e-ISSN: 2717-7505

JOMPAC

Journal of Medicine and Palliative Care

VOLUME: 4 ISSUE: 5 YEAR: 2023

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EDITORIAL

We are proud to publish the fifth issue of our journal, Journal of Medicine and Palliative Care (JOMPAC), in 2023. Our journal is published 6 issues a year. We aim to enter valuable international indexes such as SCI-Expanded, Scopus, ESCI, PubMed and contribute even more to international literature. Currently, it is included in many national and international indexes.

The quality of articles in our journal increases with each passing issue. We strive to publish articles that will contribute to the scientific literature and receive citations from international journals. I would like to thank the editors who contributed to the creation of the issues, the authors who contributed by sending articles, and everyone who contributed at any stage.

Sincerely

Prof. Dr. Aydın ÇİFCİ
Editor-in-Chief

CONTENTS

Original Article

CONTENTS

Original Article

CONTENTS

Original Article

Original Article

MEDICINE PALLIATIVE CARE

DOI: 10.47582/jompac.1342383

J Med Palliat Care. 2023;4(5):380-384

Development and progression of myopia in emmetropic children in Turkey

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Cite this article as: Kaya P. Development and progression of myopia in emmetropic children in Turkey. *J Med Palliat Care*. 2023;4(5):380-384.

Received: 13.08.2023 ◆ **Accepted**: 28.08.2023 ◆ **Published**: 27.10.2023

ABSTRACT

Aims: To investigate the development and progression of myopia in emmetrope school-aged children in Turkey.

Methods: This retrospective study included emmetrope children aged 6-18 who attended the ophthalmology clinic for regular eye and refractive examinations between 2010 and 2021. Individuals were examined at least twice for six months period. Myopia progression was calculated as the difference between the baseline and the last visit spherical equivalent refractive (SER) values. Individuals were further categorized to determine the age-specific myopia development and progression as 6-11, 12-16, and 17-18 age groups based on the school periods of the country. According to the change in SER values, individuals were classified into those who remain emmetrope and those who develop myopia.

Results: A total of 738 eyes of 369 children (222 female, 147 male) with a mean age of 9.4±2.98 (6-18) years were included in the study. The mean follow-up time of patients was 45.62±26.36 (6-130) months. The baseline mean SER value was -0.01±0.10 D (range: -0.375 and +0.375) and -0.44±0.8 (range: -5.00 and +0.375) at the final visit. The overall mean progression was -0.12±0.25 D/year (range: -2.21 and +0.36). 234 eyes (31.75%) developed myopia, and annual SER change was -0.38±0.31 D/year ($p<0.001$). 79 (35.7%) of females and 38 (25.9%) of males developed myopia with a statistical significance ($p<0.006$). There were 163 children between 6-11 years, 169 children between 12-16 years, 37 children between 17-18 years, and 41 (25.2%), 69 (40.8%), and 7 (18.9%) patients of age groups developed myopia, respectively ($p=0.15$).

Conclusion: The development and progression of myopia is more common in 12-16 ages and females. Myopia prevention recommendations should be carefully advised to predisposed age populations and females to reduce myopia progression.

Keywords: Emmetrope, myopia, development of myopia, progression of myopia, myopia in children

INTRODUCTION

Refractive error is one of the most common causes of vision loss, and myopia is becoming an epidemic because of its increasing prevalence all over the world. The worldwide prevalence of myopia and high myopia is envisaged to be 52% (almost 5 billion) and 10% (almost 1 billion) by 2050. Myopia may develop in early childhood, late teens, or adulthood.[1,2] Epidemi of myopia is defined in East and Southeast Asia, which has a prevalence in young adults of almost 80-90%.[3] Early onset of myopia has been reported to evolve more myopic refractive error or high myopia later in life.[4] High myopia may link to pathological myopia, in which choroidal, retinal, and scleral changes cause uncorrectable vision loss.[5] Despite the high prevalence in Asia countries, it was reported as almost 18% in 18-20 year-olds in European countries.[6,7] A much higher prevalence (%49.7) was reported in 12-year-old children from Sweeden.[8]

As studies on the incidence of myopia are essential to observe differences between countries and populations, the current study aims to assess the incidence and progression of myopia in school-aged children. Furthermore, the data on refractive error and the variability between gender and age were obtained from children living in Turkey.

METHODS

This retrospective study was conducted in accordance with the Declaration of Helsinki with written permission from the Zonguldak Bülent Ecevit University Non-interventional Clinical Researches Ethics Committee (Date: 06.04.2022, Decision No:2022/07). The study was carried out in Devrek State Hospital, Zonguldak, Turkey. 369 individuals

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aged 6 to 18 years and only with the diagnosis of 'emmetrope' at their first visit (taken as a baseline) were included in the study. Based on the World Health Organization (WHO) definition, we defined emmetropy as spherical equivalent refractive (SER) between <+0.50 D and >-0.50 D.[1] Patients examined at least twice with six months intervals between 2010-2021 years were evaluated. Myopia progression was calculated as the difference between the baseline and the last visit between SER values. Individuals were further categorized to determine the age-specific myopia development and progression as 6-11, 12-16, and 17-18 age groups based on the school periods of the country. According to the change in SER values, individuals were classified into those who remained emmetrope and those who developed myopia. The best corrected visual acuity was 1.0 for all patients under the correction of refractive status. Patients with other ocular diseases like uveitis, trauma, strabismus, and retinal diseases were excluded from this study.

Statistical Analysis

Descriptive and statistical analyzes were performed using IBM SPSS Statistics 21. Demographic characteristics and clinical data were expressed as mean, standard deviation, frequency, or percentage. The Kolmogorov-Smirnov test was evaluated for the normal distribution test of continuous data. Since the data were unsuitable for normal distribution, the Mann-Whitney U test was used for independent groups. Wilcoxon Signed Rank test was used for related samples, and the Kruskal Wallis test was used for multiple categorical data. The Chi-Square test is also used for suitable data. P value of 0.05 or less was considered statistically significant.

RESULTS

A total of 738 eyes of 369 children (222 female, 147 male) with a mean age of 9.4±2.98 (6-18) years were included in the study. The mean follow-up time of patients was 45.62±26.36 (6-130) months. No anisometropic patients were found during follow-up. 234 eyes of 117 patients (31.8%) developed myopia whose annual SER change was -0.38±0.31 D/year (Table 1). The mean SER value changed from -0.04±0.11 D (range: -0.375 and +0.375) to -1.35±0.87 (range: -0.50 and -0.5) during mean 49.67±21.76 (7.3-106) months follow-up of myopia developed group. Statistical significance existed between the baseline and last SER values (p<0.001). Although the first and last SER values were -0.001±0.09 D (range: -0.375 and +0.375), -0.02±0.17 D (-0.375 and +0.375) of the 'remained emmetrope' group during the 43.74±28.07 (6-130) months follow-up period, the results revealed a statistical significance (p<0.001).

Table 1. Evaluation of the number of patients who developed myopia and remained emmetrope based on gender

	Total of patients	Female	Male
Number of patients	369	222	147
Developed myopia	117 (31.8%)	79 (35.7%)	38 (25.9%)
Remained emmetrope	252 (68.2%)	143 (64.3%)	109 (74.1%)
p value		0.006*	

(*): Chi-Square test was used.

79 (35.7%) of females and 38 (25.9%) of males developed myopia, and there was statistical significance regarding the gender of patients (p<0.006) (Table 1).

The annual SER change of 234 eyes that develop myopia was -0.38 ±0.31 D (range: -0.03 and -2.21), and 504 eyes that remained emmetrope was 0.007±0.05 D (range: -0.36 and +0.37) (p<0.001) (Table 2)

The baseline mean SER value was -0.01±0.10 D (range: -0.375 and +0.375), -0.44±0.8 (range: -5.00 and +0.375) at the final visit, and the overall mean progression was -0.12±0.25 D/year (range: -2.21 and +0.36) of all the patients (Table 3).

Table 2. Evaluation of the number of eyes that developed myopia and remained emmetrope, follow-up periods, baseline, final and annual change of spherical refractive equivalent (SER) values

	N (eyes)	Follow-up period (months)	Baseline SER values	Final SER values	P value	Annual SER progression
Developed myopia	234 (31.8%)	49.67 ± 21.76 (7.3-106)	-0.04 ± 0.11 (Range: -0.375 and +0.375)	-1.35 ± 0.87 (Range: -0.50 and -0.5)	<0.001*	-0.38 ± 0.31 (Range: -0.03 and -2.21)
Remained emmetrope	504 (68.2%)	43.74 ± 28.07 (6-130)	-0.001 ± 0.09 (Range: -0.375 and +0.375)	-0.02 ± 0.17 (Range: -0.375 and + 0.375)	<0.001*	0.007 ± 0.05 (Range: -0.36 and +0.37)
p value		<0.001**	<0.001**	<0.001**		<0.001**

Results indicate as mean ± standard deviation. (*): Wilcoxon signed rank test, (**): Mann Whitney U test

Table 3. Follow-up period, baseline, and final mean spherical refractive equivalent (SER) values and myopia progression based on age, and gender

	Number of patients	Follow-up period (months)	Baseline SER values	Final SER values	P value	Annual SER progression
Total	369	45.62 ± 26.36 (6 - 130)	-0.01± 0.10 (Range: -0.375 and +0.375)	-0.44 ± 0.8 (Range: -5.00 and +0.375)	<0.001**	-0.12 ± 0.25 (Range: -2.21 and +0.36)
Age groups						
6-11	163 (44.1%)	66.86 ± 26.50 (10.5 - 130)	-0.005 ± 0.07 (Range: -0.375 and +0.375)	-0.34 ± 0.77 (Range: -4.00 and + 0.375)	<0.001**	-0.05 ± 0.11 (Range: -0.55 and + 0.21)
12-16	169 (45.9%)	42.74 ± 24.1 (6 - 111)	-0.01 ± 0.1 (Range: -0.375 and +0.375)	-0.56 ± 0.84 (Range: -5.00 and +0.375)	<0.001**	-0.14 ± 0.27 (Range: -2.21 and +0.36)
17-18	37 (10%)	32.48 ± 18.24 (6 - 70.9)	-0.03 ± 0.11 (Range: -0.375 and +0.25)	-0.31 ± 0.62 (Range: -2.50 and +0.25)	<0.001**	-0.14 ± 0.27 (Range: -1.64 and +0.30)
p value		<0.001*	=0.001*	<0.001*		<0.001*
Gender						
Females	222 (60.2%)	46.21 ± 25.83 (6 - 130)	-0.02 ± 0.1 (Range: -0.375 and +0.375)	-0.50 ± 0.81 (Range: -3.75 and +0.375)	<0.001**	-0.14 ± 0.26 (Range: -2.21 and +0.36)
Males	147 (39.8%)	44.72 ± 27.17 (6 - 128)	-0.002 ± 0.1 (Range: -0.375 and +0.375)	-0.35 ± 0.77 (Range: -5.00 and +0.375)	<0.001**	-0.1 ± 0.22 (Range: (-1.55 and +0.15)
p value		=0.321***	=0.004***	<0.001***		=0.003***

Results indicate as mean ± standard deviation. (*): Kruskal Wallis Test, (**): Wilcoxon Signed Rank Test, (***): Mann Whitney U test

The mean age of the patients was 9.57±2.6 (6-18) of that developed myopia and 9.32±3.1 (6-18) of that remained emmetrope (p=0.51) (Table 4).

Table 4. Demographic characteristics of patients who developed myopia and remained emmetrope

	Developed Myopia	Remained Emmetrope	p value
Number of patients (%)	117 (31.8%)	252 (68.2%)	
Age (min-max)	9.57 ± 2.6 (6-18)	9.32 ± 3.1 (6-18)	0.51
Female (%)	78 (67.5%)	143 (56.7%)	0.006*

Results indicate as mean ± standard deviation. (*): Chi-Square Test

When evaluated according to age, the refraction values were found to be more myopic at the last visit compared to the baseline in all groups. There were 163 children between 6-11 years, 169 children between 12-16 years, 37 children between 17-18 years, and 41 (25.2%), 69 (40.8%), and 7 (18.9%) of age groups developed myopia, respectively (p=0.15). Evaluation of myopia progression based on age revealed no statistical significance (Table 5).

Table 5. Analyses of the number of patients who developed myopia and remained emmetrope based on age

Age groups	6-11 ages	12-16 ages	17-18 ages
Number of patients	163 (44.1%)	169 (45.9%)	37 (10%)
Developed myopia	41 (25.2%)	69 (40.8%)	7 (18.9%)
Remained emmetrope	122 (74.8%)	100 (59.2%)	30 (81.1%)
p value		0.15	

DISCUSSION

This study's results indicate that myopia's incidence and progression in school-aged children varied with age and gender. Most of the individuals remained emmetrope (68.2%), and there was not a statistical difference between the developed myopia and remained emmetrope patients regarding age, but there is regarding gender. Females were more prone to developing myopia.

The incidence and progression of myopia have been evaluated in numerous studies. Annual cumulative incidence of myopia has been found more in younger age groups and among females in literature.[9,10] There has still been conflict about the onset of myopia. Fan et al.[11] and Zhou et al.[12] reported a progressive increase in incident myopia with age. Although a statistical difference was not found between age groups regarding myopia development, the 12-16 age group was more prone to develop myopia in our study. The possible reason for this finding could be the difference in follow-up time between the age groups.

With higher incidence and prevalence as reported, girls appear to be at greater risk than boys in our country. Although the conflict of gender dominance in myopia, a similar finding has been reported in the literature.[11,12] A tendency to read, write, and spend more significant time indoors of girls was reported in India. Therefore, they associated the high rates of myopia with these reasons for girls.[13] Moreover, studies show that myopia is more common but progresses more slowly in school-age girls, and the frequency is higher in boys at advanced ages.[14,15] In our study, there was a significant difference between the genders regarding myopia progression. Girls were more prone to have progression of myopia.

The present study revealed a similar annual progression of myopia values (-0.38±0.31) with those in Europe (-0.55 D), Caucasian children (aged 6 to 15 years) living in Australia (-0.31 to -0.41D), in East Asian countries like China and Singapore (-0.31 to -1.2 D) and the USA (-0.34 D to -0.50 D).[9-11,13,16] Donovan et al.[17] published a meta-analysis including 2194 participants in total; children wearing single-vision spectacles with an average age of 9.3 had a progression of -0.52 D/year (%95 CI -0.39 to -0.72 D) myopia in Europe and -0.82 D/year (%95 CI -0.71 to -0.93 D) per a year in Asia. In the ATOM1 study, 400 children aged 6-12 years with spherical equivalents of -1.00 and -6.00 D were followed for two years, and -1.20±0.69 D/2 years myopic change was detected in the non-treated atropine placebo group (n=200).[18] Wong et al.[19] reported the median progression rate of myopia as -0.16 D/year and 62% of children with myopia progressed in London, UK. In our previous study aiming to investigate the relationship between increased digital screen time and the development and progression of myopia during the COVID-19 pandemic, we found the mean annual change in spherical equivalent refractive error (SER) as -0.97±0.66 D in urban area school-aged children in Turkey.[20] The education system, location, lifestyle, and ethnicity variations among different population groups could explain the variations in myopia progression among different countries.

The limitations of this study are involving a citywide population, and it may only reflect some of the country, especially due to the known difference in myopia between urban and rural regions. In addition, the retrospective nature and non-cycloplegic refractive measurements may cause bias. Besides, this study did not evaluate the other potential factors, such as time spent outdoors, parenteral myopia, and time spent near work. Further studies involving separate data with the potential related to various factors, such as exposure to light levels/time outdoors, are required in our country.

CONCLUSION

The development and progression of myopia in school-aged Turkish children is comparable to the world. This finding of the greater progression in females emphasizes the need for regular follow-ups with short intervals and the application of anti-myopia strategies to control myopia progression. Given the potential role of geographic location on myopia progression, information on the pattern of progression of myopic refractive error across different age groups in Turkish children could help clinicians choose appropriate myopia prevention strategies.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Zonguldak Bülent Ecevit University Non-interventional Clinical Researches Ethics Committee (Date: 06.04.2022, Decision No:2022/07).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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Original Article

MEDICINE PALLIATIVE CARE

DOI: 10.47582/jompac.1340041

J Med Palliat Care. 2023;4(5):385-388

Evaluation of antibiotic susceptibility in enterococci isolated from blood culture samples

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Cite this article as: Koca Ö, Er H, Çekin Y. Evaluation of antibiotic susceptibility in enterococci isolated from blood culture samples. *J Med Palliat Care*. 2023;4(5):385-388.

Received: 09.08.2023 ◆ **Accepted**: 02.09.2023 ◆ **Published**: 27.10.2023

ABSTRACT

Aims: Increased vancomycin resistance in enterococci is an important cause of life-threatening bloodstream infections in hospitalized patients. The aim of this study is to determine the antibiotic susceptibility rates of *Enterococcus* strains isolated from blood cultures in hospitalized patients.

Methods: The antibiotic resistance rates of *Enterococcus* strains isolated from blood cultures of patients hospitalized in the service and intensive care units (ICU) between 1 January 2018 and 30 December 2022 were examined retrospectively. Blood samples were studied with the BacT/ALERT 3D culture system (Biomerieux, France). Bacterial identification was performed using conventional methods, Matrix Assisted Laser Desorption-Ionization Time-of-Flight Mass Spectrometer (MALDI-TOF MS) and VITEK 2 (Biomerieux, France) systems. Antimicrobial susceptibility tests were performed with VITEK 2 (Biomerieux, France) systems. Ampicillin, vancomycin, teicoplanin, high-level gentamicin resistance (HLGR) and linezolid susceptibility of isolated strains were evaluated according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria. Vancomycin minimal inhibitory concentration (MIC) values of vancomycin resistant strains were studied by microdilution gradient strip test (Bioanalyse).

Results: A total of 623 strains of enterococci were isolated from blood culture samples. Of the enterococci, 305 (48.9%) were identified as *Enterococcus faecalis*, 281 (45.6%) *Enterococcus faecium*, 12 (1.9%) *Enterococcus avium*, 11 (1.8%) *Enterococcus gallinarum*, 7 (1.2%) *Enterococcus casseliflavus*, 2 (0.4%) *Enterococcus durans* and 1 *Enterococcus hirae* (0.2%). Ampicillin and HLGR resistance rates of isolated *E. faecalis* strains were 11 (3.6%) and 72 (23.6%), respectively, and all strains were found to be susceptible to vancomycin, teicoplanin and linezolid. The ampicillin, vancomycin, teicoplanin and HLGR resistance rates of *E. faecium* strains were determined as 229 (81.5%), 36 (12.8%), 30 (10.7%) and 142 (50.5%), respectively, and all strains were found to be susceptible to linezolid.

Conclusion: In infections caused by enterococci, identification and determination of antibiotic susceptibility rates according to culture antibiogram results would be the right approach. Knowing the current susceptibility rates of enterococci isolated from blood culture samples in our hospital will contribute for clinicians' planning of empirical treatment.

Keywords: Enterococci, blood culture, antibiotic susceptibilities

INTRODUCTION

Enterococci are found as a flora element in human intestines. *Enterococcus faecalis* is the most common human fecal *Enterococcus* species. It can colonize the oropharynx, vagina, and skin. Because of a member of the normal intestinal flora, it causes hospital and community-acquired infections. They cause colonization, bacteremia, peritonitis, endocarditis, wound and urinary tract infections, especially in hospitalized patients.

Protein and carbohydrate virulence factors play major role in the pathogenesis of enterococcal infections. Aggregation substance released by enterococci is responsible for its attachment to heart valves and renal cells. Enterococci colonize the urinary tract, heart valves, and catheters by producing biofilms.[1,2] Although such virulence factors are more common in *Enterococcus faecalis* (*E. faecalis*) strains in the hospital setting, *Enterococcus faecium* (*E. faecium*) strains are more resistant to antibiotics.[3] Depending on the geographical location, most of the nosocomial infections due to VREs are caused by *E. faecium* and only 2-20% of them are caused by *E. faecalis* strains.[4]

In enterococcal infections, penicillin G, ampicillin, vancomycin and teicoplanin are used as cell wall-active bacteriostatic antibiotics. Gentamicin is included in the treatment as a bactericidal agent. Enterococci are intrinsically resistant to trimethoprim-sulfomethoxazole (TMP-SXT), penicillin, cephalosporin, lincosamide, and aminoglycosides.[5]

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Resistance rates in bloodstream infections caused by *E. faecalis* and *E. faecium* are increasing in hospitals and can progress with high morbidity and mortality rates. Therefore, considering the regional resistance data, appropriate and rational use of antibiotics will affect the patient's prognosis.[6]

The aim of this study is to determine the antibiotic susceptibility rates of *E. faecalis* and *E. faecium* strains isolated from the blood cultures of patients hospitalized in our hospital between 2018-2022.

METHODS

The study was carried out with the permission of Antalya Training and Research Hospital Clinical Researches Ethics Committee (Date 08.06.2023, Decision No: 8/27) All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Antibiotic resistance rates of *Enterococcus* strains isolated from blood culture samples of patients hospitalized in the service and intensive care units (ICU) of our hospital between January 1, 2018 and December 30, 2022 were examined retrospectively. Blood samples were incubated with the BacT/ALERT 3D culture system (Biomerieux, France) for 5-7 days. Gram stain was done for each sample during routine culture procedures. In addition, the samples were inoculated on 5% sheep blood agar (BA), chocolate agar (CA) and Eosin Methylene Blue agar (EMB) (RTA, Türkiye) and incubated at 37°C for 18-24 hours. Bacterial identification was performed using conventional methods, Matrix Assisted Laser Desorption-Ionization Time-of-Flight Mass Spectrometer (MALDI-TOF MS) and VITEK 2 (Biomerieux, France) systems. Antimicrobial susceptibility tests were performed with VITEK 2 (Biomerieux, France) systems in line with the manufacturer's recommendations. Ampicillin, vancomycin, teicoplanin, high-level gentamicin resistance (HLGR) and linezolid susceptibility of isolated strains were evaluated according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria. Vancomycin minimal inhibitory concentration (MIC) values of strains found to be resistant to vancomycin were studied by microdilution gradient strip test (Bioanalysis) method.

Statistical Analysis

Statistical Packages for the Social Sciences software version 22.0 (SPSS Inc., Chicago, USA) was used in the statistical analysis of the study. Antibiotic susceptibility results by years were analyzed by the Chi-square test. The degree of statistical significance (p-value) was determined as 0.05 in all analyses.

RESULTS

A total of 623 strains of enterococci were isolated from blood culture samples. Of the enterococci, 305 (48.9%) were identified as *Enterococcus faecalis*, 281 (45.6%) *Enterococcus faecium*, 12 (1.9%) *Enterococcus avium*, 11 (1.8%) *Enterococcus gallinarum*, 7 (1.2%) *Enterococcus casseliflavus*, 2 (0.4%) *Enterococcus durans* and 1 *Enterococcus hirae* (0.2%). Ampicillin and HLGR resistance rates of isolated *E. faecalis* strains were 11 (3.6%) and 72 (23.6%), respectively, and all strains were found to be susceptible to vancomycin, teicoplanin and linezolid. The ampicillin, vancomycin, teicoplanin, and HLGR resistance rates of *E. faecium* strains were determined as 229 (81.5%), 36 (12.8%), 30 (10.7%) and 142 (50.5%), respectively, and all strains were found to be susceptible to linezolid (Table 1). The MIC values of the strains found to be resistant to vancomycin with the automated system VITEK 2 were determined as >256 µg/ml with the microdilution gradient strip test. The distribution of the isolated *E. faecalis* and *E. faecium* strains according to the clinics they were isolated from is given in Table 2 and the distribution of resistance rates by years is given in Table 3.

Table 1. Resistance rates of *E. faecalis* and *E. faecium* strains

Antibiotics	*E. faecalis* (n: 305) (%)	*E. faecium* (n: 281) (%)	Toplam (n: 586) (%)
Ampicillin	11 (3.6)	229 (81.5)	240 (40.9)
Vancomycin	0	36 (12.8)	30 (6.1)
Teicoplanin	0	30 (10.7)	30 (5.1)
HLGR	72 (23.6)	142 (50.5)	214 (36.5)
Linezolid	0	0	0
Total	305	281	586

Table 2. Distribution rates of *E. faecalis* and *E. faecium* strains according to clinics from which they are isolated

Clinics	*E. faecalis* (n: 305) (%)	*E. faecium* (n: 281) (%)	Toplam (n: 586) (%)
Intensive care unit	149 (48.8)	155 (55.1)	304 (51.8)
Internal diseases	38 (12.4)	42 (14.9)	80 (13.6)
Neurology	21 (6.8)	7 (2.4)	28 (4.7)
Infectious diseases	13 (4.2)	2 (0.7)	15 (2.5)
Pediatry	10 (3.2)	4 (1.4)	14 (2.3)
Urology	3 (0.9)	5 (1.7)	8 (1.3)
Brain surgery	3 (0.9)	3 (1.0)	6 (1.0)
Cardiology	6 (1.9)	7 (2.4)	13 (2.2)
Gynecology	2 (0.6)	1 (0.3)	3 (0.5)
Cardiovascular surgery	10 (3.2)	4 (1.4)	14 (2.3)
General surgery	35 (11.4)	40 (14.2)	75 (12.7)
Thoracic surgery	10 (3.2)	2 (0.7)	12 (2.0)
Other clinics	5 (1.6)	9 (3.2)	4 (0.6)
Total	305	281	586

In our study, an increase was observed in ampicillin, HLGR, vancomycin and teicoplanin resistance over the years, and the difference between the resistance rate for teicoplanin in 2022, which was 23%, from other years was statistically significant (p:0.001).

Table 3. Distribution of *E. faecalis* and *E. faecium* strains isolated from blood cultures and antibiotic resistance by years

	E. faecalis						*E. faecium*						p value
	2018 n:64	2019 n:31	2020 n:75	2021 n:66	2022 n:69	Total n:305	2018 n:43	2019 n:45	2020 n:61	2021 n:58	2022 n:74	Total n:281	
Ampicillin	2 (3.1)	4 (12.9)	0	0	5 (7.2)	11 (3.6)	38 (88.3)	36 (80.0)	50 (81.9)	42 (72.4)	69 (93.2)	235 (83.6)	0.236
Vancomycin	0	0	0	0	0	0	3 (6.9)	3 (6.6)	8 (13.1)	3 (5.1)	13 (17.5)	30 (10.6)	0.088
Teicoplanin	0	0	0	0	0	0	3 (6.9)	1 (2.2)	3 (4.9)	6 (10.2)	17 (22.9)	30 (10.6)	0.001
HLGR*	14 (21.8)	10 (32.2)	17 (22.6)	14 (21.2)	17 (24.6)	72 (23.6)	21 (48.8)	21 (46.6)	28 (45.9)	27 (46.5)	45 (60.8)	142 (50.5)	0.362
linezolid	0	0	0	0	0	0	0	0	0	0	0	0	

*HLGR: High-level gentamicin resistance.

DISCUSSION

Enterococci cause nosocomial infections due to their ability to spread easily through patients and healthcare personnel. The increased incidence and antimicrobial resistance in enterococcal infections are important problems.[7] Many antibiotics used in the treatment of gram-positive bacterial infections are not effective in enterococcal infections. Owing to these enterococci can develop antibiotic resistance to many antibiotics intrinsically and/or acquired mechanisms. In addition, enterococci have the ability to transfer this resistance to new generations.[8-10] The increase of vancomycin-resistant enterococci (VRE) strains is particularly important.[11] For this reason, local determination of antibiotic resistance of enterococcal strains at regular intervals will guide treatment planning.[12]

Çelik et al.[6] found ampicillin resistance in enterococci isolated from blood cultures 84.8% for *E. faecium* strains and 5.2% for *E. faecalis* between 2015-2017. They found 90.7% for *E. faecium* strains and 1.6% for *E. faecalis* between 2018-2020. In a meta-analysis study examining 291 studies from different parts of the world, ampicillin resistance was found to be 78% for *E. faecium* strains and 4% for *E. faecalis* in enterococci isolated from blood cultures.[13] In our study, the ampicillin resistance rate was 81.5% for *E. faecium* strains and 3.6% for *E. faecalis*, which is consistent with the literature.

In the 1980s, enterococci developed a resistance to beta-lactam antibiotics and aminoglycosides, and vancomycin was used instead.[5] Vancomycin and teicoplanin are antibiotics that show effective activity against both *E. faecalis* and *E. faecium*.[8] Vancomycin-resistant enterococci strains were reported for the first time in 1986 from France and England.[14] In our country, vancomycin resistance was first reported from rectal swab samples by Vural et al.[15] in 1998. Later, in studies conducted in different regions, increased vancosimine resistance was reported in *Enterococcus* strains over the years. Gök et al.[3] reported vancomycin resistance to *E. faecium* at a rate of 8.2% from blood and various samples of hospitalized patients from Konya in 2020. Çelik et al.[6] did not detect vancomycin resistance in *E. faecalis* strains isolated from the blood samples of hospitalized patients in 2021, but they reported 3.3% vancomycin resistance in *E. faecium* strains. Şanlı et al.[12] reported the rates of resistance to vancomycin as 1.5% and 32.1%, respectively, in *E. faecalis* and *E. faecium* isolated from the blood culture of ICU patients in the Istanbul region in 2022.

In our study, vancomycin and teicoplanin resistance was not detected in *E. faecalis* strains isolated from blood culture. Vancomycin and teicoplanin resistance rate was 10.7% in *E. faecium* isolates. MIC values of vancomycin-resistant *E. faecium* isolates were found to be >256 µg/ml. In addition to the variability in regional data, the steady increase in resistances over the years should be noted and monitored. While evaluating the results of our study, the data in our region revealed that it is necessary to be careful about the increase in resistance over the years. In the present study, especially vancomycin and teicoplanin resistance has increased due to their widespread use in hospital infections in recent years, and the resistance rate for teicoplanin in 2022, which was found to be 23%, was found to be statistically significant compared to other years (p:0.001).

High-level aminoglycoside resistance in enterococci is mediated by aminoglycoside-modifying enzymes.[16] In a study conducted in our country, the HLGR rates in *E. faecalis* and *E. faecium* isolated from blood cultures hospitalized in the ICU were found to be 39.4% and 74.3%, respectively.[12] In another study, HLGR rates of 37% in *E. faecalis* and 62% in *E. faecium* were found in blood and various body fluid samples from hospitalized patients.17 In the presented study, the resistance rates of HLGR in *E. faecalis* and *E. faecium* were found to be 23.6% and 50.5%, respectively.

Linezolid has a broad gram positive spectrum covering methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE) and penicillin-resistant *Streptococcus pneumoniae* strains. Linezolid

is a watch and reserve drug approved by the Food and Drug Administration (FDA) to treat serious infections (infective endocarditis, bacteremia, and central nervous system infections) caused by VRE with high levels of aminoglycoside resistance.[14] In our study, similar to some studies in our country, all enterococcal strains isolated from the blood cultures of hospitalized and ICU patients were found to be susceptible to linezolid.[6,18,19] For the first time in Turkey, Aktaş et al.[20] reported resistance to linezolid at a rate of 2% in *E. faecium* isolates in rectal swab samples taken from hospitalized patients at Istanbul University Faculty of Medicine. Although linezolid is an antibiotic that is widely used in resistant enterococcal infections and has high clinical success, it is not the antibiotic of first choice in bacteremia due to its bacteriostatic nature. This may be considered as one of the reasons for the high linezolid sensitivity rates detected in blood cultures.

CONCLUSION

Although nosocomial infections due to VRE species are increasing, vancomycin is still an effective antibiotic against enterococci. In addition, linezolid, to which all strains including VRE are susceptible, is a good alternative, Knowing the current susceptibility rates of enterococci isolated from blood culture samples in our hospital will contribute to clinicians' empirical treatment planning.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Antalya Training and Research Hospital Clinical Researches Ethics Committee (Date 08.06.2023, Decision No: 8/27)

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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Original Article

MEDICINE PALLIATIVE CARE

DOI: 10.47582/jompac.1332644

J Med Palliat Care. 2023;4(5):389-394

Short and long-term safety and durability of PEG-J tube in jejunal levodopa infusion in patients with Parkinson's disease

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Cite this article as: Tenlik İ, Öztürk Ö, Arı D, et al. Short and long-term safety and durability of PEG-J tube in jejunal levodopa infusion in patients with Parkinson's disease. *J Med Palliat Care*. 2023;4(5):389-394.

Received: 09.08.2023 ◆ **Accepted**: 02.09.2023 ◆ **Published**: 27.10.2023

ABSTRACT

Aims: To investigate PEG-J related adverse events and tube durability in patients with Parkinson's disease who underwent PEG-J procedure for jejunal drug infusion.

Methods: PEG-J implanted patients, who were planned jejunal levodopa infusion, were included in the study. The demographic characteristics of the patients, tube durability, tube replacement, reason for tube replacement, number of procedures, and adverse events related to procedures were retrospectively analyzed.

Results: Thirty-four patients with a mean age of 65.7±9.8 years included in the study. The mean total PEG-J follow-up period of the patients was 33.6±21.1 months. Functions of PEG-J tubes were preserved in 82.5% at 6 months, 78.4% at 12 months, and 65.2% at 18 months. Twenty-one (% 61,8) patients required at least one PEG-J replacement. Of the PEG-J replacements, 90.4% were due to device-related adverse events. A total of 29 procedure or stoma related adverse events occurred in 21 (61.8%) patients, and a total of 28 PEG-J tube related adverse events occurred in 19 (55.9%) patients. A total of six (17.5%) early procedure-related adverse events (acute abdomen and peritonitis, prolonged bleeding, stoma leakage, stoma infection) were observed, all occurred in first 7 days. Twenty-three (67.6%) stoma-related late adverse events (stoma leakage, stoma infection, abscess) were observed. Two patients who developed peritonitis were successfully treated with conservative treatments.

Conclusion: PEG-J used for drug application is a safe method and can be used for a long time without the need for frequent replacement. Most of adverse events can be managed with conservative treatments.

Keywords: PEG-J, adverse events, Parkinson's disease, jejunal drug infusion

INTRODUCTION

Percutaneous endoscopic transgastric jejunostomy (PEG-J) is used primarily to overcome some complications that may occur due to gastric feeding in patients requiring long-term enteral nutrition, and secondarily to administer drugs that undergo gastric initial elimination when administered orally. [1,2]

In recent years, PEG-J has been widely used for continuous infusion of levodopa-carbidopa intestinal gel (LCIG) in patients with advanced Parkinson's disease who do not respond adequately to oral therapy and are not suitable for surgery.[3-6] With this method, LCIG is given as a continuous infusion directly into the jejunum with a tube that is advanced through the percutaneous endoscopic gastrostomy and extends to the proximal jejunum. In this way, undesirable fluctuations in serum levodopa level caused by gastric first elimination and problems in gastric emptying, especially in advanced Parkinson's patients, are overcome.[7] In the literature, there are few studies and limited number of patients on the early and long-term adverse events (AE) that may develop due to the PEG-J procedure used in the treatment of LCIG. The aim of this study is to investigate PEG-J related adverse events and tube durability in patients who underwent PEG-J procedure for LCIG treatment in our clinic.

METHODS

The study was carried out with the permission of Ankara City Hospital No:1 Clinical Researches Ethics Committee (Date: 20.04.2022 Decision No: E1-22-2579). All procedures were carried out in accordance with ethical rules and principles of Declaration of Helsinki.

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All patients diagnosed with Parkinson's disease who were scheduled for LCIG treatment and PEG-J implanted by the gastroenterology department in our hospital between April 2015 and April 2023 were included in the study. The LCIG treatment decision was made by the neurologist who followed the patients.

Criteria required for being a candidate for LCIG treatment and PEG-J placement were age >30 years, failure to respond to optimal oral dopaminergic therapy, and levodopa responsiveness assessed using the Levodopa Challenge test. Exclusion criteria for LCIG treatment were severe cognitive impairment, psychosis, active psychiatric illness, unresponsive Levodopa Challenge test, gastrointestinal disease or other drug use that would affect drug metabolism and lack of patient's caregiver. Exclusion criteria for PEG-J procedure were history of total gastrectomy, coagulopathy, sepsis, abdominal wall infection, ascites, lack of informed consent, gastric outlet obstruction or absence of transillumination in upper endoscopy.

The demographic characteristics of the patients, tube durability, tube replacement, reason for tube replacement, number of procedures, and AE related to the procedure were retrospectively analyzed. AE occurring in first 7 days or less were classified as early AE, and AE developing in a longer period were classified as late AE. The endpoint was tube dysfunction, tube removal for any reason and discontinuation of treatment, or death of patients for any reason. Patients who did not have data on PEG-J procedure and follow-up or who had PEG-J implantation due to enteral nutrition were not included in the study.

All patients were hospitalized before the procedure and PEG-J procedure was performed by an experienced gastroenterologist under conscious sedation provided by an anesthesiologist. Systemic antibiotic prophylaxis was administered to all patients before the procedure. Initially, endoscopy was performed to evaluate upper gastrointestinal tract. After providing skin antisepsis, a PEG tube (AbbVie 15 French PEG Kit) was placed in the region where transillumination and indentation were detected on the anterior wall of the gastric corpus-antrum junction. The inner jejunal extension tube (AbbVie 9 French intestinal tube), which was sent through the PEG tube, was held with gripping forceps and advanced to distal duodenum/proximal jejunum. Then, the endoscope was pulled back to the stomach and the gripping forceps were opened while the endoscope was inside the stomach, and the jejunal tube tip was released so that it remained in the jejunum. After the procedure, the patients in the present study were regularly checked by a nurse who was experienced in PEG-Jcare, and the control information was recorded regularly.

Statistical Analysis

IBM SPSS Statistics Version 25.0 software for Windows (IBM Corp., Armonk, NY, USA) was used to perform the statistical analysis. Descriptive statistical methods (mean, standard deviation, frequency, percentage, minimum, maximum) were used in the evaluation of the research data. The conformity of the quantitative data to the normal distribution was analyzed by Kolmogorov-Smirnov, Shapiro-Wilk test, and graphical examinations. Spearman correlation coefficient was used to compute the correlation analysis. Statistical significance was considered $p \leq 0.05$ with a confidence interval (CI) of 95%.

RESULTS

Thirty-four patients with a mean age of 65.7±9.8 years who were treated with LCIG were included in the study. Seventeen (50%) of the patients were male. Demographic characteristics of the patients are shown in Table 1.

Table 1. Demographic characteristics of patients

Total number of patients	34	
Gender	**n**	**%**
Female	17	50
Male	17	50
Age	65.7±9.8 years (48-86 years)	
Comorbid diseases	**n**	**%**
Hypertension	12	35.3
Hyperlipidemia	5	14.7
Diabetes mellitus	5	14.7
Cardiac problems	5	14.7
Osteoporosis	4	11.8
Pulmonary problems	3	8.9
Rheumatoid arthritis	1	2.9
Pernicious anemia	1	2.9
Malignancy	1	2.9

The mean total PEG-J follow-up period of the patients was 33.6±21.1 months (0-98 months). The longest period of use of a single PEG-J catheter without replacement was 52 months, and in this patient, the tube was removed while the tube was still functioning, when the patient wanted to discontinue the treatment. During the follow-up period, only one PEG-J procedure was performed in 13 patients, while two or more PEG-J procedures were performed in 21 (61.8%) patients. A total of 65 PEG-J procedures were applied (Table 2).

After initial PEG-J insertion, a total of 31 tube replacements were required due to inner jejunal tube occlusion in seven patients (Five due to drug, two due to king formation), inner jejunal tube dislocation in 10 patients, internal jejunal tube break in four patients, PEG tube damage in seven patients (Three due to

accidental cutting by the patient), peristomal infection in 2 patients, and acute abdomen and peritonitis in 1 patient. Of the PEG-J replacements, 90.4% were due to device-related AE, and 9.6% were due to procedure- or stoma-related AE. Functions of PEG-J tubes were preserved in 82.5% at 6 months, 78.4% at 12 months, and 65.2% at 18 months (Table 2).

Table 2. Number of PEG-J tubes used by patients, reasons for replacement and tube retention rate in follow-up

Average follow-up time of patients	33.6±21.1 months (0-98 months)	
Number of PEG-J used	**n (patient)**	**%**
1	13	38.2
2	14	41.2
3	5	14.7
4	1	2.9
5	1	2.9
Total	34	100
Cause of tube replacement	**n (procedure)**	**%**
Inner jejunal tube occlusion	7	22.6
Inner jejunal tube dislocation	10	32.3
Inner jejunal tube break	4	12.9
PEG tube break	7	22.6
Stoma infection	2	6.4
Acute abdomen and peritonitis	1	3.2
Total	31	100
Functional PEG-J tube ratio	**%**	
6. months	82.5	
12. months	78.4	
18. months	65.2	

Seven (20.6%) patients had no AE. A total of 29 procedure or stoma related AE occurred in 21 (61.8%) patients, and a total of 28 PEG-J tube related AE occurred in 19 (55.9%) patients. A total of six (17.5%) early procedure-related AE (acute abdomen and peritonitis, prolonged bleeding, stoma leakage, stoma infection) were observed, all occurring in first seven days. Twenty-three (67.6%) stoma-related late AE (stoma leakage, stoma infection, abscess) were detected (Table 3). There was no relation between early or late AE and comorbid diseases in the correlation analysis ($p>0.05$).

All cases with stoma leakage improved spontaneously without any intervention.

A total of 17 stoma infections and abscesses occurred in 15 patients. There was a total of 9 colonization in the wound cultures sent from 8 patients, and there was no colonization in the wound cultures of 7 patients. While Candida species were detected in five cultures; *Corynebacterium striatum*, *Enterobacter aerogenes*, *Streptococcus intermedius* and *Staphylococcus aureus* were detected in the other four cultures, respectively. While two of the patients developed two stoma infections, one stoma infection or abscess developed in the other 13 patients. Tube exchange was performed due to infection in two patients with Candida infection. In two other patients with Candida infection, the tube was removed due to prolonged infection, new PEG-J replacement was not performed because the patients wanted to discontinue the treatment. Other patients who developed infections recovered with conservative and medical treatment.

Table 3. Adverse events during follow-up

	n	Procedure %	Patient %
Stoma and procedure related early adverse events (0-7 days)			
Prolonged bleeding	1	1.5	2.9
Stoma leakage	1	1.5	2.9
Stoma infection	1	1.5	2.9
Acute abdomen	3	4.6	8.8
Total	6	9.1	17.5
Stoma and procedure related late adverse events (>7 days)			
Stoma leakage	7	10.8	20.6
Stoma infection	13	20.0	38.2
Abscess	3	4.6	8.8
Total	23	35.4	67.6
Total adverse events	29	44.5	85.1
Patient with adverse events	21		61.8
PEG-J tube related adverse events	**n**	**Procedure %**	**Patient %**
Inner jejunal tube occlusion	7	10.8	20.6
Inner jejunal tube dislocation	10	15.4	29.4
Inner jejunal tube break	4	6.1	11.8
PEG tube break	7	10.8	20.6
Total adverse events	28	43.1	82.4
Patient with adverse events	19		55.9

Acute abdomen or perforation developed in three patients. In the first patient, the tube had penetrated the left lobe of the liver, and surgically, a small liver incision was made to free the tube and the tube continued to function without replacement. In the second patient, peritonitis symptoms developed with the findings of pneumoperitoneum and intra-abdominal infectious collection, the tube was removed, and a new PEG-J was inserted when the clinical findings improved with medical treatment. In the third patient, peritonitis findings developed with pneumoperitoneum and intra-abdominal infectious collection findings, the PEG-J tube was removed, and the patient recovered with conservative methods and medical treatment without the need for surgical procedure, then the patient did not accept new PEG-J replacement.

During follow-up, mechanical ileus due to Spiegel's hernia developed in one patient and paralytic ileus due to neurological and metabolic causes in another patient, but these problems were not related to PEG-J.

Six patients died due to comorbid diseases. Three patients discontinued treatment due to complications (one patient due to peritonitis in the first week, the other two due to prolonged candida infection at 16 and 23 months). There was no death due to PEG-J procedure or tube-related complications. One patient without complications wanted to stop the treatment and the PEG-J tube was removed. At the end of the follow-up, 24 patients were still using PEG-J (Table 4).

Tablo 4. Number of patients at the end of follow-up

Patients without PEG-J exchange (n=13)	Patients without PEG-J replacement (n=21)
9 patients are still on follow-up	15 patients are still on follow-up
2 patients quit due to PEG-J complications	1 patient quit due to PEG-J complications
1 discontinued treatment without complications.	5 patients died
1 patient died	

DISCUSSION

Our study showed that PEG-J used for drug application is a safe method and can be used for a long time. 91.2% of our patients did not develop serious early complications related to the PEG-J procedure, and there was no mortality secondary to early and late complications. Conditions such as peritonitis, perforation, intestinal fistula, which are classified as severe AE in the literature, have been reported between 0-15% in different studies.[4,7-14] Viljaharju et al.[10] reported that a single case of peritonitis died among 103 patients. Cheron et al.[14] reported that one closed duodenal perforation and one intra-abdominal infectious collection were cured with conservative treatment. Ebstein et al.[13] reported that five of eight peritonitis cases treated conservatively, three of them surgically, all patients were successfully treated. All early complications observed in the present study were procedural complications that developed within first 7 days. Peritonitis and intra-abdominal infectious collection were present in two of three cases of acute abdomen. These patients recovered with medical treatment and conservative approach. Therefore, we think that conservative approaches would be more appropriate in cases of peritonitis and infectious collections without organ penetration (such as colon, small bowel, liver) in radiological imaging, if there is no finding suggesting septic shock or organ dysfunction.

During the PEG-J procedure, gastropexy is recommended to prevent serious side effects such as peritonitis and intra-abdominal abscess. However, on the contrary, other studies have reported that gastropexy application will not eliminate this risk. While no severe AE was detected after gastropexy in the study of Ishibashi et al.,[15] Yamashita et al.[16] reported that peritonitis developed in 2.9% despite gastropexy. In the present study, we detected peritonitis in 5.9% of our patients and gastropexy was not performed in any of our patients. We think that gastropexy may reduce the development of peritonitis in early period. In cases where gastropexy cannot be performed, making an incision appropriate for the diameter of the PEG catheter, and pressing the incision site more carefully while pulling the PEG tube out of the stomach through the abdominal wall may prevent the separation of the stomach and abdominal wall and the development of peritonitis and intra-abdominal infectious collections. The use of CO_2 insufflation instead of air during the procedure may reduce the development of pnomoperitoneum and therefore the risk of peritonitis. Penetration of left lob of the liver was present in one of three cases of acute abdomen in the present study. It is also important not to perform the procedure if transillumination and indentation cannot be obtained clearly, in order to avoid problems that can lead to acute abdomen, especially organ penetration.

Tube revision is required for various reasons during the follow-up of PEG-J patients. Viljaharju et al.[10] and Simoni et al.[17] found the need for at least one tube replacement in 57% and 56.6% of patients, respectively. In this study, at least one tube replacement was required at a rate of 61.8%, slightly more than in these studies. In the study by Yamashita et al.,[16] the need for tube replacement was reported in 34.9% of the patients at 12 months. In our study, tube replacement was 21.6% at 12 months and 34.8% at 18 months. We determined the durability of PEG-J tubes to be longer. Viljaharju et al. reported that over 90 percent of tube replacements were due to tube-related AE. Simoni et al.[17] also reported that 82% of the reasons for replacement were tube-related problems and the most common reason for tube replacement was inner tube dislocation. Udd et al.,[9] on the other hand, showed that the causes of tube replacement were predominantly due to tube-related AE and reported that 38% were due to accidental removal of the inner tube and 29% to the occlusion of the inner tube. In our study, similar to these studies, the majority of the replacements were related to tube-related problems and the most common cause was inner tube dislocation. Although the number of procedure- or stoma-related AE was at least as high as the number of tube-related AE, most of them responded to conservative treatments and did not require replacement.

The average number of procedures, peristomal and device-related AE per patient has been reported between 0.7 and 6 in the literature so far in patients who have been placed PEG-J for LCIG continuous infusion.[4,8,9,17] We found an average of 1.7 AE per patient. Udd et al.[9] found

71% peristomal AE and 86% tube-related AE in their patients. After accidental dislocation of the inner tube, granulation tissue formation was found to be the most common AE. Balaise et al.[4] found stoma- or procedure-related AE in 69.8% of the patients, and device-related AE in 63.5%. As common reasons: They found PEG tube dislocation with 44.4%, granuloma with 34.9%, inner tube obstruction with 31.7%, stoma infection and abscess with 30.2%, and stoma leakage with 27%. In their study, Simoni et al.[17] reported that 63.3% of the patients had AE, and they found device-related complications in 44.3% and stoma-related complications in 45.9% of them. Again, the most common complications were wound infection with 25.9% and inner tube dislocation with 18.9%. In this study, we found AE in 79.4% of our patients. Stoma- and procedure-related AE was found in 61.8% of the patients, and PEG-J tube-related AE was found in 55.9% of the patients. In our study, the main PEG-J tube related AE were inner tube dislocation, inner tube occlusion and PEG tube breaking, similar to previous studies. Half of the total AE were stoma and procedure related ones.We did not observe granulation tissue in contrast to studies[9,13,18] that detected a high rate of excessive granulation tissue. In contrast to Cococci et al.,[8] who did not report any infectious AE in their study, half of the patients in this study developed stoma infection or abscess. This finding was in line with the existing literature, and the results we found were similar to the study by Rus et al.,[18] who previously reported a 49.5% local infection rate and a 5.8% abscess rate. In earlier studies, it was reported that local infection rates were different in different centers, and the history of malignant disease, tube diameter and endoscopist experience affected the risk of infection.[19]

In the present study, only one stoma infection developed in the early period, while all remaining stoma infections and abscesses developed in the late period. This means that infections are associated with later stoma care rather than periprocedural conditions. Along with periprocedural antibiotic prophylaxis and compliance with sterile conditions during the procedure, patients and their caregivers should be well educated about stoma care and their attention should be drawn to its importance.

In the present study, wound culture was positive in half of the patients who developed peristomal infection. Patients with culture negative or bacterial colonization were treated with appropriate antibiotic therapy and conservative approach. The patient, who had previously isolated *Enterobacter aerogenes* in culture, did not respond to treatment, and candida colonization was detected in repeated culture. Four of the five patients with Candida infection were treated by removing the tube due to prolonged infection. Previous studies have shown that Candida species can colonize PEG catheters and cause serious clinical problems, especially in immunosuppressed individuals.[20-22] However, there is no evidence in the literature regarding the culture results of stoma infections developed in Parkinson's patients with PEG-J, and especially for treatment-resistant candida infections. We think that in case of treatment-resistant peristomal infections, possible Candida infection should be considered and treated with tube replacement in those who do not respond to conservative treatments.

Another stoma- and procedure-related AE that was frequently observed in the present study was stoma leakage. This AE is often caused by a large stomatal incision relative to the tube diameter or by fluid retention in the stomach. In this study, all cases with stomal leakage resolved spontaneously. Optimal size of the stoma incision, short interval and low volume diet, optimization of Parkinson's treatment and use of prokinetic agents in patients with delayed gastric emptying may reduce the incidence of stomal leakage.

One of the limitations of the present study is that it is retrospective. However, after the procedure, the patients in our study were regularly checked by a nurse experienced in PEG-J care, and the control information was recorded regularly. Another limitation of the study is the small number of patients and the absence of a control group. This study could be more powerful if the data of the patients who were placed with PEG-J for drug administration were compared with the data of the patients who were placed with PEG-J for enteral nutrition. Randomized controlled studies with larger number of patients are needed in this regard.

CONCLUSION

PEG-J used for drug application is a safe method and can be used for a long time without the need for frequent replacement. Although a few complications may develop in the early and late period, most of them can be managed with conservative treatments.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara City Hospital No:1 Clinical Researches Ethics Committee (Date: 20.04.2022 Decision No: E1-22-2579).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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Original Article

MEDICINE PALLIATIVE CARE

DOI: 10.47582/jompac.1345430

J Med Palliat Care. 2023;4(5):395-399

Colonoscopic evaluation of acromegalic patients: a single center experience

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Cite this article as: Emür Günay Y, Durak S, Coşar AM, Erkut B, Fidan S. Colonoscopic evaluation of acromegalic patients: a single center experience. *J Med Palliat Care*. 2023;4(5):395-399.

Received: 18.08.2023 ◆ **Accepted**: 04.09.2023 ◆ **Published**: 27.10.2023

ABSTRACT

Aims: To investigate the importance and necessity of colonoscopic screening in patients with acromegaly.

Methods: This study included 82 patients with acromegaly and, 82 healthy individuals as the control group who underwent screening colonoscopy in the Gastroenterology Department of Karadeniz Technical University, between January 2008-January 2021.

Results: The mean age of the patients was 45.71±12.61 years at the time of acromegaly diagnosis. 51.2% (n=42) of patients were female. Abnormal findings including evidence of polyps, and inadequate bowel preparation were significantly more common in the acromegaly group than the control($p<0,05$). The a growth hormone (GH) level measured at the time of diagnosis was significantly higher in patients with acromegaly diagnosed with inadequate bowel preparation ($p<0,05$). There was no significant difference between the two groups in non-polyp colonoscopy findings, polyp localization, histologic types and colorectal cancer.

Conclusion: The frequency of polyps is higher in patients with acromegaly than in the normal population and therefore colonoscopy screening should be performed. It would be reasonable to perform bowel preparation in patients with acromegaly (especially those with high GH at the time of diagnosis) using an approach different from standard bowel preparation, as the rate of inadequate bowel preparation is higher in this group of patients.

Keywords: Acromegaly, colonoscopy, growth hormone, colon polyps

INTRODUCTION

Acromegaly is a rare disorder caused by a GH-secreting tumor in the pituitary gland. The annual incidence is reported as 3-4 per million and the prevalence as 50-70 cases per million. Both sexes are affected equally and usually in the fifth decade of life.[1] GH secretion induces the production of insulin-like growth factor-1 (IGF-1). Both of these hormones promote protooncogene expression and cellular growth and proliferation.[2] Acromegaly is associated with higher mortality and neoplastic, cardiovascular, metabolic, and respiratory complications compared with the general population.[3]

The association between acromegaly and hyperinsulinemia resulting from abnormal glucose tolerance and insulin resistance is well established.[4] Studies have shown that people with diabetes have an increased risk of colorectal cancer than people without diabetes. Hyperinsulinemia is thought to be involved in the pathogenesis of this increase.[5] Patients with acromegaly had also been found to have an increased incidence of colon polyps.[6-8]

Earlier and more frequent colonoscopic screening is recommended because the risk of colorectal polyps and cancer is likely to develop earlier in patients with acromegaly than in the general population due to increased GH and IGF-1 levels. Guidelines for the management of acromegaly published by the American Society of Clinical Endocrinologists and the Society of Endocrinology recommend colonoscopy at the time of diagnosis of acromegaly.[9,10] Some guidelines also state that patients with acromegaly should undergo colonoscopy every 3-5 years, beginning at age forty.[7,11]

In this study, we aimed to determine the incidence of colon pathology, specifically colon cancer and colon polyps, the relationship between colon polyp location and pathology, and clinical and laboratory findings in patients with acromegaly who underwent colonoscopy and thus evaluate the need for colonoscopic screening.

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METHODS

The study was carried out with the permission of Karadeniz Technical University Ethics Committee (Date: 10.03.2022, Decision No: 161). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Eighty-two patients with acromegaly who underwent colonoscopic examinations were included in this retrospective study at Gastroenterology Department of Karadeniz Technical University Farabi Hospital between January 2008 and January 2021. As a control group, we recruited 82 patients who had undergone colonoscopy in our gastroenterology clinic for screening purposes and had no comorbidities. The demographic, histopathologic, laboratory and colonoscopic results of all patients were obtained by the hospital's electronic database in this study,retrospectively.

