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ORIGINAL RESEARCH

Bagcilar Med Bull 2025;10(2):106-115
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Evaluation of Demographic Characteristics, Working Conditions, Depression, Anxiety and Insomnia Levels of Health Workers During the COVID-19 Pandemic Period

COVID-19 Pandemisi Döneminde Sağlık Çalışanlarının Demografik Özellikleri, Çalışma Koşulları, Depresyon, Kaygı ve Uykusuzluk Düzeylerinin Değerlendirilmesi

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Abstract

Objective: The coronavirus disease-2019 (COVID-19) pandemic has caused an increase in psychiatric disorders such as depression, anxiety, insomnia, and suicidality in the community. Therefore, we aimed to determine the frequency, severity, and factors affecting depression, anxiety, and sleep disorders in healthcare workers during the pandemic.

Method: In our study, 558 healthcare workers were surveyed online, and their occupation, their status as frontline workers, their chronic diseases, their COVID-19-related training, the presence of their personal protective equipment, the frequency and duration of their shifts in pandemic units, and their exposure to negative and positive discrimination were determined. The generalized anxiety disorder 7, insomnia severity index, and center for epidemiologic studies depression scale questionnaires were administered to all patients.

Results: It was determined that 28% of the participants had insignificant clinical insomnia, 43.5% had subthreshold insomnia, 22.4% had moderate clinical insomnia, and 6.1% had severe clinical insomnia. Of the

Öz

Amaç: Koronavirüs hastalığı-2019 (COVID-19) pandemisi toplumda depresyon, anksiyete, uykusuzluk ve intihar eğilimi gibi psikiyatrik bozuklukların artmasına neden olmaktadır. Bu nedenle biz pandemi sürecinde sağlık çalışanlarında depresyon, anksiyete ve uyku bozukluklarının sıklığını, şiddetini ve etkileyen faktörleri belirlemeyi amaçladık.

Yöntem: Çalışmamızda 558 sağlık çalışanına çevrim içi anket uygulandı ve meslekleri, ön cephe çalışanı olma durumları, kronik hastalıkları, COVID-19 ile ilgili eğitimleri, kişisel koruyucu ekipman varlığı, pandemi birimlerinde vardiya sıklığı ve süresi, negatif ve pozitif ayrımcılığa maruz kalma durumları belirlendi. Tüm hastalara yaygın anksiyete bozukluğu 7, uykusuzluk şiddet indeksi ve epidemiyolojik araştırmalar merkezi depresyon ölçeği anketleri uygulandı.

Bulgular: Katılımcıların %28'inin klinik olarak önemsiz derecede uykusuzluk, %43,5'inin eşik altı uykusuzluk, %22,4'ünün orta derecede klinik uykusuzluk ve %6,1'inin ciddi klinik uykusuzluk yaşadığı belirlendi.

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Abstract

subjects, 34.9% had mild anxiety, 21.3% had moderate anxiety, and 12.5% had severe anxiety. Of the participants, 11.8% were mildly depressed, 26% were moderately depressed, and 31.4% were severely depressed. Insomnia, anxiety, and depression were more severe in women, frontline workers, those who worked shifts in COVID-19 clinics, nurses, those without personal protective equipment, those subjected to negative discrimination, and those implied by family or friends to be carriers of the virus.

Conclusion: Depression and anxiety are more frequent and severe among frontline healthcare workers during pandemic periods. Therefore, necessary social and psychological support should be provided to these individuals.

Keywords: Anxiety, COVID-19 pandemic, depression, health care workers, insomnia

Öz

Olguların %34,9'unda hafif, %21,3'ünde orta ve %12,5'inde şiddetli kaygı vardı. Katılımcıların %11,8'i hafif, %26'sı orta ve %31,4'ü şiddetli depresyondaydı. Kadınlarda, ön cephede çalışanlar, COVID-19 kliniklerinde nöbet tutanlar, hemşireler, kişisel koruyucu ekipmanı olmayanlar, negatif ayrımcılığa maruz kalanlar, aile veya arkadaşlar tarafından virüs taşıyıcısı olabileceği ima edilenlerde uykusuzluk, kaygı ve depresyon daha şiddetliydi.

Sonuç: Pandemi dönemlerinde ön saflarda çalışan sağlık çalışanlarında depresyon, anksiyete ve depresyon daha sık ve şiddetlidir. Bu nedenle bu bireylere gerekli sosyal ve psikolojik destek sağlanmalıdır.

Anahtar kelimeler: Anksiyete, COVID-19 pandemisi, depresyon, sağlık çalışanları, uykusuzluk

Introduction

On December 31, 2019, the first case of coronavirus disease-2019 (COVID-19) was reported in Wuhan city, Hubei province, China (1). This infection has affected most of the world's population and was declared a pandemic by the World Health Organization on 11 March 2020 (2). Since it was a newly emerging infection, there was uncertainty about the prevention, etiopathogenesis, clinical course, and treatment methods of COVID-19. In addition, social restrictions were implemented due to the increasing number of cases exceeding the health capacity in various countries (3). People started to spend most of their time isolated at home (3). Psychiatric disorders such as anxiety disorder and depression began to emerge in people due to the uncertainties surrounding the disease and its treatment on the one hand and the social and economic problems caused by restrictions on the other (4).

As in all pandemics, healthcare workers are on the front line of COVID-19. For long hours, they are in the same environment as patients who are known to have COVID-19. COVID-19 infection, which is known to be transmitted through droplets, is riskier for healthcare workers than for the general public due to increased viral transmission (5). The fact that infected healthcare workers accounted for 29% of all hospitalized COVID-19 patients in the early stages of the pandemic indicates this risk (6). The high number of healthcare workers who are infected and cannot continue their work due to the quarantine period or illness increases the workload of other healthcare workers. Long-term work, social loneliness, and inadequate protection measures negatively affect the mental health of healthcare workers (7).

During the pandemic period, healthcare workers, worried that they would carry the virus to their relatives and friends, tried to isolate themselves for a long time. As a result of this isolation, it started to cause psychological problems such as irritability, anger, insomnia, concentration disorder, loneliness, anxiety, depression, and suicide risk in healthcare workers (8-11). In this study, we investigated the demographic characteristics, working conditions, severity of depression, anxiety, and sleep disorders, and the factors associated with them, among healthcare workers during the COVID-19 pandemic.

Materials and Methods

Ethics committee approval was obtained for this study from the Ethics Committee of Atatürk University, dated 28.05.2020, numbered B.30.2.ATA.0.01.00/33. This study was conducted in accordance with the Helsinki Declaration, revised in 2013, "Ethical Principles for Medical Research Involving Human Subjects". The study was designed as cross-sectional, and data were collected through an online questionnaire prepared on Google forms and applied to the participants. Informed consent was obtained from all participants online before filling out the form. A questionnaire consisting of 4 subgroups including descriptive characteristics, generalized anxiety disorder-7 (GAD-7), insomnia severity index (ISI), and the center for epidemiologic studies-depression (CES-D) questionnaire was applied to 558 study participants.

The sample size was first determined for the study. Since it was conducted during the pandemic, clear information about the study population size could not be obtained.

Therefore, the total sample size was determined using the G*Power program with an effect size of 0.15, 95% power, and 5% margin of error.

Healthcare workers in wards, outpatient clinics, emergency, and intensive care units where patients diagnosed with COVID-19 were followed up were considered frontline workers. In the descriptive characteristics questionnaire, the age, gender, comorbid diseases, occupation, institution of employment, whether they received training about COVID-19 in the institution where they work, whether a frontline worker, whether they had personal protective equipment, whether shifts in the COVID-19 service, frequency and duration of shifts, whether exposed to negative or positive discrimination because of being a healthcare worker, and whether being told or implied that they might carry the virus by their family or environment were asked.

The GAD-7 questionnaire was developed by Spitzer et al. (12). Its Turkish validity and reliability were assessed by Konkan et al (13). It consists of 7 questions, with each scoring ranging from 0-3 points, and the total score is 0-21. A total score of 0-4 is considered normal, 5-9 is considered mild, 10-14 is considered moderate, and 15-21 is considered severe anxiety. A score of 10 is also the cut-off score for a possible diagnosis of generalized anxiety disorder. When the threshold for the total score of the scale is set as 10 points, the sensitivity and selectivity of the scale are 89% and 82%, respectively.

The ISI scale was developed by Bastien et al. (14). The Turkish version of the scale's validity and reliability were assessed by Boysan et al. (15). It consists of 7 questions scored between 0 to 4 and the total score is 0 to 28 points. A total score of 0-7 is clinically insignificant insomnia; 8-14 is subthreshold insomnia; 15-21 is moderate clinical insomnia; and 22-28 is severe clinical insomnia.

The Turkish validity and reliability of the CES-D scale were assessed by Tatar et al. (16). It consists of 20 questions scored 0-4; the total score is 0-60. Zero to fifteen points indicate no depression, sixteen to twenty points indicate mild depression, twenty-one to thirty points indicate moderate depression, and thirty-one or more points indicate severe depression.

Statistical Analysis

Statistical analyses were performed with NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA). Descriptive statistical methods (mean, standard deviation, median, frequency, percentage, minimum, maximum) were used to evaluate the study data. The conformity of quantitative data to normal distribution was evaluated by the Shapiro-Wilk test and graphical analysis. An Independent samples t-test was used for comparisons of quantitative variables with normal distribution between two groups, and the Mann-Whitney U test for those without normal distribution. Comparisons of quantitative variables with normal distribution between more than two groups were performed with One-Way Analysis of Variance, and Bonferroni-corrected pairwise evaluations. The Kruskal-Wallis test and Dunn-Bonferroni test were used for comparisons of quantitative variables, that did not show normal distribution, across more than two groups. Qualitative data were compared using the Pearson chi-square test, Fisher's exact test, and Fisher-Freeman-Halton exact test. Pearson correlation analysis and Spearman correlation analysis were used to evaluate the relationships between quantitative variables. Statistical significance was accepted as $p<0.05$.

Results

In our study, 558 healthcare workers, including 186 males (33.3%), and 372 females (66.7%), were evaluated. The ages of the subjects ranged between 21 and 70 years, with a mean age of 39.88±9.23 years. The participants included 55.7% physicians (n=311) 19% nurses (n=106) 6.3% midwives (n=35) 6.3% secretaries (n=35) 3.4% emergency medical technicians (EMT) (n=19) 1.1% dentists (n=6) 1.1% cleaning personnel (n=6) and 7.2% other healthcare workers (n=40). Of the participants, 16.1% (n=90) were working in family health centers (FHC), 28.9% (n=161) in public hospitals, 5.2% (n=29) in private hospitals, 0.9% (n=5) in community health centers, 41.4% (n=231) in university hospitals, and 7.5% (n=42) in other health institutions.

The answers to the descriptive survey questions asked of the participants are shown in Table 1. It was found that 27.2% (n=125) of the participants had chronic diseases. When the distribution of chronic diseases was analyzed: 46.4% (n=58) hypertension, 12% (n=15) chronic lung disease, 20% (n=25) diabetes mellitus, 12.8% (n=16) chronic heart disease, 6.4% (n=8) hypothyroidism, 2.4% (n=3) migraine. Participants had an average of 4.61±4.26 shifts per month in the units where COVID-19 patients were followed up. The duration of shifts was determined to be 10.84±4.06 hours per day.

The ISI scale scores of the subjects who participated in the study ranged between 0 and 28; the mean score was 11.17±6.13. When the ISI scale scores of the subjects were analyzed, it was determined that 28% (n=156) were clinically

Table 1. Answers to the descriptive survey questions

Question	Answers	n (%)
Do you have a chronic disease?	No	406 (72.8)
	Yes	152 (27.2)
Have you received training on COVID-19 at your institution?	No	185 (33.2)
	Yes	373 (66.8)
Do you work in services, outpatient clinics, emergency and intensive care units related to COVID-19?	No	320 (57.3)
	Yes	238 (42.7)
Do you work shifts in the COVID-19 ward?	No	419 (75.1)
	Yes	139 (24.9)
Do you have personal protective equipment?	No	21 (3.8)
	Yes	325 (58.2)
	Partially	212 (38.0)
Have you been subjected to negative discrimination because you are a healthcare worker during the pandemic?	No	384 (68.8)
	Yes	174 (31.2)
Have you been subjected to positive discrimination because you are a healthcare worker during the pandemic?	No	298 (53.5)
	Yes	259 (46.5)
Have you been told or implied by your family or others that you might carry the virus?	No	217 (38.9)
	Yes	341 (61.1)

Descriptive statistical methods were used. COVID-19: Coronavirus disease-2019

insignificant insomniacs, 43.5% (n=243) had subthreshold insomnia, 22.4% (n=125) had moderate clinical insomnia, and 6.1% (n=34) had severe clinical insomnia. Table 2 shows the relationship between the participants' descriptive characteristics and insomnia severity. A very weak negative correlation was found between the age of the participants and the total score of the ISI scale (r=-0.183; p=0.001) and between the number of seizures per month and the total score of the ISI scale (r=-0.183; p=0.001) and p=0.001, respectively). There was no statistically significant correlation between the duration of shifts and the ISI scores of the participants (p=0.29).

In the pairwise comparisons made to determine the reason for the difference in insomnia severity between professions, physicians' total ISI scale score was significantly lower than the total scores of nurses, midwives, and EMTs (p=0.001). In the analysis of differences according to institutions of employment, the ISI scale total scores of those working in public hospitals were significantly higher than those working in FHCs and university hospitals (p=0.001, p=0.002, respectively).

The scores of the participants in the GAD-7 questionnaire ranged between 0 and 18 points; the mean score was 7.58±5.16. When the GAD-7 scale scores of the participants were analyzed, 31.2% (n=174) had normal anxiety, 34.9% (n=195) had mild anxiety, 21.3% (n=119) had moderate anxiety, and 12.5% (n=70) had severe anxiety. When a total score of 10 was accepted as the cut-off score for generalized anxiety disorder, 33.9% (n=189) of the participants were found to have generalized anxiety disorder. The relationship between the answers given to the GAD-7 questionnaire and the descriptive characteristics questionnaire is shown in Table 3. There was a very weak negative correlation between the age of the participants and their total score on the GAD-7 scale (r=-0.128; p=0.002), as well as between their shift duration and the GAD-7 score (r=0.174; p=0.045). There was no statistically significant correlation between the number of days the participants were on call and their total score on the GAD-7 scale (p=0.76).

In the pair group comparisons made to explain the difference in total scores among professions in the GAD-7 questionnaire, the total score of physicians was significantly lower than that of nurses (p=0.001). When the source of the difference in the GAD-7 score according to the institution of employment was examined, employees at public hospitals had significantly higher GAD-7 scores than those working in university hospitals and FHCs (p=0.001, p=0.007; respectively).

The total score of the participants on the CES-D scale ranged between 1 and 60 points. The mean score was 24.15±12.97. When the total score obtained from the CES-D scale was analyzed, it was determined that 30.8% (n=172) had no depression, 11.8% (n=66) were mildly depressed, 26% (n=145) were moderately depressed, and 31.4% (n=175) were severely depressed. The relationship between the responses of the subjects to the descriptive questionnaire questions and the CES-D scale is shown in Table 4. There was a weak negative correlation between the age of the participants and their total score on the CES-D scale (r=-0.136; p=0.001), and a similar negative correlation between seizure duration and their total score on the CES-D scale r=0.189; p=0.029). There was no statistical correlation between the number of days of shifts and the score obtained from the CES-D scale (p=0.34).

In pairwise comparisons made to investigate the reason for the difference in the total score of the CES-D scale across different occupations, the total score of nurses was significantly higher than that of physicians and those with other duties (p=0.015, p=0.009, respectively).

Table 2. The relationship between participants' descriptive characteristics and insomnia severity index scale

Factor		Insomnia severity index total score	p-value
Gender	Male	9.34±5.77	0.001[a]
	Female	12.09±6.11	
Chronic disease	No	10.96±6.17	0.180[b]
	Yes	11.74±6.02	
Occupation	Doctor	9.62±5.47	0.001[c]
	Nurse	13.92±6.40	
	Midwife	14.43±6.64	
	Secretary	12.14±5.70	
	Emergency medical technician	15.26±6.79	
	Dentist	12.67±7.34	
	Cleaning staff	13.0±3.16	
	Others	9.83±5.61	
Institution of employment	Family health center	9.48±5.44	0.001[d]
	Public hospital	12.97±5.93	
	Private hospital	11.76±6.03	
	Community health center	11.80±8.70	
	University hospital	10.58±6.25	
	Others	10.71±6.03	
Status of receiving training on COVID-19 in the organization	No	11.89±6.10	0.053[a]
	Yes	10.82±6.12	
Status of being a frontline worker	No	10.39±5.98	0.001[a]
	Yes	12.22±6.19	
Status of being on call in COVID-19 service	No	10.41±5.84	0.001[a]
	Yes	13.47±6.43	
Ownership of personal protective equipment	No	12.24±6.21	0.004[a]
	Yes	10.46±6.05	
	Some	11.48±5.11	
Exposure to negative discrimination due to being a healthcare worker in the pandemic	No	10.12±5.80	0.001[b]
	Yes	13.49±6.21	
Exposure to positive discrimination because of being a healthcare worker during the pandemic	No	11.61±6.22	0.066[a]
	Yes	10.66±6.01	
Being told or implied by family or environment that they may carry the virus	No	9.95±5.82	0.001[b]
	Yes	11.95±6.21	

[a]: Independent samples t-test, [b]: Mann-Whitney U test, [c]: One-Way Analysis of Variance, [d]: Kruskal-Wallis test, COVID-19: Coronavirus disease-2019

In pairwise group comparisons made to examine the effect of the institutions of employment on the CES-D scale, the CES-D scale scores of those working in public hospitals were significantly higher than those working in university hospitals and FHCs, respectively (p=0.007, p=0.040).

Discussion

The COVID-19 pandemic has negatively affected individuals psychological, social, economic, and physical health. In our study, we evaluated the anxiety, insomnia, and depression status of 558 healthcare workers during the COVID-19 pandemic. We found that insomnia, anxiety, and depression were more severe in women, frontline workers (including nurses), those who did not have personal protective equipment, those who were exposed to negative discrimination, and those who were suggested by their family or environment to carry the virus.

Table 3. The relationship between participants' descriptive characteristics and GAD-7 scale

Factor		GAD-7 scale total score	p-value
Gender	Man	5.77±4.79	0.001[a]
	Female	8.49±5.12	
Chronic disease	No	7.41±5.29	0.188[b]
	Yes	8.06±4.81	
Occupation	Doctor	6.96±4.87	0.001[c]
	Nurse	9.40±5.33	
	Midwife	9.49±5.44	
	Secretary	7.63±4.98	
	Emergency medical technician	9.58±5.31	
	Dentist	7.00±2.97	
	Cleaning staff	8.83±6.94	
	Others	4.90±4.90	
Institution of employment	Family health center	6.81±4.60	0.001[d]
	Public hospital	9.16±5.11	
	Private hospital	9.17±5.46	
	Community health center	8.40±6.88	
	University hospital	6.50±4.96	
	Others	8.05±5.73	
Status of receiving training on COVID-19 in the organization	No	7.92±4.95	0.279[a]
	Yes	7.42±5.27	
Status of being a frontline worker	No	6.90±4.91	0.001[a]
	Yes	8.51±5.37	
Status of being on call in COVID-19 service	No	7.03±4.99	0.001[a]
	Yes	9.27±5.35	
Ownership of personal protective equipment	No	8.40±5.23	0.011[a]
	Yes	7.04±5.11	
	Partially	7.81±4.47	
Exposure to negative discrimination due to being a healthcare worker in the pandemic	No	6.76±5.00	0.001[b]
	Yes	9.41±5.07	
Exposure to positive discrimination because of being a healthcare worker in the pandemic	No	7.55±5.02	0.891[a]
	Yes	7.61±5.35	
Being told or implied by family or environment that they may carry the virus	No	6.53±5.06	0.001[b]
	Yes	8.26±5.13	

[a]: Independent samples t-test, [b]: Mann-Whitney U test, [c]: One-Way Analysis of Variance, [d]: Kruskal-Wallis test, COVID-19: Coronavirus disease-2019, GAD-7: Generalized anxiety disorder-7

During the previous H1N1 and SARS pandemics, it was reported that anxiety increased in the community (17). COVID-19 has also been reported to increase anxiety and stress (4,8). Fear of being infected, quarantine, newly emerging strains, an increase in COVID-19-related deaths, and not knowing when the pandemic will end are the main causes of stress and anxiety (3). Sun et al. (18) examined 44 studies evaluating anxiety in healthcare workers during the COVID-19 pandemic and reported the prevalence of anxiety as 37%. In our study, the prevalence of anxiety was found to be 68.7%. The reason for this is that our study was conducted approximately 1 year after the pandemic started in our country. Therefore, the prevalence of anxiety may have been higher in our study due to long-term social loneliness, loss of family and friends from the disease, ongoing uncertainties about the pandemic even after 1 year, and burnout caused by intense working conditions.

Table 4. The relationship between participants' descriptive characteristics and CES-D scale

Factor		CES-D scale total score	p-value
Gender	Man	19.61±11.62	0.001 [a]
	Female	26.43±13.03	
Chronic disease	No	24.14±13.33	0.947 [b]
	Yes	24.22±12.01	
Occupation	Doctor	22.89±12.63	0.004 [c]
	Nurse	27.92±14.44	
	Midwife	26.51±13.08	
	Secretary	24.89±11.73	
	Emergency medical technician	27.95±12.96	
	Dentist	22.33±11.66	
	Cleaning staff	27.67±12.66	
	Others	19.33±9.95	
Institution of employment	Family health center	21.89±12.90	0.004 [d]
	Public hospital	26.98±12.07	
	Private hospital	26.00±13.96	
	Community health center	28.40±12.52	
	University hospital	22.35±12.73	
	Others	26.38±15.10	
Status of receiving training on COVID-19 in the organization	No	25.98±12.91	0.019 [a]
	Yes	23.25±12.93	
Status of being a frontline worker	No	22.48±12.68	0.001[a]
	Yes	26.42±13.05	
Status of being on call in COVID-19 service	No	22.54±12.50	0.001[a]
	Yes	29.04±13.21	
Ownership of personal protective equipment	No	25.99±12.45	0.031[a]
	Yes	22.97±13.15	
	Partially	24.05±13.80	
Exposure to negative discrimination due to being a healthcare worker in the pandemic	No	21.76±12.34	0.001[b]
	Yes	29.46±12.79	
Exposure to positive discrimination because of being a healthcare worker in the pandemic	No	25.07±12.50	0.064[a]
	Yes	23.03±13.42	
Being told or implied by family or environment that they may carry the virus	No	21.43±12.48	0.001[b]
	Yes	25.89±13.00	

[a]: Independent samples t-test, [b]: Mann-Whitney U test, [c]: One-Way Analysis of Variance, [d]: Kruskal-Wallis test, COVID-19: Coronavirus disease-2019, CES-D: Center for epidemiologic studies-depression

COVID-19 is an infection transmitted by droplets. For this reason, the anxiety of contracting the disease is higher, especially in healthcare workers in units serving infected patients (7,19). In our study, in line with the literature, anxiety disorder was more severe in frontline workers and those who were on duty in clinics where COVID-19 patients were followed up. The lack of personal protective equipment for healthcare workers increases the risk of infection and leads to an exacerbation of stress and anxiety (20). In our study, anxiety and depression were more severe in workers without personal protective equipment.

Anxiety and depression are more common in women during the pandemic period (21,22). In our study, anxiety and depression were more severe in women. Anxiety and depression are more common in nurses who are in direct contact with patients compared to other healthcare professionals (7,23). In our study, we found that anxiety and

depression were more severe in nurses who were in contact with COVID-19 positive patients for a longer period of time than in physicians, in accordance with the literature. Conflicting results were found in studies investigating the relationship between the presence of chronic disease and anxiety severity. Karasu et al. (21) reported that anxiety increased with the presence of chronic disease. However, studies report that there is no relationship, between the presence of chronic disease and anxiety (24). We found no relationship between the presence of chronic disease and the severity of anxiety and depression.

Studies in the literature report that the level of anxiety was lower in individuals who did not receive training on COVID-19 (21). This may be attributed to the increased awareness that individuals who receive training face a serious health problem. In our study, no relationship was found between the status of receiving training on COVID-19 in the institution and anxiety severity. Since the analysis concerns the first year of the pandemic, the relationship may not have been detected because healthcare workers now have professional experience with this issue. In our country, during the pandemic, one hospital in each city with more than one hospital was designated as a COVID-19 hospital for managing COVID-19 cases. Generally, public hospitals were used as treatment centers for COVID-19. This may be the reason why anxiety levels, depression, and insomnia in individuals working in public hospitals were more severe than in those working in university hospitals, and FHC in our study.

During pandemic periods, healthcare workers are stigmatized by society due to concerns that they may transmit diseases. During the COVID-19 period, healthcare workers were also stigmatized by society (25). Stigmatization is also a factor that triggers psychiatric disorders. In our study, anxiety and depression were found to be more severe in participants who were exposed to negative discrimination during the pandemic because they were healthcare workers, and whose family or environment suggested that they could carry the virus.

Depression was reported as one of the mental disorders emerging in healthcare workers in China, the initial center of the pandemic (7). In the literature, the rate of depression in healthcare workers during the pandemic varied (23). Sahebi et al. (26) reported the rate of depression in healthcare workers as 24.8%. Moya-Salazar et al. (27) reported the prevalence of depression in 89% of healthcare workers COVID-19 care and isolation center. We found depression in 69.2% of the participants, and the severity of depression was mild in 11.8%, moderate in 26%, and severe in 31.4% of the participants. The different prevalence of depression in the studies may result from the working status units where COVID-19 cases were managed. In our study, in support of this theory, depression was more severe in frontline workers and healthcare workers who were on duty in the units where COVID-19 patients were treated or monitored compared to other healthcare workers. We found that depression was more severe in people who were not trained against COVID-19. This may be because healthcare workers do not know how to protect themselves against infection.

Stress, sleep deprivation, shift work, and fatigue often cause sleep disturbance and poor sleep quality in healthcare workers (28). In our study, we found moderate clinical insomnia in 22.4% of the participants and severe clinical insomnia in 6.1%. 43.5% of our subjects experienced subthreshold insomnia. The most important causes of insomnia in healthcare workers are shift work and long shifts. However, in our study, we found more severe insomnia in those who worked shifts, and insomnia was negatively correlated with the duration of shifts. This may be because most of our cases did not maintain shifts. In studies, sleep disturbance and poor sleep quality are more common in frontline workers (29). We found that insomnia was more severe in frontline workers.

The risk of insomnia has been reported to be higher in women than in men and higher in nurses than in other healthcare workers (30). This may be due to hormonal differences, women's workload, being higher in social life, and women's psychology being more easily affected. In our study, insomnia was found to be more severe in women and nurses. In our study, insomnia was found to be more severe in those who lacked personal protective equipment, who were exposed to negative discrimination, and who were perceived by their family or environment to carry the virus. This may be due to increased anxiety, social loneliness, and other psychological negativities triggering insomnia.

Study Limitations

The limitations in our study included not determining which department the healthcare professionals worked in before the pandemic, and not knowing the personality traits and psychological backgrounds of the participants.

Conclusion

As a result, healthcare workers are akin to soldiers on the front line during the pandemic. Therefore, negative

psychological effects are more frequent and severe in healthcare workers, especially frontline workers. Therefore, it is important to provide the necessary psychological and social support for healthcare workers during and after pandemics.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained for this study from the Ethics Committee of Atatürk University, dated 28.05.2020, numbered B.30.2.ATA.0.01.00/33. This study was conducted in accordance with the Helsinki Declaration, revised in 2013, "Ethical Principles for Medical Research Involving Human Subjects".

Informed Consent: Informed consent was obtained from all participants online before filling out the form.

Footnotes

Authorship Contributions

Concept: S.S., G.S., E.Ç.T., Z.Ö., Design: S.S., G.S., E.Ç.T., Z.Ö., Data Collection or Processing: S.S., M.B., E.Ç.T., Analysis or Interpretation: S.S., G.S., M.Ş., Y.Ç., Drafting Manuscript: S.S., M.Ş., E.Ç.T., Y.Ç., Critical Revision of Manuscript: M.B., G.S., Z.Ö.Ü., Final Approval and Accountability: S.S., G.S., E.Ç.T., M.B., M.Ş., Z.Ö., Y.Ç., Supervision: G.S., Y.Ç., Writing: S.S., G.S., E.Ç.T., M.B., M.Ş., Z.Ö., Y.Ç.

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ORIGINAL RESEARCH

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Evaluation of Eosinophil Indices in Pediatric Patients with Cow's Milk Allergy

İnek Sütü Alerjisi Olan Pediyatrik Hastalarda Eozinofil İndekslerinin Değerlendirilmesi

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Abstract

Objective: This study aimed to evaluate eosinophil indices and other inflammatory parameters in pediatric patients with cow's milk allergy (CMA), which are easily accessible and may be useful in predicting CMA.

Method: This retrospective study included 39 people in the patient group and 123 people in the control group. The records of the patients diagnosed with CMA by specific immunoglobulin E (IgE) tests were compared with patients without CMA. The study examined demographic data of the patients, including age at presentation and gender, as well as laboratory findings. The study included children under 24 months of age who underwent a specific IgE test for CMA and had simultaneous hemogram results.

Results: Neutrophil-to-eosinophil ratio (NER), derived neutrophil-to-lymphocyte ratio (dNLR), and leukocyte-to-eosinophil ratio (LER) were significantly lower in the CMA than control groups. On the other hand, eosinophil, eosinophil-to-monocyte ratio (EMR), and eosinophil-to-lymphocyte ratio (ELR) were significantly higher than control groups. Specific IgE levels were observed to have a negative correlation with LER, NER, and dNLR, and a positive correlation with eosinophil, EMR, and ELR. For a LER ≤22.2 cut-off value, sensitivity was 64.1%, and specificity was 73.2%.

Conclusion: In our study, LER and EMR seem to be useful parameters to predict CMA in children. This study's findings may indicate that leukocytes and eosinophils, could be crucial in the pathogenesis of CMA cases. Eosinophil counts and eosinophil indices, readily obtainable through a complete blood count, can serve as parameters for distinguishing CMA.

Keywords: Child, cow's milk allergy, eosinophil, eosinophil-to-monocyte ratio, leukocyte-to-eosinophil ratio

Öz

Amaç: Bu çalışmada, inek sütü alerjisi olan çocuk hastalarda, kolay erişilebilen ve inek sütü alerjisini öngörmede yararlı olabilecek eozinofil indeksleri ve diğer enflamatuvar parametrelerin değerlendirilmesi amaçlanmıştır.

Yöntem: Bu retrospektif çalışmaya hasta grubunda 39 kişi, kontrol grubunda ise 123 kişi dahil edilmiştir. Spesifik immünoglobulin E (IgE) testleri ile inek sütü alerjisi tanısı alan hastaların kayıtları, inek sütü alerjisi olmayan çocuklarla karşılaştırılmıştır. Çalışmada hastaların başvuru yaşı, cinsiyeti ve laboratuvar bulguları dahil olmak üzere demografik verileri incelenmiştir. Çalışmaya inek sütü alerjisi için spesifik IgE testi yapılan ve eş zamanlı hemogram sonuçları bulunan 24 aydan küçük çocuklar dahil edilmiştir.

Bulgular: Nötrofil-eozinofil oranı (NER), türetilmiş nötrofil-lenfosit oranı (dNLR) ve lökosit-eozinofil oranı (LER) inek sütü alerjisi olanlarda kontrol grubuna göre anlamlı derecede düşüktü. Diğer yandan, eozinofil, eozinofil-monosit oranı (EMR) ve eozinofil-lenfosit oranı (ELR) ise kontrol grubundan anlamlı derecede yüksekti. Spesifik IgE düzeylerinin LER, NER ve dNLR ile negatif korelasyon gösterdiği; eozinofil, EMR ve ELR ile pozitif korelasyon gösterdiği görülmüştür. LER ≤22,2 kesme değeri için duyarlılık %64,1, özgüllük %73,2 idi.

Sonuç: Çalışmamızda LER ve EMR'nin çocuklarda inek sütü alerjisini öngörmede yararlı parametreler olduğu görülmektedir. Bu çalışmanın bulguları, eozinofillerin yanı sıra lökositlerin de inek sütü alerjisi olgularında patogenezde önemli bir rol oynayabileceğini gösterebilir. Tam kan sayımı ile kolayca elde edilebilen eozinofil sayıları ve eozinofil indeksleri, inek sütü alerjisini ayırt etmede parametre olarak kullanılabilir.

Anahtar kelimeler: Çocuk, eozinofil, eozinofil-monosit oranı, inek sütü alerjisi, lökosit-eozinofil oranı

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Introduction

Cow's milk allergy (CMA) is an immunologic reaction to one or more milk proteins (1). CMA stands out as a prevalent form of food allergy among children aged below 24 months in developed nations (2); the prevalence in this age group was calculated to be 2-7.5% (3). Adverse reactions after cow's milk ingestion can occur at any age after birth, even in breastfed infants. The immune response to cow's milk proteins can be mediated by immunoglobulin E (IgE) or be independent of IgE (4). In most children, CMA develops with IgE-mediated reaction (5), and Th2 lymphocytes and eosinophils also play a significant role in the response of inflammation resulting from allergen binding to specific IgE (6). Platelets and neutrophils are indicators that play crucial roles in inflammation. Today, easy accessibility to these blood parameters allows them to be used to diagnose and monitor many diseases. According to studies, the platelet-lymphocyte ratio (PLR), neutrophil-lymphocyte ratio (NLR), and inflammation indices obtained from hemogram parameters are effective in diagnosing and monitoring cardiovascular diseases, malignancies, chronic inflammatory diseases, and allergic diseases like: allergic rhinitis, atopic dermatitis, and asthma (7-10).

It is crucial to avoid unnecessary initiation of elimination diets in children with CMA. The diagnosis of food allergy is still based on the principle that the causative allergen should be removed from the diet, and the symptoms should recur when added. Currently, there is no single commonly accepted diagnostic laboratory test to demonstrate an adverse immune response to cow's milk proteins (2). Although eosinophil indices have been studied in patients with allergic rhinitis, asthma and nasal polyps (10), there is an insufficient number of studies on these indices in children with CMA in the literature.

We aimed to evaluate eosinophil indices and other inflammatory parameters in pediatric patients with CMA, which are easily accessible and may be helpful in predicting CMA.

Materials and Methods

This retrospective study analyzed patient data from a University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital between September 2022 and September 2023. The records of the patients diagnosed with CMA by specific IgE tests were compared with children without CMA. The Ethical Committee of the University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital, gave its approval for the study (date: 27/10/2023, number: 2023/10/05/061). The research was carried out in accordance with the guidelines established by the Helsinki Declaration.

This research included 162 patients. The study included 39 people in the patient group and 123 age-and-gender-matched people in the control group. The study examined demographic data of the patients, including age at presentation and gender, as well as laboratory findings. The study included children under 24 months of age who underwent a specific IgE test for CMA and had simultaneous hemogram results. The study excluded parasitic diseases, malignancy, hematological diseases, and known infectious and systemic inflammatory diseases, as these conditions may affect eosinophilia levels. Systemic inflammation index (SII) was defined as (neutrophil×platelet)/lymphocyte; SIRI was defined as (neutrophil×monocyte)/lymphocyte; dNLR was defined as neutrophil count/(leukocyte count-neutrophil count); aggregate index of systemic inflammation (AISI) was defined as (neutrophil×platelet×monocyte)/lymphocyte. Eosinophil indices, including leukocyte-to-eosinophil ratio (LER), neutrophil-to-eosinophil ratio (NER), eosinophil-to-monocyte ratio (EMR), and eosinophil-to-lymphocyte ratio (ELR) were calculated based on hemogram parameters. In whole blood samples, hemogram parameters were measured by a Mindray BC-6800 Plus device (Shenzhen Mindray Bio-Medical Electronics Co), and specific IgE was measured using the chemiluminescent immunoassay method with the Immulite 2000 (Siemens Healthcare Diagnostics).

Statistical Analysis

To evaluate the normal distribution of continuous data, the Shapiro-Wilk test was employed. Continuous data were displayed as either mean with standard deviation or median with the 25th and 75th percentiles. The Mann-Whitney U test or Student's t-test was employed to compare continuous variables. The diagnostic performance of the laboratory parameters was evaluated through the receiver operating characteristic curve. The relationships between parameters were evaluated using Spearman correlation analyses. Statistical analyses were conducted using IBM SPSS v. 26.0 (IBM Corp., Armonk, NY, US) and GraphPad Prism 8.0 (GraphPad Software, San Diego, California, US). A significance level (p-value) of less than 0.05 was considered significant.

Results

The demographic data of our study are given in Table 1. There was no statistical difference in age, gender, leukocyte, platelet, monocyte, neutrophil, lymphocyte values, NLR, PLR, MLR, systemic inflammation response index, SII, and AISI between the patients with CMA and the control group (p>0.05). NER, dNLR and LER were significantly lower in the patients with CMA, whereas eosinophil, ELR and EMR were significantly higher than controls (p<0.001), as shown in Table 1 and Figure 1.

LER achieved the highest area under the curve (AUC) value of 0.716 [95% confidence interval (CI) =0.640-0.784] at a cut-off value of 22.2. EMR had an AUC value of 0.711 (95% CI=0.634-0.779) at a cut-off value of 0.30. ELR achieved an

Table 1. Comparing demographic and laboratory data between the two groups, considering the cow's milk allergy

Parameter	Control group (n=123)	Children with cow's milk allergy (n=39)	p-value
Age (months)	6 (4 to 10)	8 (5 to 11)	0.080***
Male sex, n (%)	62 (50)	22 (56)	0.638*
Specific IgE (kU/L)	0.10 (0.10 to 0.10)	0.55 (0.18 to 1.47)	**<0.001*** **
Leukocyte (10^9/L)	9.45 (7.12 to 11.5)	10.1 (8.09 to 12.1)	0.150***
Neutrophil (10^9/L)	2.53 (1.79 to 3.83)	2.33 (2.06 to 3.11)	0.380***
Platelet (10^9/L)	346 (304 to 446)	378 (289 to 453)	0.944***
Monocyte (10^9/L)	0.66 (0.55 to 0.82)	0.59 (0.49 to 0.94)	0.557***
Lymphocyte (10^9/L)	5.59±2.12	6.09±2.08	0.193**
Eosinophil (10^9/L)	0.28 (0.14 to 0.44)	0.47 (0.26 to 0.70)	**<0.001*** **
NLR	0.45 (0.31 to 0.89)	0.37 (0.26 to 0.62)	0.103***
PLR	67.8 (48.8 to 103)	58.3 (51.5 to 80.5)	0.215***
MLR	0.11 (0.09 to 0.18)	0.11 (0.07 to 0.16)	0.117***
SIRI	0.29 (0.19 to 0.66)	0.26 (0.15 to 0.42)	0.150***
SII	167 (103 to 330)	141 (103 to 189)	0.173***
AISI	115 (57.5 to 231)	91.9 (55.3 to 173)	0.161***
dNLR	0.39 (0.26 to 0.69)	0.30 (0.23 to 0.51)	**0.045*** **
LER	34.7 (21.5 to 65.1)	20.7 (14.2 to 32.5)	**<0.001*** **
NER	9.37 (5.25 to 21.2)	5.54 (3.00 to 8.25)	**<0.001*** **
ELR	0.05 (0.03 to 0.08)	0.08 (0.05 to 0.15)	**<0.001*** **
EMR	0.43 (0.17 to 0.68)	0.67 (0.42 to 1.26)	**<0.001*** **

*: Chi-square test, **: Student's t-test, ***: Mann-Whitney U test, Ig: Immunoglobulin, LER: Leukocyte-to-eosinophil ratio, NER: Neutrophil-to-eosinophil ratio, ELR: Eosinophil-to-lymphocyte ratio, EMR: Eosinophil-to-monocyte ratio, NLR: Neutrophil to lymphocyte ratio, dNLR: Derived neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, MLR: Monocyte to lymphocyte ratio, SIRI: Systemic inflammation response index, SII: Systemic inflammation index, AISI: Aggregate index of systemic inflammation

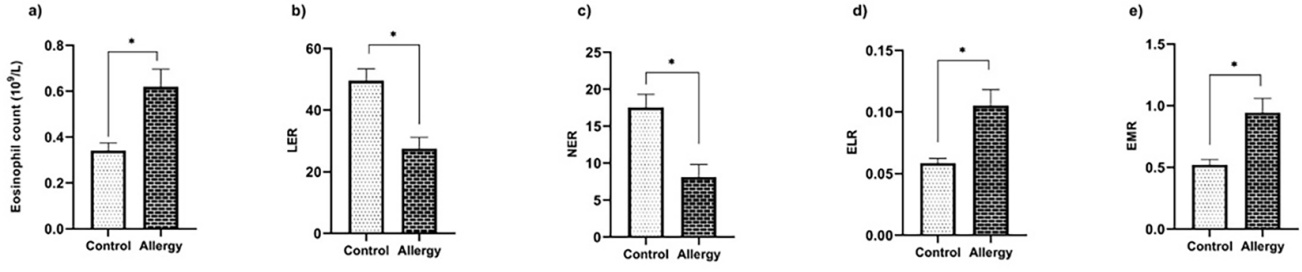

Figure 1. Comparing eosinophil and eosinophil indices between the two groups

**: p<0.001, LER: Leukocyte-to-eosinophil ratio, NER: Neutrophil-to-eosinophil ratio, ELR: Eosinophil-to-lymphocyte ratio, EMR: Eosinophil-to-monocyte ratio*

AUC value of 0.703 (95% CI =0.626-0.772) at a cut-off value of 0.06. NER achieved an AUC value of 0.703 (95% CI=0.626-0.772) at a cut-off value of 8.75 (Table 2).

