was performed at 3-month intervals in the plastic surgery and oncology outpatient clinics.

Figure 1. A. Preoperative view of the mass covering 80% of the right upper eyelid, **B.** 3.5 cm x2 cm sized excisional biopsy material, **C.** The right upper eyelid defect, **D.** First session: tarsoconjunctival interpolation flap and cheek advancement flap

Figure 2. A. Lateral canthal narrowing, **B.** Interpolation flap is shown, C. Interpolation flap separation, **D-F.** Advancement of right cheek advancement flapand upper eyelid flap to lateral canthus.

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In early and late follow-ups, muscle integrity was not impaired while blinking. There is no dry eye or lagophthalmos. The second and fourth-year follow-up images demonstrate bilateral symmetry (Figure 3) without ectropion, contracture, or lagophthalmos. No complications or recurrent lesions were observed during follow-up. The oncology council recommended radiation therapy as an adjuvant therapy.

This study is a case report, and the University of Health Sciences Turkey Ethics Committee confirmed that there was no need for ethics committee approval. The patient provided informed consent. Research related to human use was conducted in accordance with the tenets of the Helsinki Declaration.

Figure 3. The patient's dynamic pictures in the postoperative second (**A, C, E**) and forth (**B, D, F**) years demonstrate minimal deformity with optimal aesthetic and functional results

Discussion

The eyelids form a major esthetic and functional unit of the upper face. Trauma and oncologic resection are common etiologies of upper face defects. In the present case, the initial specimen obtained from the right upper eyelid tumor 5 years previously corresponded to an infected lesion. Diagnosis was delayed and misdiagnosed because of poor sebaceous differentiation.

Treatment is shaped according to the histopathological type, stage, and patient preference. However, surgery is a cornerstone in the treatment planning. After full-thickness eyelid biopsy, a wide excision with a safe surgical margin of 5 mm is recommended. When the tumor involves the bulbar conjunctiva and periorbital reconstruction is not possible, exenteration is required. A well-designed reconstruction should be designed to cover the defect after oncological resection to restore eyelid function and achieve a satisfying esthetic result. In patients with full-thickness eyelid defects, anterior and posterior lamella reconstruction should be performed. Although there are various algorithms for reconstructing eyelid skin and subcutaneous tissue (Table 1), planning is performed individually and requires the surgeon's creativity; according to the current literature, reconstruction options are still limited for total or near total upper eyelid defects. Defects occurred after excision of SGC with healthy margins that required appropriate posterior and anterior lamellar reconstruction. In similar cases, some eyelid-sharing methods, such as Cutler beard flap, Switch flap, or pericranial galeal flap, or Tenzel's semicircular flap, can be preferred (14-16). Eyelid-sharif methods inherently pose patient discomfort and temporary visual impairment but provide "like for like" reconstruction options. Other flap options, such as cheek advancement or Tenzel's semicircular flaps, have less tissue, similar to periorbital flap options. In the present case, transconjunctival interpolation and fasciocutaneous local flap were devised because of the local flap's advantages. These include tissue, color, and shape harmony. As a result, the eyelid function was improved.

Table 1. Algorithm for full-thickness upper eyelid reconstruction based on the defect size (14)	
Size of eyelid margin defect (eyelid width)	Repair
<25%	Direct closure
25-50%	Direct closure with lateral cantholysis
25-50%	Tarsal rotation flap and skin-muscle flap or skin graft
25-75%	Tarsoconjunctival graft and skin-muscle flap
33-66%	Semicircular flap with periosteal flap
50-100%	Cutler-beard flap

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Conclusion

SGC accounts for less than 1% of all skin malignancies. Diagnosis may be delayed for years due to its tendency to mimic benign eyelid lesions. To prevent high morbidity and mortality in patients with this cancer, clinicians should always be cautious in the preliminary diagnosis. Treatment methods vary from one patient to another, according to the histopathological characteristics of the tumor and its dissemination. However, wide excision and functionally, esthetically acceptable reconstruction are the basis of this treatment.

Ethics

Informed Consent: The patient provided informed consent.

Authorship Contributions

Surgical and Medical Practices: P.K., L.J.M.S., S.Ö., K.Ö., Concept: L.J.M.S., S.Ö., K.Ö., Design: L.J.M.S., S.Ö., K.Ö., Data Collection or Processing: P.K., L.J.M.S., S.Ö., K.Ö., Analysis or Interpretation: P.K., S.Ö., K.Ö., Literature Search: P.K., S.Ö., Writing: P.K., L.J.M.S., S.Ö., K.Ö.

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Surgical Treatment in Young Breast Cancer Patients is Challenging

Genç Meme Kanseri Hastalarının Cerrahi Tedavisinde Karşılaşılan Zorluklar

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Dear Editor,

Breast cancer is the most common cancer in women (1). As the proportion of breast cancer among young women (aged ≤40 years) incidence is increased up to 11% of new cases, the importance of young breast cancers is increasing (1,2).

Young breast cancer patients are mostly diagnosed late due to low mammographic sensitivity and absence of radiological breast cancer screening programs. The previous studies showed that the majority of young breast cancer patients had ductal histology (86.5%) and grade III (58.9%) tumors. Node-positive disease were observed in 50.2%, multifocality was around 27%. One third of tumors were estrogen receptor negative and one quarter was HER2 positive. They present more frequently (34.3%) with high basal-like tumors compared with older patients (20%) (3). They have higher risk of breast cancer predisposing gene mutations like *BRCA1*, *BRCA2*, *TP53*, *PALB2*, *PTEN*, *CHEK2*, *ATM*, etc. (2). As a result, breast cancer specific survival rates are lower and breast cancer recurrence risk is higher in this age group (2).

Surgery in young breast cancer patients is challenging. These patients mostly have doubts in surgical choice between mastectomy and breast conservation surgery (BCS) (4). The increased risk of death and recurrence rates direct surgeons and patients to choice more radical surgical treatments. Sun et al. (5) showed that according to surveillance, epidemiology, and end results database, by the end of the 20th century, the proportion of BCS had grown from nearly 35% to approximately 60%. However, in the 21st century, BCS gradually fell to 35% again (5). This BCS rate decrease is mostly due to increased rates of mastectomies and prophylactic mastectomies in young patients. After mastectomy young patients may face many psychosocial problems in body image, sexuality, job and fertility issues (6,7). After cancer surgery they seek reconstructive surgeries and rate of reconstruction with prothesis is increasing. This process bring out disadvantages such as loss of sensation, risk of repeat surgeries for cosmesis, increased costs, loss of ability to breast-feeding (7).

Although mastectomy surgeries supported by reconstructive techniques are increasing today, I would like to draw attention to the literature data, especially in early stage young breast cancer patients. For early stages, data from current reviews and meta-analyses showed that, breast conserving surgery provides similar overall survival rates compared to mastectomy for young breast cancer patients (5,8,9). With modern multidisciplinary management approaches, prognosis is better in young breast cancer patients nowadays (10). Considering these

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factors, radical surgical approaches in selected patient groups may be unnecessary. It should be kept in mind that, oncoplastic techniques can be applied among BCS options and better cosmetic results can be achieved even in large tumors. Reducing the diameter of the mass with neoadjuvant chemotherapy is also an effective method to achieve good cosmetic results.

A very meticulous individualized approach including cancer biology, tumor stage, genetic mutations, psychosocial effects and cost effectiveness is very important for choosing surgical treatment for young breast cancer patients.

Keywords: Breast cancer, surgery, young patient

Anahtar kelimeler: Cerrahi tedavi, genç hasta, meme kanseri

Ethics

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