Colonoscopy preparation was done with oral 250 ml of sennoside A+B. Specialist physicians with at least three years of experience performed colonoscopy with Olympus or Pentax colonoscopes. We determined the location of all polyps (e.g., rectum, sigmoid colon, descending colon, transverse colon, ascending colon, cecum) during the procedure. We defined the left colon as the rectum, sigmoid, descending colon, and the right colon as the transverse colon, ascending colon, and cecum. All polyps that underwent polypectomy were sent to the pathology laboratory for histologic diagnosis. We recorded localization, number, and histologic subtypes of polyps. Abnormal findings include polyps, hemorrhoids, colorectal carcinoma, diverticula, parasitosis, ischemic/inflammatory colitis, anal fissures and tapeworms. We assessed inadequate bowel preparation using the Boston Bowel Preparation Scale with scores of 0 and 3.

We measured serum IGF-1 with an enzyme-labeled chemiluminescent solid-phase immunometric kit (Immulite IGF-I, Siemens Medical Solutions Diagnostics, UK) using the IMMULITE 1000 system.

We measured serum GH levels with an immunoradiometric kit (IRMA) using commercially available kits (hGH- IRMA CT; RADIM, Rome, Italy). The reference ranges for GH were 0-16 ng/ml for women and 0-8 ng/ml for men.

Statistical Analysis

We used the SPSS Windows version 22 program for statistical tests. We evaluated continuous variables with histogram and Q-Q plot for normal distribution and with Shapiro-Wilk or Kolmogorov-Smirnov test for the number of variables. Normally distributed continuous variables are presented throughout the study as mean±standard deviation, and the t-test for independent variables was used to compare the two groups. Other continuous variables were presented as median (IQR), and the non-parametric Mann-Whitney U test was used to compare the groups. We presented categorical variables as frequency and percentage and used the Pearson chi-square test or Fischer exact probability test to compare the groups. Tests with a p-value of 0.05 and below at the 95% confidence interval were considered statistically significant.

RESULTS

The mean age at diagnosis of acromegaly in 82 patients who underwent screening colonoscopy was 45.71±12.61 years.51.2% (n=42) of the patients were female and 48.8% (n=40) were male. The mean age of the control group was 51.91±13.31 years, 52.4% (n=43) of the patients were female, and 47.6% (n=39) were male. There was no statistically significant difference between the acromegaly and control groups in terms of age and sex (p> 0.05) (Table 1).

Table 1. Demographic and clinical characteristics of the acromegaly and control groups

Variable	Acromegaly (n=82)	Control (n=82)	p
Age*, mean±SD	48.87±12.46	51.91±13.31	0.132
Male/Female, n (%)	40/42 (48.8/51.2)	39/43 (47.6/52.4)	1
Cases with polyps, n (%)	16 (19.5)	6 (7.3)	0.037
Surgery, n (%)	69 (84.1)		
Disease control, n (%)	45 (54.9)		
Somatostatin analog, n (%)	50 (61)		
Radiotherapy, n (%)	9 (11)		

*Based on age at the time of colonoscopy.

84.1% (n=69) of the patients with acromegaly had a history of pituitary surgery. In 13 patients who did not undergo surgery, medical treatment was given because they did not accept the operation or were at high risk for operation. The disease control was achieved in 54.9% (n=45) of the patients with surgery. While 61% (n=50) of the patients received somatostatin analogue treatment, 11% (n=9) received radiotherapy (Table 1).

Colonoscopy findings were normal in 37 (45.1%) patients with acromegaly who underwent colonoscopic examination, abnormal findings were noted in 34 (41.5%) patients, and no definite evaluation could be made in 11 (13.4%) patients because of inadequate bowel cleansing. While colonoscopy findings were normal in 75.6% (n=62) of subjects in the control group, abnormal findings were noted in 23.2% (n=19); no definite evaluation could be made in 1.2% (n=1) due

to inadequate bowel cleansing. The rates of abnormal findings [acromegaly group 42.7% (n=35) and control group 24.4% (n=20)] and inadequate bowel cleansing [acromegaly group 13.4% (n=11) and control group 1.2% (n=1)] and were statistically higher in cases with acromegaly compared to the control group (p=0.019 and p=0.005, respectively), and the detection rate for normal colonoscopic findings was significantly lower (p<0,001). (Table 2).

Table 2. Colonic localization and histological types of polyps and non-polyp findings in patients with acromegaly

	Acromegaly	Control	P
Polyp localization,n (%)			
Right colon	4 (25)	1 (16.7)	0.367
Left colon	11 (68.7)	3 (50)	0.047
Right and left colon	1 (6.3)	2 (33.4)	1
Polyp Histology, n (%)			
Tubular	15	8	0.403
Tubulovillous	3	1	0.620
Hyperplastic	2	3	1
Reactive	3	0	0.245
Inflammatory	2	0	1
Total	25	12	
Non-polyp finding,n (%)			
Hemorrhoids	13 (15.9)	10 (12.2)	0.654
Colorectal carcinoma	2 (2.4)	1 (1.2)	1
Diverticula	2 (2.4)	3 (3.7)	1
Parasitosis	2 (2.4)	0	0.497
Ischemic/inflammatory colitis	2 (2.4)	4 (4.9)	0.682
Anal fissure	1 (1.2)	2 (2.4)	1
Tapeworm	1 (1.2)	0	1
Inadequate colon cleansing	11(13.4)	1(1.2)	0.005

We detected polyps in 19.5% (n=16) of cases with acromegaly and 7.3% (n=6) of cases in the control group. The polyp detection rate was significantly higher in the acromegaly group than in the control group (p=0.037). The median number of polyps in the patients with polyps was 1 (1-4). There was no difference in age between the group with and without polyps in patients with acromegaly (p=0.562), whereas the age at polyp detection was statistically higher in the control group (mean age 60.17±4.53 vs. 51.26±13.56, p=0.002). There was no gender difference in polyp detection in the acromegaly or control groups. (p> 0.05). We found no significant difference in patients with acromegaly between cases with and without polyps in terms of time from diagnosis to colonoscopy (p=0.664). There was more than one polyp in 6 and 5 cases in patients with acromegaly and the control group, respectively.

We detected 25 polyps in 16 out of 82 patients with acromegaly who underwent colonoscopy. Of the acromegaly patients with polyps, polyps were located in the left colon in 11 (68.7%) of the patients, in the right colon in 4 patients (25%), and in both the right and left colon in 1 patient (6.3%). Rectal polyps are included in left colon polyps. If rectal polyps were evaluated separately, the most common site of polyps was the rectum with 8 (32%) polyps.

In the control group, we detected a total of 12 polyps in 6 cases, and the most common location of polyps was the sigmoid colon with four polyps (33.3%). Other polyp localizations were 1 in left colon, 3 in right colon and 2 in both right and left colon, respectively (Table 2).

Regarding the localization of polyps in the right or left colon, the left colon location of polyps was more frequent in the acromegaly group than in the control group (p=0.047) (Table 2). There was no statistically significant difference between the acromegaly and control groups in polyp localization in the rectum, sigmoid colon, descending colon, transverse colon, ascending colon, and rectum (p > 0.05).

When we evaluated the histological type of polyps, 60% (n=15) of polyps in patients with acromegaly were tubular adenomas, 12% (n=3) were tubulovillous adenomas, and 12% (n=3) were reactive polyps. There was no statistically significant difference in the evaluation of histological types of polyps in cases with and without acromegaly (p> 0.05) (Table 2).

The most common findings other than polyps in patients with acromegaly were: Hemorrhoids 15.9% (n=13), diverticula 2.4% (n=2) and parasitosis (Enterobius vermicularis) 2.4% (n=2) (Table 2). There was no statistically significant difference between the acromegaly and control groups in the frequency of non-polyp findings (p> 0.05) (Table 2).

In patients with acromegaly, we found no statistically significant difference in the presence or absence of polyps between patients depending on their concomitant systemic diseases, whether or not they underwent surgery, whether or not they were surgically cured, whether or not they received radiotherapy, and whether or not they were taking a somatostatin analog (p> 0.05) (Table 3).

When we evaluated IGF-1 and GH levels of patients with acromegaly for the presence/absence of polyps, we found no statistically significant difference in IGF-1 and GH levels at the time of diagnosis, at three months after surgery and before colonoscopy, and in GH levels at the time of diagnosis and three months after surgery (p> 0.05) (Table 3).

The GH level measured at the time of diagnosis was significantly higher in patients with acromegaly with inadequate bowel preparation (p=0.028).

Table 3. The association between the presence of polyps and the type of treatment, GH/IGF-1 levels and demographic data in patients with acromegaly

	Polyp (+)	Polyp (-)	P
Operation history, n (%)			0.711
Yes	13 (18.8)	56 (81.2)	
No	3 (23.1)	10 (15.2)	
Disease controle, n (%)			0.781
Yes	8 (17.8)	37 (82.2)	
No	8 (21.6)	29 (78.4)	
Radiotherapy history, n (%)			0.681
Yes	1 (11.1)	8 (12.1)	
No	15 (20.5)	58 (87.9)	
Use of somatostatin analogue, n (%)			0.777
Yes	9 (18)	41 (82)	
No	7 (21.9)	25 (78.1)	
Age, mean±SD	50.5±10.04	48.47±13.01	0.562
Gender, n (%)			0.583
Male	9 (22.5)	31 (77.5)	
Female	7 (16.7)	35 (83.3)	
IGF-1 (Diagnosis), mean±SD	689.27±348.73	770.58±308.51	0.445
IGF-1 (Postop 3rd month) mean±SD	385.81±279.01	340.02±206.82	0.471
IGF-1 (Colonoscopy), mean±SD	543.18±272.3	559.11±312.71	0.849
GH (Diagnosis), median (IQR)	3.62 (5)	4.12 (6)	0.83
GH (Postop 3rd month), median (IQR)	1.23 (2.77)	1.31 (1.96)	0.345

*IGF-1: Insulin-like growth factor 1, GH: Growth hormone

DISCUSSION

The frequency of polyps is higher in patients with acromegaly than in the normal population and therefore colonoscopy screening should be performed. Mortality in patients with acromegaly is higher than in the general population. With advances in treatment in recent years, mortality rates due to the disease itself have decreased. In recent studies, the most common cause of death in patients diagnosed with acromegaly is a malignancy (35%), followed by cardiac and cerebrovascular disease.[12,13]

The prevalence of colorectal polyps was 30.3% in the study by Koksal et al.[14] and 30.2% by Guistina et al.[3] In our study, this rate was 19.5%.

Studies show an increased risk of colorectal tumors and cancers in patients with acromegaly and associate this increase with high GH levels.[15,16] Although there was no significant difference in the detection rate of malignancy in patients with acromegaly compared to the control group in our study, the rate of polyps was higher in the acromegaly group than in the control group.

The difference in the rates of polyps or colorectal tumors in acromegaly patients might be related to the age at diagnosis of acromegaly, the age at which colonoscopy was performed, the timing of colonoscopy after diagnosis, and the follow-up period. Therefore, it is clear that longer follow-up studies with more patients are needed to evaluate the significance of the difference. We excluded the risk of follow-up and cancer development from the analysis because we aimed to analyze the initial screening results and not determine these details.

GH levels could be reached in only one of the patients with colon cancer, so it was not appropriate to evaluate the relationship between colon cancer and GH in our study. When we assessed the initial GH level for the presence of polyps, we found no significant difference.

Current guidelines recommend colorectal cancer screening at the time of diagnosis of acromegaly and starting at age 40 years.[17] The mean age of acromegaly patients (n=16) with polyps was 50.5±10.04 years, and the rate of patients younger than 40 years was 18.7% (n=3). These rates support the need for colonoscopic examination, regardless of age, at the earliest possible time when patients are diagnosed with acromegaly. Our two patients with acromegaly diagnosed with colorectal cancer during screening were 65 and 68 years of age.

Studies on the location of polyps in patients with acromegaly are controversial. Some studies have reported that polyps form more frequently in the right colon in patients with acromegaly.[18] In a 2020 study by Ochiai et al.,[19] significantly more polyps were detected in the sigmoid colon and rectum compared with the control group. We found no significant difference in the location and detection rate of polyps in the right and left colon in the acromegaly group compared with the control group in our study.

In another study by Wassenaar et al.,[20] it was found that the diverticulum rate was high in patients with acromegaly. In our study, it was found to be similar to the control group.

The length of the colon is increased in patients with acromegaly, and standard bowel preparation is often inadequate because the transit time of the colon is more than double.[21,22] In our study, we found that inadequate bowel preparation was significantly higher in the acromegaly group than in the control group. GH levels at the time of diagnosis were also significantly higher in patients with inadequate bowel preparation. In our study, it can be concluded that there was inadequate colon cleansing due to the increase in intestinal length and slowing of bowel movements with increased GH. Our study can be considered an original contribution to the literature and shed light on new studies on this topic because we could not find any other publication in the literature comparing GH levels in patients with acromegaly with and without inadequate bowel preparation.

This study's limitation can be a single-center and retrospective study. The inability to collect complete and sufficient data from all patients may be a problem because some of the patients were examined in our center only for colonoscopy and followed up and treated in other centers, and some patients were referred to our center for surgery from surrounding provinces and had their colorectal scans performed in the center from which they were referred. This has resulted in a small number of patients with complete data.

CONCLUSION

In this study, although the frequency of polyps was significantly higher in patients with acromegaly, we found no significant difference in colorectal cancer. We found no significant difference between the acromegaly and control groups in non-polyp colonoscopy findings, polyp location, and histological types. Since inadequate bowel preparation is more common in patients with acromegaly (especially in patients with high GH at the time of diagnosis), bowel preparation should be performed with a different approach other than standard bowel preparation. More data is required on the need for colonoscopic screening in patients with acromegaly who are at relatively higher risk for colorectal malignancy. For this reason, there is a need for multicenter and prospective studies in larger series that include colonoscopic findings, clinical and laboratory data, and compare patients with acromegaly with each other and with the control group.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Karadeniz Technical University Ethics Committee (Date: 10.03.2022, Decision No: 161).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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Original Article

MEDICINE PALLIATIVE CARE

DOI: 10.47582/jompac.1345407

J Med Palliat Care. 2023;4(5):400-405

Neutrophil-to-high-density lipoprotein ratio: an independent predictor of infarct-related artery patency in patients with acute myocardial infarction

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Cite this article as: Demirtaş B, Çetin Güven Z. Neutrophil-to-high-density lipoprotein ratio: an independent predictor of infarct-related artery patency in patients with acute myocardial infarction. *J Med Palliat Care*. 2023;4(5):400-405.

Received: 18.08.2023 ◆ **Accepted**: 06.09.2023 ◆ **Published**: 27.10.2023

ABSTRACT

Aims: The definition of an infarct-related artery (IRA) is a coronary artery occluded by a thrombus or atheroma that causes ischemia during acute myocardial infarction (AMI). Early patency of the IRA is the primary goal of treatment in patients with AMI. The neutrophil/ high-density lipoprotein cholesterol (HDL-C) ratio (NHR) has been recognized as a new inflammatory marker. We aimed to show the possible relationship between NHR and preprocedural IRA patency.

Methods: Four hundred patients were screened, and 318 were included in the study after exclusion criteria. IRA flow rate before the coronary procedure was determined according to the previously described thrombolysis in myocardial infarction (TIMI). TIMI current 0,1 and 2 patients were considered IRA non-patent, and TIMI-3 patients were considered IRA patent and were divided into two groups. Regression analysis was performed for possible parameters in predicting IRA patency, evaluated in univariable analysis, and those with p-value <0.05 were assessed in multivariable analysis.

Results: The mean age was 62.3±11.9 years, and 73.4% were male. In multivariable logistic regression analysis, high peak troponin (ng/ml) (p<0.001, OR: 0.936, 95% CIs: 0.910-0.962) and NHR (p= 0.020, OR: 0.043, 95% CIs: 0.003-0.603) levels were found to be independent predictors of patent IRA.

Conclusion: Our study investigated the relationship between IRA patency and NHR in AMI patients. The main finding of our research is that significantly higher NHR and peak troponin levels were associated with non-patent IRA patients and were independent predictors.

Keywords: Acute myocardial infarction, vascular patency, high-density lipoprotein, neutrophil

INTRODUCTION

Acute myocardial infarction (AMI) is a condition of myocardial ischemia resulting from the acute decrease in coronary artery blood flow after rupture or erosion of coronary atherosclerotic plaque. Despite modern fibrinolytic and early reperfusion treatment strategies, it is the leading cause of death in the world.[1] The definition of an infarct-related artery (IRA) is a coronary artery occluded by a thrombus or atheroma that causes ischemia during AMI.[2] Patients with ST-elevation myocardial infarction (STEMI) have transmural ischemia, and the IRA is usually occluded at admission, so early treatment strategies are of great importance. Non-ST-elevation myocardial infarction (NSTEMI) patients have subendocardial ischemia, and 30% of the IRA is occluded at admission.[3] Early provision of IRA patency has been identified as the primary goal in all treatment strategies in terms of improving prognosis. Improved ventricular performance and reduced in-hospital death rates are seen in IRA patent patients on admission.[4]

The pathophysiology of coronary artery disease (CAD) is quite complex. Inflammation, altered lipid metabolism, oxidative stress, and other processes are considered effective in pathophysiological processes. Inflammation plays an essential role in the pathogenesis of atherosclerosis and AMI.[5] The neutrophil/ high-density lipoprotein cholesterol (HDL-C) ratio (NHR) has been recognized as a new inflammatory marker. This is because neutrophils and HDL-C particles have opposing effects: while neutrophils play an active role in inflammation,[6] HDL-C has antioxidant and anti-inflammatory properties. HDL-C protects the endothelium against the effects of low-density lipoprotein cholesterol (LDL-C) and thus has an antioxidant and anti-inflammatory effect.[7] In previous

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studies, high NHR is associated with cardiovascular disease prognosis and severity. It is associated with prognosis in patients with STEMI and acute ischemic stroke.[8,9] It has also been an independent predictor of coronary artery disease severity.[10]

In our study, we aimed to show the possible relationship between NHR, this inflammatory marker is new and associated with cardiovascular disease prognosis and preprocedural IRA patency, an important prognostic indicator in outcomes such as ventricular performance and in-hospital mortality.

METHODS

The study was carried out with the permission of Ankara Etlik City Hospital No: 1 Clinical Researches Ethics Committee (Date: 05.04.2023, Decision No: 2023-047). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Our retrospective case-control study enrolled AMI patients who applied to our center between November 2022 and January 2023. Four hundred patients were analyzed, and 318 were included in the study after exclusion criteria. The diagnosis of AMI was made according to the criteria of the "Fourth Universal Myocardial Infarction Guidelines" published by the European Heart Association in 2018.[11] All patient data were obtained using the hospital's digital database. Exclusion criteria were; being under the age of 18, severe valve disease, active infection, acute liver/kidney failure, active cancer, history of inflammatory disease, receiving fibrinolytic therapy within 24 hours, and rheumatological disease.

NHR was obtained by dividing the neutrophil (10^3/ml) and serum HDL-C levels (mg/dl) received at admission. The modified Simpson method calculates the left ventricular ejection fraction (LVEF).

Coronary arteries were visualized using the standard Judkins technique. Angiographic images of the patients were obtained and evaluated via the hospital's digital PACS system. IRA was detected for each patient; patients with more than one IRA were not included in the study. Each coronary artery was visualized and evaluated in at least two planes. Two experienced cardiologists, unaware of patient groups, blindly evaluated coronary angiograms and coronary artery flow rates. Before percutaneous coronary intervention, thrombolysis in myocardial infarction (TIMI) flow grade was documented for each patient. IRA flow rate before the coronary procedure was determined according to the previously described TIMI.[12] TIMI current 0, 1 and 2 patients were considered IRA non-patent, TIMI-3 patients were considered IRA patent and were divided into two groups.[13]

Statistical Analysis

Statistical analyzes of the study were performed using SPSS 25.0 for Windows. Continuous variables were shown as mean±standard deviation. Categorical variables were given as numbers and percentages. The normal distribution of the data was evaluated with the Shapiro-Wilk test. We used Levene's test to determine the homogeneous distribution. The student-t test was used for normally distributed continuous variables fulfilling the parametric test conditions, and the Mann-Whitney U test was used to compare the variables that did not show the normal distribution and did not meet the parametric test conditions. Categorical variables were compared by χ^2 test. Receiver operating characteristic curve (ROC) analysis was used to define the optimum cut-off level of NHR and the area under the curve to estimate IRA patency. Regression analysis was performed for possible parameters in predicting IRA patency, evaluated in univariable analysis, and those with p-value <0.05 were evaluated in multivariable analysis. P<0.05 was considered to be statistically significant.

RESULTS

A total of 318 patients were included in the study, and they were divided into two groups IRA non-patent (n: 182) and IRA patent (n: 136). The mean age was 62.3±11.9 years, and 73.4% were male. Age was significantly higher in the IRA patent group (64.4±11.3 vs 60.8±12.1, p= 0.007). Hypertension history was more common in the IRA patent group (52.2% vs 40.1%, p= 0.032). Peak troponin value was significantly higher in the IRA non-patent group (14.7±10.1 vs. 6.9±8.2, p<0.001). No statistically significant difference was observed when troponin analysis was performed according to TIMI-0 vs. TIMI-1,2 subgroups in the non-patent group (15.08±10.2 vs. 13.1±10.0, p=0.198). Baseline clinical, laboratory, and angiographic characteristics between groups are shown in **Table 1**. A comparison of NHR in study groups is shown in **Figure 1**.

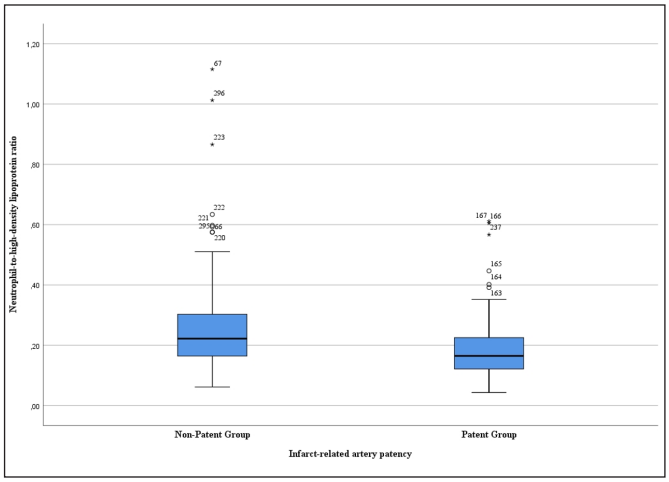

Figure 1. Comparison of NHR in study groups

Table 1. Baseline clinical, laboratory, and angiographic characteristics between groups

Variables	All patients, (n: 318)	IRA Non-patent Group, (n: 182)	IRA patent Group, (n: 136)	p
Sex, male n (%)	235 (73.4%)	139 (76.4%)	96 (70.6%)	0.245
Diabetes mellitus, n (%)	205 (64.5%)	59 (32.4%)	54 (39.7)	0.179
Hypertension, n (%)	174 (54.7%)	73 (40.1%)	71 (52.2%)	0.032
Previous history of CAD, n (%)	215 (67.6%)	51 (28.0%)	52 (38.2%)	0.054
Age, years	62.3±11.9	60.8±12.1	64.4±11.3	0.007
Serum glucose, mg/dl	151.8±72.2	155.1±73.0	147.3±71.2	0.339
Serum creatinine, mg/dl	0.92±0.34	0.91±0.31	0.92±0.36	0.751
Urea, mg/dl	35.7±17.0	35.5±17.7	36.0±16.2	0.792
Total cholesterol, mg/dl	183.0±48.0	179.3±45.6	188.0±50.8	0.113
LDL-cholesterol, mg/dl	127.0±43.6	126.3±41.9	128.0±45.9	0.740
HDL-cholesterol, mg/dl	39.6±9.9	39.3±10.1	40.0±9.8	0.504
Triglyceride, mg/dl	139.8±91.6	132.7±86.4	149.3±97.5	0.109
Sodium, mmol/L	137.3±2.9	137.0±3.0	137.7±2.7	0.036
Potassium, mmol/L	4.2±0.4	4.2±0.4	4.2±0.4	0.610
White blood cell count, 103/ml	11.22±3.83	12.25±4.03	9.84±3.07	<0.001
Hemoglobin, g/dl	13.6±1.9	13.7±1.9	13.5±1.9	0.231
Platelet count, 103/ml	256.6±74.4	259.0±78.6	253.3±68.6	0.506
Neutrophil count, 103/ml	8.35±3.79	9.36±3.98	7.00±3.05	<0.001
Lymphocyte count, 103/ml	1.97±0.90	1.97±0.97	1.98±0.80	0.943
Peak troponin, ng/ml	11.4±10.1	14.7±10.1	6.9±8.2	<0.001
NHR	0.225±0.130	0.254±0.145	0.186±0.096	<0.001
Left ventricular EF, (%)	47.2±10.7	45.3±9.8	49.8±11.5	<0.001
Infarct-related artery, n (%)				
Left anterior descending artery	126 (39.6%)	76 (41.8%)	50 (36.8)	0.368
Circumflex artery	80 (25.2%)	44 (24.2%)	36 (26.5%)	0.641
Right coronary artery	112 (35.2%)	62 (34.1%)	50 (36.8%)	0.618

CAD: coronary artery disease, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, NHR: Neutrophil to High-density lipoprotein ratio, EF: ejection fraction

In multivariable logistic regression analysis, high peak troponin (ng/ml) (p<0.001, Odds Ratio (OR): 0.936, 95% Confidence Intervals (CIs): 0.910-0.962) and NHR (p= 0.020, OR: 0.043, 95% CIs: 0.003-0.603) levels were found to be independent predictors of patent IRA. Univariable and multivariable regression analyses of potential predictive factors in determining IRA patency are shown in Table 2.

Table 2. Univariable and multivariable logistic regression analysis showing the independent predictors for the IRA patency

Variables	Univariable analysis		Multivariable analysis	
	OR (95% CI)	p	OR (95% CI)	p
Hypertension	0.613 (0.392-0.960)	0.033	0.738 (0.438-1.243)	0.254
Age, years	1.027 (1.007-1.047)	0.008	1.023 (1.000-1.046)	0.053
Sodium	1.087 (1.005-1.176)	0.037	1.065 (0.976-1.162)	0.159
Peak troponin	0.920 (0.897-0.943)	<0.001	0.936 (0.910-0.962)	<0.001
NHR	0.003 (0.000-0.037)	<0.001	0.043 (0.003-0.603)	0.020
LVEF, (%)	1.041 (1.018-1.064)	<0.001	1.020 (0.996-1.046)	0.106

OR: Odds ratio, CI: confidence interval NHR: Neutrophil to HDL ratio, LVEF: left ventricular ejection fraction

As revealed by the ROC curve analysis, the cut-off value of 0.192 for NHR predicted the non-patent IRA with a sensitivity of 61.5% and specificity of 61.8% (AUC: 0.680; CIs: 0.621-0.740; p<0.001; Figure 2).

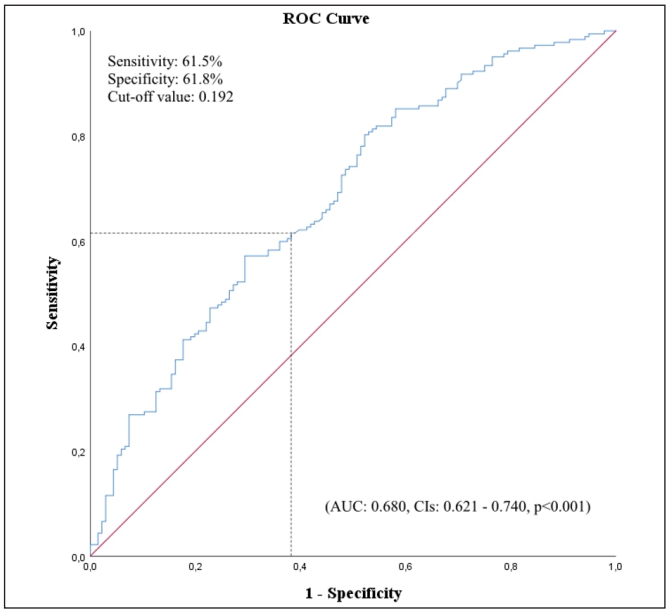

Figure 2. Receiver operating characteristics (ROC) curves of NHR associated with IRA patency

DISCUSSION

Our study investigated the relationship between IRA patency and NHR in AMI patients. The main finding of our research is that significantly higher NHR and peak troponin levels were associated with non-patent IRA patients and were independent predictors.

Troponin is a contractile protein involved in myocardial contraction. It is secreted from ischemic tissue when the coronary artery is wholly or partially occluded by atheroma or thrombus, and myocardial blood flow decreases. It has an essential place in the diagnosis of AMI. Troponin levels are significantly higher in IRA non-patent patients.[14] Although troponin values were significantly higher in the non-patent group, we found high troponin values to be an independent predictor of IRA patency.

Our study found a significantly higher age in the IRA-patent group. No studies are comparing IRA patency with age in AMI patients. A previous study also reported that preprocedural IRA patency in STEMI patients was more common in older individuals, and advanced age was an independent predictor.[15] This is consistent with the findings of our study. However, the regression analysis did not detect age as an independent predictor.

Early patency of the IRA is the primary goal of treatment in patients with AMI. Non-patent IRA at admission has been associated with poor clinical outcomes. Early provision of IRA patency is essential in preserving ventricular performance and reducing the risk of mechanical and fatal arrhythmias, especially in STEMI patients.[16] On the other hand, it was observed that IRA was non-patent at the rate of 30% at admission in NSTEMI patients.[3] IRA patency is decided according to the TIMI flow rate. TIMI-3 flow rate monitoring at admission has been associated with good clinical outcomes.[13] Stone et al.[17] found that LVEF, an important prognostic marker, was preserved in patients with IRA flow TIMI-3 and achieved better results than those with TIMI-0, 1 and 2. In our study, LVEF, an important prognostic marker in AMI patients, was significantly lower in the IRA non-patent group. Restoring early IRA patency offers the advantage of reduced infarct area, in-hospital mortality, and arrhythmia complications.[18] IRA patency in admission is also an important indicator of post-procedural patency. Failure to obtain IRA patency angiographically; a post-procedural IRA non-patent is defined as no-reflow and is a known predictor of poor prognosis.[19] For all these reasons, early estimation and restoration of IRA patency are critical in terms of prognosis. In previous studies, researchers investigated the role of different markers in predicting IRA patency at admission. In their study, Doğan et al.[20] reported that neutrophil-lymphocyte ratio, another inflammatory marker, predicts IRA patency in STEMI patients. Another study examined hematological parameters in STEMI patients who underwent primary angioplasty. The number of white blood cells (WBC), which plays a vital role in inflammation, was associated with IRA patency.[21] Our findings are similar to non-patent IRA patients' significantly higher WBC count. When the results of these studies are evaluated, it may be said that the underlying mechanism of IRA patency is inflammation.

Inflammation is essential in developing atherosclerotic plaque formation and initiating and progressing intracoronary thrombus formation in AMI.[22] Neutrophils play a crucial role in the AMI process. It is known that atherogenesis, the primary mechanism of coronary artery disease, and plaque erosion, one of the initial pathophysiological stages of AMI, are involved. After plaque erosion and rupture, the subendothelial tissue comes into contact with blood, neutrophils, and platelets rapidly collect in the lesion area, activating the coagulation cascade, and a thrombus forms.[23,24]

HDL-C has anti-inflammatory, antioxidant, antithrombotic, anti-atherosclerotic, and reverse cholesterol transport effects.[25] Atherosclerosis and stable coronary artery disease, which constitute the previous mechanism in AMI, are closely related to inflammation. Özkan et al.[26] reported in their study that the Systemic Immune-Inflammation Index predicted coronary artery severity. Because neutrophils are a cell group that has an active role in inflammation and HDL-C has anti-inflammatory effects, we can accept NHR as a new inflammatory marker that more strongly indicates inflammation. NHR, an indicator of inflammatory cells and lipid cholesterol, could be a new indicator showing inflammatory and lipid metabolism together. It has been demonstrated that NHR indicates prognosis as an inflammatory marker in patients with ischemic stroke and patients with STEMI.[8,9] NHR, a combined parameter over a single parameter, may be more comprehensive and reliable.

In light of the results of our study, we showed that NHR, an inexpensive and easily calculable biomarker, can be an independent predictor of preprocedural IRA patency status in patients presenting with AMI.

This study has some limitations. The first is that it is a single-center and retrospective study. We could not examine inflammation markers, CRP, and cytokines as they have not been routinely studied. Third, we only calculated NHR at admission and did not evaluate follow-up values. Fourth, since door-to-balloon time is not routinely recorded in AMI patients in our

center, this condition, which impacts thrombotic/antithrombotic mechanisms, could not be evaluated in our study. However, the findings of our study may be valuable for future studies and can be used in risk classification.

CONCLUSIONS

In conclusion, in this study, we found that high NHR levels were an independent predictor of non-patent IRA at presentation. Based on our findings, using NHR to estimate IRA patency in daily clinical practice may be valuable in risk and prognosis assessment. More extensive and more comprehensive studies are needed on this useful inflammatory biomarker.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara Etlik City Hospital No: 1 Clinical Researches Ethics Committee (Date: 05.04.2023, Decision No: 2023-047).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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Original Article

MEDICINE PALLIATIVE CARE

DOI: 10.47582/jompac.1343788

J Med Palliat Care. 2023;4(5):406-411

Effects of smoking on the cardiopulmonary modulation during physical exercise in middle-aged non-obese healthy individuals

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Cite this article as: Kocak A, Yıldırım O, Coşgun A, Türkkanı MH. Effects of smoking on the cardiopulmonary modulation during physical exercise in middle-aged non-obese healthy individuals. *J Med Palliat Care*. 2023;4(5):406-411.

Received: 15.08.2023 • **Accepted**: 06.09.2023 • **Published**: 27.10.2023

ABSTRACT

Aims: The aim of this study was to evaluate the overall effects of smoking and its duration on various cardiopulmonary modulation mechanisms during physical exercise in middle-aged non-obese healthy individuals.

Methods: Two hundred forty-three (142 smokers and 101 non-smokers), middle-aged, non-obese, healthy individuals were evaluated in this study. Parameters of pulmonary function including forced vital capacity (FVC), forced expiratory volume in the first second (FEV1) and FEV1/FVC ratio were evaluated using a spirometer and systolic pulmonary artery pressure (sPAP) were measured by echocardiography on rest and during various levels of exercise. A treadmill exercise test was used to assess heart rate recovery index (HRRI), the chronotropic index (CI) and the maximum rate of oxygen consumption during exercise (VO2max).

Results: Resting sPAP values were higher and FEV1, FVC and FEV1/FVC values were lower among smokers. As compared to resting values; FEV1 and FEV1/FVC ratio in smokers decreased significantly at peak exercise level (2.66±0.54 vs 2.35±0.49, p<0.01 and 81.57±8.21 vs 75.11±8.12, p<0.01 respectively). The HRRI values of all 1st, 2nd and 3rd minutes were significantly lower in the smoker group. Similar results were observed with CI and VO2max values (0.67±0.21 vs 0.76±0.19, p<0.01 and 34.91±4.63 vs 38.47±3.24, p<0.01 respectively). In addition, all mentioned parameters were significantly correlated with smoking duration.

Conclusion: Smoking is associated with a variety of adverse effects that may eventually reduce the exercise capacity of healthy individuals. These effects can manifest at early stages, and their severity correlates significantly with smoking duration.

Keywords: Smoking, physical exercise, cardiopulmonary function, chronotropic incompetence

INTRODUCTION

Smoking is a major preventable cause of morbidity and mortality worldwide due to its association with numerous pulmonary and cardiovascular diseases as well as cancer.[1] The airway obstruction and inflammatory changes of chronic obstructive lung diseases are attributed to smoking.[2] On the other hand, smoking is a well-known modifiable risk factor for atherosclerosis and cardiovascular diseases.[3]

During exercise, the body's oxygen consumption increases. In response, the cardiopulmonary system goes through physiological changes or modulation mechanisms, such as increasing cardiac output via chronotropic responses and enhancing the respiratory system's ventilatory capacity to meet body demands.[4,5] Smoking has been shown to have adverse effects on cardiac autonomic responses to exercise specifically in relation to the chronotropic responses and heart rate recovery (HRR).[6,7] The evaluation of these parameters can give an insight on cardiac modulation mechanisms during physical exercise.[8,9] Studies have also demonstrated that smoking is correlated with a decline in lung function, which consequently leads to potential limitations on an individual's daily activities and exercise capacity.[10] The evaluation of pulmonary function can be achieved using a spirometer. Furthermore, the assessment of maximal oxygen uptake (VO2max) during physical activity can provide valuable insights on individual's aerobic endurance performance. 11 In addition, smoking may also increase the pulmonary arterial pressure because of chronic hypoxia, increased pulmonary angiotensin-converting enzyme activity and increased sympathetic activation leading to chronic vasoconstriction of the pulmonary arteries.[12,13] Typically, systolic pulmonary artery pressure (sPAB) rises linearly with cardiac output;

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however, An abnormal increase in sPAB can be an early indicator of pulmonary vascular disease, which can eventually disrupt exercise capacity and respiratory health.[14]

Impaired or decreased physical activity during the middle age years can increase the risk of premature death and impede healthy aging.[15] The aim of our study was to assess the impact of smoking and its duration on diverse cardiopulmonary modulation mechanisms during physical exercise among middle-aged non-obese healthy individuals in order to provide a comprehensive understanding of the implications of smoking on physical fitness and exercise capacity.

METHODS

The study was carried out with the permission of Lokman Hekim University Scientific Researches Ethics Committee (Date: 21.12.2022, Decision No: 2022/196). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Population and Design

This retrospective study evaluated middle-aged healthy individuals who presented to our cardiology outpatient clinic between June and December 2022. Individuals with a body mass index (BMI) exceeding 30 kg/m² were not subjected to evaluation. The smoking status and the duration of smoking were documented. Fasting blood glucose, total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglyceride, and hemoglobin levels with kidney, liver, and thyroid function test results were taken from recent medical records. The demographic data of all participants was also recorded. The exclusion criteria comprised the presence of any cardiovascular, pulmonary, or other systemic diseases like hypertension or diabetes. Participants with impaired liver, renal, and thyroid function tests or electrolyte disturbances were also excluded. Consequently, a total of 243 individuals, comprising 142 smokers and 101 non-smokers, were included in the study.

Transthoracic echocardiography (TTE)

All subjects underwent two-dimensional echocardiography examination using Philips Epiq 5 device. Continuous wave (CW) Doppler of the tricuspid valve regurgitation (TR) tracing was used to measure the pressure difference between the right ventricle and the right atrium. In the simplified Bernoulli formula (P=4 [TRmax]2), the value obtained by the CW replacing over TR and the pressure difference between the right atrium and ventricle was calculated. The value obtained from the Bernoulli formula is calculated by the addition of right atrial pressure (RAP) to calculate sPAP.[16,17]

Respiratory Function Test (RFT)

The test was performed using a digital spirometer (SP10, Contec Medical, China). After deep inspiration, the subjects were asked to perform a vigorous expiration to the spirometer. The same procedure was performed three times successively. Measurements of Forced vital capacity (FVC), forced expiratory volume in the first second (FEV1) and FEV1/FVC ratio we recorded. The obtained vales from three different measurements were determined using averages. Subjects with FEV1/FVC ratio less than 70% were considered to have obstructive findings and were excluded.

Pulse Oximetry

Peripheral oxygen saturation (POS) of study participants was measured by pulse oximetry. The measurements were taken in normal room temperature. During a one-minute pulse oximetry measurement, the most frequently repeated value was recorded.

Treadmill Exercise Test (TET)

All the participants performed the TET. Before starting the test, basal sPAP, RFT, and POS values were recorded. Participants abstained from heavy eating, coffee and alcohol, and smokers from smoking two days before the test day. Drugs that are likely to influence the reliability of the test were discontinued. Blood pressure and 12-lead ECG recordings were obtained every 3 min over the course of stress testing and in the 1st, 2nd and 3rd minutes of recovery. HRRI values were obtained by subtracting the first, second, and third-minute recovery HR values from the peak HR value. Measurements of sPAP, POS, and RFT were repeated during peak exercise and after the 3rd minute of the recovery period. The chronotropic index was calculated using the formula; (Maximal HR - Resting HR)/(Predicted maximal HR - Resting HR).18 The VO2 max was calculated using the formula (Males: 3.88 + 0.056 × D and Females: 1.06 + 0.056 × D, where D= test duration in seconds).11

Statistical Analysis

The normal distribution of continuous variables was assessed using the Kolmogorov-Smirnov test and were defined as means±standard deviation. Categorical variables are commonly presented using percentages and frequencies. The Student's t-test was used to assess the differences between continuous variables, while the Chi-square test was utilized to examine associations among categorical variables. The paired samples T-test was used to compare the different values within the same group. Z test was used to compare ratios. Pearson correlation test was used to determine the correlation between the variables. P <0.05 was considered statistically significant. Statistical analysis was performed using SPSS version 24.0 (IBM Co., USA).

RESULTS

The baseline clinical features and socio-demographic characteristics showed no statistically significant differences between the study groups (Table 1). The mean smoking duration was 17.13±8.63 year. Resting sPAP values were significantly higher and the FEV1, FVC, FEV1/FVC and POS values were significantly lower in the smoker group. There was no difference between the study groups in terms of resting and peak exercise HR, but the 1st, 2nd, and 3rd minute-recovery HR were significantly higher in the smoker group. The HRRI in the smoker group was significantly lower than the non-smokers in all of 1st, 2nd and the 3rd minutes. The CI and VO2max values were significantly lower in the smoker group (Table 2). The sPAP values of the smoker group were significantly higher on peak exercise and during the recovery period. Contrarily, the peak and recovery values of all FEV1, FVC, FEV1/FVC and POS were significantly lower in the smoker group (Table 2).

AS compared to resting values, both FEV1 and FEV1/FVC ratio decreased significantly at the peak exercise level of the smoker group (2.66±0.54 vs 2.35±0.49, p<0.01 and 81.57±8.21 vs 75.11±8.12, p<0.01, respectively). This decline in respiratory function was not significant in the non-smoker group (2.84±0.49 vs 2.74±0.71, p=0.25 and 83.64±5.35 vs 82.31±2.04, p=0.21 respectively). Regarding sPAP values, there was a significant increase in sPAP values during peak exercise as compared to resting values in the smoker group (34.67±5.42 vs 44.69±7.47, p<0.01), this increase was less significant among controls (18.95±3.35 vs 20.12±3.91, p=0.023).

Table 1. Socio-demographic characteristics and baseline clinical features of study participants

Variables	Smoker Group (n=142)	Control group (n=101)	P value
Age, years	43.72±11.53	41.27±9.53	0.69
Gender			
Male, %	70.62	70.29	0,96
Female, %	29.38	29.71	0,96
BMI, kg/m²	25.35±2.73	25.52±2.91	0,64
Basal SBP, mm Hg	124.73±13.52	123.27±12.81	0,39
Basal DBP, mm Hg	74.83±8.16	75.10±7.94	0,79
Total Cholesterol, mg/dl	169.27±40.63	170.05±35.72	0,87
LDL, mg/dl	107.63±21.94	106.91±19.62	0,79
Triglycerides, mg/dl	161.63±21.73	160.95±20.83	0,8
Hemoglobin, gr/dl	14.36±2.93	14.44±2.85	0,83
Calcium, mg/dl	9.83±1.25	9.81±0.99	0,89
Sodium, mEq/L	140.94±2.94	141.07±1.89	0,69
Potassium, mEq/L	4.07±0.63	4.11±0.83	0,66
Magnesium, mg/dl	1.89±0.31	1.91±0.35	0,63

Abbr: BMI; Body Mass Index, SBP; Systolic Blood Pressure, DBP; Diastolic Blood Pressure, HR; Heart Rate, LV; Left Ventricle

Table 2. Comparison of the cardiopulmonary parameters of study participants during various levels of the treadmill exercise test

Variables	Smoker group (n=142)	Control group (n=101)	P value
On rest			
Resting HR	94.62±14.42	94.54±5.82	0.95
Resting sPAP	34.67±5.42	18.95±3.35	<0.01
Resting FEV1	2.66±0.54	2.84±0.49	0.01
Resting FVC	3.24±0.61	3.46±0.69	<0.01
Resting FEV1/FVC	81.57±8.21	83.64±5.35	0.027
Resting POS	96.01±1.72	96.59±1.24	<0.01
During peak exercise			
Peak HR	165.72±7.19	165.15±7.51	0.54
Chronotropic index	0.67±0.21	0.76±0.19	<0.01
VO2 Max	34.91±4.63	38.47±3.24	<0.01
Peak sPAP	44.69±7.47	20.12±3.91	<0.01
Peak FEV1	2.35±0.49	2.74±0.71	<0.01
Peak FVC	3.19±0.57	3.39±0.61	<0.01
Peak FEV1/FVC	75.11±8.12	82.31±2.04	<0.01
Peak POS	91.90±0.97	96.18±0.98	<0.01
During the recovery period			
1st minute Recovery HR	135.13±14.59	130.98±7.62	<0.01
2nd minute Recovery HR	118.37±14.51	111.16±6.54	<0.01
3rd minute Recovery HR	111.69±16.68	95.05±8.89	<0.01
HRRI 1st minute	30.58±11.71	34.16±8.24	<0.01
HRRI 2nd minute	47.34±13.38	53.98±7.74	<0.01
HRRI 3rd minute	54.02±17.16	70.09±10.69	<0.01
Recovery sPAP	39.37±7.36	17.19±2.27	<0.01
Recovery FEV1	2.51±0.57	2.77±0.47	<0.01
Recovery FVC	3.21±0.69	3.44±0.62	<0.01
Recovery FEV1/FVC	79.25±8.52	84.29±2.21	<0.01
Recovery POS	94.20±1.55	97.22±0.86	<0.01

Abbr: HR; Heart Rate, sPAP; systolic pulmonary artery pressure, FEV1; forced expiratory volume during the 1st second, FVC; forced vital capacity, POS; partial oxygen saturation, HRRI; heart rate recovery index

In the smoker group, there was a statistically significant negative correlation between smoking duration and the HRRI values. A significant negative correlation was also observed between smoking duration and the CI, VO2max, resting FEV1, resting FVC, resting FEV1/FVC, and resting POS values. In addition, there was a statistically significant positive correlation between smoking duration and resting sPAP values (Table 3).

Table 3. The correlations between smoking duration and parameters of cardiopulmonary function

Variables	Correlation with smoking duration	
	R-value	P-value
HRRI 1	-0.78	<0.01
HRRI 2	-0.64	<0.01
HRRI 3	-0.51	<0.01
VO2 Max	-0.38	<0.01
Chronotropic index	-0.43	<0.01
Resting sPAP	0.64	<0.01
Resting FEV1	-0.48	<0.01
Resting FVC	-0,36	<0.01
Resting FEV1/FVC	-0.41	<0.01
Resting POS	-0.38	<0.01

Abbr: HR; Heart Rate, sPAP; systolic pulmonary artery pressure, FEV1; forced expiratory volume during the 1st second, FVC; forced vital capacity, POS; partial oxygen saturation, HRRI; heart rate recovery index

DISCUSSION

The present study assessed the overall effects of smoking on the cardiopulmonary modulation mechanisms during physical exercise in middle-aged non-obese healthy individuals. Study results demonstrated that during physical exercise smokers exhibited a more significant decline in respiratory function parameters, including FEV1, FVC and FEV1/FVC with lower VO2max and POS levels, as compared to non-smokers. Furthermore, a more exagurated increase in sPAB was seen among smokers. On the other hand, the autonomic responses to exercise as evaluated by the CI and HRRI were lower in the smoker group. These variations were in correlation with smoking duration.

The effects of smoking on the pulmonary system can be attributed to a variety of factors. It promotes the destruction of alveolar walls and the expansion of air spaces distal to the terminal bronchioles, resulting in airway obstruction and diminished lung function.[2] Smoking is also known to cause fatigue of the skeletal muscles, and studies have concluded that abnormalities in skeletal muscles endurance can result in abnormalities of breathing efficiency.[19,20] Both airflow obstruction and breathing abnormalities may lead to hyperinflation and decreased exercise capacity. These consequences can be seen even in the early phases of cigarette smoking.[21] Twisk et al. reported that smoking deteriorates lung function by causing a decrease in the FVC and FEV1.[22] Another more recent study showed that smoking is associated with a significant decrease in FEV1/FVC ratio.[23] Similar findings were observed in the spirometry results of our study participants at rest. Furthermore, smoking duration was significantly correlated with all of FEV1, FVC and FEV1/FVC values at rest. While both groups experienced a decline in these parameters during peak exercise and the recovery period, study results showed that the decline in FEV1 and FEV1/FVC ratio is more significant among smokers. These findings suggests that in addition to the chronic obstructive effects of smoking on respiratory airways during rest, it can cause further deterioration of respiration during exercise, and continue even in the period of recovery. In our study, oxygen saturation levels were also measured on rest, during peak exercise and in the recovery period and similar results were observed.

Other than the pulmonary system, effects of smoking on the autonomous nervous system have been studied for a long time. Studies showed that smoking impairs the sympathetic activation and vagal modulation of the heart during exercise.[24] The increased metabolic demands during exercise are met by increasing cardiac output, which is accomplished by an increase in heart rate and stroke volume. This increase in HR is regulated by exercise induced autonomic control, where sympathetic activity increases, and vagal tone is reduced.[25] Smokers may experience chronotropic incompetence, which encounter a diminished HR response to exercise and considered as a predictor of cardiovascular mortality.[11] The smoker participants of our study had lower values of CI than non-smokers, which supports the association of smoking with chronotropic incompetence even in healthy individuals.

After the termination of exercise, sympathetic activity is withdrawn, and vagal reactivation causes the heart rate to return to baseline levels. The activation of the parasympathetic nervous system is significant in the early period after exercise, whereas the withdrawal of the sympathetic nervous system is effective in the later period.[26] Evaluating HRRI gives an idea about the parasympathetic response of the autonomic nervous system to exercise and its association with cardiovascular diseases.[27] In parallel to this, we observed a significant decrease in the HRRI rates of the 1st, 2nd, and 3rd minutes for smokers compared to nonsmokers. Since our study population is composed of healthy individuals, we can conclude that the effect of smoking on HRRI is independent from other comorbidities and that smoking can directly be responsible of exaggerating the sympathetic activity and suppressing the vagal response during physical exercise. Moreover, the parameters of autonomic modulation during exercise were all significantly correlated with smoking duration.

Another more recent predictor of cardiopulmonary function during exercise is VO2max. Studies showed that the evaluation of VO2max can be used to quantify endurance fitness and exercise capacity.[28] The smoker participants of our study had significantly lower VO2max values than non-smokers, implying a decline in physical fitness as a result of smoking. The changes in VO2max were also correlated with smoking duration.

In addition to the previous studies, we also examined the effects of smoking on the pulmonary circulation during exercise and the recovery period. Smoking is known to cause pulmonary artery remodeling and hypoxic vasoconstriction, both of which may contribute to the development of pulmonary hypertension (PH).[29] In our study, we measured the sPAP of study participants at rest and compared it to sPAP measurements taken during the peak exercise and the recovery period. At rest, sPAP values were significantly higher among smokers and resting sPAP values were correlated with smoking duration. Furthermore, smokers had significantly higher peak exercise and recovery sPAP values compared to baseline levels. Whereas the increase of sPAP in the non-smoker group was less significant. Beside the chronic morphological changes of the pulmonary vasculature,

the increased sympathetic activity seen among the smoker participants of our study may be the reason of the higher increase and the delayed fall of sPAP during exercise.[30]

The main limitation of our study was the small sample size; with a larger population, more precise data could be obtained. Moreover, the absence of randomization in the design constituted an important limitation. The impact of daily lifestyle habits, including dietary patterns, alcohol consumption, and the routine daily activity, on exercise performance was not assessed. In addition, smoking status was determined based on patients' self-reports rather than a more reliable test, such as the exhaled carbon monoxide or serum nicotine tests, which were unavailable.

CONCLUSION

Our study demonstrated that smoking is associated with a number of negative consequences that may eventually limit exercise capacity and have an adverse effect on healthy aging. These deleterious effects may start at early stage of smoking but are significantly correlated with smoking duration.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Lokman Hekim University Scientific Researches Ethics Committee (Date: 21.12.2022, Decision No: 2022/196).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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Original Article

MEDICINE PALLIATIVE CARE

DOI: 10.47582/jompac.1346527

J Med Palliat Care. 2023;4(5):412-417

Serum prealbumin levels and their association with serum albumin, calcium, magnesium, and phosphorus concentrations

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Cite this article as: Öztürk A, Demirci G. Serum prealbumin levels and their association with serum albumin, calcium, magnesium, and phosphorus concentrations. *J Med Palliat Care*. 2023;4(5):412-417.

Received: 19.08.2023 ◆ **Accepted**: 07.09.2023 ◆ **Published**: 27.10.2023

ABSTRACT

Aims: Prealbumin is a specific and sensitive marker of nutritional conditions. The aim of our study was to investigate the relationship between serum prealbumin concentrations and serum albumin, magnesium, phosphorus and calcium levels.

Methods: A total of 200 patients, 100 male and 100 female, aged 18-65 years, who applied to the Ankara Etlik City Hospital Internal Medicine Polyclinic between January 2023 and June 2023, were included in our study. The patients' prealbumin, albumin, calcium, magnesium, phosphorus, creatinine, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and complete blood count parameters (hemoglobin, white blood cell (WBC), platelet (PLT)) results were evaluated.

Results: The median prealbumin of female subjects was 0.50 g/L (0.1-1.0), while the median prealbumin of male subjects was 0.40 g/L (0.1-1.0). There was no statistically significant difference between the groups ($p>0.05$). There is a direct positive between prealbumin concentration and calcium (r: 0.75; $p<0.001$), hemoglobin (r: 0.46; $p<0.001$), LDL (r: 0.50; $p<0.001$) and HDL (r: 0.63; $p<0.001$) concentrations and an negative correlation between magnesium (r: -0.16; p:0.02) and PLT (r: -0.31; $p<0.001$). Logistic regression analysis was performed to determine the independent variables affecting prealbumin concentration. The independent variables included in the model were HDL, LDL, body mass index (BMI), creatinine, WBC, phosphorus, age, magnesium, albumin, PLT, hemoglobin, and calcium. The Nagelgerke R2 square value of the model was 0.73 and the p value of the model in ANOVA analysis was calculated as <0.001. A regression formula for prealbumin concentrations was found: Prealbumin concentration = -0.609 + (Age × -0.002) + (BMI × 0.001) + (Ca × 0.63) + (Mg × -0.020) + (P × -0.002) + (Creatinine × 0.034) + (Hb × 0.016) + (WBC × -0.004) + (HDL × 0.001) + (LDL × 0.004).

Conclusion: We think that the findings of our study will be useful in elucidating the relationship between serum prealbumin and albumin levels, which are important indicators of dietary protein intake, and serum mineral concentrations. Our study is an article that presents a regression formula for prealbumin. The diagnostic and prognostic importance of prealbumin can be further elucidated by recruiting special and larger patient groups.