In Spearman correlation, serum specific IgE levels were observed to have a negative correlation with LER (r=-0.340, p<0.001), NER (r=-0.319, p<0.001), and dNLR (r=-0.162, p=0.040), and positively correlated with eosinophil (r=0.337, p<0.001), EMR (r=0.330, p<0.001), and ELR (r=0.318, p<0.001) (Table 3).

Discussion

The study participants' age and gender were similar in all groups, ensuring that variations in inflammation marker levels can be attributed to specific factors rather than demographic differences. NER, dNLR, and LER were significantly lower in the patients with CMA. On the other hand, eosinophil, ELR, and EMR were significantly higher in the patients with CMA than in the controls. In determining the CMA group, the highest AUC was observed in LER. Moreover, LER had a higher correlation with specific IgE levels.

CMA is a prevalent food allergy among infants (11). Early recognition and appropriate management of CMA are crucial for the well-being of affected infants. The first step in the immune system's response to cow's milk protein allergy (CMPA) is a T-cell-dependent reaction (12). As a result, proinflammatory cytokines [interleukin (IL)-5, IL-13, and IL-14] are secreted by Th2 cells (13). This activates B-cells, leading to the secretion of IgE. When the same food allergen is ingested again, IgE binds to eosinophils, basophil, and mast cell surfaces and activates these cells, causing the release of mediators such as histamine that produce typical symptoms including anaphylaxis, laryngospasm, bronchospasm, angioedema, rhinitis, and urticaria within minutes to two hours (14). Allergic reactions to cow milk can be categorized into two main types: Immediate, which are typically IgE-mediated, and late-onset, encompassing both non-IgE-mediated and mixed IgE and cell-mediated reactions (15). IgE-mediated food allergy occurs with the development of food allergen-specific IgE, which develops after first contact with an allergen. Symptoms may be mild or may progress to anaphylaxis, which can be life-threatening. The oral food challenge has been regarded as the gold standard in diagnosing CMPA (16). Nevertheless, food intolerance and severe eosinophilia may cause symptoms to recur. Currently, no widely accepted diagnostic laboratory test will detect an undesirable immune system response to cow's milk proteins.

Eosinophils play a crucial role in immuno-inflammatory reactions in CMA (17). Because current indicators do not accurately represent inflammatory processes, their usefulness in this disease is limited. Thus, it is crucial to search for new biomarkers capable of detecting and

Table 2. Receiver operating curve analysis of eosinophil indices in identifying cow's milk allergy

Parameter	AUC	95 CI%	Cut-off	Sensitivity	Specificity	p-value
Eosinophil (10^9/L)	0.712	0.636 to 0.780	>0.39	66.7%	69.1%	**<0.001**
LER	0.716	0.640 to 0.784	≤22.2	64.1%	73.2%	**<0.001**
EMR	0.711	0.634 to 0.779	>0.30	92.3%	39.8%	**<0.001**
ELR	0.703	0.626 to 0.772	>0.06	64.1%	66.7%	**<0.001**
NER	0.703	0.626 to 0.772	≤8.75	79.5%	55.3%	**<0.001**

CI: Confidence interval, AUC: Area under the curve, LER: Leukocyte-to-eosinophil, EMR: Eosinophil-to-monocyte ratio, ELR: Eosinophil-to-lymphocyte ratio, NER: Neutrophil-to-eosinophil ratio

Table 3. Significant correlations between serum specific IgE levels and inflammation indices in all groups

Parameter	Specific IgE level (kU/L)	
	r	p
Eosinophil (10^9/L)	0.337	**<0.001**
LER	-0.340	**<0.001**
EMR	0.330	**<0.001**
ELR	0.318	**<0.001**
NER	-0.319	**<0.001**
dNLR	-0.162	**0.040**

LER: Leukocyte-to-eosinophil ratio, EMR: Eosinophil-to-monocyte ratio, ELR: Eosinophil-to-lymphocyte ratio, NER: Neutrophil-to-eosinophil ratio, Ig: Immunoglobulin, dNLR: Derived neutrophil-to-lymphocyte ratio

monitoring the dynamics of inflammation. Neutrophilic lipocalin associated with gelatinase (NGAL) and chemerin, markers associated with neutrophilic inflammation, was shown to be at higher levels in the CMA patient group than in the control group. Statistically significant correlations have been shown between IL-10, TNF-α, calprotectin, NGAL and WBC levels in children with CMA (18). Furthermore, the leukocyte adherence inhibition test has been proposed to discriminate antigen-specific immunoreactivity in non-IgE-mediated CMA (19). According to research, eosinophil-related indicators like eosinophil cationic protein and eosinophil protein X, were linked to intestinal inflammation in infants with atopic eczema and food allergies (20). Numerous studies have suggested that NLR and ELR could function as effective inflammatory indicators for differentiating between intermittent and persistent allergic rhinitis. Analyses have revealed that T-helper 2 lymphocytes, neutrophils, and eosinophils are all actively involved in the late-phase immune response that follows allergen exposure (21).

Study Limitations

The limitations of this study were its retrospective and single-center design. Total IgE, and clinical characteristics could not be obtained from all patient data.

Conclusion

In our study, LER and EMR seem to be useful parameters to predict CMA in children. These findings may indicate that leukocytes and eosinophils could play an important role in the pathogenesis of CMA. Eosinophil counts and eosinophil indices, readily obtainable through a complete blood count, can serve as parameters for distinguishing CMA. Understanding the immune response, particularly the role of eosinophils and leukocytes, could provide valuable insights into the pathogenesis, diagnosis, and potential predictors of tolerance in CMA. Studies on this subject are limited in the literature. We believe it will contribute to the literature. Moreover, more comprehensive studies are needed.

Ethics

Ethics Committee Approval: The Ethical Committee of the University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital, gave its approval for the study (date: 27/10/2023, number: 2023/10/05/061).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: A.K.Ç., L.D., M.E., Design: A.K.Ç., L.D., M.E., Data Collection or Processing: A.K.Ç., L.D., M.E., Analysis or Interpretation: A.K.Ç., L.D., M.E., Literature Search: A.K.Ç., L.D., M.E., Writing: A.K.Ç., L.D., M.E.

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

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ORIGINAL RESEARCH

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Effects of Patients' Adjustment to Intestinal Ostomy on Sleep Quality: A Descriptive Cross-sectional Study

Hastaların Bağırsak Ostomisine Uyumlarının Uyku Kalitesine Etkisi: Tanımlayıcı Kesitsel Bir Çalışma

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Abstract

Objective: Living with an ostomy affects the individual in many ways. The aim of the present study was to examine ostomy adaptability, sleep quality, and associated factors in patients with intestinal ostomy.

Method: This was a descriptive, cross-sectional study. The study was carried out with 45 adult patients who could perform ostomy care on their own. Study data were collected using an information form, the Pittsburgh sleep quality index, and the ostomy adjustment inventory. Obtained data were evaluated using descriptive statistical methods, variance analyses, student's t-test, correlation and regression analysis.

Results: The mean age of the patients was 58.0±17.7 years. Of them, 51% were male, 69% had a temporary ostomy, and 67% had a colostomy. The mean intestinal ostomy adjustment score of all patients was 47.1±13.9. The average sleep quality score of all patients was 7.8±4.1. Sleep quality scores between males and females were not significantly different (p=0.442). Ostomy adjustment inventory scores were 51.9±13.9 in women and 42.5±12.6 in men (p=0.023).

Conclusion: In our study, we found that patients with intestinal ostomy showed moderate adjustment to the ostomy and had poor sleep quality. It was observed that female patients had better compliance than male patients, and those who did not have ostomy problems had better compliance than those who did. The results of the present study are important in that they reveal that the patients who adapt well to ostomy may also experience sleep problems.

Keywords: Adaptability, intestinal ostomy, ostomy sleep quality

Öz

Amaç: Ostomi ile yaşamak bireyi birçok açıdan etkilemektedir. Bu çalışmanın amacı, bağırsak ostomisi olan hastalarda ostomi adaptasyonunu, uyku kalitesini ve ilişkili faktörleri incelemektir.

Yöntem: Bu araştırma tanımlayıcı, kesitsel bir çalışmadır. Örneklemi ostomi bakımını kendisi yapabilen 45 yetişkin hasta oluşturmuştur. Çalışma verileri kişisel bilgi formu, Pittsburgh uyku kalitesi indeksi ve ostomi uyum envanteri kullanılarak toplanmıştır. Elde edilen veriler tanımlayıcı istatistiksel yöntemler, varyans analizi, student t-testi, korelasyon ve regresyon analizi kullanılarak değerlendirilmiştir.

Bulgular: Hastaların yaş ortalaması 58,0±17,7 yıldır ve hastaların %51'i erkekti, %69'una geçici ostomi ve %67'sine kolostomi yapılmıştır. Tüm hastaların ortalama bağırsak ostomi uyum skoru 47,1±13,9 ve ortalama uyku kalitesi puanı 7,8±4,1 idi. Cinsiyetler arasında uyku kalitesi puanları arasında anlamlı fark yoktur (p=0,442). Ostomi uyum envanter puanı kadınlarda 51,9±13,9, erkeklerde 42,5±12,6 puandır (p=0,023).

Sonuç: Çalışmamızda bağırsak ostomisi olan hastaların ostomiye orta derecede uyum gösterdiği ve uyku kalitesinin kötü olduğu görüldü. Kadın hastaların erkek hastalara göre uyumunun daha iyi olduğu, ostomi sorunu olmayanların ise olanlara göre daha iyi uyum gösterdiği görüldü. Bu çalışmanın sonuçları, ostomiye iyi uyum sağlayan hastaların da uyku sorunları yaşayabileceğini ortaya koyması açısından önemlidir.

Anahtar kelimeler: Bağırsak ostomisi, ostomi uyumu, uyku kalitesi

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Introduction

The creation of an intestinal stoma is sometimes an inevitable necessity due to multiple reasons like cancers, chronic diseases, or traumas that affect the gastrointestinal system (1). The ostomy is created to remove the intestinal content through an aperture in the abdominal skin. This procedure requires the patient to use a fecal collector system (2,3). Among the main factors that negatively affect the life of individuals who underwent ostomy are the complications related to the ostomy itself and the surrounding tissues (2,4-6). They include problems such as bleeding, ischemia, necrosis, ostomy stenosis and retraction, prolapse, obstruction, parastomal herniation, fistula, perforation, and peristomal skin problems (1,3,5,7).

Patients may experience some psychological problems while getting used to their new bodies, with the newly created excretory pathway. As a result of ostomy surgery, individuals may experience many problems such as changes in excretion habits, lack of defecation and gas control, the presence of bad odor, dependence on an ostomy bag, change in body image perception, diminished self-respect, decreased or impaired sex life, feelings of shame, social isolation, negative feelings, loneliness, depression, and deterioration in social activities and working life (1-3). These problems could also be associated with the individual's self-care ability and the level of adaptability to ostomy (7).

Adaptation to ostomy is a continuous dynamic process in which the individual tries to deal with ostomy-related problems, alleviate negative emotions, and have control over life events caused by ostomy (8). The patient's adaptability to and acceptance of the ostomy can affect the type and incidence of ostomy complications (9). Due to the physical and mental burden effects it creates, intestinal ostomy negatively affects the daily life activities of patients and reduces their quality of life (10). However, previous studies found that the quality of life in patients with ostomy was positively correlated with the adaptation to ostomy (7,10,11).

Adequate sleep and rest are considered indicators of overall health status (12,13). Insufficient sleep and rest, on the other hand, lead to impairments in neural transmission and concentration, slowing of reflexes, impaired judgment, less participation in daily life activities, and increased restlessness, thereby reducing the quality of life (13-16). It has been shown that ostomy patients experience sleep problems (17-20) and the sleep quality of the patients is impaired (19,20). Uemura et al. (17) identified sleep problems in patients with intestinal disorders. Sleep quality of patients with ostomy also affects factors such as pain, treatment, and diagnosis. Patients with ostomy can be concerned about adverse situations such as bag rupture and leaking, contamination of clothes, bad odor, and sleeping in a position that might damage the ostomy and bag during sleeping unconsciousness (18,19). These concerns affect both deep sleep and sleep quality, which can ultimately result in insomnia.

However, to the best of our knowledge, there has been no research investigating the sleep quality and the ostomy adaptation process of ostomy patients simultaneously. The results of the present study, which examined the relationship between ostomy adaptation and sleep quality, are important in that they reveal that the patients who adapt well to ostomy may also experience sleep problems. These findings could guide patients with poor sleep quality and healthcare personel who care for them.

Aim: The aim of this study was to investigate ostomy adaptation, sleep quality and related factors in patients with intestinal ostomy.

Research Question

1- What is the level of ostomy compliance of ostomy patients?

2- What is the level of sleep quality of ostomy patients?

3- What is the level of compliance and sleep quality according to patients' ostomy characteristics?

4- What is the relationship between patients' ostomy compliance and sleep quality?

Materials and Methods

Study Design and Patients

The present study was conducted as a descriptive cross-sectional study at the General Surgery Department of Tokat Gaziosmanpaşa University Hospital. The inclusion criteria were defined as the patients who volunteered to participate in the research, who were adults between the ages of 20 and 80, who had an ostomy for more than two months, who were able to perform self-care of the ostomy, and who underwent ostomy surgery and ostomy treatment in the hospital where the research was conducted. The patients with emergency ostomy and temporary ostomy were also included.

Data Collection

Patients with intestinal ostomy were informed about the purpose of the study and invited to participate. After

their verbal and written consent was obtained, patients participating in the study completed the questionnaire forms through face-to-face interviews conducted researchers. Clinical information was retrieved from hospital files.

Data Collection Tools and Characteristics

The data of the study were collected using a questionnaire form, including demographic details, clinical information, life features and sleep quality, as well as the Pittsburgh sleep quality index (PSQI) and the ostomy adaptation inventory (OAI).

Questionnaire Form

This form was developed based on the relevant literature (18-20). The form consists of two parts, and the first part includes questions regarding patients' socio-demographic features. The latter includes characteristics of questions related to their stoma and adaptation.

The PSQI

Buysse et al. developed this scale in 1989 and Ağargün et al. (21) adapted it to Turkish in 1996. The scale's Cronbach's alpha reliability coefficient was 0.804. The PSQI evaluates sleep quality for the last month and includes 24 questions, 19 of which are self-answered. The last five questions should be answered by a spouse or roommate; these questions are only used for clinical knowledge, not for scoring. The PSQI has seven components: Subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. Each component was scored between 0 and 3. Higher scores represent negative outcomes. These seven components have a total scale score between 0 and 21. A total PSQI score of 5 or above indicates poor sleep quality (21). In the present study, the Cronbach's alpha value of the scale was 0.71.

The OAI

This self-assessment scale, including 23 items, was developed by Simmons et al. (9) to determine patients' adaptation to ostomy. Karadag et al. (22) adapted this scale to Turkish. The scale's Cronbach's alpha value was 0.93. The OAI has four subdimensions: Acceptance, anxious preoccupation, social engagement and anger. Each item is evaluated using a five-point Likert scale ranging from 0-4: Strongly agree, agree, neither agree nor disagree, disagree, and strongly disagree. A higher score for each item indicates a higher engagement. Of the items in the scale, 12, (2^{nd}, 5^{th}, 7^{th}, 8^{th}, 10^{th}, 11^{th}, 12^{th}, 13^{th}, 16^{th}, 17^{th}, 18^{th} and 21^{st} items) include negative statements and therefore are reverse-graded (9,22). In the present study, the Cronbach's alpha value of the scale was 0.85.

Statistical Analysis

Statistical Package for Social Sciences (SPSS, version 22.0, IBM Corp., Armonk, NY, USA) was used for statistical analyses. Quantitative data conformity to the normal distribution was evaluated using a Shapiro-Wilk test. Obtained data were evaluated using descriptive statistical methods (mean, standard deviation, frequency, and percentage), variance analysis, Student's t-test, correlation, and regression. The significance level was set as $p<0.05$. Based on the working hypotheses, the correlation between The OAI and The PSQI was examined, and a correlation coefficient of $r=0.527$ was calculated. Since it was a moderate correlation, the effect size was taken as 0.3. According to these values, post hoc power analysis (G*Power 3.1.9.7) was applied, (n=45). As a result of the power analysis, the post hoc power of our study was found to be 65%.

Ethical Consideration

Ethical consent was obtained from Tokat Gaziosmanpaşa University Scientific Ethics Committee (17-KEK-117, date: 01.08.2017) and written consent was obtained from the University Hospital. Written and verbal consent was obtained from all patients. The study complied with the Helsinki Declaration.

Results

This study was conducted with 45 participants with a mean age of 58.0±17.7 years. Of all patients, 51% were male, 84.8% were married, and 93.3% were not employed (Table 1). OAI scores between genders were statistically different (51.9±13.9 in women and 42.5±12.6 in men, p=0.023). The intestinal ostomy adjustment was better for women compared to men. Mean OAI scores of the patients were not associated with age (p=0.062), education level (p=0.405), marital status (p=0.952), residential area (p=0.561), or employment status (p=0.084, Table 1). There was no difference between genders for PSQI scores (p=0.442). PSQI score was not associated with age (p=0.186), education level (p=0.684), marital status (p=0.441), residential area (p=0.689), or employment status (p=0.933, Table 1).

The scale scores of the patients according to their intestinal ostomy characteristics are given in Table 2. The ostomy was due to rectal cancer in 53.3% and colon cancer in 28.9%. Ostomy was temporary in 68.9% and permanent in 31.1%.

66.7% of the ostomy patients had colostomy, while 24.4% had ileostomy. The duration of ostomy in the patients was ranging from 2 to 12 months, in 64.4%. Of all patients, 88.9% had problems around the ostomy such as peristomal skin problems (n=36), retraction in ostomy (n=2), prolapse (n=1), and bleeding (n=1) (Table 2). No difference was found in terms of the mean OAI total scale scores of the patients with respect to the reason for ostomy opening (p=0.947), ostomy duration (p=0.254), ostomy type (p=0.265), ostomy area (p=0.706), preoperative ostomy marking (p=0.709), or type of operation(p=0.604). There was a difference between average OAI scores, of the patients whether or not they had problems around the ostomy (44.8±12.8 and 65.6±7.5, respectively, p=0.001) (Table 2).

Average PSQI score of patients was not associated with the opening of the ostomy (p=0.692), ostomy duration (p=0.404), ostomy type (p=0.770), ostomy area (p=0.685), preoperative ostomy marking (p=0.583), and type of operation (p=0.669) (Table 2). The average PSQI score of patients experiencing problems around ostomy was 11.4±5.3, while patients who had no such problems had a score of 7.4±3.8 (p=0.044) (Table 2).

The average scores of scales and subscales are given in Table 3. Average OAI total scale score of the patients was 47.1±13.9. In terms of the subscales of the OAI scale, the average score was 16.5±6.9 for the acceptance subscale, 10.7±3.7 for the anxious preoccupation subscale, 9.4±3.8 for the social engagement subscale, and 4.5±2.3 for the

Table 1. Patients' demographic characteristics and scale scores (n=45)

		n (%)	Total PSQI Mean ± SD	Total OAI Mean ± SD
Gender	Female	22 (49)	8.36±2.52	51.90±13.92
	Male	23 (51)	7.39±2.86	42.56±12.66
	t‡		0.776	**2.357**
	p		0.442	**0.023***
Age (years)	20-40	6 (13.3)	6.83±2.31	36.16±8.54
	41-60	20 (44.4)	9.15±3.63	51.20±16.71
	61-80	19 (42.2)	6.84±2.70	46.31±10.11
	F†		1.754	2.976
	p		0.186	0.062
Education	None	10 (22.2)	8.5±3.27	52.3±8.89
	Primary school	25 (55.6)	8±3.69	46.12±14.86
	Middle school and above	10 (22.2)	6.9±2.81	44.5±15.64
	F†		0.384	0.925
	p		0.684	0.405
Marital status	Married	38 (84.4)	7.65±2.99	47.07±1296
	Single	7 (15.6)	9±4.29	47.42±1982
	t‡		0.777	0.060
	p		0.441	0.952
Residential area	Village	8 (17.8)	9±3.12	49.12±16.99
	Districts	26 (57.8)	7.73±3.35	48.19±12.09
	City center	11 (24.5)	7.36±2.13	43.18±16.33
	F†		0.376	0.585
	p		0.689	0.561
Working	Yes	3 (6.7)	7.77±2.05	33.66±15.5
	No	42 (93.3)	7.88±3.27	48.09±13.54
	t‡		0.085	1.770
	p		0.933	0.084

†: Variance analysis, ‡: Student's t-test,*: p<0.05, **: p<0.001, PSQI: Pittsburgh sleep quality index, OAI: Ostomy adaptation inventory, SD: Standard deviation

anger subscale. The average PSQI score of the patients was 7.8±4.1. There was a moderate correlation between the two scales (r=0.527; p<0.001) (Table 3). The relationship between the scales was examined by linear regression and was found to be 27% (R^2=0.277; p=0.000) (Table 4).

Discussion

This study was conducted to determine patients' sleep quality and adaptation to an ostomy. The main results were that the patients had a moderate level of adaptation to the ostomy and high levels of sleep problems. Patients had moderate scores related to acceptance, anxious

Table 2. Scale scores according to according to patients' intestinal ostomy characteristics

Ostomy characteristics		n (%)	Total PSQI Mean ±SD	Total OAI Mean ± SD
The reason for ostomy creation	Colon cancer	13 (28.9)	7.23±3.38	48.23±17.46
	Rectum cancer	24 (53.3)	7.87±2.46	46.66±13.78
	Other†	8 (17.7)	8.87±2.09	46.75±8.65
		F§	0.372	0.054
		p	0.692	0.947
Ostomy duration	2-12 months	29 (64.4)	7.62±3.21	46.72±15.88
	13-24 months	8 (17.8)	9.62±3.65	53.62±7.92
	25 months or more	8 (17.8)	7±3.54	42.12±8.74
		F§	0.926	1.418
		p	0.404	0.254
Ostomy type	Temporary	31 (68.9)	7.74±2.81	48.7±14.36
	Permanent	14 (31.1)	8.14±3.05	43.64±12.83
		t¶	0.295	1.130
		p	0.770	0.265
Ostomy area	Ileostomy	11 (24.4)	7.63±2.12	50.18±8.07
	Colostomy	30 (66.7)	8.16±3.19	46±15.09
	Loop colostomy	4 (8.9)	6.25±2.99	47.25±19.85
		F§	0.382	0.350
		p	0.685	0.706
Preoperative ostomy marking	Yes	18 (40)	7.38±3.03	46.16±12.11
	No	27 (60)	8.18±3.32	47.77±15.26
		t¶	0.622	0.375
		p	0.538	0.709
Operation type	Planned	34 (75.6)	7.85±3.31	48.2±14.18
	Urgent	11 (24.4)	8.5±2.59	45.6±12.6
		t¶	0.431	0.523
		p	0.669	0.604
Having problems on/around the ostomy	Yes‡	40 (88.9)	11.4±4.31	44.82±12.84
	No	5 (11.1)	7.42±2.87	65.6±7.5
		t¶	**2.078**	**3.518**
		p	**0.044***	**0.001****

†: Bladder tumors (2), injuring by weapon (2), paralytic ileus (2), rectal perforation (1) and peritoneal cancer (1), ‡: Ostomy problems: peristomal skin problems (36), retraction in ostomy (2), prolapsus (1) and bleeding (1), §: Variance analysis, ¶: Student's t-test, *: p<0.05, **: p<0.001, PSQI: Pittsburgh sleep quality index, OAI: Ostomy adaptation inventory, SD: Standard deviation

Table 3. Mean PSQI, OAI, and subdimension scores and correlation

	Mean ± SD	Min-max (min-max)†	r	p
Total PSQI	7.86±4.18	1-19 (1-21)†	**0.527**	**0.000****
Total OAI	47.13±13.96	18-79 (0-92)†		
Acceptance	16.57±6.89	8-32		
Anxiety	10.75±3.77	1-18		
Social harmony	9.44±3.87	0-16		
Anger	4.53±2.30	0-8		

†: Minimum and maximum values of scales, r: Correlation, *: p<0.05, **: p<0.001, PSQI: Pittsburgh sleep quality index, OAI: Ostomy adaptation inventory, SD: Standard deviation

Table 4. Regression analysis between scales

Independent variable	Dependent variable	R^2	F	β	t	p
OAI	**PSQI**	0.277	16.495	0.527	4.061	**0.000****

R^2: Regression analysis, F: Variance analysis, t: Student's t-test, *: p<0.05, **: p<0.001, PSQI: Pittsburgh sleep quality index, OAI: Ostomy adaptation inventory

preoccupation, social engagement, and adaptation to ostomy-related anger subscales. Most studies found patients' adaptation to ostomy to be of a moderate level (8,9,11,22-24). Creating an ostomy profoundly affects people's physical and psychosocial health, bowel function, and personal hygiene, sexual life, and body image (1,11). Considering all these factors, patients have a moderate level of ostomy compliance. Age, education level, employment status, and living place characteristics had no significant effect on the ostomy adaptation of the patients.

Gender was found to have an effect on stoma adaptation. Women had better stoma adaptation than men. This gender difference might be due to the socio-cultural characteristics and self-care abilities of women. Simmons et al. (9) found no difference between genders with regard to ostomy adaptation. Honkala and Berterö (25), in their qualitative study, found that females accepted ostomy but despite their gratitude, their lives were affected and changed radically. Their self-respect was reduced, and they felt weak, anxious and insecure (25). It could be concluded that due to the socio-cultural characteristics of women, their compliance with an ostomy is good, even though the creation of an intestinal ostomy affects women more emotionally than men.

Previous studies indicated that ostomy characteristics are significant for ostomy adaptation. Cheng et al. (26), Hu et al. (24) and Xian et al. (27), also stated that patients without a history of peristomal complications, no history of leakage with regular defecation, and better self-care ability were able to adapt better to an ostomy. Some studies mentioned that the factors that affect adaptation to ostomy include acceptance of the ostomy by the spouse, antipathy against the ostomy, peristomal complications (24), awareness of the ostomy and ostomy care, ability to do self-care, being independent (7,26), adequate time for adaptation to a new way of life and a new way of excretion (28). Similarly, our study reported that patients who have no problems around the ostomy adapt well. In our study, when the ostomy characteristics and patient adaptation were examined, it was observed that peristomal complications affect adaptation with ostomy. Peristomal complications reduce the quality of life by affecting the patient both physically and psychologically. As a result, the patient's ostomy adaptation decreases.

In terms of the association of the ostomy characteristics with patient adaptation, the duration, area and type of ostomy, preoperative ostomy marking, operation type, and the reason for ostomy creation were not associated with adaptability in this study. Adapting to an intestinal ostomy may take patients an extended time after surgery since becoming integrated with their new bodies and getting used to physical changes are quite hard (7,8,29). Ostomy duration, one of the criteria of the patients participating in the study, was set at at least two months. This period was preferred for determining adaptability and sleep quality in the patient group since it is desired that problems in the early post-operative period decrease, the wound site heals, and patients take responsibility for ostomy care themselves (30).

The patients' mean sleep quality scale score was found close to eight. A scale score of five and over indicates an impairment in sleep quality (16,21). Ostomy patients

participating in the study had a diminished sleep quality and woke frequently at night. Sleep, one of the basic needs of life, is crucial for the maintenance of physiological and psychological wellness (23). Several studies indicated that sleep quality is impaired in patients with an ostomy (31,32). In these patients, tiredness and immune system problems may occur, and the ability to fight diseases and complications becomes weakened (18-20,31,32). Thus, some symptoms may occur due to sleep deprivation, which means that nurses and healthcare staff should evaluate patients' sleep needs more closely.

The patient's age, gender, education level, and place of residence were not associated with sleep quality. In addition, there was no statistical difference between the ostomy area, ostomy type, ostomy duration of the patients, operation type, the reason for ostomy creation, and the quality of sleep. The sleep quality was generally poor in all patients. In their studies, Vorbeck et al. (19), Ceylan and Vural (18), Furukawa and Morioka (20) Avci Işik et al. (31) and Wu et al. (32) also reported sleep disorders in ostomy patients. This study found that patients experiencing problems on and around the ostomy had worse sleep quality. This indicated that patients were sacrificing and relinquish their sleep to avoid ostomy problems. It can be stated that both the ostomy itself and the ostomy bag treatment impair sleep quality.

In this study, a moderate positive relationship was observed between ostomy compliance and the sleep quality of the patients, and sleep quality predicted ostomy compliance at a rate of 27%. This result indicated that about a quarter of adjustment problems were caused by sleep. The findings indicate that sleep quality affects ostomy adaptation by 27%, and ostomy adaptation is also influenced by other factors. Previous studies found that problems on and around the ostomy could negatively affect patients' quality of life and psychological state (24,26,27,33,34). Patients may have difficulty accepting an ostomy socially and psychologically if they have negative emotions toward the created ostomy. These problems increase anxiety and cause pain and discomfort, which can affect adaptation to the ostomy by ruining patients' comfort.

Nurses and other healthcare professionals should provide the necessary support for patients with ostomy to adapt to their condition. First, it is important to determine the factors that will affect adaptation to ostomy. Nurses provide the necessary training about the preoperative and postoperative periods for individuals with ostomy to adapt (35). Nurses try to ensure adaptation by providing post-discharge care to patients with ostomy, information, consultancy services, ensuring continuity of care, building self-confidence in the patient, and empowering individuals to care for themselves (36). It is a time-consuming process for an individual to adapt to life with an ostomy. Individuals who are aware of the changes that ostomy will create in their body and their lifestyle and who can care for their ostomy will have an easier time adapting to life with an ostomy (35). Çevik et al. (37) determined that patients who had information about ostomy opening in the preoperative period had better adaptation to the ostomy than those who did not. Aminisani et al. (38) found that the compliance rate was higher in individuals who received adequate training on ostomy care than in those who did not. For this reason, patients should receive training on ostomy and be given social support. Nurses and other healthcare professionals need to evaluate the psychological and physiological dimensions of ostomy symptoms (39).

They must also assess the sleep needs of ostomy patients. Knowing the physiology of sleep and the factors that cause sleep problems will enable them to evaluate the sleep quality of their patients and to plan nursing care (40). Although patients could adjust to the ostomy, nurses should consider their sleep needs. According to the results of this study, nurses should be aware of the possibility of a relationship between ostomy adaptation and sleep quality, especially during follow-up of the patients, so that appropriate care can be provided.

Study Limitations

A major limitation of this study was that the sample included 45 individuals from one institution. The cross-sectional data reflected the participants' attitudes within a specific period. Therefore, longitudinal and qualitative studies are required to substantiate the results.

Conclusion

This study indicated that the sleep quality of the patients with intestinal ostomy was poor. Patients reported a moderate level of ostomy adaptation. Adaptation to the ostomy does not necessarily indicate better sleep quality. The results of the present study are important in that it revealed that the patients who adapt well to ostomy may also experience sleep problems.

Ethics

Ethics Committee Approval: Ethical consent was obtained from Tokat Gaziosmanpaşa University Scientific Ethics

Committee (17-KEK-117, date: 01.08.2017) written consent was obtained from the University Hospital. The study complied with the Helsinki Declaration.

Informed Consent: Written and verbal consent was obtained from all patients.

Footnotes

Authorship Contributions

Concept: Ş.E., İ.O., A.A., Design: Ş.E., İ.O., A.A., Data Collection or Processing: Ş.E., İ.O., A.A., Analysis or Interpretation: Ş.E., İ.O., A.A., Literature Search: Ş.E., İ.O., A.A., Writing: Ş.E., İ.O., A.A.

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ORIGINAL RESEARCH

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Medical Ethics-based Intensive Care Unit Admission Evaluation Using Fuzzy Logic for COVID-19-like Pandemic

COVID-19 Benzeri Pandemi için Bulanık Mantık Kullanarak Tıbbi Etik Temelli Yoğun Bakım Ünitesi Kabul Değerlendirmesi

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Abstract

Objective: In this study, a novel fuzzy logic model for intensive care unit (ICU) admission was developed by including not only the medical patient information but also medical ethics to aid in decision-making during pandemic respiratory infectious conditions such as Coronavirus disease-2019 to fill the gap in the literature.

Method: A two-stage fuzzy rule base incorporating experts' experiences was developed to reach a fair decision to prioritize patients for ICU admission. Age, oxygen saturation, and comorbidities were considered as medical risk factors, while the survival probability, discharge period expectancy, and life-cycle principle were considered as ethical parameters.

Results: The ranking score of fair admission is verified by the experts' decisions. As an important validation of the study, an excellent agreement was obtained between the experts' scores and the results of the fuzzy logic algorithm informed by medical information and medical ethics. The scores estimated from the fuzzy logic algorithm were highly positively correlated with those obtained from experts, having r=1 and p<0.01.

Conclusion: The final decision should be left to the responsible doctor in charge. The proposed algorithm is extensible to different numbers and types of medical inputs, ethical perspectives, and the severity of pandemic situations.

Keywords: Fair admission, fuzzy logic, intensive care unit, medical ethics, medical information

Öz

Amaç: Bu çalışmada, literatürdeki boşluğu doldurmak amacıyla, Koronavirüs hastalığı-2019 gibi pandemik solunum yolu enfeksiyonu durumlarında karara katkıda bulunmak amacıyla sadece tıbbi hasta bilgilerinin değil tıp etiğinin de dahil edilmesiyle yoğun bakım ünitesine (YBÜ) kabul için yeni bir bulanık mantık modeli geliştirilmiştir.

Yöntem: YBÜ'ye kabul için hastaları önceliklendirmek amacıyla adil bir karar vermeye ulaşmak amacıyla uzmanın deneyiminden yararlanılarak iki aşamalı bir bulanık kural tablosu geliştirildi. Tıbbi risk faktörleri olarak yaş, oksijen saturasyonu ve komorbiditeler dikkate alınırken, etik parametreler olarak hayatta kalma olasılığı, taburculuk süresi beklentisi ve yaşam döngüsü ilkesi dikkate alındı.

Bulgular: Adil kabul sıralama puanı uzmanların kararlarıyla doğrulanmaktadır. Çalışmanın önemli bir doğrulaması olarak, uzmanların puanları ile hasta hakkındaki tıbbi bilgi, klinik bulgular ve tıp etiğinin yönettiği bulanık mantık algoritmasının sonuçları arasında mükemmel bir uyum elde edildi. Bulanık mantık algoritmasından elde edilen puanlar, uzmandan elde edilen puanlarla yüksek düzeyde pozitif korelasyon göstermiştir (r=1 ve p<0,01).

Sonuç: Nihai karar sorumlu hekime bırakılmalıdır. Önerilen algoritma farklı sayıda ve türdeki tıbbi girdilere, etik bakış açılarına ve pandemik durumların şiddetine göre genişletilebilir.

Anahtar kelimeler: Adil kabul, bulanık mantık, medikal etik, tıbbi bilgi, yoğun bakım ünitesi

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Introduction

The intensive care unit (ICU) provides life support for critically ill patients. Therefore, admission decisions are the most vital phase of the triage. These units often face the risk of not being able to respond to the growing need for medical teams and allocating equipment. The Coronavirus disease-2019 (COVID-19) pandemic has made it clear that intensive care services need to be supported such that they can provide solutions to sudden peak demands using scientific innovation and proactive strategies. Admissions to the ICU at the beginning of the COVID-19 pandemic, due to decisions based on emotional and social status, revealed the need to use appropriate ethical criteria as well as medical ones. It is necessary to develop an objective, correct, logical, fast and ethically appropriate decision-making method for admission (1,2). For example, Cesari and Proietti (1) discuss the valuable experience they have had after the COVID-19 pandemic hit Italy. In their study, they cite the clinical ethics recommendations for allocating treatment in exceptional resource-limited situations by the Italian Society of Anesthesia, Analgesia and Intensive Care, including i) setting an age limit for allocation in ICU, and ii) considering the patient's comorbidities and functional status. They conclude that there is a need for the implementation of ethical principles into decisional algorithms and that these should be integrated into pandemic preparation globally.

It is difficult to identify patients who are likely to benefit from admission to the ICU. Sabetian et al. (3) developed models based on machine learning to estimate the ICU requirement of patients with COVID-19. Certain risk factors can influence ICU triage. In literature, factors such as patients' age, comorbidities, chronic health status, ICU occupancy rate, oxygen saturation (SaO_2 level), respiratory rate, pulse rate, and presence of life-threatening conditions have been reported (2,4-6). Bates and Young (7) proposed a fuzzy logic algorithm to promote decision making in the ICU by considering only arterial blood pressure and urine output. Fernandes et al. (8) utilized a machine learning approach to identify emergency department patients with a high ICU admission rate. Polilli et al. (9) performed a retrospective study to build a risk score for the decision-making process at the emergency department using logistic regression and Cox modelling by using demographic and clinical data.

The ICU admission process should be ethically satisfactory in all aspects. The main motivation of this study is the search for a method to create a fair and non-discriminatory decision approach in the provision of life support in ICU services. Childress et al. (10) and Annas (11) draw attention to the fact that today's traditional medical ethics principle of respect for patient autonomy, beneficence, not harming, and justice are insufficient when ICU scarcity arises in public health crises or disasters resulting in a tremendous increase in the patient population. White et al. (12) pointed out that admission decisions for ICUs in inadequate conditions should also be based on strong moral criteria such as distributive justice, focus on the common social benefit, certainty of criteria, transparency, sensitivity, and rationality. They confirm the use of maximizing life-years, life-cycle principle, and using multiple principles in an allocation strategy.

In literature, various hospitalization criteria for reaching ICU utilities and the high insufficiency caused by the pandemic conditions have been taken as the basis of the medical ethics debates so far (13). Childress and Beauchamp (14) mostly stated that the utilitarian approach, which emphasizes maximizing net social utility, and the equality approach, which emphasizes that people should have equal opportunities, are the most prominent in the distribution policies of scarce medical treatments, and they suggested combining these two. Persad et al. (15) consider maximizing benefits, which is an important Utilitarian value, and explain it through strategies such as saving the most lives, saving the most life years, and using a prognosis-oriented strategy during medical resource scarcity. Rubio et al. (2) emphasized those patients' refusing the ICU treatment; expressed in advance directives should be taken into account. They suggested avoiding medical futility, saving the maximum number of lives and life-years, and maximizing the chance of living all stages of life, for the allocation strategy of scarce intensive care treatment in times of crisis. Norwegian nurses' and physicians' perceptions of the needs of significant others in ICUs validate that four factors: "attentiveness and assurance", "taking care of themselves", "involvement", and "information and predictability" effectively address these needs (16).

Halvorsen et al. (17), reported that significant others could induce unintentional discrimination of ICU patients. Family members who were demanding received more time and attention for both themselves and the patient. Patients' and families' status and position and/or an interesting medical diagnosis seemed to govern the clinicians' priorities of patients and families, consciously as well as unconsciously, and the principle of justice was violated. As reported by

Oerlemans et al. (18), sometimes the pressure of the need for ICU results in ethical problems such as refusing the admission or transferring the patient to another ICU far away after his medical stabilization, which sometimes worsens the patient's situation.

White et al. (12,19) criticized the existing ICU allocation strategies in possible pandemic crises and evaluated some ethical approaches such as broad social value, maximizing the life-years, the life cycle principle, and multiplier effect. They reached a conclusion that only focusing on saving the maximum number of lives is not satisfactory, whereas the life cycle principle is acceptable from the ethical point of view. There should be studies for ethically permissible allocation strategies, both to identify the most acceptable approach and to achieve the greatest possible extent of a fair process of decision making (12,19).

After a public health situation caused by the COVID-19 pandemic in Spain, Rubio et al. (2) also reported a consensus among 18 scientific societies and 5 institutes/chairs of bioethics and palliative care on a reference framework document with general ethical recommendations. These are i) maximizing survival after hospital discharge and the number of life-years saved, considering that chronological age should not be the only element to take into account, ii) triage should be based on principles of distributive justice, prioritizing the best "cost/opportunity" ratio and proportionality, not hospitalizing patients with minimum benefits foreseen, such as patients with advanced disease-related limited life expectancy.

Many medical applications, such as computer-aided clinical decision support systems (CDSS), have been studied so far. CDSS provide patient-specific information and advice to healthcare professionals and patients. The decision-making methods of these systems can be divided into four categories: algorithms (20,21), multi-criteria decision-making methods (22), statistical methods (23), and artificial intelligence methods (24).

Uncertainties can rarely be avoided in solving real-world problems. In such cases, fuzzy logic is a useful tool in solving problems. Fuzzy logic approaches have been successfully used in a variety of disciplines, including medicine. Data in linguistic format are frequently encountered in the field of medicine. The linguistic description of the same phenomenon may differ between people. In situations where there are uncertainties in human judgment, fuzzy logic concepts can be used to obtain approximate information. Thus, experts' knowledge and experience can be utilized in the decision-making process.

Ethical decision-making often involves a choice between distinct alternatives with the structure of a dilemma. There is always fuzziness and ambiguity in human thinking. Thus, fuzzy logic-based approaches are accepted as the most similar to human thought processes in terms of their ability to make appropriate decisions based on linguistic non-specific data (25).

In a previous study, it was aimed to propose a computer-aided method using a fuzzy logic algorithm for patient admission to the ICU in order to achieve fair prioritization among different patients (26). The aim is to develop a fuzzy logic algorithm that can be used for obtaining accurate priority scores among disparate patients from objective parameters. Both medical information and ethical parameters were taken into account for the two-stage consecutive fuzzy logic algorithm. As a result, it became possible to make ethical and objective decisions regarding the admission of patients to the ICU independent of subjective decisions of medical staff.