Keywords: Prealbumin, albumin, calcium, magnesium, phosphorus

INTRODUCTION

Prealbumin is an important protein mainly found in blood and has a molecular weight of 55 kDa. Although most of it is synthesised in hepatocytes, a very small amount originates from tissues such as pancreas.[1] This protein is also known and named as transthyretin because of its thyroid hormones and vitamin A binding properties.[2] Prealbumin is a specific and sensitive marker of nutritional conditions.[3,4] The half-life of prealbumin is approximately 60 hours. It is even more valuable in showing short-term nutritional differences in the human body due to this short half-life.[5] In individuals over 18 years of age, the reference range for this protein is 0.2-0.4 g/L.[4] Prealbumin is also a negative acute phase reactant. Therefore, laboratory data of these protein concentrations should be carefully evaluated. If there are other conditions accompanying the patient, it may lead to erroneous interpretations. For example, serum prealbumin level may decrease significantly in severe infections, inflammatory conditions and traumatic conditions.[6] Since this molecule undergoes various post translational modifications, its association with many important diseases such as Alzheimer's disease and familial amyloidic neuropathy has been shown.[7,8] In addition, there are studies reporting the association of prealbumin with the prognosis of many diseases such as COVID-19 mortality, liver transplantation, acute pancreatitis, gastric cancer, hepatocellular carcinoma and breast cancer.[9-16]

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Serum albumin levels are also related with inflammatory processes and nutritional conditions.[17] Just like prealbumin, albumin is a negative acute phase reactant and its serum levels decrease in the presence of inflammation and inadequate nutrition.[18] Albumin has a longer half-life compared to prealbumin and is synthesised more slowly in the liver.[5,19]

Calcium (Ca), phosphorus (P) and magnesium (Mg) play important roles in the growth and metabolism of many tissues including bone.[20] The extracellular fraction of calcium binds especially to serum albumin.[21] However, it has long been established that a part of calcium also binds to prealbumin with an affinity similar to albumin.[22] Since calcium binds to both albumin and the nutritional marker prealbumin and its levels change with nutritional status, an important relationship network is in question. Magnesium and phosphorus, like calcium, are essential for bone mineralisation and many cellular functions.[23] Therefore, all proteins in question have a close relationship with each other both functionally and quantitatively.

After all the reasons and mechanisms described above, we thought that prealbumin concentrations may be related with serum albumin, magnesium, phosphorus and calcium levels and that we may obtain new data or formulae. In summary, the aim of our study was to investigate the possible relationship between serum prealbumin concentrations and serum albumin, magnesium, phosphorus and calcium levels.

METHODS

The study was carried out with the permission of Ankara Bilkent City Hospital No: 1 Clinical Researches Ethics Committee (Date: 30.11.2022, Decision Number: E1/3061/2022). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design and Study Population

This is a retrospective observational study a total of 200 patients, 100 male and 100 female, aged 18-65 years, who applied to the Ankara Etlik City Hospital Internal Medicine Polyclinic between January 2023 and June 2023, were included in our study. Individuals whose serum albumin, prealbumin, magnesium, phosphorus and calcium parameters, as well as routine biochemistry and complete blood counts were reported simultaneously in the central biochemistry laboratory were included in our study. The inclusion and exclusion criteria are as follows.

Inclusion criteria: Age between 18 and 65 years, no known psychotic illness, no diagnosis of alcoholism, no chronic inflammatory liver disease, no chronic drug use, no history of malignant neoplasia, and liver function tests (alanine aminotransferase (ALT), aspartate) Aminotransferase (AST), gamma-glutamyl transferase (GGT), prothrombin time (PT), direct bilirubin, total bilirubin) within normal limits.

Exclusion criteria: People who did not have the above-mentioned characteristics were excluded from our study.

Demographic information and laboratory results of the patients were obtained electronically through the laboratory information system (LIS). According to the World Health Organisation recommendations, the study groups were grouped according to BMI levels as underweight (<18.5), normal (18.5-24.9), pre-obesity (25.0-29.9), obesity class I (30.0-34.9), obesity class II (35.0-39.9) and obesity class III (≥40.0).[24] Ankara Etlik City Hospital coordinator chief physician permission was also obtained for the use of patient data. Since the ethics committee was not yet ready when our hospital was newly established, ethics committee permission was obtained from the Ethics Committee of Ankara City Hospital.

Laboratory Analysis

The patients' prealbumin, albumin, calcium, magnesium, phosphorus, creatinine, low-density lipoprotein (LDL), high-density lipoprotein (HDL), PT and complete blood count parameters (hemoglobin, white blood cell (WBC), platelet (PLT) results were evaluated. The routine operation of our laboratory when performing the tests whose results we evaluated in our study is as follows. Venous blood and whole blood samples are taken from these individuals after 10-12 hours of fasting. 8-10 mL of venous blood is collected in a tube containing clot activator and gel, then waited for 20-30 minutes and centrifuged at 1500-2000 g for 10 minutes to obtain a serum sample. Biochemical parameters are measured using these serum samples and analysed on a Roche Cobas c 702 (Roche Diagnostics GmbH, Mannheim, Germany) autoanalyzer. These autoanalysers measure prealbumin by immunoturbidimetric method, albumin by colorimetric method (using bromocresol green), calcium, magnesium and phosphorus by colorimetric method, ALT and AST by photomeric method and GGT, LDL and HDL by colorimetric enzyme method. PT is measured with the cobas t 711 (Roche Diagnostics GmbH, Mannheim, Germany) autoanalyser. For complete blood count, a whole blood sample is collected in a purple capped tube containing K-EDTA and analysed on a Sysmex XN1000 (Sysmex corp. Kobe, Japan). In this device, hemoglobin is measured by photometric method, platelets by optical scattering and impedance method and WBC by fluorescence dyed light scattering method. In addition to these parameters, demographic information such as age and gender were obtained from LIS.

Statistical Analysis

Data were analysed using the statistical package programme Analyze-It for Microsoft Excel 5.80.2. The suitability of the data for normal distribution was determined by Shapiro-Wilk test. Categorical variables were shown as (n,%), data with and without normal distribution were expressed as mean SD and median (min-max), respectively. Comparison of prealbumin and categorical variables was evaluated by t test if the data were normally distributed and by Mann-Whitney U test or Kruskal-Wallis test if the data were not normally distributed. The relationship between prealbumin and laboratory parameters was evaluated by Pearson correlation test. Independent risk factors affecting prealbumin level were investigated by linear regression test. Statistical significance level was stated as p<0.05.

RESULTS

Demographic and laboratory characteristics of the study group are presented in Table 1. The median prealbumin of female subjects was 0.50 g/L (0.1-1.0), while the median prealbumin of male subjects was 0.40 g/L (0.1-1.0). There was no statistically significant difference between the groups (p=0.53; evaluated by Mann-Whitney U test). According to BMI levels, the subjects were grouped as underweight, normal, pre-obesity, obesity class I, obesity class II and obesity class III. The median prealbumin values of the groups were 0.5 g/L (0.1-0.9); 0.4 g/L (0.1-1.0); 0.4 g/L (0.1-1.0); 0.4 g/L (0.1-1.0); 0.5 g/L (0.1-0.9) and 0.4 g/L (0.1-1.0), respectively. There was no statistically significant difference between the groups (p=0.54). Table 2 shows the correlation relationship between prealbumin and laboratory parameters. There is a direct positive between prealbumin concentration and calcium (r: 0.75; p<0.001), hemoglobin (r: 0.46; p<0.001), LDL (r: 0.50; p<0.001) and HDL (r: 0.63; p<0.001) concentrations and an negative correlation between magnesium (r: -0.16; p:0.02) and PLT (r: -0.31; p<0.001).

Table 1. Demographic and laboratory characteristics of the study group

Parameters		
Gender (n.%)	Female	100 (50.0%)
	Male	100 (50.0%)
Age (year)		41.0 (18.0-65.0)
BMI (kg/m2)		27.8 (14.1-40.6)
Prealbumin (g/L)		0.5 (0.1-1.0)
Albumin (g/L)		44.0 (20.0-64.0)
Calcium (mg/dl)		10.1 ±1.8
Magnesium (mg/dl)		2.70 (0.9-4.30)
Phosphorus (mg/dl)		4.6 (1.6-6.7)
Creatinin (mg/dl)		1.0 (0.5-1.4)
Hemoglobin (g/dl)		14.0 (9.2-18.0)
WBC (cell/µl)		8.1 (2.4-15.4)
PLT (cell/µl)		320.0 (132.0-597.0)
LDL (mg/dl)		105.0 (49.0-197.0)
HDL (mg/dl)		53.0 (20.0-82.0)

Categorical variables were shown as (n.%), data with and without normal distribution were expressed as mean SD and median (min-max), respectively. WBC: White blood cell; PLT: Platelet; LDL: Low-density lipoprotein; HDL: High-density lipoprotein

Table 2. Correlation relationship between prealbumin and laboratory parameters

Variable		Prealbumin	Albumin	Calcium	Magnesium	Phosporus	Creatinin	Hemoglobin	WBC	PLT	LDL	HDL
Prealbumin	Pearson	(-)										
	p value	(-)										
Albumin	Pearson	-0.04	(-)									
	p value	0.56	(-)									
Calcium	Pearson	0.75	0.10	(-)								
	p value	<0.001	0.13	(-)								
Magnesium	Pearson	-0.16	-0.40	-0.06	(-)							
	p value	0.02	0.51	0.34	(-)							
Phosporus	Pearson	0.05	0.05	0.08	-0.02	(-)						
	p value	0.42	0.50	0.21	0.74	(-)						
Creatinin	Pearson	0.05	0.04	0.02	0.02	0.06	(-)					
	p	0.47	0.54	0.76	0.74	0.29	(-)					
Hemoglobin	Pearson	0.46	-0.03	0.36	0.02	0.03	-0.06	(-)				
	p	<0.001	0.64	<0.001	0.73	0.04	0.13	(-)				
WBC	Pearson	-0.03	-0.01	0.01	-0.01	0.06	0.01	-0.07	(-)			
	p	0.67	0.11	0.84	0.09	0.39	0.90	0.19	(-)			
PLT	Pearson	-0.31	0.04	-0.25	0.06	-0.05	0.12	-0.21	-0.08	(-)		
	p	<0.001	0.53	<0.001	0.33	0.58	0.34	0.76	<0.001	(-)		
LDL	Pearson	0.50	-0.06	0.39	-0.07	0.10	0.09	0.28	0.04	0.04	(-)	
	p	<0.001	0.33	<0.001	0.09	0.36	0.81	0.31	<0.001	0.56	(-)	
HDL	Pearson	0.63	-0.01	0.50	-0.01	0.00	0.02	0.32	0.01	-0.26	0.31	(-)
	p	<0.001	0.80	<0.001	0.33	0.46	0.06	<0.001	0.21	<0.001	<0.001	(-)

WBC: White blood cell; PLT: Platelet; LDL: Low-density lipoprotein; HDL: High-density lipoprotein. Bolded numbers are the results considered statistically significant (p<0.05).

Logistic regression analysis was performed to determine the independent variables affecting prealbumin concentration. The independent variables included in the model were HDL, LDL, BMI, creatinine, WBC, phosphorus, age, magnesium, albumin, PLT, hemoglobin, and calcium. The Nagelgerke R2 square value of the model was 0.73 and the p value of the model in ANOVA analysis was calculated as <0.001. A summary of the model is presented in Table 3. Age, calcium, magnesium, hemoglobin, HDL and LDL cholesterol are the values that affect prealbumin concentration independently of other variables. The regression equation is shown in Formula 1.

Formula 1: Prealbumin concentration = -0.609 + (Age × -0.002) + (BMI × 0.001) + (Ca × 0.63) + (Mg × -0.020) + (P × -0.002) + (Creatinine × 0.034) + (Hb × 0.016) + (WBC × -0.004) + (HDL × 0.001) + (LDL × 0.004)

Table 3. Independent variables affecting prealbumin concentration

Variable	B	Sig	95% CI
Constant	-0.609	.000	(-.836 ; -.382)
Age	-0.002	.027	(-.003; .000)
Albumin	.000	.777	(-.001; .002)
Body mass index	.001	.616	(-.002; .003)
Calcium	.063	.000	(.051; .760)
Magnesium	-.020	.032	(-.038; -.002)
Phosporus	-.002	.720	(-.015; .020)
Creatinin	.034	.332	(-.035; .102)
Hemoglobin	.016	.001	(.007; .025)
WBC	-.004	.121	(-.009; .001)
PLT	.000	.023	(.000; .000)
HDL	.001	.000	(.001; .002)
LDL	.004	.000	(.003; .006)

WBC: White blood cell; PLT: Platelet; LDL: Low-density lipoprotein; HDL: High-density lipoprotein. CI: Confidence Interval, Bolded numbers are the results considered statistically significant (p<0.05).

DISCUSSION

Prealbumin, also known as transthyretin, is a specific marker of nutritional status and is a protein associated with the pathogenesis and prognosis of many diseases. The first striking finding was the negative correlation between magnesium and platelets and prealbumin. A negative correlation between prealbumin and PLT may be due to reactive thrombocytosis in malnutrition, just as in iron deficiency anaemia. However, the negative correlation between prealbumin and magnesium contrary to the literature was an unexpected result for us.[25,26] Changes in nutritional conditions may cause significant changes in free magnesium concentrations by affecting prealbumin and albumin levels. Since approximately one third of serum magnesium is bound to proteins, especially albumin, molecular interactions, which are not yet known and may be revealed in further research, may have produced this negative correlation.[27] In addition, we showed that serum prealbumin concentrations were positively correlated with calcium, LDL, HDL and hemoglobin levels. Our study also provides a specific formula for estimating serum prealbumin levels. In this formula, serum prealbumin level is calculated by using the patient's age, hemoglobin, LDL, HDL, magnesium, calcium, and age parameters. Our aim in searching for a regression formula is to predict the prealbumin concentration with related parameters in laboratories where measurement of prealbumin concentration cannot be performed.

In a study conducted with hemodialysis patients, Chertow et al.[28] reported that serum prealbumin values were directly correlated with albumin values. In addition, in this study, prealbumin was shown to have prognostic importance in hemodialysis patients. The superior aspects of our study are the correlation of serum prealbumin concentrations not only with albumin but also with parameters such as calcium, magnesium, phosphorus, LDL, HDL and hemoglobin and the development of a special formula to predict prealbumin levels. However, the lack of a specific disease group and the lack of investigation of prognostic significance are the negative aspects of our study.

In a study conducted in 2017 on 664 women with osteoporosis in China, serum prealbumin levels were shown to be directly correlated with bone mineral density (BMD).[29] In this study, it was found that serum prealbumin concentrations decreased as BMD decreased. Although a specific patient population was selected in this study, the fact that the correlation of BMD and prealbumin with molecules that play important roles in bone mineralisation such as serum calcium, magnesium and phosphorus was not investigated was a negative factor compared to our study.

The study conducted by Xiu et al.[30] in 2019 in osteoporotic patients with type 2 diabetes mellitus showed that prealbumin levels were higher in those without osteoporosis and that low prealbumin levels increased the risk of osteoporosis. Therefore, this study re-emphasised that a poor nutritional status increases the risk of osteoporosis. The selection of a specific patient group as in other studies is a superior feature of this study, but it also has negative aspects compared to our study. These negative aspects are that the correlation between prealbumin and parameters such as albumin, calcium, magnesium, phosphorus, hemoglobin, HDL and LDL was not investigated.

Handcox et al.[31] performed a retrospective observational study looking at serum prealbumin, albumin, magnesium and phosphorus levels in orthopaedic trauma patients. In this study, it was reported that

orthopaedic traumas were experienced more frequently and wound complications were observed more frequently in patients with low prealbumin levels. This study could not show a correlation between magnesium and phosphorus and these pathologies. In our study, the correlation of prealbumin with calcium and magnesium was shown.

Study Limitations

Our study had limitations such as small population size, lack of a specific disease group, lack of power analysis, being a retrospective study, and multifactorial and variable prealbumin metabolism. In addition, it should not be forgotten that external validation of the formula we have put forward should be done.

Strengths of the study: The strengths of our study include an extensive and up-to-date review of the literature on the subject, highlighting many possible relationships with prealbumin, calculating the correlation with many parameters, introducing a new formula that can be used in hospitals where prealbumin cannot be measured and effective statistical analysis.

CONCLUSION

In our study, we showed that serum prealbumin concentrations were positively correlated with calcium, LDL, HDL and hemoglobin levels and negatively correlated with magnesium and platelet levels. Although some of our findings differ from a few studies in the literature, this article may be a guide for new and further studies. We think that the findings of our study will be useful in elucidating the relationship between serum prealbumin and albumin levels, which are important indicators of dietary protein intake, and serum mineral concentrations. The fact that there are not many studies on this subject in the literature makes our study more valuable. Multicentre and long-term studies may be useful to generalise our results. Our study is the first manuscript to present a regression formula for prealbumin. The diagnostic and prognostic importance of prealbumin can be demonstrated in studies with different disease groups and groups of completely healthy volunteers.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara Bilkent City Hospital No: 1 Clinical Researches Ethics Committee (Date: 30.11.2022; Decision Number: E1/3061/2022).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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Original Article

MEDICINE PALLIATIVE CARE

DOI: 10.47582/jompac.1345829

J Med Palliat Care. 2023;4(5):418-422

Evaluation of serum neopterin levels in patients with Graves disease

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Cite this article as: Gürcü S, Yorulmaz G, Kocatürk E, et al. Evaluation of serum neopterin levels in patients with Graves disease. *J Med Palliat Care*. 2023;4(5):418-422.

Received: 18.08.2023 ◆ **Accepted**: 08.09.2023 ◆ **Published**: 27.10.2023

ABSTRACT

Aims: Graves' disease is a disease with an autoimmune basis in which the synthesis and release of thyroid hormone from the thyroid gland increases. Interferon-gamma (IFN-γ) released from activated T lymphocytes causes macrophages to produce neopterin (NPT), increasing its concentration in serum and other body fluids. There is a relationship between NPT and the production of free oxygen radicals by these cells. In this study, it was aimed to measure serum NPT levels in individuals with Graves' disease.

Methods: The study included 13 newly diagnosed Graves' patients (neopterin levels were measured at the time of first diagnosis and at the 3rd month of treatment) and 16 Graves' patients who were followed up in endocrinology outpatient clinics for at least one year. NPT levels of 23 healthy individuals without any disease were taken as the control group. Free triiodothyronine (T3), free thyroxine (T4), thyroglobulin, and thyroid stimulating hormone (TSH) levels were measured in the blood samples of the participants.

Results: Serum NPT levels were found to be higher in Graves' patients compared to the control group (6.66 nmol/L in newly diagnosed patients, 9.24 nmol/L in patients at the 3rd month of treatment, 10.68 nmol/L in patients followed for one year or more, 1.44 nmol/L in the control group, respectively, $p < 0.05$).

Conclusion: Monitoring NPT levels in serum and other body fluids can be used to evaluate the diagnosis, prognosis, and treatment efficacy of autoimmune diseases. In addition, NPT can be suggested as a potential biomarker to determine disease stage, treatment efficacy, and immunological remission status, as well as the diagnosis of Graves' disease.

Keywords: Neopterin, Graves disease, hyperthyroidism, cellular immunity, T helper cells

INTRODUCTION

Graves disease is an autoimmune disease of the thyroid gland that can lead to hyperthyroidism. It was pointed out that Graves disease affects 1-1.5% of the population, and also, 4 out of 5 cases of hyperthyroidism are due to Graves disease. Graves disease is more common in women and adults older than 30.[1-3]

Infiltration of thyroid-antigen-specific T-cells into the thyroid gland and development of autoantibodies (TSH-R-Ab) against thyroid-stimulating hormone receptor (TSH-R) are involved in the pathogenesis of Graves disease. Activation of thyroid-stimulating hormone receptors by autoantibodies enhances intracellular cyclic AMP production, mediating thyroid hyperplasia and inappropriate thyroid hormone secretion.[4-6]

Neopterin (NPT), a pteridine, is an oxidized metabolite of tetrahydrobiopterin (BH_4) produced by activated macrophages. There is growing interest in considering NPT as a biomarker in infectious and inflammatory diseases and malignancies. The innate immune system activation leads to the stimulation of T-helper 1 cells, which secrete interleukin-2 (IL-2), interferon-γ (IFN-γ), and tumor necrosis factor-α (TNF-α) and regulate tissue damage by the cellular immune response. During the inflammatory conditions, NPT is generated from BH_4, which has antioxidant effects with GTP cyclohydroxylase enzyme in macrophages induced with IFN-γ secreted from T-helper 1 cells. It can be put forward to NPT is considered a convenient biomarker to monitor immune activation in inflammatory conditions because the produced amount of NPT is closely related to immune system activation, and it can be easily measured in biological fluids.[7,8]

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Although it was a different study, our aim in this study was to compare Graves patients with high disease activity at different stages with a healthy control group with biochemical and hematological parameters.[9]

METHODS

The study was carried out with the permission of Eskisehir Osmangazi University Non-interventional Clinical Researches Ethics Committee (Date: 03.11.2020, Decision No: 2020-10). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study was conducted with 29 patients with Graves disease and 23 healthy volunteers. Patients over 18 years of age and without kidney failure or kidney damage were included in the study. Patients with autoimmune diseases other than Graves disease that would affect serum NPT levels, active acute or chronic viral/bacterial infection, and malignancy were excluded from the study. Graves disease was determined with undetectable TSH levels, elevated serum free T4 and free T3 concentrations, positive TSH receptor antibodies, and goiter and increased blood flow on thyroid ultrasound.[10]

According to the disease's duration, Graves disease patients were classified as 16 newly diagnosed and 13 as follow-up patients. The volunteer participants of the study were chosen from patients admitted to the Endocrinology outpatient clinic of Eskişehir Osmangazi University Hospital between December 2020-April 2021.

We evaluated newly diagnosed patients two times, at the first diagnosis and in the 3rd month of the treatment, to investigate the immunological response of these patients to anti-thyroid therapy. The other 13 patients with Graves (FUPG group) were previously diagnosed and were not in remission yet. According to the recommendations in the 2018 European Thyroid Association Guidelines, considering the severity of the disease and adjusting the dose, methimazole treatment was started, and methimazole treatment was continued in the FUPG, in accordance with the guideline recommendation.[1]

Blood samples collected from the participants were centrifuged at 3500 rpm for 10 minutes and stored at-80°C for measurements.

Serum neopterin concentrations were analyzed with commercial enzyme-linked immunosorbent assay (ELISA) kits (Human Neopterin Assay Kit, Bioassay Technology Laboratory, China) according to the manufacturer's instructions. Optical density was measured at 450 nm with a microplate reader (Spectra Max M2, England). Serum neopterin levels were expressed as nmol/L.

In all cases, free thyroxine (T4), free triiodothyronine (T3), thyrotropin (TSH), anti-TG, and anti-TPO were determined by Electro Chemiluminescent immunoassay and serum C-reactive protein (CRP) levels were measured by immunoturbidimetric method (Cobas e801 Roche Diagnostics, Mannheim, Germany) commercially available kits (T4, T3, TSH, anti-TPO, CBC analyses were performed on Sysmex XN 1000 hematology analyzers (Sysmex Corporation, Kobe Japan). Erythrocyte sedimentation rate (ESR) was studied by the Westergren method in a fully automated Vacuplus ESR-120 (Ankara, Turkey) analyzer.

Data were presented as mean±standard error mean. The conformity of the data to the normal distribution was evaluated with Shapiro-Wilks or Kolmogorov-Smirnov test. Data were statistically analyzed using the Kruskal-Wallis Test post hoc Bonferroni. Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) 21. If $p<0.05$, the difference between the means was considered significant.

RESULTS

The patients with Graves disease included in this study were classified as newly diagnosed Graves patients (NDG) and followed-up Graves patients (FUPG). The N numbers of the participants and the mean values of their ages are given in Table 1. There was no significant difference in terms of age, gender, and BMIs between the groups. The followed-up Graves patients (FUPG) had 2.6 mean disease years from diagnosis.

Table 1. Demographic data of the participants. Data were presented as mean±SEM

		Control	NDG	FUPG	p
N		23	16	13	
Age (year)		44.3±10.7	43.1±12.6	39±14.5	>0.05
Gender	Male Female	10 (43.5%) 13 (56.5%)	6 (37.5%) 10 (62.5%)	4 (30.8%) 9 (69.2%)	>0.05
BMI		21.1±2.0	19.6±2.1	20.6±2.6	>0.05

NDG: New diagnosed Graves patients (The BMI of this group was calculated at month 0), FUPG: Follow-up Graves patients, BMI: Body mass index.

We measured the levels of free triiodothyronine (T3), free thyroxine (T4), thyroglobulin, and thyroid-stimulating hormone (TSH) in the blood samples of the participants. There is a significant increase in the free T3 and T4 levels of the blood samples of the NDG group compared to that of healthy individuals. Furthermore, the blood TSH levels of NDG and FUPG groups were found significantly diminished compared to healthy individuals. It was indicated that the decreased TSH levels accompanying enhanced free T3 and T4 levels in blood samples of the participants in the NDG and FUPG groups compared to control confirmed that the participants in the NDG and FUPG groups had uncontrolled hyperthyroidism (Table 2). TSH receptor antibody, anti-TPO, and anti-thyroglobulin blood levels of the participants in the NDG and FUPG groups were found to be greater than that of the control group, as detailed in Table 2.

Table 2. The thyroid function tests, thyroid autoantibody levels, biochemical data, and hemogram findings of the participants. Data were presented as mean±SEM. *p<0,05, compared to control

Thyroid tests	Control	NDG		FUPG
		0th month	3rd Month	
N	23	16		13
TSH (0.27-4.2 IU/ml)	1.6±0.6	0.0*	0.9±1.0*	0.1±0.3*
T3 (2.3-4.5 pg/ml)	3.3±0.7	12.3±9.8*	5.4±3.5*	4.0±1.2*
T4 (0.93-1.7 ng/dl)	1.2±0.4	2.4±1.6*	1.5±0.8*	1.8±0.8*
TSH receptor antibody (0-1,5 U/L)	0.3±0.2	6.8±4.6*	5.3±6.0*	7.3±6.1*
Anti-TPO (0-34 IU/ml)	7.0±10.2	185.1±157.5*	-	84±92.9*
Anti-thyroglobulin (0-115 IU/ml)	38.1±104.1	132.4±129.7*	-	90.7±126.5*
Thyroglobulin (3,5-77 ng/ml)	23.5±20.7	73.9±59.6	-	107.9±50
Blood data of the participants	**Control**	**NDG (0th month)**		**FUPG**
Calcium (8,6-10,2 mg/dl)	9.2±0.4	9.7±0.4+		9.6±0.40
Albumin (3,5-5,2 g/dl)	4.6±0.3	4.3±0.2+		4.4±0.4
Phosphorus (2,7-4,5 mg/dl)	3.5±0.5	3.9±0.9+		3.9±1.0
Alkaline phosphatase (0-104 U/L)	69.6±32.4	97.6±24.2*+		70.0±31.7
AST (0-31 U/L)	17.1±3.5	21.1±10.1+		21.4±9.7
ALT (0-33 U/L)	21±13.3	24.7±22.7+		25.0±18.0
Hemoglobin (g/dl)	14.3±1.6	13.6±1+		13.6±1.6
Leukocyte (10^3/ul)	7.2±2.1	7.0±1.9+		6.9±2.6
Neutrophil (10^3/ul)	4.1±1.6	3.6±1.0+		4.0±1.6
Lymphocyte (10^3/ul)	2.3±0.8	2.7±1.1+		2.6±1.1
Platelets (10^3/ul)	269.1±60.4	288.1±45.6+		272.6±71.6

TSH: Thyroid stimulating hormone, T3: Free Triiodothyronine, T4: Free thyroxine, TSH Receptor Antibody: Anti-thyroid stimulating hormone receptor antibodies, Anti-TPO: Anti-thyroid peroxidase antibodies, AST: Aspartate transaminase, ALT: Alanine transaminase. + (The data of this group was obtained at month 0)

The serum NPT levels of the participants in the NDG and FUPG groups were considerably higher than the control group, as listed in Table 3 and Figure 1. Although the groups were similar in terms of age, gender, and BMI, when neopterin was compared between the groups, it was determined that age, gender, and BMI were not confounding factors (p>0.05). ESR and CRP levels, which are commonly used to evaluate inflammation, were found to be similar between the patient and control groups. In contrast, neopterin levels were found to differ significantly between the groups, being higher in the patient groups.

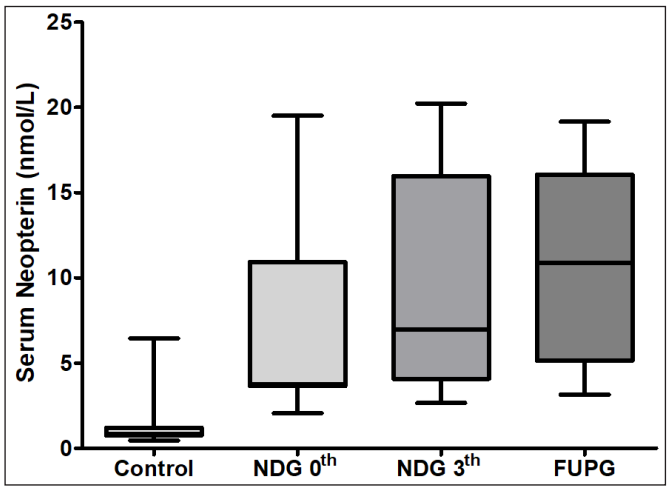

Figure 1. Serum NPT of participants
NDG: New diagnosed Graves patients (0th month, 3rd month), FUPG: Follow-up Graves patients.

Table 3. NPT, ESR, and CRP levels of participants. Data were presented as mean±SEM. *p<0,05, compared to control

		N	Serum neopterin (nmol/L)	ESR (0-10 mm/h)	CRP (0-5 mg/L)
Control		23	1.44±1.45	9.8±4.9	1.3±1.0
NDG	0th month	16	6.66±5.28*	11.7±6.7	1.9±1.3
	3rd month	16	9.24±6.12*	10.6±4.2	1.8±1.3
FUPG		13	10.68±5.63*	12.2±5.5	2.0±1.2

NPT: Neopterin, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein.

Despite the high TRAb values in the NDG and FUPG groups, we could not detect a relationship between TRAb values and neopterin levels (r=-0.270, p:0.377).

DISCUSSION

NPT, considered a biomarker, is attracting widespread interest in the diagnosis of infectious inflammatory diseases and malignancies. Immune activation stimulates T-lymphocytes to secrete cytokines like IL-2 and IFN-γ. NPT is produced in macrophages activated with IFN-γ secreted from T-lymphocytes in inflammatory conditions. Increased generation of reactive oxidative substances in inflammatory conditions enhances the production of NPT obtained from BH_4, which plays an important role in defense mechanisms against oxidative stress.[7,8]

Various studies indicate that serum NPT levels are consistent with the severity and progression of infectious and inflammatory diseases and malignancies. The highest

serum NPT levels were determined in the acute phase of inflammatory diseases such as rheumatoid arthritis (RA), Crohn's disease, ulcerative colitis, autoimmune thyroiditis, systemic lupus erythematosus, and early-onset autoimmune diabetes. Also, it was established that NPT levels in biological fluids changed with disease severity and expansion.[8,9,11] Another previous research established that the NPT levels in synovial fluid samples of RA patients were greater than in control groups. A considerable increase in NPT levels in synovial fluid samples of RA patients was detected compared to those with osteoarthritis. The relative increase in NPT levels in synovial fluid samples of RA patients accounted for cellular stimulation of immune reaction.[12] In contrast, serum NPT levels were found to be higher in serum samples of the patients with systemic lupus erythematosus (SLE) compared to the control. On the other hand, a marked increase was determined in synovial fluid samples of RA patients compared to healthy individuals in the same study.[13] Therefore, previous research conducted with Arshadi et al.[14] indicated that the disease activity determined with the DAS-CRP method in the patients with RA demonstrated a correlation with the plasma NPT levels compared to healthy individuals. The evidence points to the likelihood that NPT is a sensitive marker for the activity of inflammatory diseases arising from macrophage activation induced by T-lymphocytes.

The results obtained from this study indicated that serum NPT levels of the patients with Graves disease displayed a marked increase compared to healthy individuals. Also, it was determined that the serum NPT level of the patients with followed-up Graves disease (FUPG group) was found to be higher than that of the patients who have newly diagnosed Graves disease (NDG group). These results are unlike the evidence in the literature, which suggested that serum NPT levels were decreased with treatment.[15,16] The marked increase in serum NPT levels of the followed-up Graves disease patients may be attributed to enhanced disease activity by the cellular immune response against thyroidal tissue. Neopterin is released from macrophages with the stimulation of IFN-γ released from T helper cells. Major histocompatibility antigen (MHC) class II, which provides antigen presentation to T helper cells in healthy individuals, is expressed only on antigen-presenting cells (APCs), not thyroid cells. It is thought that thyroid cells also express MHC class II molecules (notably HLA-DR molecules) with the stimulation of interferon released by any thyroidal T cell in Graves' patients, exacerbating the already established thyroid autoimmunity.[17]

In a previous study conducted by Wagner et al.[9] serum NPT levels, considered a T-lymphocyte/monocyte axis function biomarker, were determined to be greater in the patients with Graves disease or autoimmune thyroiditis compared to healthy individuals and the patients with nontoxic goiter. However, contrary to our results obtained from this study, no significant difference in serum NPT levels was established between the different stages of Graves disease, such as newly diagnosed, treated, remission, and relapse. Although it has been suggested that the NPT levels may increase due to increased thyroid volume and macrophage numbers in Graves disease, no correlation was found between them in that study. Similarly, no relationship was found between NPT and thyroid volume in Schomburg et al.'s study.[18]

Zantut-Wittmann et al.'s[19] study showed ATDs reduced HLA-DR expression in follicular cells in fine-needle aspiration biopsy samples of Graves patients with controlled thyrotoxicosis. Therefore, NPT levels associated with HLA-DR expression can be expected to decrease as the duration of ATD treatment increases. In our study, while NDG 0 months had not yet received ATD, NDG 3 months and FUPG patients received ATD but were not yet in a euthyroid state. Since we worked with patients with uncontrolled thyrotoxicosis, we may have concluded that NPT levels are higher with longer disease duration and that ATD treatment does not reduce NPT. In Schomburg's study[18], no significant difference was found in NPT levels between Graves patients who received and did not receive ATD. Although our study lacks a group that did not receive ATD, we can say that ATD treatment does not significantly affect NPT levels in patients who have not yet reached remission.

The TRAb, anti-TPO, and anti-thyroglobulin antibody levels of the NDG and FUPG groups participants were higher than the control group in our study. Since only the patients in the active phase of the disease were included in the study, and the disease control was not complete in the FUPG group, TRAb values were very similar to those in the NDG group. NPT levels in biological fluids are altered with T-lymphocyte/monocyte activation in autoimmune reactions. Considering the high NPT levels, our study showed that the antibody formation against thyroidal proteins like TSH-receptor, TPO, and thyroglobulin in patients with Graves disease results from the activation of CD4+ T-helper lymphocytes. In recent research by our study group, NPT levels were found to be lower in patients with subacute thyroiditis than in controls. It was inferred that CD8+ cytotoxic T-lymphocytes in the thyroidal tissue have a pivotal role in the immune reaction in subacute thyroiditis rather than CD4+ T-helper cells. Also, it was assumed that lower serum NPT levels in the patients with subacute thyroiditis were associated with the involvement of HLA-B*35- MHC class I in the pathogenesis of subacute thyroiditis.[11,20]

Neopterin shows the extent of inflammation related to cellular immunity and can sometimes result differently from the general inflammatory markers ESR and CRP. In our study, there was no difference in ESR and CRP

between the patient and the control groups and intergroup comparisons of the patients. Still, the difference in NPT levels reveals that NPT is a unique inflammatory marker.

The present descriptive research has some limitations that the sample size was not sufficient. Our results are promising and should be verified in a larger cohort of patients with Graves disease, including those in remission and those with relapses. Further investigations should focus on the local NPT production in the thyroidal tissue.

CONCLUSION

It is conceivable that monitoring NPT levels in biological fluids could provide compelling evidence in evaluating the diagnosis, prognosis, and treatment efficacy of autoimmune diseases. Also, NPT might be put forward as a potential biomarker to determine the diagnosis, disease stage, treatment efficacy, and immunological remission status of Graves disease.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Eskisehir Osmangazi University Non-interventional Clinical Researches Ethics Committee (Date: 03.11.2020, Decision No: 2020-10).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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Original Article

MEDICINE PALLIATIVE CARE

DOI: 10.47582/jompac.1347667

J Med Palliat Care. 2023;4(5):423-430

Evaluation of laboratory and radiological imaging results in terms of hospitalization and mortality in acute pancreatitis cases

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Cite this article as: Akın B, Demirci B, Coşkun A. Evaluation of laboratory and radiological imaging results in terms of hospitalization and mortality in acute pancreatitis cases. *J Med Palliat Care*. 2023;4(5):423-430.

Received: 22.08.2023 ◆ **Accepted**: 16.09.2023 ◆ **Published**: 27.10.2023

ABSTRACT

Aims: Acute pancreatitis (AP) is a common diagnosis in emergency services and is very important in terms of morbidity and mortality. It was aimed to evaluate the relationship of laboratory and imaging findings of AP cases with hospitalization and mortality outcomes.

Methods: This retrospective study was conducted with 225 cases over the age of 18 who applied to the emergency department between 1 September 2020 and 1 March 2021. Age, gender, laboratory and imaging data of the patients were recorded and evaluated on groups formed according to hospitalization and mortality status.

Results: The mean age of 225 acute pancreatitis cases was 54.10±19.07 years, and 116 (51.6%) were female. 169 (75.1%) individuals were hospitalized and seven (3.1%) patients resulted in mortality. Age was associated with mortality (p<0.001). Lipase levels in the mortality group were substantially higher, with 3474.71±3013.69 U/L (p= 0.046). Similarly, elevated urea was found to be related with mortality (p=0.019). On ultrasonography, pancreatic edema was found to be associated with mortality (p=0.012). The presence of intrahapatic bill duct dilatation (p=0.002), pancreatic edema (p=0.045) and peripancreatic fluid (p=0.009) in magnetic resonance cholangiopancreatography (MRCP) was significant at hospitalization. Tomography and MRCP findings did not correlate with mortality.

Conclusion: Laboratory parameters and imaging findings in the emergency department may be predictive of hospitalization and mortality outcomes in AP.

Keywords: Acute pancreatitis, emergency department, laboratory, imaging methods, hospitalization, mortality

INTRODUCTION

Acute pancreatitis (AP) is a prevalent gastrointestinal disorder with a high global incidence, frequently leading to emergency department visits and hospital admissions.[1] According to recent research, the prevalence of acute pancreatitis (AP) ranges from 4.9 to 73.4 instances per 100,000 individuals globally.[2] Its annual cost can reach 2.6 billion dollars and it is observed quite widely.[3] Although the mortality for AP in the general population remains constant, its incidence is increasing due to diagnostic methods and ease of admission.[2] There is currently no established pharmacological intervention that has been empirically validated. AP is a pathological condition that can be clinically detected in the absence of systemic manifestations. This condition can lead to both local and systemic inflammatory responses, organ dysfunction, pancreatic necrosis, and ultimately, mortality.[4]

While gallstones and alcohol are the etiology of 80% of AP cases, the remaining are less common causes such as drug reactions, pancreatic solid and cystic malignancies, and hypertriglyceridemia.[5] The diagnosis of AP necessitates the presence of prototypical abdominal pain, high levels of serum amylase and/or lipase that exceed three times the upper limit of normal, and/or the identification of at least two diagnostic abnormalities on abdominal imaging.[6,7] Patients commonly experience pain in the central epigastric region and the upper right quadrant. The sensation of discomfort has the potential to extend towards the posterior region or laterally. The object in question may possess characteristics reminiscent to a belt, with the knife being affixed in a manner that allows it to remain in a fixed position. In order to establish a diagnosis for the disease, it is necessary to consider the collective evaluation of anamnesis, physical examination, laboratory tests, and radiographic investigations.[8,9] In emergency medical care, ultrasonography (USG), contrast-enhanced abdominal computed tomography (CT), and magnetic resonance cholangio-pancreatography (MRCP) are favored diagnostic modalities with hemogram and biochemical indicators.

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The clinical presentation ranges from a mild version that exhibits a prompt response to medical intervention, to a severe form characterized by systemic manifestations, sepsis, and multi-organ failure. The majority of patients exhibit a modest trajectory, leading to prompt clinical amelioration due to the implementation of moderate fluid resuscitation, pain and nausea treatment, and early initiation of oral feeding. In its severe form, which constitutes 20-30% of the patient group, hospital mortality rates can reach approximately 15%.[10] Infected necrosis affects mortality considerably, and mortality is 35.2% in cases with organ failure and infected necrosis, while mortality is at a lower level of 1.4% if there is infected necrosis without organ failure.[11]

The aim of early evaluation, diagnosis and treatment is to minimize complications and prevent morbidity and mortality. Today, although various diagnostic tests and imaging techniques are applied to direct the diagnosis, some delays can still be observed in the diagnosis and treatment of AP patients. Therefore, there is a constant need for studies on high-sensitivity biochemical biomarkers and imaging methods that can more rapidly and specifically evaluate the pathogenesis, diagnosis and prognosis of the disease in AP.

In this study, we aimed to contribute to the literature by evaluating the hospitalization and mortality status of acute pancreatitis cases, along with laboratory and imaging results.

METHODS

The study was carried out with the permission of İstanbul Prof. Dr. Cemil Taşcıoğlu City Hospital Clinical Researches Ethics Committee (Date: 08.03.2021, Decision No: 105) All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design and Population

The research encompassed a population of 225 individuals (116 females, 109 males) with a mean age of 54.10±19.07 years and a range of 18 to 94 years. These participants were diagnosed with acute pancreatitis in the emergency department during the period from 1 September 2020 to 1 March 2021. The inclusion criteria for this study required participants to be above the age of eighteen. The hospital where the study was conducted is a tertiary education and research hospital, and all records of patients' anamnesis, physical examination, laboratory and imaging reports are available in the electronic data system.

The diagnosis of acute pancreatitis was established based on the fulfillment of two affirmative criteria: the presence of abdominal pain that aligns with the symptoms associated with the disease, biochemical evidence indicating the existence of pancreatitis, and the identification of distinctive observations on abdominal imaging. As the biochemical proof of AP, a serum amylase and/or lipase three times or more above the normal value was accepted as diagnostic. Patients over the age of 18 who met these criteria, who did not have the diagnoses in the exclusion criteria and whose data in the hospital registry system were complete, were included in the study.

Patients with trauma, salivary gland disease, non-pancreatic infection, isolated cholecystitis, isolated choledoclithiasis, chronic pancreatitis, gastroenteritis, inflammatory bowel disease, obstructive bowel disease, celiac disease, pheochromocytoma, sarcoidosis, macroamylasemia, macrolipazemia, renal failure, malignancy clinic or history and under the age of 18 were excluded from the study. In addition, cases with missing data in the data recording system were not included in the study.

Age, gender, white blood cell (WBC), lymphocyte (LYM), neutrophil (NEU), urea, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transferase (GGT), lactate dehydrogenase (LDH) were included in the patient case forms. Amylase, lipase and C-reactive protein (CRP) values were recorded. The presence of USG, CT, and MRCP examinations of the patients were recorded. The findings of the patients who underwent USG were evaluated in five groups: Gallbladder wall thickness increase (GWT), Gallstone (GS), intrahepatic bile duct dilatation (IBD), pancreatic edema (PE), peripancreatic fluid (PPF). CT and MRCP findings were evaluated in six groups by evaluating pancreatic density increase/heterogeneity (PDI) in addition to the findings on USG. Hospitalization status and duration and mortality status of the patients were also recorded. The patients were evaluated by dividing them into two groups according to their hospitalization and mortality status.

Laboratory Design

Blood samples were collected from patients who were hospitalized to the emergency room with a preliminary diagnosis of AP in order to conduct hemogram, biochemistry, and C-reactive protein tests. The study examined the parameters measured upon admission to the emergency department, which provided a range of 45 to 90 minutes.

The hemogram was assessed utilizing a Beckman Coulter Automated CBC Analyzer, manufactured by Beckman Coulter, Inc. in Fullerton, CA, USA. The blood samples were subjected to biochemical analysis using the Cobas 6000 instrument (specifically, the C6000-Core module from the Cobas c-501 series, manufactured by Hitachi and distributed by Roche, USA).

Statistical Analysis

The data acquired from the study were analyzed using the SPSS 20 software package developed by SPSS Inc., based in Chicago, IL, USA. The investigation of the normal distributions of the variables involved the utilization of the Kolmogorov-Smirnov test. The descriptive statistics were reported in the form of mean ± standard deviation or median (minimum-maximum) for continuous variables, and as the count and percentage (%) for nominal variables. The Mann-Whitney U test was employed to analyze the disparities between groups due to the non-normal distribution of the variables. The use of chi-square analysis was employed to investigate the associations among groups of nominal variables. Statistical significance was determined by considering values below the significance level of 0.05 throughout the interpretation of the results.

RESULTS

The study included a total of 225 cases of acute pancreatitis, with a mean age of 54.10±19.07 years. Among these cases, 116 individuals (51.6%) were identified as women. Out of the total number of patients, 169 individuals (75.1%) were hospitalized, while 56 patients (24.9%) were released from the emergency department. There was no significant association found between age (p=0.362) and gender (p=0.308) with hospitalization. The mean duration of hospitalized patients was 4.75±3.83 days. In the hospitalization group, amylase was 964±1101.1 U/L (p<0.001), lipase was 1902.34±2199.99 U/L (p<0.001) and there was a significant increase in hospitalized patients. The GGT value was 232.98±297.24 U/L in the hospitalization group and was significant (p=0.021). Total bilirubin value was significantly higher in the hospitalization group with 2.16±3.02 mg/dl (p=0.018). Other laboratory parameters were not associated with hospitalizations (Table 1).

The mean age of the survival group was 53.24±18.71 years, and 81.00±6.80 years in the mortality group (p<0.001). Seven (3.1%) cases resulted in mortality. Of the cases that resulted in mortality, 6 (2.7%) were female (p=0.070). The duration of hospitalization was found to be 7.43±2.64 days, with a statistically significant increase observed in the mortality group (p=0.002). Although there was no observed association between amylase values and death, it was found that lipase levels were considerably elevated in the group who had mortality, with an average of 3474.71±3013.69 U/L (p=0.046). In addition, high urea was also evaluated to be associated with mortality (p=0.019). All hemogram and biochemistry parameters evaluated except urea and lipase were not associated with mortality (Table 2).

Table 1. The relationship of hospitalization with age, gender and laboratory parameters

	All Patients n(%)	Hospitalization (-) n(%)	Hospitalization (+) n(%)	p value
Gender				0.308
Female	116(51.6)	31(13.8)	85(37.8)	
Male	109(48.4)	25(11.1)	84(37.3)	
Total	225(100)	56(24.9)	169(75.1)	
	Mean ±SD	**Mean ±SD**	**Mean ±SD**	
Age (year)	54.10±19.07	52.07±18.31	54.77±19.32	0.362
Hospitalization Time (day)	3.59±3.90		4.75±3.83	
Laboratory Findings				
WBC(10^3/µl)	11.12±4.77	10.46±4.59	11.34±4.83	0.156
NEU(10^3/µl)	8.42±4.55	7.52±4.15	8.72±4.66	0.053
LYM(10^3/µl)	1.81±1.09	2.01±1.49	1.74±0.92	0.379
Urea (mg/dl)	49.36±55.28	47.71±47.78	49.90±57.67	0.764
ALT(U/L)	153.16±296.90	117.73±170.51	164.90±327.81	0.061
AST(U/L)	172.05±453.86	123.98±188.98	187.98±511.79	0.069
GGT (U/L)	218.51±292.09	174.86±273.86	232.98±297.24	0.021
LDH (U/L)	441.37±928.27	377.71±365.78	462.46±1050.38	0.088
Amylase (U/L)	855.74±1084.76	529.03±972.06	964±1101.01	<0.001
Lipase (U/L)	1700.02±2138.51	1089.44±2095.69	1902.34±2119.99	<0.001
CRP (mg/dl)	41.37±65.84	27.79±51.24	45.87±69.56	0.039
Direct Bilirubin (mg/dl)	0.96±1.59	0.72±1.29	1.04±1.67	0.218
Total Bilirubin (mg/dl)	2.02±2.89	1.59±2.43	2.16±3.02	0.018
Sodium (mEq/L)	135.77±4.92	135.11±4.89	135.99±4.92	0.278
Potassium (mEq/L)	4.28±0.66	4.26±0.65	4.28±0.66	0.659

SD: standard deviation, WBC: White Blood Cell, NEU: Neutrophil, LYM: Lymphocyte, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, GGT: gamma glutamyl transferase, LDH: Lactate dehydrogenase, CRP: C-Reactive Protein, p:Statistical significance (<0.05)

Table 2. Relationship of mortality with age, gender and laboratory parameters

	Mortality (-) n(%)	Mortality (+) n(%)	p value
Gender			0.070
Female	110(48.9)	6(2.7)	
Male	108(48)	1(0.4)	
Total	218(96.9)	7(3.1)	
	Mean ±SD	**Mean ±SD**	
Age (year)	53.24±18.71	81.00±6.80	<0.001
HosiptalizationTime (day)	3.47±3.88	7.43±2.64	0.002
Laboratory Findings			
WBC(10^3/µl)	11.07±4.79	12.56±4.36	0.286
NEU(10^3/µl)	8.37±4.55	10.28±4.84	0.217
LYM(10^3/µl)	1.81±1.11	1.68±0.80	0.904
Urea (mg/dl)	46.90±50.01	125.88±128.72	0.019
ALT(U/L)	155.44±300.95	82.14±95.92	0.481
AST(U/L)	171.50±459.37	189.14±240.93	0.662
GGT (U/L)	221.90±295.03	113.00±153.76	0.181
LDH (U/L)	438.22±940.21	539.28±432.42	0.156
Amylase (U/L)	849.71±1092.44	1043.71±851.82	0.264
Lipase (U/L)	1643.04±2089.20	3474.71±3013.69	0.046
CRP (mg/dl)	39.66±61.94	94.56±140.27	0.330
Direct Bilirubin (mg/dl)	0.98±1.61	0.42±0.31	0.908
Total Bilirubin (mg/dl)	2.05±2.93	1.12±0.66	0.848
Sodium (mEq/L)	135.72±4.95	137.43±3.78	0.556
Potassium (mEq/L)	4.27±0.66	4.47±0.55	0.115

SD: standard deviation, WBC: White Blood Cell, NEU: Neutrophil, LYM: Lymphocyte, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, GGT: gamma glutamyl transferase, LDH: Lactate dehydrogenase, CRP: C-Reactive Protein, p:Statistical significance (<0.05)

In the evaluation of hospitalization and mortality with imaging results, USG findings were not associated with hospitalization, but pancreatic edema was found to be associated with mortality (p=0.012). CT and MRCP findings were not associated with the mortality of the cases. Gallbladder wall thickness increase (p=0.016) and increase in pancreatic density and heterogeneity (p=0.038) hospitalizations were associated as CT findings. In addition, the presence of intrahapatic bill duct dilatation (p=0.002), pancreatic edema (p=0.045) and peripancreatic fluid (p=0.009) in MRCP was also evaluated as associated with hospitalization (Table 3).

Figure 1 displays the analysis of mortality through the Receiver Operating Characteristic (ROC) curve. Based on the findings of this analysis, it has been determined that there are optimal cut-off values for amylase and lipase in predicting the development of mortality. The amylase test demonstrated a sensitivity of 47.9% and a specificity of 44.5%, with an area under the curve (AUC) of 0.624 (95% confidence interval: 0.414-0.834, p=0.264). On the other hand, the lipase test showed a sensitivity of 71.4% and a specificity of 69.3%, with an AUC of 0.722 (95% confidence interval: 0.529-0.915, p=0.046). These results were observed when the values exceeded 45%.

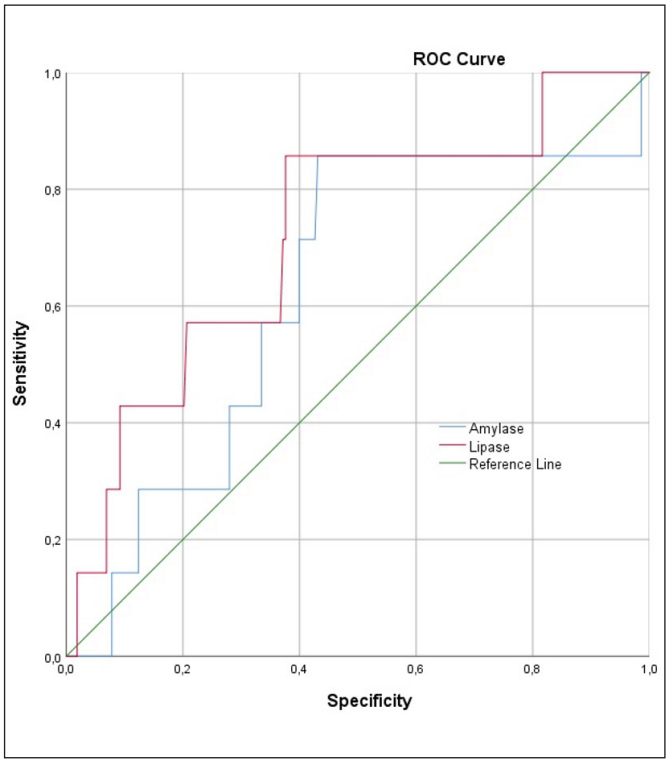

Figure 1. ROC Curve in terms of the relationship of amylase and lipase values with mortality

Table 3. Relation of hospitalization and mortality presence with gender and imaging findings

		H(-) n(%)	H(+) n(%)	Total n(%)	p value	M(-) n(%)	M(+) n(%)	Total n(%)	p value
Ultrasonography									
USG	No	14 (6.2)	14 (6.2)	28 (12.4)	0.002	28 (12.4)	0 (0)	28 (12.4)	0.389
	Yes	42 (18.7)	155 (68.9)	197 (87.6)		190 (84.4)	7 (3.1)	197 (87.6)	
GWT	No	52 (23.1)	145 (64.4)	197 (87.6)	0.122	191 (84.9)	6 (2.7)	197 (87.6)	0.611
	Yes	4 (1.8)	24 (10.7)	28 (12.4)		27 (12)	1 (0.4)	28 (12.4)	
GS	No	42 (18.7)	105 (46.7)	147 (65.3)	0.054	143 (63.6)	4 (1.8)	147 (65.3)	0.460
	Yes	14 (6.2)	64 (28.4)	78 (34.7)		75 (33.3)	3 (1.3)	78 (34.7)	
IBD	No	48 (21.3)	126 (56)	174 (77.3)	0.058	169 (75.1)	5 (2.2)	174 (77.3)	0.497
	Yes	8 (3.6)	43 (19.1)	51 (22.7)		49 (21.8)	2 (0.9)	51 (22.7)	
PE	No	55 (24.4)	164 (72.9)	219 (97.3)	0.535	214 (95.1)	5 (2.2)	219 (97.3)	0.012
	Yes	1 (0.4)	5 (2.2)	6 (2.7)		4 (1.8)	2 (0.9)	6 (2.7)	
PPF	No	55 (24.4)	159 (70.7)	214 (95.1)	0.192	209 (92.9)	5 (2.2)	214 (95.1)	0.040
	Yes	1 (0.4)	10 (4.4)	11 (4.9)		9 (4)	2 (0.9)	11 (4.9)	
Computerized tomography									
CT	No	42 (18.7)	83 (36.9)	125 (55.6)	0.001	120 (53.3)	5 (2.2)	125 (55.6)	0.324
	Yes	14 (6.2)	86 (38.2)	100 (44.4)		98 (43.6)	2 (0.9)	100 (44.4)	
GWT	No	56 (24.9)	155 (68.9)	211 (93.8)	0.016	204 (90.7)	7 (3.1)	211 (93.8)	0.634
	Yes	0 (0)	14 (6.2)	14 (6.2)		14 (6.2)	0 (0)	14 (6.2)	
GS	No	54 (24)	157 (69.8)	211 (93.8)	0.276	205 (91.1)	6 (2.7)	211 (93.8)	0.366
	Yes	2 (0.9)	12 (5.3)	14 (6.2)		13 (5.8)	1 (0.4)	14 (6.2)	
IBD	No	54 (24)	155 (68.9)	209 (92.9)	0.190	202 (89.8)	7 (3.1)	209 (92.9)	0.592
	Yes	2 (0.9)	14 (6.2)	16 (7.1)		16 (7.1)	0 (0)	16 (7.1)	
PE	No	52 (23.1)	155 (68.9)	207 (92)	0.521	201 (89.3)	6 (2.7)	207 (92)	0.447
	Yes	4 (1.8)	14 (6.2)	18 (8)		17/7.6)	1 (0.4)	18 (8)	
PPF	No	54 (24)	152 (67.6)	206 (91.6)	0.103	199 (88.4)	7 (3.1)	206 (91.6)	0.535
	Yes	2 (0.9)	17 (7.6)	19 (8.4)		19 (8.4)	0 (0)	19 (8.4)	
PDI	No	51 (22.7)	135 (60)	186 (82.7)	0.038	180 (80)	6 (2.7)	186 (82.7)	0.651
	Yes	5 (2.2)	34 (15.1)	39 (17.3)		38 (16.9)	1 (0.4)	39 (17.3)	
Magnetic resonance imaging									
MRCP	No	48 (21.3)	106 (47.1)	154 (68.4)	0.001	148 (65.8)	6 (2.7)	154 (68.4)	0.293
	Yes	8 (3.6)	63 (28)	71 (31.6)		70 (31.1)	1 (0.4)	71 (31.6)	
GWT	No	53 (23.6)	154 (68.4)	207 (92)	0.300	200 (88.9)	7 (3.1)	207 (92)	0.553
	Yes	3 (1.3)	15 (6.7)	18 (8)		18 (8)	0 (0)	18 (8)	
GS	No	51 (22.7)	139 (61.8)	190 (84.4)	0.082	183 (81.3)	7 (3.1)	190 (84.4)	0.301
	Yes	5 (2.2)	30 (13.3)	35 (15.6)		35 (15.6)	0 (0)	35 (15.6)	
IBD	No	53 (23.6)	131 (58.2)	184 (81.8)	0.002	178 (79.1)	6 (2.7)	184 (81.8)	0.626
	Yes	3 (1.3)	38 (16.9)	41 (18.2)		40 (17.8)	1 (0.4)	41 (18.2)	
PE	No	55 (24.4)	153 (68)	208 (92.4)	0.045	201 (89.3)	7 (3.1)	208 (92.4)	0.573
	Yes	1 (0.4)	16 (7.1)	17 (7.6)		17 (7.6)	0 (0)	17 (7.6)	
PPF	No	56 (24.9)	153 (68)	209 (92.9)	0.009	202 (89.8)	7 (3.1)	209 (92.9)	0.592
	Yes	0 (0)	16 (7.1)	16 (7.1)		16 (7.1)	0 (0)	16 (7.1)	
PDI	No	55 (24.4)	155 (68.9)	210 (93.3)	0.075	204 (90.7)	6 (2.7)	210 (93.3)	0.387
	Yes	1 (0.4)	14 (6.2)	15 (6.7)		14 (6.2)	1 (0.4)	15 (6.7)	
Total		56 (24.9)	169 (75.1)	225 (100)		218 (96.9)	7 (3.1)	225 (100)	

H: Hospitalization, M: Mortality, GWT: Gallbladder Wall Thickness Increase, GS: Gallstone, IBD: Intrahepatic Bile Duct Dilatation, PE: Pancreatic Edema, PDI: Pancreatic Density Increase/heterogeneity, PPF: Peripancreatic Fluid, USG: Ultrasonography, CT: Computerized Tomography, MRCP: Magnetic Resonance Cholangiopancreatography, p:Statistical significance (<0.05)

DISCUSSION

In AP, which is an inflammatory condition that can cause even multi-systemic organ failure with a severe mortality rate, laboratory analysis is essential in addition to anamnesis and physical examination for appropriate evaluation.[12] It is also very important to make the diagnosis of AP quickly, to start the treatment early and to prevent the complications that may develop. Although many different biomarkers are used in the diagnosis of AP, there is still no biomarker with high sensitivity and specificity. There are also no clear ideas about how the results will affect the prognosis. In addition to basic laboratory diagnostic parameters, imaging methods are also very important in terms of both diagnosis and treatment. We aimed to evaluate whether some laboratory parameters, especially amylase and lipase, and imaging options applied to the patients could give an idea about the hospitalization and mortality status of the patients.

Although the mean age in our study was similar to other studies in the literature, it had a wide age range of 18-94 years. The wide age range is important in terms of considering AP in the differential diagnosis of all ages. While some studies have reported that acute pancreatitis is more common in women, some studies have found that AP is more common in men.[13-15]

Despite the absence of a statistically significant disparity, our investigation revealed that the proportion of female patients was 51.6%, indicating a higher representation compared to other groups. The study conducted by Shen et al. examined the impact of gender on mortality in a sample of 13,110 AP patients. The results indicated a statistically significant association between gender and mortality, with men exhibiting greater mortality rates.[16] In our study, there was a significant increase in mortality with age, similar to other studies. Although no statistically significant correlation was observed between mortality and gender, 6 (2.7%) of 7 (3.1%) cases resulted in mortality were women.

According to the results of a study, the average length of hospital stay for AP-related hospitalizations was 6.4 days in 1997 and 4.7 days in 2003.[3] In a retrospective observational study of 232 patients presenting with the first mild acute pancreatitis attack, Francisco et al.[17] examined the factors associated with long hospital stay in mild acute pancreatitis. In this study, the mean hospital stay was 8 days.

In our study, the average length of stay was 4.75 days only in patients hospitalized, while it was 3.6 days among all pancreatitis patients. The observed reduction in length of stay can likely be attributed to advancements in the comprehension of the pathophysiology of AP, enhanced identification of complications at an earlier stage, superior management strategies for these complications, and a heightened realization of the imperative to mitigate healthcare expenditures. White blood cells (WBCs) play a crucial role in the initiation and regulation of the inflammatory response. Hematopoietic stem cells, which are multipotent cells located in the bone marrow, serve as the source and origin of all WBCs. White blood cells play many roles in the promotion and regulation of inflammation.[18] According to reports, there exists a correlation between elevated leukocyte count, specifically a rise in WBC count, and mortality. Especially the fact that pancreatic necrosis leads to the development of systemic inflammatory response syndrome emphasizes the importance of leukocytes and WBC in pancreatitis.[19] Contrary to this information, in our study, no relationship was found between WBC and hospitalization and mortality.

As it is known, AP is an inflammatory process and in a study conducted with CRP, one of the markers showing inflammation, it was stated that CRP values of >190 mg/dl could indicate the severity of acute pancreatitis.[20] In another study, Sternby et al.[21] mentioned that CRP can be used to differentiate between moderate and severe pancreatitis. In our study, it was determined that high CRP value was associated with hospitalization in AP cases.

In the research of Faisst et al.,[22] high BUN values at admission and an increase in BUN values during the course of the disease in patients with acute necrotizing pancreatitis were found to be associated with long stays in the ICU (≥14 days), and mortality was significantly increased in these patients. Renal failure was also found to be an important risk factor prolonging hospital stay. Francisco et al.[23] also reported in their study that urea was associated with hospitalization and long stay. Although urea was not associated with hospitalization in our study, it was observed that it had a significant effect on mortality.

The sensitivity of lipase level surpasses that of amylase level. Amylase is synthesized in the salivary glands and can be found at normal levels in individuals with recurrent alcoholic pancreatitis.[23] Pancreatitis can be diagnosed when the levels of lipase or amylase exceed three times the upper limit of the normal range.[24] According to a report, there is no observed correlation between blood amylase and lipase levels and the clinical severity of acute pancreatitis.[25] Although there are studies evaluating the relationship of amylase and lipase with the severity of the disease, in our study, in which hospitalization and mortality were evaluated, both amylase velipase is associated with hospitalization. This can be attributed to the fact that these two parameters are already in the diagnostic criteria. However, in addition to hospitalization, lipase was also associated with mortality in our study.

Imaging methods are very important in AP, both in the diagnosis, in the determination of complications and in the treatment process. Patients' need for abdominal imaging and procedures such as CT and MRCP have been associated with long hospital stays.[17] In the study, USG was evaluated in 197 (87.6%) of our cases, CT in 100 (44.4%) and MRCP in 71 (31.6%) of our cases. While USG, CT and MRCP examination were not associated with mortality in our study, all three were found to be associated with hospitalization. According to the study conducted by Greenberg et al.,[26] it is strongly recommended, with high levels of evidence, that USG should be conducted as the initial diagnostic procedure for all patients presenting with acute pancreatitis. The primary objective of this procedure is to identify the presence of gallstones and/or stones in the common bile duct, as well as to assess the condition of the biliary tract. In the research conducted by Karaca and Oktay,[27] abdominal USG was conducted on all individuals in the emergency department. The USG findings indicated pancreatitis in 30 patients (25.9%), while it did not indicate pancreatitis in 61 patients (52.6%). Additionally, 25 patients (21%) had

inconclusive USG results regarding pancreatitis. In our study, USG findings were not associated with hospitalization, but the presence of pancreatic edema on USG was associated with mortality. We attribute the absence of this relationship in CT and MRCP to the fact that advanced edema can be seen on USG and this is associated with an unfavorable prognosis. The efficacy of abdominal USG in pancreatic imaging may be constrained by factors such as the presence of intestinal gas and obesity. Indeed, it can be postulated that the solicitation of abdominal ultrasonography in the emergency department has the potential to impede patient care in this specific cohort. Nevertheless, it is our contention that abdominal USG ought to be administered to all individuals presenting with acute pancreatitis in the emergency department. This is because it plays a significant role in the care of patients with acute pancreatitis and aids in ruling out surgical or alternative etiologies of acute abdominal pain. Contrast-enhanced CT is the gold standard for the diagnosis and evaluation of acute pancreatitis.[28] CT defines anatomical structures better and can reveal complications such as pancreatic inflammation and necrosis. CT is also helpful in determining clinical severity and prognosis, with a diagnostic value of 75–90% for acute pancreatitis.[29,30] MRI and MRCP are good choices for demonstrating pancreatobiliary anomalies because they take multislice images. MRCP is important in elucidating the biliary etiology of pancreatitis. The ideal imaging time for MRCP is when pancreatic edema regresses and the acute attack subsides.[31]

We did not find any detailed study in which CT and MRCP findings were associated with mortality. In our study, we found that none of the findings were associated with mortality in the evaluation made according to the hospitalization and mortality status of the patients. However, increase in gallbladder wall thickness and increase in pancreatic density/heterogeneity in CT, enlargement of intrahepatic bile ducts, pancreatic edema and peripancreatic fluid in MRCP were associated with hospitalization.

Study Limitations

The study had some limitations. The most important of these limitations is related to the retrospective and single-center planning of the study. The information of the patients was obtained from the hospital electronic database and the files in the hospital archive. The exclusion of some of the patients from the study due to errors and deficiencies in the recording of these data may also be a limitation in reducing the effectiveness of the study.

CONCLUSION

Acute pancreatitis is a frequent cause of admission to emergency departments and is still an important problem in morbidity and mortality. Correct diagnosis and early treatment are very important. Being able to use laboratory and imaging methods correctly and being able to make an evaluation in the direction of predicting prognosis and mortality contributes positively to the process. Although there are many studies in terms of clinical severity, laboratory, imaging and prognosis, studies are limited in terms of the effectiveness of laboratory and imaging results in hospitalization and mortality. Amylase, lipase, GGT and Significantly elevated CRP results were observed in patients who were hospitalized. In terms of mortality, especially high urea and lipase values should be a warning in acute pancreatitis. In imaging methods, some findings are significant in hospitalized patients, but no CT or MRCP finding that will give an idea about mortality has been detected. However, the presence of edema and peripancreatic fluid in the pancreas on USG should be a warning for mortality. Prospective studies are needed on the clinical and prognostic effects of laboratory and imaging parameters in AP.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of İstanbul Prof. Dr. Cemil Taşcıoğlu City Hospital Clinical Researches Ethics Committee (Date: 08.03.2021, Decision No: 105)

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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Original Article

MEDICINE PALLIATIVE CARE

DOI: 10.47582/jompac.1349901

J Med Palliat Care. 2023;4(5):431-435

Evaluation of electrocardiographic arrhythmogenicity markers in patients with type 2 diabetes mellitus

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Cite this article as: Kıraç CO. Evaluation of electrocardiographic arrhythmogenicity markers in patients with type 2 diabetes mellitus. *J Med Palliat Care*. 2023;4(5):431-435.

Received: 25.08.2023 ◆ **Accepted**: 18.09.2023 ◆ **Published**: 27.10.2023

ABSTRACT

Aims: Diabetes mellitus (DM) is a chronic disease that progresses with hyperglycemia and the proinflammatory process. The most common complication of DM is cardiovascular disease, and it is known that the risk of arrhythmia increases in patients with DM. The aim of our study was to evaluate the correlation of electrocardiographic arrhythmogenicity markers with HbA1c and fasting blood glucose.

Methods: The study included 77 type 2 DM patients and 76 healthy individuals as a control group. Body mass index, HbA1c value, and fasting blood glucose level were recorded for all patients. Corrected QT (QTc), T peak-T end intervals (Tp-e), and Tp-e/QTc values were calculated from 12-lead electrocardiography (ECG). The results were evaluated statistically.

Results: The Tp-e interval ($p<0.001$), QTc interval ($p<0.05$), and Tp-e/QTc ratio ($p<0.001$) were significantly prolonged within the DM group compared to the control group.

Conclusion: ECG, an inexpensive and reliable diagnostic method, can be used to evaluate the risk of arrhythmia in DM patients. This study concluded that QTc, Tp-e interval, and Tp-e/QTc ratio are markers that can be used to predict arrhythmia risk in DM patients.

Keywords: Arrhythmia, diabetes mellitus, HbA1c, QTc, T peak-T end interval, Tp-e/QTc

INTRODUCTION

Type 2 diabetes mellitus (DM) is a complex metabolic disease that progresses with beta cell destruction and insulin resistance, resulting in hyperglycemia.[1] The most common cause of morbidity and mortality in DM is cardiovascular disease. Prospective studies show that the risk of coronary artery disease and myocardial infarction in patients with DM increases 1-3 times in men and 2-5 times in women compared to healthy individuals.[2] Another cardiac complication seen in patients with DM is ventricular arrhythmia. Cardiac autonomic neuropathy is seen in approximately 30% of patients with DM.[3] Impaired autonomic regulation in patients with DM causes increased activation of the sympathetic system and is associated with ventricular arrhythmia independent of coronary artery disease, heart failure, and hypertension.[4] In addition to autonomic neuropathy, the prothrombotic and proinflammatory process seen in patients with DM also contributes to the development of atherosclerosis, increasing the risk of silent infarcts and arrhythmia.[5] Many studies have shown that an electrocardiogram (ECG) can be used to predict the risk of cardiac arrhythmia in patients with DM. QTc is one of the most commonly used predictors in these studies.[6,7] QTc prolongation has been shown to be an independent predictor of cardiovascular mortality in patients with DM.[8] Two other recently studied markers, the T peak-T end interval (Tp-e) and the Tp-e/QT ratio, are also increasingly used.[9,10] Tp-e has been reported in previous studies to be able to show transmural repolarization. Tp-e is measured independently from the QRS complex, and the Tp-e interval measurement is considered superior to that of QTc duration.[11]

The aim of this study was to determine the relationship between QTc, Tp-e, and the Tp-e/QTc ratio, which are among the arrhythmogenicity indices, and blood glucose regulation in patients with DM.

METHODS

The study was carried out with the permission of Kahramanmaraş Sütçü İmam University Clinical Researches Ethics Committee (Date: 01.12.2021, Decision No: 01). This study was conducted in our institution between January and June 2022. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

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Patients with type 2 DM who applied to an endocrinology and metabolic diseases outpatient clinic for a routine check were included in this cross-sectional study. The patients included in the study were between the ages of 18-65. Blood pressure measurements were taken during the physical examination, and patients who were normotensive without medication or under medication were included in the study. The exclusion criteria were as follows: 1) patients using beta-blockers, calcium channel blockers, or antiarrhythmic drugs; 2) patients with renal dysfunction or electrolyte imbalance; 3) patients with any history of arrhythmia, known coronary artery disease, heart valve disease, pacemaker implantation, or cardiomyopathy; 4) patients with thyroid dysfunction; 5) patients with clinical and/or laboratory findings suggestive of infection; 6) patients using cigarettes, alcohol, and recreational drugs; 7) patients with a diagnosis of malignancy; and 8) pregnant patients.

For the control group, healthy individuals who did not have a history of chronic disease, met the inclusion and exclusion criteria, applied to our hospital for a check-up, and were age- and gender-matched with the patient group were included.

Venous blood samples were taken in the morning after 12 hours of fasting. Biochemical analyses of fasting blood glucose and hemoglobin A1c (HbA1c) were performed. Weight and height measurements were taken, and body mass index (BMI) was calculated as the ratio of weight to height squared (kg/m2).

The 12-lead ECGs of the individuals under study were evaluated. A resting ECG was recorded at 50 mm/sec paper speed (Nihon Kohden ECG-1250 electrocardiograph). The Tp-e interval was defined by the tangential method. The QT interval was descriptive of the time from the onset of the QRS complex to the point where the T wave reversed from baseline. The QTc interval was computed by the Bazett's formula.[12] Precordial V5 lead was applied to these measurements. The evaluation of ECGs in the study was performed by an endocrinologist who had training in cardiology and had previous studies on ECG.

Statistical Analysis

We conducted all analyses utilizing R software, version 4.0.4, developed by the R Foundation for Statistical Computing in Vienna, Austria. Continuous variables were presented as mean±standard deviation, or as median (interquartile range), while categorical variables were expressed as counts (n) and proportions (%). To compare continuous variables between groups, either the Student t-test or the Mann-Whitney U test was employed, based on the normality distribution of the data. Categorical variables were assessed for group differences using the Chi-square test. For numerical variables with a homogeneous distribution, correlation coefficients were calculated using the Pearson test, and for those with a non-homogeneous distribution, the Spearman test was utilized. Statistical significance was considered for two-tailed p-values less than 0.05.

RESULTS

Table 1 shows the baseline clinical and laboratory characteristics of both the patients with DM and control groups. A total of 153 patients were included in the study, including 88 women (57.5%) with a mean age of 43±13.2 years and 65 men (42.5%) with a mean age of 44.5±11.2 years. Among them, the control group consisted of 76 patients while the DM group consisted of 77 patients. Notably, no significant differences were observed between the groups in terms of gender, age, or BMI.

As expected, the DM group had increased fasting glucose and HbA1c levels compared to the control group ($p<0.05$). In addition, the Tp-e interval ($p<0.001$), the QTc interval ($p<0.05$), and the Tp-e/QTc ratio were significantly prolonged within the DM group compared to the control group.

When performing a correlation analysis within the DM patient cohort, Tp-e intervals were found to have significant positive correlations with duration of DM ($r=0.423$, $p<0.001$), BMI ($r=0.339$, $p=0.003$), and

Table 1. Comparing basic characteristics and laboratory data between groups

	Total (n=153)	Controls (n=76)	Cases (n=77)	p
Sex (female), n(%)	88(57.5)	46(60.5)	42(54.5)	0.514
Age (years)	46.2 ± 11.7	44.1 ± 9.7	48.3 ± 13.6	0.065
BMI kg/m²	27(24-29)	27.1(24.3-29)	27(24-29)	0.427
DM Duration (years)	-------	-------	8(5-11)	-------
Fasting glucose, mg/dl	102(88-135)	92(78-102)	130(100-194)	<0.001
HbA1c, mg/dl	6.3(5.7-8.3)	5.7(5.5-6)	8(7.2-10)	<0.001
QTc (ms)	415(409-423)	413(409-420)	418(410-425)	0.039
Tpeak-tend (ms)	84(76-89)	78(73-84)	88(82-95)	<0.001
Tpeak-tend/QTc	0.20(0.18-0.21)	0.18(0.17-0.20)	0.21(0.19-0.22)	<0.001

BMI: Body Mass Index, DM: Diabetes Mellitus, QTc: corrected QT p < .05, ** p < .01, *** p < .001

HbA1c values (r=0.463, p<0.001) as shown in **Figure 1**. Likewise, the QTc interval showed significant positive correlations with BMI (r=0.367, p=0.001) and HbA1c (r=0.306, p=0.007), while no correlation was found between QTc and the duration of DM (r=0.171, p=0.136). The Tp-e/QTc ratio was positively correlated with DM duration (r=0.370, p=0.001) and HbA1c levels (r=0.369, p=0.001), while there was no significant correlation between Tp-e/QTc ratio and BMI (r=0.220, p=0.055) (**Table 2**).

DISCUSSION

The sudden cardiac death rate for patients with DM is 2-10 times higher than for the general population, but the underlying causes are still unclear.[13] Arrhythmias are thought to be the most important cause of sudden cardiac death, and QTc prolongation is one of the most important arrhythmia markers for DM patients.[14] Similar to previous studies, our study found a significant prolongation of QTc between the DM and control groups.[9,10,14] A study by Stern et al.[15] on 265 patients showed that besides the presence of DM, the patients' blood sugar regulation and BMI values were directly related to QTc prolongation. The authors determined that high HbA1c and obesity cause cardiac autonomic dysfunction, resulting in an increased risk of arrhythmia. Similarly, we observed that both HbA1c levels and BMI were positively correlated with QTc. Many studies have shown that a high fasting blood glucose level is a risk factor for QTc prolongation in patients with DM.[14-16] However, our study revealed no significant relationship between QTc and fasting blood glucose. This may be due to the limited number of patients in our study, but it may also be because the blood glucose regulation of the patients included in the study was relatively well controlled. As a result, the fasting blood glucose levels of our patients were close to normal. In the literature, we could not find any study evaluating the relationship between DM duration and QTc interval; however, Agarwal et al.[17] showed that the duration of DM increases the risk of atrial fibrillation. In our study, we found no significant relationship between DM duration and QTc interval, but there was a significant positive correlation between DM duration and both Tp-e and the Tp-e/QTc ratio.

Tp-e and the Tp-e/QTc ratio are two of the ventricular arrhythmia markers frequently studied in the last decade, and in some clinical conditions, these markers have been shown to be more useful for predicting cardiac arrhythmias than QTc.[18] Similarly, our comparison of the DM and control groups

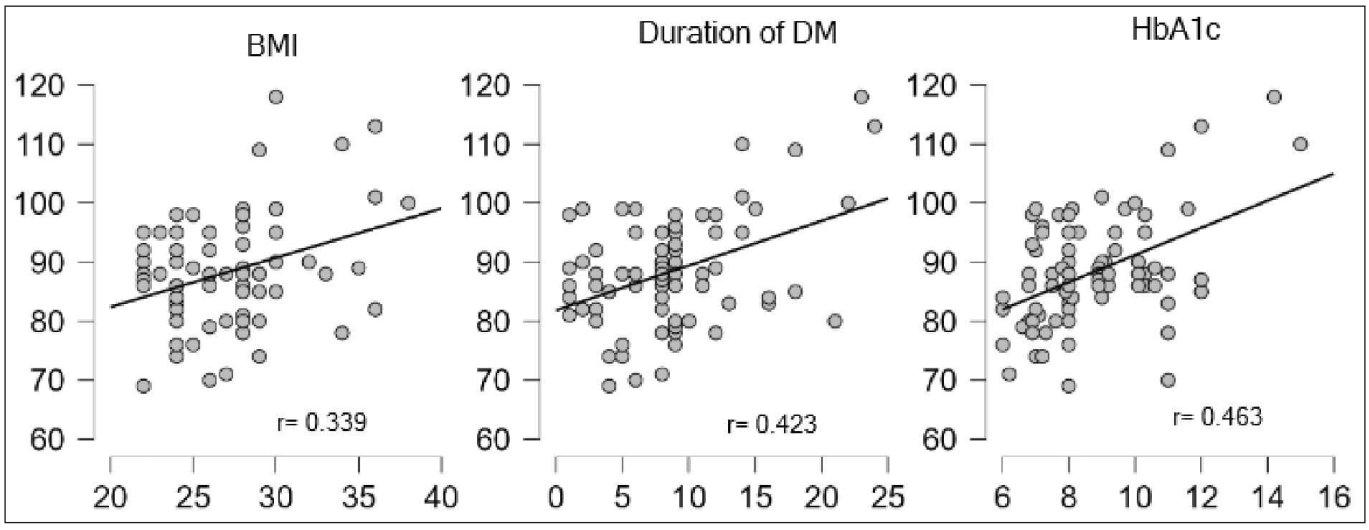

Figure 1. Positive Correlation Between Body Mass Index (BMI), Duration of Diabetes Mellitus (Years) and HbA1c Values With The Tpeak Tend Interval (Tp-e).

Table 2. Correlation matrix between variables

Variable		QTC	Tpe	Tpe/QTc	Duration of DM	HbA1c	BKI	Glucose
Duration of DM	r-value	0.171	0.423***	0.370***	—			
	p-value	0.136	<.001	<.001	—			
HbA1c	r-value	0.306**	0.463***	0.369***	0.311**	—		
	p-value	0.007	<.001	<.001	0.006	—		
BMI	r-value	0.367**	0.339**	0.220	0.327**	0.215	—	
	p-value	0.001	0.003	0.055	0.004	0.061	—	
Fasting glucose	r-value	0.033	-0.155	-0.160	-0.048	0.087	0.057	—
	p-value	0.776	0.179	0.166	0.682	0.454	0.622	—

BMI: Body Mass Index, DM: Diabetes Mellitus * p < .05, ** p < .01, *** p < .001

showed that Tp-e and Tp-e/QTc gave more significant results than QTc. In previous studies, it was observed that Tp-e and Tp-e/QTc are directly related to HbA1c and fasting blood glucose levels in patients with DM.[9,10] Similar results were seen in the study by Ardahanlı et al.[19] on prediabetic patients, in which it was theorized that silent ischemic heart diseases may occur in the prediabetic period, so the risk of ventricular arrhythmia increases with an increased transmural dispersion of repolarization. Similarly, we found a positive correlation between HbA1c and Tp-e and Tp-e/QTc. However, unlike previous studies, we found no relationship between fasting blood glucose and arrhythmogenicity indices, which again may be due to the relatively regulated blood glucose levels of the DM group included in our study.

Conflicting results have been seen in studies evaluating the relationship between the duration of DM and cardiac complications. While some studies have shown that the risk of subclinical and clinical cardiovascular disease increases with longer durations of DM,[20,21] some studies have not found any association.[22] In our study, Tp-e and Tp-e/QTc were found to be directly related to the duration of DM, independent of blood glucose regulation.

Previous studies have shown that obesity increases the risk of arrhythmia, and that both Tp-e and Tp-e/QTc increase in obese patients.[23,24] There is a pathophysiology of increased risk of arrhythmia with obesity; especially in the early stages of obesity, there is thought to be a decrease in cardiac remodeling and an increase in fibrosis.[25] In addition, cardiometabolic risk due to increased sympathetic activity increases in obesity.[26] Similarly, we found a positive correlation between Tp-e and BMI.

Study Limitations

This research had some limitations. First, the sample size was relatively small, so there is a need to conduct this study in a larger population. Second, it used a cross-sectional research method and had no long-term patient follow-up. Also not including diabetic patients with arrhythmia as a third group in the study is a factor that reduces the power of the study. Finally, some of the patients included in the study had chronic diseases, such as hypertension and hyperlipidemia, apart from DM. We included normotensive patients in the study, but we had to disregard the effect of chronic diseases other than DM on the arrhythmia markers. Therefore, further studies with more isolated and larger patient groups are needed to reveal the pathophysiology of arrhythmia in patients with DM.

CONCLUSION

The most common cause of mortality due to DM is cardiovascular complications. One of these complications is arrhythmia. Because it is an inexpensive and reliable diagnostic method, ECG should be used in the evaluation of cardiac complications in DM patients. As a result of our study, QTc, Tp-e interval and Tp-e/QTc ratio are markers that can be used to predict arrhythmia risk in patients with DM.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kahramanmaraş Sütçü İmam University Clinical Researches Ethics Committee (Date: 01.12.2021, Decision No: 01)

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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Original Article

MEDICINE PALLIATIVE CARE

DOI: 10.47582/jompac.1340956

J Med Palliat Care. 2023;4(5):436-443

An examination of rational drug use and traditional complementary medicine in patients hospitalized because of gastrointestinal system bleeding

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Cite this article as: Afşar F, Erdoğan H, Küçük N, Karaali Z, Bölüktaş RP. An examination of rational drug use and traditional complementary medicine in patients hospitalized because of gastrointestinal system bleeding. *J Med Palliat Care*. 2023;4(5):436-443.

Received: 10.08.2023 ◆ **Accepted**: 19.09.2023 ◆ **Published**: 27.10.2023

ABSTRACT

Aims: The aim of this study was to determine the knowledge levels of rational drug use, the attitudes toward traditional and complementary medicine, and the relationship between these in patients admitted to the Internal Medicine Clinic because of gastrointestinal system bleeding.

Methods: This descriptive, cross-sectional study was conducted with 124 patients hospitalized in the Internal Medicine Clinic of a training and research hospital with a diagnosis of gastrointestinal bleeding between 10.07.2022 and 10.12.2022.

An information form including demographic and clinical characteristics, the Rational Drug Use Scale (RDUS), and the Complementary, Alternative, and Conventional Medicine Attitudes Scale (CACMAS) were applied to the patients. The data obtained were analyzed statistically using SPSS vn. 23.0 software.

Results: For the whole sample of patients hospitalized with a diagnosis of gastrointestinal system bleeding, the mean RDUS points were determined to be 19.8±4.17 and the mean total CACMAS points were 96.76±15. In the subscales of the CACMAS, the mean points were determined to be 28.15±9.42 for philosophical congruence with complementary medicine, 23.23±10.39 for dissatisfaction with conventional medicine, and 45.38±8.18 for holistic balance. A statistically significant negative correlation was found between rational drug use and dissatisfaction with conventional medicine ($p \leq 0.001$), and a statistically significant positive correlation was found between rational drug use and holistic balance ($p \leq 0.001$). A backward-step regression analysis was performed to measure the relationship between rational drug use and the three quantitative variables of the CACMAS. The linear equation of the relationship to the second model was found to be statistically significant ($p \leq 0.001$).

Conclusion: The results of this study demonstrated that rational drug use was low and that rational drug use had a proportionate effect on holistic balance in patients hospitalized in the Internal Medicine Clinic because of gastrointestinal bleeding.

Keywords: gastrointestinal bleeding, rational drug use, alternative medicine, patient

INTRODUCTION

Gastrointestinal bleeding, which has a high mortality rate, is a common medical emergency that requires hospitalization and a multidisciplinary approach for diagnosis and treatment.[1,2] The mortality rate during hospitalization has been reported to be 7% worldwide. Previous studies have shown that H.pylori infection and the use of non-steroid anti-inflammatory drugs (NSAIDs) are the leading risk factors for gastrointestinal system bleeding and that the risk of complications in patients with bleeding is increased 4-fold in those who use NSAIDs and 2-fold in those who use aspirin. The first approach to patients presenting with suspected gastrointestinal system bleeding should be the questioning of the use of oral anticoagulants, antiplatelet drugs, and NSAIDs. Of these drugs, the use of NSAIDs without prescription is extremely widespread.[3,4]

Although NSAIDs are the most frequently recommended drugs for symptomatic relief in the treatment of pain, fever, and inflammation, they are drugs which are often used without a prescription.[5] It has been reported that an estimated 29% of fatal peptic ulcer complications, especially in elderly patients, may be associated with NSAIDs.[6] Aspirin is fundamentally an NSAID and is often used without prescription as it is thought to be effective in preventing cardiovascular diseases (CVD), and reducing morbidity and mortality.[7,8]

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However, in the decision to use low-dose aspirin for the prevention of CVD in clinical practice, the bleeding risks of the individual should be carefully evaluated and in those taking prophylactic low-dose aspirin, combined use together with an acid-suppressing agent is recommended.[9]

The interest in traditional and complementary medicine has increased in recent years. Herbal methods are the most commonly used. Therapeutic plants and their chemical components have started to be used in the prevention and treatment of many diseases. However, in addition to the beneficial effects of herbal products, it is also known that they can contain dangerous bioactive elements. It is important that the efficacy on systems of the products used and interaction with other drugs are supported by evidence-based studies.[10,11] Previous studies have shown that some plants have the potential to intervene in blood clotting. Various regulations have been made in Turkey and throughout the world in general on the subject of plants with this effect, but they continue to be used without supervision. When more than one plant is used at the same time, or especially when it is used with drugs, this can lead to severe side effects and even toxicity.[12] Uncontrolled drug use and/or the use of traditional complementary medicine methods, especially to get rid of symptoms of pain, is a common thing right now.[13] Although there are studies on drugs and plants that may cause gastrointestinal bleeding, no study has been found that evaluates this. Although there are studies in the literature on drugs and plants that may cause gastrointestinal bleeding, no study has been found that evaluates the attitudes of patients with gastrointestinal bleeding regarding rational drug use and complementary medicine practices. The aim of this study was to determine the relationship between rational drug use and traditional and complementary medicine in patients hospitalized in the Internal Medicine Clinic because of gastrointestinal bleeding.

METHODS

The study was carried out with the permission of Başakşehir Çam and Sakura City Clinical Researches Ethics Committee (Date: 06.07.2022, Decision No: 218). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This descriptive, cross-sectional study was conducted with 124 patients hospitalized in the Internal Medicine Clinic of a training and research hospital with a diagnosis of gastrointestinal bleeding between 10.07.2022 and 10.12.2022. It was calculated to be necessary to include 110 patients in the t test family (linear bivariate regression) using 0.85 power, 0.05 error, and 0.25 slope H1.

An information form including demographic and clinical characteristics, the Rational Drug Use Scale (RDUS), and the Complementary, Alternative, and Conventional Medicine Attitudes Scale (CACMAS) were applied to the patients. The Rational Drug Use Scale (RDUS) of 21 items in a single subscale was developed in 2018 by Demirtaş et al.[14] to measure knowledge about rational drug use. Responses are given as "yes", "no", I don't know, and the total points range from 0-42. In the original version of the rational drug use scale, a score of ≥ 35 points is accepted as knowledge of rational drug use. A score of ≥35 points is accepted as knowledge of rational drug use. The Cronbach alpha value of the original scale was 0.79, and this value was determined to be 0.80 in this study. The Complementary, Alternative, and Conventional Medicine Attitudes Scale (CACMAS) was developed by McFadden et al. in 2010, and validity and reliability studies of the Turkish version were conducted in 2016 by Köse, Ekerbiçer, and Erkorkmaz.[15] The responses to the scale items are on a 7-point Likert-type scale ranging from 1= I completely disagree to 7= I completely agree, to give a total score in the range of 1-189 points. The scale has 27 items in 3 subscales of Philosophical Congruence with Complementary and Alternative Medicine with 8 items (nos: 5,7,9,18,19,21,22,24; 1-56 points); Dissatisfaction with Conventional Medicine with 10 items (nos: 1, 4, 8, 11, 14, 16, 17, 20, 26, 27; 1-70 points); and Holistic Balance with 9 items (nos: 2, 3, 6, 10, 12, 13, 15, 23, 25; 1-63 points). Reverse scoring is applied to 5 items (nos: 1, 4, 8, 9, 26). Higher total scores obtained from this scale indicate a more positive attitude toward complementary and alternative medicine. The Cronbach's alpha value of the original scale and in the current study was determined to be 0.80.

Statistical Analysis

The data obtained in the study were analyzed statistically using G*Power 3.1.9. and IBM SPSS vn. 23.0 software. Following evaluation of the conformity of data to the normal distribution with the Kolmogorov-Smirnov test, parametric tests were applied to data showing a normal distribution and non-parametric tests to data not conforming to the normal distribution. The sociodemographic data were stated as mean±standard deviation (SD), median, minimum- maximum values, number (n), and percentage (%). In the comparisons of two groups of continuous data, the Student's t-test was used, and correlations were examined with the Pearson correlation coefficient. A value of $p<0.05$ was accepted as the level of statistical significance.

RESULTS

The patients hospitalized in the Internal Medicine Clinic because of gastrointestinal system (GIS) bleeding were determined to have a mean age of 59.17±16.04 years; 102 (82.2%) patients had an education level of primary school; 96 (77.42%) were married; 100 (80.65%) had an income of an average level; and 88 (71%) were determined to have a chronic disease.

Of the total 124 patients hospitalized in the Internal Medicine Clinic because of GIS bleeding, 92 (74.2%) did not use anticoagulants, 118 (95.2%) used stomach protection, 88 (71%) reported regular drug use, 63 (50.8%) took painkillers only when they were in pain, and 41 (33.1%) used aspirin (Table 1).

Table 1. The sociodemographic characteristics and clinical findings of the patients (n=124)

Characteristic Features	N	Percentage
Age	59.17±16.04	
Gender		
Female	55	44.4%
Male	69	55.6%
Education		
Primary school	102	82.3%
High School	12	9.7%
University	10	8.1%
Marital status		
Married	96	77.4%
Single	12	9.7%
Divoced/Widowed	16	12.9%
Income level		
Low income	12	9.7%
Middle income	100	80.6%
High income	12	9.7%
Chronic disease		
Present	88	71%
Absent	36	29%
Number of chronic diseases		
None	36	29.0%
One	40	32.3%
2 or more	48	38.7%
Anticoagulant use		
Non-use	92	74.2%
Antiagregan	12	9.7%
Antikoagülan	20	16.1%
Stomach protection use		
Present	118	95.2%
Absent	6	4.8%
Regular drug use		
Use	88	71.0%
Non-use	36	%29
Painkiller		
Use	63	%50.8
Non-use	61	%49.2
Aspirin		
Use	41	33.1%
Non-use	83	66.9%

The mean systolic blood pressure was determined to be 115.85±14.76, and the mean diastolic blood pressure was 68.32±10.92 (Table 2).

Table 2. Blood pressure values of the patients (N=124)

	N	Min	Max	Mean±SD	Median
Systolic BP	124	87	147	115.85±14.76	120
Diastolic BP	124	45	96	68.32±10.92	68

For the whole sample of patients hospitalized with a diagnosis of gastrointestinal system bleeding, the mean RDUS points were determined to be 19.8±4.17 and the mean total CACMAS points were 96.76±15. In the subscales of the CACMAS, the mean points were determined to be 28.15±9.42 for philosophical congruence with complementary and alternative medicine 23.23±10.39 for dissatisfaction with conventional medicine, and 45.38±8.18 for holistic balance (Table 3).

Table 3. The Rational Drug Use and CACMAS scores of the patients (N=124)

	N	Min	Max	Mean±SD	Median
Rational Drug Use	124	7	30	19.8±4.17	21
CACMAS subscale scores					
Philosophical congruence with CAM	124	12	52	28.15±9.42	27.00
Dissatisfaction with conventional medicine	124	10	50	23.23±10.39	20.00
Holistic balance	124	31	58	45.38±8.18	46.50
Total	124	72	132	96.76±15	97.50

*CAM: complementary and alternative medicine

In the female patients hospitalized because of GIS bleeding, the RDUS points (20.33±4.37, p:0.04), and CACMAS subscale points of dissatisfaction with conventional medicine (26.04±9.74, p: 0.03), and holistic balance (47.24±7.33, p: 0.02) were found to be significantly higher than in males. In the male patients, the CACMAS subscale mean points for philosophical congruence with complementary and alternative medicine were determined to be significantly higher (29.77±9.52, p:0.03). No statistically significant difference was determined between the RDUS points and the CACMAS points according to education level. When examined according to marital status, the CACMAS subscale mean points for philosophical congruence with complementary and alternative medicine (36.33±9.06, p:0.002) and the total CACMAS points (104.67±12.5; p: 0.004) were determined to be statistically significantly higher in patients who were single compared to those who were married. The mean RDUS score of patients with a good income status (22.17±4.02, p:0.03) was higher than that of the other groups; the patients

with a low income had higher mean points in the CACMAS subscale of dissatisfaction with conventional medicine (30±15.17, p: 0.03), and these differences showed statistical significance (p<0.05). No statistically significant correlation was determined between the presence or number of chronic diseases and the RDUS and total CACMAS points (p>0.005), (Table 4).

The CACMAS subscale points of philosophical congruence with complementary and alternative medicine of the patients who used anticoagulants (32.95±10.77; p:0.04) were determined to be statistically significantly high. No statistically significant correlation was determined between the status of using stomach protection and the RDUS and CACMAS points (p>0.005), (Table 4).

The total CACMAS points (98.66±14.76; p:0.03) and the holistic balance CACMAS subscale points 846.49±8.34; p:0.02) of the patients who reported regular drug use were determined to be statistically significantly higher compared to those of the patients who did not use drugs regularly. The RDUS points of patients who did not use painkillers (21.21±4.00, p:0.01), and the CACMAS subscale points of dissatisfaction with conventional medicine of the patients who only took painkillers when they were in pain (26±10.67; p:0.01) were statistically significantly high (Table 4).

Table 4. Correlations between the demographic characteristics and the clinical findings of the patients and the RDUS and CACMAS scores (N=124)

	Rational drug use		Philosophical congruence with CAM		Dissatisfaction with conventional medicine		Holistic balance		CACMAS Total points	
Gender										
Female	20.33±4.37	0.208	26.13± 8.97	0.032*	26.04±9.74	0.007*	47.24±7.33	0.023*	99.4±15.41	0.080
Male	19.38±3.98		29.77± 9.52		20.99±10.42		43.9±8.56		94.65±14.43	
Education										
Primary school	19.71±4.48	0.942	28.36± 8.82	0.607	23.73±10.56	0.39	45.06±8.29	0.48	97.15±14.84	0.349
High school	20.58±1.78		26.67± 14.71		18.17±6.09		46.08±6.3		90.92±18.11	
University	19.8±2.62		27.8±8.44		24.2±11.85		47.8±9.3		99.8±11.96	
Marital status										
Married	19.68±4.2	0.325	28.01± 9.43	0.002*	23.75±10.09	0.384	45.34±8.62	0.659	97.1±14.24	0.004*
Single	19±5.26		36.33± 9.06		21.33±8.86		47±7.68		104.67± 12.5	
Divoced/widowed	21.13±2.85		22.88± 4.6		21.5±13.22		44.38± 5.56		88.75± 18.08	
Income level										
Low income	21±3.77	0.032*	25.67± 4.96	0.221	30±15.17	0.156	44.33±6.97	0.411	100±18.59	0.581
Middle income	19.37±4.14		27.95± 9.46		22.88± 9.61		45.15±8.39		95.98±14.6	
High income	22.17±4.02		32.33± 11.66		19.33± 8.81		48.33±7.33		100±14.93	
Chronic disease										
Absent	19.33±3.08	0.429	28.56± 8.8	0.762	21.25± 11.07	0.177	46.5±8.06	0.331	96.31±15.11	0.831
Present	19.99±4.54		27.99± 9.7		24.03± 10.05		44.92±8.23		96.94±15.03	
Number of chronic diseases										
None	19.33±3.08	0.203	28.56± 8.8	0.485	21.25± 11.07	0.117	46.5±8.06	0.044*	96.31±15.11	0.767
One	20.48±4.61		26.95± 11.09		25.13± 10.24		43.2±5.89		95.28±15.06	
2 or more	19.58±4.49		28.85± 8.39		23.13± 9.91		46.35±9.59		98.33±15.03	
Anticoagulant use										
Non-use	19.64±4.06	0.397	27.36± 8.65	0.065	22.9±10.74	0.48	44.76±8.4	0.153	95.02±15.34	0.035*
Antiagregan	21.42±1.56		26.25± 11.02		22.25± 8.04		49.83±5.08		98.33±11.59	
Anticoagulant	19.55±5.49		32.95± 10.77		25.3±10.17		45.55±8.11		103.8±13.54	
Stomach protection										
Use	19.75±4.19	0.535	27.74± 9.04	0.183	23.37± 10.49	0.487	45.18±8.1	0.226	96.29±14.96	0.122
Non-use	20.83±3.76		36.33± 13.56		20.33± 8.52		49.33±9.56		106±13.65	
Regular drug use										
Use	20.34±4.48	0.023*	28.99± 10.02	0.123	23.18±9.99	0.942	46.49± 8.34	0.018*	98.66± 14.76	0.027*
Non-use	18.47±2.92		26.11± 7.51		23.33±11.45		42.67±7.18		92.11±14.75	
Painkiller use										
1 every 2 days	20.48±4.17	0.01*	27.78± 12.83	0.58	21.22±8.95	0.01*	47.09±5.46	0.25	96.09±16.05	0.14
When there is pain	18.7±4.01		28.98± 7.14		26±10.67		44.21±9.31		99.19±14.54	
Non-use	21.21 ±4		27± 10.44		19.84±9.64		46.29±7.38		93.13±14.72	
Aspirin use										
Use	19.49± 3.1	0.562	29.83± 9.46	0.165	22.49±10.37	0.580	46.12±8.76	0.479	98.44±13.82	0.383
Non-use	19.95± 4.61		27.33± 9.34		23.59±10.44		45.01±7.9		95.93±15.56	

A statistically significant positive correlation was found between mean systolic blood pressure values and the mean CACMAS subscale points of philosophical congruence with complementary and alternative medicine (p:0.009), and a statistically significant negative correlation with the mean subscale points of dissatisfaction with conventional medicine (p:0.000). The mean diastolic blood pressure values were determined to be statistically significantly positively correlated with the mean subscale points of philosophical congruence with complementary and alternative medicine (p:0.015), and negatively correlated with the mean subscale points of dissatisfaction with conventional medicine (p:0.000), (Table 5).

Table 5. Correlations between the blood pressure values and the RDUS and CACMAS points (N=124)

		Age	Systolic BP	Diastolic BP
Rational Drug Use	r*	0.094	0.111	0.039
	P	0.298	0.255	0.689
Philosophical congruence with CAM	r*	-0.145	0.253**	0.236**
	P	0.108	0.009	0.015
Dissatisfaction with conventional medicine	r*	0.104	-0.356**	-0.358**
	P	0.249	0.000	0.000
Holistic balance	r*	0.006	0.054	-0.084
	P	0.947	0.579	0.391
Total	r*	-0.016	-0.023	-0.114
	P	0.864	0.818	0.246

*Pearson correlation coefficient, **statistically significant

The relationships between the RDUS points and the CACMAS total points and subscale points were evaluated with correlation analysis. No statistically significant correlation was found between the RDUS points and the subscale of philosophical congruence with complementary and alternative medicine (p=0.444). A statistically significant negative correlation was determined between the RDUS points and the subscale of dissatisfaction with conventional medicine (r=-0.381, p<0.001), and a statistically significant positive correlation was found between rational drug use and holistic balance (r=0.472;p<0.001) (Figure 1).

A backward step regression analysis was performed to measure the relationship between rational drug use and the three quantitative variables of the CACMAS. The linear equation of the relationship to the second model was found to be statistically significant (F=21.759, p<0.001).

The equation showed equivalence of RDUS=13.124-0.90 Dissatisfaction with Conventional Medicine + 0.193 Holistic Balance (p<0.001, p=0.010, respectively). The subscale of philosophical congruence with complementary and alternative medicine was not found to have a statistically significant effect on RDUS (p=0.164). An increase of 1 unit in the dissatisfaction with conventional medicine subscale reduced the RDUS points by 0.90 and an increase of 1 unit in the holistic balance subscale increased the RDUS points by 0.193, as a result of which the RDUS score was calculated as 13.28.

DISCUSSION

The non-rational use of drugs causes a decrease in patient compliance with treatment, drug interactions, the development of resistance to some drugs, prolongation or recurrence of diseases, an increase in the frequency of adverse events, and an increase in treatment costs. One of the most important problems in the non-rational use of drugs is the use of analgesics without a prescription.16 In a study of 542 patients presenting at an Internal Medicine polyclinic, it was reported that 51.8% of adults used drugs without a prescription, and 88.6% of the unprescribed drugs were painkillers.[17] In another study of 2842 students in a Health Sciences Faculty, 52.1% of the students stated that they used painkillers without a prescription, and the percentage of students with a high income level using painkillers was lower than that of other income groups.[18] Although the rational drug use points of the current study patients who used drugs regularly were high, the scores were determined to be below the RDUS cutoff value of 35 points. Patients who

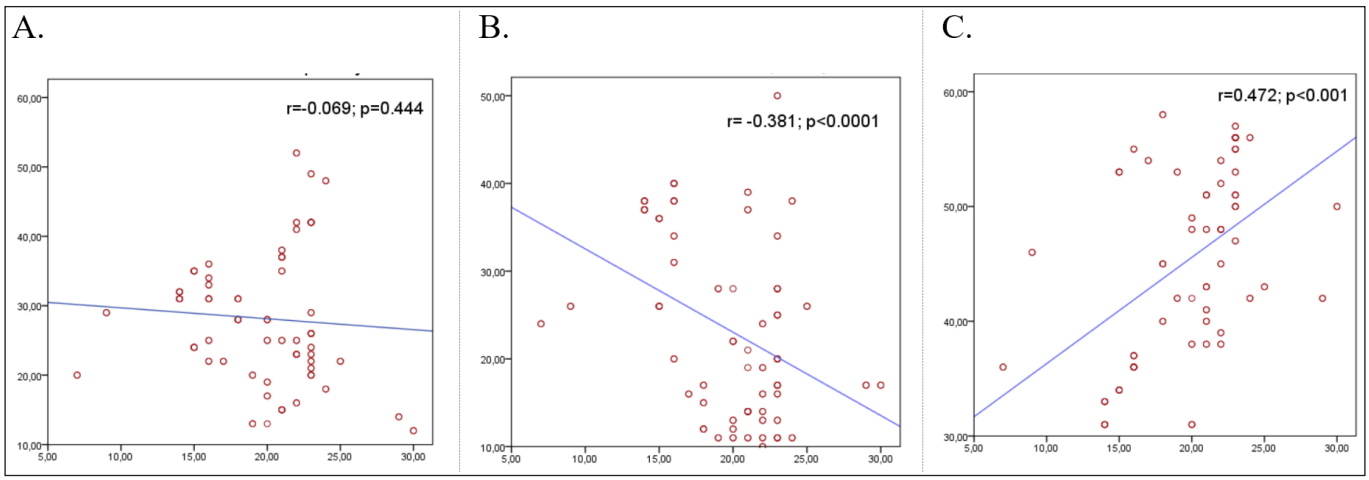

Figure 1. Graphic representations of the correlations between Rational Drug Use and (A)Philosophical Congruence with CAM, (B) Dissatisfaction with Conventional Medicine, and (C) Holistic Balance

used painkillers only when they were in pain were found to have lower RDUS points, which was thought to be due to conscious behavior to relieve the negative condition created by pain and focus on the outcome of pain relief.

Aspirin is one of the drugs most often used in the general population because of its analgesic, anti-inflammatory, anti-pyretic, and anti-aggregant effects. In literature, aspirin has been shown to be an independent risk factor for the first occurrence of GIS bleeding, other than varices.[4] A study of 119 patients who presented at family practitioners reported that 42% were using aspirin as they wished.[19] In another population-based study related to low-dose aspirin users, the incidence of lower GIS bleeding was higher than the incidence of upper GIS bleeding, but the incidence rates of GIS bleeding and 30-day mortality rates of hospitalized patients were lower for those with lower GIS bleeding than for those with upper GIS bleeding.[20] It was seen that 33.1% of the current study patients were using aspirin, but no statistically significant difference was determined between those using and not using aspirin in respect of the RDUS points. Aspirin is a readily available over-the-counter drug and is widely used in the general population. Unconscious use of aspirin at high doses is absolutely a serious risk factor for upper GIS bleeding. Therefore, it is important that society is informed and awareness is created within the framework of health education before these negative outcomes emerge.

The use of traditional and complementary medicine methods is increasing in many countries. The reasons for people wanting to benefit from complementary and alternative medicine include conformity with cultures, lower cost, easy availability, that they are not interventional procedures, and that they seem to be promising for chronic, psychiatric, and terminal diseases.[21] Özer et al.[22] examined the attitudes to complementary and alternative medicine of patients presenting at the Internal Medicine Polyclinic, and reported total CACMAS mean points of 115.78±18.81, philosophical congruence with complementary and alternative medicine subscale points of mean 35.54±8.81, dissatisfaction with conventional medicine subscale points of 35.54±10.28, and holistic balance subscale points of 44.7±8.25. While the philosophical congruence with complementary and alternative medicine and dissatisfaction with conventional medicine subscale points were lower in the current study, the holistic balance points were similar at a mean 45.38±8.18.

Under the umbrella term alternative and complementary treatment, herbal products have started to be widely used. Although there are few reports of the side-effects of herbal products known as complementary and alternative , it has been reported in the literature that biological-based products obtained from unreliable sources can cause a toxic effect or drug interactions.[23] In a study of 348 patients presenting at a family health center, it was determined that 47.1% of the study participants were interested in herbal treatments and applied these, and 19.8% used complementary and alternative medicine-herbal treatment-first when they became ill. It was also determined that females used herbal products at a higher rate than males.[24]

In another study of 196 adults with digestive system problems, 53.8% reported that they used diet and herbal products for these GIS problems.[25]

In a study in Sweden, 1029 patients presenting at the emergency department were questioned about their use of alternative medicine. It was determined that 72.9% of the patients applied alternative medicine at some time in their lives, and the middle-aged female group with a middle-school level of education, and those who used drugs without a prescription used alternative medicine more.[26] The behaviours and attitudes to complementary and alternative medicine were examined in a study of 700 patients presenting at a university hospital, and it was reported that females, females with a high income level, those with poor health perception and chronic disease, and those with knowledge about the use of complementary treatments had higher alternative medicine attitude points than the other groups.[27] The use of complementary and alternative medicine and the associated behaviours and attitudes were examined in a study of 110 immigrants, and it was reported that females and those with a chronic disease showed greater complementary and alternative medicine use behaviour and attitudes.[28] In another study by Kaur et al.,[29] 29.3% of the study population in Malaysia stated that they had used complementary and alternative medicine health services at some time in their life, and more females than males (23.9% vs. 19.3%) reported that they had benefitted more from complementary and alternative medicine practices.[29]

In our study, traditional complementary medicine attitude scores are seen to be high. In addition, the study determined that greater attitudes wardcomplementary and alternative medicine were found in females than in males and in single patients compared to those who were married. Moreover, the holistic balance subscale points were determined to be higher in patients with two or more chronic diseases. Nowadays, it seems that there is a tendency to use complementary medicine for health maintenance and aesthetic purposes, especially in the female and single population. It is thought that the results of our study are due to the fact that women are prone to using alternative medicine methods even without being sick. The RDUS points of the patients who did not

use painkillers were found to be high, and the subscale points of dissatisfaction with conventional medicine were found to be high in those who only used painkillers when they were in pain. This suggested that there was a relationship between rational drug use and not obtaining the expected effect from the use of random painkillers without a doctor's prescription. The RDUS points were higher in patients with a good income level, and the dissatisfaction with conventional medicine subscale points were high in those with a low income. When it is considered that a good income level is in parallel with educational level and access to healthcare services, the data obtained on this point were to be expected. The CACMAS subscale points of philosophical congruence with complementary and alternative medicine were determined to be high in those who used anticoagulant drugs. This was attributed to anticoagulants being taken on prescription and requiring continuous follow-up. The total CACMAS points and holistic balance subscale points were determined to be higher in patients who used drugs regularly compared to those who did not. This could be thought to be due to the fact that, with the thought of lifetime dependency, those who have to take drugs continuously may be directed to alternative treatments and show an interest in complementary and alternative medicine.

Limitations of the Research

The limitations of the study are that the research was conducted in a single hospital and that the sample size could not be expanded due to the researcher leaving the institution.