Materials and Methods

Medical Information and Ethics Evaluation Software

In the creation of a fair ICU admission computer software model, appropriate methods and approaches from different disciplines were studied. The Utilitarian approach and ethical principles are preferred in relation to patient information management in medical ethics, along with fuzzy logic as a decision tool, and they are used to incorporate both medical and ethical principles in justice.

Medical Patient Information Based Medical Ethics

As cited before, the strategies to maximize the number of lives saved and to maximize life-years are considered important in times of ICU scarcity. The Utilitarian Theory is broadly accepted for the allocation and distribution, of scarce treatments such as life-sustaining technology in public health crises. Non-discriminative fair decisions must be the main goal (27). Although the effect of the Utilitarian approach has decreased in medical ethics of today, where respect for patient autonomy comes to the fore, it continues to be effective in some special areas such as public health. The theory focuses on the benefit of maximization of utility and results. In this respect, it pursues the ideal of increasing the general welfare and spreading happiness (28). The principled approach of medical ethics contributes to developing a balanced and reasonable strategy for the protection of both individuals and society in routine circumstances. It is based on generally accepted moral

principles and medical tradition, emphasizing respect for autonomy, non-maleficence, beneficence, and justice. The principle of respect for patient autonomy is effectively embedded in medical practice, with the patient making their own medical decisions, after being informed by the physicians. The physician must obtain patients' decisions, desire, or preferences about life-sustaining treatment according to the legislation.

After satisfying the arguments above, the accepted ethical measures, such as survival probability, discharge period expectancy, and life-cycle principle (years to live by reaching an equality in individuals' whole life-cycle), have been used in the decision algorithm. The decision-making process of experts and the fuzzy logic algorithm representing their decisions have been forced to obey the principles reflecting the Utilitarian Method when encountering medical inputs of age, SaO_2 level, and comorbidities. Additionally, they consider the beneficence and non-maleficence principles of Childress and Beauchamp (14) for COVID-19 ICU insufficiency.

Fuzzy Logic

There are difficulties in transferring the personal experience and knowledge of the expert to conventional decision-making methods, which are necessary in cases without agreement among disciplines on criteria. In such cases, fuzzy logic rule tables are a highly effective means of incorporating the expert's contribution into the decision-making process. Fuzzy inference is the process of mapping a given input to output through a fuzzy logic based reasoning mechanism constituted of if-then rules, membership functions, and fuzzy logic operations such as if "input 1" and "input 2" and "input 3" then "output". A fuzzy inference system has four main steps. These are fuzzification, fuzzy rules, fuzzy inference, and defuzzification. In this study, Mamdani fuzzy inference was used. The fuzzy set defines and converts the result of the if-then rule into membership values during the fuzzification step of this inference.

Computer Software Design

The computer software algorithm of the proposed method with a two-stage fuzzy logic decision mechanism, is presented in Figure 1. It is important to emphasize that even the measure of ethical principles, based on medical patient information. Therefore, a brand new computer-aided decision-making software that is based on medical information and produces the effects of selected ethical measures, which are i) probability of survival, ii) ICU discharge period expectancy, iii) Life-cycle principle based years (left). After the ICU experts confirmed the first stage fuzzy logic decision unit algorithm and the outputs of these measures, these outputs will be used in the second stage of fuzzy logic decision unit to obtain a fair admission priority ranking. Figure 2 shows a two-stage fuzzy decision-making process sequentially. The first stage is a multi-input multi-output (MIMO) with three inputs (age, SaO_2 level, and comorbidities) and three outputs (survival rate expectancy, discharge period expectancy, and years to live after recovery based on life-cycle principles). The second stage is a multi-input single-output (MISO) system with three inputs from the first stage and one output of a priority score for ICU admission.

The membership functions of the inputs and output of MIMO and MISO are given in Figures 3, 4, respectively. Their ranges were determined using information from the most experienced ICU doctors in their field.

The first input variable is age, and it is categorized as young, mature, and old. ICU candidates were further categorized in the second input as having severe hypoxemia, moderate hypoxemia, mild hypoxemia, and normal based on their SaO_2 levels. The survival probability is the first output, and it is classified as low, medium, or high depending on the patients' likelihood of survival with intensive care treatment based on the ICU experts' information. The discharge period, which is the second output of MIMO, shows the

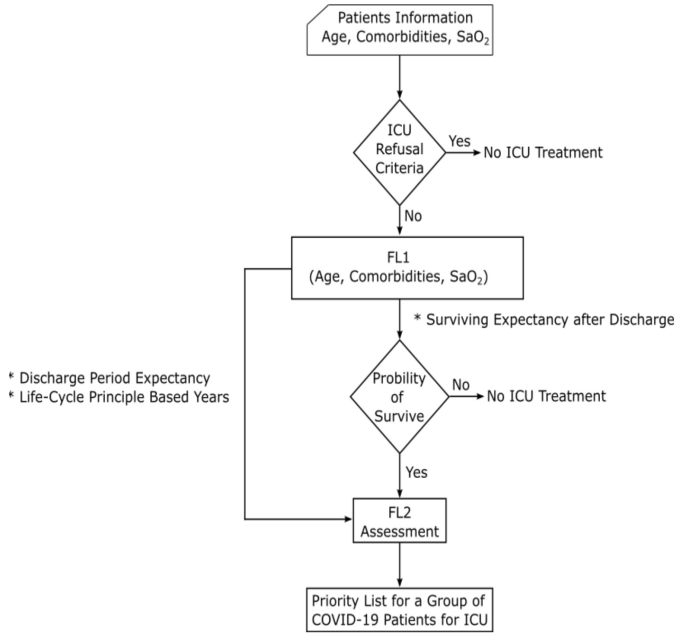


Figure 1. Computer software algorithm
ICU: Intensive care unit, COVID-19: Coronavirus disease-2019

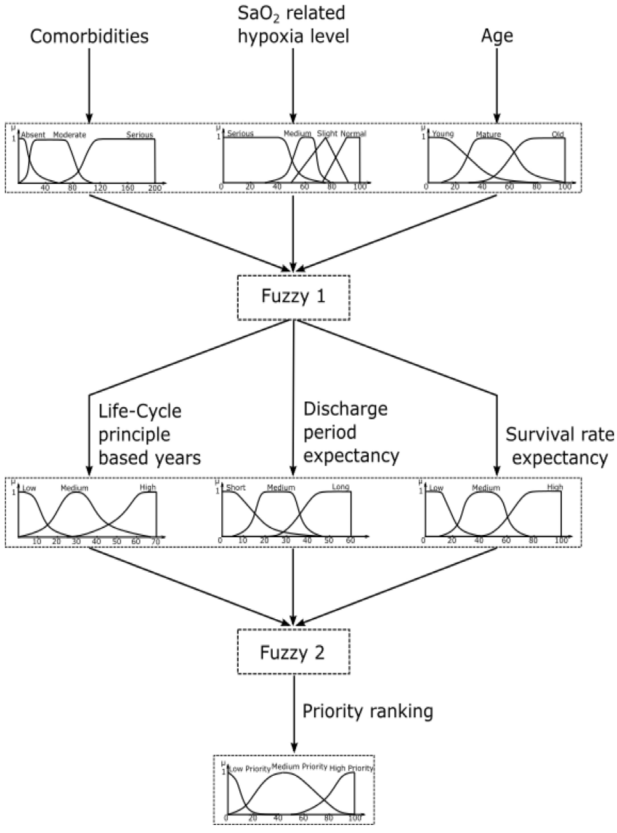
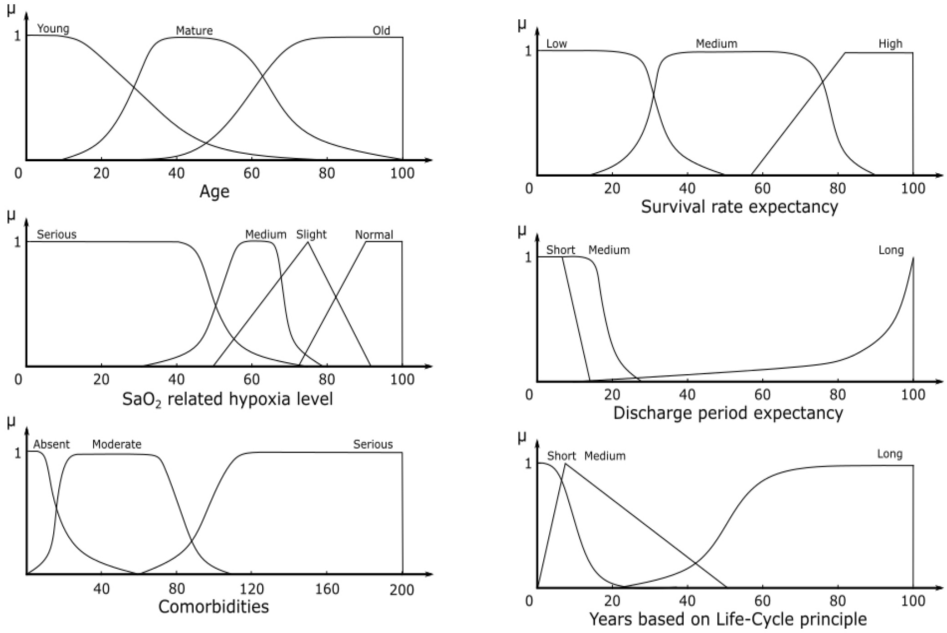


Figure 2. Fuzzy logic flowchart used in admission decision

patients' possible length of stay in the ICU and is classified into three categories: short, medium, and long. Life-cycle principle-based years left is the final output and it shows the life expectancy after discharge from the intensive care unit, which is categorized into three categories: Short, medium, and long as shown in Figure 3. The comorbidities of the patients were chosen as the last input and were divided into three categories (absent, moderate, and serious) depending on whether they were major or minor. Cardiac, pulmonary, renal, liver disease, and diabetes mellitus were considered as major criteria, while body mass index (≥30 kg/m^2), smoking, and others were considered as minor criteria (29). Table 1 shows how major and minor diseases were quantified based on membership limits. These scores are needed for related fuzzy logic input regarding comorbidities. Then, the total comorbidity score was computed by considering the severity of major and minor diseases that patients had.

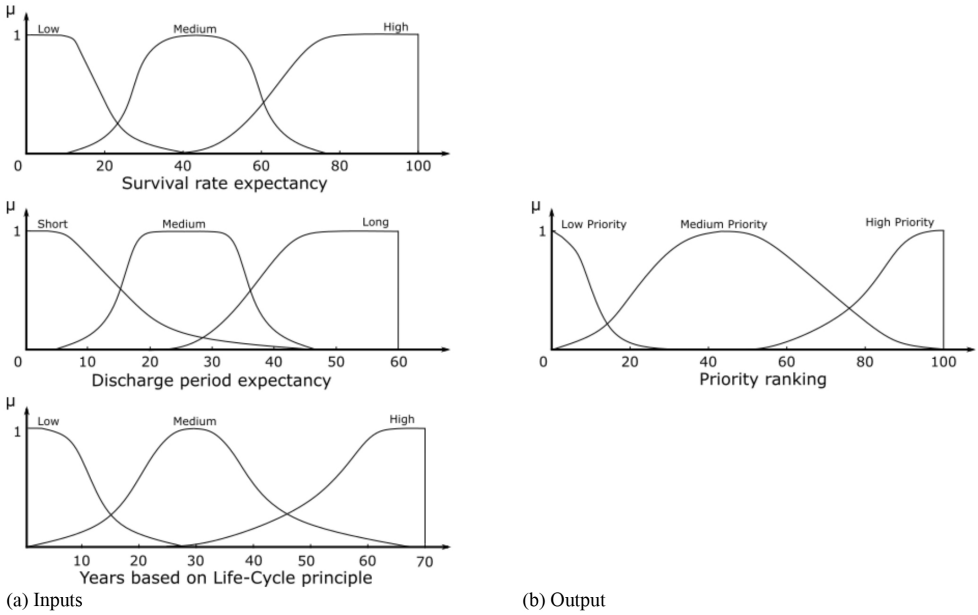
The second stage input variables are first stage output variables, and their crisp values are used in the inference system of MISO with a new membership function of the related variables. The priority score, which is the final output of this study, is obtained as a crisp value from the second stage. This output is divided into three categories: low, medium, and high priority. The second-stage fuzzy logic membership functions are presented in Figure 4.



(a) Inputs

(b) Outputs

Figure 3. Membership functions for the first fuzzy logic assessment



(a) Inputs (b) Output

Figure 4. Membership functions for the second and final fuzzy logic assessment

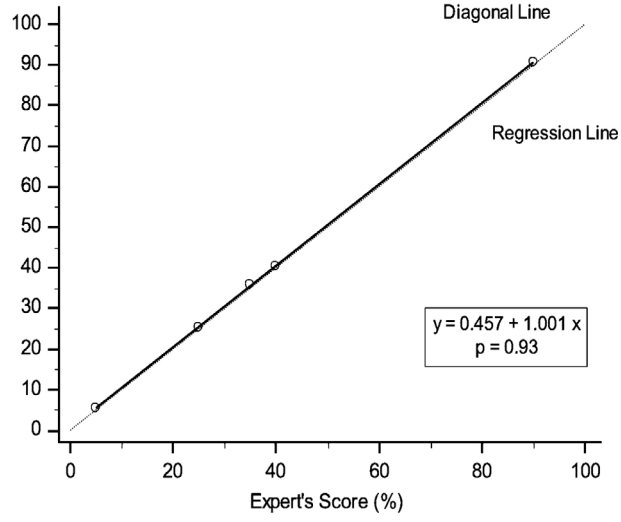


Figure 5. Comparison of expert's score and fuzzy logic score with Passing-Bablok analysis

To design the rule base for the admission of ICU candidates, the influence of each parameter on the admission of patients to the ICU was determined by referring to the experiences of eminent ICU experts. The underlying logic of these rules was that the patient's possibility of ICU admission increased with the severity of his/her status, which was represented as inputs. The proposed fuzzy system had 36 rules at the first stage (Table 2) and 27 rules at the second stage (Table 3).

Statistical Analysis

Passing and Bablok (30) regression analysis was employed to evaluate the agreement between the scores obtained from the proposed fuzzy logic algorithm and those from the expert assessment. This method is particularly robust for assessing the linearity and agreement between two measurement methods without assuming normality or equal variance. Statistical significance level was set to $p<0.05$.

Ethics

The patient data used in our study were not taken from real patients; instead, a data set was created by consulting expert physicians for possible scenarios. Therefore, since the study does not include real patient data, there is no need to obtain ethics committee approval.

Results

Tables 4, 5 demonstrate the patient scores, calculated by the first phase of the proposed fuzzy logic decision-making method, and the ICU experts' scores. Comorbidity scores were calculated using Table 1, based on the patients' major and minor diseases. Patient data are hypothetical, and offered by a very experienced expert who is the head of a 36-bed ICU. The proposed fuzzy decision-making process was challenged and tested using these potentially critical patient data representing real pandemic conditions.

Table 1. Additive score of the major and minor diseases to be used in third input of the first stage

Number of major comorbidities	Score	Number of minor comorbidities	Score
1	50	1	5
2	80	2	10
3	120	3	15
4 and more	170	4 and more	20 and 30

The survival rate expectancy, ICU discharge period expectancy, and years to live after discharge based on the life-cycle principle estimated by the fuzzy logic algorithm are presented in Table 4. It is seen that the experts' average evaluation scores are in good harmony with those obtained from fuzzy logic software.

The priority scores for ICU admission of the candidates estimated by the second phase of the fuzzy logic algorithm

Table 2. Fuzzy decision rules of the first stage

Age	SaO_2 related hypoxemia	Comorbidities	Survival rate expectancy	Discharge period expectancy	Years to live after recovery
Young	Serious	Absent	Medium	Short	Long
Young	Serious	Moderate	Medium	Medium	Long
Young	Serious	Serious	Low	Long	Medium
Young	Medium	Absent	High	Short	Long
Young	Medium	Moderate	Medium	Medium	Long
Young	Medium	Serious	Medium	Long	Long
Young	Slight	Absent	High	Short	Long
Young	Slight	Moderate	High	Medium	Long
Young	Slight	Serious	Medium	Medium	Long
Young	Normal	Absent	High	Short	Long
Young	Normal	Moderate	High	Medium	Long
Young	Normal	Serious	Medium	Medium	Long
Mature	Serious	Absent	Medium	Medium	Medium
Mature	Serious	Moderate	Medium	Medium	Medium
Mature	Serious	Serious	Low	Long	Short
Mature	Medium	Absent	Medium	Medium	Medium
Mature	Medium	Moderate	Medium	Medium	Medium
Mature	Medium	Serious	Low	Long	Medium
Mature	Slight	Absent	Medium	Short	Medium
Mature	Slight	Moderate	Medium	Medium	Medium
Mature	Slight	Serious	Low	Long	Medium
Mature	Normal	Absent	High	Short	Medium
Mature	Normal	Moderate	Medium	Medium	Medium
Mature	Normal	Serious	Low	Long	Medium
Old	Serious	Absent	Medium	Long	Short
Old	Serious	Moderate	Low	Long	Short
Old	Serious	Serious	Low	Long	Short
Old	Medium	Absent	Medium	Long	Short
Old	Medium	Moderate	Low	Long	Short
Old	Medium	Serious	Low	Long	Short
Old	Slight	Absent	Medium	Medium	Medium
Old	Slight	Moderate	Low	Long	Short
Old	Slight	Serious	Low	Long	Short
Old	Normal	Absent	High	Medium	Medium
Old	Normal	Moderate	Low	Long	Short
Old	Normal	Serious	Low	Long	Short

are also provided in Table 5. Priority score indicates the candidate priority ranking for ICU admission in justice, depending on both medical records and medical ethics evaluation, which is based on survival rate expectancy, discharge period expectancy, and life cycle principle, considering these factors were also derived from patients' medical records. The priority order is presented from highest to lowest score. There has been a perfect match, as an important verification of the study, between the experts' scores and the medical ethics dominated fuzzy logic algorithm.

Table 3. Fuzzy decision rules of the second stage

Survival rate expectancy	Years to live after recovery	Discharge period expectancy	Priority ranking
Low	Short	Short	Low priority
Low	Short	Medium	Low priority
Low	Short	Long	Low priority
Low	Medium	Short	Low priority
Low	Medium	Medium	Low priority
Low	Medium	Long	Low priority
Low	Long	Short	Medium priority
Low	Long	Medium	Medium priority
Low	Long	Long	Low priority
Medium	Short	Short	Low priority
Medium	Short	Medium	Low priority
Medium	Short	Long	Low priority
Medium	Medium	Short	Medium priority
Medium	Medium	Medium	Low priority
Medium	Medium	Long	Low priority
Medium	Long	Short	High priority
Medium	Long	Medium	High priority
Medium	Long	Long	Medium priority
High	Short	Short	Low priority
High	Short	Medium	Low priority
High	Short	Long	Low priority
High	Medium	Short	High priority
High	Medium	Medium	Medium priority
High	Medium	Long	Low priority
High	Long	Short	High priority
High	Long	Medium	High priority
High	Long	Long	Medium priority

Agreement between experts' scores and fuzzy logic scores was evaluated by Passing and Bablok (30) regression analysis. The scores estimated from the proposed fuzzy logic algorithm were highly positively correlated with those obtained from an expert, having r=1 and p<0.01. r and p are the correlation coefficient and the cumulative sum control chart test p-value, respectively, as presented in Figure 5.

Discussion

The admission of candidates to the ICU is a critical decision and depends on patients' medical records. It is experienced that evaluation has been depended on medical experts' experiences, certain ethical parameters and sometimes possibly affected by subjective considerations such as cultural, social, psychological priorities of the locals during pandemic. The decision must not be affected by non-medical and non-ethical factors. Therefore, it was aimed to develop a computer-aided algorithm to determine a fair priority ranking of the candidates to the ICU by using objective parameters, in terms of medical and ethics ones, for Coronavirus-like pandemic conditions such as COVID-19. Medical information dominated ethical principles have been effective in experts' decisions such as saving more lives, maximizing the life-years after discharge and life-cycle principle. Survival rate expectancy, ICU discharge period expectancy and years to live after discharge (a measure for life-cycle principle) were obtained from medical patient

Table 4. Fuzzy logic ICU admission scores and experts' scores for the first stage

Patient no.	SaO_2 related hypoxemia	Age (years)	Comorbidities		Survival rate expectancy (%)		ICU discharge period expectancy (days)		Years to live after ICU discharge	
			Number of minor diseases	Number of major diseases	Expert's scores	Fuzzy scores	Expert's scores	Fuzzy scores	Expert's scores	Fuzzy scores
1	55	18	0	0	80	79.95	7	7.03	60	64
2	70	40	0	2	50	54.14	14	16.24	24	27
3	65	54	1	2	40	40.79	21	22.35	17	12.2
4	60	68	2	1	35	34.35	24	23.43	10	6.68
5	55	82	3	0	30	24.01	30	27.34	3	3.67

ICU: Intensive care unit

Table 5. Fuzzy logic ICU admission scores and experts' scores for the second stage

Patient No.	Survival rate expectancy (%)	ICU discharge period expectancy (days)	Years to live after ICU discharge (years)	Priority ranking	
				Expert's* scores	Fuzzy logic score
1	80	7	60	90	90.6
2	50	14	24	40	40.5
3	40	21	17	35	35.8
4	35	24	10	25	25.2
5	30	30	3	5	5.5

*: Expert estimates the survival rate expectancy, ICU discharge period expectancy, years to live after ICU discharge and achieves his scores. The fuzzy logic mimics the decision process. ICU: Intensive care unit

information, namely age, SaO_2 and comorbidities. Ethical basis on which consensus has been formed in literature for ICU scarcity conditions were imposed in the decision of the proposed fuzzy logic algorithm software and verified that these admission decisions are also compatible with the experts' decision.

It was taken into account that survival rate expectancy, discharge period expectancy, and life-cycle principle-based years to live after ICU discharge were dependent on the patients' age, SaO_2 level, and comorbidities.

Several research studies considered only patients' medical information for the decision-making process using different algorithms and machine learning methods. Patients' age, comorbidities, chronic health status, ICU occupancy rate, SaO_2 level, respiratory rate, pulse rate, and presence of life-threatening conditions are important parameters affecting the admission of patients to the ICU (2,4-6). Patients' age, SaO_2 and comorbidities have been used among the medical parameters. In addition to existing literature, ethical parameters in terms of survival rate expectancy, ICU discharge period expectancy, and years to live after ICU discharge have also been considered. Since the ICU admission process should be ethically satisfactory in all aspects, it was crucial to consider both medical and ethical parameters. The pros and cons of this study are presented. Designing a two-step fuzzy logic algorithm and increasing the number of inputs placed a significant burden on determining the rule table and model. However, the results were in perfect agreement with the expert's opinion and clearly demonstrated the effectiveness of the developed algorithm.

Study Limitations

The medical data and ethical criteria are international medical factors globally accepted in respiratory infectious conditions, such as pandemics like COVID-19. On the other hand, similar pandemic diseases might need the evaluation of medical measures with different weights within a fuzzy logic algorithm. For example, younger ages might be a more significant factor. But the body and the construction of the fuzzy logic software presented in this study can be adopted to new pandemics easily because it is an open-source computer program. Of course, during this adaptation period the programmer needs the guidance and approval of the eminent experts. The other limitation is the undeniable legal responsibility of the ICU personnel in command. One must not forget that the outputs of the software must not have a dominant effect in decision making, and everybody needs to follow the instructions of the responsible personnel.

Conclusion

This brand-new fair fuzzy logic algorithm will contribute to the decision processes of intensive care specialists. It can easily be revised with subsequent studies according to the scarcity of ICU resources and different ethical approaches. Taking into account risk factors and medical ethics principles, it is a strong candidate to help ensure fair ICU admission by imitating the decision-making process of very experienced ICU doctors during the COVID-19 pandemic as well as other respiratory infectious pandemics, without causing any ethical debates and accusations.

Ethics

Ethics Committee Approval: The patient data used in our study were not taken from real patients; instead, a data set was created by consulting expert physicians for possible scenarios. Therefore, since the study does not include real patient data, there is no need to obtain ethics committee approval.

Informed Consent: The patient data used in our study were not taken from real patients.

Footnotes

Authorship Contributions

Concept: S.Y., N.Y., Design: S.Y., D.K., B.S., N.Y., Data Collection or Processing: Z.S., D.K., B.S., Analysis or Interpretation: S.Y., D.K., B.S., Z.S., Literature Search: S.Y., D.K., B.S., Writing: S.Y., D.K., B.S.

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

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ORIGINAL RESEARCH

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Assessment of Retinal Nerve Fiber Layer Thickness Strabismic and Anisometropic Amblyopia Cases

Şaşılık ve Anizometropik Ambliyopi Olgularında Retinal Sinir Lifi Tabaka Kalınlığının Değerlendirilmesi

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Abstract

Objective: The aim of this study was to determine whether differences exist in retinal nerve fiber layer (RNFL) thickness between amblyopic eyes and non-amblyopic eyes of patients with strabismic amblyopia and anisometropic amblyopia using optical coherence tomography (OCT), as well as healthy eyes in a control group.

Method: Thirty-six cases of unilateral anisometropic amblyopia, 40 cases of unilateral amblyopia with strabismus, and 42 healthy individuals were included. Patient history, demographic characteristics, and mean RNFL thickness values across quadrants were recorded using OCT.

Results: A total of 118 participants were enrolled in the study, comprising 54 males and 64 females, with an average age of 16.25±9.05 years. Analysis of mean and quadrant RNFL thickness values revealed no statistically significant differences between amblyopic eyes, non-amblyopic eyes, and the control group (p>0.05). Similarly, there was no significant variation in RNFL thickness in the amblyopic eyes of patients with strabismic and anisometropic amblyopia compared to their non-amblyopic eyes or to the control group (p>0.05). However, participants with anisometropic amblyopia had a thicker mean RNFL when compared to those with strabismic amblyopia (p>0.05). Although there was a tendency for increased RNFL thickness across all quadrants in individuals with anisometropic amblyopia, this difference did not reach statistical significance (p<0.05).

Conclusion: RNFL thickness was found to be similar in amblyopic and normal eyes. While existing studies have highlighted the impact of amblyopia on the RNFL, further investigations that consider additional factors are warranted.

Keywords: Anisometropia, amblyopia, retinal nerve fiber layer, strabismus

Öz

Amaç: Bu çalışmanın amacı, şaşılık ambliyopisi ve anizometropik ambliyopisi olan hastaların ambliyopik gözleri ile ambliyopi olmayan gözleri ve kontrol grubundaki sağlam gözler arasında retina sinir lifi tabakası (RSLT) kalınlığında farklılık olup olmadığını optik koherens tomografi (OKT) kullanarak araştırmaktır.

Yöntem: Kırk, tek taraflı şaşılık ambliyopisi olan, 36 tek taraflı anizometropik ambliyopi ve 42 sağlıklı birey çalışmaya dahil edildi. Tüm olguların öykü, ortalama ve kadran RSLT kalınlığı değerleri OKT kullanılarak kaydedildi.

Bulgular: Çalışmaya 64'ü kadın, 54'ü erkek olmak üzere toplam 118 kişi dahil edildi. Ortalama yaş 16,25±9,05 yıldı. Tek taraflı ambliyopili olguların ambliyopili gözlerinin ortalama ve kadran RSLT kalınlığı değerleri ambliyopisi olmayan gözlerle ve kontrol grubunun sağ gözleriyle karşılaştırıldığında istatistiksel olarak anlamlı bir fark gözlenmedi (p>0,05). Hem şaşılık hem de anizometropik ambliyopili olguların ambliyopili gözleri arasında, ambliyopisi olmayan gözlere veya kontrol grubunun sağ gözlerine göre ortalama ve kadran RSLT kalınlığı açısından anlamlı bir fark yoktu (p>0,05). Şaşılık ambliyopili olguların ambliyopik gözleri anizometropik ambliyopili olgularla karşılaştırıldığında, anizometropik ambliyopili olgularda anlamlı derecede daha kalın ortalama RSLT kalınlığı gözlendi (p>0,05). Anizometropik ambliyopili olgularda şaşılık ambliyopili olgularla karşılaştırıldığında dört kadranda da RSLT'nin kalınlaşması yönünde bir eğilim olmasına rağmen bu fark istatistiksel olarak anlamlı değildi (p<0,05).

Sonuç: Çalışmamızın sonuçları, ambliyopik ve sağlıklı gözler arasında RSLT kalınlığı açısından anlamlı bir fark olmadığını göstermektedir. Şu ana kadar yapılan çalışmalar ambliyopinin RSLT üzerindeki etkilerini göstermiştir. Ancak bu alanda farklı faktörlerin dikkate alındığı daha fazla araştırmaya ihtiyaç vardır.

Anahtar kelimeler: Ambliyopi, anizometropi, retina sinir lifi tabakası, şaşılık

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Introduction

Amblyopia is a condition characterized by significantly reduced visual acuity, which may result from severe visual deprivation or abnormal binocular interactions during visual development (1). The prevalence of amblyopia ranges from 1% to 5% in studies of large populations (2-6). Amblyopia is not solely an eye-related issue; it can also be considered a form of brain dysfunction caused by exposure to abnormal visual stimuli. In amblyopic eyes, a decrease in contrast sensitivity, distortion of object shapes, and diminished spatial localization perception are commonly observed (7). There are three primary causes of amblyopia: Anisometropic amblyopia, strabismic amblyopia, and stimulus deprivation amblyopia. Anisometropic amblyopia may occur independently or in conjunction with strabismic amblyopia (8). Optical coherence tomography (OCT) facilitates the detailed evaluation of retinal structures, including retinal nerve fiber thickness (RNFL), macular volume, and macular thickness. Advancements in OCT technology allow for an in-depth examination of retinal layers, RNFL, and the choroid layer (9). Studies investigating the relationship between amblyopia and RNFL thickness have yielded mixed results. While some researchers found no significant differences in RNFL thickness between amblyopic and healthy eyes (10,11), others reported notable variations in RNFL thickness in anisometropic amblyopic eyes compared to normal eyes (12,13).

The objective of this study is to determine whether RNFL thickness varies between amblyopic eyes and non-amblyopic eyes in patients diagnosed with strabismic and anisometropic amblyopia, using OCT technology.

Materials and Methods

This study was designed retrospective and cross-sectional. For the study, 40 strabismic patients with unilateral amblyopia, 36 anisometropic patients with unilateral amblyopia, and 42 healthy subjects who were admitted to İstanbul Okmeydanı Training and Research Hospital between January 2008 and January 2013 were included in the study. Approval was obtained from the İstanbul Okmeydanı Training and Research Hospital Ethics Committee with the decision dated 07/06/2013 and numbered 89, following the rules of the Declaration of Helsinki.

Inclusion criteria were as follows:

- Best-corrected visual acuity ≥20/20 in the better eye.
- Age range: 7 to 40 years.
- Intraocular pressure (IOP) <20 mmHg in both eyes.
- Clear ocular environment.
- Normal fundus examination.
- Unilateral amblyopia due to strabismus or anisometropia.

Exclusion criteria were as follows:

Subjects with organic eye disease; a history of intraocular surgery; opacity in the optic axis; a history of neurological disease; any retinal or optic nerve pathology; a history of glaucoma; IOP higher than 21 mmHg; nystagmus; non-communicable diseases; and age less than seven years were excluded.

Based on these criteria, the participants were divided into three groups according to the type of amblyopia:

- Group I: This group included forty patients with strabismic amblyopia and a shift of more than ten prism diopters.
- Group II: Thirty-six patients with hypermetropic anisometropic amblyopia and a refractive difference of at least two diopters between the two eyes were included in this group.
- Group III: Forty-two patients with complete visual acuity in both eyes and no ophthalmic or systemic disease were included in this group. The right eye values of the individuals were used in the study.

A detailed medical history was recorded, and uncorrected and best-corrected visual acuity, measured with the Snellen chart, and IOP, measured with a Topcon CT.80A pneumotonometer, were also recorded. The distance and near shifts of strabismic patients were recorded in prism diopters. Anterior segment and fundus examinations of all patients with fully dilated pupils were recorded. RNFL measurements were recorded by a single examiner using the Cirrus HD-OCT (model 4000, software version 5.1.1.6, Carl Zeiss Meditec, Inc.) with fully dilated pupils. Cases with an OCT signal strength of less than five were not included in the study. The average, superior, nasal, inferior, and temporal quadrant RNFL thicknesses were recorded in all cases.

Amblyopia cases were divided into three groups: mild, moderate, and severe in terms of best-corrected visual acuity measured from the Snellen chart by correcting the refractive error.

Statistical Analysis

Data from all cases were entered into SPSS (Statistical Package for Social Science, Worldwide Headquarters SPSS

Inc.) 20.0 for statistical analysis. Means, standard deviations, proportions, and frequencies were used for descriptive statistics of the data. The Kolmogorov-Smirnov test was used to test the distribution of variables. ANOVA (Tukey test) and Kruskal-Wallis (Mann-Whitney U test) were used to analyze quantitative data. The paired sample t-test and the Wilcoxon test were used for repeated measurements. The chi-square test was used to analyze qualitative data.

Results

Demographics

A total of 118 cases were analyzed, with a mean age of 16.25±9.05 years (range: 7-40 years).

- Group 1 (strabismic amblyopia): Mean age 14.05±6.89 years (range: 7-27 years).
- Group 2 (anisometropic amblyopia): Mean age 18.89±11.02 years (range: 7-40 years).
- Group 3 (control): Mean age 16.10±8.62 years (range: 7-32 years).

Gender distribution:

- 64 participants (54.2%) were female.
- 54 participants (45.8%) were male.

There was no statistically significant difference in age or gender among the groups (Table 1).

When grouped according to visual acuity, in Group 1, 16 cases (40%) were classified as severe amblyopia, 14 cases (35%) as moderate amblyopia, and 10 cases (25%) as mild amblyopia. In Group 2, 16 cases (44.4%) were classified as severe amblyopia, 10 cases (27.8%) as moderate amblyopia, and 10 cases (27.8%) as mild amblyopia. No statistically significant difference in the degree of amblyopia was observed between Groups 1 and 2 based on visual acuity (Table 2).

Overall RNFL Thickness

The mean RNFL thickness in the amblyopic eyes of 76 patients with unilateral amblyopia was 95.81±13.33 µm, compared to 94.92±13.94 µm in their normal eyes. This difference was not statistically significant (p>0.05).

RNFL thickness in the four quadrants for amblyopic versus non-amblyopic eyes:

- Temporal: 65.50±21.18 µm vs. 66.23±14.23 µm.
- Nasal: 70.39±14.39 µm vs. 68.97±13.93 µm.
- Superior: 119.18±22.28 µm vs. 119.89±22.28 µm.
- Inferior: 126.60±20.28 µm vs. 126.10±22.78 µm.

No statistically significant difference was found between the quadrants (p>0.05). Similarly, no significant disparity was observed when comparing amblyopic eyes with the control group (Table 3).

Group-specific RNFL Findings

1. Group 1 (strabismic amblyopia):

- Mean RNFL thickness:
- Amblyopic eyes: 92.95±13.81 µm.
- Normal eyes: 90.55±14.04 µm.
- Quadrant thicknesses in amblyopic vs. normal eyes:
- Temporal: 63.80±13.21 µm vs. 63.00±11.46 µm.
- Nasal: 68.40±16.14 µm vs. 64.25±12.82 µm.
- Superior: 121.55±25.64 µm vs. 114.05±22.90 µm.
- Inferior: 124.60±22.69 µm vs. 120.50±24.04 µm.

No significant differences were found between amblyopic and normal eyes, nor when compared to the control group (p>0.05, Table 4).

2. Group 2 (anisometropic amblyopia):

- Mean RNFL thickness:
- Amblyopic eyes: 99.00±12.19 µm.
- Normal eyes: 99.77±12.26 µm.
- Quadrant thicknesses in amblyopic vs. normal eyes:

Table 1. The demographic characteristics of the cases

	Age	Sex			
		Female		Male	
		n	%	n	%
Group 1	14.05±6.89	22	54.2	18	45.8
Group 2	18.89±11.02	20	55.6	16	44.4
Group 3	16.10±8.62	22	52.4	20	47.6
p	0.104	0.955			

Table 2. Distribution of amblyopia severity within the groups

Visual acuity	Group 1		Group 2		p
	n	%	n	%	
Severe	16	40.0	16	44.4	
Moderate	14	35.0	10	27.8	0.796
Mild	10	25.0	10	27.8	

- Temporal: 67.38±27.57 µm vs. 69.83±16.20 µm.
- Nasal: 72.61±11.98 µm vs. 74.22±13.38 µm.
- Superior: 122.50±18.14 µm vs. 126.38±20.39 µm.
- Inferior: 128.83±17.28 µm vs. 132.33±19.79 µm.

There was no statistically significant difference between amblyopic and normal eyes and control group (p>0.05, Table 4).

Comparative Analysis Between Groups

- When comparing amblyopic eyes in Group 1 (strabismic amblyopia) and Group 2 (anisometropic amblyopia), anisometropic amblyopic eyes exhibited a significantly thicker mean RNFL (p<0.05).
- Although RNFL thickness in anisometropic amblyopic eyes appeared greater in all four quadrants, this variance was not statistically significant (p>0.05, Table 4).

Discussion

Amblyopia is known to cause many histologic changes in the LGN and visual cortex. In its pathogenesis, the balance of binocular competition is disturbed because the afferent pathways of the dominant eye stimulate more neurons in the visual cortex, resulting in decreased visual acuity in the non-dominant eye (14). RNFL thickness is affected by various parameters such as race, age, and sex. There may be many reasons for different results in different studies on this topic. These may include the use of different devices (e.g., OCT with a temporal analysis system or OCT with Fourier principle), measurements performed by different clinicians, insufficient numbers of subjects enrolled in the study, or unequal gender distribution. In our study, there was no statistically significant disparity in terms of age and gender. After the detection of changes in the LGC and visual cortex, it has been a matter of curiosity whether amblyopia causes changes in the retina, and many studies have been conducted in this direction. A study conducted with 37 patients in 2009 found no statistically significant variance in the average and 4-quadrant RNFL thickness between amblyopic and healthy eyes. However, it was reported that the results could not be generalized to all amblyopes because the study did not involve patients with high degrees of amblyopia and patients with deprivation amblyopia (15). In our study, when amblyopic eyes (strabismic and anisometropic) were compared with normal eyes, no significant difference was observed between the mean RNFL thickness and 4-quadrant RNFL thicknesses. When the amblyopic eyes (strabismic and anisometropic) were compared with the right eye of the control group, no significant difference was observed in the mean RNFL thickness and in the thickness of the four quadrants. In our study, when the amblyopic eyes of strabismic and anisometropic amblyopes were compared, the RNFL of the anisometropic group was thicker than that of the strabismic group. This finding is consistent with those of both Repka et al. (15) and Kee et al. (16). Kavitha et al. (17) conducted a study utilizing the Fourier OCT in children and found that there was no discernible variance in RNFL thickness among patients with unilateral anisometropic amblyopia. Furthermore, they observed that there was no substantial alteration in RNFL thickness following one year

Table 3. Average and quadrant thickness values of the ampliyopia eye, fellow eye and control group

RNFL thickness	Ambliyopia eye	Fellow eye	Control group	P1	P2
Mean	95.81±13.33	94.92±13.94	95.80±10.98	0.470	0.998
Temporal	65.50±21.18	66.23±14.23	67.66±11.30	0.610	0.540
Nasal	70.39±14.39	68.97±13.93	69.28±10.61	0.377	0.663
Superior	119.18±22.28	119.89±22.28	123.04±21.21	0.790	0.361
Inferior	126.60±20.28	126.10±22.78	124.66±13.85	0.824	0.582

P1: Ambliyopia and fellow eye, P2: Ambliyopia and control group, RNFL: Retinal nerve fiber layer

Table 4. Comparing the thickness of RSLT between groups

RNFL thickness	Group 1	Group 2	Group 3	P1	P2
Mean	92.95±13.81	99.00±12.19	95.80±10.98	0.048	0.228
Temporal	63.80±13.21	67.38±27.57	67.66±11.30	0.465	0.953
Nasal	68.40±16.14	72.61±11.98	69.28±10.61	0.205	0.198
Superior	114.05±22.90	122.50±18.14	123.04±21.21	0.081	0.151
Inferior	120.50±24.04	128.83±17.28	124.66±13.85	0.090	0.241

P1: Group 1 and group 2, P2: Group 2 and group 3, RNFL: Retinal nerve fiber layer

of closure therapy (17). Huynh et al. (18) conducted a study using OCT temporal analysis and found no disparity in RNFL thickness among patients with unilateral amblyopia. In studies conducted in our country, similar to our study, Yazıcı et al. (19) compared the RNFL thickness of amblyopic and normal eyes of 114 patients, 67 of whom were strabismic, 35 of whom were anisometropic, and 12 of whom had deprivation amblyopia, using OCT with a temporal analysis system, and found no significant disparity in any quadrant. In the study conducted by Soyugelen et al. (20) using Fourier principle OCT in children aged 5-23 years, there was no difference between RNFL thicknesses. Similarly, Ulaş et al. (21) evaluated 32 unilateral anisometropic amblyopic patients with Fourier-domain OCT. They reported that the global, nasal, and inferonasal segments of the RNFL were thicker in anisometropic amblyopic eyes than in eyes with good vision. Contrary to the above studies, Soydan et al. (22) used OCT with a temporal analysis system in 50 unilateral anisometropic amblyopes and 50 normal subjects aged 5-62 years. The study revealed that the RNFL thickness was greater in anisometropic amblyopic cases compared with the control groups, and increased hyperopia and decreased axial length may have contributed to the difference between the groups (22). In the study by Yen et al. (12), the RNFL of 20 strabismic and 18 anisometropic amblyopic cases and 17 non-amblyopic anisometropic control cases was measured by OCT (Model 2000). The average RNFL of amblyopic eyes was determined to be significantly thicker than that of normal eyes. In line with the findings of this study, there was no significant variance in the RNFL between the amblyopic eyes of individuals with strabismic amblyopia and normal eyes, whereas those with anisometropic amblyopia exhibited a significantly thicker RNFL compared to normal eyes. Within the control group, no significant distinction in RNFL values was observed between the eye with high refractive error and its counterpart. In light of these findings, Yen et al. (12) explained the thick RNFL in amblyopic eyes with the theory that the postnatal decrease in ganglion cell numbers requires a sharper focus according to the stimulus. However, because this is not possible in amblyopic subjects, the necessary decrease does not occur. They also attributed the difference between the strabismic and anisometropic groups to the fact that neuronal loss in amblyopia is different depending on the etiology, and but suggested that new histopathologic studies were needed to confirm this (12). Yoon et al. (13) examined macular thickness and RNFL in 31 hypermetropic anisometropic amblyopic patients using OCT (Model 3000) and found that the mean RNFL was significantly thicker in amblyopic eyes (115.2±9.7 μm) than in normal eyes (109.6±8.4 μm). Again, based on these findings, they suggested that amblyopia has the potential to impact the RNFL while not affecting macular thickness. Other studies, including postmortem studies, should support this. In the literature, it has been emphasized that neural tissue loss may vary depending on the etiology of amblyopia (13). This is supported by the fact that in deprivation amblyopia and anisometropic amblyopia, there is a decrease in the LGC in monocular and binocularly innervated regions, whereas in strabismic amblyopia, there is a decrease only in binocularly innervated regions (23,24). Salchow et al. (25) showed that a refractive error of 1 diopter causes an increase in RNFL thickness of approximately 1.67 μm. Therefore, we should consider that this increase in thickness in anisometropic cases may be due to the effect of refractive error on RNFL measurement. In a recent study, it was determined that the retinal nerve fiber layer (RNFL) of 35 eyes —comprising healthy, amblyopic, and single-vessel anisometropic eyes— between the ages of 6 and 63 years was examined using OCT. It was found that there was no significant difference between the RNFL studies of amblyopic eyes and the eyes of healthy subjects (26). In a study conducted in our country in 2022, the thickness of the RNFL in 111 pediatric patients with unilateral amblyopia due to anisometropia or strabismus, was investigated using OCT. It was found that the RNFL thickness of the superior, nasal, and temporal quadrants did not differ significantly. The study suggested that in amblyopic patients, there may be some damage in higher visual pathways such as the lateral geniculate nucleus and visual cortex rather than structural damage in the retina (27).

Study Limitations

The limitation of this study is that the amblyopic patients' data were obtained from medical sources of our hospital. Another limitation is that the role of strabismus in the degree of amblyopia and retinal development may have affected the RNFL thickness measurements. However, the important feature of our study is that the groups are similar in terms of number, demographics, and long-term data collection.

Conclusion

In our research, we found no substantial variance in the RNFL thickness of amblyopic and non-amblyopic eyes, both between amblyopic patients and between normal subjects. Studies on the effect of amblyopia on the RNFL have yielded different results. These differences may be due to the age factor, amblyopia type and severity, the insufficient

number of cases, and the position of the scanning ring used during OCT. Further research is needed in this area, taking into account different factors.

Ethics

Ethics Committee Approval: Approval was obtained from the İstanbul Okmeydanı Training and Research Hospital Ethics Committee with the decision dated 07/06/2013 and numbered 89, following the rules of the Declaration of Helsinki.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

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

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

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ORIGINAL RESEARCH

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Assessment of Disease Codes Reliability in Emergency Department Patients

Acil Servise Başvuran Hastalarda Tanı Kodlarının Güvenilirliğinin Araştırılması

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Abstract

Objective: In modern times, data obtained through international classification of diseases (ICD) codes from hospital automation systems are frequently used in studies on epidemiology, surveillance, and survival. The reliability of these data is critically important for the accuracy of the studies. This study aims to investigate the accuracy of emergency department diagnoses for patients who requested urology consultations and to reveal their reliability.

Method: Records of patients who requested urology consultations after presenting to the emergency department within the past year were retrospectively screened through the hospital automation system. The green, yellow, and red zone presentations were classified according to the time of day, and the compatibility of the patients' emergency diagnoses with the diagnoses in the urology clinic was evaluated.

Results: A total of 2.197 patients [1.660 (75.56%) men and 537 (24.44%) women] with an average age of 50.59±23.10 (range: 1-98) years, who requested urology consultations in the emergency department, were included in the study. Of the patients seen in the urology clinic, 637 (28.99%) were referred from the green zone, 703 (32.04%) from the yellow zone, 221 (10.10%) from the red zone, and 636 (28.86%) from other branches. Of the patients, 1.623 (73.87%) presented between 08:00 and 16:00, 406 (18.48%) between 16:00 and 00:00, and 168 (7.64%) between 00:00 and 08:00.

Öz

Amaç: Günümüzde epidemiyoloji, sürveyans ve sağkalım gibi çalışmalarda sıklıkla hastane otomasyon sistemleri üzerinden uluslararası hastalık tanı sınıflandırma (ICD) kodları kullanılarak elde edilen veriler kullanılmaktadır. Bu verilerin güvenilirliği çalışmaların doğruluğu açısından ciddi önem taşımaktadır. Bu çalışmada acil servis başvurusunda üroloji konsültasyonu istenen hastaların acil servis tanılarının doğruluğunu araştırarak güvenilirliklerini ortaya koymayı amaçladık.

Yöntem: Hastane otomasyon sistemi üzerinden son bir yıl içinde acil servis başvurusu sonrası üroloji konsültasyonu istenen hastalarının kayıtları geriye dönük olarak tarandı. Yeşil, sarı ve kırmızı alan başvuruları gün içindeki başvuru zamanına göre tasnif edilerek hastaların acil tanıları ile üroloji polikliniğindeki tanılarının uyumu değerlendirildi.

Bulgular: Acil servis başvurusunda üroloji konsültasyonu istenen, ortalama yaşı 50,59±23,10 (1-98 arası) yıl olan toplam 2,197 hasta [1,660 (%75,56) erkek ve 537 (%24,44) kadın] çalışmaya dahil edildi. Üroloji polikliniğinde görülen hastaların 637'si (%28,99) yeşil alandan, 703'ü (%32,04) sarı alandan, 221'i (%10,10) kırmızı alandan ve 636'sı (28,86) diğer branşlardan yönlendirilmişti. Hastaların 1623'ü (%73,87) saat 08:00-16:00 arası, 406'sı (%18,48) 16:00-00:00 arası ve 168'i (%7,64) 00:00-08:00 arasında başvurmuştu. Üroloji konsültasyon isteklerindeki hasta ICD kodları ile ürolojik değerlendirme sonrası hastaların aldıkları ICD kodları

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The ICD codes of patients who requested urology consultations were found to have statistically significant compatibility with the ICD codes of patients after urological evaluation (kappa: 0.863, p<0.05). This significant compatibility was also observed in the evaluations classified based on the unit and hours of consultation requests.

Conclusion: The reliability of diagnosis codes is high even in high-volume areas like emergency departments. These results have inspired the creation of secure databases that will provide a source for diagnosis code-based studies in our country.

Keywords: Emergency department, International classification of diseases code, national database, renal colic

istatistiksel olarak anlamlı derecede uyumlu saptanmıştır (kappa: 0,863, p<0,05). Konsültasyon atılan birim ve konsültasyon atılan saatler göz önüne alınarak yapılan sınıflandırılmış değerlendirmelerde de anlamlı uyumluluğun devam ettiği görülmüştür.

Sonuç: Tanı kodu güvenilirliği acil servis gibi yüksek yoğunluklu hasta başvurusu olan alanlarda dahi yüksektir. Bu sonuçlar ülkemizde tanı koduna dayalı çalışmaların yapılmasına kaynak sağlayacak güvenli veri tabanlarının oluşturulmasına ilham vermiştir.

Anahtar kelimeler: Acil servis, renal kolik, ulusal veri tabanı, uluslararası hastalık tanı sınıflandırma kodu

Introduction

For more than a century, the international classification of diseases (ICD) has had a wide range of global uses. Through data reported and coded with ICD, critical information on the scope, causes, and consequences of diseases and deaths is provided globally (1,2). The statistics obtained from these data support service planning, quality and safety management, healthcare research, and payment systems (2). Therefore, the reliability of the data is critically important. Problems in data entry due to excessive workload, insufficient staff, or lack of experience threaten data reliability. There is no study in our country testing the reliability of these data that will provide a source for the planned national database application. In this study, we aimed to assess the reliability of emergency department diagnoses by investigating the accuracy of diagnoses of presenting patients where high-intensity service delivery occurs.

Materials and Methods

After obtaining data usage permission from the Local Ethics Committee (University of Health Sciences Turkey, Gaziosmanpaşa Training and Research Hospital Clinical Research Ethics Committee, date: 16.08.2023, no: 118), records of patients who requested urology consultations after presenting to the emergency department within the past year prior to the approval date were retrospectively screened through the hospital automation system (Sarus® Hospital Information System, Technoritma Software Services Inc., Ankara, Turkey). The records were classified separately as emergency area presentations in the categories of green, yellow, red, and other (internal medicine, surgery, pediatrics), taking into account the time of day. Data such as age, gender, and the ICD codes entered in the consultation request and response were recorded separately. The compatibility of the patients' emergency department diagnoses by the triage physician with the diagnoses made after further examination and evaluation in the urology clinic was evaluated.

Statistical Analysis

In this study, statistical analyses were performed using the NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA) package. In addition to descriptive statistical methods (mean, standard deviation), the compatibility between the groups was evaluated using Cohen's kappa analysis. The results were evaluated at a significance level of p<0.05.

Results

In the past year, urology consultation requests were made for 2.218 patients from emergency areas, but urology consultations were not conducted for 21 patients. A total of 2.197 patients [1.660 (75.56%) men and 537 (24.44%) women] with an average age of 50.59±23.10 (range: 1-98) years were included in the study. Of the patients seen in the urology clinic, 637 (28.99%) were referred from the green zone, 703 (32.04%) from the yellow zone, 221 (10.10%) from the red zone, and 636 (28.86%) from other branches. Of the patients, 1.623 (73.87%) presented between 08:00-16:00, 406 (18.48%) between 16:00-00:00, and 168 (7.64%) between 00:00-08:00, (Table 1). Patients were most frequently consulted with 13 different ICD codes, with "Hematuria; R31" being the most common, and after urological evaluation, the most common diagnosis was "Renal colic; N23" (Table 2). The ICD codes of patients who requested urology consultations from emergency areas were found to have a statistically significant compatibility with the ICD codes of patients after urological evaluation (kappa: 0.863, p<0.05). This significant compatibility was also observed in the classified evaluations in terms of the unit and hours of consultation requests (Table 1). Although the decrease was statistically significant, it was found that the compatibility

rate decreased during peak hours of patient volume (08:00-16:00 kappa: 0.856, 16:00-00:00 kappa: 0.878, 00:00-08:00 kappa: 0.887).

Discussion

Data coded and reported using the ICD offer standard terminology and classification, in a conceptual framework independent of language and culture (1). Through this, ICD-based national data systems have been developed to determine priorities by analyzing data on incidence and mortality rate, especially in situations threatening public health like cancer. After the National Cancer Institute of America launched the SEER (Surveillance, Epidemiology, and End Results) program in 1973, the World Health Organization published the International Classification of Diseases-Oncology (ICD-O) in 1976 (3,4). ICD-O was approved in our country in 2013 and came into force in 2016 (5). However, the recent pandemic has revealed that systems collecting only cancer cases are insufficient. Comprehensive databases providing data on acute and chronic diseases affecting public health are still lacking. In our study, the reliability of ICD codes in automation systems that will also provide sources for non-oncology databases was evaluated through a pilot study. Even in departments with relatively higher patient volume, such as the emergency department, diagnostic reliability was found to be high.

In programs with comprehensive and continuous data entry, like national databases, ensuring data reliability at the beginning is important, but it is also crucial to design the process in a way that allows for continuous testing of data reliability (6). Our study found that, although statistically significant, data reliability slightly decreased during peak hours of patient volume. The high accuracy of urological diagnoses was thought to be related to the lower patient volume in the urology consultation area compared to clinics. In addition to facilitating data entry into automation systems, it was concluded that employing a sufficient and competent workforce might be effective in ensuring data security. Providing optimal workforces and physical conditions was thought to facilitate the monitoring of dynamic data flow.

Study Limitations

The data from our study are too limited to support the claim that sufficient reliability has been achieved for the creation of national database programs. This necessitates multicenter, high-volume studies. Our study conducted in

Table 1. Compatibility of urological and emergency ICD codes with Cohen kappa analysis

	n	Kappa	p-value
UROLOGY /ICD EMERGENCY Green Zone_08:00am-16:00pm	498	0.785	<0.05
UROLOGY /ICD EMERGENCY Green Zone_16:00pm-:00pm	102	0.834	<0.05
UROLOGY /ICD EMERGENCY Green Zone_00:00pm-08:00am	37	0.790	<0.05
UROLOGY /ICD EMERGENCY Yellow Zone_08:00am-16:00pm	444	0.831	<0.05
UROLOGY /ICD EMERGENCY Yellow Zone_16:00pm-:00pm	178	0.867	<0.05
UROLOGY /ICD EMERGENCY Yellow Zone_00:00pm-08:00am	81	0.902	<0.05
UROLOGY /ICD EMERGENCY Red Zone_08:00am-16:00pm	110	0.836	<0.05
UROLOGY /ICD EMERGENCY Red Zone_16:00pm-:00pm	67	0.879	<0.05
UROLOGY /ICD EMERGENCY Red Zone_00:00pm-08:00am	44	0.949	<0.05
UROLOGY /ICD EMERGENCY Others Zone_08:00am-16:00pm	571	0.939	<0.05
UROLOGY /ICD EMERGENCY Others Zone_16:00pm-:00pm	59	0.981	<0.05
UROLOGY /ICD EMERGENCY Others Zone_00:00pm-08:00am	6	0.760	<0.05
UROLOGY /ICD EMERGENCY_Green Zone_Total	637	0.794	<0.05
UROLOGY /ICD EMERGENCY_Yellow Zone_Total	703	0.849	<0.05
UROLOGY /ICD EMERGENCY_Red Zone_Total	221	0.873	<0.05
UROLOGY /ICD EMERGENCY_Others Zone_Total	636	0.942	<0.05
UROLOGY /ICD EMERGENCY_08:00am-16:00pm_Total	1623	0.856	<0.05
UROLOGY /ICD EMERGENCY_16:00pm-00:00pm_Total	406	0.878	<0.05
UROLOGY /ICD EMERGENCY_00:00pm-08:00am_Total	168	0.887	<0.05
UROLOGY /ICD EMERGENCY_Total	2197	0.863	<0.05

ICD: International classification of diseases, Others zone: General surgery, internal medicine, pediatry

Table 2. Distribution of urological and emergency ICD codes

Emergency ICD	Urology ICD													
	C62	N17	N20	N23	N30	N39	N44	N45	R10	R30	R31	R33	S37	Total
C62	12													12
N17		75		20										95
N20			288											288
N23				66					36					102
N30				25	219									244
N39				45		216								261
N44							40							40
N45								200						200
R10				52					80					132
R30				36						132				168
R31				45							294			339
R33				12								288		300
S37													16	16
Total	12	75	288	301	219	216	40	200	116	132	294	288	16	2197

C62: Malignant neoplasm of testis, N17: Acute renal failure, N20: Calculus of kidney and ureter, N23: Unspecified renal colic, N30: Cystitis, N39: Other disorders of urinary system (urinary tract infection, proteinuria or incontinence), N44: Torsion of testis, N45: Orchitis and epididymitis, R10: Abdominal and pelvic pain, R30: Pain associated with micturition, R31: Unspecified haematuria, R33: Retention of urine, S37: Injury of urinary and pelvic organs

the busy emergency department serves as a pilot study that will pave the way for similar studies in different clinics.

Conclusion

The reliability of diagnosis codes is high even in high-volume areas like emergency departments. These results have inspired the creation of secure databases that will provide a source for diagnosis code-based studies for non-cancer entities affecting public health in our country.

Ethics

Ethics Committee Approval: After obtaining data usage permission from the Local Ethics Committee (University of Health Sciences Turkey, Gaziosmanpaşa Training and Research Hospital Clinical Research Ethics Committee, date: 16.08.2023, no: 118).

Informed Consent: Retrospective studyç.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.G., S.K., M.G.K., M.G., S.S., S.Sü., S.Y., M.M.D., E.K., E.Y., A.Y.M., Concept: S.G., S.K., M.G.K., M.G., S.S., S.Sü., S.Y., M.M.D., E.K., E.Y., A.Y.M., Design: S.G., S.K., M.G.K., M.G., S.S., S.Sü., S.Y., M.M.D., E.K., E.Y., A.Y.M., Data Collection or Processing: S.G., S.K., M.G.K., M.G., S.S., S.Sü., S.Y., M.M.D., E.K., E.Y., A.Y.M., Analysis or Interpretation: S.G., S.K., M.G.K., M.G., S.S., S.Sü., S.Y., M.M.D., E.K., E.Y., A.Y.M., Literature Search: S.G., S.K., M.G.K., M.G., S.S., S.Sü., S.Y., M.M.D., E.K., E.Y., A.Y.M., Writing: S.G., S.K., M.G.K., M.G., S.S., S.Sü., S.Y., M.M.D., E.K., E.Y., A.Y.M.

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ORIGINAL RESEARCH

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Evaluation of Surgical Approaches in Patients Presenting with Hemoptysis

Hemoptizi ile Başvuru Sonrası Opere Edilen Hastaların Değerlendirilmesi

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Abstract

Objective: Hemoptysis is the expectoration of blood from the lower respiratory tract. Since the definitive treatment of hemoptysis often involves surgical intervention targeting the underlying disease, the initial assessment and preparation for surgical treatment are of critical importance.

Method: In our study, we retrospectively evaluated the data of patients who presented to the emergency department with hemoptysis and were operated on after being consulted by the department of thoracic surgery between 2012 and 2018. Patients were divided into groups: Those who underwent emergency surgery within the first 24 hours after hospitalization, those who underwent sub-elective surgery between the 1st and 3rd days, and those who underwent elective surgery on the 4th day and later.

Results: Of the 82 patients in our study, 60 (73.2%) were male and 22 (26.8%) were female. Hemoptysis was most frequently observed attributable to bronchiectasis (39%). During the preparation process for surgery, bronchial artery embolization (BAE) was performed on 16 patients (19.5%). The amount of hemoptysis in patients who underwent BAE was found to be statistically significantly higher (p=0.016). A total of 21 patients (25.6%) developed complications, none of whom had undergone pneumonectomy. Complications were found to be related to the amount of hemoptysis and length of hospital stay, but not to the

Öz

Amaç: Hemoptizi alt solunum yollarındaki kanamanın ekspektorasyonudur. Hemoptizinin kesin tedavisi altta yatan hastalığa yönelik cerrahi olduğu için ilk değerlendirme ve bu değerlendirmeye göre cerrahi tedaviye hazırlık süreci önem arz etmektedir.

Yöntem: Çalışmamızda 2012-2018 yılları arasında hemoptizi nedeniyle acil servise başvuran ve göğüs cerrahisine konsülte edildikten sonra opere edilen hastaların verileri retrospektif olarak değerlendirildi. Hastalar, başvuru sonrası ilk 24 saat içerisinde acil opere edilenler, 1-3. günler arasında subelektif opere edilenler ve 4. gün ve sonrasında elektif olarak opere edilenler olmak üzere gruplara ayrıldı.

Bulgular: Çalışmamızdaki 82 hastanın, 60'ı (%73,2) erkek, 22'si (%26,8) kadındı. En sık bronşiektazi (%39) nedeniyle hemoptizi izlendi. Operasyona hazırlık sürecinde 16 hastaya (%19,5) bronşiyal arter embolizasyonu (BAE) gerçekleştirildi. BAE uygulanan hastaların hemoptizi miktarı istatistiksel olarak anlamlı derecede yüksek hesaplandı (p=0,016). Toplamda 21 hastada (%25,6) komplikasyon gelişti, hiçbiri pnömonektomi uygulanan hasta değildi. Komplikasyonların hemoptizi miktarı ve yatış süresi ile ilişkiliyken BAE uygulaması ile ilişkisi olmadığı tespit edildi (sırasıyla p=0,017, p<0,001 ve p=1,000). Komplikasyon gelişen hastaların oranı elektif grupta (%28,6) diğer gruplara göre düşük bulundu ama istatistiksel olarak anlamlı fark saptanmadı (p=0,594). İki hastada (%2,4) cerrahi mortalite izlendi.

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Abstract

application of BAE (p=0.017, p<0.001, and p=1.000, respectively). The proportion of patients who developed complications was lower in the elective group (28.6%) compared to other groups, but this difference was not statistically significant (p=0.594). Surgical mortality was observed in two patients (2.4%).

Conclusion: Although medical treatment and BAE play a significant role, in controlling the clinical condition preoperatively, the definitive treatment for hemoptysis is surgery targeting the underlying disease. In suitable patients, emergency surgery and complete resections such as pneumonectomy can be performed with acceptable rates of complications and mortality.

Keywords: Bronchial artery embolization, hemoptysis, surgery

Öz

Sonuç: Preoperatif dönemde medikal tedavi ve BAE klinik durumun kontrolünde önemli rol oynasa da hemoptizinin tedavisi altta yatan hastalığa yönelik cerrahidir. Uygun hastalarda acil cerrahi ve pnömonektomi gibi komplet rezeksiyonlar, kabul edilebilir komplikasyon ve mortalite oranlarıyla uygulanabilir.

Anahtar kelimeler: Bronşial arter embolizasyonu, cerrahi, hemoptizi

Introduction

Hemoptysis is defined as the expectoration of blood from the lower respiratory tract. It ranges from the blood-stained sputum to life-threatening clinical conditions (1). In past years, hemoptysis was classified based on the volume of blood expectorated, and treatment options were tiered accordingly (2). Presently, the predominant perspective is that the volume may be overestimated or underestimated due to the patient ingesting blood (2,3). Therefore, the assessment of hemoptysis should incorporate a thorough consideration of the patient's clinical status. The average anatomical deads pace volume in the respiratory system is approximately 150 milliliters (mL). Consequently, even minimal volumes of hemorrhage can pose a significant threat to life.

The source of hemoptysis is the bronchial artery or its branches in 90% of cases. Controlling the bleeding focus is critically important during the initial phase of treatment (1-3). Advancements in interventional bronchoscopic and radiological procedures have significantly altered the criteria for surgical treatment indications. These interventional procedures are especially advantageous in mitigating the increased mortality particularly associated with emergency surgery. Specifically, bronchial artery embolization (BAE) has been reported to successfully halt bleeding in the initial stage in 73-98% of cases (4,5). However, non-surgical treatments have a high probability of hemoptysis recurrence. In cases of life-threatening hemoptysis resulting in blood gas exchange abnormalities, the mortality rate can escalate to 50-85%. Therefore, the definitive treatment for hemoptysis is stil considered to be surgical (1-5). In this study, we aimed to evaluate the outcomes of surgical operations performed on patients presenting to the emergency department with an attack of hemoptysis, based on the timing of surgery and in combination with interventional procedures.

Materials and Methods

The study enrolled patients who underwent surgery following their admission to the emergency department with hemoptysis between 2012 and 2018. The study protocol was approved by the Local Ethics Committee of University of Health Sciences Turkey, Ankara Atatürk Sanatory Training and Research Hospital under decision number 2012-KAEK-15/2743. The study was conducted in accordance with the principles of the World Medical Association Declaration of Helsinki. Patients' age, gender, amount of hemoptysis, diagnosis and treatment methods, treatment processes, and outcomes were retrospectively evaluated. Those under 18 years of age, patients with incomplete data, individuals who did not consent to participate in the study, patients with hemoptysis due to trauma, and those whose treatment involved methods other than surgical intervention were excluded from the study.

Preoperative Patient Management

The time intervals until surgery were grouped as follows: Patients in Group 1 underwent surgery with in the first 24 hours after admission to the hospital, patients in Group 2 were operated on between days 1 to 3 after initial assessment, and patients in Group 3 underwent elective surgery ≥4 days after hemoptysis was controlled. The surgical timing was determined based on the patient's cardiopulmonary readiness and the localization of the bleeding focus. Patients were closely monitored in the intensive care unit until surgery. Only 13 patients had the bleeding focus identified in the emergency department and were immediately operated on after stabilizing cardiopulmonary

(Group 1). All patients underwent computed tomography. In Groups 2 and 3, BAE was performed if the bleeding could not be controlled with medical treatment or if there was no decrease in hemoptysis volume. Patients were managed to maintain a hemoglobin level ≥7 g/dL, with blood transfusion and fresh frozen plasma administration as needed. Medical oxygen and intravenous nutritional support were provided to all patients in the intensive care unit. Medical treatment included broad-spectrum antibiotics, antitussive agents, vitamin K, and tranexamic acid. Patients with difficulty maintaining airway patency were managed with intubation. Biochemical parameters, complete blood counts, and coagulation tests were regularly monitored in all patients. Prior to surgery, all patients underwent flexible bronchoscopy to maintain airway patency, and in an attempt to visualize the bleeding site. Cryotherapy for bronchial lesions was performed using rigid bronchoscopy in only two patients. Following double-lumen intubation, 12 patients underwent video-assisted thoracic surgery in the standard lateral decubitus position, while others underwent open surgery.

Statistical Analysis

All analyses of the study were conducted using the SPSS version 24.0 software package. Descriptive statistics were presented as the number of units (n), percentage (%), and mean ± standard deviation for age. Independent two-sample t-tests or Mann-Whitney U tests were used for continuous numerical variables between two groups. One-Way ANOVA or Kruskal-Wallis tests were employed for continuous numerical variables among multiple groups. The distribution of categorical variables among groups was evaluated using Pearson's chi-square test. A p-value less than 0.05 was considered statistically significant for all comparisons.

Results

Demographic and Clinicopathological Findings

In our study, out of 82 patients, 60 (73.2%) were male and 22 (26.8%) were female. The mean age was 49.32±16.40 years. The median amount of hemoptysis was 200 cc (min: 20 - max: 800). The etiology included bronchiectasis in 32 patients (39%), hydatid cyst in 12 patients (14.6%), malignancy in 11 patients (13.4%), and sequelae of previous tuberculosis in 10 patients (12.2%). The median time from hospital admission to operation was 2 days (min: 0 - max: 30). Right lower lobectomy was performed in eighteen patients (22%), left lower lobectomy in fourteen patients (17.1%), and cystotomy and capitonnage in ten patients (12.2%). The median duration from operation to discharge was 7 days (min: 1 - max: 21). Overall, complications occurred in 21 patients (25.6%), with prolonged air leak identified as the most prevalent complication, observed in eight patients (9.8%). Surgical mortality was observed in two patients (2.4%). All demographic and clinicopathological findings are summarized in Table 1. Bronchoscopic image of a patient with hemoptysis is shown in Figure 1, while theetiology of patients is presented in Figure 2.

Comparison of Operation Periods

There were 13 patients (15.9%) in Group 1, 38 patients (46.3%) in Group 2, and 31 patients (37.8%) in Group 3. Although Group 3 had a lower median hemoptysis amount compared to the other groups, no statistically significant difference was found (p=0.312). The rate of patients developing complications was lower in Group 3 (19.4%) compared to other groups, but this difference was not statistically significant (p=0.594). There were no statistically significant differences among groups in terms of age, gender, intubation, and median hospital stay after surgery (Table 2).

BAE

Sixteen patients (19.5%) underwent BAE. Although the mean age was higher in patients who did not undergo BAE (50.47±16.41 years), this difference was not statistically significant (p=0.198). The amount of hemoptysis was significantly higher in patients who underwent BAE (p=0.016). No significant association was found between BAE and the duration from admission to surgery, length of hospital stay, and complications (Table 3).

Postoperative Complications

The average age of patients manifesting complications (53.33±14.06 years) was higher, although no statistically significant difference was found (p=0.195). In patients with complications, the median hemoptysis volume (250 cc) was significantly higher (p=0.017). Additionally, hospital stay duration and intubation rate were found to be significantly higher in this patient group (p<0.001 and p=0.035, respectively) (Table 4).

Discussion

Hemoptysis is a rare condition, with prevalence reported to range from 0.2% to 14% (2). In a study conducted in France, it was found to constitute 0.2% of all hospital admissions (4). Its etiology varies depending on geographical and

Table 1. General information of patients

Parameter	n (%)
Gender	
Female	22 (26.8)
Male	60 (73.2)
Age (years)	49.32±16.40
Hemoptysis amount (cc)	200 (20-800)
Bronchial artery embolization	
Yes	16 (19.5)
No	66 (80.5)
Time of operation	
Group 1 (Emergency)	13 (15.9)
Group 2 (Subelective)	38 (46.3)
Group 3 (Elective)	31 (37.8)
Intubation	
Yes	6 (7.3)
No	76 (92.7)
Surgical preference	
Open surgery	70 (85.4)
VATS	12 (14.6)
Surgical side	
Right	55 (67.1)
Left	27 (32.9)
Operation	
Right lower lobectomy	18 (22)
Left lower lobectomy	14 (17.1)
Cystotomy and capitonnage	10 (12.2)
Right upper lobectomy	9 (11)
Middle lobectomy	7 (8.5)
Left upper lobectomy	7 (8.5)
Pneumonectomy	6 (7.3)
Segmentectomy	5 (6.1)
Wedge resection	2 (2.4)
Cryotherapy	2 (2.4)
Cavitectomy	1 (1.2)
Aortobronchial fistula repair	1 (1.2)
Time until surgery (days)	2 (0-30)
Hospital stay after surgery (days)	7 (1-21)
Complications	
Prolonged air leak	8 (9.8)
Pneumonia	4 (4.9)
Bleeding	2 (2.4)
Ischemic/toxic hepatitis	1 (1.2)
Pulmonary thromboembolism	1 (1.2)
Acute renal failure	1 (1.2)
Atrial fibrillation	1 (1.2)
Wound site infection	1 (1.2)
Empyema	1 (1.2)
Depression	1 (1.2)
Surgical mortality	
Present	2 (2.4)
Absent	80 (97.6)

VATS: Video-assisted thoracic surgery

seasonal conditions (2). Tuberculosis is generally prevalent in developing and under-developed countries, while malignancy is more common in developed countries. Although rankings may vary, bronchiectasis, tuberculosis sequelae, and malignancies are commonly reported causes (1-6). The proportion of hemoptysis with unknown etiology is also known to be around 10-20% (1-6). In our study, we found that bronchiectasis, hydatid cyst, malignancies, and tuberculosis sequelae were the most common causes of hemoptysis. Pulmonary hydatid cyst causing hemoptysis has been reported in case reports and case series (7-9). It is noteworthy that hydatid cyst ranks second among the leading causes, likely due to our country's endemic regions for hydatid disease (10-11).

Determining the etiology of hemoptysis is as important as determining its treatment plan. In our study, BAE was performed in 16 patients (19.5%) to stabilize the patients before surgical treatment. These patients had a higher level of hemoptysis than those who did not undergo BAE. Previous studies on surgical treatments for hemoptysis have raised concerns about high morbidity and mortality rates, highlighting the importance of interventional radiology. BAE is now commonly preferred as a first-line treatment option to control bleeding (1,4-6). Although effective in controlling bleeding in 75-94% of cases, the treatment has reported recurrence rates of bleeding between 9-29% (3,12-14). Therefore, BAE is considered a temporary treatment until stable conditions for surgical treatment are achieved, rather than a definitive treatment (1,3,6). We also believe that BAE is one of the most important tools in preparing patients for surgical treatment when hemoptysis does not decrease or even increases despite medical treatment.

In the periods leading up to surgical treatment, we observed lower median hemoptysis amounts, intubation rates, and complication rates in Group 3. Studies have reported that emergency surgery increases complication rates in hemoptysis (1). Our data were consistent with literature findings, suggesting that prolonging the time from hospital admission to surgery reduces complications. Additionally, studies have reported that procedures such as emergency pneumonectomy increase complication and mortality rates. In our study, no complications or mortality were observed in patients undergoing pneumonectomy. Patient condition and severity of the lesion may play a more significant role (1). Studies with larger subgroups of patients are needed to explore factors such as intraoperative conditions, comorbidities, and surgical techniques that may affect complication and mortality rates.

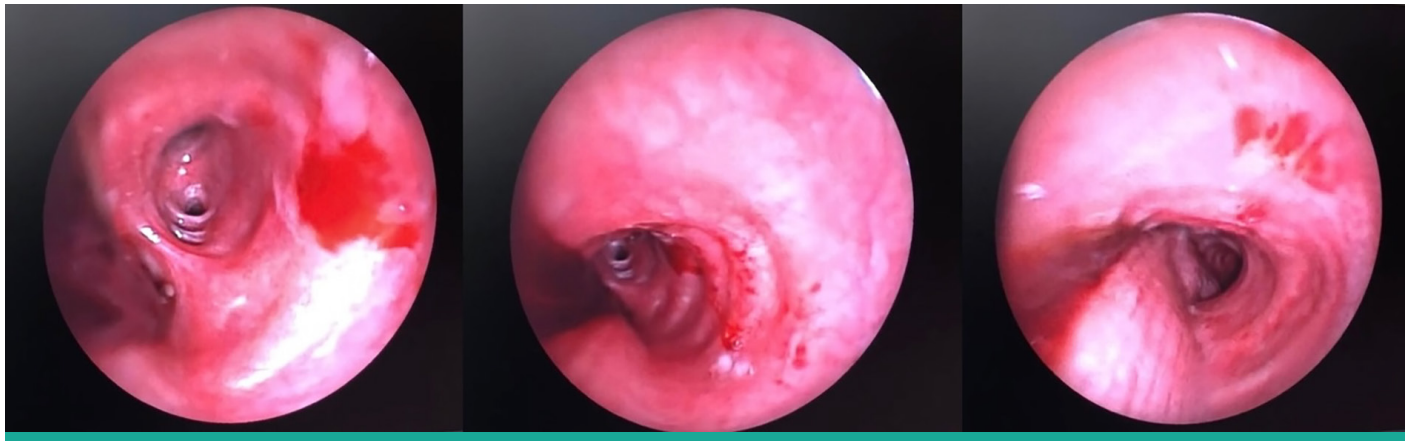

Figure 1. Sequential fiberoptic bronchoscopy images of a hematoma originating from the left lower lobe and extending to the trachea in a patient presenting to the emergency department with hemoptysis

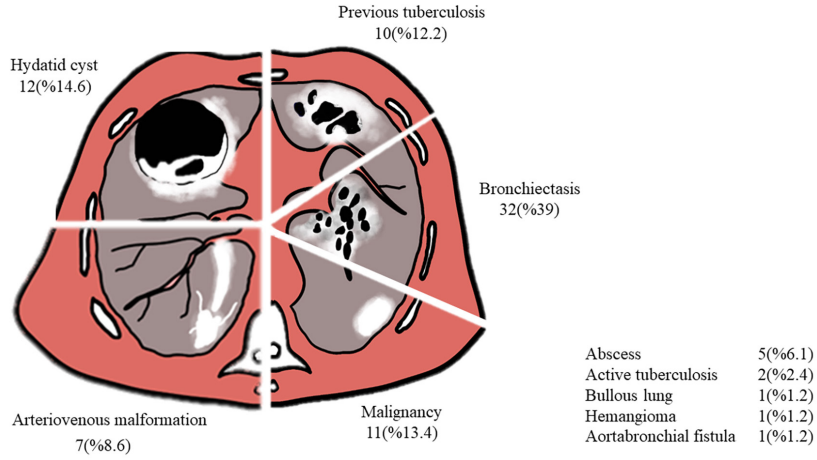

Figure 2. Etiology of hemoptysis

Table 2. Comparison of time intervals until surgery among groups

	Time elapsed until surgery			p
	Group 1	**Group 2**	**Group 3**	
Gender				
Female	4 (30.8)	11 (28.9)	7 (22.6)	0.789
Male	9 (69.2)	27 (71.1)	24 (77.4)	
Age **(year)**				
$\bar{x}$ ± SD	45.54±14.39	47.32±17.35	53.35±15.61	0.210
Hemoptysis amount **(cc)**				0.312
M (min-max)	200 (100-700)	200 (50-800)	150 (20-400)	
Intubation				0.362
Present	2 (15.4)	3 (7.9)	1 (3.2)	
Absent	11 (84.6)	35 (92.1)	30 (96.8)	
Postoperative length of stay, **(day)**				0.397
M (min-max)	6 (2-17)	7 (1-21)	7 (2-21)	
Complications				0.594
Present	4 (30.8)	11 (28.9)	6 (19.4)	
Absent	9 (69.2)	27 (71.1)	25 (80.6)	

Patient numbers and percentages (in parentheses) are indicated in rows. $\bar{x}$: Mean, SD: Standard deviation, M: median, cc: Cubic centimeter, p: Statistical value

Table 3. Information regarding bronchial artery embolization.

	Bronchial artery embolization		p
	Present	Abset	
Gender			
Female	4 (25)	18 (27.3)	0.854
Male	12 (75)	48 (72.7)	
Age, (year)			0.198
χ ± SD	44.56±15.94	50.47±16.41	
Hemoptysis amount (cc)			0,016
M (min-max)	250 (100-800)	150 (20-700)	
Intubation			0.855
Present	1 (16.7)	5 (7.6)	
Absent	5 (83.3)	61 (92.4)	
Time until surgery (day)			0.357
M (min-max)	2.5 (1-10)	2 (0-30)	
Postoperative length of stay (day)			0.911
M (min-max)	7 (1-19)	7 (2-21)	
Complications			0.950
Present	17 (25.8)	4 (25)	
Absent	49 (74.2)	12 (75)	

Patient numbers and percentages (in parentheses) are indicated in rows. χ : Mean, SD: Standard deviation, M: Median, cc: Cubic centimeter, p: Statistical value, statistically significant p-value is bolded

Table 4. Evaluation of parameters with postoperative complications

Parameters	Postoperative complications		
	Absent n (%)	Present n (%)	p
Age (year)	47.93±17.01	53.33±14.06	0.195
Gender			
Male	45 (73.8%)	15 (71.4%)	0.835
Female	16 (26.2%)	6 (28.6%)	
DSA			
Absent	49 (80.3%)	17 (81%)	1.000
Present	12 (19.7%)	4 (19%)	
Hemoptysis amount (cc)	175 (min: 20, max: 700)	250 (min: 50, max: 800)	0.017
Postoperative length of stay (day)	6 (min: 1, max: 12)	11 (min: 4, max: 21)	<0.001
Intubation			
Present	59 (96.7%)	17 (81%)	0.035
Absent	2 (3.3%)	4 (19%)	

In our study, 25.6% of patients developed complications during the postoperative period. We found that patients who developed complications had higher age, volume of hemoptysis, intubation rates, post-surgery hospital stay, and mortality rates. Similarly, complications are commonly observed in hemoptysis surgeries. The most common complications in the postoperative period include recurrent hemoptysis, prolonged air leakage, bronchopleural fistula, empyema, and prolonged mechanical ventilator need (1,2). Our findings were similar to those reported in the literature. Our postoperative mortality rate (2.4%) was lower compared to rates reported in the literature, which range from 3.2% to 27%. The most important factors affecting mortality are reported to be emergency surgery, intubation, pneumonectomy, and postoperative intensive care unit stay (3,4,6,12).

Study Limitations

This study has limitations as a retrospective, single-center study without random distribution among groups. We believe that studies with a larger number of patients could yield statistically more significant results.

Conclusion

In conclusion, the definitive treatment for hemoptysis is surgery for the underlying disease. Patient-based approaches should be developed to ensure surgical treatment at the most appropriate time; importance should be given to preoperative patient management. In patients who can be managed electively, medical treatment and BAE can be used as strong tools in the preoperative period. Emergency surgery and complete resection options, including pneumonectomy, should not be avoided in suitable patients.

Ethics

Ethics Committee Approval: The study protocol was approved by the Local Ethics Committee of University of Health Sciences Turkey, Ankara Atatürk Sanatory Training and Research Hospital under decision number 2012-KAEK-15/2743. The study was conducted in accordance with the principles of the World Medical Association Declaration of Helsinki.

Informed Consent: Since our study is a retrospective research article and no additional examination or procedure was performed on the patient group, there is no need for a patient consent form.

Footnotes

Authorship Contributions

Concept: M.A.B., S.Ş.E.G., Design: M.A.B., S.Ş.E.G., Data Collection or Processing: G.P.M., M.Ç., M.Ö., Analysis or Interpretation: İ.T., K.B.Ç., N.S., Drafting Manuscript: İ.T., K.B.Ç., G.P.M., M.Ç., N.S., Critical Revision of Manuscript: M.Ö., M.A.B., S.Ş.E.G., Final Approval and Accountability: İ.T., M.Ç., M.A.B., S.Ş.E.G., Technical or Material Support: M.Ö., N.S., G.P.M., K.B.Ç., Writing: İ.T., M.Ç., M.A.B., S.Ş.E.G.