CONCLUSION

The results of this study demonstrated that rational drug use was low and that rational drug use had a directly proportional effect on holistic balance in patients hospitalized in the Internal Medicine Clinic because of gastrointestinal bleeding. It can be considered that the development of preventative healthcare services with health education related to rational drug use to prevent the development of gastrointestinal bleeding would have a positive effect on hospitalizations. In this context, it is important that nurses, who take a leading role in health education, are knowledgeable about rational drug use and traditional and complementary treatment methods.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Başakşehir Çam and Sakura City Clinical Researches Ethics Committee (Date: 06.07.2022, Decision No: 218).

Informed Consent: Written consent was obtained from the patient participating in this study.

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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Original Article

MEDICINE PALLIATIVE CARE

DOI: 10.47582/jompac.1347537

J Med Palliat Care. 2023;4(5):444-450

The importance of social media use and interpersonal factors in suicidal ideas

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Cite this article as: Kocakaya H, Arslan K. The importance of social media use and interpersonal factors in suicidal ideas. *J Med Palliat Care*. 2023;4(5):444-450.

Received: 21.08.2023 ◆ **Accepted**: 19.09.2023 ◆ **Published**: 27.10.2023

ABSTRACT

Aims: Every year, more than 800.000 individuals die by suicide as a global public health issue. In our study, we aimed to evaluate the relationship between suicidal ideation and interpersonal needs, acquired suicidal efficacy, and social media use in the context of Psychological Suicide Theory.

Methods: This cross-sectional study was conducted with 450 individuals. Participants were contacted through online platforms (Whatsapp and e-mail). The sociodemographic form (gender, age, education, income level, which social media platforms they prefer, their daily social media usage time, what kind of news they follow on social media), Interpersonal Needs Questionnaire (INQ), Acquired Suicide Capability - Fear of Death Scale, (ACSS-FAD), Beck Hopelessness Scale (BHS) and Social Media Use Scale (SMUIS) were applied to the volunteers who gave consent to participate in the study. The research was approved by the Kırıkkale University Faculty of Medicine Non-Interventional Research Ethics Committee.

Results: A total of 450 individuals, 308 (68.4%) women and 142 (31.6%) men, participated in the study, with an average age of 26.19±7.81. 9.3% (n=42) of the participants had a history of suicide attempt. Half of the participants (50.7%) reported that the suicide news attracted their attention and affected them, and 22.4% reported following the suicide news on social media. It was observed that those who had suicide attempts had significantly higher scores on the SMUIS and INQ ($p=0.002$, $p<0.001$). Those who followed suicide news on social media were found to have substantially higher SMUIS, INQ, and ACSS-FAD scores ($p<0.001$, $p<0.001$, $p=0.029$). Hierarchical regression analysis was utilized to evaluate factors assumed to have an effect on acquired suicidal efficacy. According to this; social media use was found to be effective on acquired suicide capability- death fearlessness (($\beta=.295$, $t(450)=6.01$, $p<0.001$)).

Conclusion: Social media use and interpersonal needs among those who attempted suicide were found to be significantly higher. Additionally, the use of social media has been found to be the most effective factor in finding suicide capability-fearlessness about death.

Keywords: Interpersonal needs, suicide capability, thwarted belongingness, perceived burdensomeness

INTRODUCTION

Suicidal behavior, which includes death, attempts, plans and thoughts, is a universal problem that affects the individual, family and society due to its consequences. Approximately one million people end their lives by suicide each year. Suicidal behaviors that do not result in death are known to be 10-20 times more common.[1] Nationally, suicide was among the 10 leading causes of death among people aged 10-64 years in the United States in 2020 and was the second leading cause of death among adults aged 25-34 years.[2]

It has been reported that suicide attempts are also common among the youth of our country; 32.8%-45% of the youth have thought of suicide at least once in their lives, and 7%-11% have attempted suicide at least once in their lives.[3] Despite this, studies on this subject are relatively few due to the fact that suicidal behavior is a difficult subject to study, that working with suicidal individuals involves safety problems, and that it is impossible to work with individuals who have succeeded in suicidal behavior. At this point, the Interpersonal Psychological Theory of Suicide (IPIK) has been put forward in order to understand suicide, its causes and relationships, and to develop methods to prevent suicide. According to the theory, it is stated that perceived burdensomeness and thwarted belongingness increase suicidal thoughts in individuals, but acquired suicide capability for behavior is also required.[4] Therefore, social connection and its disruption play a critical role

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in suicidal thoughts. In addition, it has been reported that negative interactions mediated by social media may contribute to suicidal thoughts by preventing the sense of belonging in general, although not as much as negative face-to-face interactions.[5]

Social media platforms or social networking sites consist of online websites or mobile phone applications that allow users to share information, messages and multimedia content with relatives, friends and strangers.[6] It has been reported that social media applications such as Facebook, Google, Youtube, Twitter and Instagram are the most preferred applications by users in our country.[7] Social media provides opportunities such as following technological developments, producing content, and creating networks by coming together with like-minded people.[8] However, transferring needs such as communication, self-expression, and entertainment to the virtual environment can trigger addiction to social media and cause people to experience some mental problems by living in isolation from social life.[9] In addition, providing false and harmful information about mental illnesses on social media (Twitter, Facebook, etc.) may increase the tendency for prejudice and stigmatization in society and prevent individuals with mental illnesses (schizophrenia, bipolar disorder, etc.) from receiving treatment. The study examining society's perspective on schizophrenia and stigma via Twitter confirms this view.[10] Similar results were reported in the study where society's perspective on mental illness and bipolar disorder was evaluated via Twitter.[11] In another study, time spent on social media was found to lead to an increase in depression and anxiety symptoms, harmful social comparisons, and a decrease in subjective well-being. However, when the literature is analyzed, it is also found that people at risk of suicide are affected by the suicide news they encounter on social media.[12] Suicides on social media have a greater negative impact on individuals, particularly those who use the Internet for suicidal purposes, are less likely to seek help and have less social support. The fact that suicide has a contagious effect may help to explain this situation.[13] The study by Brown et al.[14] also showed that social media sites are used to talk about suicide, search for content about suicide, and share experiences about suicide or self-harm through photos and videos. This situation suggests that social media use may also pose a risk of suicide for individuals without a diagnosis of mental illness.

In light of this information, we aimed to evaluate the relationship between suicidal ideation and interpersonal needs, acquired suicidal efficacy, and social media use in the context of Psychological Suicide Theory.

METHODS

The study was carried out with the permission of the Kırıkkale University Non-interventional Clinical Researches Ethics Committee (Date: 27.04.2022, Decision No: 2022.04.15). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design

This cross-sectional study was conducted at Kırıkkale University Faculty of Medicine, Department of Psychiatry. The study sample consisted of 450 individuals aged 18-45. Individuals were reached via online platforms (Whatsapp, e-mail) and informed about the study. Individuals who completed the consent form and online questionnaires after the information was included in the study. Inclusion criteria; I) Not receiving psychiatric treatment for any reason in the past or at the time of the study, II) Not receiving treatment for a chronic medical condition, III) Not using alcohol and substances.

Data Collection Tools

The sociodemographic form (gender, age, marital status, education, income status, which social media platforms they prefer, their daily social media usage time, what kind of news they follow on social media), interpersonal needs questionnaire (INQ), acquired suicide capability - fear of death scale, (ACSS-FAD), Beck hopelessness scale (BHS) and Social media use scale were applied to the volunteers who gave consent to participate in the study.

Interpersonal needs questionnaire (INQ): It is a 10-item self-report scale to measure the perceived burdensomeness and thwarted belongingness, which are perceived as two factors that make people suicidal.[15] While five of the INQ items measure perceived burdensomeness, the other five measure thwarted belongingness. Participants responded on a 7-point Likert-type scale. A higher total score on the scale is associated with an increase in interpersonal needs. In the Turkish adaptation and psychometric research conducted in Turkey, the internal consistency reliability coefficient was found to be 0.90 for perceived burdensomeness and 0.79 for thwarted belongingness. Turkish validity and reliability study was conducted by Eskin et al.[16]

Acquired suicide capability - fear of death scale, (ACSS-FAD): It is a short scale created by Ribeiro et al.[17] by taking 7 items from the 20-item Acquired Suicide Efficacy Scale. Participants respond on a 7-point Likert-type scale. An increase in the total score obtained from the scale is associated with an increase in fearlessness of death. In the Turkish adaptation and psychometric research conducted in our country, the internal consistency reliability coefficient was found to be 0.85.[16]

Social media use integration scale (SMUIS): The original form of the scale was developed by Jenkins-Guarnieri, Wright, and Johnson.[18] The scale includes a 6-point scale from 1: Strongly Disagree to 6: Strongly Agree. The 8th item in the scale is reverse scored. Higher scores indicate higher levels of social media use. The Cronbach's alpha internal consistency reliability coefficients of the original form of the Social Media Use Scale were 0.89 for the social integration and emotional connection subscale, 0.83 for the integration with social routines subscale, and 0.91 for the whole scale.[19]

Beck hopelessness scale (BHS): It was developed by Beck et al. to measure hopelessness. It includes 20 items answered as "Yes" and "No". It was adapted into Turkish by Durak et al.[20] and found to be adequate. IPS scores vary between 0 and 20 and high scores indicate excessive feelings of hopelessness.[21]

Statistical Analysis

Statistical Package For Social Science (SPSS) 24.0 package program was used for data analysis. The Kolmogorov-Smirnov test examined the normality assumption. Independent groups t-test, correlation analysis, and regression analysis techniques were used to examine whether there were differences between groups. The analysis began by determining the prerequisites for the regression analysis of the scale scores. As a result of the analysis of the graphs, it was determined that the scores obtained from the dependent variable Acquired Suicide Capability - Fear of Death Scale (ACSS-FAD) showed a linear relationship with the scores of the predictor variables Interpersonal Needs Questionnaire, Beck Hopelessness Scale (BHS) and Social Media Use Scale. Factors thought to have an effect on acquired suicidal competence (income, age, education, SMUIS, INQ, BHS, and ACSS-FAD) were evaluated by hierarchical regression analysis.

RESULTS

A total of 450 individuals, 308 (68.4%) women and 142 (31.6%) men, participated in the study, with an average age of 26.19±7.81. It was observed that 64.7% of the participants were undergraduates, 27.8% were middle school-high school, 3.8% were postgraduate, and 3.8% were primary school graduates. When income status is analyzed, almost half (43.6%) are below the minimum wage. The majority (67.1%) live in the city center. 9.3% (n=42) of the participants had a history of suicide attempt. The time spent on social media was 60-180 minutes (40.4%), and the most used platforms were Instagram (60%), Whatsapp (18%), and Youtube (13.3%). Half of the participants (50.7%) reported that the suicide news attracted their attention and affected them, and 22.4% reported following the suicide news on social media.

Table 1. Demographic characteristics of the participants (n=450)

Variables	Number (n)	Percentage (%)
Gender		
Female	308	68.4
Age		
18-30	339	75.3
31-44	100	22.4
45-55	11	2.3
Mean (SD) Range	26.19±7.81	
Education		
Primary	17	3.8
Middle-High	125	27.8
University	291	64.7
Graduate	17	3.8
Occupation		
Student	240	53.3
Officer	116	25.8
Housewife	50	11.1
Worker	44	9.8
Income Level		
<4800 TL	196	43.6
4800-7000 TL	153	34
>7000 TL	101	22.4
Living Space		
Province	302	67.1
District	130	28.9
Village	18	4
Was there a suicide attempt?		
Yes	42	9.3
No	408	90.7
Social media time		
15-60 min.	73	16.2
60-180 min.	182	40.4
>180 min	195	43.3
The platform with the most time spent		
Instagram	270	60
Whatsapp	81	18
Youtube	60	13.3
Twitter	31	6.9
Facebook	8	1.8
Do suicide get your attention?		
Yes	228	50.7
No	222	49.3
Do you follow suicide news on social media?		
Yes	101	22.4
No	349	77.6
Are you affected by news of suicide on social media		
Yes	228	50.7
No	222	49.3

SD: Standard Deviation

The relationships between the scales were evaluated by correlation analysis. Accordingly, there was a positive correlation between social media use and acquired fear of death (r=0.302; p<0.001). A negative correlation was observed between acquired fear of death and age (r =-0.144; p<0.001).

Table 2. The correlations between social media usage, interpersonal need, acquired fear of death and sociodemographic variables

Variables	1	2	3	4	5	6	7	8
Age	1							
Education level	-.215**	1						
SMUIS	-.324**	-.004	1					
INQ	-.214**	-.067	.219**	1				
Perceived burdensomeness	-.233**	-.017	.188**	.865**	1			
Thwarted belongingness	-.181**	-.086	.186**	.834**	-.160**	1		
BHS	.008	.241**	-.157**	-.140**	-.160**	-.176**	1	
ACSS-FAD	-.144**	.037	.302**	.019	.003	.030	-.026	1

Abbreviations: SMUIS: Social Media Usage Scale INQ: Interpersonal Needs Questionnaire, ACSS-FAD: Acquired Suicide Capability - Fear of Death Scale, BHS: Beck Hopelessness Scale, *p<0.05, **p<0.001

The t-test was used to evaluate whether there was a significant difference in the participants' scores according to their suicide attempt in terms of the SMUIS, the INQ, the BHS and the ACSS-FAD scores. Accordingly, it was observed that those who had suicide attempts had significantly higher scores on the SMUIS and INQ (t=3.19; p=0.002; t= 4.88 p<0.001). (Table 3). According to the participants, the status of following suicide news on social media, the SMUIS, the INQ, the BHS and the ACSS-FAD scores were evaluated by t-test. accordingly, it was observed that those who followed suicide news on social media had significantly higher scores on the SMUIS, INQ and ACSS-FAD scales (t=3.67; p< 0.001; t=4.36 p<0.001; t=2.19; p=0.029, respectively) (Table 4).

Table 3. Evaluation of scale scores according to suicide attempts with the independent t-test

Scales	Attempted suicide	N	Mean (SD)	T test results		
				t	Cohen's d	p
SMUIS	Yes No	42 408	35.45(11.12) 30.52(9.37)	3.19	1.00	.002
INQ	Yes No	42 408	35.95(14.49) 27.25(10.60)	4.88	1.00	.000
BHS	Yes No	42 408	10.62(2.68) 10.60(2.50)	.045	NA	.964
ACSS-FAD	Yes No	42 408	28.19(9.19) 27.14(9.99)	.651	NA	.515

SMUIS: Social Media Usage Scale INQ: Interpersonal needs questionnaire, ACSS-FAD: Acquired suicide capability - fear of death scale, BHS: Beck Hopelessness Scale, p<0.05, p<0.001

Table 4. Evaluation of scale scores according to the status of following suicide news on social media with the independent t-test

Scales	Following suicide news on social media	N	Mean (SD)	T-test results		
				t	Cohen's d	p
SMUIS	Yes No	101 349	34.04(10.99) 30.09(9.03)	3.67	0.530	.000
INQ	Yes No	101 349	32.30(12.30) 26.84(10.69)	4.36	0.706	.000
BHS	Yes No	101 349	10.26(2.54) 10.70(2.50)	-1.56	NA	.118
ACSS-FAD	Yes No	101 349	29.13(10.56) 26.69(9.65)	2.19	0.674	.029

SMUIS: Social media usage scale INQ: Interpersonal needs questionnaire, ACSS-FAD: Acquired suicide capability - fear of death scale, BHS: Beck hopelessness scale, p<0.05, p<0.001.

In our study, factors thought to have an effect on acquired suicidal competence (income, age, education, SMUIS, INQ, BHS and ACSS-FAD) were evaluated by hierarchical regression analysis. Socio-demographic variables included in the analysis at the first step and explained 2% of the variance in the model. In addition, INQ and BHS were also included in the analysis but were found not to predict the model significantly (β=-.058, t(450)=6.76, p≤0.05, β=.009, t(450)=6.61, p≤ 0.05, respectively). It was seen that the contribution of the Social Media Use Scale added in the last step to the model was significant and explained 48% of the variance ((β=.295, t(450)=6.01, p<0.001)).

Table 5. Evaluation of factors thought to have an effect on acquired suicidal ability by multiple hierarchical regression analysis

Model	Predictor	B	SE B	β	p	R2	ΔR2
1	Constant Age Income Education	31.392 -.192 .346 .027	2.99 .064 .623 .783	 -.152 .027 .006	.000 .003 .579 .898	.022	.015
2	INQ	-.046	.042	-.052	.276	.022	.013
3	BHS	.019	.187	.005	.919	.023	.012
4	SMUI	.307	.050	.299	.000	.099	.086

SMUIS: Social media usage scale INQ: Interpersonal needs questionnaire, ACSS-FAD: Acquired suicide capability - fear of death scale, BHS: Beck hopelessness scale, p<0.05, p<0.001

DISCUSSION

In the context of Interpersonal Psychological Theory of Suicide, we examined the relationship between social media use and suicidal behavior in our study. Social media use and interpersonal needs were found to be substantially higher among those who attempted suicide. In addition, as the use of social media increased, interpersonal needs and acquired suicide capability-fearlessness about death-increased. It has been observed that the most effective factor in acquired suicide capability -fearlessness about death is the use of social media.

Every year, more than 800.000 individuals die by suicide is a global public health issue. Studies show that suicide is among the top four causes of death worldwide among young people aged 15-29.[1] Studies show that suicide is

among the top four causes of death worldwide among young people aged 15-29. It has been reported that suicidal behavior is an important public health problem in our country, and 7-11% of young people attempt suicide at least once in their lifetime.[3] Similarly, in our study, 9.3% of the participants were found to have attempted suicide. In a study (n=1262) conducted with university students in our country, it was seen that approximately 42% of the sample had suicidal thoughts and 7% had attempted suicide.[22] In another study, it was reported that 45% of 1203 university students had suicidal thoughts and 11% had attempted suicide.[23] In this respect, our result was similar to the literature.

Interpersonal suicide theory is one of the most important models for understanding the development of suicidal thinking and behavior. According to the theory, the factors that push a person towards suicidal ideation are thwarted belongingness and perceived burdensomeness.[24] In this context, it has been reported that social connections are important and breaking social ties is critical. It has been reported that negative interactions mediated by social media may contribute to suicidal ideation by preventing the sense of belongingness.[5] Social media is generally defined as any digital tool that allows social interaction. In our study, it was seen that the platforms where the most time was spent were Instagram, WhatsApp, and YouTube. A survey of USA youth under 30 found that 95% prefer YouTube, 70% Facebook, 71% Instagram, 65% Snapchat, 48% TikTok, and 42% Twitter.25 In a recent study conducted with young people (N=1537) living in 12 provinces of Turkey, it was reported that the most used social media platforms were Instagram, YouTube and Twitter, respectively.[7] Our study's sample group was older, but the findings were consistent with previous research.

Although social media offers the opportunity to follow developments, come together with similar people, network, etc., the virtualization of social life may cause mental problems.[6] In this context, in our study, it was seen that individuals with a history of suicide attempts had significantly higher scores on social media use, perceived burdensomeness and thwarted belongingness. This may be explained by the fact that these individuals see social media as a shelter and are more suicidal due to the lack of communication with others and the deterioration of their previous relationships. In a study examining the interpersonal and internal determinants of suicidal thoughts and behaviors in university students (n=655), it was reported that the perceived burdensomeness and thwarted belongingness are associated with suicidal ideation.[26] In another study conducted in China (n=2320), it was reported that perceived burdensomeness and thwarted belongingness have a mediating role in the relationship between shame and suicidal ideation.[27] In a study evaluating the factors contributing to the idea of death in older adults, it was reported that perceived burdensomeness was associated with the idea of death.[28] In a recent meta-analysis study, the use of social media and suicidal thoughts and behaviors were examined. Accordingly, it has been reported that both exposure to content related to self-harming thoughts and behaviors and the creation of this content are related to suicidal plans and behaviors.[29] Although our study did not examine what content the patients were exposed to on social media, it is known that it is easy to access this content on social media.

Social media, often used for purposes such as receiving news, accessing information, leisure, socializing, and entertainment, has been shown to have an impact on suicidal behavior.[9] In our study, it was observed that individuals who follow suicide news on social media have higher social media use, perceived burdensomeness, thwarted belongingness, and acquired suicide capability-death fearlessness compared to other individuals. This may be explained by the fact that suicidal individuals express their distress in an anonymous and easily accessible environment and interact with similar individuals.[30] Online media use has the potential to be damaging in this regard since it might normalize suicidal conduct, trigger behavior (i.e., contagion), stimulate competitive behavior, and provide knowledge on suicide techniques. Also, victims of cyberbullying are almost three times more likely to attempt suicide and are twice as likely to have suicidal thoughts compared to non-victims.[31]

According to the Interpersonal Suicide Theory, a third factor contributing to suicidal behavior is acquired capability for suicide. The capacity has been proven to increase following exposure to terrible events and nonfatal self-harming behaviors.[16] In addition, the number of self-harm behaviors and the low reaction to these behaviors increase the risk of suicide in people who engage in self-harm behaviors. Especially, men are less afraid of death than women because of their social gender patterns, military service, law enforcement, and participation in more dangerous activities.[32]

In our study, factors that are thought to have an effect on acquired suicidal efficacy (gender, age, education, social media use, perceived burdensomeness and thwarted belongingness) were evaluated with hierarchical regression analysis. According to the analysis, social media use was found to be effective in acquired suicide capability- death fearlessness. This may be explained by the fact that people who are exposed to painful life events are more able to communicate with similar-minded people on social media platforms and support

each other in terms of suicidal behavior. In a study that evaluated suicide rates in various age groups after an online series in which suicide was depicted fictionally, it was reported that suicides had increased, especially among young people.[33] Consistent with the results of the aforementioned study, a distinct inquiry carried out in Canada also observed an increase in suicide rates, with a special emphasis on incidents involving the youth population.[34] Nevertheless, the available data regarding this topic is limited, thus requiring the conduct of longitudinal investigations.

The evaluation of the findings of the current study should take into consideration its limitations. First, the current study is cross-sectional in design. In order to gain a deeper understanding of potential causal links between variables, it will be necessary to conduct longitudinal and experimental investigations. Another limitation is the use of self-report scales when evaluating.

CONCLUSION

In the context of Interpersonal Psychological Theory of Suicide, we examined the relationship between social media use and suicidal behavior in our study. Social media use and interpersonal needs were found to be substantially higher among those who attempted suicide. In addition, as the use of social media increased, interpersonal needs and acquired suicide capability -fearlessness about death increased. It has been observed that the most effective factor in acquiring suicide capability -fearlessness about death is the use of social media. Our study is a pioneering study and further studies on this subject are needed. The choice of social media platforms on which individuals spend their time is of great importance, considering the fundamental role these platforms play in our daily lives. Particularly, content that may affect suicidal behavior and thoughts should be kept away from people who are at suicide risk. In addition, the presentation of suicide news on social media should be framed and not encouraged.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the Kırıkkale University Non-interventional Clinical Researches Ethics Committee (Date: 27.04.2022, Decision No: 2022.04.15).

Informed Consent: All participants signed consent informed to participate in the study.

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

Acknowledgements: The authors would like to appreciate the patients participation in this study

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Original Article

MEDICINE PALLIATIVE CARE

DOI: 10.47582/jompac.1346655

J Med Palliat Care. 2023;4(5):451-455

Effect of bilateral cochlear implants on language development in children aged 2-7 years

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Cite this article as: Kurt E. Effect of bilateral cochlear implants on language development in children aged 2-7 years. *J Med Palliat Care*. 2023;4(5):451-455.

Received: 20.08.2023 ◆ **Accepted**: 19.09.2023 ◆ **Published**: 27.10.2023

ABSTRACT

Aims: Pediatric patients with bilateral total sensorineural hearing loss have very poor or no language development compared to their peers. The hearing and language development of these patients is usually managed via cochlear implants (CIs).

Methods: This study examined the factors that affect the language development of children aged 24-84 months who have undergone CI surgery. The language development outcomes of patients with bilateral CIs and patients with unilateral CIs were compared. The participants were receiving regular hearing rehabilitation training and had undergone unilateral or bilateral CI surgery at various centers. Their language development was evaluated using the Turkish adaptation of the Test of Early Language Development-3 (TELD-3).

Results: The expressive language development of the patients with unilateral implants was delayed by 14.0±18.1 months, while the expressive language development of patients with bilateral implants was delayed by 2.8±8.7 months. This difference was statistically significant (p=0.025).

Conclusion: Although the levels of receptive language development of patients with bilateral and unilateral CIs were similar, the expressive language development of patients with bilateral CIs was better. We recommend that bilateral CI surgery be performed in a single session for patients with congenital bilateral total sensorineural hearing loss.

Keywords: Cochlear implant, language development, speech therapy

INTRODUCTION

Hearing loss experienced before language development can negatively affect the child's perception and expressive language development. With early diagnosis, the negative factors that affect language development can be resolved by starting hearing aid use and hearing rehabilitation early.[1] Patients who do not benefit from hearing aids are evaluated for cochlear implant (CI) surgery. CI surgery has been performed in many centers in Turkey since 1987. There are individual differences in the receptive and expressive language development of children with CIs, and many factors affect language development.[2] Factors independent of CI surgery such as duration of device use before CI surgery, age at which CI surgery was performed, hearing rehabilitation, auditory neuropathy, cochlear anomalies, number of active electrodes, and appropriate programming all affect language development.[3] Many studies have indicated that the most important factor affecting language development is CI surgery performed at an early age and that the language development of pediatric patients who underwent CI surgery before the age of 1 year reaches the level of their healthy peers in a very short time.[4] Language development among pediatric patients who underwent CI surgery at older ages reaches the level of their healthy peers after a longer duration of time and sometimes may not match the language development level of healthy peers. It is known that hearing age also plays an important role in language development alongside chronological age.[5] Education after CI surgery also affects language development in children. It is known that the language development of children receiving verbal education is faster than the language development of children receiving sign language education. Although numerous studies have been conducted in Turkey on the effects of CI surgery on the auditory perception skills of children with hearing loss and the factors that affect this, studies of the language development of children with hearing loss who underwent CI surgery are limited. Thus, this study aimed to evaluate the language development of children with hearing loss who are enrolled in the same educational institution at the preschool level and use unilateral or bilateral CIs and to examine the factors affecting their language development.

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METHODS

The study was carried out with the permission of the Adıyaman University Non-interventional Clinical Researches Ethics Committee (Date: 18.01.2022, Decision No: 2022/1-5). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design and Study Sample

Sixty-eight pediatric patients aged 24-84 months who used CIs and received preschool education at the private Yekta Education and Rehabilitation Center were included in the study. The families of the patients were informed about the study and their written permission was obtained. All of the children were diagnosed with bilateral total sensorineural hearing loss at birth, did not benefit from hearing aids, used unilateral or bilateral CIs, and underwent CI surgeries at different centers. Patients who had bilateral CIs underwent surgery in a single session, during which the CI devices were attached to both of their ears. Twelve patients who were syndromic, received CIs after meningitis, or had auditory neuropathies or other comorbidities were excluded from the study. The patients included in the study used CI devices with different processors. All of the patients were receiving verbal education and did not receive sign language education. The language development of the patients was evaluated using the Turkish adaptation of the Test of Early Language Development-3 (TELD-3).

Statistical Analysis

Statistical analyses were performed with IBM SPSS Statistics 22 (IBM Corp., Armonk, NY, USA). Categorical descriptive data were presented as numbers and percentages and continuous data were presented as means ± standard deviations (mean±SD). The conformity of continuous variables to normal distribution was evaluated by the Shapiro-Wilk test. The Mann-Whitney U test was used for comparisons of two variables and the Kruskal-Wallis test was used for comparisons of more than two variables. The Spearman correlation test was used to examine the relationships between continuous variables. A statistical significance level of $p<0.05$ was accepted as significant in all analyses. The delay duration was calculated in months by subtracting the speaking age of the patients from their chronological ages.

RESULTS

A total of 68 patients were included in the study. Thirty-two of the patients (47.1%) had 1 or 2 siblings and 36 of the patients (52.9%) had 3 or 4 siblings. The financial status of 6 (8.8%) of the patients' families was good, while 58 of the patients' families (85.3%) had moderate and 4 of the patients' families (5.9%) had poor financial status. The mothers of 46 of the patients (67.6%) had primary education, while 22 of them (32.4%) had high school education. The fathers of 10 of the patients (14.7%) had primary education, while 58 of them (85.3%) had high school education. Twenty-eight (41.2%) of the patients had unilateral CIs and 40 (58.8%) of the patients had bilateral CIs. The average chronological age of the patients was 71.9±17.8 months, their average right-side hearing age was 21.7±8.4 months, and their average left-side hearing age was 32.5±18.4 months. The average receptive language age of the patients was 68.6±18.6 months and their average expressive language age was 64.5±20.1 months (Table 1).

Table 1. Characteristics of the patients included in the study

	Number	%
Number of siblings		
1-2	32	47.1
3-4	36	52.9
Financial status		
Good	6	8.8
Moderate	58	85.3
Poor	4	5.9
Education level of mother		
Primary school	46	67.6
High school	22	32.4
Education level of father		
Primary school	10	14.7
High school	58	85.3
Implant location		
Unilateral	28	41.2
Bilateral	40	58.8
	Mean±SD	
Chronological age (months)	71.9±17.8	
Right-side hearing age (months)	21.7±8.4	
Left-side hearing age (months)	32.5±18.4	
Receptive language age (months)	68.6±18.6	

The average chronological age of patients who underwent unilateral CI surgery was 70.6±17.8 months, while the average chronological age of patients who underwent bilateral CI surgery was 72.9±18.3 months, with no statistically significant difference (p=0.616). The average right-side hearing age of the patients who underwent unilateral CI surgery was 24.5±10.4 months, while the average right-side hearing age of patients who underwent bilateral CI surgery was 19.8±6.2 months, with no statistically significant difference (p=0.290). The average left-side hearing age of patients who underwent unilateral CI surgery could not be measured, while the average left-side hearing age of patients who underwent bilateral CI surgery was 32.5±18.4 months. The average receptive language age of patients who underwent unilateral CI surgery was 63.6±17.5 months, while the average receptive language age of patients who underwent bilateral CI surgery was 72.2±18.9 months, with no statistically significant difference (p=0.148) (Table 2).

Table 2. Comparison of the ages of patients according to implant location

	Unilateral Mean±SD	Bilateral Mean±SD	p*
Chronological age (months)	70.6±17.8	72.9±18.3	0.616
Right-side hearing age (months)	24.5±10.4	19.8±6.2	0.290
Left-side hearing age (months)	-	32.5±18.4	-
Receptive language age (months)	63.6±17.5	72.2±18.9	0.148
Expressive language age (months)	56.6±18.0	70.1±19.9	0.061

*Mann-Whitney U test was applied.

Patients who underwent unilateral CI surgery had an average of 46.1±18.3 months of delay in right-side hearing, while patients who underwent bilateral CI surgery had an average of 53.1±15.7 months of delay in right-side hearing, with no statistically significant difference (p=0.192). Patients who underwent bilateral CI surgery had an average of 41.9±19.4 months of delay in left-side hearing. Patients who underwent unilateral CI surgery had an average of 7.0±16.4 months of delay in receptive language, while patients who underwent bilateral CI surgery had an average of 0.8±6.1 months of delay in receptive language, with no statistically significant difference (p=0.259). Patients who underwent unilateral CI surgery had an average of 14.0±18.1 months of delay in expressive language, while patients who underwent bilateral CI surgery had an average of 2.8±8.7 months of delay in expressive language, which constituted a statistically significant difference (p=0.025) (Table 3, Figure 1).

Table 3. Comparison of development delay of patients according to implant location

	Unilateral Mean±SD	Bilateral Mean±SD	p*
Right-side hearing delay (months)	46.1±18.3	53.1±15.7	0.192
Left-side hearing delay (months)	-	41.9±19.4	-
Receptive language delay (months)	7.0±16.4	0.8±6.1	0.259
Expressive language delay (months)	14.0±18.1	2.8±8.7	0.025

*Mann-Whitney U test was applied.

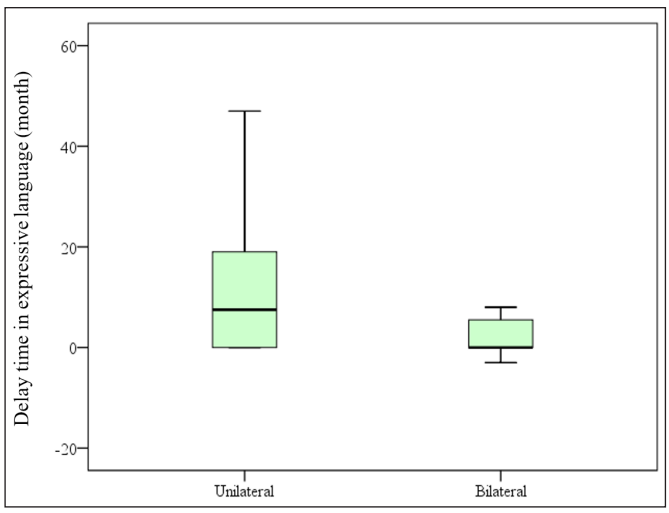

Figure 1. Comparison of delay in expressive language according to implant location

There was no significant difference in delay according to number of siblings or the financial status or education levels of the mothers and fathers of the patients (p>0.05) (Table 4). It was found that there were significant positive correlations between chronological age and right-side hearing age, receptive language age, expressive language age, right-side hearing delay, and left-side hearing delay. Significant positive correlations between both right-side hearing age and left-side hearing age and receptive language age and expressive language age were also found. Significant positive correlations were observed for left-side hearing age, receptive language age, and expressive language age. Significant positive relationships were found among receptive language age, expressive language age, and right-side hearing delay, and negative positive relationships were found for receptive language age, receptive language delay, and expressive language delay. A significant positive relationship was determined between expressive language age and right-side hearing delay and a significant negative relationship between expressive language age and expressive language delay. A significant positive relationship was found between right-side hearing delay and left-side hearing delay. A significant positive relationship was also found between receptive language delay and expressive language delay (Table 5).

DISCUSSION

It is thought that this study, which evaluates factors that affect the language development of pediatric patients with CIs and compares the language development of patients with bilateral CIs and unilateral CIs, will greatly contribute to the literature.

Various factors affect language development in children. These include gender, the social environment and family, socioeconomic factors, brain health, intelligence, the educational status of the family, bilingualism, play, and physical health. Language development is directly proportional to intelligence and mental development.[6-8]

Studies of factors that affect language development in children with CIs are limited in number in the literature. When the data of the current study were compared with the findings reported in the literature, it was seen that quite similar results were obtained. It was found in this study that there is a highly significant relationship between age and language skills. This finding is compatible with the literature and is to be expected since it is known that language is a learned skill that develops with age.[9,10] Alongside age, the duration of implant use was also found to be highly correlated with language skill development. These results are consistent with the results in the literature.[11]

Table 4. Comparison of delay according to other parameters

	Right-side hearing delay		Left-side hearing delay		Receptive language delay		Expressive language delay	
	Mean±SD	p	Mean±SD	p	Mean±SD	p	Mean±SD	p
Number of siblings		0.266*		0.075*		0.055*		0.059*
1-2	46.6±16.9		35.6±19.4		-1.1±4.2		2.3±3.9	
3-4	53.4±16.8		50.5±16.9		7.2±14.7		11.9±18.3	
Financial status		0.152**		0.714**		0.670**		0.264**
Good	38.0±23.1		53.0		0.7±1.2		5.3±3.5	
Moderate	52.6±16.1		41.3±19.8		3.4±12.5		7.2±15.3	
Poor	34.5±7.8		-		6.5±9.2		13.5±7.8	
Education level of mother		0.383*		0.559*		0.077*		0.971*
Primary school	51.8±17.3		40.3±21.5		5.8±13.4		9.0±17.0	
High school	46.8±16.3		46.4±12.7		-1.8±4.1		4.2±4.6	
Education level of father		0.962*		0.737*		0.539*		0.232*
Primary school	50.6±15.6		54.0		10.8±19.6		15.2±19.3	
High school	50.1±17.4		41.2±19.7		2.0±9.8		6.1±13.2	

Table 5. Correlations between relevant measured ages

		Chronological age	Right-side hearing age	Left-side hearing age	Receptive language age	Expressive language age	Right-side hearing delay	Left-side hearing delay	Receptive language delay
Right-side hearing age	r	0.350							
	p	0.043							
Left-side hearing age	r	0.395	0.487						
	p	0.094	0.035						
Receptive language age	r	0.706	0.486	0.515					
	p	0.000	0.004	0.024					
Expressive language age	r	0.648	0.465	0.536	0.955				
	p	0.000	0.006	0.018	0.000				
Right-side hearing delay	r	0.886	-0.038	0.270	0.584	0.533			
	p	0.000	0.832	0.264	0.000	0.001			
Left-side hearing delay	r	0.568	0.277	-0.339	0.361	0.321	0.530		
	p	0.011	0.251	0.155	0.129	0.180	0.019		
Receptive language delay	r	0.257	0.090	-0.243	-0.368	-0.335	0.186	0.225	
	p	0.143	0.612	0.317	0.032	0.053	0.292	0.354	
Expressive language delay	r	0.054	0.036	-0.423	-0.437	-0.572	0.039	0.302	0.681
	P	0.762	0.842	0.071	0.010	0.000	0.826	0.209	0.000

Spearman correlation analysis was applied.

In this study, it was found that the expressive language development of patients with unilateral implants was delayed by 14.0±18.1 months, while the expressive language development of patients with bilateral implants was delayed by 2.8±8.7 months, which constituted a significant difference. This may be due to the fact that bimodal hearing is more effective for language development than monomodal hearing, and due to clearer perceptions of sounds and direction.

In their study, Erva et al.[6] found that patients who underwent bilateral CI surgeries in a single session had better phoneme distinction compared to patients who underwent unilateral CI surgeries. In the current study, it was found that the levels of auditory perception of the groups were similar, while the expressive language of bilateral CI patients was better than that of unilateral CI patients.

In their study on the hearing quality and quality of life of patients with unilateral and bilateral CIs, Sivonen et al.[7] found that the hearing quality and quality of life of patients with bilateral CIs was better than that of patients with unilateral CIs. In the present study, the expressive language development and quality of life of bilateral CI patients were also found to be better than those of unilateral CI patients.

According to the study of Baronson et al.[8] The results of the analysis of hearing performance in children and adolescents with unilateral and bilateral CI were significantly better in patients with bilateral CI compared to patients with unilateral CI. It was also found that the hearing performances of patients who had previously undergone unilateral CI surgeries significantly increased after another CI was inserted into the other ear. Similarly, in the present study, it was found that bilateral CI patients had better expressive language performance.

In the study conducted by Li et al.[12] it was determined that bilateral cochlear implants performed simultaneously, especially in noisy environments, improved hearing performance and quality of life more than unilateral or sequential cochlear implant recipients. The results were similar to the findings in our study.

According to the study conducted by Virzob et al.[13] It was determined that bilateral cochlear implantation provided a significant improvement in quality of life by significantly increasing speech perception, speech production, and reading success. The results were similar to the findings in our study.

In the study by Almeida et al.[14] Bilateral cochlear implants in children provided better speech perception in quiet and noisy environments compared to unilateral cochlear implants, regardless of the age of surgery and the duration of use of the cochlear implant. The use of a hearing aid before cochlear implant positively affected speech perception performance in both quiet and noise. The results were similar to the findings in our study.

The limitations of this study included patients using CI devices with different processors, the number of active electrodes not being taken into account, the rehabilitation and education being given by different educators, and the number of patients participating in the study being low.

CONCLUSION

There are various factors that affect language development in hearing-impaired children, such as gender, age at onset of hearing loss, age at starting rehabilitation and duration of rehabilitation, duration of device use before CI surgery, age at which CI surgery was performed, having unilateral or bilateral CIs, education levels of the parents, and number of siblings. In this study, it was concluded that although the receptive language development was similar in pediatric patients with bilateral and unilateral CIs, the expressive language development of patients with bilateral CIs was better than that of patients with unilateral CIs. As a result, bilateral CI surgery conducted in a single session is of great benefit for the expressive language development of children with congenital bilateral total hearing loss.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the Adıyaman University Non-interventional Clinical Researches Ethics Committee (Date: 18.01.2022, Decision No: 2022/1-5).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

Acknowledgements: The authors would like to appreciate the patients participation in this study

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Original Article

MEDICINE PALLIATIVE CARE

DOI: 10.47582/jompac.1341423

J Med Palliat Care. 2023;4(5):456-465

Retrospective analysis of clinical characteristics, diagnosis, treatment and complications of children with acute pancreatitis: results of a single center

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Cite this article as: Başkocagil E, Gümüş M, Yorulmaz A, Emiroğlu HH. Retrospective analysis of clinical characteristics, diagnosis, treatment and complications of children with acute pancreatitis: results of a single center. *J Med Palliat Care*. 2023;4(5):456-465.

Received: 11.08.2023 ◆ **Accepted**: 20.09.2023 ◆ **Published**: 27.10.2023

ABSTRACT

Aims: In the present study, the purpose was to evaluate the demographic and clinical data of pediatric patients, who had pancreatitis, who were followed up as outpatients or in the wards, and to evaluate the treatment modalities used along with nutritional status, length of hospital stays, and complications.

Methods: This study was carried out by retrospectively evaluating the files of 166 patients identified by INSPPIRE Criteria who were followed up at the Department of Pediatric Gastroenterology, Faculty of Medicine, at Selçuk University between 2011 and 2021. The age, gender, height, weight, known disease, drugs used, follow-up periods by us, complaints on admission, the etiological reason for the diagnosis, type of pancreatitis, length of hospital stay, treatment modalities applied, and complications of the patients were recorded. The PAPPS Scores, Ranson Admission Scores, and Ranson 48th hour Scores of the patients were analyzed.

Results: A total of 120 patients (72.3%) had AP, 25 patients (15.1%) had CP, and 21 patient (12.7%) had ARP. According to the Atlanta Criteria, 82.5% were mild and 17.5% were moderate. The most common complaint was abdominal pain and the most common cause was found to be idiopathic. There was a weak and positive correlation between the PAPPS Score, Ranson Admission Score, and length of hospital stay.

Conclusion: In the diagnosis and follow-up of pancreatitis, it is important to determine the severity of the disease and to reveal the etiology. Establishing and applying standard approaches for early diagnosis and treatment of patients will lead to prognostic improvement and prevent related complications.

Keywords: Pancreatitis, children, INSPPIRE criteria, PAPPS score, Ranson score

INTRODUCTION

Pancreatitis is an inflammation type occurring in the pancreatic tissue after the activation of enzymes because of various reasons.[1,2] The incidence of Acute Pancreatitis (AP) is 34/100000 and the incidence of Chronic Pancreatitis (CP) is 10/100000 in the general population.[3,4] Damage to pancreatic acinar cells is detected because of various reasons in the pathophysiology of AP. A local inflammatory response occurs after the release of pancreatic inflammatory cytokines with acinar cell injury. The magnitude of the inflammatory response determines the clinical severity and possible complications (e.g., pancreatic necrosis, shock, and distant organ ailure).[2,5]

The International Study Group of Pediatric Pancreatitis: In Search for a Cure (INSPPIRE) Group defined [0]Acute Pancreatitis (AP), Acute Recurrent Pancreatitis (ARP), and Chronic Pancreatitis (CP) in children in 2012.[6] Typical abdominal pain, serum AP was defined as having amylase and/or lipase levels 3-fold or higher than normal and two findings suggesting acute pancreatitis in imaging methods. ARP is defined as two or more attacks in which all findings completely return to normal between attacks. For CP, it is sufficient to have characteristic imaging findings as well as abdominal pain and endocrine/exocrine insufficiency findings consistent with pancreatitis.[6-8] Abdominal Ultrasonography (USI), Computed Tomography (CT), and Magnetic Resonance Cholangio-Pancreaticography (MRCP) among imaging methods are employed for diagnosis to show the etiology and complications.[9,10] Analgesia, pancreatic rest, intravenous fluid therapy, and monitoring for complications are essential in the treatment.

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It is still a problem to determine in advance which cases will progress with severe clinical findings or complications, and therefore, how many days of treatment will be needed in the hospital. In the present study, the purpose was to evaluate the demographic and clinical data of pediatric patients who had pancreatitis who were followed up as outpatients or in the wards and to evaluate the treatment modalities used along with nutritional status, length of hospital stays, and complications.

METHODS

The study was carried out with the permission of the Selçuk University Local Ethics Committee (Date: 24.03.2021, Decision No: 2021/164). All procedurs were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Group and Protocol

A total of 166 patients who had AP, ARP, and CP followed up in the Department of Pediatric Gastroenterology, Faculty of Medicine, Selçuk University, between 2011 and 2021, were included in the study. The data of the patients in the study group were reviewed retrospectively by examining the patient files and records in the Hospital Computer System.

The pancreatitis types were identified based on the criteria of INSPPIRE[6]. At least two of the following findings were considered CP; abdominal pain suggestive of pancreatitis, serum amylase and/or lipase values greater than 3-fold the upper limit of normal; at least two AP episodes and >1-month pain-free period between episodes or amylase-lipase values returning to normal values between episodes were considered ARP; exocrine and/or endocrine pancreatic insufficiency or at least one of the findings that abdominal pain suggestive of pancreatitis and radiological imaging findings consistent with CP were considered CP. The data of ARP patients during the last attack period were recorded in the study.

The age, gender, height, weight, known disease, drugs used, follow-up periods by us, complaints on admission, the etiological reason for the diagnosis, type of pancreatitis, length of hospital stay, treatment modalities applied, and complications of the patients were recorded along with previously known chronic diseases, the drugs they used, and the presence of active infection. Etiological factors were considered according to the history given at the time of admission, and laboratory and radiological findings. Patients whose cause could not be detected and who were using drugs were recorded as drug-induced pancreatitis in case of clinical and laboratory improvement following the discontinuation of the drugs. Etiological evaluation of traumatic pancreatitis was made according to the anamnesis.

Complete blood count, biochemistry values, ESR, and CRP blood test results were recorded at admission and at the 48th hour. The upper limit of amylase value was 53 U/L and 67 U/L for lipase. Abdominal USI, MRCP (if any), and abdominal CT findings were recorded from the Hospital Automation System.

The treatments applied were recorded by scanning the Epicrisis in the Hospital Automation System and the digital system. It was recorded how many days the treatment was started and how many days it was administered to the patients who were started on Total Parenteral Nutrition (TPN). It was evaluated on which day the feeding of the patients whose oral intake was discontinued was started, and on which day the diet was switched to Diet 3. It was also examined which group of patients needed surgery.

The number of days the patients needed to stay in the hospital, whether they were hospitalized in the Intensive Care Unit, whether complications developed, and on which day the complications developed and regressed were examined. The patients were grouped as mild, moderate, and severe according to the Atlanta, PAPPS, and Ranson Criteria.[11,12]

Statistical Analysis

The IBM SPSS Statistics 20 package program was used for statistical analysis. Whether the variables of the analysis showed normal distribution was examined with the Kolmogorov-Smirnov Test.The Student's t-test was used in the statistical analysis of the paired groups in independent groups to examine the relationships between the variables that had normal distribution, and the Mann-Whitney U-Test was used for the variables that did not have normal distribution.The One-Way Analysis of Variance was used in the analysis of the data with normal distribution in the analysis of more than two groups, and the Kruskal-Wallis Analysis and Shapiro-Wilk Analysis was used in the analysis of the data that did not comply with normal distribution. The categorical variables were compared by using the Chi-Square Test and the significance level was taken as $p<0.05$.

RESULTS

A total of 166 patients who were followed up with the diagnosis of Acute Pancreatitis, Acute Recurrent Pancreatitis, and Chronic Pancreatitis with history, clinical, laboratory findings, and radiological imaging results were included in the study 92 (55.4%) female and 74(44.6%) male with an F/M ratio of 1:24). The mean age of the female group was 9.92±5.29 years and the mean age of the males was 10.85±4.52.When the mean age was compared according to gender, it was not found statistically significant (p:0.223). The demographic characteristics of the patients and their distribution according to pancreatitis types are given in **Table 1**.

Table 1. The distribution of the demographic characteristics of the patients according to pancreatitis types

	Acute Pancreatitis n (%)	Chronic Pancreatitis n (%)	Recurren Pancreatitis n (%)	Total n (%)	P
Gender					0.691
Girl	67 (40.3)	15 (9)	10 (6)	92 (55.4)	
Boy	53 (31.9)	10 (6)	11 (6.6)	74 (44.6)	
Age Group					0.498
1-5 age	30 (76.9)	3 (7.7)	6 (15.4)	39 (23.5)	
6-10 age	27 (65.9)	9 (22.0)	5 (12.1)	41 (24.7)	
>11 age	63 (73.3)	13 (15.1)	10 (11.6)	86 (51.8)	
BMI					0.010
<18.5	56[a] (70.9)	13[a] (16.5)	10[a] (12.6)	79 (60.8)	
18.5-24.9	27[a] (69.3)	10[a] (25.6)	2[a] (5.1)	39 (30.0)	
>25.0	7[a] (58.3)	0[a] (0)	5[b] (41.7)	12 (9.2)	
Application complaints					
Abdominal pain	95 (57.2%)	22 (13.2%)	20 (12%)	137 (82.5)	0.095
Nausea and vomiting	89 (53.6%)	18 (10.8%)	14 (8.4%)	121 (72.9)	0.771
Lack of appetite	74 (44.5%)	16 (9.6%)	12 (7.2%)	102 (61.4)	0.521
Fever	27 (16.2%)[a]	1 (0.6%)[b]	2 (1.2%)[b]	30 (23.1)	0.021
Other	14 (8.4%)	2 (1.2%)	1 (0.6%)	17 (10.2)	0.741
Jaundice	6 (3.6%)	1 (0.6%)	1 (0.6%)	8 (4.8)	0.648
Etiology					
Idiopathic	38 (56.6)	14 (21.2)	14 (21.2)	66 (39.8)	
Infection	47 (100)	0 (0)	0 (0)	47 (28.3)	
Pancreaticobiliary	15 (68.2)	5 (22.7)	2 (9.1)	22 (13.3)	
Drugs	7 (77.8)	1 (11.1)	1 (11.1)	9 (5.4)	
Trauma	8 (100)	0 (0)	0 (0)	8 (4.8)	
Systemic diseases	4 (57.1)	2 (28.6)	1 (14.3)	7 (4.2)	
Genetic	0 (0)	3 (50.0)	3 (50.0)	6 (3.6)	
Metabolic causes	1 (100)	0 (0)	0 (0)	1 (0.6)	
Total	120 (72.3)	25 (15.1)	21 (12.6)	166 (100)	

There is no difference between values with the same letter

According to the diagnostic criteria, 120 patients (72.3%) were considered AP, 25 patients (15.1%) CP, and 21 patients (12.7%) ARP. It was found that patients who had ARP relapsed at the earliest 1 month, at the latest 36 months later.

The most common complaint was abdominal pain in 137 (82.5%) cases at admission.When the admission complaints were evaluated according to the pancreatitis types, it was found that fever was more common in patients who had AP when compared to other pancreatitis types at a statistically significant level (p<0.021) (Table 1). When the location of the pain was evaluated, it was found that the epigastric region and around the navel were the first areas of pain, and when the relationship with food was examined, it was determined that most of them were not associated with food.

When the etiologies were examined, the most common cause was found to be idiopathic at a rate of 39.7% (n:66) (Table 1).When those who had infection etiology were examined according to subgroups, 16 (9.7%) had acute gastroenteritis, 16 (9.7%) had upper respiratory tract infection, and 3 (1.8%) had lower respiratory tract infection. Gallstones were detected in 9 (5.4%) of pancreaticobiliary pancreatitis, biliary sludge in 4 (2.4%), pancreatic divisium in 3 (1.8%), choledochal stones in 3 (1.8%), common bile duct cysts were seen in 2 (1.2%), and a duodenal diverticulum in 1 (0.6%). When those who had systemic diseases in the etiology were examined, 4 (2.4%) had cystic fibrosis and 3 (1.8%) had Inflammatory Bowel Disease. When the etiology of drug use was evaluated, 3 (1.8%) non-steroidal anti-inflammatory, 2 (1.2%) oral contraceptives, 1 (0.6%) antiepileptic, 1 (0.6%) SSRI, 1 (0.6%) used antipsychotics (Risperidone), and 1 (0.6%) used 5-aminosalicylic acid (meselazine). When those with genetic disease etiology were analyzed according to subgroups, 2 (1.2%) had PRSS-1 gene mutations, 2 (1.2%) had CFTR gene mutations, and 1 (0.6%) had PRSS-1 and CFTR gene mutations.

The mean age at diagnosis of the patients according to pancreatitis types was also analyzed. The age was not statistically significant at diagnosis when compared according to pancreatitis types (p:0.868). The anthropometric characteristics of the patients and the distribution of hematological and biochemical parameters according to pancreatitis types are given in Table 2.

Table 2. The anthropometric characteristics of the patients, the distribution of the hematological and biochemical parameters according to pancreatitis types

	Acute Pancreatitis		Chronic Pancreatitis		Recurrent Pancreatitis		p
	Mean±SD	Median (Min-max)	Mean±SD	Median (Min-max)	Mean±SD	Median (Min-max)	
Age n (years)	10.24±5.18	11 (1-17)	11±3.96	11 (3-17)	10.19±4.94	10 (3-17)	0.868
BW persentile	28.5±31.81	15.5 (1-99)	31.71±27.8	26.5 (1-88)	47.11±38.19	30 (1-99)	0.154
Lenght persentile	31.41±30.62	18.5 (1-99)	35.76±26.6	31 (1-86)	41.06±34.53	34 (1-99)	0.517
BMI (kg/m^2)	17.93±4.42	17.04 (11-33.79)	17.88±2.63	17.85 (13.78-22.21)	20.01±6.96	16.93 (12.9-31.96)	0.488
WBC (10^3/ul)	10.36±5.11	9.4 (1.8-29.8)	9.87±4.16	8.6 (5.1-20.7)	10.58±4.8	10.4 (2.9-19.6)	0.780
Hemoglobin (g/dl)	12.58±2.15	12.85 (6.1-16.7)	12.74±1.95	12.8 (8.4-17.2)	13.35±1.72	13.4 (10.1-16.7)	0.930
Platelet (mm^3)	308.2±124.07	308 (30-835)	334.12±120.76	335 (88-625)	331.95±95.61	314.5 (166-524)	0.199
Neutrophil (10^3/L)	6.95±4.72	5.9 (1.1-23.1)	221.54±1074.27	5.4 (2.7-5378)	6.96±4.39	5.9 (0.9-17.4)	0.752
CRP (mg/dl)	15±33.08[a]	3.65 (0.1-205)	8.34±21.39[b]	1.4 (0.1-98)	3.17±4.04[c]	1.55 (0.1-14)	0.017
Sedim (mm/h)	15.97±15.02	12.5 (2-56)	14.18±13.8	10.5 (2-53)	9.6±5.45	10 (2-20)	0.743
Calcium (mg/dl)	9.48±0.71	9.5 (6.3-11.1)	9.72±0.61	9.7 (8.7-10.8)	9.88±0.59	9.9 (8.4-10.9)	0.133
Phosphorus (mg/dl)	4.26±0.92	4.3 (1.1-6.4)	4.7±1.02	4.6 (3-7.5)	4.48±0.86	4.5 (2.3-5.8)	0.071
Urea (mg/dl)	26.89±23.92	21 (5-170)	25.75±8.78	24 (14-44)	22.74±5.83	22 (13-37)	0.156
Creatinin (mg/dl)	0.58±0.54	0.51 (0.11-4.3)	0.49±0.17	0.47 (0.24-0.92)	0.49±0.19	0.44 (0.23-0.93)	0.675
LDH (U/L)	394.29±804.82[a]	253 (100-6524)	225.15±48.59[b]	234.5 (144-329)	261.24±55.54[b]	242 (185-361)	0.021
T. bilirubin (mg/dl)	0.85±1.19	0.56 (0.09-9.7)	1.3±3.7	0.44 (0.16-17.8)	0.68±0.65	0.43 (0.2-2.88)	0.269
D. bilirubin(mg/dl)	0.3±0.51	0.14 (0.01-3.7)	0.56±2.09	0.1 (0.05-9.9)	0.29±0.44	0.12 (0.06-1.92)	0.061
Albumin (g/dl)	4.12±0.55	4.2 (2.7-5.2)	4.26±0.46	4.4 (2.9-5)	4.33±0.54	4.4 (3.1-5.4)	0.521
Triglyceride (mmol/L)	130.5±173.29	89 (32-1368)	83.86±45.43	68 (30-216)	101.47±46.21	93 (40-201)	0.080
Glucose (mg/dl)	105.6±83.49	91 (24-798)	101.13±15.43	98.5 (78-137)	152.67±250.43	91.5 (65-1154)	0.067
ALT (IU/L)	63.15±169.45	17 (3-1530)	29.64±41.05	15 (7-171)	26.48±34.69	16 (7-153)	0.440
AST (IU/L)	112.42±466.69	30 (10-4881)	39.8±45.23	23 (16-227)	36.86±32.04	27 (14-143)	0.655
GGT (U/L)	54.9±140.34	15 (3-1243)	18.76±17.18	14 (4-87)	56.74±125.68	13.5 (8-529)	0.177
ALP (IU/L)	186.38±112.21	152 (43-665)	231.12±147.4	231 (35-686)	189.06±121.3	141.5 (75-444)	0.309
Amylase (U/L)	597.59±1166.17	234 (20-10110)	551.84±662	227 (63-2551)	808.48±710.29	346 (152-2249)	0.099
Lipase (U/L)	1241.37±4288.07	327.5 (4-45552)	916.76±1231.27	318 (11-4415)	1691.24±2001.65	446 (30-6709)	0.357

BW: Body Weight ; BMI; Body Mass Index; SDS: Standart Deviation Score; WBC: White Blood Cell; CRP: C Reactive Protein; Sedim: Sedimentation; LDH: Lactat Dehyrogenase, ALT: Alanin aminotransferase ; AST: Aspartat Aminotransferase,; GGT: Gama Glutamil Transferase; ALP: Alcalen Phosphatase. There is no difference between values with the same letter

When the radiological imaging results were evaluated, it was found that 155 (93.37%) of the patients were evaluated with USI and 102 of them were evaluated as normal (61.44%). Abdominal USI, CT, and MRI findings are given in **Table 3**.The comparison of the complete blood count and biochemical values of the patients at admission to the hospital and at the 48 th hour is given in **Table 4**.