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ORIGINAL RESEARCH

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Can CRP/Albumin Ratio, a non-Invasive Test, Predict the Severity of Acute Pancreatitis?

Non-invaziv Bir Test Olan CRP/Albümin Oranı Akut Pankreatitin Ciddiyetini Öngörebilir mi?

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Abstract

Objective: We intended to determine the relationship between the severity and clinical outcomes of acute pancreatitis and the C-reactive protein (CRP)/albumin ratio (CAR).

Method: A total of 580 patients with acute pancreatitis, treated in the ınternal medicine clinic, were reviewed retrospectively. According to the revised Atlanta criteria, the patients were categorized into three groups: Mild, moderate, and severe pancreatitis. The CAR, hospital stay duration, requirement for intensive care, and mortality rates were compared among these groups.

Results: The CAR was associated with severe acute pancreatitis [odds ratio 1.04; 95% confidence interval (CI): 1.03-1.06; p<0.001]. To identify the severe pancreatitis group according to the Atlanta criteria, the CRP/albumin level was determined to be >15.59 with a sensitivity of 96.77% and a specificity of 75.32%. The area under the ROC curve for the CAR in severe acute pancreatitis was 0.89 (95% CI: 0.87-0.92). When comparing the areas under the curve for albumin, CRP, and the CAR in identifying severe disease according to the Atlanta criteria, the CAR was statistically significantly higher than CRP and marginally different from albumin.

Conclusion: The CAR, which is easily obtainable and a non-invasive test, can be used as a marker in addition to existing risk scores to determine acute pancreatitis severity.

Keywords: Acute pancreatitis, albumin, C-reactive protein

Öz

Amaç: Akut pankreatitin ciddiyetini ve klinik sonuçları ile C-reaktif protein (CRP)/albümin oranı (CAO) arasındaki ilişkiyi belirlemeyi amaçladık.

Yöntem: İç hastalıkları kliniğinde yatırılarak tedavi gören toplam 580 akut pankreatitli hasta retrospektif olarak değerlendirildi. Hastalar revize Atlanta kriterlerine göre hafif, orta ve şiddetli pankreatit olarak 3 gruba ayrıldı. Bu gruplar arasında CAO, hastanede yatış süresi, yoğun bakım yatış ihtiyacı ve mortalite oranları karşılaştırıldı.

Bulgular: CAO şiddetli akut pankreatit ile ilişkili saptandı [olasılık oranı 1,04; %95 güven aralığı (GA): 1,03-1,06; p<0,001]. Atlanta kriterlerine göre şiddetli pankreatit hasta grubunu belirlemede CRP/albümin düzeyi %96,77 sensivite, %75,32 spesifite ile >15,59 olarak saptandı. Şiddetli akut pankreatitte CAO'nun ROC eğrisi altında kalan alan 0,89 (%95 GA: 0,87-0,92) idi. Albümin, CRP, CAO'nun Atlanta kriterlerine göre şiddetli hastalığı saptamada eğri altındaki alanlarını karşılaştırmada CAO, CRP'ye göre istatistiksel olarak anlamlı yüksek, albümin ile sınırda farklı saptandı.

Sonuç: Kolaylıkla bakılabilen ve non-invaziv bir test olan CAO akut pankreatitin ciddiyetini belirlemek için mevcut risk skorlarına ek olarak bir marker olarak kullanılabilir.

Anahtar kelimeler: Albümin, akut pankreatit, C-reaktif protein

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Introduction

Acute pancreatitis is a severe condition with a rising incidence globally. While most cases of acute pancreatitis are mild, it can sometimes progress to severe forms that may result in mortality. Thus, identifying potentially severe cases of acute pancreatitis early is essential.

Various risk scores, such as APACHE, Atlanta, bedside index of severity in acute pancreatitis (BISAP), and Ranson, are utilized to assess the severity of acute pancreatitis (1-4). However, due to their comprehensive nature, these risk scores are not widely used at the bedside. No scoring system has been established as the gold standard.

C-reactive protein (CRP) and albumin are commonly used inflammatory markers to assess the severity of various diseases. During inflammation, CRP levels rise while albumin levels drop. Albumin levels can be influenced by malnutrition. Therefore, instead of using CRP or albumin alone, the CRP/albumin ratio (CAR) is becoming an emerging marker for assessing disease seriousness (5-7). However, there is no definitive threshold value for the CAR in assessing acute pancreatitis seriousness.

In our study, we examined the usability of the CAR in determining the severity, and fatality of acute pancreatitis. In doing so, we evaluated the feasibility of using the CAR as a cost-effective test for assessing the seriousness and outcome of acute pancreatitis in hospitals with limited diagnostic facilities.

Materials and Methods

The research examined 580 cases, with acute pancreatitis admitted to the Internal Medicine Clinic at a specific hospital between January 1, 2021, and January 1, 2024. This research was conducted in accordance with the Declaration of Helsinki. Participants were briefed regarding the research, and their written consent was acquired.

Patients aged 18 years and older, regardless of gender, were part of the study. This research was performed as a retrospective analysis. The diagnosis of acute pancreatitis and the severity of the disease were made based on the revised Atlanta criteria (2).

The seriousness of the disease was evaluated based on the revised Atlanta criteria and BISAP scores (2,3).

The study investigated the relationship between the CRP/albumin ratio and severe pancreatitis, as well as its components in patients with acute pancreatitis. Data collected included patients' age, gender, smoking status, alcohol consumption, comorbid chronic diseases, etiology of acute pancreatitis, BISAP score, and classification of pancreatitis severity based on the revised Atlanta criteria (mild, moderate, severe). Biochemical and hemogram parameters were recorded. The serum CAR was determined by dividing the CRP level (mg/L) by the serum albumin level (g/L). The CRP/albumin ratio was analyzed from blood samples taken on the day admission to the emergency department. Additionally, data on the requirement for intensive care unit (ICU) admission, duration of hospitalization, and mortality were documented.

Exclusion criteria were defined as patients younger than 18, pregnant individuals, those with chronic pancreatitis, and those with post-ERCP pancreatitis.

For this research, approval was issued by University of Health Sciences Turkey, Şişli Hamidiye Etfal Training and Research Hospital's Ethics Committee under protocol number 4424 on June 11, 2024.

Statistical Analysis

Statistical analysis was conducted using SPSS version 15.0 for Windows. Descriptive statistics were reported as counts and percentages for categorical variables, and as mean, standard deviation, minimum, maximum, and median for numerical variables. Proportions in the groups were compared using the chi-square test. Numerical variables were compared using the Student's t-test for two independent groups and the One-Way ANOVA test for more than two independent groups, provided that normal distribution conditions were satisfied. When normal distribution conditions were not met, the Mann-Whitney U test and the Kruskal-Wallis test were employed for comparisons. Post-hoc analyses for non-parametric tests with more than two groups were performed using the Mann-Whitney U test, and a Bonferroni correction was applied. Determinants were examined using logistic regression analysis. Cut-off values were determined using ROC curve analysis. The level of significance was set at α=0.05.

Results

The average age of the participants was 71.8±15.3 years (range 21-100). Of the participants, 42.6% were male and 57.4% were female. The most common etiology was gallstones, followed by idiopathic causes. According to the revised Atlanta criteria, 51% of the 580 patients had mild acute pancreatitis (n=294), 44% had moderate acute pancreatitis (n=255), and 5% had severe acute pancreatitis (n=31).

Patients with severe pancreatitis exhibited a higher average age (Table 1). In subgroup analyses, patients with moderate pancreatitis had markedly higher average ages compared to those with mild pancreatitis while patients with severe pancreatitis had significantly higher average ages compared to those with mild pancreatitis. However, while the mean age of cases with severe pancreatitis was numerically higher than that with moderate pancreatitis, the difference did not reach significance (Table 2).

The hospital stay duration was notably shorter in cases with mild pancreatitis compared to cases with moderate and severe pancreatitis. No marked difference was found in the hospital stay duration between cases with moderate and severe pancreatitis (Table 2).

When comparing ICU stay durations, patients with mild and moderate pancreatitis had shorter stays than those with severe pancreatitis. No ICU admissions were observed in patients with mild pancreatitis (Table 2).

Laboratory values such as leukocyte count, urea, and creatinine were lower in cases of mild pancreatitis compared to moderate and severe pancreatitis cases. Additionally, lactate dehydrogenase (LDH) levels were markedly elevated in severe pancreatitis cases compared to mild and moderate cases (Table 2, 3).

CRP and CRP/albumin levels were markedly elevated in cases with severe pancreatitis compared to mild and moderate pancreatitis, and were also higher in cases with moderate pancreatitis compared to mild pancreatitis. Albumin levels were markedly lower in severe pancreatitis cases compared to mild and moderate pancreatitis, and lower in moderate pancreatitis cases, compared to mild pancreatitis (Table 2, 3).

Table 1. Clinical characteristics of acute pancreatitis patients classified according to the revised Atlanta criteria

		Total	Revised Atlanta classification							
			Mild		Moderately		Severe		p	
Age Mean ± SD min-max (median)		71.8±15.3 21-100 (74)		66.6±18.2 21-97 (71)		76.7±8.8 46-100 (76)		80.2±8.2 66-96 (81)		**<0.001**
Gender n (%)	Female	333	57.4	165	56.1	151	59.2	17	54.8	0.732
	Male	247	42.6	129	43.9	104	40.8	14	45.2	
Smoking n (%)		178	30.7	100	34.0	68	26.7	10	32.3	0.174
Alcohol n (%)		53	9.1	37	12.6	15	5.9	1	3.2	**0.012**
Comorbidity n (%)	Diabetes mellitus	174	30.0	83	28.2	85	33.3	6	19.4	0.177
	Hypertension	367	63.3	163	55.4	186	72.9	18	58.1	**<0.001**
	Chronic renal disease	50	8.6	21	7.1	27	10.6	2	6.5	0.324
	†COPD	79	13.6	36	12.2	36	14.1	7	22.6	0.267
	Cerebrocascular disease	48	8.3	15	5.1	27	10.6	6	19.4	**0.005**
	Ischemic heart disease	126	21.7	51	17.3	71	27.8	4	12.9	**0.006**
	Malignancy	61	10.5	24	8.2	31	12.2	6	19.4	0.081
	Cholecystectomy history	56	9.7	29	9.9	24	9.4	3	9.7	0.984
Etiology	Gallstones	437	75.3	215	73.1	199	78.0	23	74.2	0.407
	Hypertriglyceridemia	2	0.3	2	0.7	0	0.0	0	0.0	0.554
	Alcohol	13	2.2	12	4.1	1	0.4	0	0.0	**0.010**
	Drug	9	1.6	2	0.7	6	2.4	1	3.2	0.153
	Idiopathic	114	19.7	64	21.8	45	17.6	5	16.1	0.422
	Necrotizing pancreatitis	8	1.4	0	0.0	3	1.2	5	16.1	**<0.001**
Bedside Index	≥3	259	44.7	67	22.8	161	63.1	31	100	**<0.001**
	<3	321	55.3	227	77.2	94	36.9	0	0.0	
Mortality n (%)		24	4.1	0	0.0	8	3.1	16	51.6	**<0.001**
‡**LOHS** Mean ± SD min-max (median)		8.3±5.7 1-42 (7)		5.3±2.2 2-15 (5)		11.2±6.1 1-42 (10)		12.5±9.3 1-35 (12)		**<0.001**
§**ICUS** Mean ± SD min-max (median)		0.4±2.5 0-32 (0)		0.0±0.0 0-0 (0)		0.1±0.8 0-12 (0)		6.9±8.3 0-32 (4)		**<0.001**

†: Chronic obstructive pulmonary disease (COPD), ‡: Length of hospital stay, days, §: Length of ıntensive care unit stay, days, SD: Standard deviation

Table 2. Subgroup analyzes

	Mild vs. Moderately	Mild vs. Severe	Moderately vs. Severe
	p†	p†	p†
Age	**<0.001**	**<0.001**	0.046
‡LOHS	**<0.001**	**<0.001**	0.742
§ICUS	**0.016**	**<0.001**	**<0.001**
Leukocyte	**<0.001**	**<0.001**	0.018
Hemoglobin	**0.016**	0.027	0.221
Hematocrit	0.109	0.077	0.219
Urea	**<0.001**	**<0.001**	0.559
Creatinine	**<0.001**	**<0.001**	0.498
ALT	0.208	0.219	0.437
AST	0.670	0.982	0.931
LDH	0.934	**0.007**	**0.006**
Amylase	0.398	0.350	0.561
Lipase	**0.014**	0.898	0.333
Total bilirubin	0.030	0.124	0.477
Direct bilirubin	0.167	**0.012**	0.057
CRP/albumin	**<0.001**	**<0.001**	**<0.001**
CRP	**<0.001**	**<0.001**	**<0.001**
Albumin	**<0.001**	**<0.001**	**<0.001**

†: Mann-Whitney U test Bonferroni's Correction p<0.017, ‡: Length of hospital stay, days, §: Length of intensive care unit stay, days, ALT: Alanine transaminase, AST: Aspartate transaminase, LDH: Lactate dehydrogenase, CRP: C-reactive protein

The predictive effect of laboratory levels on patients with severe acute pancreatitis, based on the Atlanta criteria, was analyzed using univariate logistic regression analysis. It was found that increases in leukocytes, total bilirubin, direct bilirubin, CAR, and CRP were risk factors for severe disease, while an increase in albumin was recognized as a protective factor. When analyzed using multivariate logistic regression, an increase in albumin was recognized as a shielding factor (Table 4).

When acute pancreatitis patients were separated into two groups -individuals who stayed in the general ward and individuals who required ICU admission and/or died- laboratory values including leukocyte count, urea, creatinine, LDH, total bilirubin, direct bilirubin, CRP, and the CAR were markedly elevated in the ICU admission and/or mortality group. Albumin value was significantly lower in this group (Table 5).

The CAR was found to be >15.59 with a sensitivity of 96.77% and specificity of 75.32% for identifying severe pancreatitis cases according to the Atlanta criteria (Figure 1).

In comparing the areas under the receiver operating characteristic curve for albumin, CRP, and the CAR in identifying severe disease according to the Atlanta criteria, the CAR was determined to be significantly higher than CRP and not significantly different from albumin (Figure 2).

Discussion

Most individuals with acute pancreatitis have a mild course that is self-limiting, but it can also progress to a severe course that may result in mortality. Therefore, it is essential to recognize cases of acute pancreatitis that may develop a severe course in advance.

In a study by Kazmi et al. (8), similar to our findings, the CRP/albumin ratio was found to have greater sensitivity than CRP alone in determining severe pancreatitis in cases with acute pancreatitis.

In Kaplan et al.'s (9) study on cases with acute pancreatitis, the CAR was elevated in patients who did not survive compared to those who did. Our study also found that the CRP and CRP/albumin ratios were significantly elevated in cases that resulted in death.

In a systematic review performed by Tarar et al. (10), similar to our study, the CAR at hospital admission in cases with acute pancreatitis was found to correlate with

Table 3. Laboratory characteristics of acute pancreatitis patients classified according to the revised Atlanta criteria

		Revised Atlanta classification			
	Total	Mild	Moderately	Severe	
	Mean ± SD Min-max (median)	Mean ± SD Min-max (median)	Mean ± SD Min-max (median)	Mean ± SD Min-max (median)	p†
Leukocyte, 10^3 mm^3	23.6±27.9 2.8-67.2 (11.3)	11.1±5.3 4.2-67.2 (10.1)	12.9±5.0 2.8-32.3 (12.3)	15.6±6.5 3.3-26.18 (14.8)	**<0.001**
Hemoglobin, g/dL	12.8±1.9 7.1-18.2 (12.8)	13.0±1.9 7.1-18.2 (13.1)	12.6±1.8 7.1-17.6 (12.7)	12.2±2.0 9.2-16.3 (12.3)	**0.016**
Hematocrit, %	38.3±5.2 20.1-52.3 (38.5)	38.6±5.1 20.1-52.3 (39)	38.1±5.1 20.2-50.8 (38.2)	36.9±5.8 27.8-47.7 (36.7)	0.131‡
Urea, mg/dL	46.8±30.3 12-271 (40)	35.8±18.7 12-198 (33)	58.1±36.3 20-271 (50)	57.8±27.4 22-151 (51)	**<0.001**
Creatinine, mg/dL	1.10±0.91 0.32-12.78 (0.88)	0.88±0.60 0.32-7.23 (0.78)	1.32±1.14 0.45-12.78 (1.04)	1.29±0.62 0.51-3.07 (1.18)	**<0.001**
ALT, u/L	107.4±110.5 5-750 (66.5)	115.1±116.5 7-750 (73)	100.9±104.7 5-515 (63)	87.5±95.1 7-387 (51)	0.267
AST, u/L	89.7±102.5 6-731 (46)	92.2±102.0 10-557 (46.5)	86.4±102.4 6-731 (47)	92.1±109.7 10-439 (43)	0.917
LDH, u/L	281.2±166.7 116-2484 (231)	276.6±138.1 118-885 (223)	278.9±192.6 116-2484 (233)	342.9±175.9 167-813 (297)	**0.019**
Amylase, u/L	819.2±798.7 78-9244 (606)	829.0±924.5 78-9244 (572)	796.2±629.3 107-3651 (622)	918.1±770.1 103-3282 (703)	0.513
Lipase, u/L	1456.2±1535.9 99-9772 (1001.5)	1629.7±1711.0 112-9772 (1072)	1254.2±1300.4 99-8801 (909)	1455.9±1380.1 100-5414 (1183)	**0.044**
Total bilirubin, mg/dL	1.54±1.68 0.14-16.66 (0.94)	1.35±1.43 0.15-11.73 (0.89)	1.62±1.52 0.14-8.58 (1.03)	2.66±3.58 0.37-16.66 (1.08)	0.050
Direct bilirubin, mg/dL	0.92±1.39 0.02-14.63 (0.36)	0.80±1.22 0.02-10.83 (0.34)	0.94±1.25 0.05-7.89 (0.37)	1.96±2.93 0.10-14.63 (0.58)	**0.029**
CRP/albumin	15.0±22.2 0.1-131.4 (4.4)	2.7±3.8 0.1-30.3 (1.2)	24.6±23.3 0.4-131.4 (15.4)	52.0±33.0 8.8-123.5 (40.3)	**<0.001**
CRP, mg/L	49.5±71.3 0.4-494.1 (16.2)	10.2±14.5 0.4-130.7 (4.6)	82.1±75.5 1.4-426 (53.0)	155.6±109.7 30-494.1 (119)	**<0.001**
Albumin, g/L	3.60±0.48 1.85-5.1 (3.64)	3.78±0.40 2.60-5.10 (3.8)	3.46±0.44 1.85-4.54 (3.50)	3.01±0.53 1.96-4 (3)	**<0.001**

†: Kruskal-Wallis test, ‡: One-Way ANOVA, ALT: Alanine transaminase, AST: Aspartate transaminase, LDH: Lactate dehydrogenase, CRP: C-reactive protein, SD: Standard deviation

Table 4. Univariate and multivariate logistic regression analysis for predicting severe acute pancreatitis according to the Atlanta criteria based on laboratory levels

Variables	Univariate			Multivariate		
	p	OR	95% CI	p	OR	95% CI
Leukocyte	**0.003**	1.085	1.028-1.144	0.321	0.851	0.620-1.170
Hemoglobin	0.112	0.946	0.883-1.013	0.585	0.970	0.869-1.083
Creatinine	0.235	1.176	0.900-1.536	0.436	1.304	0.669-2.540
ALT	0.304	0.998	0.994-1.002	0.069	0.994	0.988-1.000
LDH	0.060	1.001	1.000-1.003	0.816	1.000	0.998-1.002
Total bilirubin	**0.001**	1.276	1.105-1.474	0.833	0.945	0.560-1.595
Direct bilirubin	**<0.001**	1.349	1.140-1.596	0.051	1.837	0.998-3.380
CRP/albumin	**<0.001**	1.045	1.032-1.057	0.266	0.942	0.849-1.046
CRP	**<0.001**	1.012	1.009-1.016	0.120	1.027	0.993-1.062
Albumin	**<0.001**	0.084	0.039-0.184	**0.005**	0.055	0.007-0.426

CI: Confidence interval, OR: Odds ratio, CRP: C-reactive protein, ALT: Alanine transaminase, LDH: Lactate dehydrogenase

Table 5. Comparison of laboratory characteristics between acute pancreatitis patients with ICU admission and/or mortality and those with ward admission

	Hospital ward stay	In-hospital mortality and/or ICU stay	
	Mean ± SD Min-max (median)	Mean ± SD Min-max (median)	p†
Leukocyte, 10^3 mm^3	11.9±5.2 2.76-67.2 (11.11)	15.3±6.6 3.3-26.2 (14.1)	**0.001**
Hemoglobin, g/dL	12.8±1.9 7.1-18.2 (12.8)	12.5±1.9 9.2-16.3 (12.6)	0.295‡
Hematokrit, %	38.3±5.1 20.1-52.3 (38.6)	37.9±5.6 27.8-47.7 (37.8)	0.565‡
Urea, mg/dL	45.3±28.5 12-265 (39)	64.6±44.1 22-271 (53)	**<0.001**
Creatinine, mg/dL	1.07±0.89 0.32-12.78 (0.87)	1.42±1.08 0.51-7.21 (1.16)	**0.001**
ALT, u/L	107.7±111.0 5-750 (68)	102.7±105.6 7-400 (63)	0.807
AST, u/L	88.0±101.1 6-731 (45)	110.0±117.4 10-439 (55)	0.224
LDH, u/L	270.7±133.5 116-911 (227)	411.2±369.2 167-2484 (301)	**<0.001**
Amylase, u/L	807.2±797.1 78-9244 (601)	971.8±813.4 103-3417 (783.5)	0.189
Lipase, u/L	1451.2±1553.1 99-9772 (991)	1519.9±1310.0 100-5414 (1227)	0.256
Total bilirubin, mg/dL	1.46±1.47 0.14-11.73 (0.92)	2.57±3.16 0.37-16.66 (1.25)	**0.039**
Direct bilirubin, mg/dL	0.86±1.23 0.02-10.83 (0.35)	1.74±2.57 0.10-14.63 (0.58)	**0.005**
CRP/albumin	12.5±19.2 0.1-131.4 (3.7)	45.9±32.1 2.3-123.5 (37.8)	**<0.001**
CRP, mg/L	42.3±62.6 0.38-425.96 (13.3)	140.6±104.4 7.3-494.1 (116.7)	**<0.001**
Albumin, g/L	3.63±0.45 1.85-5.10 (3.7)	3.11±0.51 1.96-4.17 (3.15)	**<0.001**

†: Mann-Whitney U test, ‡: Student's t-test, SD: Standard deviation, ALT: Alanine transaminase, AST: Aspartate transaminase, LDH: Lactate dehydrogenase, CRP: C-reactive protein, ICU: Intensive care unit

a more severe disease course, higher mortality, and longer hospital stay.

In Behera et al.'s (11) study involving 116 patients with acute pancreatitis, the CAR was observed to predict severe acute pancreatitis, and it was an independent determinant of mortality.

Yılmaz and Kandemir's (12) study involving 264 cases with acute pancreatitis, the CAR was identified as markedly elevated in the severe pancreatitis cases compared to the moderately severe pancreatitis cases. The Ranson score was utilized to assess the severity of pancreatitis (12).

In Saad et al.'s (13) review of acute pancreatitis patients, the CAR measured at admission was elevated in cases with severe acute pancreatitis compared to those with mild to moderate cases. Additionally, the CAR was markedly elevated in patients who did not survive compared to those who did (13).

In a review and meta-analysis by Mariadi et al. (14) involving 2.244 cases with acute pancreatitis, the CAR was elevated in severe acute pancreatitis cases relative to mild to moderate cases. The ratio was also markedly elevated in patients who did not survive compared to those who did (14).

Zhao et al.'s (15) study on 284 cases with acute pancreatitis found that the CAR measured on the second day was linked to severe acute pancreatitis and mortality. The ratio on the third day was linked to higher severity, pancreatic necrosis, organ dysfunction, and mortality (15). In our research, the CAR was evaluated only at the time of hospital admission.

In Piñerúa-Gonsálvez et al.'s (16) study involving 722 cases with acute pancreatitis, the CAR was linked to severe cases. The optimal cut-off value to estimate severe acute pancreatitis was 7.51, with a sensitivity of 63.4% and specificity of 65.6%. Although the sensitivity and specificity are low, the CRP/albumin ratio may still serve as an additional marker in evaluating the prognosis of acute pancreatitis (16). In our research, the optimal cut-off value for the CAR to identify severe acute pancreatitis cases based on the Atlanta criteria was determined to be 15.59, with a sensitivity of 96.77% and a specificity of 75.32%.

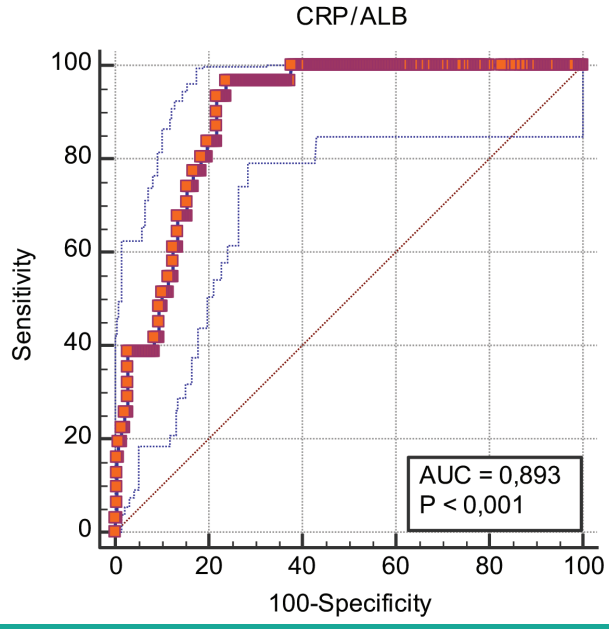

Figure 1. ROC curve for determining the risk of severe pancreatitis using the CRP/albumin ratio

CRP: C-reactive protein, AUC: Area under the curve, ROC: Receiver operating characteristic, ALB: Albumin

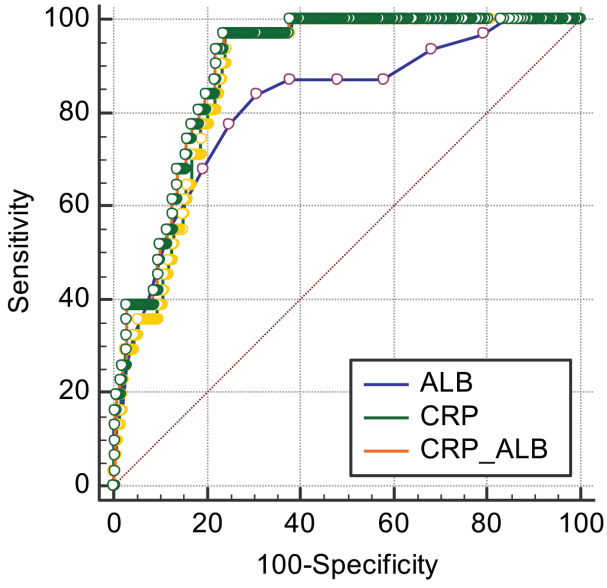

Figure 2. ROC curve of albumin, CRP and CRP/albumin ratio to determine the risk of severe pancreatitis

CRP: C-reactive protein, ROC: Receiver operating characteristic, ALB: Albumin

In the research by Yogesh et al. (17) involving 150 cases with acute pancreatitis classified based on the Atlanta criteria, the CAR was more elevated in cases with severe acute pancreatitis than in those with mild pancreatitis. At a cut-off value of 0.25, the CAR had a sensitivity of 85% and a specificity of 80% in forecasting organ failure (17). In our research, the CAR was elevated in severe pancreatitis cases compared to mild and moderate pancreatitis and was higher in moderate pancreatitis cases compared to mild pancreatitis.

In Karabuga et al.'s (18) study involving 500 patients with acute pancreatitis, the CAR, neutrophil to lymphocyte ratio, platelet-lymphocyte ratio, and red cell distribution width values were markedly elevated in severe acute pancreatitis cases compared to mild acute pancreatitis cases based on the BISAP score.

The study by Ghaffar et al. (19), identified a marked connection between the severity of acute pancreatitis and the CAR. This ratio can be particularly useful in assessing the severity of acute pancreatitis in resource-limited settings (19).

In a study investigating the CAR as a determinant of mortality in critically ill cases, the CAR was found to predict mortality better than CRP alone (20). In our study, the CRP and CRP/albumin values were markedly elevated among patients who died or were admitted to the ICU compared to those who were admitted to the general ward with acute pancreatitis. Therefore, we believe that the CRP/albumin level can be used during initial hospital admission to predict severe pancreatitis and mortality.

Consequently, I would like to present a summary of all the studies referenced in my article regarding acute pancreatitis and the CRP/CAR in one comprehensive table, including sample sizes, pancreatitis etiologies, patient outcomes, and the countries of origin (Table 6).

Study Limitations

This study's limitations include its single-center design and the relatively small sample size. The tests were conducted only at the time of the patients' initial hospital admission, and repeated measurements were not evaluated.

Table 6. Summary of studies on C-reactive protein/albumin ratio (CAR) in acute pancreatitis: Etiologies, patient outcomes, and diagnostic performance

Study name	Sample sizes	Pancreatitis etiologies	Patient outcomes	The countries of origin
Kazmi et al. (8)	225	N/A	CAR >4.35: Sensitivity 87%, Accuracy 76% (SAP)	Pakistan
Kaplan et al. (9)	192	Gallstone 80.2%, Alcohol 2.6%, Hypertriglyceridemia 1.6%, Hereditary 9.4%, ERCP 1.6%, Other 4.7%	CAR >16.28: Sensitivity 92.1%, Specificity 58% (mortality)	Turkey
Tarar et al. (10)	956	N/A	CAR at admission linked to SAP, longer hospital stay, higher mortality	United Kingdom
Behera et al. (11)	116	Alcohol 46.6%, Biliary 38.8%, Idiopathic 6%, Post ERCP 5.1%	CAR predicts mortality and AP severity	India
Yılmaz and Kandemir (12)	264	N/A	CAR higher in severe vs. moderate	Turkey
Saaad et al. (13)	2244	N/A	CAR higher in severe AP and non-survivors	Egypt
Mariadi et al. (14)	2244	N/A	CAR higher in severe AP and non-survivors	Indonesia
Zhao et al. (15)	284	Gallstone 54.23%, Hyperlipidemia 24.30%, Alcohol 4.58%, Other 21.48%	Day 2 CAR linked to SAP and mortality	China
Piñerúa-Gonsálvez et al. (16)	722	N/A	CAR optimal cut-off for predicting SAP: 7.51	Spain
Yogesh et al. (17)	150	Alcohol 60%, Biliary 23%, Others 17%	CAR higher in severe vs mild AP. At 0.25 cut-off: Sn 85%, Sp 80% for organ failure	India
Karabuga et al. (18)	500	Biliary 72.20%, Non-biliary 27.80%	CAR: Sn 71.43%, Sp 70.88% for predicting SAP	Turkey
Ghaffar et al. (19)	N/A	N/A	CAR strongly correlates with AP severity	Pakistan, Congo, Kenya

Prospective studies are essential to evaluate the function of the CAR in the course of acute pancreatitis.

Conclusion

We believe that the CAR measured at the time of hospital admission can serve as an additional marker to existing risk scores and can evaluate the seriousness and prognosis of acute pancreatitis as a cost-effective test in hospitals with limited diagnostic facilities.

Ethics

Ethics Committee Approval: For this research, approval was issued by University of Health Sciences Turkey, Şişli Hamidiye Etfal Training and Research Hospital's Ethics Committee under protocol number 4424 on June 11, 2024.

Informed Consent: Participants were briefed regarding the research, and their written consent was acquired.

Footnotes

Authorship Contributions

Concept: A.Ç., Design: A.Ç., Data Collection or Processing: A.Ç., Ç.E., Analysis or Interpretation: A.Ç., Ç.E., Literature Search: A.Ç., Ç.E., Writing: A.Ç., Ç.E.

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

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ORIGINAL RESEARCH

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Glomus Tumors of 20 Cases' Experience

Glomus Tümörlerinde 20 Olguluk Deneyim

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Abstract

Objective: This study aimed to analyze the clinical characteristics, surgical outcomes, and long-term follow-up of glomus tumors in a single-center experience.

Method: A retrospective analysis was conducted on 20 patients who underwent surgery for histologically confirmed glomus tumors between 2013 and 2023. Patient demographics, tumor characteristics, clinical presentation, radiological findings, surgical outcomes, and follow-up data were collected and analyzed.

Results: The cohort consisted of 75% females, with a mean age of 45.5±17.3 years. Most tumors (85%) were located in the hand, with 65% in the subungual region. The most common symptoms were tenderness (100%), visible tumor (85%), cold sensitivity (80%), and pain (70%). Radiological findings were positive in 70% of cases. The median tumor size was 0.6 cm, with significantly larger tumors in males compared to females (p=0.0245). The median preoperative duration was two years, and the median follow-up was 3.5 years. A 5% recurrence rate was observed post-surgery.

Conclusion: This study provides valuable insights into the clinical presentation and surgical management of glomus tumors. The findings highlight the effectiveness of surgical excision, with a low recurrence rate. The correlation between positive radiological findings and longer preoperative duration suggests potential diagnostic delays, emphasizing the need for increased awareness and prompt intervention in suspected cases.

Keywords: Clinical characteristics, glomus tumor, hand tumors, long-term follow-up, radiological findings, subungual tumors, surgical excision

Öz

Amaç: Bu çalışmada tek merkezli bir deneyimde glomus tümörlerinin klinik özellikleri, cerrahi sonuçları ve uzun dönem takiplerinin analiz edilmesi amaçlandı.

Yöntem: 2013-2023 yılları arasında histolojik olarak doğrulanmış glomus tümörü nedeniyle ameliyat edilen 20 hasta üzerinde retrospektif bir analiz yapıldı. Hasta demografisi, tümör özellikleri, klinik prezentasyon, radyolojik bulgular, cerrahi sonuçlar ve takip verileri toplandı ve analiz edildi.

Bulgular: Kohort, ortalama yaşı 45,5±17,3 yıl olan %75 kadın hastadan oluşuyordu. Tümörlerin çoğu (%85) elde ve %65'i subungual bölgede yerleşmişti. En yaygın semptomlar hassasiyet (%100), görünür tümör (%85), soğuk hassasiyeti (%80) ve ağrı (%70) idi. Radyolojik bulgular olguların %70'inde pozitifti. Ortanca tümör boyutu 0,6 cm idi ve erkeklerde kadınlara kıyasla anlamlı olarak daha büyük tümörler vardı (p=0,0245). Ameliyat öncesi medyan süre iki yıl ve medyan takip süresi 3,5 yıldı. Cerrahi sonrası %5 nüks oranı gözlendi.

Sonuç: Bu çalışma glomus tümörlerinin klinik görünümü ve cerrahi yönetimi hakkında değerli bilgiler sağlamaktadır. Bulgular, düşük nüks oranı ile cerrahi eksizyonun etkinliğini vurgulamaktadır. Pozitif radyolojik bulgular ve daha uzun preoperative sure arasındaki korelasyon, potansiyel tanısal gecikmelere işaret etmekte ve şüpheli olgularda farkındalığın artırılması ve hızlı müdahale ihtiyacını vurgulamaktadır.

Anahtar kelimeler: Cerrahi eksizyon, el tümörleri, glomus tümörü, klinik özellikler, radyolojik bulgular, subungual tümörler, uzun dönem takip

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Introduction

Glomus tumors are rare neoplasms arising from the glomus body in the dermis, which provides thermoregulation (1,2). Glomus bodies are specialized neuromyoarterial structures with a delicate network of arteriovenous anastomoses regulating blood flow through the skin to control blood pressure and temperature. First described by Wood (3) in 1812, glomus tumours were identified as subcutaneous nodules on the fingers of the upper extremities(1,2). Subsequently, case reports occurred in various parts of the body, including internal organs such as the stomach and kidney (1,4). Clinically, glomus tumors are difficult to diagnose. Non-specific symptoms and usual physical examination findings often lead to misdiagnosis and incorrect treatment. Some patients may experience prolonged pain due to delays in diagnosis. The difficulty in diagnosis is often due to the small size of the tumor; the lesion may not be visible on physical examination and radiological imaging (5). In 1972, Roberte and Arnoldt (6) described the classic symptoms of glomus tumors as pain, tenderness and cold sensitivity. These three symptoms have been shown to allow for diagnosis in 90% of patients (7). Physical examination findings include Love's test (needle tip tenderness) and Hildreth's sign (decrease in pain/sensitivity after inflation of a tourniquet above systolic blood pressure proximal to the tumour) (8-10).

In addition to the clinical findings, radiological imaging is used to confirm the diagnosis. Scalloping of the bone can be seen on plain radiographs, albeit at a low rate (11). High-resolution magnetic resonance imaging (MRIs) are useful for detecting small tumors during diagnosis (12). However, there are also tumors that are not detected on MRI but are seen intraoperatively and excised. Studies have shown that high-resolution ultrasound is also useful for diagnosis (13).

Glomus tumors are histologically well-circumscribed nodules consisting of uniform round cells that are typically located perivascularly. These tumors are composed of glomus cells, blood vessels, and smooth muscle cells. Based on the distribution of these three components, they are divided into three histological subtypes: Glomus solid tumors, glomangiomas, and glomangiomyomas. There are very few smooth muscle and blood vessel components in glomus tumors. Blood vessels are prominent in glomangiomas. Smooth muscles and blood vessels are equally dominant in glomangiomyomas (14).

With our comprehensive analysis, we hope to provide valuable insights into the management of glomus tumors. We are pleased to present a series of 20 glomus tumor cases, one of the largest case series from a single institution. Our study aimed to elucidate the clinical features of this rare neoplasm.

Materials and Methods

Patient Selection

A retrospective analysis was conducted on the medical records of 20 individuals who underwent surgical treatment for glomus tumors at our orthopedic and trauma center from 2013 to 2023. The investigation took place in a single tertiary healthcare facility, with the research protocol receiving approval from the Institutional Ethics Committee of University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital (protocol number: 2024/04/03/040, date: 29/04/2024). To be included in the study, participants had to be at least 18 years old, have a histologically confirmed glomus tumor diagnosis, and have a minimum one-year follow-up period. The study excluded patients with insufficient follow-up documentation or uncertain pathological diagnoses. Initially, 23 potential candidates were identified from hospital records. However, three were subsequently excluded due to lack of clinical follow-up. The final study group comprised 20 patients with confirmed glomus tumors, all of whom underwent surgery and received clinical follow-up care from a single orthopedic surgeon at the aforementioned tertiary care hospital.

Data Collection

A comprehensive database system was developed to compile various details using hospital records. This form included patient demographics, preoperative imaging results, thorough surgical notes, and physical examination findings of the affected area. The collected information encompassed the patient's age, gender, tumor location, duration of symptoms before surgery, tumor recurrence as a postoperative issue, length of follow-up after surgery, patient's dominant hand, any history of injury, and imaging study results.

Operation

A single surgeon performed all operations. Surgical procedures involved making incisions in the appropriate anatomical area of the lesion, adhering to oncological surgery principles. The surgeon prioritized removing masses in one piece while carefully preserving crucial nearby structures, such as the nail bed, and ensuring no satellite lesions remained (Figure 1).

The excised masses were then preserved for pathological examination. For subungual region masses, the surgeon first removed the nail; then made a longitudinal incision in the nail bed and nail fold. Following mass excision, the area was repaired using two 4-0 vicryl sutures, and the previously removed nail was placed over the wound to serve as a biological dressing (Figure 2).

Histopathological Analysis

A single pathologist conducted the histopathological evaluation of the specimens. The largest dimension and visual characteristics of the tumors were documented macroscopically. Standard tissue processing methods, along with hematoxylin and eosin staining and immunohistochemical analyses, were employed on the samples. Microscopic examination confirmed the diagnosis of glomus tumors. All findings were documented in the patient records.

Follow-up

Post-operative care involved unrestricted movement and the initiation of active motion once pain subsided. Patients underwent examination and wound site evaluation after two weeks, with subsequent follow-up appointments scheduled. During these visits, patients reported that the area where the nail was surgically removed had healed naturally during later dressings, and a new nail had emerged. The follow-up sessions documented various complications, including recurrence, limitations in joint mobility, nail abnormalities, nail discomfort, sensitivity, and issues at the wound site. The duration of follow-up ranged from 13 to 110 months.

Statistical Analysis

The GraphPad Instat ver. 3.06 (GraphPad Inc, CA, USA) software was used to conduct statistical analyses. To determine the distribution of variables, the Kolmogorov-Smirnov test was used. For comparing two normally distributed continuous variables, an unpaired t-test was applied, while One-Way Analysis of Variance (ANOVA) was used for comparing more than two such variables. In cases of non-normally distributed continuous variables, the Mann-Whitney U test was employed for comparing two groups, and the Kruskal-Wallis test was used for more than two variables. Comparisons of categorical variables were made using the chi-squared test for Independence. A p-value of less than 0.05 was considered statistically significant.

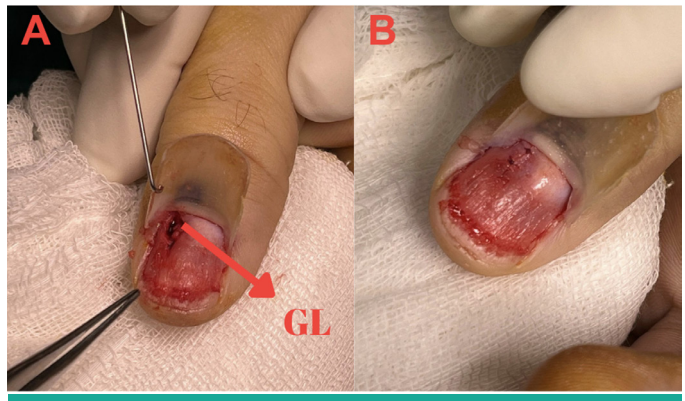

Figure 1. A: Intraoperative image of a glomus tumour (GL) in the nail bed of the thumb of the hand, B: Image of nail bed repair after GL excision

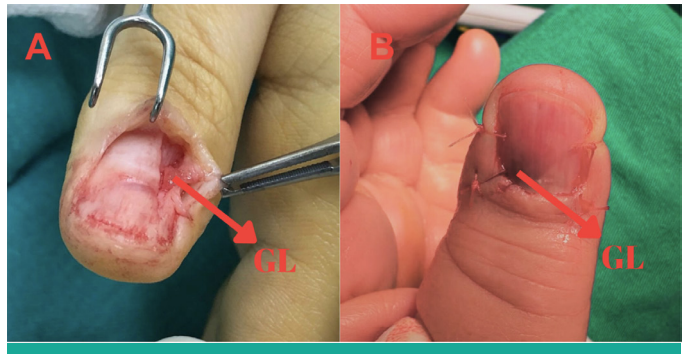

Figure 2. A: Intraoperative image of a glomus tumour (GL) in the nail bed of the thumb, B: Replacement of the nail as a biological dressing after excision of GL. Note the discolouration of the nail bed

Results

Twenty patients were evaluated. The mean age was 45.5±17.3 years, with 75% of the cohort comprising female participants and 25% male participants. Most of the tumors were located in the hand (85%), with 65% of these tumors specifically in the subungual region. On histological examination, the tumors were identified as glomus tumors in 90% of the cases, with the remaining 10% classified as glomangiomas (Table 1). The most frequently reported symptoms were tenderness (100%), the presence of a visible tumor (85%), cold sensitivity (80%), and pain (70%). Nail changes were observed in 20% of the patients (Figure 3). A history of trauma was documented in 10% of the cases. Radiological findings were positive in 70% of patients, with a median tumour size of 0.6 cm (range: 0.3-2.0 cm). The median preoperative duration was two years (range: 0.25-10 years), and the median follow-up duration was three and a half years (range: one to nine years). Recurrence was observed in one patient, representing 5% of the total number of cases.

Table 1. Demographics and clinicopathological features of all patients

		Total (n=20)
Age, mean ± SD	Year	45.5±17.3
Gender, n (%)	Male Female	5 (25) 15 (75)
Tumor location, n (%)	Hand Fingernail Subcutaneous region Others*	17 (85) 13 (65) 4 (20) 3 (15)
Side, n (%)	Left Right	13 (65) 7 (35)
Type of tumor, n (%)	Glomus Glomangioma	18 (90) 2 (10)
Symptoms, n (%)	Pain Tenderness Cold sensitivity Visible tumor Nail changes	14 (70) 20 (100) 16 (80) 17 (85) 4 (20)
History of trauma, n (%)		2 (10)
Radiological findings, n (%)		14 (70)
Tumor size, median [range]	Largest dimension (cm)	0.6 [0.3-2.0]
Preoperative duration, median [range]	Year	2 [0.25-10]
Duration of follow-up, median [range]	Year	3.5 [1-9]
Recurrence, n (%)		1 (5)

SD: Standard deviation, *: 1 case in knee, 1 case in shoulder and 1 case in cruris

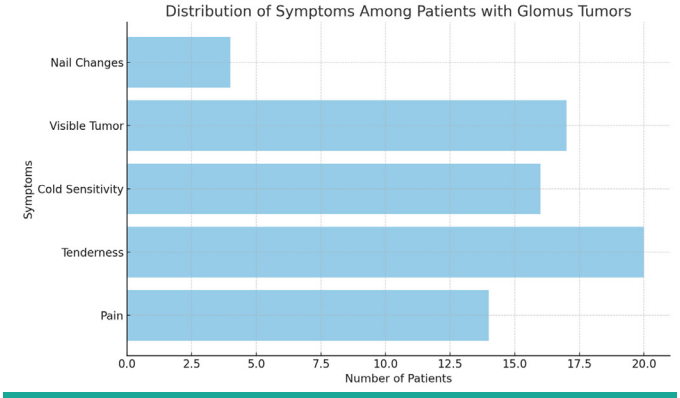

Figure 3. Distribution of symptoms among patients with glomus tumors. The bar chart illustrates the frequency of various symptoms observed in patients with glomus tumors. Tenderness was the most common symptom, reported by 100% of the patients, followed by visible tumors (85%), cold sensitivity (80%), and pain (70%). Nail changes were observed in 20% of the patients

A comparison of the sexes revealed no significant differences in mean age (p=0.898) but a significant difference in tumor location (p=0.0114). However, a significant difference was observed in tumor size between the two sexes. Median tumour size was 6 mm. The median size of the tumors was 1.0 cm (range: 0.9-2.0 cm); in males, it was 0.5 cm (range: 0.3-0.7 cm), in females (p=0.0245). Recurrence was observed in 6.6% of the female patients, whereas no recurrence was noted in the male patients (Table 2).

Radiological Findings

A comparison of patients based on the presence of radiological findings revealed no significant differences in terms of age (p=0.444), sex (p=0.573), or tumor size (p>0.999). However, the preoperative duration was significantly longer in patients with positive radiological findings [median: 3.0 years (range: 0.5-10.0 years)] than in those without [median: 1.0 year (range: 0.25-2.0 years) (p=0.0261)]. Recurrence was observed in 7.1% of the patients with radiological findings, whereas no recurrence was noted in those without such findings (Table 3).

Discussion

The most significant aspect of our study is that it is one of the largest single-center series with a long follow-up period (15,16). One of the most significant findings was that 70% of patients exhibited radiological findings, which increased in prevalence in correlation with the duration of preoperative waiting time.

Demographic data indicated a higher prevalence of glomus tumors in women (75%), which is consistent with existing literature (17,18). The mean age of 45.5±17.3 years suggests that glomus tumors predominantly affect middle-aged adults.

Glomus tumors can present at a wide range of anatomical sites beyond the classic subungual location. The literature documents cases of glomus tumors in various extradigital and visceral sites, which can pose diagnostic challenges due to their rarity and potential for atypical presentation. Recognition of these diverse locations is crucial for accurate diagnosis and management of glomus tumors (19,20). The majority of tumors were located in the hand (85%), with a particular predilection for the subungual region (65%). This localization pattern aligns with previous studies reporting that glomus tumors typically occur in the distal extremities.

Regarding symptomatology, tenderness (100%), visible tumor (85%), cold sensitivity (80%), and pain (70%) were the most frequently reported complaints. This symptom profile is consistent with the classic triad described by Roberte and Arnoldt (6), underscoring the importance of high clinical suspicion in the diagnosis of glomus tumours.

Imaging techniques, such as ultrasonography and MRI, play a significant role, with MRI being particularly valuable for identifying small tumors and assessing their extent. The literature suggests that while MRI is a powerful diagnostic tool, its performance can be enhanced with additional techniques such as MR angiography to overcome its

Table 2. Comparison of demographics and clinicopathological features of patients according to the gender

		Male (n=5)	Female (n=15)	p-value
Age, mean ± SD	Year	46.6±23.8	45.1±15.7	0.898
Tumor location, n (%)	Hand	2 (40)	15 (100)	0.0114
	Fingernail	2 (40)	11 (73.3)	0.417
	Subcutaneous region	0 (0)	4 (26.7)	0.519
	Others	3 (60)*	0 (0)	0.0114
Side, n (%)	Left	4 (80)	9 (60)	0.787
	Right	1 (20)	6 (40)	
Type of tumor, n (%)	Glomus	4 (80)	14 (93.3)	0.389
	Glomangioma	1 (20)	1 (6.7)	
Symptoms, n (%)	Pain	3 (60)	11 (73.3)	0.573
	Tenderness	5 (100)	15 (100)	-
	Cold sensitivity	3 (60)	13 (86.7)	0.519
	Visible tumor	2 (40)	15 (100)	0.0114
	Nail changes	1 (20)	3 (20)	1.00
History of trauma, n (%)		1 (20)	1 (6.7)	0.389
Radiological findings, n (%)		3 (60)	11 (73.3)	0.573
Tumor size,median [range]	Largest dimension (cm)	1.0 [0.9-2.0]	0.5 [0.3-0.7]	0.0245
Preoperative duration, median [range]	Year	1.0 [0.25-8.0]	2.0 [0.5-10.0]	0.570
Duration of follow-up, median [range]	Year	3.0 [1.0-7.0]	4.0 [1.0-9.0]	0.590
Recurrence, n (%)		0 (0)	1 (6.6)	0.554

Mann-Whitney U test or Unpaired t-test with Welch correction and chi-square,*: 1 case in knee, 1 case in shoulder and 1 case in cruris, SD: Standard deviation

Table 3. Comparison of demographics and clinicopathological features of patients according to the presence of radiological findings

		Without finding (n=6)	With finding (n=14)	p-value
Age, mean ± SD	Year	39.8±22.1	47.9±15.2	0.444
Gender, n (%)	Male	2 (33.3)	3 (21.4)	0.573
	Female	4 (66.7)	11(78.6)	
Tumor location, n (%)	Hand	5 (83.3)	12 (85.7)	0.891
	Fingernail	3 (50)	10 (71.4)	0.682
	Subcutaneous region	2 (33.3)	2 (14.3)	0.714
	Others*	1 (16.7)	2 (14.3)	0.891
Side, n (%)	Left	4 (66.7)	9 (64.3)	0.919
	Right	2 (33.3)	5 (35.7)	
Type of tumor, n (%)	Glomus	5 (83.3)	13 (92.9)	0.515
	Glomangioma	1 (16.7)	1 (7.1)	
Symptoms, n (%)	Pain	5 (83.3)	9 (64.3)	0.750
	Tenderness	6 (100)	14 (100)	-
	Cold sensitivity	5 (83.3)	11 (78.6)	0.807
	Visible tumor	5 (83.3)	12 (85.7)	0.891
	Nail changes	1 (16.7)	3 (21.4)	0.807
History of trauma, n (%)		0 (0)	2 (14.3)	0.871
Tumor size,median [range]	Largest dimension (cm)	0.6 [0.3-2.0]	0.6 [0.3-1.3]	>0.999
Preoperative duration, median [range]	Year	1.0 [0.25-2.0]	3.0 [0.5-10.0]	0.0261
Duration of follow-up, median [range]	Year	4.0 [2.0-7.0]	3.0 [1.0-9.0]	0.323
Recurrence, n (%)		0 (0)	1 (7.1)	0.502

Mann-Whitney U test or Unpaired t-test with Welch correction and chi-square, *: 1 case in knee, 1 case in shoulder and 1 case in cruris, SD: Standard deviation

limitations (21,22). Radiological findings were positive in 70% of patients, suggesting that imaging modalities can be beneficial in diagnosis, but may not be sufficient for a definitive diagnosis. Notably, patients with radiological findings had a longer preoperative symptom duration (median, 3 years vs. 1 year; p=0.0261), indicating potential diagnostic delays.

The significant difference in tumor size between genders (median 1.0 cm in males, 0.5 cm in females, p=0.0245) is noteworthy and may warrant further investigation. A comparison with similar studies in the literature reveals that the tumour size is larger than that reported (median 6 mm) (15,23). It was observed that the tumour size was larger in cases where a long preoperative waiting time had elapsed. It was therefore assumed that there was a direct correlation between tumour size and the length of time spent in preoperative waiting.

Current literature on recurrence rates following surgical intervention for glomus tumors is limited due to the rarity of these neoplasms. However, available studies generally indicate that surgical excision is an effective treatment modality, associated with low recurrence rates. Notably, in cases of subungual glomus tumors, surgical excision has been reported to alleviate symptoms with infrequent recurrence during follow-up period (24,25). The recurrence rate was 5%, which is consistent with the rates reported in the literature and demonstrates the efficacy of surgical excision as a treatment modality.

Study Limitations

It should be noted that our study is subject to certain limitations, including the relatively small number of patients included and the retrospective nature of the study. Furthermore, a comparison of preoperative and postoperative pain and functional scores was not possible.

Conclusion

This study provides valuable insights into the clinical characteristics and surgical outcomes of glomus tumors, drawing from a substantial single-center series with extended follow-up. Key findings include a predominance in female patients and in the hand, particularly in the subungual region, and the observation of the classic symptom triad in the majority of patients. Positive radiological findings were present in 70% of cases and correlated with a longer preoperative duration, while larger tumors were observed in male patients. The investigation reported a low recurrence rate of 5% following surgical excision, underscoring the effectiveness of this treatment approach.

Ethics

Ethics Committee Approval: The investigation took place in a single tertiary healthcare facility, with the research protocol receiving approval from the Institutional Ethics Committee of University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital (protocol number: 2024/04/03/040, date: 29/04/2024).

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

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.U., Concept: O.B., N.Y.E., Design: O.B., Data Collection or Processing: N.Y.E., Analysis or Interpretation: N.Y.E., O.B., Literature Search: M.U., Writing: M.U.

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

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ORIGINAL RESEARCH

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Evaluation of Patients with Inhalant Allergen Sensitivity Detected by Skin Prick Test

Deri Prick Testinde İnhalen Allerjen Duyarlılığı Saptanan Hastaların Retrospektif Değerlendirilmesi

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Abstract

Objective: Atopy refers to an individual's predisposition to develop allergies. Allergens can cause asthma, allergic rhinitis (AR), and atopic dermatitis (AD). The allergy skin prick test (SPT) is a safe, easy-to-apply, and cost-effective diagnostic tool for detecting sensitivity to allergens. This study aims to evaluate the relationships between identified allergen sensitivities, age groups, presenting complaints, and clinical diagnoses in patients who underwent SPT.

Method: The results of 2413 patients who underwent SPT in University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital's Pediatric Allergy Unit between March 1, 2012, and February 28, 2014, were retrospectively evaluated.

Results: The ages of the cases ranged from 1.7 to 17.5 months, with a mean age of 7.76±2.93 years. Of the cases, 990 (41.03%) were female and 1423 (58.97%) were male. Asthma was diagnosed in 1064 patients, AR in 186 patients, and both asthma and AR in 1163 patients. Among the 2413 SPT results evaluated, 576 were negative, while at least one allergen sensitivity was detected in 1837 prick tests. The most common presenting complaint was cough in 2145 patients (88.93%), and the most frequent allergen sensitivity was against *Dermatophagoides pteronyssinus* at 57.4%. Thirty-nine patients had AD accompanying their existing diagnoses, with AD most commonly observed alongside AR at 6.5%.

Conclusion: Our study found that the most common allergen sensitivity was against house dust mites. Identifying sensitivity to aeroallergens via SPT and protecting patients from these allergens forms the cornerstone of treatment in children diagnosed with allergic diseases such as asthma, AR, and AD.

Keywords: Allergen sensitivity, allergic diseases, skin prick test

Öz

Amaç: Atopi, bir kişinin allerji gelişimine eğilimli olması halidir. Allerjenler; astım, allerjik rinit (AR) ve atopik dermatite (AD) neden olur. Allerji deri prik testi (DPT) allerjene karşı duyarlılığı saptamada güvenli, kolay uygulanabilir ve düşük maliyetli bir tanı aracıdır. Çalışmamızda DPT uygulanan hastaların saptanan allerjen duyarlılığı, yaş grupları, başvuru şikayetleri ve klinik tanıları arasındaki ilişkilerin değerlendirilmesi amaçlanmıştır.

Yöntem: Sağlık Bilimleri Üniversitesi, Bakırköy Dr. Sadi Konuk Eğitim ve Araştırma Hastanesi, Çocuk Alerji Polikliniği'nde 1 Mart 2012-28 Şubat 2014 tarihleri arasında DPT uygulanan 2413 hastanın sonuçları retrospektif olarak değerlendirilmiştir.

Bulgular: Çalışmaya alınan olguların yaşları 1,7 ile 17,5 yaş arasında değişmekte olup ortalama yaş 7,76±2,93 yıldır. Olguların 990'ı (%41,03) kız, 1423'ü (%58,97) erkektir. Hastaların 1064'üne astım, 186'sına AR ve 1163'üne astım+ AR tanısı konulmuştur. Değerlendirilen 2413 DPT sonucunun 576'sı negatif olarak sonuçlanmış, 1837 prik testinde en az bir allerjen duyarlılığı saptanmıştır. En sık başvuru şikayeti 2145 hastada (%88,93) öksürük olmuş, en sık allerjen duyarlılığı %57,4 ile *Dermatophagoides pteronyssinus*'a karşı saptanmıştır. Otuz dokuz hastanın mevcut tanılarına AD tanısı da eşlik etmiş olup AD %6,5 ile en sık AR ile beraber görülmüştür.

Sonuç: Çalışmamızda en sık alerjen duyarlılığı ev tozu akarlarına karşı saptanmıştır. Astım, AR ve AD gibi alerjik hastalık tanısı alan çocuklarda DPT ile aeroallerjenlere karşı duyarlılığın belirlenmesi ve hastaların allerjenlerden korunması tedavinin temelini oluşturmaktadır.

Anahtar kelimeler: Allerjen duyarlılığı, allerjik hastalıklar, deri prik testi

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Introduction

Atopy refers to an individual's predisposition to develop allergies due to their genetic characteristics. It is characterized by the tendency to produce IgE antibodies in response to low-dose allergens, usually proteins. These allergens cause asthma, allergic rhinitis (AR), and atopic dermatitis (AD), and according to the World Health Organization and World Allergy Organization, approximately 40% of the world's population is estimated to be atopic (1). The interaction of personal and environmental factors results in atopic diseases, with genetic predisposition being the most significant personal factor. Environmental factors include respiratory allergens, diet, infections, cigarette smoke, and air pollution (2).

Upon inhalation, skin contact, or oral ingestion of antigens, the body becomes sensitized due to the activation of mast cells and the production of vasoactive mediators in the tissues. When the sensitized body is exposed to the allergen a second time, vasodilation, increased vascular permeability, and mucus secretion occur. These mediators cause AR in the nasal mucosa, allergic asthma in the lungs, and urticaria on the skin. Diagnosing these diseases involves supporting the findings from the patient's history and physical examination with laboratory tests (3-5).

The skin prick test (SPT) is a widely used, easy, rapid, and reliable method for diagnosing allergies (6,7). A positive skin test indicates the presence of specific immunoglobulin (Ig) E on dermal mast cells (8). SPT is a crucial diagnostic tool for detecting allergen sensitivity due to its safety, relatively easy application, and low cost (9).

This study aims to evaluate the relationships between age groups, presenting complaints, identified allergen sensitivities, and clinical diagnoses in patients who underwent SPT in University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital's Pediatric Allergy Unit between March 2012 and February 2014.

Materials and Methods

This study included patients who were followed up with diagnoses of asthma, AR, and AD and underwent SPT in the Pediatric Allergy and Immunology Unit of University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital between March 2012 and February 2014. Skin prick tests were performed on all patients by a pediatric immunology and allergy specialist, and the results were evaluated by the same physician. Histamine (1.0 mg/mL) was used as a positive control, and standard saline was used as a negative control. All results were evaluated at the 20th minute, when the reaction was at its peak. If the largest diameter of the resulting induration was 3 mm or larger, the positive control was 3 mm or larger, and there was no reaction at the negative control application site, the prick test was considered positive. After obtaining ethical committee of University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital approval, the results of the skin prick tests conducted were retrospectively evaluated (approval date: 05.05.2014, decision number: 2014/07/33).

Statistical Analysis

Statistical analyses in this study were performed using NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA). In evaluating the data, descriptive statistical methods (mean, standard deviation) were used, as well as One-Way Analysis of Variance for comparisons between groups, independent t-test for comparisons between two groups, and chi-square and Fisher's exact tests for qualitative data comparisons. The results were evaluated at a significance level of $p<0.05$.

Results

The study included the prick test results of 2413 cases conducted between March 1, 2012, and February 28, 2014, at the Pediatric Allergy and Immunology Clinic of University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital. The ages of the cases ranged from 1.7 to 17.5 months, with a mean age of 7.76±2.93 months. Of the cases, 990 (41.03%) were female, and 1423 (58.97%) were male. The mean age for female cases is 7.77±2.88 years (2-16.66 years), while for male cases, the mean age is 7.76±2.97 years (1.75-17.53 years).

Examining the initial presenting complaints, cough was noted in 2145 patients (88.9%), wheezing in 938 patients (38.8%), and nasal symptoms in 1385 patients (57.4%). The occurrence of cough or wheezing as the initial complaint was significantly more common in patients with asthma and asthma+AR (p=0.0001). Nasal symptoms were more frequently observed as the presenting complaint in patients with AR and asthma+AR, also showing statistical significance (p=0.0001) (Table 1).

Among the 2413 evaluated SPT results, 576 were negative. The remaining 1837 tests revealed sensitivity to at least one allergen. In our study, house dust mites were the most frequently detected allergens, with a higher prevalence

in patients diagnosed with both asthma and AR, showing statistical significance ($p<0.05$). The distribution of allergen sensitivities by diagnosis is shown in Table 2.

In 39 patients who underwent SPT, AD was also present in addition to their existing diagnoses. Of these, 26 were male and 13 were female. Among asthmatic patients, 19 (1.8%) also had AD. Among AR patients, 12 (6.5%) had AD, and among those with both asthma and AR, 8 (0.7%) had AD.

In the evaluation of patients with positive allergen sensitivity according to their symptoms, the most common presenting complaint was cough, followed by nasal symptoms. Wheezing was found at a higher rate in patients with cat and dog epithelium sensitivity compared to other allergen sensitivities. The distribution of symptoms according to allergen sensitivities is presented in Table 3.

Table 1. Distribution of initial presenting complaints according to diagnoses

Initial complaint	Asthma (n, %)	AR (n, %)	Asthma + AR (n, %)	p
Cough	978 (91.9%)	107 (57.5%)	1060 (91.2%)	0.0001[a]
Wheezing	439 (41.2%)	19 (10.2%)	480 (41.3%)	0.0001[a]
Nasal symptoms	404 (37.9%)	150 (80.6%)	831 (71.5%)	0.0001[a]

[a]: Chi-square test, AR: Allergic rhinitis

Table 2. Distribution of allergen sensitivities according to diagnoses in patients undergoing skin prick tests (%)

Allergen	Asthma (n, %)	AR (n, %)	Asthma + AR (n, %)	p	AD (n, %)	p	Total (n, %)
Dermatophagoides farinae	554 (52.07)	88 (47.31)	740 (63.63)	**0.0001[a]**	19 (48.72)	0.277	1401 (58.06)
Dermatophagoides pteronyssinus	560 (52.63)	89 (47.85)	738 (63.46)	**0.0001[a]**	20 (51.28)	0.431	1407 (58.30)
Grass pollens	455 (42.76)	80 (43.01)	650 (55.89)	**0.0001[a]**	16 (41.03)	0.307	1201 (49.77)
Trees-1 (early flowering)	394 (37.03)	69 (37.10)	520 (44.71)	**0.001**	18 (46.15)	0.486	1001 (41.48)
Trees-2 (mid-season flowering)	267 (25.09)	38 (20.43)	365 (31.38)	**0.0001[a]**	4 (10.26)	**0.014[b]**	674 (27.93)
Weed pollens	181 (17.01)	21 (11.29)	229 (19.69)	**0.013**	7 (17.95)	0.990	438 (18.15)
Grass and cereal pollens	146 (13.73)	23 (12.37)	196 (16.85)	0.067	3 (7.69)	0.191	368 (15.25)
Molds	125 (11.75)	17 (13.5)	157 (13.5)	0.171	1 (2.56)	0.060	300 (12.43)
Cat epithelium	3 (0.28)	1 (0.54)	15 (1.29)	**0.025[b]**	0 (0)	0.575	19 (0.78)
Dog epithelium	1 (0.09)	0 (0)	13 (1.12)	**0.004[b]**	0 (0)	0.630	14 (0.58)
Budgerigar feathers	110 (10.34)	12 (6.45)	108 (9.29)	0.231	3 (7.69)	0.693	233 (9.65)
Cockroach	98 (9.21)	9 (4.84)	111 (9.55)	0.111	2 (5.13)	0.390	220 (9.11)

[a]: Independent t-test, [b]: Fisher's exact test, AR: Allergic rhinitis, AD: Atopic dermatitis

Table 3. Symptom distribution according to allergen sensitivities (%)

Allergen (n)	Cough (n, %)	Wheezing (n, %)	Nasal symptoms (n, %)
Dermatophagoides farinae (1384)	1209 (87.35)	541 (39.08)	873 (63.07)
Dermatophagoides pteronyssinus (1389)	1212 (87.25)	544 (39.16)	881 (63.42)
Grass pollens (1186)	1026 (86.50)	453 (38.19)	763 (64.33)
Trees-1 (early flowering) (1398)	859 (61.44)	388 (27.75)	530 (37.91)
Trees-2 (mid-season flowering) (671)	589 (87.77)	270 (40.23)	426 (63.48)
Weed pollens (431)	377 (87.47)	162 (37.5)	261 (60.55)
Grass and cereal pollens (365)	309 (84.65)	137 (37.53)	238 (65.20)
Molds (299)	255 (85.28)	107 (35.78)	187 (62.54)
Cat epithelium (19)	16 (84.21)	13 (68.42)	11 (57.89)
Dog epithelium (14)	13 (92.85)	9 (64.28)	13 (92.85)
Budgerigar feathers (230)	209 (90.86)	82 (35.65)	150 (65.21)
Cockroach (218)	201 (92.20)	79 (36.23)	129 (59.17)

Discussion

In recent years, there has been a significant increase in the prevalence of allergic diseases and asthma. To compare studies on this subject, the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaires have been used (10,11). ISAAC surveys from different regions have reported wide variations in the prevalence of allergic diseases and asthma, with rates observed at 20% in the Unites States of America, 1.6% in Indonesia, and 36.8% in the United Kingdom (12). The increase in allergic diseases has been attributed to high socioeconomic status and good hygiene conditions, though genetic predisposition and environmental factors also play a role in the etiology along with the hygiene hypothesis (13,14).

SPT is a widely used, inexpensive, easy, quick, and reliable diagnostic method for allergic diseases. The primary purpose of performing SPT is to evaluate type I hypersensitivity reactions in the skin. Histamine plays a major role in the allergic skin test response. Many allergens in our environment, such as house dust, pollens, molds, and animal epithelia, can cause disease in sensitive individuals. SPT results can be used to map allergen sensitivity.

In our study, we retrospectively evaluated the SPT results of 2413 patients performed between March 2012 and February 2014 at University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital. SPT was negative in 23.8% of patients, while 76.2% showed sensitivity to at least one allergen. Nam and Lee (15) found a general positive SPT response rate of 59.8% in patients over the age of 10, with most allergen sensitivities decreasing with age. Şahiner et al. (16) reported a positive SPT rate of 35.1%. In İstanbul, Küçükosmanoğlu et al. (17) found a 17.2% positivity rate in children's allergy skin tests, while İğde et al. (18) reported a rate of 45.9% in the Central Black Sea Region. The positivity rates of SPT in various regions of our country have ranged from 17% to 64% (3,17-22). In terms of diagnoses, 44% of the patients were diagnosed with asthma, 7.7% with AR, and 58.9% with both asthma and AR. Kulalert et al. (23) conducted a study in Thailand between 2020-2021 with 688 children. They found that 667 children (96.95%) were diagnosed with allergic rhinitis (AR) and 209 children (30.38%) with asthma. According to the DPT (skin prick test) results, more than 95% positivity was observed (23).

In a study by Topal et al. (22), the most common aeroallergens in children diagnosed with asthma and AR in the Malatya Region were grass/cereal pollen mixtures (48.9%) and weed pollen mixtures (48.5%). Additionally, 44.1% of patients had eosinophilia, and 69.6% had total IgE levels ≥100 IU/dL (22). The high sensitivity to grass/cereal pollens in hot and dry regions explains the frequent detection of this sensitivity in the Malatya Region. Similarly, studies in hot and dry climates have also found the most common sensitivity to be to grass/cereal pollens.

In a study conducted by Canbal (20) the most frequent sensitivity among children with allergic asthma and AR in the Karaman Region was found to be to wild grasses at a rate of 26.4%. Among the patients with allergic reactions to wild grass pollens, 80% showed positivity for meadow grass and couch grass. Allergens were classified into indoor and outdoor allergens, with the highest sensitivity indoors being to house dust mites (14.1%) (20). These mites, which are strong immunogens, are more commonly found in poorly ventilated, cramped, energy-efficient homes. In the same region, a study by Şahiner et al. (16) revealed that grass was the most frequently encountered allergen, followed by house dust mites. In our study, sensitivity to grass pollen was found to be 63.63%, to weed pollen 19.69%, and to grass and cereal pollen 16.85%. In Nassikas et al.'s (24) study, the relationship between pollen sensitivity and lung function was evaluated, and it was shown that concomitant diagnoses of asthma and AR in patients with pollen sensitivity affected their lung functions.

In our study, the most common positive response was to house dust mites (*D. pteronyssinus* 57.48% and *D. farinae* 57.27%). Two different studies conducted in China have shown that the most commonly detected aeroallergens were *D. pteronyssinus* and *D. farinae*. In these studies, it was found that sensitivity to *D. pteronyssinus* and *D. farinae* was significantly higher in males and in patients diagnosed with both asthma and AR (25,26). In the Central Black Sea Region, İğde et al. (18) found the highest allergen sensitivity to be 97% for house dust mites, with no significant differences in allergen frequency among various respiratory allergic diseases. The frequency of sensitivity to house dust mites in atopic individuals was found to be normally distributed at 52.5±13.44% across Turkey (18). Katotomichelakis et al. (27) also found house dust mites to be the most common aeroallergen sensitivity in children with AR in Northeast Greece.

In the Eastern Black Sea Region, Ayvaz et al. (3) reported the highest positive rates in SPT results for grass and weed pollens, followed by house dust mites. The high prevalence of house dust mites in the Black Sea Region, along with the region's vegetation and climate conditions, explains the

frequent positive results for grass, weed, tree, and house dust mite pollens (3).

Similar findings to our study were observed by Küçükosmanoğlu et al. (17) in İstanbul, where house dust mites were the most common sensitivity, followed by grass pollens. The study emphasized the importance of indoor allergens in the development of asthma due to children's increased time spent indoors and the direct impact of indoor factors on the respiratory system (17).

Araz's (19) evaluation of children with chronic cough showed that 57.1% of patients had sensitivity to at least one allergen. The data were expected to contribute to the identification of allergen distribution in the region and provide insights into the etiology of chronic cough (19).

In adults, a study found sensitivities of 71% to mites, 42% to molds, and 36% to grass pollens. A negative correlation between age and sensitivity to grass pollens was reported. The study also found sensitivities of 32% to cockroaches, 22% to animal epithelia, and 42% to molds, with a close relationship between molds, animal epithelia, and asthma (28). In a study conducted by Khreesha et al. (29) in Jordan, olive pollen was identified as the most common allergen in both pediatric and adult populations. The study also demonstrated that sensitivity to aeroallergens decreased with increasing age (29).

Çölgeçen et al. (30) showed that aeroallergens, through inhalation or direct skin contact, exacerbated the disease in some patients with AD, with clinical symptoms reducing after allergen exposure ceased. The study recommended first investigating triggering agents, followed by SPT or specific IgE antibody testing. In patients with AD, 73.2% showed sensitivity to wheat pollen, attributed to the prevalence of farming in the region (30). In the study by Wongpiyabovorn et al. (31), it was observed that house dust mites, specifically *D. pteronyssinus* and *D. farinae*, showed a high level of correlation between the SPT results and specific IgE levels. Baykan et al. (32) found rye pollen sensitivity to be the second most common after grass pollen, linked to the frequent harvesting of rye in the Central Anatolia Region.

Although SPT results have a sensitivity close to 100%, their specificity remains around 50%, necessitating support from specific IgE measurements.

Karabulut et al. (33) evaluated SPT results based on meteorological and demographic characteristics and found that 46.1% of patients were housewives, 9.6% were healthcare workers, 18.1% were teachers, and 26.3% were from other professions. The most common sensitivities were to tree pollen mixtures (49.7%) and grass pollen mixtures (48.6%). House dust mite sensitivity (60.7%) was second among housewives, attributed to frequent exposure to indoor allergens. Sensitivity to tree pollens was highest during months with low humidity and rainfall. Nasal and eye symptoms were significantly higher among housewives and healthcare workers, while respiratory and skin symptoms were common among housewives. Correlations were found between nasal itching and headache with house dust mites, and eye symptoms with year-round allergens like house dust, cockroaches, molds, and egg whites (33).

Conclusion

In conclusion, our study found the most common allergen sensitivity to be against house dust mites and grass pollen. SPT results reflect the characteristics of the regions where they are performed. Identifying aeroallergen sensitivity in children diagnosed with asthma, AR, and AD using SPT plays a key role in their treatment and follow-up.

Ethics

Ethics Committee Approval: After obtaining ethical committee of University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital approval, the results of the skin prick tests conducted were retrospectively evaluated (approval date: 05.05.2014, decision number: 2014/07/33).

Informed Consent: Informed consent was obtained from all individual participants included inthe study.

Footnotes

Authorship Contributions

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

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

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ORIGINAL RESEARCH

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Corticosteroid Use in Severe COVID-19 and Factors Associated with Secondary Infection and Mortality Among Patients Admitted to the Intensive Care Unit

Yoğun Bakım Ünitesinde Takip Edilen COVID-19 Hastalarında Kortikosteroid Kullanımının Sekonder Enfeksiyon Üzerine Etkisi

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Abstract

Objective: To assess the outcomes of corticosteroid usage in Coronavirus disease-2019 (COVID-19) patients treated in the intensive care unit (ICU) and determine factors associated with secondary infection and mortality.

Method: This retrospective analysis involved data from patients admitted to the ICU for COVID-19 treatment between April 1, 2020, and December 31, 2021. The medical records of 114 patients who received corticosteroids and the records of 94 patients who did not, were comprehensively reviewed, and information about demographic characteristics, clinical features, and laboratory results was recorded.

Results: The 28-day mortality rate was 52.9% (n=110), the overall mortality was 61.5% (n=128), and secondary infection occurred in 52.9% (n=110) of COVID-19 ICU patients. Steroid users had longer ICU stays (p=0.001), longer intubation periods (p<0.001), a higher need for positive inotropic therapy (p<0.001), and higher APACHE II scores (p=0.014). Overall mortality was higher in steroid recipients (p=0.001), while 28-day mortality was similar (p=0.061). The frequency of secondary infections in COVID-19 ICU patients was significantly higher in the steroid group (p=0.003). Multivariable logistic regression analysis indicated that extended ICU stays [odds ratio (OR): 1.174] and prolonged intubation (OR: 1.317) were independently associated with secondary infections. Similarly, older age (OR: 1.079), need for renal replacement therapy (OR: 7.600), need for positive inotropic therapy (OR: 25.627), and high SOFA score (OR: 1.528) were independently associated with mortality.

Öz

Amaç: Yoğun bakım ünitesinde (YBÜ) tedavi gören Koronavirüs hastalığı-2019 (COVID-19) hastalarında kortikosteroid kullanımının sonuçlarını değerlendirmek ve ikincil enfeksiyon ve mortalite ile ilişkili faktörleri belirlemektir.

Yöntem: Bu retrospektif analiz, 1 Nisan 2020-31 Aralık 2021 tarihleri arasında COVID-19 tedavisi için kabul edilen hastaların verilerini içermektedir. Kortikosteroid alan 114 ve almayan 94 hastanın tıbbi kayıtları kapsamlı bir şekilde incelenerek demografik özellikleri, klinik özellikleri ve laboratuvar sonuçlarına ilişkin bilgiler kaydedildi.

Bulgular: Hastaların 28 günlük mortalite oranı %52,9 (n=110), genel mortalite %61,5 (n=128) ve sekonder enfeksiyon %52,9 (n=110) olarak gerçekleşti. Steroid kullananlarda yoğun bakımda kalış süresi (p=0,001) daha uzun, entübasyon süreleri (p<0,001) daha uzun, pozitif inotropik tedavi ihtiyacı daha yüksek (p<0,001) ve APACHE II skorları daha yüksekti (p=0,014). Genel mortalite steroid alanlarda daha yüksekti (p=0,001), 28 günlük mortalite ise benzerdi (p=0,061). COVID-19 yoğun bakım hastalarında sekonder enfeksiyon sıklığı steroid grubunda anlamlı olarak daha yüksekti (p=0,003). Çok değişkenli lojistik regresyon analizi, yoğun bakımda uzun süreli kalış süresinin [olasılık oranı (OO): 1,174] ve uzun süreli entübasyonun (OO: 1,317) ikincil enfeksiyonlarla bağımsız olarak ilişkili olduğunu gösterdi. Benzer şekilde ileri yaş (OO: 1,079), renal replasman tedavisi ihtiyacı (OO: 7,600), pozitif inotropik tedavi ihtiyacı (OR: 25,627) ve yüksek SOFA skoru (OO: 1,528) bağımsız olarak mortaliteyle ilişkiliydi.

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Abstract

Conclusion: According to the findings of the study, although corticosteroid use in severe COVID-19 cases does not appear to increase the risk of secondary infections or mortality, the decision to use corticosteroids should be made with careful consideration of the patient's clinical condition. Additionally, more comprehensive and in-depth studies on the use of corticosteroids in COVID-19 patients are needed.

Keywords: Anti-inflammatory agents, Coronavirus infections, COVID-19, COVID-19 drug treatment, dexamethasone, methylprednisolone

Öz

Sonuç: Çalışmanın bulgularına göre, şiddetli COVID-19 olgularında kortikosteroid kullanımı sekonder enfeksiyon veya mortalite riskini artırmıyor gibi görünse de, kortikosteroid kullanım kararı olgunun klinik durumuna göre titizlikle verilmelidir. Ayrıca, COVID-19 hastalarında kortikosteroid kullanımına dair daha geniş kapsamlı ve derinlemesine araştırmalara ihtiyaç duyulmaktadır.

Anahtar kelimeler: Anti-enflamatuar ajanlar, COVID-19, COVID-19 da kullanılan ilaç tedavileri, deksametazon, Koronavirüs enfeksiyonu, metilprednizolon

Introduction

The clinical presentation of Coronavirus disease-2019 (COVID-19) ranges from asymptomatic/mild respiratory disease to severe pneumonia, hypoxemic lung failure, multi-system organ dysfunction, and death (1). Studies performed early in the pandemic demonstrated that acute respiratory distress syndrome (ARDS) occurred in approximately 17-41% of cases (2,3), while cytokine release syndrome was also implicated in severe COVID-19 (4). Furthermore, postmortem data showed that patients who died due to COVID-19 had high levels of inflammatory cytokines, tissue necrosis and interstitial macrophage and monocyte infiltrations in the lung, heart and gastrointestinal mucosa (5). Even during the initial waves of the pandemic, these data showed the importance of alleviating extreme immune activity in COVID-19, which encouraged trials focusing on anti-inflammatory therapies (4). Various agents have been used for this purpose, including immunoglobulin, colchicine, janus kinase inhibitor inhibitors, interleukin (IL)-6 inhibitors, IL-1 inhibitors, anti-tumor necrosis factor-α agents, and corticosteroids (6).

Corticosteroids, which exert broad anti-inflammatory effects, are potent immunomodulatory medications that alleviate hyperinflammation (7). Initially, the World Health Organization (WHO) and infectious disease authorities had recommended avoiding systemic corticosteroids in COVID-19 patients due to limited improvements in mortality and the fact that prior studies involving patients with severe Middle-East respiratory syndrome (MERS) had shown delayed RNA clearance with glucocorticoids (8,9). Today, WHO recommends corticosteroids in severe or critical COVID-19 patients, especially in COVID-19 cases requiring respiratory support (10,11). This shift in guidance emerged as a result of numerous studies and meta-analyses that shared clinical evidence for the benefits of corticotherapy in patients with severe COVID-19 (2,7,12,13). Nonetheless, for the beneficial use of corticosteroids, COVID-19 patients need to be well targeted because patients requiring low-flow oxygen do not appear to experience the same benefits as those receiving ventilation or high-flow oxygen support (14).

As the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) virus continues to mutate over time, the possible role of glucocorticoids in different virus mutations will remain a topic of interest [15). Reviewing evidence to offer insights into the efficacy and safety of corticosteroids in the evolving landscape of COVID-19 can provide valuable guidance for future clinical interventions. In this study, we aimed to investigate the relationship between corticosteroids and clinical outcomes in patients followed up in the intensive care unit (ICU) due to COVID-19.

Materials and Methods

The medical records of patients diagnosed with COVID-19 who were admitted to the ICU of our Anesthesia Department, between 1 April 2020 and 31 December 2021, were examined. Inclusion criteria were: Having at least one positive SARS-CoV-2 polymerase chain reaction test in nasopharyngeal or oropharyngeal swab samples; being followed up in the ICU; and being 18 years of age or older. Exclusion criteria were pregnancy, malignancy, immunodeficiency, chronic organ failure, being in the postoperative period, receiving immunosuppressive/anti-cytokine therapy, secondary infection before treatment, culture growth in the ICU, ICU stay of less than 48 hours, and age younger than 18 years. The study plan was approved by the University of Health Sciences Turkey, Kanuni Sultan Süleyman Training and Research Hospital, Clinical Research Ethics Committee (date/number: February 2022/#2022/34).