The hospital stays of the patients ranged from 1 to 50 days (mean 10.5±8.47).The distribution of the length of stay in the wards and Intensive Care Units of the patients is given in **Table 5**.

When the treatment methods used were evaluated, 159 (95.78%) received saline intravenous fluid, 146 (87.95%) proton pump inhibitor, 65 (39.15%) TPN, 59 (%35,54) octreotide, 55 (33.13%) antibiotics, and 30 (18.07%) analgesics and 6 of the patients (3.61%) required surgical intervention. The distribution of the treatment modalities of the patients according to pancreatitis types is given in **Table 6**. Although the mean hospital stay was 6.77 days in patients who did not use octreotide, it was 17.27 days in patients who used octreotide.A statistically significant difference was detected in the comparisons (p<0.001). It was found that 14 (53.54%) of the patients who developed complications were given octreotide treatment.The most commonly used antibiotic was Meropenem (n:23; 42.6%). Other antibiotics used for pancreatitis were Cefotaxime, Teicoplanin, Piperacilin-Tazobactam, Metronidazole, Ceftriaxone, Sulfaxide, and Cefepime.

When complications were evaluated, peripancreatic fluid was detected in 15 (57.7%), pancreatic edema was detected in 5 (19.3%), pseudocyst in 3 (11.5%), and pancreatic necrosis in 3 (11.5%).When the development of complications was evaluated according to pancreatitis types, 18 (69.2%) were diagnosed with AP, 5 (19.2%) with CP, and 3 (11.6%) with ARP at a statistically insignificant level (p: 0.808). When the length of stay between the groups with and without complications was evaluated, it was 9.78 days in the group without complications and 14.38 days in the group that developed complications. When compared statistically, a significant difference was detected in this respect (p: 0.010). The duration of hospitalization in the Intensive Care Unit was found to be 2.0 days in the group without complications, and it was 2.50 days in the group that developed complications. There were no significant differences in this respect (p: 0.591). The time to start enteral feeding was 3.65 days in the group without complications and 5.00 days in the group with complications, and there were no statistically significant differences (p 0.151).

Table 3. The Abdominal Ultrasonography, Computed Tomography, and Magnetic Resonance Imaging findings of the patients

	N	%
USI Findings		
Normal	102	61.44
Biliary Sludge	13	7.83
Increase in pancreatic size	11	6.62
Gallstone	11	6.62
Peripancreatic fluid	10	6.02
Pancreas could not be evaluated	9	5.42
Pancreatic edema	7	4.21
Increased pancreatic echogenicity	6	3.61
Lymphadenopathy	5	3.01
Choledochal duct width	5	3.01
Pancreas cyst	3	1.8
Pancreatic duct dilatation	2	1.2
Choledochal cyst	1	0.6
CT Findings		
Normal	15	9.03
Increase in pancreatic size	8	4.81
Peripancreatic fluid	6	3.61
Pancreatic edema	3	1.8
Gallstone	2	1.2
Pancreatic duct dilatation	2	1.2
Pancreatic necrosis	2	1.2
Pancreatic density changes	1	0.6
Lymphadenopathy	1	0.6
Bile duct dilatation	1	0.6
MR Findings		
Normal	63	37.95
Increase in pancreatic size	18	10.84
Peripancreatic fluid	13	7.83
Pancreatic duct dilatation	12	7.22
Bile duct dilatation	10	6.02
Pancreatic echogenicity changes	9	5.42
Gallstone	8	4.81
Pancreatic pseudocyst	3	1.8
Choledochal cyst	2	1.2
Pancreatic necrosis	2	1.2
Pancreatic atrophy	2	1.2
Pancreas divisium	2	1.2

Table 5. The distribution of ward and intensive care unit hospitalization times of the patients who participated in the study

Hospitalization Duration	**Mean±SD**	**Median (Min-max)**	**p**
Gender			0.751
Girl	10.41±8.48	8.00 (1-50)	
Boy	10.72±8.37	8.00 (1-42)	
Total	10.56±8.47	8.00 (1-50)	
Age Group			0.336
1-5 age	9.82±7.44	8 (1-30)	
6-10 age	12.20±9.45	10 (1-50)	
>11 age	10.09±8.41	7 (1-42)	
Type of Pancreatitis			0.758
Acute Pancreatitis	10.63±8.57	8 (1-50)	
Chronic Pancreatitis	9.76±7.70	6 (2-30)	
Recurrent Pancreatitis	11.05±8.71	8 (1-31)	
Duration of Intensive Care Hospitalization	**Mean±SD**	**Median (Min-max)**	**p**
Gender			0.849
Girl	2.0±1.22	2 (1-3)	
Boy	2.2±1.92	2 (1-5)	
Total	2.1±1.52	2 (1-5)	
Age Group			0.098
1-5 age	2.0±0.81	2 (1-3)	
6-10 age	4.00±1.41	4 (3-5)	
>11 age	1.25±1.50	1 (0-3)	
Type of Pancreatitis			0.526
Acute Pancreatitis	1.71±1.25	2 (1-3)	
Chronic Pancreatitis	3.0±1.0	3 (1-3)	
Recurrent Pancreatitis	3±2.83	3 (1-5)	

Table 4. The comparison of the complete blood counts and biochemical values of the patients with the values at admission to the hospital and at the 48th hour

	At the time of admission to hospital		**After 48 hours**		
	Mean±SD	**Median (Min-max)**	**Mean±SD**	**Median (Min-max)**	**p**
WBC (10^3/ul)	10.31±4.91	9.25 (1.8-29.8)	7.81±3.58	6.85 (1.75-20)	0.001
Hemoglobin (g/dl)	12.7±2.08	12.9 (6.1-17.2)	12.09±2.01	12.5 (6.7-17.3)	0.001
Platelet (mm^3)	315.09±120.31	313 (30-835)	299.03±113.88	279 (40-867)	0.004
Neutrophil (10^3/L)	39.66±419.44	5.85 (0.9-5378)	4.98±4.39	4.1 (0.5-40.9)	0.293
Calcium (mg/dl)	9.56±0.69	9.6 (6.3-11.1)	9.31±0.64	9.4 (7.2-11)	0.001
Phosphorus (mg/dl)	4.36±0.94	4.3 (1.1-7.5)	4.26±0.97	4.35 (1-7.4)	0.209
Urea (mg/dl)	26.18±20.63	22 (5-170)	21.56±17.44	18 (2-149)	0.001
Creatinin (mg/dl)	0.55±0.47	0.48 (0.11-4.3)	0.77±2.98	0.46 (0.04-37)	0.366
LDH (U/L)	352.47±688.72	249 (100-6524)	325.1±522.53	234.5 (105-4530)	0.085
Total Bil (mg/dl)	0.9±1.77	0.52 (0.09-17.8)	0.91±1.64	0.59 (0.1-17)	0.285
Direkt Bil (mg/dl)	0.34±0.93	0.13 (0.01-9.9)	0.31±0.89	0.13 (0.03-9.2)	0.073
Albümin (g/dl)	4.17±0.54	4.3 (2.7-5.4)	3.83±0.49	3.8 (2.6-4.9)	0.001
ALT (IU/L)	53.41±145.95	16 (3-1530)	59.57±247.07	14 (3-2817)	0.652
AST (IU/L)	91.8±397.8	27 (10-4881)	87.13±501.26	24 (8-6111)	0.510
GGT (U/L)	49.45±127.31	15 (3-1243)	53.31±112.86	15 (1-825)	0.846
ALP (IU/L)	193.91±119.81	153 (35-686)	176.65±119.82	143 (38-918)	0.016
Amylase (U/L)	617.38±1054.18	239.5 (20-10110)	211.64±191.11	151 (13-971)	0.001
Lipase (U/L)	1249.39±3742.88	334.5 (4-45552)	263.14±292.23	178 (4-1484)	0.001

WBC: White Blood Cell; CRP: C Reactive Protein; LDH: Lactat Dehyrogenase, ALT: Alanin aminotransferase ; AST: Aspartat Aminotransferase,; GGT: Gama Glutamil Transferase; ALP: Alcalen Phosphatase.

Table 6. The distribution of the treatments applied to the patients according to pancreatitis types

		Acute Pancreatitis[a]	Chronic Pancreatitis[b]	Recurrent Pancreatitis[b]	Total	p
		n (%)	n (%)	n (%)	n (%)	
Hydration	+ -	5 (71.4) 115 (72.3)	0 (0) 25 (15.7)	2 (28.6) 19 (12.0)	7 (4.2) 159 (95.8)	0.277
TPN	- +	72 (71.3) 48 (73.8)	19 (18.8) 6 (9.2)	10 (9.9) 11 (19.9)	101 (60.8) 65 (39.2)	0.134
PPI	- +	13 (65.0) 107 73.3	5 (25.0) 20 (13.7)	2 (10.0) 19 (13.0)	20 (12.0) 146 (88.0)	0.410
Octreotide	- +	80 (74.8) 40 (67.8)	19 (17.8) 6 (10.2)	8 (7.4) 13 (22.0)	107 (64.5) 59 (35.5)	0.018
Antibiotics	- +	76 (68.4) 44 (80.0)	20 (18.0) 5 (9.1)	15 (13.6) 6 (10.9)	111 (66.9) 55 (33.1)	0.244
Analgesic	- +	98 (73.7) 20 (66.6)	19 (14.3) 5 (16.7)	16 (12.0) 5 (16.7)	133 (81.6) 30 818.4)	0.716
Surgical intervention	Not required Required	116 (72.5) 4 (66.6)	24 (15.0) 1 (16.7)	20 (12.5) 1 (16.7)	160 (96.4) 6 (3.6)	0.736
		Mean ±SD	**Mean ±SD**	**Mean ±SD**	**Mean ±SD**	**p**
Time to start feeding (days)		3.92±3.27	3.67±2.03	4.17±2.6	3.92±3.02	0.592
Time to start normal feeding (Day) (Regime 3)		7.02±5.28	6.41±3.81	7.89±4.85	7.06±5.03	0.510
Time to start TPN (Day)		2.85±3.05	2.0±1.73	2.36±1.8	2.70±2.77	0.663
Duration of TPN (Day)		6.88±5.38	6.6±2.61	7.82±5.9	7.02±5.26	0.759
The day the amylase value starts to decrease		2.73± 2.07	2.0.5± 1.55	2.39±0.69	2.65±1.84	0.914
The day the lipase value starts to decrease		3.39±0.69	2.8 ±1.7	2.82±1.46	3.08±2.45	0.989
Day of normalization of lipase value		16.05±21.2	10.86±15.02	17.81 ±19.14	13.68±30.17	0.257
Day of normalization of amylase value		11.60±15.2	9.47±12.98	31.33±77.78	15.71±20.42	0.236

TPN: Total Parenteral Nutrition; PPI: Proton Pump Inhıbıtor. There is no difference between values with the same letter

When the patients were evaluated according to the Atlanta Criteria, 137 (82.5%) were mild and 29 (17.5%) were moderate.There was no patient in the severe disease group. When the duration of hospitalization was evaluated according to the Atlanta Criteria, it was found to be 9.77 days in the mild group and 13.93 days in the middle group, and a statistically significant difference was detected when compared statistically (p: 0.016). The PAPPS Scores, Ranson Admission Scores, and Ranson 48 th hour Scores of the patients were analyzed. The PAPPS Score was Mean±SD was 0.6±0.92. The Ranson Admission Score was Mean±SD 0.31±0.63, and the Ranson Score at the 48 th hour was 0.17±0.39.The Ranson Score of the patients decreased at a significant level (p: 0.012). There was a weak and positive correlation between the PAPPS Score, Ranson Admission Score, and length of hospital stay (p:0.001, r:0.365, p:0.007, r: 0.210, respectively). No relationship was detected in terms of length of hospital stay in Ranson 48th hour scoring.

No deaths occurred because of AP, and there was no progression to chronic pancreatitis and endocrine pancreatic insufficiency in any of the patients.The patients who were included in the study were followed up in the Pediatric Gastroenterology Clinic for an average of 12.76±18.45 months (1.0-99.0). Recurrence was detected in 21 (12.65%) patients and 10 (47.61%) of these patients had acute pancreatitis attacks twice, 7 (33.33%) 3 times, 2 (9.52%) 4 times, 2 (9.52%) 5 times.

DISCUSSION

In recent years, the incidence of pancreatic diseases during childhood has been increasing because of the increasing awareness of physicians.[13] Recovery is observed in the majority of patients without complications and recurrent pancreatitis attacks are seen in 15-35% of patients and CP may develop.[14,15]

AP can be seen in all age groups.In a study conducted by Nydegger et al. with 279 pediatric patients, the mean age was found to be 10 years at presentation and the number of male patients was 1.4 -fold higher than that of female patients.[4] In a meta-analysis that was published in 2016, the mean age was found to be 9.2±2.4 years and it was reported that female patients were more common.[16] Similarly, in the present study, the mean age was found to be 10.34±4.97 years. The rate of female patients to male patients was 1:24.

A total of 50% of the patients were diagnosed with AP, 21% with ARP, and 29% with CP in a 12-year study conducted by Poddar et al.[7] Similarly, in the present study, the majority of patients had AP and 72.3% of them were identified as AP, 15.1% as CP and 12.7% as ARP. The fact that the diagnosis age of patients with CP was higher than those with ARP and AP, and patients with CP were more than those with ARP, were associated with the chronicity of ARP and AP over time.

Regarding pancreatitis, abdominal pain, and vomiting are the leading findings that suggest the disease.In the study conducted by Werlin et al.[15] abdominal pain was detected in 45 (80%) patients, and it was reported that it was most common in the epigastric region, followed by the right upper quadrant and the right lower quadrant. Vomiting was reported in 96 (53%) patients in the same study.[15] Similarly, the most common complaint of patients was abdominal pain in 137 (82.5%) patients in the present study.Other complaints were nausea-vomiting in 121 (72.89%) and anorexia in 102 patients (61.44%). In the present study, among the patients who had abdominal pain, the pain was in the epigastric region in 57 (34.3%) patients, around the navel in 47 (28.3%), on the back in 22 16.05%)patients, both in the epigastric and umbilical region in 14 (10.21%) patients, and in the right lower quadrant in 6 (4.37%) cases. In the study that was conducted by Park et al.[17] it was reported that older children presented with complaints of abdominal pain and nausea-vomiting more than younger children, and the frequency of nausea/vomiting was 93.4% and 78.1%, respectively. Similarly, it was observed in the present study that abdominal pain was more common in older children and fever was more common in younger children. The reason for this was considered that the younger age group could not describe abdominal pain and infections were more common in the etiology. When evaluated according to pancreatitis type, it was found that fever was statistically higher than other pancreatitis types in the complaints of patients with AP. The reason for this is that infection is frequently seen in the etiology of AP.

Although the cause of pancreatitis is often gallstones and alcohol in the adult age group, systemic diseases, gallbladder disease, drugs, infection, and idiopathy in the pediatric age group. Genetic mutations and metabolic diseases were detected less frequently in the etiology.[18] In the study that was conducted by Park et al.[17] the most common cause was reported as biliary diseases (32.6%), drugs (32.6%), and idiopathic (20%).The most common causes were idiopathic (52%), traumas (21%), and pancreaticobiliary causes (10%) in Poddar's study.[7] In the present study, 66 (39.7%) of the patients who were diagnosed with pancreatitis had idiopathic causes, and infection was found to be the cause in 47 (28.3%). Although there have been developments in the diagnosis and examination in the field of healthcare in recent years, the etiology of many cases of pancreatitis cannot be clarified yet.

Many infectious agents can cause pancreatitis.[21] When the subgroups of the patients who had infectious etiology were examined in the present study, 16 (9.7%) had gastroenteritis, 16 (9.7%) had URTI, 3 (3.0%) had LRTI, 12 (7.2%) had other causes of infection.There are few data on the development of AP as a complication of Coronavirus Disease-19 (COVID-19) infection.[20] One of the patients who were included in the present study had abdominal pain complaints during COVID-19 and the patient was evaluated as FP according to INSPREE Criteria.

When pancreaticobiliary causes were evaluated, gallstones, biliary sludge, choledochal cysts, choledochal stones, and pancreatic divisium were frequently detected.[17] In the study that was conducted by Ma et al.[21] gallstones were detected at a rate of 55%, biliary sludge at 21%, and structural anomalies at 24% among biliary causes. Similarly, in the present study, pancreaticobiliary etiology was detected at a rate of 13.2%, and when those with biliary origin were examined, gallstones were found in 40%, biliary sludge in 18.1%, and structural anomalies in 16.6%.

One of the common causes of pancreatitis is drugs. Many drugs have been accused in this respect.[22] In the present study, drugs were evaluated as the cause in 9 (5.4%) patients, NSAIDs in 3 (1.8%), oral contraceptives in 2 (0.12%), valproic acid in 1 (0.6%), SSRIs in 1 (0.6%), antipsychotic medication (risperidone) in 1 (0.6%), and 5-aminosalicylic acid (mesalazine) in 1 patient.

Traumas (e.g., blunt traumas, abuse, post-ERCP, post-pancreaticobiliary surgery) were evaluated as a cause of AP with a frequency of 8-60% in the literature.[15] In the present study, 8 (4.8%) patients were found to be traumatized in etiology (blunt traumas in 4, after the replacement of the gastrostomy tube in 1 because of the insertion of the probe in front of the papilla in the duodenum, after electric shock in 1 patient, after gastrostomy tube opening and Nissen Fundoplication Surgery in 2). Traumas were less common in the etiology in the present study compared to the literature data, and it was considered that this was because trauma patients applied to the adult emergency and pediatric surgery department of our hospital.

Imaging is the first choice used in the diagnosis of pancreatitis because USI is a non-invasive and reliable diagnostic tool.[23-25] In the study that was conducted by Werlin et al.[15] USI imaging was performed in 50% of the patients who had suspected pancreatitis, and it was evaluated as normal in 75%. In the present study, 155 (93.37%) of the patients were screened with USI in the first step because it was reliable and did not contain radiation. Although 102 (61.44%) of our patients were evaluated as normal, 13 (7.83%) had bile sludge, 11 (6.62%) had increased pancreatic size, 11 (6.62%) had gallstones, and 10 (6.02%) had peripancreatic fluid.

Abdominal CT is more valuable than ultrasound in the diagnosis and for the determination of complications. Its use in pediatric patients is avoided because it contains radiation.[5] In a study that was conducted with pediatric pancreatitis patients, 73% of the patients underwent CT imaging, and pancreatic edema was detected in 38%, gallstones, biliary sludge, and cholecystitis in 17%, and necrosed pancreas in 6%.[26] In the present study, 34 of the patients (20.48%) underwent CT imaging, 15 (9.03%) were normal, and increased pancreatic size was detected most frequently in eight (4.81%) patients. In the present study, pancreatic parenchyma was normal in USI in 1 of the patients who had pancreatic necrosis, the pancreatic parenchyma was slightly heterogeneous and there was peripancreatic fluid in the other, and necrosis was observed in the CT scans performed on the same day. In 3 patients whose USI was normal, peripancreatic fluid, pancreatic duct dilatation, and gallstones were detected on CT imaging. Even if the USI is normal, further imaging must be performed in patients who are considered to develop complications.

MRI shows pancreatic inflammation earlier than other imaging methods and is often employed in etiology research rather than diagnosis.[27] MRI was performed in 107 (64.45%) of our patients, and on all patients who were diagnosed with CP and ARP. It was normal in 63 of our patients (37.95%), increased pancreatic size was most common in 18 (10.84%) patients, followed by peripancreatic fluid in 13 (7.83%) patients.Among the 11 patients who had normal findings USI, peripancreatic fluid was detected in 5, pancreatic enlargement in 4, and pancreatic duct dilatation in 2 in MRI. These results show the superiority of MRI and CT over USI in etiology and complication research.

Although the etiology is investigated in the first step in patients who are diagnosed with pancreatitis, oral intake must be stopped to rest the pancreas, and fluid replacement therapy should be started to prevent complications.[11] In the study that was conducted by Appak et al.[28] oral intake was discontinued in all patients at admission and opened within an average of four days.Similar to our study results, oral intake was opened in an average of three days. The mean time of switching to Diet 3 was determined as 7.06±5.03 days and oral intake was initially discontinued in 159 (95.78%) patients, and saline intravenous fluid containing sodium concentration appropriate for their age was administered.In a study conducted in our country, TPN was started in 32.2% of the patients for an average of 15.1±12.6 days.[30] A total of 65 (39.2%) of our patients received TPN whose onset time was 2.70±2.77 days and duration was 7.02±5.26 days. When TPN onset and duration of time were compared according to pancreatitis types, no significant differences were detected.

It was reported in the clinical report published by the NASPGHAN Pancreatitis Committee that the average hospitalization duration of pediatric patients who had pancreatitis was mostly between 2.8-8 days, and most of the patients were infants and children younger than 6 years old.[29] In the present study, the median hospital stay of the patients was 8 days, and the mean hospitalization duration was 10.5±8.47 days. When the duration of hospitalization was analyzed according to age groups, it was found that the maximum duration of hospitalization was 12.15±9.52 days in children who were aged 6-10 years.A total of 8 (4.8%) patients who were included in the study were followed up in the Intensive Care Unit and the mean hospital stay was 2.10±1.5 days. Two patients were admitted to the Intensive Care Unit for 2 days after a choledochal-enterostomy because of a choledochal cyst, and one patient was hospitalized because of severe malnutrition. Two patients developed sepsis and 3 patients developed AP because of systemic diseases during their follow-ups in the intensive care unit.

In the study conducted by Sweeny et al.[30] it was reported that 70% of ARP patients recurred in the first five months. In the present study, it was found that the patients relapsed in an average of 11.50±10.70 months, which was associated with the disruption of intermittent check-ups although the families were informed in this respect.

In their study conducted with 110 patients who had complications, Poddar et al.[7] found peripancreatic fluid in 41% and pseudocyst in 54%. Peripancreatic fluid was detected in 15 (57.7%) patients who developed complications in our study, pancreatic edema was detected in 5 (19.3%), pseudocyst in 3 (11.5%), and pancreatic necrosis was detected in 3 (11.5%) patients.

According to the Atlanta Scoring Criteria, the average hospital stay was reported to be 9.77 days in the mild group and 13.93 days in the moderate group. Although the mean Ranson Score was 0.31±0.63 at admission, the mean Ranson Score was calculated as 0.17±0.39 at 48 hours. The Ranson Scores of the patients decreased significantly (p=0.012). A weak and positive correlation was detected in the PAPPS Scores and Ranson Admission Scores of the patients.

The limitations of the present study were that it had a retrospective design and included the results of a single center. Further multicenter prospective studies are needed to develop scoring systems to determine disease severity and prognosis.

CONCLUSION

In the diagnosis and follow-up of acute pancreatitis, it is important to determine the severity of the disease and to uncover its etiology. Accurate and effective use of clinical and laboratory findings and radiological examination results of patients who apply to healthcare institutions with the preliminary diagnosis of acute pancreatitis, which still has no specific treatment and can be fatal, is essential for rapid diagnosis. Establishing and applying standard approaches for early diagnosis and treatment of patients will lead to prognostic improvement and prevent related complications.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the Selçuk University Local Ethics Committee (Date: 24.03.2021, Decision No: 2021/164).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

Acknowledgements: This Publication is related to thesis with reference number 10520437 (YOKSİS Tez Merkezi)

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Original Article

MEDICINE PALLIATIVE CARE

DOI: 10.47582/jompac.1348792

J Med Palliat Care. 2023;4(5):466-471

Correlation between spinopelvic angles and radiological findings of lumbar spondylolisthesis patients

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Cite this article as: Yücel E, Akyuva Y. Correlation between spinopelvic angles and radiological findings of lumbar spondylolisthesis patients. *J Med Palliat Care*. 2023;4(5):466-471.

Received: 23.08.2023 ◆ **Accepted**: 20.09.2023 ◆ **Published**: 27.10.2023

ABSTRACT

Aims: Spondylolisthesis is a deformity in which the upper segment is displaced anteriorly or posteriorly in the spine relative to the lower segment. In this pathology, which often causes instability, surgical treatment may be required. Also, patient's radiological images should be evaluated carefully before treatment. We aimed to analyze clinical and radiological data with spinopelvic angles of the lumbar spondylolisthesis patients in our research.

Methods: 6593 patients who applied to the neurosurgery outpatient clinic with complaints of low back pain between January 2019 - December 2022 were retrospectively analyzed. The radiological findings of patients with spondylolisthesis, whose lumbar MRI and lumbar CT were obtained appropriately along with X-ray were evaluated in detail. Age, gender, listhesis level and degree, Cobb angle, pelvic incidence, pelvic tilt, sacral slope angle, Modic degeneration, vacuum phenomenon, annulus rupture, Schmorl nodule, facet hypertrophy, osteophyte, maximum AP central canal diameter and joint lysis has been examined in these patient tests. The relationships of these data with each other were evaluated statistically.

Results: 58 female and 5 male patients were found to be eligible for the study. Mean age was 59 (min 22, max 81). Grade 1 listhesis was detected in 52 of the patients. Listhesis was observed at the level of L5-S1 in 31 patients, L4-L5 in 24 patients and L3-L4 in 8 patients. A direct correlation was found between age and vacuum phenomenon, osteophyte, presence of L5-S1 listesis and lysis. Similar correlation was found between pelvic incidence and sacral slop angle, facet hypertrophy and Modic type 2 degeneration. Also, there was a direct correlation between pelvic incidence and pelvic tilt; between facet hypertrophy and vacuum phenomenon and lysis; ligamentum hypertrophy and vacuum phenomenon; and facet hypertrophy and lower level listesis (p 0.05).

Conclusion: Spondylolisthesis is an important problem that requires treatment in spine surgery. Radiologically determined parameters can give important knowledge about the severity of this pathology. These findings should be taken into consideration in the treatment of spondylolisthesis.

Keywords: Spondylolisthesis, radiological parameter, spinal deformity, instability, spinopelvic angles

INTRODUCTION

Spondylolisthesis develops after the vertebrae move forward or backward on each other.[1] It usually occurs at the L4-5 level and rarely in adjacent segments. Degenerative spondylolisthesis is common in women after the age of 50.[2] The reason for its frequent occurrence in women is known to be the more ligament laxity than men. In women, especially during pregnancy, maternal hormones increase joint laxity and initiate a pathological process for spondylolisthesis.[3] It appears as a wide clinical spectrum ranging from simple mechanical low back pain to progressive neurological deficits and radiological findings. It is a serious public health problem as it causes workforce loss.[4]

In degenerative lumbar spondylolisthesis, pathologies begin with intervertebral disc and facet joint degeneration. After the development of degenerative disc disease, most of the loads on the lumbar region are transferred to the facet joints. After this microinstability caused by progressive degeneration, hypertrophy and osteophyte formation begins in the facet joint. After this change, the tension and ligament loosening occurring in the facet capsule may lead to forward or lateral shifts in the vertebrale column. Other radiological findings such as disc space height loss, facet hypertorophy, ligamentum flavum hypertrophy, subchondral sclerosis, osteophyte formation, spinal stenosis and foraminal stenosis may accompany the spondylolisthesis.[5-7] Age, gender, occupation, trauma are the main known causes of spondylolisthesis, and although

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there are many studies on this topic, a clear relationship has not yet been absolutely established between clinical and radiological findings and spinopelvic angles in terms of the development of spondylolisthesis.[8-12] In our study, radiological findings, spinopelvic angles and clinical findings in patients with spondylolisthesis were evaluated and compared in detail.

METHODS

The study was carried out with the permission of the Hatay Mustafa Kemal University Non-interventional Researches Ethics Committee (Date: 01.09.2022, Decision No: 32). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

6593 patients who applied to the neurosurgery outpatient clinic with complaints of back and leg pain between January 2019 and December 2022 were retrospectively analyzed. Among the patients with spondylolisthesis, X-ray (lateral, anteroposterior), lumbar magnetic resonance imaging (MRI- 1.5 T T2, T1 sequence sagittal, T2 sequence axial section) and lumbar computed tomography (CT- sagittal-axial-coronal section) were obtained from 63 patients having appropriate radiological tests and evaluated in detail. Patients with a previous history of spinal surgery, spinal tumor, congenital malformation or major trauma exposure were not included in the study. The common feature of the patients was lumbar degenerative spondylolisthesis. In these patients, age, gender, listhesis level, listhesis degree, Modic degeneration, presence of osteophyte, facet hypertrophy, maximum antero-posterior central canal (MAPCC) length, pelvic incidence (PI), pelvic tilt (PT), sacral slope (SS) angles, vacuum phenomenon, Cobb angle, joint lysis, anulus rupture, Schmorl nodule and the relationships between these data were evaluated statistically.

PI, PT, SS and Cobb angles were calculated using the Clear Canvas program from one researcher who is dealing with spine surgery. While performing lumbar CT of the patients, it had been checked that CT was taken from the upper end plate of the L1 vertebra to the femoral head of pelvis. The PI was determined by calculating the angle between the vertical line drawn down from the midline of the sacral plateau in the sagittal plane and the line drawn from the same point to the femoral head (**Figure 1A**).[13] The SS was calculated as the angle between the sacral plateau and the horizontal plane (**Figure 1B**). PT was found by calculating the angle between the line drawn from the midpoint of the sacral plateau to the femoral head and the vertical plane (**Figure 1C**).[14] Scoliosis angle was determined with the plane drawn from the upper and lower ends of scoliosis in patients with lumbar scoliosis (**Figure 1D**).[15] Listhesis level (**Figure 2A, 2B**) and degree (**Figure 2A, 2B**), Modic degeneration type (**Figure 3**), vacuum phenomenon (**Figure 4A**), MAPCC diameter at the listhesis level (**Figure 4B**), ligamentum flavum thickness (**Figure 4C**), facet degeneration (**Figure 4D**), osteophyte (**Figure 4E**) and Schmorl nodule (**Figure 4F**) were evaluated from lumbar MRI and CT images of the patients.

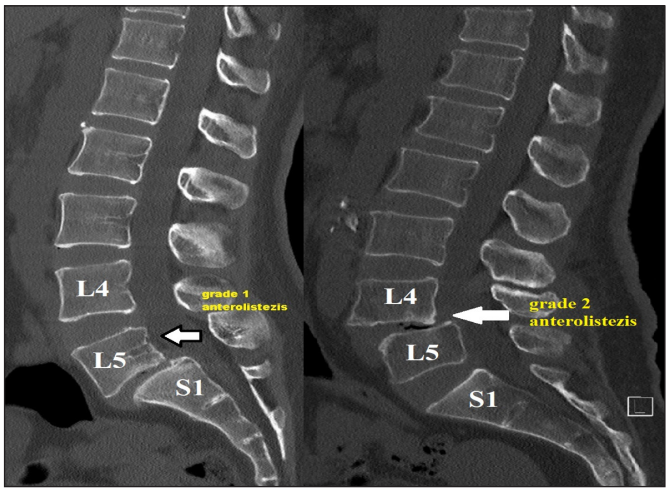

Figure 2

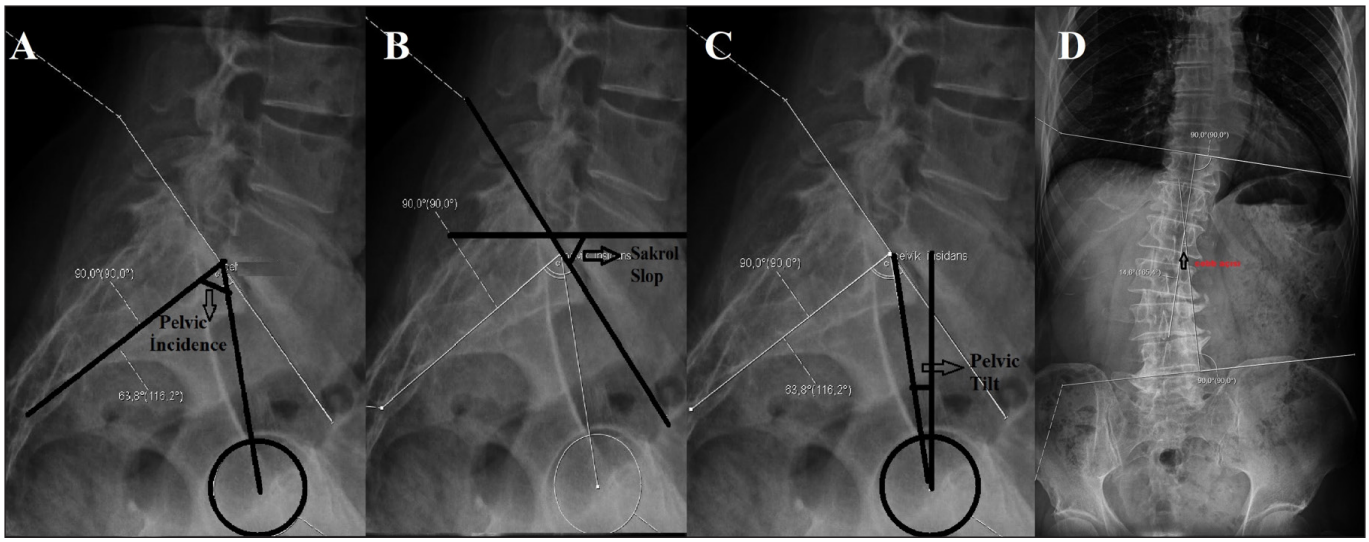

Figure 1

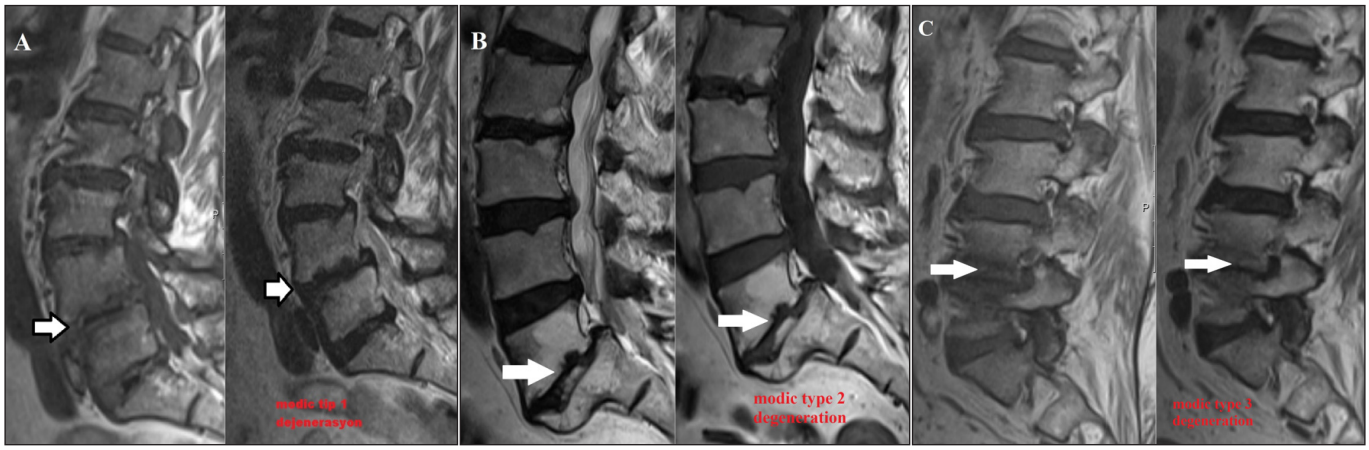

Figure 3

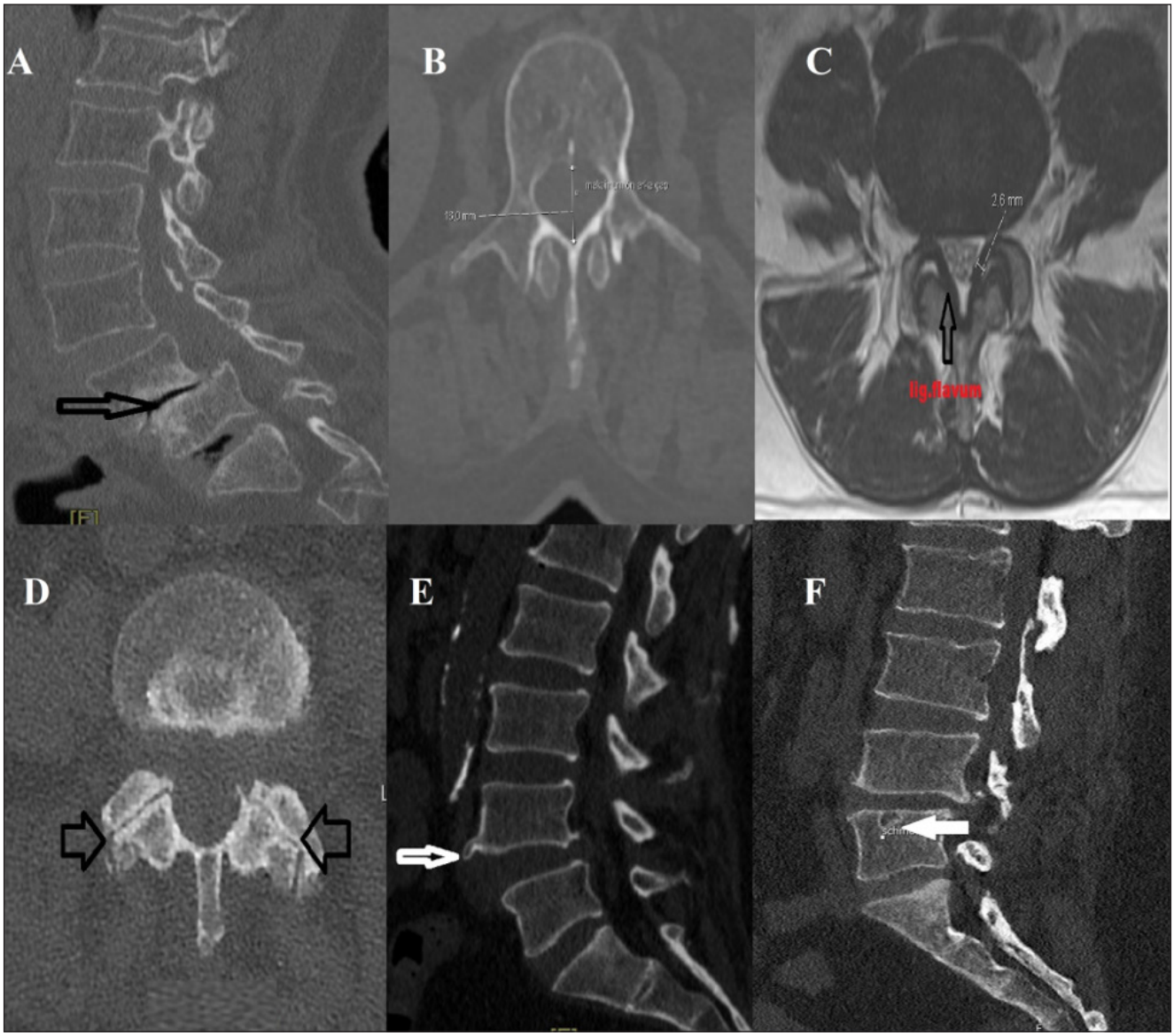

Figure 4

Statistical Analysis

SPSS v21.0 for Windows (IBM Corp., Armonk, NY, USA) was used to analyze data. Means±standard deviations were used for normally distributed continuous variables [p>0.05 in Kolmogorov-Smirnov test or Shapiro-Wilk]. Correlation between facet hypertrophy, Modic degeneration, anulus rupture, vacuum phenomenon, MAPCC, spondylolisthesis levels, lysis defect and spinopelvic angle in the groups was measured by the Pearson correlation test (r). A p value below 0.05 was regarded as statistically significant.

RESULTS

The population of our study consists of 58 females and 5 males, totally 63 patients. Grade 1 spondylolisthesis was detected in 52 patients, and grade II spondylolisthesis in 11 patients. Spondylolisthesis was present at L5-S1 level in 31 patients, L4-L5 in 24 patients, and L3-L4 in 8 patients. The mean age was found to be 56.89±12.21 years. The mean SS angle was 36.89±7.66, the PT angle was 22.73±3.64, and the PI angle was 68.37±7.79. Local lumbar Cobb angle was found to be 34.22±5.28 degrees in patients with degenerative scoliosis (n: 8). When the axial sections were examined, it was seen that MAPCC (CT) was 15.59±5.67 mm and the thickness of the ligamentum flavum (MRI) was 4.71±1.29 mm. Facet hypertrophy was detected in 42 patients. Nine patients had type 1, 24 patients had type 2, and three patients had type 3 Modic degeneration. Modic degeneration was not detected in 27 patients. Vacuum phenomenon was seen in 32, anterior osteophyte in 48, anulus rupture in 11, and Schmorl nodule in 16 patients (Table).

Table. Demographic and radiological information of patients

Gender	
Male	5
Female	58
Grade	
I	52
II	11
Level	
L3-4	8
L4-5	24
L5-S1	31
Average age	56.89 ±12.21
Pelvic parameters	
Sacral Slope	36.89 ±7.66
Pelvic Tilt	22.73±3.64
Pelvic Incidence	68.37 ±7.79
Local cobb angle	34.22 ±5.28
Maximum antero-posterior central canal	15.59 ±5.67
Ligamentum flavum thickness	4.71 ±1.29
Facet hypertrophy	
+	42
-	21
Modic degeneration	
-	27
I	9
II	24
III	3
Vacuum phenomenon	32
Anterior osteophyte	48
Annulus rupture	11
Schmorl nodule	16

There was a negative correlation between SS and facet hypertrophy, and a weak positive correlation with Modic degeneration (r=-0.383, p=0.003 and r=0.310, p=0.01, respectively). There was a negative correlation between PI and anulus rupture (r=-0.327, p=0.013). There was a weak negative correlation between facet hypertrophy and Modic degeneration, vacuum phenomena (r=-0.347, p=0.008 and r=-0.275, p=0.039, respectively). There was a weak negative correlation between MAPCC and flavum thickness (r=-0.311, p=0.018). There was a weak positive correlation between vacuum phenomenon and disc level, lysis defect (r=0.309, p=0.019 and r=0.312, p=0.018, respectively). There was a weak negative correlation between lysis defect and facet hypertrophy, and weak positive correlation between Modic degeneration and vacuum phenomenon (r=-0.365, p=0.005, r=0.325, p=0.014 and r=0.312, p=0.018, respectively). There was a moderate positive correlation between lysis defect and disc level (r=0.555 p=0.0001).

DISCUSSION

Studies on spondylolisthesis found that the PI was greater before dislocation and degeneration began, so lumbar lordosis and also the SS angle were higher in patients than in the normal population. With the increase of lumbar lordosis, an excessive load is placed on the posterior facet joints. This mechanical stress on the facet joints results in facet arthrosis. After facet arthrosis, the SS angle is affected and causes a situation predisposing to listhesis. Spondylolisthesis is followed by intervertebral disc degeneration and collapse. Sagittal vertical axis shifts forward. As a result of compensatory mechanism in degenerative spondylolisthesis cases; pelvic retroversion is expected with a decrease in the SS angle and an increase in the PT angle.[16-18] Therefore, it is important to plan the treatment by considering the accompanying radiological findings of the evaluation for the spine and pelvis in patients with spondylolisthesis.

Pelvic morphology and spinopelvic balance abnormalities are among the most important factors causing the development of spondylolisthesis. Legaye et al.[19] reported the PI as 50.2±10.6 in the normal elderly population, while this angle was 62±11 in patients with listhesis. Also, Liu[20] and Funao[21] likewise showed that PI was higher than the normal population in their study. In our study, the PI was found to be 68.37±7.79, consistent with the literature. Likewise, the data in our study support that the PT angle is higher (22.73±3.64) and the SS angle is lower (36.89±7.66) than the range of the normal elderly population in the literature.

The data of our study showed that the spinopelvic parameters are different from the normal population in accordance with other studies in the literature. These results, although not proven, support that they develop due to a compensatory mechanism in spondylolisthesis. Kırceli at al.[22] emphasized in their study that LL and SS

angles may be a predisposing factor for the development of disc degeneration. Ergun at al.[23] found that the degree and risk of intervertebral disc degeneration and herniation increases in parallel to the decrease in sacral kyphosis and LL, and to the increase in SS angle. Considering that spondylolisthesis is a pathology that develops on the basis of intervertebral disc degeneration, the data in our study support that the spinopelvic angles change depending on the compensatory mechanism.

Lazenec et al.[17] mentioned about the relationship between radiological parameters and postoperative pain in lumbosacral fusion. Spinopelvic angles are disrupted in patients with spondylolisthesis. These patients usually complain of ongoing postoperative pain. In our study, distorted spinopelvic angles were found as compared to the normal population. At the same time, it was thought that the positive correlation in our study between spondylolisthesis and radiological findings such as Modic degeneration, joint lysis, vacuum phenomenon indicates more bone damage. These datas suggested that before the surgery surgical team should evaluate the patient better, and the patient's satisfaction from the treatment could be increased by performing peroperative corrective interventions, if necessary.

In our study, there was a negative correlation between spondylolisthesis and facet hypertrophy, anulus rupture; and a positive correlation between Modic degeneration and osteophytes. These findings showed us that the possibility of listhesis development is reduced after facet hypertrophy, secondary to this stronger bone formation. On the contrary, it is concluded that if facet hypertrophy does not develop, lysis occurs after with microtraumas, the Modic degeneration process starts after traumas in the vertebra, and osteophyte development is seen secondary to the efforts to reconstruct the bony column. Grobler et al.[18] argued that lumbar facet morphology is one of the most important etiological factors in the development of spondylolisthesis and facet degeneration has a major determinant role in this issue, in accordance with the data in our study.

There was no clear relationship between the symptoms caused by spondylolisthesis and central canal stenosis. However, in our study, a negative correlation was found between facet hypertrophy and listhesis, and the central canal anteroposterior distance was found in the normal population range. Although it is named as lumbar degenerative spondylolisthesis, when compared to the studies on spinal stenosis in the literature; both ligamentum flavum thickness and MAPCC values are close to the normal population in spondylolisthesis patients. Considering that Modic type 1 and type 2 degenerations are more frequently detected in our patients, it is thought that the pathological degenerative processes due to inflammatory and fatty degeneration resulting from microtrauma are the main determinants.

Especially joint laxity and pregnancy are the most important factors in the development of spondylolisthesis in the female population.[4] Therefore, it is expected to be more common in women. In our study, 58 patients (92%) consisted of women, in parallel to the literature. Our study was conducted on patients who were admitted to a local hospital that appeals to the socioculturally lower class. The common feature of female patients in this population was the high body mass index (BMI) and the presence of multiple birth history. In cases of obesity and multiple pregnancy, the load carried by the pelvis increases towards the anterior due to the displacement of the center of gravity. Since our study is a retrospective study, the BMI and number of births of these patients could not be included in our study. However, while L4-L5 listhesis was observed more frequently in the normal population, it was thought that the higher prevalence of L5-S1 listhesis (n: 31) in our study may be related to this issue.

Some studies in the literature emphasize that more frequently seen spondylolisthesis in women cannot be explained by paraspinal muscle mass and ligament laxity. Also, pelvic type and morphometry may be an important factor in the development of spondylolisthesis. Boulay at al.[24] stated in their study on 12 anatomic pelvis specimens that, pelvis morphology can be used to examine the relationship between pelvis anatomy and spinal curves. In addition, they believe that the pelvis type could be one of the predisposing factors in degenerative spinal pathologies.

In our study, scoliosis was found in 8 patients. Cobb angles were determined between Min:25.7°- Max:45.6° (34.22±5.28). In our study, scoliosis with a minor degree were ignored, and scoliosis greater than 20° were included. These values indicate that spondylolisthesis may be not only be a sagittal but also an axial balance pathology. Seitsalo at al.[25] stated that scoliosis accelerates degeneration and is a disease associated with spondylolisthesis. He reported that the rate of scoliosis with listhesis was higher when minor angle scoliosis was taken into account.

Limitation

Our study is retrospective in nature, and therefore, not all requested information could be obtained from the patients. Information regarding the BMI values and the number of pregnancies of the patients was not recorded in the system; hence, it could not be included in the research data. Data pertaining to patients' pain, functional status, and neurological deficits, as well as instability findings in dynamic radiographs, were not mentioned in the study because they were not archived in the patient files.

CONCLUSION

Spondylolisthesis often requires treatment. Radiologically determined parameters can give important clues regarding the severity of this pathology. When evaluating a patient with spondylolisthesis, it is important to measure the spinopelvic parameters. Detailed radiological evaluation is required treatment planning of spondylolisthesis.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the Hatay Mustafa Kemal University Non-interventional Researches Ethics Committee (Date: 01.09.2022, Decision No: 32).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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Original Article

MEDICINE PALLIATIVE CARE

DOI: 10.47582/jompac.1342127

J Med Palliat Care. 2023;4(5):472-477

Comparative evaluation of retrograde intrarenal surgery using ureteral access sheath and fluoroscopy: a retrospective analysis on kidney stone treatment

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Cite this article as: Doğan K. Comparative evaluation of retrograde intrarenal surgery using ureteral access sheath and fluoroscopy: a retrospective analysis on kidney stone treatment. *J Med Palliat Care*. 2023;4(5):472-477.

Received: 12.08.2023 ◆ **Accepted**: 22.09.2023 ◆ **Published**: 27.10.2023

ABSTRACT

Aims: This study aimed to investigate the outcomes of retrograde intrarenal surgery (RIRS) with and without the utilization of ureteral access sheath (UAS) and fluoroscopy for treating kidney stones and its implications on postoperative complications.

Methods: Employing a retrospective design, we analyzed the records of 314 patients subjected to RIRS due to kidney stones. Patients were categorized into two groups based on the application of fluoroscopy and UAS (Group 1) versus non-application (Group 2). Various metrics, including stone-free rates, residual stone rates, and postoperative complications, were compared between the groups.

Results: The results showed no significant differences between the two groups regarding patient age, stone size, and several demographic parameters. However, there was a considerable reduction in operation duration in Group 2 (20.96±5.97 minutes) compared to Group 1 (26.15±5.41 minutes), where UAS and fluoroscopy were applied, with p=0.001. Furthermore, post-treatment results highlighted a decline in residual stone rates and an enhancement in stone-free rates, though differences between groups were not significant. The incidence of postoperative complications, like fever, urinary tract infections, and ureteral stenosis, was assessed, revealing no differences between the two groups.

Conclusion: The application of RIRS without UAS and fluoroscopy appears to be a promising approach to treating kidney stones, offering similar outcomes regarding stone removal efficacy and postoperative complications compared to the traditional method with UAS and fluoroscopy. This research emphasizes the potential of a less invasive method, warranting further studies to understand its broad implications.

Keywords: Retrograde intrarenal surgery, kidney stone, ureteral access sheath, fluoroscopy

INTRODUCTION

Endourological advances in recent years have ushered in transformative changes in the management and treatment paradigms for renal calculi.[1] The evolution of ureteroscopy tools and state-of-the-art laser technologies has elevated retrograde intrarenal surgery (RIRS) as a predominant therapeutic choice for renal stones.[2] Current literature underscores the efficacy and reliability of RIRS, demonstrating its minimal invasiveness, high success ratios, and remarkably infrequent occurrences of significant postoperative complications.[3,4]

The widespread adoption of RIRS across numerous medical institutions can be attributed to its innate non-invasive nature, complemented by an impressive success trajectory.[5] A prototypical RIRS procedure entails placing a ureteral access sheath (UAS) under fluoroscopic guidance, ensuring renal accessibility via a flexible ureterorenoscope (fURS), and executing lithotripsy utilizing a holmium laser.[6,7] Nevertheless, the utilization of UAS is not devoid of potential risks.[8] Clinical outcomes have reported complications, such as ureteral wall abrasions, ischemic insults to the ureteral wall, and even the rare yet severe ureteral avulsion.[9]

A consequential concern emerging from the protracted use of fluoroscopy pertains to the lurking genetic mutation threats, potentially precipitating oncogenic transformations in patients and the attending medical personnel.[10] While existing literature delves into the comparative surgical outcomes of exclusive UAS or fluoroscopy usage against non-usage protocols, a conspicuous gap remains.[11] Juxtaposed surgical procedures incorporating both UAS and fluoroscopy against those devoid of both modalities were areas with limited research. Our research aims to discern the

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necessity of employing both UAS and fluoroscopy in RIRS, thus adding a perspective and novel contribution to the endourological discourse.

METHODS

The study was carried out with the permission of the İstinye University Clinical Researches Ethics Committee (Date: 26.05.2021, Decision 2/2021.K-32). All procedures were carried out under the ethical rules and the principles of the Declaration of Helsinki.

Study Design

We performed a retrospective assessment, poring over the records of patients who underwent RIRS for renal calculi treatment. All these surgical interventions were orchestrated under the expertise of a singular surgeon skilled in RIRS. Out of the pool, 314 patients conformed to our stringent inclusion criteria and were ushered into the study.

Patient Selection

Patients eligible for the study had renal calculi with a diameter less than 2 cm or those greater than 2 cm but were deemed unfit for Percutaneous Nephrolithotomy (PNL). Furthermore, only individuals aged over 18 years were considered. On the other side of the spectrum, those excluded from the study were those with stones larger than 2 cm that was compatible with PNL, those under 18 years, cases with concurrent ureteral stones, those with detected renal anomalies like Bifid pelvis, calyceal diverticulum, horseshoe kidney, ectopic kidney, duplicated system, and those who underwent a non-lithotripsy surgical procedure with RIRS, such as Endopyelotomy.