The medical records of the patients were examined in detail, and information on demographic characteristics, clinical features, and laboratory results relative to patients with and without corticosteroid therapy in addition to standard

treatment were recorded. Baseline values of laboratory measurements (IL-6, D-dimer, ferritin, fibrinogen) were recorded and longitudinal samples were assessed to determine the lowest, highest, and average values for several inflammatory parameters [C-reactive protein (CRP), procalcitonin, complete blood count parameters]. The emergence of secondary infection and mortality (28-day mortality and total mortality) was recorded as outcomes of interest.

All patients included in the study received the standard care specified in the COVID-19 treatment guideline published by the Ministry of Health, and the COVID-19 anticytokine, anti-inflammatory treatment guideline. Favipiravir, as antiviral treatment, and low molecular weight heparin as deep vein thrombosis prophylaxis were administered to all patients without contraindications. Corticosteroid treatment was initiated in patients with ARDS whose clinical condition worsened and whose oxygen demand or acute phase reactants had increased. The standardized daily therapy was 300 mg methylprednisolone or 56.3 mg dexamethasone (equivalent to 1500 mg hydrocortisone). According to respiratory symptoms and peripheral partial oxygen saturation values, patients were given oxygen support with a face mask, reservoir mask, or high-flow nasal cannula. When these interventions were inadequate, patients received non-invasive or invasive mechanical ventilation support. Fluid therapy was administered according to the fluid status of the patient, and vasopressor support was initiated in patients who did not respond to fluid therapy. Blood, urine, tracheal aspirate, and, if necessary, wound site cultures were obtained when there were findings suggestive of secondary infection (new onset fever, leukocyte count of ≥12,000, procalcitonin value of ≥0.5). The results of these cultures were recorded, and the patients received empirical antibiotic therapy to cover detected or possible microorganisms.

APACHE II Score

The APACHE II score developed by Knaus et al. (16) is widely used to assess disease severity and mortality in patients hospitalized in intensive care units. A total score is calculated using the acute physiologic score, age, and parameters indicating chronic disease status. Although the theoretical maximum score is 71, it is rarely seen above 50. An increase in the total score indicates a negative change in health status and is associated with an increased risk of mortality (16).

Sequential Organ Failure Assessment (SOFA)

SOFA was developed by the European Society of Intensive Care Medicine in 1996 to assess the acute morbidity of critical illness by defining the degree of organ failure due to sepsis. A total score can be calculated by summing the scores given to six organ systems (respiratory, cardiovascular, central nervous system, renal, coagulation, and liver) ranging from 0 to 4. The total score can be up to 24, and mortality increases as the score increases (17).

Statistical Analysis

Two-tailed p-values of less than 0.05 were considered statistically significant. SPSS version 25.0 (IBM, Armonk, NY, USA) was used for statistical analysis. The Kolmogorov-Smirnov test was used to examine the conformity of the variables to normal distribution. Descriptive statistics were presented using median (25^{th}-75^{th} percentile) for non-normally distributed continuous variables and frequency (percentage) for categorical variables. Due to non-normal distributions, continuous variables were analyzed with the Mann-Whitney U test. Categorical variables were analyzed with the Pearson chi-square test or Fisher's Exact test. Logistic regression analyses were performed to determine significant factors independently associated with secondary infection or mortality. Variables were analyzed using univariable logistic regression , and statistically significant variables were included in multivariable logistic regression.

Results

A total of 208 COVID-19 patients treated in the ICU were included in this study. One hundred-fourteen (54.8%) had received steroid treatment and 94 (45.2%) had not received steroid treatment. Overall, 59.1% were male, 40.9% were female, and the median age was 68 (55-76) (range: 27-89) years. The 28-day mortality rate was 52.9% (n=110), the overall mortality was 61.5% (n=128), and the secondary infection rate was 52.9% (n=110). Length of ICU stay and intubation were 12 (2-57) days and 6 (0-57) days, respectively. Age (p=0.788) and sex distribution (p=0.653) were similar in the steroid and non-steroid groups. The frequency of comorbidities (p=0.029), especially neurological disease (p=0.020), was higher in the non-steroid group. The length of ICU stay (p=0.001), the length of intubation (p<0.001), and the frequency of needing positive inotropic therapy (p<0.001) were higher in steroid users. While the overall mortality rate was significantly higher in the steroid group (p=0.001), the groups were similar in terms of 28-day mortality rate (p=0.061). APACHE II score, was significantly higher in the steroid group (p=0.014), while there was no

difference in terms of SOFA score (p=0.968). There was no difference between the groups in terms of baseline values for CRP (0.393), procalcitonin (p=0.338), leukocyte count (p=0.965), neutrophil count (p=0.390), IL-6 (p=0.313), D-dimer (p=0.501), ferritin (p=0.071) and fibrinogen (p=0.096). Baseline lymphocyte (p=0.001) and monocyte counts (p<0.001) were lower in the steroid group (Table 1).

Table 1. Summary of demographics, outcomes and laboratory measurements with regard to steroid use

		Steroid use		
	All patients (n=208)	**No (n=94)**	**Yes (n=114)**	**p**
Age	68 (55-76)	67 (54-76)	68 (55-76)	0.788
Sex				
Male	123 (59.1%)	54 (57.5%)	69 (60.5%)	0.653
Female	85 (40.9%)	40 (42.5%)	45 (39.5%)	
Comorbidity (1)	164 (78.9%)	81 (86.2%)	83 (72.8%)	0.029
Cardiovascular diseases	118 (56.7%)	60 (63.8%)	58 (50.9%)	0.061
Endocrine disorders	75 (36.1%)	37 (39.4%)	38 (33.3%)	0.368
Respiratory diseases	44 (21.2%)	21 (22.3%)	23 (20.2%)	0.834
Organ failure	22 (10.6%)	13 (13.8%)	9 (7.9%)	0.247
Neurological diseases	32 (15.4%)	21 (22.3%)	11 (9.7%)	0.020
Others*	12 (5.7%)	4 (4.3%)	8 (7.0%)	0.581
Length of stay in ICU, days	12 (7-20)	10.5 (5-18)	13 (10-23)	0.001
Duration of intubation, days	6 (0-13.5)	2 (0-11)	9 (2-16)	<0.001
Renal replacement therapy need	51 (24.5%)	20 (21.3%)	31 (27.2%)	0.409
Positive inotropic therapy need	131 (63.0%)	46 (48.9%)	85 (74.6%)	<0.001
28-days mortality	110 (52.9%)	43 (45.7%)	67 (58.8%)	0.061
Overall mortality	128 (61.5%)	46 (48.9%)	82 (71.9%)	0.001
APACHE II score	21.5 (15.0-29.0)	19.0 (14.0-29.0)	24.5 (18.0-30.0)	0.014
SOFA score	5.0 (4.0-8.5)	5.5 (4.0-9.0)	5.0 (4.0-8.0)	0.968
CRP				
Baseline	138.0 (79.9-224.4)	129.3 (68.2-214.4)	140.2 (84.1-232.1)	0.393
Lowest	39.0 (17.2-86.4)	59.71 (23.9-139.9)	28.2 (14.2-51.9)	<0.001
Highest	241.8 (145.4-346.9)	233.8 (121.5-349.9)	248.4 (162.8-338.5)	0.294
Average	122.61 (76.6-191.9)	144.0 (78.9-211.2)	114.2 (74.2-161.9)	0.106
Procalcitonin				
Baseline	0.32 (0.14-1.00)	0.31 (0.16-0.97)	0.33 (0.12-1.02)	0.338
Lowest	0.14 (0.07-0.39)	0.19 (0.08-0.55)	0.10 (0.06-0.29)	0.014
Highest	3.13 (0.52-14.36)	2.42 (0.31-13.30)	4.53 (0.85-14.87)	0.302
Average	1.02 (0.22-3.67)	0.76 (0.20-4.50)	1.13 (0.24-3.25)	0.902
Leukocyte (x10^3)				
Baseline	9.5 (7.1-13.6)	9.3 (7.4-13.6)	9.8 (6.8-13.6)	0.965
Lowest	7.0 (5.2-9.0)	7.0 (5.1-9.2)	7.02 (5.4-9.0)	0.900
Highest	16.9 (11.6-24.4)	14.3 (10.2-21.7)	21.7 (13.7-26.7)	<0.001
Average	11.4 (8.8-15.3)	10.3 (7.9-13.7)	12.0 (9.7-16.0)	0.011
Neutrophil (x10^3)				
Baseline	8.1 (5.7-13.1)	8.0 (6.1-11.5)	8.7 (5.4-13.2)	0.390
Lowest	5.6 (3.7-7.6)	5.1 (3.2-7.9)	5.7 (4.5-7.5)	0.285
Highest	15.6 (10.3-22.4)	12.7 (8.5-19.6)	19.8 (13.2-23.63)	<0.001
Average	10.0 (7.1-14.1)	8.6 (5.7-12.6)	10.2 (7.9-14.8)	0.004

Table 1. Continued

		Steroid use		
	All patients (n=208)	**No (n=94)**	**Yes (n=114)**	**p**
Lymphocyte (x10³)				
Baseline	0.70 (0.60-1.15)	0.95 (0.60-1.40)	0.70 (0.60-0.90)	0.001
Lowest	0.40 (0.30-0.65)	0.60 (0.40-0.90)	0.30 (0.30-0.50)	<0.001
Highest	1.80 (1.10-2.90)	1.65 (1.10-2.40)	1.90 (1.10-2.90)	0.182
Average	1.07 (0.65-1.28)	1.09 (0.73-1.61)	1.02 (0.60-1.07)	0.001
Monocyte (x10³)				
Baseline	0.38 (0.27-0.63)	0.48 (0.34-0.78)	0.34 (0.25-0.48)	<0.001
Lowest	0.25 (0.16-0.39)	0.33 (0.21-0.50)	0.21 (0.13-0.29)	<0.001
Highest	0.91 (0.66-1.35)	0.91 (0.57-1.29)	0.90 (0.67-1.35)	0.474
Average	0.59 (0.40-0.74)	0.65 (0.43-0.82)	0.57 (0.38-0.70)	0.059
LDH, baseline	473.5 (328-651.5)	383 (295-560)	531 (366-695)	<0.001
IL-6, baseline	96.5 (44.3-235.6)	84.0 (43.3-207.2)	97.5 (48.1-275.6)	0.313
D-dimer, baseline	1.9 (1.0-4.3)	2.1 (1.0-4.6)	1.8 (1.0-3.9)	0.501
Ferritin, baseline	650.4 (318.8-1302.0)	540.8 (234.9-1224.0)	732.95 (362.9-1370.0)	0.071
Fibrinogen, baseline	580.5 (442-729)	519 (426-681)	589 (479-738)	0.096

Descriptive statistics were presented by using median (25th-75th percentile) for non-normally distributed continuous variables and frequency (percentage) for categorical variables. (1) Patients may have more than one of the followings.
*Others: Rheumatologic disease, Behçet's disease, psychiatric disease, Down syndrome, multiple myeloma, prostate hyperplasia, ICU: Intensive care unit, IL: Interleukin, LDH: Lactate dehydrogenase, CRP: C-reactive protein, SOFA: Sequential Organ Failure Assessment

The frequency of secondary infection was significantly higher in the steroid group (p=0.003). There was no difference between the groups in terms of blood culture positivity (p=0.169), but urine culture positivity (p=0.035) and *Klebsiella pneumoniae* in urine culture (p=0.001) were more common in steroid recipients. The frequency of tracheal culture positivity (p=0.001) and *Klebsiella pneumoniae* presence in tracheal cultures (p<0.001) was significantly higher in steroid recipients (Table 2).

Multivariable logistic regression revealed that longer stay in the ICU [odds ratio (OR): 1.174, 95% confidence interval (CI): 1.070-1.287, p=0.001] and longer intubation duration (OR: 1.317, 95% CI: 1.150-1.509, p<0.001) were independently associated with secondary infection likelihood. In the univariate analysis, corticosteroid use was found to be associated with an increased risk of secondary infections, while in the multivariate analysis, no significant relationship was observed between corticosteroid use and the risk of secondary infections (OR: 0.828, 95% CI: 0.329-2.084, p=0.689) (Table 3).

Multivariable logistic regression revealed that higher age (OR: 1.079, 95% CI: 1.027-1.134, p=0.003), need for renal replacement therapy (OR: 7.600, 95% CI: 1.380-41.843, p=0.020), need for positive inotropic therapy (OR: 25.627, 95% CI: 6.261-104.902, p<0.001), and high SOFA score (OR: 1.528, 95% CI: 1.098-2.125, p=0.012) were independently associated with mortality likelihood. While corticosteroid use was found to increase mortality in the univariate analysis, it was not identified as one of the factors influencing mortality in the multivariate analysis (OR: 2.005, 95% CI: 0.579-6.944, p=0.272) (Table 4).

Discussion

The COVID-19 pandemic has placed an unforeseen burden on the global health system, requiring the world to react quickly to find different solutions, both for preventive and therapeutic purposes. One of the agents used for this purpose is a corticosteroid, which has strong anti-inflammatory properties (18). Systemic glucocorticoids are not routinely indicated in COVID-19, and their use is limited to cases with severe complications such as ARDS or the so-called "cytokine storm" (19). In this study, we examined a group of patients who were admitted for severe COVID-19 and received steroids (or not) based on available guidelines. We also investigated factors associated with mortality and secondary infections. Our data showed that steroid recipients had longer ICU stay and intubation periods, as well as higher APACHE II scores and increased inflammatory parameters. Notably, steroid recipients also had higher frequencies of positivity for urine and tracheal cultures - largely as a result of increased *Klebsiella*

Table 2. Summary of secondary infection and culture results with regard to steroid use

		Steroid use		
	All patients (n=208)	**No (n=94)**	**Yes (n=114)**	**p**
Secondary infection	110 (52.9%)	39 (41.5%)	71 (62.3%)	0.003
Blood culture positivity (1)	62 (29.8%)	23 (24.5%)	39 (34.2%)	0.169
Acinetobacter baumannii	13 (6.3%)	5 (5.3%)	8 (7.0%)	0.829
Klebsiella pneumoniae	30 (14.4%)	9 (9.6%)	21 (18.4%)	0.108
Corynebacterium spp.	3 (1.4%)	1 (1.1%)	2 (1.8%)	1.000
Candida spp.	21 (10.1%)	9 (9.6%)	12 (10.5%)	1.000
Pseudomonas aeruginosa	1 (0.5%)	0 (0.0%)	1 (0.9%)	1.000
Escherichia coli	3 (1.4%)	0 (0.0%)	3 (2.6%)	0.253
Enterococcus spp.	4 (1.9%)	2 (2.1%)	2 (1.8%)	1.000
Staphylococcus spp.	8 (3.9%)	3 (3.2%)	5 (4.4%)	0.732
Enterobacter spp.	1 (0.5%)	1 (1.1%)	0 (0.0%)	0.452
Others*	1 (0.5%)	1 (1.1%)	0 (0.0%)	0.452
Urine culture positivity (1)	63 (30.3%)	21 (22.3%)	42 (36.8%)	0.035
Acinetobacter baumannii	3 (1.4%)	1 (1.1%)	2 (1.8%)	1.000
Klebsiella pneumoniae	19 (9.1%)	1 (1.1%)	18 (15.8%)	0.001
Corynebacterium spp.	1 (0.5%)	1 (1.1%)	0 (0.0%)	0.452
Candida spp.	26 (12.5%)	8 (8.5%)	18 (15.8%)	0.171
Pseudomonas aeruginosa	1 (0.5%)	1 (1.1%)	0 (0.0%)	0.452
Escherichia coli	8 (3.9%)	4 (4.3%)	4 (3.5%)	1.000
Enterococcus spp.	7 (3.4%)	5 (5.3%)	2 (1.8%)	0.248
Staphylococcus spp.	2 (1.0%)	1 (1.1%)	1 (0.9%)	1.000
Enterobacter spp.	4 (1.9%)	1 (1.1%)	3 (2.6%)	0.628
Others	1 (0.5%)	0 (0.0%)	1 (0.9%)	1.000
Tracheal aspirate culture (1)	74 (35.6%)	22 (23.4%)	52 (45.6%)	0.001
Acinetobacter baumannii	19 (9.1%)	8 (8.5%)	11 (9.7%)	0.967
Klebsiella pneumoniae	36 (17.3%)	6 (6.4%)	30 (26.3%)	<0.001
Corynebacterium spp.	5 (2.4%)	4 (4.3%)	1 (0.9%)	0.178
Candida spp.	23 (11.1%)	6 (6.4%)	17 (14.9%)	0.084
Pseudomonas aeruginosa	3 (1.4%)	1 (1.1%)	2 (1.8%)	1.000
Escherichia coli	4 (1.9%)	1 (1.1%)	3 (2.6%)	0.628
Enterococcus spp.	1 (0.5%)	1 (1.1%)	0 (0.0%)	0.452
Staphylococcus spp.	5 (2.4%)	2 (2.1%)	3 (2.6%)	1.000
Enterobacter spp.	1 (0.5%)	0 (0.0%)	1 (0.9%)	1.000
Others	4 (1.9%)	0 (0.0%)	4 (3.5%)	0.128

Descriptive statistics were presented using frequency (percentage) for categorical variables. (1) Culture positivity counts are based on culture specimens and are calculated separately; thus, total numbers exceed patient counts.
*Others: Proteus mirabilis, moellerella wisconsensis, stenotrophomonas maltophilia, blastoschizomyces capitatus, gemella haemolysans, stenotrophomonas maltophilia

pneumoniae prevalence. Finally, the multivariate analyses revealed that steroid use was not independently associated with the development of secondary infections or mortality.

A meta-analysis of 20,197 patients reported that findings from both observational studies and randomized controlled trials confirmed the beneficial effect of corticosteroids on reducing the need for mechanical ventilation (12). Despite the presence of several large studies and meta-analyses on the topic, there are various studies with notable outcomes and notable findings. Tomazini et al. (20) reported that there was no difference in the duration of mechanical ventilation at 28 days with dexamethasone use among COVID-19 patients with moderate/severe ARDS. Sarkar et al. (21) reported that systemic steroid treatment was not effective in reducing the length of hospital stay. In a study

Table 3. Odds ratios for secondary infection, logistic regression analysis results

	Univariable		Multivariable	
	OR (95% CI)	p	OR (95% CI)	p
Age	1.012 (0.993-1.032)	0.209		
Sex, Female	1.276 (0.732-2.225)	0.389		
Any comorbidity	1.158 (0.595-2.254)	0.666		
Cardiovascular diseases	1.226 (0.708-2.125)	0.467		
Endocrine disorders	0.870 (0.494-1.534)	0.630		
Respiratory diseases	0.685 (0.351-1.337)	0.268		
Organ failure	0.879 (0.363-2.127)	0.775		
Neurological diseases	0.872 (0.411-1.853)	0.722		
Other comorbidity	1.264 (0.388-4.119)	0.697		
Length of stay in ICU, days	1.245 (1.167-1.329)	<0.001	1.174 (1.070-1.287)	0.001
Duration of intubation, days	1.416 (1.291-1.552)	<0.001	1.317 (1.150-1.509)	<0.001
Renal replacement therapy need	2.692 (1.365-5.308)	0.004	1.360 (0.444-4.161)	0.590
Positive inotropic therapy need	10.907 (5.515-21.574)	<0.001	1.644 (0.558-4.839)	0.367
Steroid use	2.329 (1.332-4.070)	0.003	0.828 (0.329-2.084)	0.689
APACHE II score	1.005 (0.980-1.032)	0.682		
SOFA score	1.125 (1.030-1.229)	0.009	1.025 (0.872-1.205)	0.765
CRP, baseline	1.005 (1.002-1.008)	0.001	1.002 (0.997-1.007)	0.445
Procalcitonin, baseline	1.012 (0.982-1.043)	0.431		
Leukocyte ($x10^3$), baseline	0.991 (0.947-1.036)	0.685		
Neutrophil ($x10^3$), baseline	1.006 (0.959-1.055)	0.805		
Lymphocyte ($x10^3$), baseline	0.783 (0.488-1.256)	0.310		
Monocyte ($x10^3$), baseline	0.690 (0.336-1.415)	0.311		
LDH, baseline	1.000 (0.999-1.001)	0.655		
IL-6, baseline	1.000 (1.000-1.000)	0.362		
D-dimer, baseline	1.023 (0.990-1.058)	0.176		
Ferritin, baseline	1.000 (1.000-1.000)	0.727		
Fibrinogen, baseline	1.000 (0.999-1.001)	0.587		
Nagelkerke R^2	-		0.699	

OR: Odds ratio, CI: Confidence interval, ICU: Intensive care unit, IL: Interleukin, LDH: Lactate dehydrogenase, CRP: C-reactive protein, SOFA: Sequential Organ Failure Assessment

conducted by Emgin et al. (22) with COVID-19 patients in the ICU, the length of stay was reported to be longer in patients who received dexamethasone treatment. In the present study, ICU stay, intubation duration, need for positive inotropic therapy, and APACHE-II score were higher in steroid-treated patients. These relationships are not surprising as the present study included patients who had severe COVID-19 (admitted to the ICU) and steroid recipients were those who required advanced treatment due to their clinical and laboratory prognosis.

Secondary bacteremia is an important complication that can lead to a poor prognosis in COVID-19 patients and requires an appropriate treatment strategy, especially for patients with concomitant predisposing factors. Given that steroids can frequently obscure infection indicators by reducing body temperature and levels of acute phase proteins like CRP, it is essential to be cautious about potential secondary infections and conduct thorough assessments when employing steroid treatment for COVID-19 (23). Contrary to the results of a previous study evaluating the follow-up of MERS coronavirus infection in the ICU (8), no increased risk of bacterial infection or delayed viral clearance was reported when using corticosteroids in managing COVID-19 patients requiring oxygen support (7,19). Corticosteroids are reported to be important options in criticallyill COVID-19 patients, particularly since they have been suggested to have no impact on secondary infection (24). Similarly, Abelenda-Alonso et al.

Table 4. Odds ratios for mortality, logistic regression analysis results

	Univariable		Multivariable	
	OR (95% CI)	p	OR (95% CI)	p
Age	1.050 (1.027-1.073)	<0.001	1.079 (1.027-1.134)	0.003
Sex, female	1.153 (0.652-2.040)	0.624		
Any comorbidity	2.056 (1.049-4.031)	0.036	0.713 (0.138-3.675)	0.686
Cardiovascular diseases	1.322 (0.753-2.322)	0.331		
Endocrine disorders	0.987 (0.552-1.765)	0.964		
Respiratory diseases	0.779 (0.397-1.531)	0.469		
Organ failure	0.892 (0.363-2.193)	0.803		
Neurological diseases	1.728 (0.755-3.953)	0.195		
Other comorbidity	1.267 (0.369-4.352)	0.707		
Length of stay in ICU, days	1.024 (0.995-1.054)	0.107		
Duration of intubation, days	1.219 (1.144-1.298)	<0.001	1.041 (0.965-1.122)	0.302
Renal replacement therapy need	3.853 (1.756-8.451)	0.001	7.600 (1.380-41.843)	0.020
Positive inotropic therapy need	35.385 (16.009-78.209)	<0.001	25.627 (6.261-104.902)	<0.001
Steroid use	2.674 (1.505-4.751)	0.001	2.005 (0.579-6.944)	0.272
Seconder infection	7.105 (3.775-13.372)	<0.001	0.977 (0.220-4.336)	0.976
APACHE II score	1.075 (1.039-1.113)	<0.001	1.016 (0.949-1.087)	0.656
SOFA score	1.526 (1.315-1.771)	<0.001	1.528 (1.098-2.125)	0.012
CRP, baseline	1.007 (1.003-1.010)	<0.001	1.004 (0.998-1.011)	0.193
Procalcitonin, baseline	0.974 (0.931-1.019)	0.255		
Leukocyte ($x10^3$), baseline	1.008 (0.962-1.056)	0.735		
Neutrophil ($x10^3$), baseline	1.018 (0.968-1.070)	0.490		
Lymphocyte ($x10^3$), baseline	0.983 (0.817-1.183)	0.860		
Monocyte ($x10^3$), baseline	0.362 (0.166-0.790)	0.011	0.402 (0.060-2.710)	0.349
LDH, baseline	1.003 (1.001-1.004)	<0.001	1.000 (0.998-1.002)	0.988
IL-6, baseline	1.000 (1.000-1.000)	0.618		
D-dimer, baseline	1.041 (0.998-1.086)	0.063		
Ferritin, baseline	1.000 (1.000-1.000)	0.707		
Fibrinogen, baseline	1.003 (1.001-1.004)	0.001	1.002 (0.999-1.006)	0.232
Nagelkerke R^2	-		0.775	

OR: Odds ratio, CI: Confidence interval, ICU: Intensive care unit, IL: Interleukin, LDH: Lactate dehydrogenase, CRP: C-reactive protein, SOFA: Sequential Organ Failure Assessment

(25) reported that there was no association between steroid use and the development of nosocomial bloodstream infections in patients with severe COVID-19 pneumonia. In a study evaluating the outcomes of COVID-19 patients admitted to the ICU in two different hospitals, it was reported that immunosuppressive treatments such as steroids and tocilizumab were not associated with an increased risk of bacteremia. In addition, it was reported that those who developed bacteremia among COVID-19 patients in the ICU had a higher SOFA score, were intubated more frequently and for longer durations, stayed in the ICU longer, and had higher mortality (26). In the present study, although the prevalence of secondary infection was found to be higher in steroid recipients compared to non-recipients, in multivariable analysis, we found that this increase in secondary infection was independently associated with longer ICU stay and longer intubation. There was no independent relationship between steroid use and the risk of secondary infection. Our results are consistent with the information in the literature. However, this does not change the fact that the decision to use corticosteroids should be made cautiously to prevent the risk of secondary infections. This is because there are also studies in the literature reporting opposite results. In a study evaluating COVID-19 patients admitted to an ICU, dexamethasone treatment was associated with a threefold

increase in the risk of pulmonary aspergillosis (27). In a retrospective study, it was reported that steroid treatment increased the risk of non-respiratory nosocomial bacterial infections, while male sex, advanced age, and ICU need were found to be risk factors for bacteremia (23). Of note, both studies centered around specific pathogens (23,27) which may explain the differences in results. In addition, prophylactic antimicrobial treatment protocols can vary from institution to institution, and it is possible that other factors contributed to these conflicting findings, including drug access, management guidelines, and antibiotic resistance patterns.

In COVID-19, corticosteroids (dexamethasone, hydrocortisone or methylprednisolone) have been reported to increase the chances of survival (7). The RECOVERY study was the first to evaluate the effect of dexamethasone treatment on mortality in COVID-19 patients who required oxygen therapy or mechanical ventilation. The authors reported that 28-day mortality was lower with dexamethasone (6 mg once daily for up to 10 days) in patients who received invasive mechanical ventilation or oxygen support; but no difference was found in patients without respiratory support (2). In a prospective meta-analysis by the WHO Rapid Evidence Assessment for COVID-19 Treatments Working Group, evaluating data from 12 countries from February 26, 2020 to June 9, 2020, it was reported that systemic corticosteroids were associated with lower 28-day all-cause mortality in patients with critical COVID-19 compared to usual care or placebo (13). In another retrospective study of COVID-19 patients in the ICU, corticosteroid administration was found to significantly reduce the likelihood of 28-day mortality (24). A recent meta-analysis evaluating the results of fifteen randomized controlled trials reported that in patients with severe and critical COVID-19, glucocorticoid therapy reduced the risk of all-cause mortality compared to conventional therapy, but no difference was found in those with mild disease (15). In another meta-analysis, mortality was shown to be significantly reduced with the use of corticosteroids (12). In the present study, mortality was higher in severe COVID-19 cases with steroid use in univariate analyses. However, in the multivariable model, this significance disappeared, and the use of steroids in treatment was not one of the factors independently affecting the risk of mortality. Factors identified included higher age, higher SOFA score, need for positive inotropic drugs, and need for renal replacement therapy. There are other studies reporting similar results. In a meta-analysis evaluating the efficacy and safety of steroids in COVID-19 (with data from randomized controlled trials and cohorts), there was no association between systemic glucocorticoid use and mortality in COVID-19 patients (21). Tomazini et al. (20) reported no difference in 28-day mortality among recipients and non-recipients of dexamethasone therapy after being diagnosed with moderate or severe ARDS. In contrast, a previous meta-analysis reported that overall mortality increased with the use of glucocorticoids in hospitalized patients who did not need respiratory support (28). Despite varying levels of evidence and partially conflicting results, it is evident that corticosteroids should not be used in COVID-19 cases that do not require respiratory support, but this therapy must be considered in patients requiring respiratory support. In patients requiring respiratory support, particularly those with advanced age, renal replacement therapy, positive inotropic therapy, and high SOFA scores, the decision to use corticosteroids should be made with caution. The variables included in the model used for the analyses may have influenced the results obtained in the study. Additionally, differences in the type, dose, and duration of corticosteroid protocols may further explain the heterogeneity in the reported evidence.When reviewing the existing literature regarding the use of steroids in COVID-19 cases, it is clear that physicians must exercise caution when making decisions about steroid utilization. The primary determining factor for initiating corticosteroid therapy in COVID-19 appears to be the requirement for respiratory support and overall clinical condition. Nonetheless, the decision for corticosteroid treatment should not be solely based on the severity of disease, but should also include consideration of the benefits and risks on a case-by-case basis (19). Although corticosteroids are currently widely used in the treatment of severe COVID-19 patients on respiratory support, many aspects of their use, such as the preferred agent, optimal dose and duration of treatment, are yet to be clarified (7). In addition, we believe that it is important to continuously update the information on this issue. It should be noted that the use of steroids in this population may have negative effects on both mortality and secondary infections. To better prepare for future outbreaks and reduce mortality among COVID-19 patients, a global effort is essential to develop novel treatments targeting both the clinical aspects of COVID-19 and the hyperinflammatory response triggered by the infection.

Study Limitations

This study has notable limitations, including its retrospective and single-center design, which restricts the generalization of results. A significant constraint is the absence of specific

data regarding the decision to administer steroids to COVID-19 ICU patients. The variation in clinical severity between patient groups may have influenced the findings. Additionally, the study did not investigate different types, doses, or durations of corticosteroid treatment. The study also did not consider various SARS-CoV-2 variants. Despite these limitations, the data provide valuable insights into corticosteroid use in treating severe COVID-19 cases.

Conclusion

Our results demonstrated that while corticosteroid use in critically ill COVID-19 patients was associated with increased mortality and secondary infections in univariate analyses, this association was not confirmed in multivariate analyses. The primary independent factors contributing to an increased risk of secondary infections were identified as prolonged ICU stay and extended duration of intubation. Furthermore, advanced age, the need for renal replacement therapy, the requirement for positive inotropic support, and a high SOFA score were determined to be independent predictors of increased mortality. In this context, it can be concluded that decisions regarding the use of corticosteroids in severe COVID-19 cases should be made with careful consideration of the individual clinical condition of each patient. To assess whether the effects of corticosteroid use are influenced by SARS-CoV-2 variants or other factors, broader and more comprehensive prospective studies involving various viral variants are needed.

Ethics

Ethics Committee Approval: The study plan was approved by the University of Health Sciences Turkey, Kanuni Sultan Süleyman Training and Research Hospital, Clinical Research Ethics Committee (date/number: February 2022/#2022/34).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: P.K.E., E.K., A.S.Ş., Concept: A.S.Ş., Design: A.S.Ş., Data Collection or Processing: P.K.E., Analysis or Interpretation: P.K.E., A.S.Ş., Literature Search: P.K.E., Writing: P.K.E., E.K., A.S.Ş.

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ORIGINAL RESEARCH

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The Role of Colposcopy in Women with Normal Cytology and High-risk Human Papilloma Virus Positivity, Except for Types 16 and 18

Normal Sitolojisi Olan ve Tip 16 ve 18 Dışında Yüksek Riskli İnsan Papilloma Virüsü Pozitifliği Olan Kadınlarda Kolposkopinin Rolü

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Abstract

Objective: The main objective of present study was to evaluate the role of colposcopy in women with normal cytology and positivity for high risk human papilloma virus (HPV), except types 16 and 18.

Method: A retrospective analysis was conducted on a cohort of women who presented to the clinic for colposcopy between January 2018 and December 2023. These women had normal cytology and positivity for high risk HPV, except types 16 and 18. The demographic data and colposcopy results were obtained from the patient files and the electronic database of the gynaecological oncology clinic.

Results: A total of 1,646 women underwent colposcopy during the specified period. Four hundred-thirty (26.1%) women exhibited positivity for high risk HPV, except types 16 and 18, and normal cytology. A total of 41 patients (9.5%) were found to have cervical intraepithelial neoplasia (CIN)2+ (CIN2, CIN3, or invasive cancer) lesions. Among 41 women with CIN2+ lesions, 22% were found to have multiple infections, 17% had HPV other-x (subgroup could not be obtained), 17% had HPV type 31, and 12% had HPV type 51 positivity. The detection rate of CIN2+ lesions was highest in the group of women with HPV 31 positivity. Cervical biopsy and endocervical biopsy, revealed CIN2+ lesions in 21.7% (n=5/23) and 8.7% (n=2/23) of women with HPV type 31 positivity, respectively.

Conclusion: Women with high-risk HPV (except types 16 and 18) and normal cytology have a significantly increased risk of high-grade cervical lesions.

Keywords: Cervical cancer, cervical screening, cervical precancerous lesions, colposcopy, human papilloma virus

Öz

Amaç: Bu çalışmanın ana amacı, sitolojisi normal olan ve tip 16-18 dışı yüksek riskli human papilloma virüs (HPV) pozitifliği olan kadınlarda kolposkopinin rolünü değerlendirmektir.

Yöntem: Ocak 2018 ile Aralık 2023 tarihleri arasında kliniğe kolposkopi için başvuran kadınlardan oluşan bir kohort üzerinde retrospektif bir analiz yapılmıştır. Çalışmaya dahil edilen kadınların sitolojileri normaldi ve tip 16-18 dışı yüksek riskli HPV pozitifliği vardı. Demografik veriler ve kolposkopi sonuçları hasta dosyalarından ve jinekolojik onkoloji kliniğinin elektronik veri tabanından elde edildi.

Bulgular: Belirtilen dönem arasında toplam 1.646 kadına kolposkopi yapılmıştır. Dört yüz otuz (%26,1) kadında tip 16-18 dışı yüksek riskli HPV pozitifliği ve normal sitoloji saptandı. Kırk bir (%9,5) hastada servikal intraepitelyal neoplazi (CIN)2+ (CIN2,CIN2 ya da inavziv kanser) lezyon saptandı. CIN2+ lezyonu olan 41 kadının %22'sinde çoklu enfeksiyon, %17'sinde HPV diğer-x (alt grup tespit edilemedi), %17'sinde HPV tip 31 ve %12'sinde HPV tip 51 pozitifliği saptandı. CIN2+ lezyonların saptanma oranı HPV 31 pozitifliği olan kadın grubunda en yüksekti. HPV tip 31 pozitifliği olan kadınların sırasıyla %21,7'sinde (5/23) ve %8,7'sinde (2/23) servikal biyopsi ve endoservikal küretaj materyalinde CIN2 lezyonlar saptanmıştır.

Sonuç: Anormal sitolojisi olmayan ve tip 16-18 dışı yüksek riskli HPV taşıyan kadınlarda, yüksek dereceli servikal preinvaziv lezyon riski belirgin şekilde artmaktadır.

Anahtar kelimeler: İnsan papilloma virüsü, kolposkopi, serviks kanseri, servikal prekanseröz lezyonlar, servikal tarama

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Introduction

Historically, the understanding of the pathogenesis of cervical cancer has led to the realisation, that the application of appropriate screening methods can facilitate the detection of precancerous lesions, thereby reducing the incidence of cervical cancer with early, appropriate interventions. The discovery of the Papanicolaou (Pap) smear by Dr. George Pap and the subsequent implementation of cervical cytology for cervical cancer screening demonstrated that the incidence of cervical cancer can be reduced. Furthermore, the identification of human papilloma virus (HPV) as a viral infectious agent strongly associated with cervical cancer facilitated the development of highly sensitive HPV screening tests with or without cervical cytology for cervical cancer screening (1).

HPV is a non-enveloped double-stranded DNA virus. To date, approximately 40 distinct HPV types with a proclivity for the anogenital region have been identified. Of these, 15 types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82) are classified as high-risk (HR), three types (26, 53, 66) are considered probable HR, and 12 types (6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, and 89) are classified as low-risk. HPV16 is associated with 50-60% of cervical cancers, while HPV18 is linked to 10-15%. The remaining HR HPV types are responsible for 25-40% of cervical cancer cases (2,3).

In the context of cervical cancer screening programmes, the majority of HPV tests examine 14 HR HPV genotypes. The combination of HR HPV positivity with cytological results has resulted in the formulation of a number of management guidelines. In this context, the American Society for Colposcopy and Cervical Pathology (ASCCP) published the initially proposed guidelines for the management of abnormal cervical cancer screening results in 2012 and subsequently updated these guidelines in 2019 (4,5). A review of cervical cancer screening programmes at the country level reveals that the majority of cases occur in women with HR HPV positivity and normal cytology results (6-8). In accordance with the aforementioned guidelines for the management of women with HR HPV positivity, the presence of HPV types 16 and 18 with normal cervical cytology necessitates a colposcopic examination. However, in the case of positivity for HR HPV, except types 16 and 18 (other HR HPV) and normal cervical cytology, a recommendation is made for retesting after a one-year interval (4,5). Nevertheless, the optimal management of women with positivity for other HR HPV and normal cytology remains a topic of contention.

A screening strategy based on repeated testing for women with positivity for other HR HPV may present a significant challenge due to low participation rates and loss to follow-up. Moreover, some studies have indicated that the risk of developing high-grade cervical lesions in patients with positivity for other HR HPV may be comparable or even higher than that of HPV type 18 (9,10). Additionally, the false-negative rate of cervical cytology has been reported to be approximately 15-65% (11). This high rate raises questions regarding the follow-up of cases that test positive for other HR HPV and have normal cytology after one year by non-invasive methods, given the possibility of an increased risk for cervical high-grade lesions and cervical cancer.

In order to address these concerns, a retrospective study was conducted to evaluate the role of colposcopy in women with normal cytology and positivity for other HR HPV. Furthermore, the association of positivity for other HR HPV with high-grade cervical lesions was discussed separately.

Materials and Methods

A retrospective analysis was conducted on women who had visited the clinic for colposcopy between January 2018 and December 2023. The cohort comprised women with positivity for other HR HPV and normal cytology. The age range was determined to be from 18 to 80 years. The patients were divided into three groups according to the HPV types: HPV other-x (patients for whom the HPV other subgroup could not be obtained), HPV multiple infection (patients with more than one HPV other subgroup), and HPV 31, HPV 33, etc. (patients positive for a single known HPV other subgroup).

The HPV test employed was Hybrid Capture 2 (Qiagen), which is the reference test routinely utilised in numerous laboratories. In cases where the Hybrid Capture2 (Qiagen) test indicated the presence of HPV, genotyping was conducted using the CLART kit (Genomica). The analysis excluded patients who had undergone hysterectomy, those diagnosed with gynaecological cancer, those younger than 18 years of age, those older than 80 years of age, and for whom colposcopy results were not available. Data on patients who underwent colposcopy in our institution were collected from patient files and the electronic database systems. The demographic data, including age, menopausal status, pathological results of colposcopically directed biopsies, and endocervical curettage (ECC) were obtained. The study was initiated following the approval of the Ethics Committee of the University of Health Sciences Turkey,

Antalya Training and Research Hospital, dated 10 October 2024 and numbered 2024-319. The study was conducted in accordance with the ethical principles set forth in the Declaration of Helsinki.

The colposcopic examination database was evaluated to ascertain whether the colposcopy was conducted adequately. All colposcopies were conducted by gynaecological oncologists during the specified period. A colposcopic evaluation was conducted subsequent to the administration of a 3% acetic acid solution to the cervix. Cervical biopsies were taken in the presence of lesions suspicious for cervical intraepithelial neoplasia (CIN) on colposcopic examination. Additionally, random biopsies were sometimes taken at the discretion of the colposcopist in the absence of abnormal colposcopic findings. When colposcopy was inadequate, ECC was performed in cases where the cervix was obscured by haemorrhage, inflammation, or scar tissue; when the squamocolumnar junction was not visible or only partially visible; when the transformation zone was type 3; or when the visualised lesion extended into the endocervical canal. Additionally, ECC was performed at the discretion of the colposcopist in the absence of the aforementioned factors. ECC was performed with a Novak curette, whereby the entire endocervical canal was scraped and subsequently processed as a histopathological specimen.

In this manuscript, the pathological results of the specimens, either cervical biopsies or ECC, were assessed in two categories in accordance with the threshold for treatment at our centre: Those below the CIN2 level and those at or above the CIN2 level, including CIN2, CIN3 and invasive cancer (CIN2+).

Statistical Analysis

SPSS version 22.0 was used for the analysis of the data. Descriptive statistics were used. The binary variables were reported as counts and percentages.

Results

A total of 1,646 women underwent colposcopy between the specified period. Of these, 333 (20.2%) women exhibited HPV 16/18 positivity and normal cytology, and 430 (26.1%) women exhibited positivity for other HR HPV and normal cytology. The data set comprised 430 women, obtained from the electronic records of the institution. The analysis was conducted on a total of 430 women. The median age of the cohort was 44 years (range, 30-65 years). Amongst the women whose menopausal status was known, 63% were premenopausal. The distribution of HPV subtypes is presented in Table 1.

The colposcopic findings were reported as normal in 207 women (48.1%), inadequate in 12 women (2.8%), and abnormal in 211 women (49.1%). A total of 41 (9.5%) patients were found to have CIN2+ lesions. Cervical biopsy revealed CIN2+ lesions in 29 women (6.7%), while ECC revealed CIN2+ lesions in 12 women (2.8%) (Tables 2, 3).

Table 1. The distribution of HPV subgroups

HPV type	n	(%)
HPV other-x*	110	25.6
HPV multiple**	125	29.1
HPV 31	23	5.3
HPV 52	31	7.2
HPV 56	22	5.1
HPV 35	16	3.7
HPV 33	7	1.6
HPV 51	36	8.4
HPV 68	12	2.8
HPV 45	14	3.3
HPV 39	11	2.6
HPV 58	18	4.2
HPV 59	5	1.2
Total	430	100

*: Patients whose HPV other subgroup couldn't be obtained, **: Patients who had more than one HPV other subgroups, HPV: Human papilloma virus

Table 2. The distribution of cervical biopsy results with regard to HPV subtypes

	Cervical biopsy, n (%)		
HPV type	Not performed	Negative	CIN2+CIN3
HPV other-x*	65 (59.1)	39 (35.5)	6 (5.5)
HPV multiple**	54 (43.2)	65 (52)	6 (4.8)
HPV 31	8 (34.8)	10 (43.5)	5 (21.7)
HPV 52	10 (32.3)	18 (58.1)	3 (9.7)
HPV 56	11 (50)	9 (40.9)	2 (9.1)
HPV 35	7 (43.8)	8 (50)	1 (6.3)
HPV 33	5 (71.4)	1 (14.3)	1 (14.3)
HPV 51	20 (55.6)	13 (36.1)	3 (8.3)
HPV 68	6 (50)	6 (50)	0 (0)
HPV 45	7 (50)	5 (35.7)	2 (14.3)
HPV 39	6 (54.5)	5 (45.5)	0 (0)
HPV 58	13 (72.2)	5 (27.8)	0 (0)
HPV 59	1 (20)	4 (80)	0 (0)
Total	213 (49.5)	188 (43.7)	29 (6.7)

*: Patients whose HPV other subgroup couldn't be obtained, **: Patients who had more than one HPV other subgroups, HPV: Human papilloma virus, CIN: Cervical intraepithelial neoplasia

No women presented with invasive cancer. Conization was recommended for 41 women (9.5%) and was performed on 34 women (7.9%).

Tables 2, 3 present the details of the cervical biopsy and ECC results with regard to HPV subtypes. Of the 41 patients with CIN2+ lesions, 22% were found to have multiple infections, 17% had HPV other-x (subgroup could not be obtained), 17% had HPV type 31, and 12% had HPV type 51 positivity. The detection rate of CIN2+ lesions was highest in the group of women with HPV 31 positivity. Cervical biopsy and ECC revealed CIN2+ lesions in 21.7% (n=5/23) and 8.7% (n=2/23) of women with HPV type 31 positivity, respectively (Tables 2, 3). Overall, a CIN2+ lesion was identified in seven (30.4%) of the 23 women with HPV type 31-positive disease.

Conization identified a CIN2+ lesion in 24 (72.7%) of the 34 women who underwent this procedure. The results of conisation according to the HPV subtypes are presented in Table 4.

Discussion

In the present study, CIN2+ lesions were identified in 41 of 430 (9.5%) women with positivity for other HR HPV and normal cervical cytology. Furthermore our study revealed that 17% of women with CIN2+ lesions were HPV type 31 positive, and that CIN2+ lesions developed in 7 (30.4%) of 23 patients with HPV type 31 positivity.

Table 3. The distribution of ECC results with regard to HPV subtypes

	ECC, n (%)		
HPV type	**Not performed**	**Negative**	**CIN2+CIN3**
HPV other-x*	36 (32.7)	73 (66.4)	1 (0.9)
HPV multiple**	29 (23.2)	91 (72.8)	5 (4)
HPV 31	8 (34.8)	13 (56.5)	2 (8.7)
HPV 52	6 (19.4)	25 (80.6)	0 (0)
HPV 56	5 (22.7)	16 (72.7)	1 (4.5)
HPV 35	2 (12.5)	14 (87.5)	0 (0)
HPV 33	0 (0)	6 (85.7)	1 (14.3)
HPV 51	5 (13.9)	29 (80.6)	2 (5.6)
HPV 68	3 (25)	9 (75)	0 (0)
HPV 45	5 (35.7)	9 (64.3)	0 (0)
HPV 39	5 (45.5)	6 (54.5)	0 (0)
HPV 58	4 (22.2)	14 (77.8)	0 (0)
HPV 59	1 (20)	4 (80)	0 (0)
Total	109 (25.3)	309 (71.9)	12 (2.8)

*: Patients whose HPV other subgroup couldn't be obtained, **: Patients who had more than one HPV other subgroups, HPV: Human papilloma virus, CIN: Cervical intraepithelial neoplasia, ECC: Endocervical curettage

Table 4. Pathology of conisation results according to HPV subgroups

	Pathology of conisation		Total
HPV type	**Negative**	**CIN2+**	
HPV other-x*	2 (28.6%)	5 (71.4%)	7 (100%)
HPV multiple**	2 (33.3%)	4 (66.7%)	6 (100%)
HPV 31	0 (0%)	5 (100%)	5 (100%)
HPV 52	2 (66.7%)	1 (33.3%)	3 (100%)
HPV 56	2 (66.7%)	1 (33.3%)	3 (100%)
HPV 35	0 (0%)	1 (100%)	1 (100%)
HPV 33	0 (0%)	1 (100%)	1 (100%)
HPV 51	0 (0%)	5 (100%)	5 (100%)
HPV 45	1 (50%)	1 (50%)	2 (100%)
Total	9 (27.3%)	24 (72.7%)	33 (100%)

*: Patients whose HPV other subgroup couldn't be obtained, **: Patients who had more than one HPV other subgroups, HPV: Human papilloma virus, CIN: Cervical intraepithelial neoplasia

In cervical cancer screening programmes, the most frequently observed positive screening results are HR HPV positivity with normal cytology. The rate in the literature ranged from 6.7% to 14.9% (12-15). In settings where colposcopy services are inadequate, referring women with HR HPV positivity, with normal cytology, to colposcopy will present a substantial challenge for healthcare systems. It is therefore of great importance to ensure that women who are to be referred for colposcopy are selected appropriately. In the present study, 20.2% of the women who were referred for colposcopy tested positive for HPV 16/18 and had normal cytology, while 26.1% tested positive for positivity for other HR HPV and had normal cytology. Although a higher proportion was identified in the present study than in previous literature, this was because only women who underwent colposcopy were included. Nevertheless, in the present study, a significant proportion of the total colposcopy load consisted of women with HR HPV positivity and normal cytology, as reported in the literature.

In the 2019 ASCCP guideline on risk-based management of abnormal cervical cancer screening results, the clinical action threshold for colposcopy was set at an immediate CIN3+ risk above 4%. In this guideline, the immediate risks of CIN 2+ and CIN 3+ lesions for women with HPV type 16 positivity and normal cytology are 7.82% and 5.30%, respectively, compared to 5.56% and 3% for women with HPV type 18 positivity and normal cytology, respectively (5). Although the immediate risk of CIN3+ for HPV type

18 positivity and normal cytology remains below the clinical action threshold for colposcopy, there is a rationale for excluding HPV18 as the second most important carcinogenic type. This is because HPV18 is linked to cervical adenocarcinoma, which is not effectively identified by cytology. In the present study, the rate of CIN2+ lesion detection in women with other HR HPV positivity was found to be 9.5%. A review of the literature revealed a considerable range in the reported rate, with figures varying between 5% and 15% (16-19). It is believed that this extensive range can be attributed to the number of patients included in the studies (97 to 1,332 women). However, it is hypothesised that a significant proportion of high-grade cervical lesions may go undetected in women with other HR positivity for HPV, and normal cytology, who do not undergo colposcopic examination.

In April 2014, the US Food and Drug Administration approved the cobas® 4800HPV test as an option for primary screening. This test provides genotyping information for HPV16/18 and also allows the identification of the other 12 high risk HPV types (20). The use of genotyping has enabled the determination of the prevalence of HR HPV genotypes in different geographical regions. The studies investigating the distribution of HR HPV genotypes in women with normal cervical cytology in Asian and African populations found that the five most frequently detected genotypes were 16, 52, 58, 18, and 33, and 16, 58, 52, 35 and 18, respectively (21,22). In the present study, the frequency distribution of the five most common HR positivity types of HPV in individuals with normal cytology was as follows: Multiple infection (29.1%), HPV other-x (genotyping could not be obtained) (25.6%), HPV type 51 (8.4%), HPV type 52 (7.2%), and HPV type 31 (5.3%). The identification of the distribution of oncogenic HR HPV genotypes in different regions highlights the need to develop management guidelines tailored to these variations. We believe this approach is crucial for the effective management of abnormal results from the cervical cancer screening programme, including women who are positive for other HR HPV, with normal cytology.

In the context of the development of precancerous and cancerous lesions, a comprehensive understanding of the geographical distribution of HR HPV genotypes, as well as their oncogenic potential, is of great importance. The prevalence of oncogenic HR HPV genotypes in precancerous and cancerous lesions can be employed as an indicator of oncogenic potential. In the present study, the most frequently identified other HR HPV genotypes in women with normal cytology and CIN2+ lesions were HPV multiple infection (26%), HPV other-x positivity (17%), HPV type 31 (17%) and HPV type 51 (12%), in descending order of prevalence. Furthermore, it is noteworthy that a CIN2+ lesion was identified in seven (30.4%) of the 23 women with HPV type 31-positive disease. The development of high-grade cervical lesions in women who are positive for other HR HPV types and normal cytology has been the subject of only a limited number of studies. However, in the majority of these studies, positivity for other HR HPV was grouped together, and their association with high-grade cervical lesions was subjected to statistical analysis as a single group (16,18,19). In accordance with the findings of the present study, a previous study conducted by Kabaca et al. (17) investigated women with normal cytology and positivity for other HR HPV. HPV type 31 and HPV type 51 positivity were observed in 19.5% and 10.6% of those with CIN2+ lesions, respectively. In studies conducted by Schiffman et al. (23) and Zhang et al. (24) on women with HR HPV infection and normal cytological findings, Schiffman et al. (23) observed that the most common HPV types after HPV type 16 in women with CIN3+ lesions were HPV types 31 and 52, with a frequency of 13.9% and 11.2%, respectively. Similarly, Zhang et al. (24) observed that the most common HPV types after HPV type 16 in women with CIN2+ lesions were HPV types 52 and 58, with a frequency of 13.7% and 12.7%, respectively (23). In the light of the data mentioned above, it can be suggested that some HR HPV genotypes may exhibit a higher prevalence and a greater oncogenic capacity than HPV type 18, considering both geographical distribution and oncogenic potential. Consequently, these genotypes with non-invasive methods may permit the omission of unnecessary follow-up procedures for cervical high-grade lesions. In this respect, the present study emphasises the need to reconsider the role of colposcopy in women with other HR HPV positivity and normal cytology, particularly HPV type 31, which has a comparable risk to HPV 18. It requires that these women be evaluated by colposcopy and, if suspected, cervical biopsies, rather than retesting by co-test one year later, contrary to current management guidelines.

Study Strengths

One of the strengths of the current study is that it is one of the few studies to specifically evaluate colposcopy outcomes in women with other HR HPV types positivity, and normal cytology.

Furthermore, the present study is important for understanding the distribution of other HR HPV genotypes

and their oncogenic potential, as it categorises other HR HPV genotypes into specific groups and subjects them to statistical analysis.

The present study contributes to the management of women infected with other HR HPV in the absence of abnormal cytology, as it presents data from a cohort of women referred for colposcopy from a specific region of Turkey, thereby providing valuable insights into the distribution of other HR HPV genotypes.

Study Limitations

The limitations of the present study are firstly, that the study population was relatively small and limited to patients admitted to a single center. As a result, the findings of the current study cannot be generalised beyond this context. Secondly, the retrospective design of the study did not allow for an adequate analysis of prognostic variables and management strategies.

Furthermore, HPV genotyping using the CLART kit (Genomica) revealed that a significant proportion of the study population exhibited a HR HPV type labeled as other-x (where the genotype could not be obtained), precluding the possibility of establishing a correlation with HPV-specific genotypes.

Conclusion

The risk of high-grade cervical preinvasive lesions is markedly increased in women positive for other HR HPV in the absence of abnormal cytology. It is crucial not to ignore this risk. The necessity of retesting these women after one year, in accordance with established guidelines, is open to question, particularly in view of regional differences in the incidence of HR HPV genotypes and the need to consider the capacity of individual genotypes to develop preinvasive lesions. The findings of this study indicate that, despite the potential increase in the number of colposcopies performed, referring women with normal cytology infected with other HR HPV to colposcopy results in a higher incidence of high-grade cervical preinvasive lesions being detected. It can be reasonably assumed that this will result in a reduction in the incidence of cervical cancer, which is the primary goal of cervical cancer screening programmes.

Ethics

Ethics Committee Approval: The study was initiated following the approval of the Ethics Committee of the University of Health Sciences Turkey, Antalya Training and Research Hospital, dated 10 October 2024 and numbered 2024-319. The study was conducted in accordance with the ethical principles set forth in the Declaration of Helsinki.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: N.Y., A.A., M.G., Me.G., T.T., I.Ü., Concept: N.Y., Me.G., T.T., I.Ü., Design: N.Y., A.A., M.G., T.T., I.Ü., Data Collection or Processing: N.Y., A.A., M.G., Me.G., Analysis or Interpretation: N.Y., Me.G., T.T., I.Ü., Literature Search: N.Y., A.A., M.G., Writing: N.Y., I.Ü.

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REVIEW

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Anesthetic Drug Used by Şerafeddin Sabuncuoğlu in the 15th Century: Murkid

15. Yüzyılda Şerafeddin Sabuncuoğlu'nun Kullandığı Anestezik İlaç: Mürkid

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Abstract

In this review, it was aimed to investigate Sabuncuoğlu's contributions to surgery and the anesthetic effects of almond (Amygdalus communis, Prunus dulcis, Prunus amygdalus) and Mandragora autumnalis plants in the mixture called murkid, which he used for anesthesia and analgesia during surgery, in terms of modern medical pharmacognosy. The surgical techniques that Sabuncuoğlu applied was investigated in the light of the literature in detail together with the mixture called Murkid. Using reference sources, it was investigated Sabuncuoğlu's contributions to surgery and the anesthetic effects of almond (Amygdalus communis, Prunus dulcis, Prunus amygdalus) and Mandragora autumnalis herbs in the mixture called murkid, in terms of modern medical pharmacognosy. Murkid is a mixture that was discovered hundreds of years ago and was found to be very effective when evaluated during its time. However, it is toxic if the dose is not adjusted. Also it has dose dependent side effects such as blurred vision, headache, skin rash, vomiting, and tachycardia. Almond is considered to be from the Latin species "Amygdalus communis" in the "Rosaceae" family. Bitter almond seeds should not be consumed. The seed contains "laetrile" known as vitamin B17 and antitumor "taxifolin". Its leaves are used in the treatment of diabetes. Sabuncuoğlu is a Turkish physician who successfully applied and transferred some of the surgical techniques and anesthesia practices used today from centuries ago, far ahead of his time. There is a need for studies on the use of the active ingredients contained in Murkid in the field of anesthesia in modern medicine.

Keywords: Anesthesia, history of medicine, Murkid, Şerafeddin Sabuncuoğlu

Öz

Bu derlemede, Sabuncuoğlu'nun cerrahiye katkıları ve cerrahi esnasında anestezi ve analjezi amaçlı kullanmış olduğu murkid adlı karışımdaki badem (Amygdalus communis, Prunus dulcis, Prunus amygdalus) ve adamotu (Mandragora autumnalis) bitkilerinin, modern tıbbi farmakognozi açısından, anestezik etkilerinin araştırılması amaçlanmıştır. Sabuncuoğlu'nun uyguladığı cerrahi teknikler, Murkid adı verilen karışımla birlikte literatür ışığında detaylı bir şekilde incelenmiştir. Referans kaynaklardan yararlanılarak Sabuncuoğlu'nun cerrahiye katkıları ve mürşit adı verilen karışımdaki badem (Amygdalus communis, Prunus dulcis, Prunus amygdalus) ve Mandragora autumnalis bitkilerinin anestezik etkileri modern tıbbi farmakognozi açısından araştırılmıştır. Murkid, yüzlerce yıl önce keşfedilen ve kendi döneminde değerlendirildiğinde oldukça etkili olduğu görülen bir karışımdır. Fakat doz ayarı yapılmadığında toksiktir. Ayrıca doza bağlı; bulanık görme, baş ağrısı, deride kızarıklık, kusma, taşikardi gibi yan etkilere sahiptir. Badem, "Rosaceae" familyasında yer alan latince "Amygdalus communis" türünden kabul edilmektedir. Badem çekirdeklerinin acı olanları tüketilmemelidir. Tohum B17 vitamini olarak bilinen "laetrile" ve antitümör "taksifolin"i içermektedir. Yaprakları diyabet tedavisinde kullanılmaktadır. Sabuncuoğlu, günümüzde kullanılan cerrahi tekniklerinin ve anestezi uygulamalarının bir kısmını zamanının çok ötesinde, yüzyıllar öncesinden başarı ile uygulamış ve nakletmiş bir Türk tıp adamdır. Murkid'in barındırdığı etken maddelerin modern tıpta anestezi alanında kullanımı ile ilgili çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Anestezi, Murkid, Şerafeddin Sabuncuoğlu, tıp tarihi

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Introduction

Şerafettin Sabuncuoğlu is an important Turkish physician who lived in Amasya between 1385 and 1468(?) in the Ottoman Empire period. In his time Amasya was one of the most important health centers. His grandfather Sabuncuoğlu Hacı İlyas Çelebi and his father Ali Çelebi were also chief physicians in Amasya before him. Medical developments in the Ottoman Empire continued as a legacy of the Seljuk Empire. At that time, medical madrasahs and hospitals were important institutions of health services. The hospital located in Amasya was called "Asylum", "Bimarhane", "Şifahane" among the people and in the 19th century it was converted just into "Asylum" that is psychiatric hospital (1,2).

Sabuncuoğlu contributed to the medical community with four of his works. Among his works, "Cerrahiyetü'l-Haniyye" is the most important. This work includes surgical instruments, devices and colorful pictures of surgical treatment techniques. An important feature of this work that, it is written in an clear Turkish. Because although he writes and reads in Persian and Arabic well, at that time the surgeons were illiterate and the Anatolian people mostly spoke Turkish. Although Cerrahiyetü'l-Haniyye is the first illustrated medical book in the Islamic world, it is known that it was inspired by Albucasis's surgery textbook Al-Tasrif. This book is dedicated to the Ottoman empirer of the period, Fatih Sultan Mehmet (3,4).

In terms of anesthesia and pain, Sabuncuoğlu recommends medical treatments for low back pain and sciatica, headache, toothache, sinusitis and eye pain (5). He used a herbal mixture called Murkid to provide superficial anesthesia for patients who needed surgery. Murkid, which is obtained by mixing the plant known as Mandrake among the people with almond oil, has analgesic and sedative characteristics.

According to the World Health Organization, approximately 80% of people all over the world still use herbs for their health problems. It is known that this rate is higher in developing countries such as Turkey (6). In this review it was aimed to investigate Sabuncuoğlu's contributions to surgery and the anesthetic effects of herbs almond (Amygdalus communis, Prunus dulcis, Prunus amygdalus) and Mandrake (Mandragora autumnalis), that in the mixture called murkid, which he used for anesthesia and analgesia during surgery, in terms of modern medical pharmacognosy.

Sabuncuoğlu's surgical techniques, he used in the light of the literature and discussed in his great work called "Cerrahiyetü'l-Haniyye", made a significant contribution to the surgical techniques of that time, were investigated in detail, as well as the mixture called Murkid, which he used and suggested for anesthesia centuries ago. This mixture consists of almond oil and Mandrake. Based on this content, almond extracts (oil) and Mandrake, which are widely used in various areas today, were evaluated in terms of its medical and traditional indications and the active ingredients and phytochemicals it contains, with reference to many herbal medicine monographs such as the Turkish Medicines and Medical Devices Agency (TITCK), pfaf.org (7-9).

Using reference sources, the anesthesia-analgesia and sedative effects of almond oil and Mandrake on human health were investigated. In addition to the medical use of these herbal extracts, their traditional uses, which are frequently used in different ways in almost every society and civilization as old as human history, are also taken into consideration.

Approximately 168 surgical instruments and 138 surgical and medical approaches were drawn or depicted in Cerrahiyetü'l-Haniyye. It contains cautery technique, some surgical procedures, orthopedic fractures/dislocations, and cream, lotion and pomade recipes from medical treatments. In terms of content, this work includes some neurology, urology, orthopedics, neurosurgery, ophthalmology, plastic reconstructive aesthetic surgery, general surgery, obstetrics, oncology, thoracic surgery, dermatology and algology treatments.

Murkid is a mixture that was discovered hundreds of years ago and was found to be very effective when evaluated during its time. Although murkid is not a medicine used directly today, it has historical importance and has contributed to medical developments. Almond is considered to be from the Latin species "Amygdalus communis" in the "Rosaceae" family. There are synonyms named Prunus amygdalus and Prunus dulcis. It is classified as morphologically and biologically in various ways. Bitter almond seeds should not be consumed. Today, the oil extracted from its seeds, is used for medicinal purposes. The seed contains "laetrile", known as vitamin B17, and antitumor "taxifolin". Its leaves are used in the treatment of diabetes. Almond oils are used for dry skin in aromatherapy. TITCK; recommends to use carefully in hypoglycemic patients and discontinue 2 weeks before surgery. There is a small amount of hydrogen cyanide in its leaves and seeds. Low doses of hydrogen cyanide stimulate breathing and improve digestion. It is also used in cancer treatment. However, high doses may cause respiratory arrest and death (2,10,11).

Mandrake is known as "adam otu" in Anatolia because its roots resemble humanbeing. Mandragora Autumnalis, commonly known as "Mandrake", is in the "Solanaceae" family. Only one species grows in Anatolia. Some authors consider it is the same as Mandragora Officinarum. Even though they are different species, they have similar effects because they are from the same subfamily. It contains hyoscyamine and scopolamine alkaloids. Thus, it also has anticholinergic, hypnotic and hallucinogenic effects. In the past, it was used to treat depression, mania, and stomach ulcers. It can cause amnesia and reduce bronchial secretion. Mandrake was used for surgical anesthesia until the 19th century. However, it is toxic if the dose is not adjusted. Also it has dose dependent side effects such as blurred vision, headache, skin rash, vomiting, and tachycardia (2,10,12).

Surgery and anesthesia have evolved together through centuries. The development of surgical techniques and the birth of modern anesthesia are in the same time. If we look at the content of Sabuncuoğlu's Cerrahiyetü'l-Haniyye from the perspective of today's modern medicine: In Sabuncuoğlu's studies in neurosurgery; on spinal dislocations, sciatic nerve, and approaches to back pain are shown with drawings (5,13). In general surgery treatments of hemorrhoids, anal fissure, perianal abscess, and inguinal hernia are depicted (14). The approach to the treatment of circumcision, urethral stenosis, imperforate anus, hypospadias, epispadias, urethral atresia, and perianal abscess in pediatric surgery are depicted and explained (15). Normal birth and manipulations related to obstetrics (16); treatment of upper and lower extremity fractures and dislocations related to orthopedics and traumatology (17) are explained with drawings. The treatment of rib fractures, pneumothorax, and sternal fractures related to thoracic surgery is written (18). In addition to the treatment of maxillofacial injuries, gynecomastia, and hermaphrodism diseases related to plastic reconstructive and aesthetic surgery (19), treatment methods of urological surgery (20,21) are described. Dermatological treatments (22), treatment of proptosis, hypopyon, chalazion and pannus in ophthalmic surgery (23) procedures related to the treatment of varicose veins (24) and approaches to oncological surgery (25) methods are explained. In addition; he described acupuncture points and application methods (26). Some of these treatments have continued to be used till today.

It was unthinkable that Sabuncuoğlu, who described many surgical techniques mentioned above, did not know the importance of anesthesia for surgical procedures. For this purpose, he described Murkid. The "Mandrake" in Murkid has been described before in the Hittite tablets, in Ancient Egypt, in ancient legends, in the famous Materia Medica of Diascorides, in the Bible and in Medieval Europe and also mentioned by Hippocrates. In many cultures it was associated with fertility. Mandrake, which has been the subject of many legends in the past due to its hallucinogenic effects, has a long medical history and superstitions played an important role during the time it was used. It was used by witches, especially in Europe. That is why it is less used today. Leaving aside its bad reputation, it can be used in the appropriate dosage and duration under the supervision of healthcare professionals (Figure 1) (27).

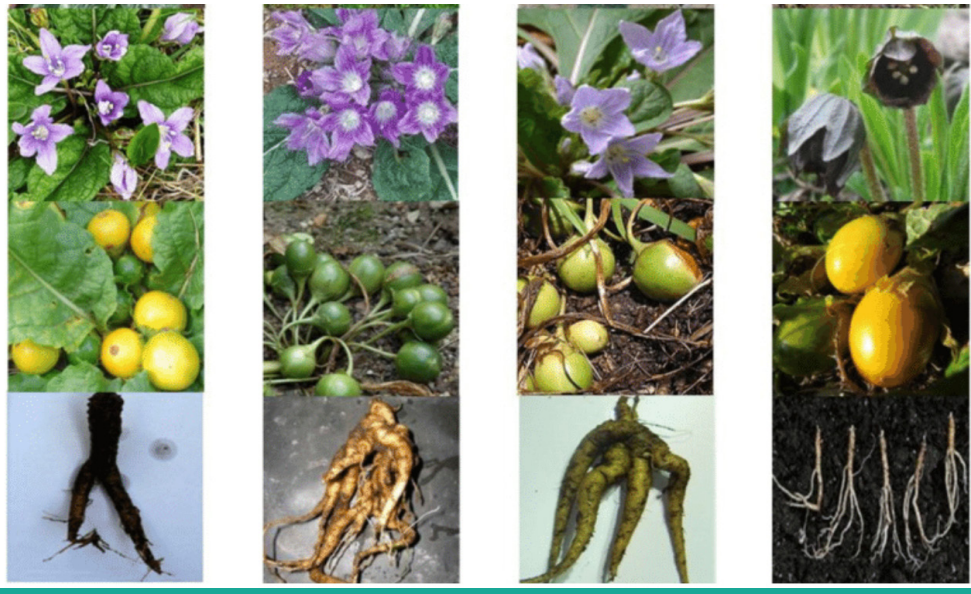

Figure 1. Different parts of *Mandragora officinarum* (28)

In this review when we examine the current pharmacognosy resources available, it is seen that medical practices, as in every field of science from past to present, are based on improving the previous ones. Sabuncuoğlu suggested that Murkid, which is a mixture of mandrake and almond oil, should be used for a certain dose and duration, the drug dose should be adjusted according to patient's weight, and stated that the patient should be followed up for a certain period after the surgical procedure. In this respect, it is seen that Şerafettin Sabuncuoğlu implemented some of the methods applied today and postoperative patient follow-up at that time (2,13).

Today, authors have stated that in the traditional medicinal use of both mandrake and almond (especially its seed), dose adjustments should be applied as with all medicines. Especially due to their high hydrogen cyanide content, it is stated that bitter ones of the almond seeds should not be consumed. When we examine the current monographs, it has been seen that the combined use of mandrake and almond oil has synergistic effects.

When we examine the ingredients, phytochemicals in the Murkid, it is seen that they are a perfect mixture according to the conditions of that time due to their sinergistic effects in terms of analgesia, amnesia, hypnotism, decreased secretion, blood glucose control and hemodynamic stabilization for both surgical intervention and anesthesia.

Conclusion

Sabuncuoğlu is a Turkish physician who has successfully applied and transplanted some of the surgical techniques and anesthesia practices used today, far ahead of his time, centuries ago. He continues to inspire today's scientists with the illumination of his works. There is a need for further studies on the use of the active ingredients contained in Murkid in the field of anesthesia in modern medicine.

Ethics

Footnotes

Authorship Contributions

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

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

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CASE REPORT

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A Rare Cause of Acute Kidney Injury Following Coronary Angiography: Cholesterol Crystal Embolus

Koroner Anjiyografi Sonrası Gelişen Akut Böbrek Hasarının Nadir Bir Nedeni: Kolesterol Kristal Embolisi

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Abstract

Cholesterol crystal embolus (CCE) is characterized by atheroembolization of the small vessels of the kidney, skin, brain, eye, gastrointestinal system, and extremities with crystal emboli originating from atherosclerotic plaques. It may develop spontaneously or after a cardiovascular intervention, other invasive procedures or subsequent to anticoagulant or thrombolytic therapy. Subacute renal injury is the most common clinical presentation. Skin involvement is the most frequent extrarenal manifestation associated with this condition. We present a case of CCE presented with subacute kidney injury following coronary angiography.

Keywords: Acute renal injury, cholesterol crystal embolus, coronary angiography

Öz

Kolesterol kristal embolisi (KKE), aterosklerotik plaklardan kaynaklanan kristal emboliler ile böbrek, deri, beyin, göz, gastrointestinal sistem ve ekstremitelerdeki küçük damarların ateroembolizasyonu ile karakterizedir. Kendiliğinden gelişebileceği gibi bir kardiyovasküler girişim, diğer invaziv işlemler ve antikoagülan veya trombolitik tedavi sonrasında da gelişebilir. Subaküt böbrek hasarı en sık görülen klinik tablodur. Bu tabloya eşlik eden böbrek dışı bulgular arasında en sık karşılaşılan bulgu deri tutulumudur. Biz koroner anjiyografi sonrası gelişen ve subakut böbrek yetmezliği ile prezente olan bir KKE olgusunu sunuyoruz

Anahtar kelimeler: Akut böbrek hasarı, kolesterol kristal embolisi, koroner anjiyografi

Introduction

Acute kidney injury (AKI) is characterized by a sudden deterioration of renal function, indicated by elevated serum creatinine levels and decreased urine output, especially oliguria. This condition typically lasts up to 7 days. Additionally, renal dysfunction may persist beyond the acute phase and can lead to the development of both acute and chronic kidney disease (1,2).

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Among three types of AKI, prerenal AKI is the most common subgroup, which accounts for 60% of all AKI, and is mainly associated with hypovolemia and develops as a result of the adaptation of structurally normal kidneys to reduced blood flow. Secondly, intrarenal AKI results from structural damage to the renal tubules, glomeruli, interstitium, or vasculature, and accounts for up to 40% of cases. Finally, less frequently, postrenal AKI occurs due to obstruction of the urinary outflow tract and constitutes 5% of all cases (3).

Cholesterol crystal embolization (CCE) is a multisystemic disease that occurs due to the rupture of atherosclerotic plaques, leading to the release of cholesterol crystals (CCs) and atheromatous material into the circulation. While it is most commonly induced iatrogenically by invasive procedures, it can also occur spontaneously. Embolized CCs become lodged in smaller arterioles, causing varying degrees of ischemia and triggering an inflammatory response in target organs. This process primarily affects the kidneys, skin, gastrointestinal system, and central nervous system (4).Despite significant variability among studies, the incidence of clinically apparent CCE has been reported to range from 0.09% to 2.9%. Autopsy studies have reported CCE in 0.31-2.4% of cases, though its prevalence is significantly higher (12-77%) in selected populations, particularly elderly patients who died following aortic surgery or aortography. CCE is frequently missed in many cases, and the actual incidence is probably much higher than what has been reported (5).

A case of CCE that develops after cardiovascular intervention is presented in this report. Written informed consent was received from the patient.

Case Report

A 59-year-old male patient presented to our emergency department with a complaint of dyspnea. He had a known history of smoking, along with diagnoses of diabetes mellitus, coronary artery disease, and hypertension. Three weeks before his admission, he underwent two consecutive coronary angiographies which were performed 2 days apart; the first for diagnostic purposes and the second for stent placement.

On physical examination, decreased breath sounds in the lower pulmonary segments and bilateral pretibial edema were noted. Laboratory tests revealed AKI and hyponatremia (urea: 165 mg/dL, creatinine: 5.6 mg/dL, sodium: 126 mmol/L). Thoracic tomography showed bilateral pleural effusion. The patient was hospitalized for evaluation and treatment with a preliminary diagnosis of acute kidney failure.

On the third day of hospitalization, the patient developed a blue discoloration on his fingernails and foot soles (Figure 1). Considering the patient's history of an angiographic intervention three weeks prior to hospital admission and subsequent initiation of antiplatelet therapy, the observed finding was deemed suggestive of blue toe syndrome (BTS) and potentially attributable to CCE. However, due to the history of acute coronary stent placement and ongoing clopidogrel therapy, renal biopsy was contraindicated for confirming the presence of CCE.

Since Hollenhorst plaques (HP) are specific for CCE and their diagnosis does not require an invasive procedure, an ophthalmology consultation was requested. Fundoscopic examination revealed three HP in the right eye (Figure 2).

The patient who required intermittent dialysis and whose renal function did not improve was discharged with the recommendation of dialysis maintenance therapy and outpatient follow-up. Four days post-discharge, the patient developed Coronavirus disease-2019 (COVID-19) pneumonia and required hospitalization. The patient

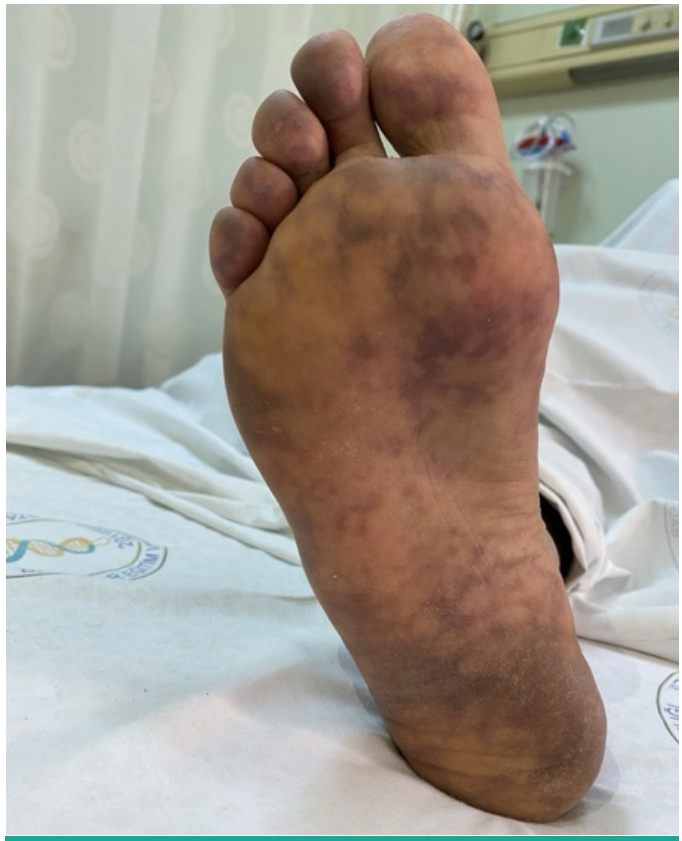

Figure 1. Cyanotic appearance with blue-purple discoloration on the toes and sole of the right foot

passed away due to respiratory failure from COVID-19 on the fifth day of hospitalization. Consequently, long-term follow-up could not be performed.

Discussion

Antemortem diagnosis of CCE is difficult and requires a high degree of suspicion. Identification of risk factors, recognition of clinical findings and consideration of CCE in the differential diagnosis of AKI in patients that underwent certain cardiovascular interventions is of vital importance. A triad consists of a triggering factor including history of coronary angiography, the presence of acute or subacute AKI and the occurrence peripheral crystal embolization in especially male, white and older than 60 years of age patients strongly suggestive of the diagnosis. Contrast nephropathy, small vessel vasculitis, drug-induced interstitial nephritis, and subacute bacterial endocarditis are among the differential diagnoses (6). Our patient, similar to cases reported in the literature, was a 60-year-old male who developed CCE following coronary angiography. However, the presence of HP in our patient was a significant finding supporting the diagnosis.

Histopathologic identification of atheroembolic renal injury is crucial to confirm antemortem diagnosis; however, in case of contraindications for biopsy and when the diagnostic procedures are properly conducted, only 20% of cases require kidney biopsy (7). Moreover, tissue samples taken from the retina, skin, or the muscle may provide clues (8). In patients for whom a biopsy cannot be performed, fundoscopy can be used to confirm the diagnosis if HP are detected.

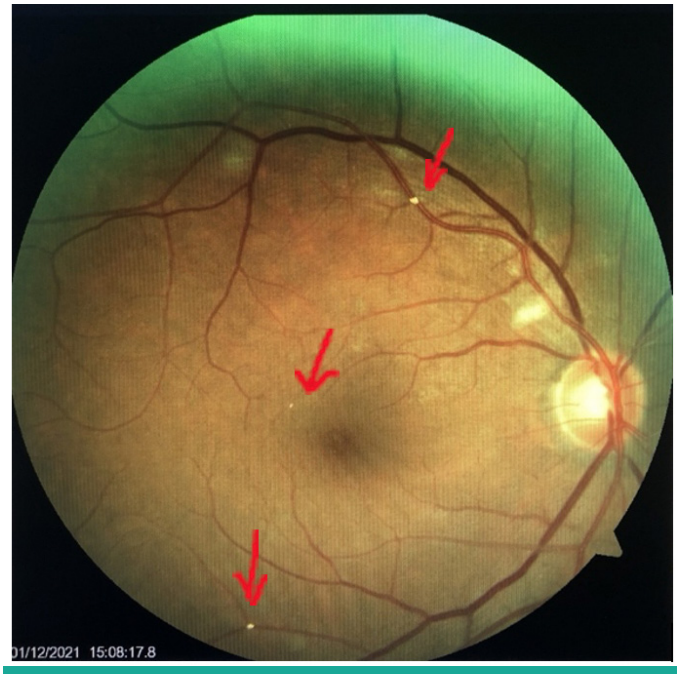

Figure 2. Fundoscopic examination showing 3 Hollenhorst plaques which are arterioler deposition of cholesterol embolus

In this case, CCE must be differentiated from contrast-induced nephropathy (CIN) and vasculitis. CIN is defined as a ≥0.5 mg/dL or >25% increase in the level of creatinine, which sustains for at least 2 to 5 days, in the absence of other identifiable factors, and it is usually initiated within 48 to 72 hours of the administration of an iodinated contrast agent. On the other hand, atheroembolic renal injury has a late onset and long duration and has a poor prognosis, compared to CIN (9). The timing of the AKI, which occurred three weeks after the coronary angiography procedure, combined with the lack of improvement in renal function, led to the exclusion of CIN as a potential diagnosis.

Vasculitis may mimic CCE due to overlapping features such as eosinophilia, elevated sedimentation rate, and multiorgan involvement. However, urine sediment analysis can help differentiate between the two (10). In our case, the absence of nephritic-type urine sediment findings and the presence of non-specific urine sediment led to the exclusion of vasculitis in the differential diagnosis.

In CCE, the skin is the most commonly affected organ outside the kidneys. The most frequent cutaneous findings are BTS and livedo reticularis (11). The main pathophysiologic mechanism in BTS (Figure 1) is embolism of small vessels, sluggish blood flow to nail-bed, and red cell extravasation that cause non-blanchable discolouration (12). In the present case, the development of BTS findings raised the suspicion of CCE, leading to further diagnostic investigations and treatment planning.

Cholesterol emboli originate from the carotid arteries, and because the ophthalmic artery is the first branch of the internal carotid artery, CCE may cause HP, which can be observed by fundoscopic examination (13). In a patient presenting with BTS and a history of coronary angiography, fundoscopic examination was performed to confirm the diagnosis, and HP were detected.

Although there are promising studies with corticosteroids, lipid-lowering agents, and prostacyclin, no curative treatment is available for CCE at present. Thus, treatment approaches are symptomatic and should be aimed at preventing the development of the disorder. However, Belenfant et al. (14) recommended discontinuation of

anticoagulation and avoidance of unncessary surgery or interventions, initiating angiotensin II antagonists or vasodilators the treatment of hypertension, volume control by loop diuretics or hemodialysis, parenteral nutrition and steroid therapy to improve abdominal discomfort. Considering the profit and loss account before starting anticoagulation or performing a surgery or a radiologic intervention is the mainstay of the preventive strategy.

The prognosis of CCE is generally poor, with a renal function recovery rate of 21-28%. The short-term (one-year) survival rate is around 87%; however, it remarkably decreases to 52% by the fourth year. The major cause of death is cardiovascular complications, rather than renal problems. The predictors of mortality are diabetes, advanced age, history of cardiovascular disease, eosinophilia, baseline renal functions and rapid deterioration of renal functions (15,16).

In conclusion, CCE is a rare but serious cause of AKI that should be considered in patients with a history of cardiovascular interventions. Early recognition of clinical findings and imaging techniques such as BTS and HP is essential for timely diagnosis and management. Treatment is largely supportive, and early diagnosis along with preventive measures may reduce mortality.

Ethics

Informed Consent: Written consent was received from the patient.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.M., N.G., A.E.A., Concept: S.M., R.S.T., H.Ç., A.E.A., Design: S.M., N.G., E.I.Ş., C.R., Data Collection or Processing: S.M., A.E.A., H.Ç., R.S.T., Analysis or Interpretation: N.G., A.E.A., R.S.T., Literature Search: A.E.A, C.R., E.I.Ş., H.Ç., Writing: S.M., A.E.A., C.R., E.I.Ş., N.G.

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