Grouping and Measurements

The cohort was bifurcated into two distinct segments for analytical ease. The first ensemble, Group 1, encapsulated patients subject to fluoroscopy and UAS techniques. Conversely, Group 2 pooled patients who were spared these procedures. The dimensional attributes of the stones were ascertained via a trifecta of plain radiography, ultrasonography (USG), and low-dose CT, with the calculative methodologies aligned with the protocols stipulated by the European Urology Guideline. In both groups, an initial entry was made with rigid URS, advancing up to the ureteropelvic junction to check for any ureter pathology or the presence of a stone, after which either UAS or flexible URS was deployed. We meticulously cataloged a plethora of metrics ranging from demographic data, stone characteristics such as its dimensions and locational attributes, the duration of the operation, the span under fluoroscopy, the length of the hospital sojourn, the CT-determined value of the stone, the stone clearance rate, and the incidence of residual stones. In addition, we kept a vigilant tab on postoperative complications, categorizing them in alignment with the nuanced Dindo-Clavien classification. All operations routinely utilized UAS and fluoroscopy; however, based on subsequent observations that the procedural outcomes were comparable irrespective of UAS usage, my approach evolved to primarily exclude UAS, with fluoroscopy being reserved exclusively for cases necessitating UAS placement.

Preoperative and Postoperative Assessments

In the run-up to the surgical endeavor, a comprehensive urinalysis and urine culture were deemed mandatory for all subjects. Patients manifesting signs of urinary infections were earmarked for a preliminary bout of antibiotic therapy. Once cleared, the surgical intervention was given the green light. Postoperative stone evaluations employed an amalgam of direct urinary system radiography and ultrasonography. A month post the surgical foray, these parameters were again brought under the scanner via CT, followed by an extended vigil spanning two years to monitor any lurking complications.

Surgical protocol

Each surgery was prefaced with 1g of ceftriaxone IV administration, and the operations were executed under the aegis of spinal anesthesia. The surgical modus operandi for both Group 1 and Group 2 bore subtle distinctions, detailed as follows: In Group 1, the UAS technique was harnessed along with the c-arm fluoroscopy device. After this, the stone was accessed with fURS, followed by a holmium laser fragmentation. For Group 2, a similar preliminary inspection was conducted using a rigid ureteroscope. The stone location was mapped using the preoperative CT, allowing for direct observation and access. Stones were fragmented using a holmium laser (Quanta Litho® 35 w Milan, İtaly 2015) in dusting or hard stone mode (0.8- 1.2 joules, 8-12 Hz).

Statistical analysis

The statistical analysis of the study was done by SPSS (IBM Corp., Armonk, NY, USA) v25. We employed the Shapiro-Wilk test to assess the distribution patterns of our numerical data. This allowed us to determine whether our data conformed to the normal distribution or deviated from it. We utilized the Mann-Whitney U test for datasets that did not adhere to a normal distribution, as it is specifically tailored for such situations. We resorted to the Pearson chi-square and Fisher's Exact tests for our categorical data, which includes data types typically organized into distinct categories or groups. These tests are instrumental in

determining relationships or associations between categorical variables. In our analysis, a p-value (probability value) less than 0.05 was taken as the threshold for statistical significance. Furthermore, to ensure the reliability and precision of our findings, we operated within a 95% confidence interval.

RESULTS

There was no difference between the groups in terms of patient age and the stone size; the data were found to be 39.96±10.44 years, 17.98±2,02 mm in group 1, and 38.67±11.12 years, 17.53±2,47 mm in group 2, respectively. Demographic data were examined in Table 1, and no difference was found between the groups according to the gender distribution, CT value of stones (Hounsfield units), the location, and the opacity of stones. No difference was observed in the previous stone surgery, the Extracorporeal Shock Wave Lithotripsy (ESWL), and the preop DJ stent (Table 1).

Table 1. Demographic data of the patients

Parameters	Group 1 (n=165)	Group 2 (n=149)	P value
Age (years)(SD)	39.96±10.44	38.6±11.12	0.33
Gender n (%)			
Female	81 (49.09%)	76(51%)	0.77
Male	84 (50.9%)	73(49%)	
Stone size (mm) (SD)	17.98±4.15	17.53±4.63	0.22
Hounsfield Units of Stone	913.87±238.24	895.55±237.3	0.32
Location of Stones n (%)			
Upper calyx and middle calyx	20 (12.12%)	17 (11.4%)	0.93
Pelvis	113 (68.48%)	104 (69.7%)	
Lower calyx	32 (19.4%)	28 (18.9%)	
Opacity of Stones n (%)			
Opaque	156 (94.55%)	137 (92%)	0.35
Non-opaque	9 (5.45%)	12 (8%)	
History of surgery n (%)	24 (14.54%)	19 (12%)	0.66
History of ESWL n (%)	43 (26.06%)	37 (24.8%)	0.82
Preoperative DJ presence n (%)	61 (36.96%)	52 (34.89%)	0.43

Group 1: Cases with Fluoroscopy and Ureteral Access Sheath
Group 2: Cases without Fluoroscopy and Ureteral Access Sheath
n: number of the patients, BMI: body mass index, SD: standart deviation, * p<0.05 value was accepted as significant

When we look at the postoperative first-day clinical results, residue, and stone-free rates were 35.15% and 64.84% in the patients in Group 1. These rates were 28.85% and 71.14% in Group 2 (p=0.15 and p=0.7). Residual stone rates decreased from 35.15% to 23.63% in Group 1 and 28.85% to 17.44% in Group 2 one month after the procedure (p=0.123). Stone-free rates increased from 64.84% to 76.36% in Group 1 and from 71.14% to 82.55% in Group 2. (p=0.17). No s rate was changed between groups in the postoperative first month (p=0.17) (Table 2).

Table 2. Comparison of the postoperative first-day and first-month clinical results between the groups

Parameters	Group 1 (n=165)	Group 2 (n=149)	P value
Residue stone n (%)	58 (35.15%)	43 (28.85%)	0.15
Stone free n (%)	107 (64.84%)	106 (71.14%)	0.7
Parameters (1st Month)			
Residue stone n (%)	39 (23.63%)	26 (17.44%)	0.123
Stone free n (%)	126 (76.36%)	123 (82.55%)	0.17

Group 1: Cases with Fluoroscopy and Ureteral Access Sheath
Group 2: Cases without Fluoroscopy and Ureteral Access Sheath
n: number of patients. * p<0.05 value was accepted as significant

The operation duration was 26.15±5.41 minutes in Group 1 (where the ureteral access sheath and fluoroscopy were used), and the use of fluoroscopy was more extended with 58.23 ± 24.11 seconds; this duration was 20.96±5.97 minutes in Group 2, where they were not used (p=0.001) (Table 3).

There was no difference between the groups in terms of postoperative hospital stay (p=0.09) and DJ stent implantations (p=0.43) (Table 3).

Table 3. Comparison of intraoperative and postoperative data

Parameters	Group 1 (n=165)	Group 2 (n=149)	P value
Operation Duration (min)	26.15±5.41	20.96±5.97	0.001
Fluoroscopy Duration (sec)	58.23±24.11	0	0.001
Hospital Stay Duration (days)	0.98±0.23	1.03±0.2	0.09
The Presence of Postoperative DJ Stent			0.43
Yes	46 (27.87%)	41 (27.51%)	
No	119 (72.12%)	108 (72.48%)	
Ureteral stenosis			0.125
Yes	4 (2%)	0 (0.0%)	
No	160 (98%)	149 (100%)	

Group 1: Cases with Fluoroscopy and Ureteral Access Sheath
Group 2: Cases without Fluoroscopy and Ureteral Access Sheath
Sec: Seconds, Min: Minute, n: number of the patients

Postoperative complications are shown in Table 4 following the modified clavien classification. Fever requiring postoperative antipyretic treatment was observed in 21 (12.72%) patients in Group 1 and 11 (7.3%) patients in Group 2 (p=0.12). Urinary tract infections were detected in 12 (7.27%) patients in Group 1 and 7 (4.6%) patients in Group 2 (p=0.35), and they were treated with appropriate antibiotics. Steinstrasse was detected in three (1.8%) of the patients in Group 1 and four (2.6%) of the patients in Group 2, and the patients were treated with rigid ureterorenoscopy (p=0.71). Ureteral stenosis developed in 4 patients in group 1 postoperatively, one of them was treated with a DJ stent, and when the stenosis did not improve with the DJ stent, the patients were treated with open ureteroureterostomy (p=0.25). In Group 1, urosepsis was detected in one (0.6%) of the patients, and they were treated with appropriate antibiotics and DJ stent implantation (p=1) (Table 4).

Table 4. Comparison of complications of the groups according to Clavien classification

Grades	Complication	Group 1	Group 2	P value
Grade 1	Fever requiring antipyretics	21(12.72%)	11 (7.3%)	0.12
Grade 2	Urinary system infections	12(7.27%)	7(4.6%)	0.35
Grade 3a		0	0	1.0
Grade 3b	Open ureteroureterostomy due to ureteral stenosis	3 (1.8%)	0	0.25
	Rigid ureterorenoscopy due to steinstrasse	3 (1.8%)	4 (2.6%)	0.71
Grade 4a		0	0	1.0
Grade 4b	Urosepsis	1 (0.6%)	0	1.0
Grade 5		0	0	1.0

Group 1: Cases with Fluoroscopy and Ureteral Access Sheath
Group 2: Cases without Fluoroscopy and Ureteral Access Sheath

DISCUSSION

The landscape of urological interventions, particularly RIRS, is replete with advancements in technique and technology, promising more effective and safer surgeries. While commonplace, integration of tools like UAS and fluoroscopy often goes unchallenged, potentially leading us to overlook potential complications or over-reliance. The present research explores the nuanced intricacies of using UAS and fluoroscopy in RIRS, challenging established norms and setting the stage for more informed clinical choices. With this study, we not only take a step towards enriching the literature on the non-routine use of UAS and fluoroscopy but also stand as the pioneering research examining the effects of both UAS and fluoroscopy on concomitant and non-used drugs.

RIRS, PNL, and ESWL are preferred treatments for stones shorter than 2 cm.[12] The advantages of RIRS are that it is non-invasive, incurring shorter hospital stays, less bleeding, and less parenchymal damage;[13] these have made RIRS a more preferable treatment option than PNL for stones shorter than two cm.[14] In addition to such technological developments as improved image quality and increased mobility in flexible URS, the expanded surgical experience of urologists has made the operations safe and effective without using fluoroscopy and the ureteral access sheath.[7] A prospective study by Lima et al.[15] observed urosepsis in 7 of 8 patients where complications existed related to the use of UAS; pain due to stent was observed in 2 patients in the group without UAS, and there was no difference in complication rates between the groups. Damar et al.[16] found in examining the complication rates with and without the use of UAS that there was no difference between the two groups.

Many publications show that using UAS during RIRS reduces intrarenal pressure, achieving better visibility and minimizing damage to the kidney.[17] When the rates of complications were examined, they were observed to be lower in the UAS group; this was thought to be due to decreased intrarenal pelvic pressure in the UAS group. Our study did not use a basket catheter for stone extraction, so we did not need re-entry in either group. Our SFR rates were similar in both groups, as we turned the stones into dust or millimetric fragments with the painting method. Our stone-free rates in RIRS with and without ureteral access sheath were 88.48 and 82.55% upon one-month follow-up, with no difference observed between the groups. While our study observed no difference in hospital stay duration, surgery duration was shorter in the group where UAS was not used. Similarly, in the studies by Lima et al.,[15] surgery duration was shorter where UAS was not used.

Our data indicates that UAS use prolongs surgery duration and fluoroscopy duration. The reduced operation time in the non-UAS group may be attributable to the time saved during UAS placement and the time often consumed towards the end of the procedure in attempts to extract residual fragments using a basket. Recently, with the development of laser devices, stone-free rates have increased. In a study by Sari et al.,[18] stone-free rates in RIRS using a 20-watt and 30-watt laser device were higher than the stone-free rates in lithotripsy performed in dusting mode with a 30-watt device, although both devices were used at the same power and frequency. Stones are pulverized by the dusting technique or fragmented into such small pieces that they pass through the ureter without requiring extraction. Thus stone-free rates are high in RIRS performed without the access sheath. Our stone-free rates are high despite not performing stone extraction because we turn the stones into dust or millimetric fragments.

In some studies comparing the results of operations performed without fluoroscopy, no significant difference was found in stone-free rate and complication development.[10,19,20] When we compare the patient groups with and without fluoroscopy, our stone-free and complication rates show that we can perform effective surgery without fluoroscopy. Studies in the literature compare surgeries performed with and without the use of fluoroscopy alone, those performed with and without the use of UAS alone, and the results of the surgeries performed without fluoroscopy and UAS. In our standard practice, whenever UAS is employed, fluoroscopy is invariably used in conjunction; conversely, if UAS is not used, fluoroscopy is also omitted, ensuring that neither tool was utilized independently of the other. Unlike previous studies, our study compared a group in which fluoroscopy and UAS were used with a group in which neither was used.

When we compared the group in which fluoroscopy and UAS were used and the group in which neither were used, we found no difference in the rates of stone-free and major complications; we observed a higher rate of minor complications in the group in which UAS was used. We think that stone-free rates may have increased due to the experienced surgeons breaking the stones into smaller pieces and finding and breaking up possible residual stones. A urologist who frequently uses flexible ureterorenoscopy in daily practice should review UAS and fluoroscopy. Our study found that using UAS and fluoroscopy did not significantly affect success and complications. Therefore, it may be necessary to reassess whether using UAS and fluoroscopy is mandatory. Considering that successful results can be obtained without using UAS and fluoroscopy, reducing the use of these methods may be considered. However, it is essential to make an individualized assessment for each patient and situation and to consider clinical experience. However, long-term randomized controlled studies with more patients are required for more precise results.

This research breaks new ground by being the inaugural examination of the combined utilization of UAS and fluoroscopy versus their omission in RIRS surgeries. It robustly underscores the salient point that surgeons with ample experience can potentially sidestep fluoroscopy, hence mitigating associated radiation risks. An innovative approach to pulverizing stones was instrumental in achieving commendable stone-free rates, even without stone extraction. However, certain limitations are palpable. In the group where UAS was not used, periodic water evacuation was performed from within the flexible URS during the procedure to reduce kidney pressure and dust particles, resulting in no observed difference in the patients' pain levels. The groundbreaking nature of this study means there is a dearth of comparable literature to benchmark against. Furthermore, results might be intricately linked to the proficiency of the surgeons involved, raising questions about wider generalizability. The study's methodology, which eschewed using a basket catheter for stone extraction, also necessitates careful consideration. While these challenges are pertinent, it is essential to juxtapose them with the study's inherent strengths, ensuring a well-rounded understanding. As we delve deeper into these specifics, we aim to present readers with a comprehensive view of the advantages and constraints of our research. While the study undeniably propounds the rethinking of routine UAS and fluoroscopy usage in RIRS, it is prudent to acknowledge the pressing need for expansive, longitudinal research to authenticate these preliminary findings further.

CONCLUSION

The study determined similar stone-free and complication rates between groups with and without fluoroscopy and UAS, and the procedure could be performed successfully and reliably in both groups. While patients are protected from complications that may develop due to UAS, proper stone mapping with preoperative CT will eliminate the need for fluoroscopy and protect the operating team and the surgeon from the adverse effects of radiation.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the İstinye University Clinical Researches Ethics Committee (Date: 26.05.2021, Decision 2/2021.K-32).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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Original Article

MEDICINE PALLIATIVE CARE

DOI: 10.47582/jompac.1333813

J Med Palliat Care. 2023;4(5):478-484

Exploring health literacy and associated factors among individuals registered in family health centers in Batman province

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Cite this article as: Bulut Çelik S, Erten Bucaktepe PG. Exploring health literacy and associated factors among individuals registered in family health centers in Batman province. *J Med Palliat Care*. 2023;4(5):478-484.

Received: 28.07.2023 ◆ **Accepted**: 22.09.2023 ◆ **Published**: 27.10.2023

ABSTRACT

Aims: Health literacy is often defined as one's capacity to obtain, interpret, and understand basic health information and services to preserve, improve, or recover their health and their ability to make the right choices regarding their health. In this study, we attempted to explore health literacy and associated factors among individuals registered in primary health centers.

Methods: We carried out this cross-sectional study with individuals registered in family health centers in Batman province between October 2018 and March 2019. After obtaining ethical approval from the relevant ethics committee, we collected the data from the participants with a sociodemographic information form and the Turkish version of the European Health Literacy Survey Questionnaire (HLS-EU-Q).

Results: Our findings revealed that 62.3% (n=301) of the participants were females, 52.0% (n=251) held an undergraduate or higher degree, and 17.6% (n=85) had a high monthly income. The participants' mean age was 33.1±11.8 years (18-78 years), and 62.1% (n=300) were younger than 35 years. We discovered that the younger participants (p=0.003), those with higher educational attainment (p=0.001), and those without chronic disease (p=0.005) had significantly greater health literacy. Given gender and other sociodemographic characteristics demonstrating significant relationships with health literacy, our logistic regression findings also showed that income level, perceived socioeconomic and health status, and reading enjoyment had significant impacts on the participants' sufficient/excellent health literacy level.

Conclusion: Thus, the results of this research and prospective studies would further facilitate developing policies for boosting health literacy to protect public health and alleviate inequalities in accessing healthcare services.

Keywords: Health literacy, primary care, research

INTRODUCTION

Although advancements in science and technology have improved the diagnosis and treatment capacity in modern medicine, preventive medicine practices in primary care are recognized as fundamental in preventing and treating diseases.[1] In addition to environmental and genetic factors, one's health-oriented behaviors become key in preventing disorders and promoting health.[2] Moreover, healthcare systems expect individuals to undertake the responsibility of preserving their health, understanding essential medical information, and making decisions for their health to some extent, which underlines the concept of health literacy.[1]

The concept of health literacy has emerged to explain the impact of health education and communication on health outcomes.[3] It is indeed grounded on social, personal, and cognitive skills required for reading, numerical processing, problem-solving, decision-making, information seeking, and interacting to function in the healthcare system.[4] Health literacy was first coined in the 1970s and has been subjected to different definitions since then. In 2013, the World Health Organization (WHO) defined health literacy as: "Health literacy is linked to one's knowledge, motivation, and competence to access, understand, evaluate, and practice health information to make judgments and decisions regarding health care, disease prevention, and health promotion to maintain or improve their quality of life throughout their lives.".[5] Finally, it was defined in 2020 as: "Health literacy is the degree to which individuals can find, understand, and use information and services to inform themselves and others about health-related decisions."[6]

It may be essential to reveal the health literacy level in a community to improve the health of every citizen and plan an appropriate allocation of healthcare services.[7,8] In addition, an increase in community-wide health literacy is

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thought to end up with the more efficient use of healthcare services.[4,9] Besides, uncovering health literacy levels and associated factors among people may play a significant role in alleviating inequalities in accessing healthcare services.[10] Apparent societal factors (e.g., healthcare and education systems and sociocultural characteristics) are known to affect one's demand for healthcare services as well as their perceptions of and behaviors about their health, highlighting an evident need for efforts to contribute to individuals' health literacy.[11] Therefore, the present study attempted to explore health literacy and associated factors among individuals registered in primary family health centers in Batman province. Thus, we think that new health policies can be developed for more efficient use of healthcare services by revealing the levels of health literacy among people and related factors.

METHODS

The study was carried out with the permission of the Batman Province Public Hospital Clinical Researches Ethics Committee (Date: 13.06.2018, Decision No: 111). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

We carried out this cross-sectional study with individuals registered in family health centers in Batman province between October 2018 and March 2019. According to TUIK 2017 data, 411251 (206665 male, 204586 female) people older than 18 years reside in the center of Batman Province (www.tuik.gov.tr) and this population had been taken into consideration for sample size. Using the G*Power 3.1.9.7 program, we calculated the minimum sample size to be attained as 220 at a 95% confidence interval (CI) and type I error level of 0.05 within a Batman-based population older than 18 years. In calculating the sample size, since health literacy was mostly evaluated by dividing into groups according to literacy levels in previous studies, the chi-square test as a proportion-based statistical method and the medium effect size in more than two groups were taken into account. Stratified random sampling method according to age, gender, income and social status, was used in the selection of the sample. Accordingly, we recruited 483 participants for the study upon obtaining their written and verbal consent. Persons who were literate, had no mental problems that could affect their understanding or perception of reality, and agreed to fill out the questionnaire were included in the study.

Then, we collected the data using a sociodemographic information form covering questions about participants' sociodemographic characteristics, general health status, and use of healthcare institutions and the Turkish version of the European Health Literacy Survey Questionnaire (HLS-EU-Q).[2]

We grouped the participants' ages and categorized their reading enjoyment and perceived socioeconomic status (SES) scored between 1-10. Moreover, we calculated their body mass indexes (BMI) by dividing their body weights in kilograms by the square of their heights in meters and categorized BMIs as normal-underweight (<25.0) and overweight-obese (≥25.0).

The European Health Literacy Project Consortium designed the HLS-EU-Q as a self-report instrument to assess people's health literacy levels.[12] In their study, Abacıgil et al. explored the validity and reliability of the HLS-EU-Q in the Turkish context and reported the internal consistency of the scale (Cronbach's α) to be 0.95.[13,14] In this study, the internal consistency coefficient of the scale was calculated as 0.968 (quite reliable). The 4-point Likert-type instrument (1=Very difficult, 4=Very easy) consists of 47 items within three subscales (health care, disease prevention, and health promotion). Whereas one can obtain a minimum of 47 points and a maximum of 188 points, we standardized the total score between 0 (lowest health literacy) and 50 (highest health literacy) points, as in the original study, for ease of calculation using the following formula:

Index=[mean score-1 (lowest possible value of the mean)] × [50/3 (range of mean score)]

Accordingly, we evaluated the participants' health literacy levels in the following four categories by their HLS-EU-Q scores:

- 0-25: insufficient health literacy
- >25-33: problematic/restricted health literacy
- >33-42: sufficient health literacy
- >42-50: excellent health literacy

While presenting continuous variables as means (M) and standard deviations (SD), we demonstrate categorical variables as numbers (n) and percentages (%). A series of chi-square tests were performed to compare participants' health literacy levels by their sociodemographic characteristics. We dichotomized the four categories of health literacy as insufficient/problematic health literacy and sufficient/excellent health literacy and performed a multivariate binary logistic regression analysis to the variables with statistically significance level of $p < 0.25$ in univariate analyses to uncover the predictors of sufficient/excellent health literacy. We analyzed the data using SPSS 26.0 (IBM Corp., Armonk, NY, USA) Program and accepted a p-value of <0.05 as statistically significant.

RESULTS

We found that 62.3% (n=301) of the participants were females, 52.0% (n=251) held an undergraduate or higher degree, and 17.6% (n=85) had a high monthly income.

The participants' mean age was 33.1±11.8 years (18-78 years), and 62.1% (n=300) were younger than 35 years. The participants' sociodemographic characteristics are presented in Table 1. While 190 participants (39.4%) perceived their SES as good, the rate of those perceiving their health status as excellent was 23.8% (n=115). Besides, 136 (28.2%) reported receiving assistance while reading and writing, and 70 (14.5%) had no reading habit.

When it comes to the participants' scores on the HLS-EU-Q, we found that while 41.8% (n=202) of the participants had insufficient/problematic health literacy, 38.7% (n=187) had sufficient/excellent health literacy (sufficient health literacy with 26.1% (n=126) and excellent health literacy with 12.6% (n=61); Table 2). Our findings demonstrated that the younger participants (p=0.003), those with higher educational attainment (p=0.001), and those without chronic disease (p=0.005) had significantly greater health literacy (Table 3). Moreover, we found significantly higher health literacy levels in those with high perceived SES (p<0.001), those with high reading enjoyment (p<0.001), those with a reading habit (p=0.001), and those with excellent perceived health (p<0.001; Table 3 and Table 4).

Table 2. Participants' scores on the HLS-EU-Q and its subscales

Scores	M±SD	Insufficient n (%)	Problematic n (%)	Sufficient n (%)	Excellent n (%)
Health care	33.1±8.5	79 (16.4)	157 (32.5)	171 (35.4)	76 (15.7)
Disease prevention	33.3±9.7	105 (21.7)	172 (35.6)	135 (28.0)	71 (14.7)
Health promotion	30.4±10.0	146 (30.2)	134 (27.7)	143 (29.6)	60 (12.4)
Total score	31.6±8.7	94 (19.5)	202 (41.8)	126 (26.1)	61 (12.6)

Considering gender and other sociodemographic characteristics that yielded significant results in univariate analyses, our regression results also showed that income level, perceived SES and health status, and reading enjoyment had significant effects on the participants' sufficient/excellent health literacy level (Table 5). Accordingly, sufficient/excellent health literacy was nearly twice as high for those with monthly income surpassing their expenditures than those without (Odds Ratio (OR)=1.925; 95% CI=1.052-3.521; p=0.034), 2.5 times as high for those with excellent perceived health than those with bad perceived health (OR=2.564; 95% CI=1.384-4.751; p=0.003), twice as high for those with high perceived SES than those with low perceived SES (OR=2.016; 95% CI=1.154-3.525; p=0.014), and twice as high for those with moderate reading enjoyment (OR=2.244; 95% CI=1.090-3.758; p=0.026) and 2.1 as high for those with high reading enjoyment (OR=2.143, 95% CI=1.158-3.966; p=0.015) compared to those with poor reading enjoyment.

Table 1. Participants' sociodemographic characteristics

Characteristics	n	%	M±SD
Gender			
Male	182	37.7%	
Female	301	62.3%	
Age (years)			33.1±11.8 (18-78)
18-24	123	25.5%	
25-34	177	36.6%	
35-44	109	22.6%	
45-54	44	9.1%	
≥55	30	6.2%	
Educational attainment			
High school and below	232	48.0%	
Undergraduate and above	251	52.0%	
Marital status			
Married	291	60.2%	
Unmarried	251	39.8%	
Place of residence (the longest time)			
Village/Town	38	7.9%	
City	381	78.9%	
Metropolitan city	64	13.3%	
Occupation			
Civil servant	220	45.5%	
Student	80	16.6%	
Other	183	37.9%	
Household income			
Income < Expenditures	159	32.9%	
Income=Expenditures	239	49.5%	
Income > Expenditures	85	17.6%	
BMI			24.4±4.3
< 25.0	303	62.7%	
≥ 25.0	180	37.3%	
Chronic disease			
Yes	84	17.4%	
No	399	82.6%	
Number of households			4.9±2.4 (1-17)
1-3	149	30.8%	
6-7	186	38.6%	
8-10	148	30.6%	
Health insurance			
No or Green Card	59	12.2%	
Yes	424	87.8%	
Perceived social status (1 to 10)			6.8±2.0
1-5	132	27.3%	
6-7	161	33.3%	
8-10	190	39.4%	
Receiving assistance while reading and writing			
Sometimes/Always	136	28.2%	
Seldom/Never	347	71.8%	
Reading enjoyment (1 to 10)			6.5±2.8
1-4	121	25.1%	
5-7	163	33.7%	
8-10	199	41.2%	
Frequency of reading			
Never	70	14.5%	
Sometimes/Frequently	413	85.5%	
Perceived health status			
Excellent	115	23.8%	
Good/Fair	229	47.4%	
Bad	139	28.8%	
The most trusted source of health information			
Healthcare workers	335	69.4%	
Other	148	30.6%	
Preliminary healthcare provider			
Family health centers	164	34.0%	
State hospitals	185	38.3%	
Private hospitals	134	27.7%	
Frequency of application to health institutions			
≤1 per month	405	83.9%	
>1 per month	78	16.1%	

Table 3. Participants' scores on the HLS-EU-Q and its subscales by their sociodemographic characteristics

Sociodemographic characteristics	HL Score M±SD	Insufficient n (%)	Problematic n (%)	Sufficient n (%)	Excellent n (%)	p*
Gender						0.610
Male	31.8±8.8	30 (16.5)	78 (42.9)	51 (28.0)	23 (12.6)	
Female	31.5±8.6	64 (71.3)	124 (41.2)	75 (24.9)	38 (12.6)	
Age (years)						0.003
18-24	32.0±7.7	20 (16.3)	54 843.9)	36 (29.3)	13 (10.6)	
25-34	32.4±8.4	27 (15.3)	75 (42.4)	50 (28.2)	25 (14.1)	
35-44	32.2±9.2	22 (20.2)	45 (41.3)	24 (22.0)	18 (16.5)	
45-54	29.8±9.2	9 (20.5)	19 (43.2)	13 (29.5)	3 (6.8)	
≥ 55	25.6±9.6	16 (53.3)	9 (30.0)	3 (10.0)	2 (6.7)	
Educational attainment						0.001
High school or below	30.1±8.4	55 (23.7)	97 (42.7)	62 (26.7)	16 (6.9)	
Undergraduate or above	33.0±8.8	39 (15.5)	103 (41.0)	64 (85.5)	45 (17.9)	
Marital status						0.503
Married	31.1±9.1	63 (21.6)	120 (41.2)	73 (25.1)	35 (12.0)	
Unmarried	32.4±8.0	31 (16.1)	82 (42.7)	53 (27.69)	26 (13.5)	
Place of residence (the longest time)						0.077
Village/Town	28.1±8.3	12 (31.6)	17 (44.7)	9 (23.7)	0 (0%)	
City	31.7±8.7	73 (19.2)	161 (42.3)	95 (24.9)	52 (13.6)	
Metropolitan city	33.0±8.3	9 (14.1)	24 (37.5)	22 (34.4)	9 (14.1)	
Occupation						0.076
Civil servant	32.8±8.8	36 (16.4)	86 (39.1)	60 (27.3)	38 (17.3)	
Student	31.5±7.2	14 (17.59	38 (47.5)	21 (26.3)	7 (8.8)	
Other	30.2±9.0	44 (24.0)	78 (42.6)	45 (24.6)	16 (8.7)	
Household income						0.131
Income < Expenditures	30.0±9.0	36 (22.6)	71 (44.7)	38 (23.9)	14 (8.8)	
Income=Expenditures	31.8±8.5	46 (19.2)	102 (42.7)	59 (24.7)	32 (13.4)	
Income > Expenditures	34.1±8.2	12 (14.1)	29 (34.1)	29 (34.1)	15 (17.6)	
BMI						0.061
< 25.0	32.3±8.5	49 (16.2)	127 (41.9)	83 (27.4)	44 (14.5)	
≥ 25	30.4±8.9	45 (25.0)	75 (41.7)	43 (23.9)	17 (9.4)	
Chronic disease						0.005
Yes	28.5±9.9	27 (32.1)	35 (41.7)	14 (16.7)	8 (9.5)	
No	32.2±8.3	67 (16.8)	167 (41.9)	112 (28.1)	53 (13.3)	
Number of households						0.478
1-3	32.1±8.9	30 (20.1)	60 (40.3)	36 (24.2)	23 (15.4)	
4-5	32.4±8.3	30 (16.1)	82 (44.1)	49 (26.3)	25 (13.4)	
≥ 6	30.2±8.9	34 (23.0)	60 (40.5)	41 (27.7)	13 (8.8)	
Health insurance						0.511
No/Green Card	30.3±10.7	15 (25.4)	20 (33.9)	16 (27.1)	8 (13.6)	
Yes	31.8±8.4	79 (18.6)	182 (42.7)	110 (25.9)	53 (12.5)	

* χ 2 test used

Table 4. Participants' scores on the HLS-EU-Q and its subscales by their sociodemographic characteristics

Sociodemographic characteristics	HL Score M±SD	Inadequate n (%)	Problematic n (%)	Sufficient n (%)	Excellent n (%)	p*
Perceived social status						<0.001
1-5	27.8±9.9	46 (34.8)	56 (42.4)	18 (13.6)	12 (9.1)	
6-7	31.9±7.2	27 (16.8	70 (43.5)	50 (31.1)	14 (8.7)	
8-10	34.0±8.0	21 (11.1)	76 (40.0)	58 (30.5)	35 (18.4)	
Receiving assistance while reading and writing						0.927
Sometimes/ always	31.7±8.6	27 (19.9)	55 (40.4)	38 (27.9)	16 (11.8)	
Seldom/ never	31.6±8.7	67 (19.3)	147 (42.4)	88 (25.4)	45 (13.0)	
Reading enjoyment						<0.001
1-4	28.2±8.9	37 (30.6)	55 (45.5)	22 (18.2)	7 (5.8)	
5-7	32.1±7.3	25 (15.3)	71 (43.6)	51 (31.3)	16 (9.8)	
8-10	33.2±9.1	32 (16.1)	76 (38.2)	53 (26.1)	38 (19.1)	
Frequency of reading						0.001
Never	27.3±9.4	25 (35.7)	28 (40.0)	14 (20.0)	3 (4.3)	
Sometimes/ Frequently	32.3±8.4	69 (16.7)	174 (42.1)	112 (27.2)	58 (14.0)	
Perceived health status						<0.001
Excellent	34.1±7.7	15 (13.0)	37 (32.2)	43 (37.4)	20 (17.4)	
Good/Fair	31.9±7.8	37 (16.2)	104 (45.4)	63 (27.5)	25 (10.9)	
Bad	29.1±10.0	42 (30.2)	61 (43.9)	20 (14.4)	16 (11.5)	
The most trusted source of health information						0.479
Healthcare workers	31.8±8.7	59 (17.6)	142 (42.4)	90 (26.9)	44 (13.1)	
Other	31.2±8.7	35 (23.6)	60 (40.5)	36 (24.3)	17 (11.5)	
Preliminary healthcare provider						0.943
Family health centers	31.7±8.8	33 (20.1)	67 (40.9)	43 (26.2)	21 (12.8)	
State hospitals	31.8±8.9	32 (17.3)	77 (41.6)	52 (28.1)	24 (13.0)	
Private hospitals	31.1±8.4	29 (21.6)	58 (43.3)	31 (23.1)	16 (11.9)	
Frequency of application to health institutions						0.124
≤1 per month	32.1±8.4	72 (17.8)	169 (41.7)	110 (27.2)	50 (13.3)	
>1 per month	28.9±9.7	22 (28.2)	33 (42.3)	16 (20.5)	7 (9.0)	

* χ 2 test used

Table 5. Multivariate logistic regression analysis for predictors of sufficient/excellent health literacy

HLS-EU-Q Scores	B (SE)	Wald	AOR	95% CI	p*
Gender					
Male			1		
Female	0.035 (0.232)	0.023	1.036	0.657-1.634	0.879
Age (years)					
18-24			1		
25-34	-0.260 (0.341)	0.582	0.771	0.395-1.504	0.446
35-44	-0.286 (0.385)	0.554	0.751	0.353-1.597	0.457
45-54	-0.112 (0.483)	0.054	0.894	0.347-2.303	0.816
≥55	-0.456 (0.642)	0.505	0.634	0.180-2.230	0.477
Educational attainment					
High school and below			1		
Undergraduate and above	-0.039 (0.272)	0.021	0.961	0.564-1.640	0.085
Occupation					
Civil servant			1		
Student	-0.585 (0.425)	1.894	0.557	0.242-1.282	0.169
Other	-0.126 (0.259)	0.237	0.881	0.530-1.466	0.627
Place of residence (the longest time)					
Village/Town			1		
City	0.534 (0.447)	1.429	1.706	0.711-4.094	0.232
Metropolitan city	0.817 (0.512)	2.543	2.263	0.829-6.177	0.111
Household income					
Income < Expenditures			1		
Income=Expenditures	0.138 (0.231)	0.355	1.148	0.730-1.805	0.551
Income > Expenditures	0.655 (0.308)	4.515	1.925	1.052-3.521	0.034
Perceived health status					
Bad			1		
Good/Fair	0.217 (0.269)	0.650	1.242	0.733-2.106	0.420
Excellent	0.942 (0.315)	8.958	2.564	1.384-4,751	0.003
BMI					
< 25.0			1		
≥ 25.0	-0.215 (0.246)	0.762	0.807	0.498-1.307	0.383
Chronic disease					
Yes			1		
No	0.195 (0.333)	0.342	1.215	0.633-2.332	0.559
Frequency of application to health institutions					
≤1 per month			1		
>1 per month	0.016 (0.301)	0.003	1.016	0.563-1.835	0.957
Perceived social status					
1-5			1		
6-7	0.395 (0.286)	1.905	1.485	0.847-2.602	0.168
8-10	0.701 (0.285)	6.057	2.016	1.154-3.525	0.014
Frequency of reading					
Never			1		
Sometimes/Frequently	-0.094 (0.369)	0.065	0.910	0.442-1.875	0.798
Reading enjoyment					
1-4			1		
5-7	0.705 (0.316)	4.983	2.024	1.090-3.758	0.026
8-10	0.762 (0.314)	5.893	2.143	1.158-3.966	0.015
Model (χ2(22), p)	59.281, p < 0.001				
Hosmer-Lemeshow Test, p	0.251				
Nagelkerke, R2	15.7%				
Classified cases (%)	67.3%				

*Binary logistic regression analysis; AOR: Adjusted Odds Ratio; CI: Confidence Interval; SE: Standard Error

DISCUSSION

The 2014 Türkiye Health Literacy Survey revealed that only one-third of the population had sufficient or excellent health literacy. In the same survey, health literacy was found to be significantly lower in women and those older than 65 years, and there was an inverse correlation between health literacy and age and education level.[16] The findings of a study in primary health centers in Bursa suggested that the rate of those with sufficient health literacy varied between 28.1% and 58.7% by the instrument used, that the most prominent sociodemographic characteristics associated with health literacy became education, that vocabulary and reading skills were more effective factors in health literacy than numerical skills, and that those scoring the lowest in health literacy were women, primary school graduates, low-gainers, and older adults.[27] A previous study in Edirne concluded positive correlations between health literacy and educational attainment, the number of books read per year, the number of newspapers read per week, and monthly income.[8] In another study, the researchers found that low-income patients were able to understand drug leaflets and leaflets about their diseases less.[28] A Portugal-based study in primary health centers suggested that high health literacy is associated with better education and income.[29] Similarly, health literacy was previously found to be higher in participants with a higher income level.[30] In our study, we discovered that the participants with a monthly income surpassing their expenditures had about twice the level of health literacy compared to those with a low monthly income, which may be since those with a higher income level are likely to enjoy more opportunities to access health-related information and services. In this regard, relevant state bodies may consider deploying efforts to promote health literacy in society and ensure equal health-related conditions for every citizen.

It is known that the majority of deaths of all ages worldwide are due to chronic diseases. Failure to comply with healthy living principles and practices facilitates the development of various chronic diseases. Substantial evidence underlined that insufficient health literacy is associated with poor health outcomes, adverse health behavior, and increased costs in chronic diseases.[31] Besides, health literacy is closely related to protection from modifiable risk factors and non-communicable conditions.[17] In our study, we discovered that the younger participants, those with higher educational attainment, and those without chronic disease had significantly greater health literacy. Thus, higher health literacy is thought to contribute to the general health status of society and help cut the expenditures for chronic diseases.

CONCLUSION

In a nutshell, we deem it necessary to reveal health literacy levels and associated factors among individuals for the sake of promoting a contemporary understanding of health to protect and improve health across the world. Moreover, relevant state bodies are recommended to introduce policies to improve health literacy levels in Turkish society to maintain public health and improve inequalities in accessing healthcare services.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the Batman Province Public Hospital Clinical Researches Ethics Committee (Date: 13.06.2018, Decision No: 111).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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Original Article

MEDICINE PALLIATIVE CARE

DOI: 10.47582/jompac.1350661

J Med Palliat Care. 2023;4(5):485-491

The effect of maximum tumor diameter and 18F-FDG PET/CT imaging status on overall survival in Hodgkin lymphoma patients

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Cite this article as: Gürsoy V, Göktuğ MR, Hunutlu FÇ, et al. The effect of maximum tumor diameter and 18F-FDG PET/CT imaging status on overall survival in Hodgkin lymphoma patients. *J Med Palliat Care*. 2023;4(5):485-491.

Received: 27.08.2023 ◆ **Accepted**: 25.09.2023 ◆ **Published**: 27.10.2023

ABSTRACT

Aims: This research aims to determine the impact of maximum tumor diameter and FDG PET CT status at the time of diagnosis on survival outcomes and to identify prognostic factors that influence treatment response and survival.

Methods: 239 patients with a diagnosis of Hodgkin lymphoma participated in the study. Clinical characteristics, treatment responses, and prognostic factors influencing survival were retrospectively analyzed from patient medical records.

Results: There were 136 (56.9%) male patients and 103 (43.1%) female patients, who participated in the study. Of these patients, 202 (84.5%) survived, while 37 (15.5%) died during the study period. When surviving patients and non-survivor patients were compared, the deceased patients had a higher mean age (p=0.003), a higher prevalence of spleen involvement and B symptoms (p=0.011 and p=0.001, respectively), lower albumin levels (p=0.008), higher beta-2 microglobulin levels (p=0.001), and more bone marrow involvement (p=0.006). A fourfold increase in mortality was seen in patients with beta-2 microglobulin levels >2920 mg/L, and a 3.188-fold increase in mortality was seen in patients with spleen involvement.

Conclusion: In conclusion, beta-2 microglobulin >2920 mg/L, the presence of spleen involvement, the presence of relapse, and the presence of progressive or refractory disease in FDG PET CT were significant prognostic factors for 1st, 3rd, and 5th-year survival rates in patients with Hodgkin lymphoma. In addition, there was no correlation between survival rate and maximum tumor diameter as measured by FDG-PET or CT.

Keywords: Hodgkin lymphoma, clinical indicators, prognostic factors, FDG PET CT

INTRODUCTION

Hodgkin lymphoma (HL) is a B-cell lymphoma that accounts for 10%-15% of all lymphomas. It has a bimodal age distribution in the 3rd and 6th decades. HL is one of the most common malignancies in young adults and one of the best-treated cancers, with a cure rate of 90%.[1,2] Current treatment options for HL include chemotherapy and radiotherapy regimens, depending on the stage of the disease. A high cure rate in early-stage Hodgkin lymphoma (HL) is a big step forward in hemato-oncology.[3] But late side effects of treatment may put long-term disease free survival (DFS) and health at risk.[4] Individualized approaches to treatment become more important. [18F]-fluorodeoxy-D-glucose positron emission tomography (FDG-PET/CT) is an imaging system that can be used to demonstrate the metabolic activity of a tumor. Therefore, it is used to evaluate the response to treatment during HL treatment. As one of the first applications of personalized medicine, PET-guided approaches have been tested and successfully implemented in HL clinical practice. FDG-PET/CT is commonly used to monitor treatment response in HL patients. In HL, the early treatment response measured by [18F]-fluorodeoxyglucose (FDG) positron emission tomography (PET) has become a potent indicator of prognosis.[5] Pet-guided treatments in Hodgkin lymphoma have become widely accepted after prospective studies with a large number of patients and a high level of evidence have been conducted on this subject.[6,7] However, the relationship between FDG-PET/CT maximum standardized uptake value (SUVmax) and treatment response or overall survival values is not clear in the literature. For the majority of patients, who achieved a complete

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response following treatment, neither clinical status nor imaging techniques alone accurately predicted disease relapse and survival.[8,9] There is a need for research on additional biomarkers that influence survival and treatment response. In the era of PET-adapted therapy, uncertainty still surrounds the prognostic significance of tumor volume in the HL. Treatment response and disease overall survival in Hodgkin lymphoma patients are thought to be related to maximum tumor diameter and maximum FDG PET-CT SUV uptake at the time of diagnosis.[10,11] The purpose of this study is to assess the prognostic factors influencing treatment response and survival, as well as to demonstrate the effects of maximum tumor diameter and FDG PET CT status at the time of diagnosis on survival outcomes.

METHODS

This retrospective study was carried out with the permission of the Uludağ University Faculty of Medicine Clinical Researches Ethics Committee (Date: 19.02.2020, Decision No: 2020-3/8). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study included 239 patients, who presented to the Adult Hematology Outpatient Clinic between January 2010 and January 2020 with a diagnosis of Hodgkin lymphoma. Patients' archived medical records were retrospectively analyzed for epidemiological information, clinical characteristics, treatment responses, and prognostic factors influencing survival. The birth date, disease onset age, disease duration, clinical findings, and biochemical results of each patient were evaluated. The maximum tumor diameter and SUVmax values at the time of diagnosis were determined by analyzing the system's stored radiological images. Patients with missing information were excluded from the study.

Statistical analysis

SPSS 25.0 (IBM Corporation, Armonk, New York, United States) and Medcalc 14 (Acacialaan 22, B-8400 Ostend, Belgium) programs were used to analyze the variables. The conformity of the data to the normal distribution was evaluated with the Shapiro-Wilk Francia test, while the homogeneity of variance was evaluated with the Levene test. In the comparison of two groups according to quantitative variables, the Mann Whitney U test, one of the non-parametric tests, was tested using Monte Carlo simulation results, while the Independent Two Samples T test, one of the parametric methods, was tested using the Boostrap method. The Pearson Chi-Square, Fisher Exact, and Fisher Freeman Halton tests were used to compare categorical variables using the Monte Carlo Simulation technique.The resulting categorical variables were compared in Kaplan Meier (log rank) analysis. Variables with $p<0.10$ in Kaplan Meier analysis were taken and modeled using the backward elimination method in Cox regression analysis. The variables were analyzed at a 95% confidence level, and a p-value of less than 0.05 was considered significant. Quantitative variables were expressed as mean (standard deviation) and median (minimum/maximum) in the tables, while categorical variables were shown as n (%).

RESULTS

There were 136 (56.9%) male patients and 103 (43.1%) female patients, who reviewed retrospectively. The mean age of the patients was 41.53±15.9. Of the patients, 202 (84.5%) survived, while 37 (15.5%) died during the study period. In total, 126 (55.3%) of the patients had the nodular sclerosis subtype of Hodgkin lymphoma, while 40 (17.5%) had the mixed cellular variant. Only 26 patients (11.1%) had involvement in the spleen and 15 patients (6.5%) had bulky disease. Only 19 (12.8%) of the patients had bone marrow involvement, and only 19 (7.9%) of the patients had comorbidities. Chemotherapy treatment was applied to every patient, but only 26 patients (11.6%) received radiotherapy. **Table 1** shows the regions of lymph node involvement based on FDG-PET CT and CT scans, along with the distribution of clinical status following treatment. The patients participating in the study were receiving similar treatments.

Table 2 shows the findings of the routine blood tests and disease datasets that were performed on the patients. CT analysis confirmed a maximum tumor diameter of 38.93±20.97 millimeters. The patients were monitored for a total of 69.12±44.25 months during the follow-up period. When the surviving patients and the patients who died were compared, the dead patients had a higher mean age (p=0.003), a greater prevalence of spleen involvement and B symptoms (p=0.011 and p=0.001, respectively), lower albumin levels (p=0.008), higher beta-2 microglobulin levels (p=0.001), and greater bone marrow involvement (p=0.006). In addition, the deceased patients had a lower mean albumin level In addition, the FDG PET CT evaluation after treatment revealed significant differences between the two groups in terms of the progression or refractoriness of the disease, as well as partial and complete response. There was no statistical difference between maximum tumor diameter in FDG PET CT or CT (**Table 3**).

Table 1. Baseline characteristics of patients with Hodgkin lymphoma

	n (%)
Mortality	
Alive	202 (84.5)
Exitus	37 (15.5)
Gender	
Male	136 (56.9)
Female	103 (43.1)
Hodgkin Lymphoma Subtype	
Lymphocyte-Rich	15 (6.6)
Nodular Sclerosis	126 (55.3)
Classical	33 (14.5)
Mix Cellular	40 (17.5)
Nodular Lymphocyte Predominant	11 (4.8)
Lymphocyte Depleted	3 (1.3)
Extralymphatic involvement	
Absent	209 (88.9)
Present	26 (11.1)
Spleen involvement	
Absent	193 (83.5)
Present	38 (16.5)
Bulky Disease	
Absent	216 (93.5)
Present	15 (6.5)
B Symptoms	
Absent	127 (55)
Present	104 (45)
Co-morbidity	
Absent	220 (92.1)
Present	19 (7.9)
Major involvement region in PET-CT	
Cervical region	54 (46.6)
Mediastinum	40 (34.5)
Abdominal	5 (4.3)
Pelvic and inguinal	7 (6)
Bone	2 (1.7)
Axilla	8 (6.9)
Major involvement region in CT	
Cervical region	40 (49.4)
Mediastinum	19 (23.5)
Abdominal	8 (9.9)
Pelvic and inguinal	10 (12.3)
Axilla	4 (4.9)
Bone marrow involvement	
Absent	130 (87.2)
Present	19 (12.8)
Radiotherapy	
Not performed	198 (88.4)
Performed	26 (11.6)
PET-CT Results after treatment	
Progressive or refractory disease	25 (11.4)
Partial response	5 (2.3)
Complete response	188 (85.5)
Unknown	2 (0.9)
Relapse	
Present	66 (30.6)
Absent	150 (69.4)

Table 2. Blood routine examination and disases indexes of patients with Hodgkin lymphoma

	Mean (SD.)	Median (min-max)
Age	41.53 (15.9)	39 (18-82)
White blood cell	10569.97 (6511.93)	9140 (1100-38800)
Lymphocyte	2114.01 (1452.76)	1910 (207-17700)
Monocyte	739.35 (475.65)	616 (10-3520)
Hemoglobin	12.23 (2.05)	12.3 (5.7-17.6)
Albumin g/dl	4.05 (0.51)	4.15 (2-5.1)
Lactate dehydrogenase	229.74 (84.72)	204 (118-587)
Beta 2 microglobulin	2382.9 (1237.27)	2011 (702-8330)
Erythrocyte sedimentation rate	44.48 (32.24)	38 (2-120)
Creatinin	0.76 (0.27)	0.71 (0.4-3.6)
Maximum tumor diameter in FDG PET CT	37.08 (30.46)	18.9 (10.2-99)
Maximum tumor diameter in CT	38.93 (20.97)	31 (13-130)
Chemotherapy session count	6.33 (1.78)	6 (2-12)
Follow up duration (Month)	69.12 (44.25)	67 (1-364)

SD.:Standart deviation, min:minimum, max: Maximum

The cut-off values were determined between the statistically significant numerical values (age, beta-2 microglobulin, albumin) between both groups. These cut-off values were >47 for age, 2920 mg/L for beta-2 microglobulin, and 3.6 for albumin. Considering the diagnostic accuracy of these cut-off values, it was 0.647 for albumin for age and 0.649 for beta-2 microglobulin (AUC). (**Table 4**). **Table 5** provides an analysis of survival based on patient and disease variables. Age ≤47 years, an albumin value >3.6, beta-2 microglobulin values ≤2920 mg/L, absence of spleen, the absence of B symptoms, the absence of bone marrow involvement, the presence of a complete response, and the absence of relapse were statistically associated with increased life expectancy. The stages of the patients were examined at the time of diagnosis. At the time of diagnosis, the stages were evaluated as favorable, unfavorable and advanced. The survival rate of patients in the advanced stage was significantly lower. (p <0.001). Those with beta-2 microglobulin levels >2920 mg/L had a fourfold higher mortality rate than those with beta-2 microglobulin levels greater than >2920 mg/L. Those with spleen involvement had a 3.188-fold higher mortality rate. The mortality odds ratio for each subgroup appeared to be less than one at the end of the treatment period, indicating a protective factor. When compared to those who progress, those who had a complete response after treatment had a 7.8 times higher mortality rate (**Table 6**).

Table 3. The effect of the disease and patients' charecteristics in terms of living status

	Alive (n=202)	Exitus (n=37)	p
Age, median (min/max)	36.5 (18/82)	50 (19/79)	0.003[u]
Gender (Female), n (%)	90 (44.6)	13 (35.1)	0.367[c]
Hodgkin lymphomca subtype, n (%)			0.943[ff]
Lymphocyte-Rich	14 (7.3)	1 (2.7)	
Nodular Sclerosis	104 (54.5)	22 (59.5)	
Classical	28 (14.7)	5 (13.5)	
Mix Cellular	33 (17.3)	7 (18.9)	
Nodular lymphoycte predominant	9 (4.7)	2 (5.4)	
Lymphocye Depleted	3 (1.6)	0 (0)	
Presence of extralymphatic involvement,n(%)	20 (10)	6 (17.6)	0.232[f]
Presence of spleen involvement, n (%)	27 (13.7)	11 (32.4)	0.011[c]
Presence of Bulky Mass, n (%)	13 (6.6)	2 (5.9)	0.999[f]
Presence of B symptoms, n (%)	80 (40.6)	24 (70.6)	0.001[c]
Iliac and inguinal lymph node involvement , n (%)			0.553[ff]
Absent	168 (85.3)	29 (85.3)	
Iliac and inguinal lymph node involvement	6 (3)	2 (5.9)	
Iliac involvement	8 (4.1)	0 (0)	
Inguinal involvement	15 (7.6)	3 (8.8)	
Co-morbidity, n (%)	15 (7.4)	4 (10.8)	0.507[f]
White blood cell count, median (min/max)	9085 (1380/38800)	10300 (1100/27280)	0.734[u]
Lymphocyte, median (min/max)	1910 (277/17700)	1830 (207/6180)	0.584[u]
Monocyte, median (min/max)	607 (10/3520)	661.5 (177/1840)	0.598[u]
Hemoglobin, mean (SD.)	12.3 (2.08)	11.84 (1.78)	0.215[t]
Albumin, median (min/max)	4.2 (2/5.1)	4 (2.4/4.6)	0.008[u]
Lactate dehydrogenase, median (min/max)	202.5 (118/587)	216 (153/549)	0.193[u]
Beta 2-microglobulin, median (min/max)	1948.5 (702/8330)	3053 (1323/5206)	0.001[u]
Eritrocyte sedimantation rate, median (min/max)	39 (2/120)	32.5 (2/105)	0.597[u]
Creatinin, median (min/max)	0.7 (0.4/2.11)	0.79 (0.49/3.6)	0.217[u]
Max tumor diameter in FDG PET CT (mm), median (min/max)	18.1 (10.2/99)	25 (11/98)	0.383[u]
Max tumor diameter inCT (mm), median (min/max)	31.5 (15/130)	28 (13/100)	0.688[u]
Bone marrow involvement, n (%)			0.006[f]
Absent	112 (91.1)	18 (69.2)	
Present	11 (8.9)	8 (30.8)	
Chemotherapy session count	6 (2/12)	8 (2/8)	0.107[u]
Radiotherapy administration , n (%)	24 (12.6)	2 (5.9)	0.385[f]
FDG PET CT after treatment, n (%)			0.001[ff]
Progressive/Refractory disease	16 (8.5)	9 (29)	
Partial response	3 (1.6)	2 (6.5)	
Complete response	169 (89.4)	19 (61.3)	
Unknown	1 (0.5)	1 (3.2)	
Relaps presence, n (%)	40 (21.6)	26 (83.9)	<0.001[c]
Systemic Inflamatory Response Index (SIRI)	209.66 (1.02/6679.78)	190.71 (41.83/2239.11)	0.944[u]
Systemic Inflamatory Index (SII)	86.58 (0.04/3473.48)	104.51 (11.84/1638.41)	0.458[u]

[u] Mann Whitney-U Test (Monte Carlo), [c] Chi Square Test (Monte Carlo), [ff] Fisher Freeman Halton Test (Monte Carlo), [f] Fisher Exact Test (Monte Carlo), [t] Independent Two Samples T Test (Boostrap), SD.:Standard Deviation, min: Minimum, max: Maximum

Table 4. Determination of cut-off values for predicting mortality according to Age, Albumin and Beta 2 microglobulin variables

Reference: Exitus	Cut off	Sensitivity	Specificity	+PPV	-PPV	AUC±SE.	P Value
Age	>47	59.46	67.33	25	90.1	0.647±0.054	0.007
Albumin g/dl	≤ 3.6	41.94	85.56	32.5	89.9	0.649±0.053	0.005
Beta 2 Microbulin mg/L	>2920	61.9	85.06	36.1	94.2	0.714±0.068	0.002

ROC (Receiver Operating Curve) Analysis (Honley&Mc Nell-Youden index J), AUC: Area under the ROC curve, SE: Standard Error, +PV: Positive Predictive Value, -PV: Negative Predictive Value

Table 5. Survival analysis results according to patient and disease characteristics

	Alive	Exitus	Estimate Survival	Estimate Proportion Surviving at the	P value
	n (%)	n (%)	Mean±SE.	1/3/5 years	
Age					0.012
≤ 47	136 (67.3)	15 (40.5)	238.021±58.575	97.3/95.9/93.0	
>47	66 (32.7)	22 (59.5)	158.694±13.619	93.1/81.9/75.7	
Albumin					<0.001
>3.6	175 (86.6)	24 (64.9)	206.388±34.623	98.0/96.8/95.6	
≤ 3.6	27 (13.4)	13 (35.1)	91.808±8.645	82.4/49.0/49.0	
Beta 2-microglobulin					<0.001
≤ 2920	131 (64.9)	8 (21.6)	211.92±6.44	100.0/99.2/97.1	
>2920	71 (35.1)	29 (78.4)	175.041±38.526	90.0/80.9/73.6	
Spleen involvement					0.003
Absent	170 (86.3)	23 (67.6)	205.101±34.631	96.9/95.7/93.1	
Present	27 (13.7)	11 (32.4)	110.559±10.346	89.1/61.7/61.7	
B symptoms					0.001
Absent	117 (59.4)	10 (29.4)	269.489±43.624	99.2/97.4/92.8	
Present	80 (40.6)	24 (70.6)	129.626±7.976	92.3/86.5/79.3	
Bone marrow involvement					0.011
Absent	112 (91.1)	18 (69.2)	197.249±7.099	96.1/91.7/86.6	
Present	11 (8.9)	8 (30.8)	95.789±10.608	94.7/89.5/78.3	
FDG PET CT status. after treatment					<0.001
Progressive/Refractory disease	16 (8.5)	9 (29.0)	64.485±8.384	92.0/43.1/43.1	
Partial response	3 (1.6)	2 (6.5)	85.750±25.398	100.0/75.0/50.0	
Complete response	169 (89.4)	19 (61.3)	207.4343±34.451	98.9/98.9/96.1	
Unknown	1 (0.5)	1 (3.2)	60.00±38.891	50.0/50.0/50.0	
Relapse					<0.001
Absent	145 (78.4)	5 (16.1)	346.810±8.012	98.7/98.7/97.7	
Present	40 (21.6)	26 (83.9)	118.919±13.303	92.1/68.2/42.1	
Stages at the diagnosis					0.001
Favorable	50 (25.4)	2 (5.9)	136.957±3.463	100.0/94.0/94.0	
Unfavorable	62 (31.5)	4 (11.8)	152.507±5.017	100.0/90.9/90.9	
Advanced	85 (43.1)	28 (82.4)	170.733±28.986	92.0/87.0/81.1	

Kaplan Meier Test;Log Rank (Mantel-Cox), SE.: Standard Error

Table 6: Cox regression analysis of variables affecting mortality

Independent Variables	B±Sh	p value	Odds Ratio (95% C.I.)
Beta-2 Microglobulin (<2920) mg/L	1.387±0.548	0.011	4.002 [1.368-11.709]
Spleen Involvement	1.159±0.507	0.022	3.188 [1.18-8.614]
PET-CT evaluation after treatment		0,001	
Progressive/Refractory Disease vs Complete response	2.054±0.581	<0.001	7.81 [2.49-24.39]
Partial response vs Complete response	2.401±0.932	0,010	10.99 [1.77-66.66]
Progressive/Refractory Disease vs Partial response	0.347±0.872	0.690	1.41 [0.26-7.81]
Relapse	1.736±0.64	0.007	5.677 [1.62-19.889]
Estimate Proportion Surviving at the 1/3/5 years (Sh.): 99.8 (0.002)/99.0 (0.007)/96.0 (0.019)-Base Line Hazard: 0.325			

Cox Regression-Stepwise (Wald) Model, C.I.: Confidence interval B: regression coefficients SE.: Standard Error

DISCUSSION

In HL, the overall survival rate exceeds 90%.[3,12] These excellent results, however, have the drawback of an increased risk of long-term toxicity as a result of chemotherapy and/or radiation.[4] In addition, 10 to 30 percent of patients are refractory to treatment or experience recurrence. Researchers have identified a number of factors that decrease the survival rate in HL over the past decades.[10] In our study, when the patients, who died during the study, were compared with the patients who survived, the surviving patients were younger, had less spleen involvement and B symptoms, higher albumin values, lower beta-2 microglobulin values, and less bone marrow involvement. Moreover, these variables affect the survival rates of patients in the first, third, and fifth years. In the International Prognostic Score for Hodgkin Lymphoma, being over the age of 45 is scored as unfavorable. In addition, according to the European Organization for Research and Treatment of Cancer (EORTC), being over the age of 50 is considered

unfavorable.[13] In our study, in patients over 47 years of age, 1, 3, and 5 year estimated survival rates were significantly higher than those in patients under ≤47 years of age. Depending on the subtype, the disease characteristics of HL patients can vary significantly. However, it is known that survival rates decline with age. Our findings are consistent with the literature.

In HD, the spleen is usually considered a nodal organ. Rarely does Hodgkin lymphoma affect only the spleen. Splenic involvement is found in 30-40% of HD patients at the time of diagnosis.[14] In the early stages of Hodgkin's lymphoma, the spleen is the organ most often affected by occult disease. The German Hodgkin Lymphoma Study Group looked at 391 patients in limited early clinical stages. In 21% of these, laparotomy found occult abdominal lymphoma, and in 86.6%, the spleen was affected.[15] In our study, in the presence of spleen involvement, the mortality rate was 3.188 times higher. In addition, according to the findings of the German Hodgkin Lymphoma Study Group, involvement of the spleen and bone marrow occurs in advanced stages 3-4 of the disease.[16] In our study, the decrease in survival rates in patients with spleen and bone marrow involvement is consistent with the literature. The German Hodgkin Lymphoma Study Group, and the European Organization for Research and Treatment of Cancer evaluated the presence of B symptoms as unfavorable factors.[17,18] Likewise, in our study, the survival rate was lower in those with B symptoms. Hypoalbuminemia and higher beta-2 microglobulin can be used to determine the disease as unfavorable and may point to the presence of cancer-related inflammation in the body.[19,20] In our study, the mortality rate of patients with beta 2 globulin levels higher than 2920 mg/L was found to be four times higher than that of those with beta 2 globulin levels lower than 2920 mg/L.

PET-CT-based treatment response assessment has recently become a widely accepted method. In spite of the progress that has been made in standardizing the use of PET/CT in lymphoma, there are still challenges to be faced, most notably with regard to the limited positive predictive value.[21] The presence of relapsed or refractory disease following a PET-CT examination results in a significant reduction in survival rates. Tumor mass has long been considered to be prognostic in HL, but uncertainty remains regarding the significance and definition of the mass in the era of PET-adapted evaluation. In addition, the connection between the maximum tumor diameter measured by FDG PET/CT and the patient's likelihood of survival is not yet fully understood. In early-stage HL patients, Illidge et al.[10] demonstrated that there is a correlation between the maximum tumor diameter and both relapse and complete metabolic response. There are also studies that report that the relationship cannot be precisely defined. Existing relapsed or refractory disease after PET-CT examination significantly reduces survival rates. Some studies indicate that the size of the tumor at the time of diagnosis has an effect on survival rates, but other studies say the opposite.[21-23] In our study, there was no association between survival and the maximum diameter value of the tumor as measured by FDG-PET or CT. Furthermore, the location of the tumor with the maximum tumor diameter at the time of diagnosis did not affect survival. The primary limitations of this study may be that the computed tomography and FDG PET CT scans were done by different specialists, there was a lack of standardization in the range widths of the examined image sections, and all Hodgkin lymphoma subtypes were evaluated at once.

CONCLUSION

Beta-2 microglobulin >2920 mg/L , the presence of spleen involvement, the presence of relapse (n;66, 28%, Estimate Survival, Mean±SE.; 118.919±13.303), and having a progressive or refractory disease evaluation after treatment with FDG PET CT were the most relevant independent prognostic factors for the 1st, 2nd, and 5th-year survival rates with Hodgkin's lymphoma patients. In addition, no correlation was detected between the survival rate and the maximum tumor diameter as measured by FDG-PET or CT.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the Uludağ University Faculty of Medicine Clinical Researches Ethics Committee (Date: 19.02.2020, Decision No: 2020-3/8).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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Original Article

MEDICINE PALLIATIVE CARE

DOI: 10.47582/jompac.1342558

J Med Palliat Care. 2023;4(5):492-498

Trauma symptoms, sleep quality and related factors in the early post-earthquake period

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Cite this article as: Öztürk HM, Daymaz D, Kocakaya H, Akkoyun AZ, Saygun M. Trauma symptoms, sleep quality and related factors in the early post-earthquake period. *J Med Palliat Care*. 2023;4(5):492-498.

Received: 14.08.2023 ◆ **Accepted**: 25.09.2023 ◆ **Published**: 27.10.2023

ABSTRACT

Aim: Traumatic life events such as earthquake are frequently encountered problems both in our country and all over the world. The aim of this study was to determine sleep quality, trauma level and related factors and to evaluate the effects of gender, damage status and losses in adults who were admitted to the psychiatry outpatient clinic among individuals who were placed six thousand kilometers far away from their residence in Kırıkkale University student dormitories immediately after the 6 February 2023 earthquakes that affected a wide geography in Turkey.

Methods: 64 volunteers were included in the study between March 2023 and June 2023. After the participants' complaints and sociodemographic characteristics were questioned, the Pittsburgh Sleep Quality Index (PSQI) and the Scale That Determines the Level of the Trauma after the Earthquake (PETLDS) were applied to the participants to determine their sleep quality and trauma levels after the earthquake.

Results: The mean age of the participants was 45.5±15.5, and 75.0% of them were women. Fear/anxiety and insomnia were the most frequently reported complaints by the participants. The mean of the participants' PSQI scores was 10.5±4.4, and 43 participants (79.6%) had poor sleep quality in the last month. The mean score of the participants' PETLDS was determined as 76.6±17.9. When the subscales were examined, it was determined that the emotional limitation and cognitive restructuring scores were higher than the behavioral, affective and sleep problems. When the participants were compared in terms of damage in their homes, it was found that the participants with moderately or more damaged houses had statistically higher emotional, cognitive restructuring and sleep problems and total trauma scores compared to the participants with a solid or slightly damaged house (respectively; p=.017, p=.023, p=.010, p=.040). Individuals with moderately or more damaged houses had higher PSQI scores but this difference did not reach statistical significance (p=.061). However, parameters such as age, female gender, history of psychiatric illness, loss of loved ones, damage status of house, and PSQI score did not yield an association with high-level trauma symptoms (PETLDS score above 52.3) in univariate logistic regression analysis.

Conclusion: Female gender, young age, damage status of house, losing loved ones and history of psychiatric illness are associated with high-level trauma symptoms and poor sleep quality after the early period of earthquake with no statistical significance.

Keywords: Earthquake, public health, sleep disorders, trauma

INTRODUCTION

Traumatic life events are frequently encountered problems both in our country and all over the world. Approximately 2/3 of people in the general population experience a significant traumatic event at any time in their lives. Disasters are traumatic events that many people experience and can lead to extensive physical and mental health problems.[1,2] Although natural disasters affect many people at the same time, according to World Mental Health Survey data, the prevalence of traumatic stress symptoms after natural disasters is between 0.01-3.8%.[3,4]

Earthquakes have an important place among natural disasters because they are effective in a wide area, occur suddenly, are unpredictable, affect large masses due to the destruction, death and injuries they cause, create many additional problems and can also create chronic effects due to aftershocks.[5-7] Among natural disasters, the type of disaster that causes the most loss of life and property is earthquake, and 90% of our country's territory, 95% of the population and 75% of industrial zones are on the earthquake

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zone.[6,8] Problems such as infrastructure inadequacies, failure to meet basic needs, disruption of health services, failure to solve the housing problem quickly, continuation of aftershocks, failure to ensure the return of life to its natural flow, inability of earthquake victims to reach their relatives and disruption of funeral procedures make the destructive effects of the earthquake massive and lead to prolongation of the trauma period.[8]

When the factors associated with trauma symptoms that develop after disasters are examined, it has been shown that factors such as female gender, past/comorbid psychiatric diagnosis, low social support, and degree of exposure to the disaster may be risk factors.[1] Some researchers have shown that variables such as the level of damage in the location of the earthquake, loss of relatives, and forced displacement may be effective on trauma symptoms.[4,6,8] Depending on the magnitude of the earthquake, there may be individual differences in the reactions of those exposed to the disaster, and these symptoms can be classified as emotional, physical, cognitive and social.[9,10] Acute stress reactions such as shock, fear, helplessness, anger, shame and guilt, inability to focus, emotional blunting, forgetfulness, images and memories of the earthquake, restlessness, tension, weakness, startle, palpitations, nausea, changes in sleep and appetite, intolerance, social isolation, feeling lonely and insecure can be seen immediately after the earthquake.[9,11-13]

When the literature was examined, it was observed that most of the psychosocial studies conducted after the earthquake were conducted after a certain period after the earthquake. However, many studies emphasise the importance of assessments to be made in the acute period after the earthquake in terms of the development of psychopathology and the effectiveness of therapeutic approaches.[14] The aim of this study was to determine sleep quality, trauma level and related factors and to evaluate the effects of gender, damage status and losses in 64 adults who were admitted to the psychiatry outpatient clinic among individuals who were placed in Kırıkkale University student dormitories immediately after the 6 February 2023 earthquakes that affected a wide geography in Turkey.

METHODS

The study was carried out with the permission of the Kırıkkale University Non-interventional Clinical Researches Ethics Committee (Date: 29.03.2023, Decision No: 2023.03.18). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Written informed consent was obtained from the participants.

The population of this descriptive study consisted of earthquake-affected individuals who left the city where they experienced the earthquake and were placed in Kırıkkale University student dormitories immediately after the earthquakes whose epicentres were Kahramanmaras, Pazarcik or Elbistan on 6 February 2023 and who applied to Kırıkkale University Faculty of Medicine Psychiatry Outpatient Clinic between March 2023 and June 2023 and agreed to participate in the study. The aim of the study was to evaluate the socio-demographic characteristics and complaints of the volunteers, to determine their sleep quality and post-earthquake trauma levels and to determine the related factors affecting them.

As a data source, a personal information form prepared by the researchers, consisting of fifteen questions inquiring some socio-demographic characteristics of earthquake-affected individuals such as age, gender, marital status, education level, and the province where the earthquake occurred was applied to participants. Afterwards, the Pittsburgh Sleep Quality Index (PSQI) and the Scale That Determines the Level of the Trauma after the Earthquake (PETLDS) were used to determine their sleep quality and the level of trauma they experienced after the earthquake.

Developed by Tanhan and Kayri in 2013, PETLDS is a five-point Likert-type measurement tool that measures the trauma symptoms experienced by individuals after the earthquake. The scale consists of 20 items and 5 dimensions ('behaviour problems', 'emotive limitedness', 'affective', 'cognitive structures', 'sleep problems'). The internal consistency coefficient calculated to determine the reliability of the scale was found to be .87. A score in the range of 52.3±5.1 corresponds to a threshold value indicating that individuals are traumatised. A score above or below this value indicates a high or low level in showing post-earthquake traumatic symptoms.[15]

The PSQI was developed by Buysse et al.[16] in 1989 and adapted into Turkish language by Agargun et al.[17] The PSQI is a 19-item self-report scale that assesses sleep quality and sleep disturbance in the past one month. The scale consists of 24 questions. 19 questions are self-report questions, and the other 5 questions are questions to be answered by the spouse or roommate. The 18 scored questions of the scale consist of 7 components: Subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, sleep medication use and daytime dysfunction. Each component is evaluated on a 0–3-point scale. The total score of 7 components gives the total score of the scale. The total score ranges from 0-21. A total score greater than 5 indicates poor sleep quality.

Statistical Analysis

Statistical analysis of the study were performed with SPSS 20.0 package programme. After descriptive statistical analyses, the results were expressed as percentage distribution or mean ± standard deviation. The normal distribution of the data was analysed using the Kolmogorov-Smirnov test. Independent sample t test was used for intergroup comparisons. Logistic regression analysis was performed to evaluate predictors of high-level trauma symptoms (PETLDS score above 52.3). Variables that could be associated with high-level trauma symptoms such as age, gender, psychiatric illness history, damage status of house, loss of loved ones and PSQI score were tested in logistic regression analysis and a p value <.1 was considered as significant for univariate tests. For all statistical analyses, significance level was accepted as p value <.05.

RESULTS

Of the 64 participants, 48 were female (75.0%) and 51 were married (79.7%). The mean age of the participants was 45.5±15.5 and the age range varied between 18 and 79. While 34.4% of the participants stated their education level as primary school, the rate of university graduates was 26.6% and the rate of high school graduates was 17.2%. 23 (37.0%) of the participants stated that they experienced the earthquake in Hatay, 19 (30.6%) in Kahramanmaras, 9 (14.5%) in Malatya, 6 (9.6%) in Adiyaman, 3 (4.8%) in Osmaniye and 2 (3.2%) in Gaziantep. 39.1% of the participants stated that the place where they stayed was severely damaged during the earthquake, and 9.4% stated that the building was destroyed. 39 people (60.9%) stated that they lost at least one relative due to the earthquake. Three of the participants stated that they lost their mother, one of them lost their father, two of them lost their siblings, and one of them lost their spouse; 25 of them lost their close relatives, and 17 of them lost their close friends (Table 1).

When participants were asked about the symptoms for applying to Kırıkkale University Faculty of Medicine Psychiatry Outpatient Clinic, the most common complaints were fear/anxiety (n=39, 67.1%) and sleep disturbance (n=34, 58.5%). Anorexia was reported by 7 people and other complaints included inability to stay still, inability to enter a closed area, shortness of breath, nervousness, reluctance, numbness in the mouth and jaw, restlessness, startle, crying, palpitations, and irritability. Twenty-four of the participants (39.3%) stated that they had a previous history of psychiatric illness (Table 2).

Table 1. Distribution of socio-demographic characteristics of participants

Characteristics	n	%
Gender		
Woman	48	75.0
Man	16	25.0
Marital status		
Single	10	15.6
Married	51	79.7
Divorced/Deceased	3	4.7
Education status		
Illiterate	4	6.3
Literate	4	6.3
Primary School	22	34.4
Middle School	6	9.4
High School	11	17.2
University	17	26.6
Location during the earthquake		
Adiyaman	6	9.6
Gaziantep	2	3.2
Osmaniye	3	4.8
Malatya	9	14.5
Kahramanmaras	19	30.6
Hatay	23	37.0
Damage to the residence during the earthquake		
Slightly damaged	18	28.1
Moderately damaged	15	23.4
Heavily damaged	25	39.1
Destroyed	6	9.4
Loss of loved ones due to earthquake		
Yes	39	60.9
No	25	39.1

Table 2. Distribution of participants' reasons for applying to mental health and diseases outpatient clinics and having a history of psychiatric disease

Applicant's complaint*	n	%
Sleep disturbance	34	58.5
Fear/anxiety	39	67.1
Loss of appetite	7	12.0
Other**	19	32.6
History of psychiatric illness***		
Yes	24	39.3
No	37	60.7

*Six of the participants did not specify any complaints, and there were participants with more than one complaint. **Other: Restlessness, startle, palpitations, crying, irritability. ***Three of the participants did not state whether they had a history of psychiatric illness.

The mean PSQI score of the participants was calculated as 10.5±4.4. Since the cut-off score of the scale was 5, it was determined that 43 participants (79.6%) had poor sleep quality in the last month. The mean score of the participants in the PETLDS was calculated as 76.6±17.9. When the subscales were examined, it was found that emotive limitedness and cognitive structures scores were higher than behaviour problems, affective and sleep problems (Table 3).

Table 3. Distribution of participants' PETLDS and PSQI scores

	Mean ± Standard Deviation
PSQI	10.5±4.4
PETLDS	76.6±17.9
Behaviour Problems	13.3±4.1
Emotive Limitedness	18.1±8.8
Affective	14.0±4.5
Cognitive Structures	18.2±3.7
Sleep Problems	12.8±3.6

PSQI = The Pittsburgh Sleep Quality Index, PETLDS= The Scale That Determines the Level of the Trauma after the Earthquake.

When the participants were compared in terms of damage to their homes, it was found that the participants with moderate or more damaged homes had statistically higher affective, cognitive structures, sleep problems and total trauma scores than the participants with intact or slightly damaged homes (p=.017, p=.023, p=.010, p=.040, respectively). The PSQI scores of individuals with medium or more damaged houses were found to be higher, but this difference did not reach statistical significance (p=.061) (Table 4).

Table 4. The relationship between the damage status of the houses of the participants and their PETLDS and PSQI scores

	Intact/ slightly damaged (n=17)	Moderately/ heavily damaged/ demolished (n=45)	p value
PSQI	8.6±4.8	11.2±4.1	.061
PETLDS	69.3±26.8	79.3±12.5	.040*
Behavioural problems	11.8±4.1	13.8±4.1	.092
Excitement limitation	18.2±14.7	18.1±5.4	.961
Affective	11.8±4.2	14.8±4.4	.017*
Cognitive structuring	16.4±6.1	18.8±1.9	.023*
Sleep problems	10.9±4.9	13.6±2.7	.010*

PSQI = The Pittsburgh Sleep Quality Index, PETLDS = The Scale That Determines the Level of the Trauma after the Earthquake.

All parameters including age (OR: 1.04, 95% CI: 0.98-1.10, p=.190) female gender (OR: 3.66, 95% CI: 0.65-20.53, p=.139), history of psychiatric illness (OR: 0.27, 95% CI: 0.04-1.62, p=.153), loss of loved ones (OR: 0.83, 95% CI: 0.14-4.94, p=.841), damage status of house (OR: 2.6, 95% CI: 0.13-50.04, p=.190) and PSQI score (OR: 1.11, 95% CI: 0.86-1.43, p=.412) did not yield an association with high-level trauma symptoms in univariate logistic regression analysis (Table 5).

Table 5. Associates of high-level trauma symptoms by logistic regression analysis

	Univariate	
	Odds Ratio (95%CI)	P value
Age	1.04 (0.98-1.10)	.190
Gender	3.66 (0.65-20.53)	.139
Psychiatric illness history	0.27 (0.04-1.62)	.153
Loss of loved ones	0.83 (0.14-4.94)	.841
Damage status of house	2.60 (0.13-50.04)	.527
PSQI score	1.11 (0.86-1.43)	.412

PSQI = The Pittsburgh sleep quality index

DISCUSSION

In our study, post-earthquake trauma symptoms, sleep quality and related factors were examined in individuals who were affected by the earthquakes whose epicentres were Pazarcik and Elbistan districts of Kahramanmaras, respectively, on 6 February 2023 and who had to change their cities and settled in Kırıkkale University student dormitories, which is approximately six hundred kilometres away from the epicentres of earthquakes. We found that female gender, young age, damage status of house, losing loved ones and history of psychiatric illness are associated with high-level trauma and poor sleep quality after the early period of earthquake with no statistical significance.

According to our descriptive results obtained, the mean PETLDS total score of the individuals was calculated as 76.6±17.9 and in this direction, it was determined that the participants were traumatised after the earthquake. The score range of 52.3±5.1 to be taken from PETLDS indicates a threshold value pointing that individuals were traumatized after the earthquake.[15] It was found that the mean scores of the excitement limitedness and cognitive structuring sub-dimensions were higher (18.1±8.8, 18.2±3.7, respectively) than the mean scores of the behavioural, affective and sleep problems sub-dimensions (13.3±4.1, 14.0±4.5, 12.8±3.6, respectively). Similar results were obtained in a recent study using the PETLDS.[18] According to the results of research conducted by Aynur Karabacak Celik, excitement limitedness and cognitive structuring scores were higher (16.9±5.4, 17.0±3.2, respectively) than other sub-dimensions of PETLDS.[18] Since items in sub-dimension of 'excitement limitedness' mostly contain hopelessness and depressive elements (e.g., 'It feels like life has no meaning anymore', 'I feel very helpless/powerless'); this can be expected to be higher in the individuals affected by earthquake. Besides, 'cognitive structuring' contains anxiety related items such as 'I am irritated because of the thought that an earthquake will occur at any moment', 'I am worried about the future'. It is known that anxiety and depressive symptoms are very common in people at post-earthquake period.[19,20] In this context, high scores of cognitive structuring and excitement limitedness in our study are consistent with the literature.

In a study conducted in China, Jiang et al.[21] demonstrated that 83.2% of the participants had sleep problems according to PSQI scores. In our study, the PSQI scores of the individuals exposed to earthquake were found to be high (10.5±4.4) and a total of 43 (79.6%) individuals scored greater than 5 which indicates poor sleep quality. This higher rate of sleep disturbances seen in the early period after natural disasters may be related to decreased sense of security and avoidance behaviour.[12] Increasing

line of evidence show that sleep disturbance is a core feature of PTSD rather than an accompanying symptom. Furthermore, post-earthquake sleep quality of individuals was significantly predictive of anxiety, depression, and PTSD development as shown in studies. [21]

In studies investigating the psychological effects of earthquakes, it has been emphasised that anxiety, depression, dissociation, physical symptoms and sleep disorders may be observed in individuals after an earthquake.[12,22] In the results of studies conducted shortly after the Iranian earthquake in 2017, it was found that individuals affected by earthquake experienced anxiety with 70%, stress with 60%, depressive symptoms with 41.5% and sleep disorders with 20%.[19] In a study, the first three most common symptoms after the earthquake were sadness 75%, sleep disturbance 75% and anxiety 61%.[20] In a study conducted after the Elazığ earthquake, Bilici et al.[8] found fear as the most common complaint (73.3%). Similarly, the two most common symptoms in our study were fear/anxiety (n=39, 67.1%) and sleep disturbance (n=34, 58.5%).

The extent to which individuals will be affected by the earthquake is generally parallel to how close they are to the epicentre. Individuals who were injured in the earthquake, lost their relatives, had their homes/workplaces destroyed, were buried under the rubble, and whose neighbourhood was destroyed may be more emotionally affected.[12] In studies conducted after the Van 2019 earthquake, it was found that the post-traumatic stress symptoms of the participants were significantly different in terms of the variables of loss of relatives in the earthquake, experiencing the earthquake, damage of the house they live in and being buried under the rubble.[6,23] According to the research conducted in two different regions of Marmara after the Istanbul earthquake, Basoglu et al.[24] suggested that damage to home was significant but weak predictor of traumatic stress symptoms. In our study, individuals with more severe damage in their homes were found to have higher scores on the PETLDS (total score: 79.3±12.5, p=.04; sleep problems sub-dimension:13.6±2.7, p=.01) and PSQI (11.2±4.1, p=.61).

In the literature, it has been shown that there is a relationship between female gender and past/comorbid psychiatric diagnosis and traumatic symptoms.[1,20] Approximately three-quarters of the individuals who participated in this study were women (n=48) , and although not statistically significant, women had higher scores on the PETLDS and PSQI (77,5±18.1, p=.48; 10.6±4.7, p=.70, respectively). In our study, 24 individuals with a psychiatric history had higher scores on the PETLDS and PSQI, but this difference was not statistically significant (78,8±17.6, p=.21; 11.1±4.1, p=.22, respectively). The mean age of the participants in our study was 45.5±15.5 years and the age range were between 18 and 79 years. Although younger participants aged under 45 had higher PETLDS and PSQI scores (77,2±19.1, p=.77; 11.1±4.3, p=.35, respectively), no significant relationship was found between age and trauma level and sleep disturbance. While previous studies have indicated that being young is a risk factor for trauma symptoms, the fact that the sample of our study consisted mostly of middle-aged and older participants may have caused the effect of age not to be shown.4 Studies investigating the relationship between loss of a relative in an earthquake and psychiatric symptoms have yielded conflicting results.[12,20] In our study, trauma and sleep scores of individuals who lost a relative in the earthquake were lower (75,8±15.0, p=.66; 10.5±4.3, p=.97, respectively), but not statistically significant.

Furthermore, we aimed to evaluate whether the abovementioned parameters such as age, gender, history of psychiatric illness, loss of loved ones, damage status of house and PSQI score predict high-level trauma symptoms through logistic regression analysis. Nevertheless, none of the parameters included in univariate tests yielded a statistically significant relationship with high-level trauma symptoms which could be due to observative nature, descriptive design and small number of participants compared to other studies.[4,6,24] It should be underlined that evaluation of the participants at the early period, small number of participants and conducting the study far from the epicentre of the earthquake might have been reasons for failed regression analysis. For example, a previous study showed that the psychological reactions of individuals after damaging traumas are not in the dimension of the severity of the events. The concept of posttraumatic growth can be defined as positive psychological changes that develop after challenging life events.6 It may be considered that the low scores observed in our study may be related to posttraumatic growth.

There are many studies in the literature published from Turkey and the world that evaluated psychiatric disorders of individuals after earthquakes.[2,4-6,8,19-21,23,24] At this point, it is reasonable to question the scientific contribution of our study. Because the earthquakes that occurred on 6th February of 2023 affected a very wide geographical region and one of the largest earthquakes ever experienced in Turkey, evaluation of individuals that suffered from this disaster can contribute to national scientific data of Turkey. On the other hand, the participants of our study have moved approximately six hundred kilometres away from their residencies and lived in student dormitories of a university for a while. To our knowledge, there is no data in the literature both from

Turkey as well as the world that evaluated the psychiatric status of such individuals. From this perspective, our data can give valuable insights to scientific literature.

The most important limitation of our study is that the participants could not be followed up longitudinally and could not be evaluated in terms of the rates of development of Acute Stress Disorder (ASD) and PTSD. Exploratory and descriptive design of the study is a significant limitation that limits to make firm conclusions about trauma symptoms related with earthquake. In longitudinal research dataset, we could explore the principal relationship between sleep disturbances and psychiatric disorders. In addition, the past trauma history of the participants was not questioned. Therefore, impact of past trauma on the development and severity of trauma symptoms could not be assessed. Also sample size of our study is small, which could be due to the study was conducted in a city located far from the epicentre of the earthquake. It should be underlined that, according to the relevant literature, most of the post-earthquake studies were conducted long after the trauma. Despite the small sample size, the fact that the examination was conducted in the early period is a strength of our study. Additionally, it is emphasized that evaluation in the early period is important in terms of the development of psychopathology and the effectiveness of therapeutic approaches.[8,21] Future prospective, well-designed and statistically powered studies are needed to clarify the long-term prevalence of psychiatric morbidity among individuals after major disasters. In line with this, our observational and descriptive study results should be considered hypothesis-generating only. On the other hand, whether providing education to the individuals about the symptoms they may experience and coping methods in the early period after the earthquakes should be the subject of future studies.

CONCLUSION

The earthquakes that occurred in our country on and after 6 February 2023 covered a large area and resulted in millions of people being directly affected and the rest of the society being indirectly affected at various levels. Our study results indicate that being female, at a younger age, damage status of house, losing loved ones and history of psychiatric illness are associated with high-level trauma and poor sleep quality after the early period of earthquake with no statistical significance.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the Kırıkkale University Non-interventional Clinical Researches Ethics Committee (Date: 29.03.2023, Decision No: 2023.03.18).

Informed Consent: Written informed consent was obtained from the participants.

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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Original Article

MEDICINE PALLIATIVE CARE

DOI: 10.47582/jompac.1350147

J Med Palliat Care. 2023;4(5):499-504

Urea-to-hemoglobin ratio for patients with upper gastrointestinal bleeding

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Cite this article as: Yeşil B, Sevim B. Urea-to-hemoglobin ratio for patients with upper gastrointestinal bleeding. *J Med Palliat Care*. 2023;4(5):499-504.

Received: 25.08.2023 ◆ **Accepted**: 26.09.2023 ◆ **Published**: 27.10.2023

ABSTRACT

Aims: Upper gastrointestinal bleeding develops due to various pathologies in a wide region, including esophagus, stomach, and duodenum. The clinical presentation is highly variable between patients and can rapidly deteriorate and even be fatal without follow-up. Medical agents, endoscopic interventions, and surgery may be required in the treatment of the patient, and a high blood transfusion may be required. The accurate identification of patients who are at a higher risk and require immediate attention is crucial for the appropriate management of patient care. The ratio of urea to hemoglobin (UHR) has been identified as a potentially valuable tool for determining the necessity of endoscopy due to its simplicity, quick applicability, and reliability.

Methods: This was a single-center retrospective study in which 361 patients treated for upper gastrointestinal bleeding were investigated. Age and gender data, endoscopy records, and blood tests of the patients were analyzed within the scope of the study. Median UHR values were significantly higher in intensive care indication, endoscopic indications, and blood transfusion indications ($p<0.05$).

Results: The majority of patients were male, with 72.3%. The median age was 56 years (15-96). Peptic ulcer (70.9%) was the most common etiologic cause, and angioectasia (6.65%) was the second most common etiologic cause. Intensive care follow-up was required in 29.1%, erythrocyte replacement in 36.01%, and endoscopic treatment in 46.81% of patients. 13 patients died (3.6%). The median value was 58 for urea, 10.50 for hemoglobin and 5.75 for UHR.

Conclusion: Upper gastrointestinal bleeding is a variable and rapidly deteriorating clinical entity. Patients may not always be encountered under ideal conditions and may need to be managed with limited resources. Therefore, there is a need for easy-to-access, rapid, and reliable auxiliary techniques to differentiate patients who may need urgent treatment and interventions from others. Urea and Urea/hemoglobin ratio fulfill these requirements, and their significance in terms of upper gastrointestinal bleeding should be investigated.

Keywords: Gastrointestinal hemorrhage, peptic ulcer, emergency intervention, endoscopy, urea

INTRODUCTION

Upper gastrointestinal bleeding (UGIB) defines hemorrhages that develop due to pathologies in the gastrointestinal tract up to the ligament of Treitz.[1] Many pathologies that may cause bleeding in this region, including esophagus, stomach, and duodenum, have been described. Although these pathologies differ in terms of the way they occur and the severity of the clinic they cause, the basic goals in the management of these clinics are the same. When bleeding is detected, hemodynamic stabilization of the patient should be targeted, preparation should be made for the need for resuscitation and transfusion, proton pump inhibitor and somatostatin treatment should be started in selected patients, and intervention should be planned to identify and stop the bleeding focus.[2]

While around 80% of instances of upper gastrointestinal bleeding (UGIB) exhibit spontaneous recovery, it is important to note that 13% of these cases may result in mortality.[2,3] Given the diverse range of clinical presentations and the potential for acute manifestations, it is imperative to ascertain the relative risk and prioritize patients accordingly, taking into account both individual patient well-being and the overall clinic population. This is particularly important due to the frequency of bleeding incidents and the limited capacity for simultaneous endoscopic procedures. Hence, there exists a must for methodologies capable of forecasting which patients necessitate a blood transfusion due to their severity, as well as identifying those who require an expedited endoscopy. These procedures should possess attributes

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of simplicity, expediency, and sufficient accuracy to be effectively employed in emergency scenarios. The scope of blood tests that may be conducted in emergency scenarios and yield prompt answers is constrained. However, existing literature suggests that certain available assays can provide indirect indications regarding the extent of bleeding and the clinical status.

Urea is a blood test that can be easily and rapidly studied, even in centers with the most limited facilities. Although it is known as an integral part of renal function tests, it has been widely observed to give abnormal results in gastrointestinal bleeding. There are data showing a significant correlation between elevated urea and mortality in patients with UGIB.[4] Considering the effect of uremia on intestinal mucosa and platelet functions, the value of urea in predicting prognosis and the need for treatment in these patients should be investigated.[5]

Tomizawa et al.[6] reported that patients with higher BUN levels may have more severe upper GI bleeding. In a study in 2020 study reported that urea level was an independent predictor of positive endoscopic findings in upper GI bleeding and that early endoscopic intervention should be considered in patients with elevated urea levels.[7] Some studies have used the BUN/Creatinine ratio as an index to differentiate between upper and lower GI bleeding and have shown that a higher BUN/Cr ratio is associated with a higher likelihood of upper GI bleeding.[8,9]

In cases of ongoing bleeding in any area of the body, a decrease in hemoglobin levels is expected. Since both urea and hemoglobin levels are known to change in bleeding states, we thought that a ratio derived from them might be meaningful in upper GI bleeding.

Based on this, we aimed to investigate and reveal the relationship between urea/hemoglobin ratio (UHR) and upper gastrointestinal bleeding and the possible clinical significance of these bleedings.

METHODS

The study was carried out with the permission of the Batman Training and Research Hospital Scientific Researches Ethics Committee (Date: 22.12.2022, Decision No: 324). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This study was conducted retrospectively and single-center in the Gastroenterology Clinic of Batman Dünya Hospital. Patients who were treated in our clinic between January 2010 and December 2022 and were diagnosed with upper gastrointestinal tract bleeding for any reason other than variceal bleeding were included in the study. Patients presenting with variceal bleeding or having nephrological comorbidities (defined as patients with a creatinine value above 1.3 mg/dl at the time of admission) were excluded from the study. Similarly, patients who presented to the outpatient clinic with anemia and who had no evidence of active GI bleeding were not included in the study. The study included 361 patients who met the definition and were treated on those dates. Age and gender data, endoscopy records, and blood tests of the patients were analyzed within the scope of the study.

Patient data collected within the scope of the study were analyzed with IBM Statistical Package for the Social Sciences (SPSS 25.0-IBM, NY, USA) for Windows 25.0 package program. Frequency and percentage for categorical data, and median, minimum, and maximum for continuous data, were given as descriptive values. The conformity of the data to the Gaussian distribution was analyzed by the Kolmogorov-Smirnov test. For intergroup comparisons, the Mann Whitney U-Test was used for two groups, and the Kruskal-Wallis H-Test was used for more than two groups. The relationship between urea/hemoglobin ratio (UHR) and the risk of peptic ulcer bleeding was evaluated by Spearman's correlation analysis. Results were considered statistically significant when the p value was less than 0.05.

RESULTS

The evaluation encompassed a total of 361 patients. **Table 1** displays the distribution of demographic and clinical findings among the patients. Upon analysis of the table, it becomes evident that a significant proportion of the patients were of the male gender, accounting for 72.3% of the total population. The median age of the population under study was 56 years, with a range spanning from 15 to 96 years. The most prevalent etiologic cause of peptic ulcer was found to be 70.9%, whereas angioectasia was identified as the second most common etiologic cause, accounting for 6.65% of cases. A total of 36.39% of the patients exhibited the presence of at least one comorbid disease, with coronary artery disease being the most prevalent among them, affecting 12.46% of the patients. A follow-up in the intensive care unit was necessary for 29.1% of the cases, while erythrocyte replacement was required in 36.01% of the cases, and endoscopic therapy was necessary in 46.81% of the cases. During the subsequent assessment, a total of 13 patients, accounting for 3.6% of the sample, experienced mortality. The median values for urea, hemoglobin, and UHR were 58, 10.50, and 5.75, respectively.

Table 1. Distribution of demographic and clinical findings of the patients

N:361	n (%) or Median (Min-Max)
Gender	
Male	261 (72.3)
Female	100 (27.7)
Age, year	56 (15-96)
Etiology of Bleeding	
Peptic Ulcer	256 (70.9)
Forrest 1a	13
Forrest 1b	42
Forrest 2a	59
Forrest 2b	10
Forrest 2c	38
Forrest 3	94
Erosive gastritis	23 (6.37)
Angioectasia	24 (6.65)
Hemorrhagic gastritis	6 (1.66)
Mallory-Weiss	14 (3.88)
Upper GI cancer	14 (3.88)
GIST	2 (0.55)
Dieulafoy	4 (1.11)
Esophagitis	2 (0.55)
Esophageal ulcer	8 (2.22)
Post-ERCP	2 (0.55)
Post-polypectomy	1 (0.28)
Cameron ulcer	2 (0.55)
Marginal ulcer	2 (0.55)
Swallowed blood (haemoptysis)	1 (0.28)
Place of Hospitalization	
Service	256 (70.9)
Intensive care	105 (29.1)
Medicine	
NSAIDs (ASA and others)	78 (21.61)
Antiaggregant/Anticoagulant	46 (12.74)
Comorbidity	131 (36.39)
Diabetes mellitus	19 (5.26)
Hypertension	27 (7.48)
Coronary artery disease	45 (12.46)
Cerebrovascular disease	7 (1.94)
Chronic obstructive pulmonary disease	2 (0.55)
Arrhythmia	4 (1.11)
Heart valve surgery	8 (2.22)
Gastric surgery	12 (3.32)
Cancer (non-gastric)	8 (2.22)
Erythrocyte Replacement	160 (44.32)
Endoscopic Treatment	169 (46.81)
Last Status	
Alive	348 (96.4)
Deceased	13 (3.6)
Laboratory	
Urea (mg/dl)	58 (11-182)
Creatinine (mg/dl)	0.90 (0.30-1.30)
Albumin (g/dl)	3.70 (1.20-5.29)
INR	1.11 (0.86-12.20)
White blood cell (µl)	9680 (1400-35130)
Neutrophil (µl)	6730 (1700-32870)
Lymphocyte (µl)	1900 (100-10300)
Hemoglobin (g/dl)	10.50 (3.20-18.30)
Platelets (µl)	241.50 (32-888)
UHR	5.75 (0.79-26.01)

Table 2 presents an analysis of probable fluctuations in the urea to hemoglobin ratio among the participants in the study, considering specific variables that are hypothesized to impact this ratio. It was determined that there was no significant difference between genders (p=0.46). Median UHR values were found to be significantly higher in patients who required intensive care follow-up, underwent endoscopic treatment, received erythrocyte administration, and were older than 65 years (p<0.05). In the comparison of peptic ulcer bleeding and other etiologies, UHR was found to be significantly higher in the peptic ulcer group (p<0.001).

Table 2. Distribution of urea/hemoglobin ratio by variables

Variable	UHR Median (Min-Max)	p
Gender		0.46
Male	5.80 (1.21-21.76)	
Female	5.71 (0.79-26.01)	
Age		<0.001
<65	5.05 (0.79-11-7.79)	
≥65	7.68 (1.38-26.01)	
Intensive care follow-up		<0.001
Yes	6.77 (1.62-26.01)	
No	5.22 (0.79-22.98)	
Endoscopic treatment requirement		0.01
Yes	6.10 (0.79-21.76)	
No	5.23 (1.05-26.01)	
Erythrocyte replacement requirement		<0.001
Yes	7.37 (1.38-26.01)	
No	4.17 (0.79-18.02)	
Etiology of bleeding		<0.001
P. Ulcer	6.09 (1.24-26.01)	
Other	4.04 (0.79-22.98)	
Result		0.01
Alive	5.70 (0.79-26.01)	
Deceased	8.60 (2.78-19.13)	

Table 3 shows the relationship between bleeding risk groups and the ratio of urea to hemoglobin. The findings revealed that as the risk level grew, there was a corresponding increase in the ratio of urea to hemoglobin. The correlation analysis revealed a positive, low-level linear association between UHR and the bleeding risk of peptic ulcer (Table 4). The statistical analysis, which employed post-hoc Bonferroni correction, indicated that the observed disparity can be ascribed to the differentiation between the low- and high-risk groups (p=0.013).

Table 3. Urea/hemoglobin ratio according to bleeding risk in peptic ulcer patients

Bleeding risk according to forrest classification	UHR Median (Min-Max)	p
Low	5.48 (1.24-17.65)	
Middle	6.03 (1.25-26.01)	0.04
High	7.00 (1.48-21.76)	

Table 4. Correlation analysis results between peptic ulcer bleeding risk and UHR			
			UHR
Spearman's correlation	Bleeding risk	r p N	.149 0.017 256

Table 5 displays the findings of the analysis that assessed the potential disparity between the groups receiving erythrocyte replacement and those not receiving erythrocyte replacement in relation to UHR, based on baseline hemoglobin values. It is evident that the UHR is significantly greater in the groups that had erythrocyte replacement, regardless of the hemoglobin cut-off levels (p<0.001).

Table 5. Comparison of UHR of those with erythrocyte requirement at follow-up according to baseline hemoglobin levels

	Erythrocyte replacement (n)	UHR Median (Min-Max)	p
Hemoglobin ≥10 (n:213)	Yes (54) No (159)	6.77 (1.38-14.23) 3.58 (0.79-18.02)	<0.001
Hemoglobin ≥7 (n:329)	Yes (130) No (199)	7.02 (1.38-11-19.99) 4.06 (0.79-18.02)	<0.001

DISCUSSION

With a wide spectrum of causes and clinical severity, UGIB is a difficult clinic for clinicians to manage. Treatment of patients is initiated before the nature of the disease is understood and is not known until endoscopy is performed. It is therefore difficult to predict which patients need further treatment more than others and when. Nevertheless, despite all the obstacles, the clinician has to make decisions about intervention with endoscopy, follow-up in the intensive care unit, and early initiation of transfusion, based on the limited findings available to him and needs techniques to support him in this regard.

The age distribution of the cases in our study was quite wide (15-96) and the mean age was 56 years. 72.3% of our patients were male. In a study of UGIB cases conducted in France, the mean age was 63 years, and 2130 cases were male and 1073 cases were female.[5] Although the mean ages were slightly different, they were similarly high, and the difference may be due to demographic differences in life expectancy and age. In terms of gender, the cases were similarly dominated by males. The most common cause of non-variceal UGIB is peptic ulcer.[10] Similar to the literature, peptic ulcer was the most common etiologic cause in our study. In a study conducted by Falcão et al.[11] in 2021, the intensive care unit follow-up rate was reported as 35.6%. Our patients required intensive care unit follow-up at a rate close to this rate (29.1%). Based on this, we performed further analysis in terms of our hypothesis, considering that our study group was in rough agreement with the literature.

In our study, the median value was 58 for urea, 10.50 for hemoglobin and 5.75 for UHR. As far as we know, there is no study directly examining the relationship between UHR and UGIB in the literature, so we tried to compare them indirectly. In a study examining upper and lower gastrointestinal bleeding in Japan, mean hemoglobin was 10.1 g/dl and serum urea nitrogen (BUN) was 21.1 mg/dl in patients with UGIB.12 Based on this data, urea was calculated as 45.153 (BUN was multiplied by 2.14 for conversion to urea), and UHR was calculated as 4.47 and found to be similar to our study.

In the United Kingdom, a study was conducted on early blood transfusion in cases of acute UGIB, and it was observed that 38 of 57 patients with urea values below 6.5 mmol/L at admission did not need blood transfusion in the early period, and this data was statistically significant.[13]

In a retrospective study conducted in Japan to predict the need for emergency endoscopy, the importance of hemoglobin and urea was emphasized.[14] Various factors were examined for the need for hemostatic treatment and blood pressure (p=0.0283), BUN (p<0.001), hemoglobin (p=0.0037), hematemesis (p=0.0030) and pulse (p=0.0137) were found to be directly related. Based on this, hematemesis, pulse rate above 100 beats per minute, hemoglobin below 10 g/dl, blood pressure below 100 mmHg, and BUN values of 22.4 mg/dl and above were determined as indicators associated with the need for endoscopic treatment, and a new scoring system was proposed.

Urea and hemoglobin are used in the Glasgow-Blatchford score, which is one of the severity scores of UGIB. In this score, elevated urea and low hemoglobin cause the patient to have a higher score and are associated with severe UGIB.[15] There are studies showing an association between low hemoglobin and mortality.[16] In our study, UHR was found to be associated with disease severity indicators and mortality. The Forrest classification has been used for risk stratification in nonvariceal ulcer bleeding and is associated with the risk of rebleeding.[17] de Groot et al.[18] reported that there was no relationship between Forrest classification and mortality. The existing literature does not contain any research that have examined the correlation between the urea/hemoglobin ratio and the likelihood of experiencing peptic ulcer bleeding. During the course of our investigation, it was noted that there was a substantial increase in the urea to hemoglobin ratio in instances of peptic ulcer

bleeding. Moreover, a low-level positive correlation was observed between the risk of bleeding as per the Forrest classification and the extent of UHR. Our study is the first to report this relationship.

In patients with upper GI bleeding, erythrocyte replacement is recommended so that hemoglobin is 7-9 g/dl.[19] The European Society of Gastrointestinal Endoscopy (ESGE) recommends a more liberal erythrocyte transfusion strategy in hemodynamically stable patients with acute UGIB and a history of acute or chronic cardiovascular disease, with a hemoglobin threshold of ≤8 g/dl triggering erythrocyte transfusion and a target hemoglobin ≥ 10 g/dl.[20] In our evaluation to need for erythrocyte replacement in the follow-up according to the baseline hemoglobin level, patients with high UHR needed erythrocytes in the follow-up for both cut-off values (7 g/dl and 10 g/dl).

In the study conducted by Kiringa et al.[4] in which UGIB cases were examined, uremia was found in almost half of the cases (44.6%), and it was observed that patients with uremia had a more mortal course (OR 5.4, 95% CI 1.57-18.53, p-value 0.007). Based on this data, it can be claimed that uremia is associated with bleeding and mortality. In our study, median UHR values were found to be significantly higher in patients who required intensive care follow-up, underwent endoscopic treatment, received erythrocyte transfusions, and were older than 65 years; in summary, in patients at high risk of mortality ($p<0.05$).

CONCLUSION

Upper gastrointestinal bleeding (UGIB) remains a complex and challenging condition until the diagnostic procedure of an endoscopy is performed. There are a number of possibilities, including spontaneous cessation of small ulcer bleeding, persistent bleeding from a pulsatile artery, and the presence of a malignant condition. Regardless of the underlying cause, the primary goal of treatment is to maintain hemodynamics and rapidly identify and treat the underlying cause. We assessed UHR in our study to identify patients who are at high risk and require urgent attention for endoscopy. Research findings suggest a significant link between UHR and bleeding. This association is of great importance for understanding and predicting the magnitude and severity of hemorrhagic events. Based on the analysis of the data we collected, it is recommended that the urea/hemoglobin ratio be used as an important prognostic indicator in determining the need for endoscopy, blood transfusion, and subsequent intensive care unit monitoring in cases of upper gastrointestinal bleeding. This recommendation emphasizes the need to incorporate this ratio into routine clinical practice.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the Batman Training and Research Hospital Scientific Researches Ethics Committee (Date: 22.12.2022, Decision No: 324).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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Original Article

MEDICINE PALLIATIVE CARE

DOI: 10.47582/jompac.1346914

J Med Palliat Care. 2023;4(5):505-510

Does end-tidal carbon dioxide monitoring in gastrointestinal endoscopy have a clinical advantage?

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Cite this article as: Özden MGN, Karslı S, Bakan N. Does end-tidal carbon dioxide monitoring in gastrointestinal endoscopy have a clinical advantage?. *J Med Palliat Care*. 2023;4(5):505-510.

Received: 20.08.2023 ◆ **Accepted**: 26.09.2023 ◆ **Published**: 27.10.2023

ABSTRACT

Aims: In current guidelines recommended CO_2 monitoring for patient safety and comfort in sedation for gastrointestinal endoscopy. We aimed to investigate whether carbon dioxide monitoring, which was developed for the early detection of adverse respiratory events shows the expected benefit in its clinical use.

Methods: ASA I-II patients, average age 48±15, were divided into two groups, standard monitoring was performed on Group S (n=30), and $EtCO_2$, Integrated Pulmonary Index measurements were added to the Group K (n=30). Patients received Fentanyl 1µgr/kg, propofol 1 mg/kg and propofol 10-30 mg in a bolus by providing BIS to be 60-85. Adverse respiratory events were recorded. The time to Fast-tracking score being 14 was recorded and patients with two consecutive Fast-tracking scores of 14 were discharged. Patient satisfaction was questioned the next day.

Results: There is no difference between groups in heart rate and mean arterial pressure, and decreased during the procedure compared to baseline in both groups. While $EtCO_2$ was similar at all times, IPI was lower than baseline. While the processing time was 21±6 in Group S, it was 38±11 in Group K. No adverse respiratory events occurred. Recovery heart rates, peripheral oxygen saturation, mean arterial pressure and scores were similar. There was no difference in patient satisfaction.

Conclusions: There wasn't a clinical advantage with measuring $EtCO_2$ added to the standard monitoring in gastrointestinal tract endoscopy. We believe that more studies are needed on optimum monitoring during moderate sedation in patients with less clinical risk.

Keywords: Capnography, gastrointestinal endoscopy, sedation.

Oral Presentation: 1st International Anesthesiology and Reanimation Symposium (it was included in the oral presentation competition)

INTRODUCTION

Endoscopic interventions are very important in the investigation of the gastrointestinal tract and in the diagnosis of pathologies. However, these procedures can be uncomfortable and painful for the patient. Sedation is required for patient comfort and ease of invention.[1]

Sedation is applied to relieve the patient's anxiety and discomfort by creating a depression at the conscious level, to ensure the best application of the procedure, and to prevent the patient from remembering the procedure. For safe sedation, patients need close observation and appropriate monitoring should be provided for this.[2]

Sedation applied for gastrointestinal procedures is moderate sedation that responds to verbal or tactile stimuli, does not require airway intervention, provides adequate spontaneous breathing, and preserves cardiac functions.[3] However, deep sedation or general anesthesia situations requiring intervention may occur during moderate sedation.

In recent years, monitoring techniques showing ventilation by measuring end-tidal carbon dioxide and sedation level by measuring electrical activity of brain have been developed. In current guidelines, CO_2 monitoring is recommended for moderate and deep sedation.[4] The formation of deep sedation or general anesthesia and the undesirable respiratory events prolong the recovery time of the patients after the invention.[5]

In our study, we aimed to investigate whether carbon dioxide monitoring, which was developed for the early detection of adverse respiratory events that may develop in patients who received moderate sedation during the endoscopic intervention in the gastrointestinal system, shows the expected benefit in its clinical use.

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METHODS

This prospective randomized study was carried out with the permission of the Health Sciences University Sureyyapasa Chest Diseases and Thoracic Surgery Training and Research Hospital Clinical Researches Ethics Committee (Date: 09.05.2019, Decision No: 053). The necessary informed consents of the patients were completed before the procedure. All procedures were carried out under the ethical rules and the principles of the Declaration of Helsinki.

The study was completed with a total of 60 ASA I-II patients, aged between 18-70 years, undergoing esophagogastroduodenoscopy in an education and research hospital. Patients with heart disease, lung disease, liver failure, kidney failure, psychiatric drug use, history of malignancy, morbidly obese, pregnant or breastfeeding patients were not included in the study. The study was finished with 60 patients who were sedated during the gastrointestinal endoscopy examination between May and December 2019. Randomization was performed by the computer as Group S (n=30) with standard monitoring and Group K (n=30) with end-tidal carbon dioxide ($EtCO_2$) monitoring in addition to standard monitoring. While the heart rate (HR), mean arterial pressure (MAP), peripheral oxygen saturation (SpO_2) measurements and respiratory rate (RR) were recorded in Group S patients; $EtCO_2$, RR, SpO_2, HR and Integrated Pulmonary Index (IPI) interval data were recorded by the capnography (Capnostream® 20p/Covidien) in Group K patients in the endoscopy unit. The IPI score is calculated by the device, and the actual figures of $EtCO_2$, RR and SpO_2, PR values are reduced to a number by mathematical analysis. The device is evaluated in 6 categories ranging from 1 to 10 IPI Score. As seen in the figure; Between 5-10 green areas (safe), 3-4 yellow areas (requiring intervention) and 1-2 red areas (requiring urgent intervention) are accepted (Figure 1).

IPI	Patient Status
10	Normal
8-9	Within normal range
7	Close to normal range – requires attention
5-6	Requires attention and may require intervention
3-4	Requires intervention
1-2	Requires immediate intervention

Figure 1. IPI (integrated pulmonary index)

Ronen M, Weissbrod R Overdyk FJ, Ajizian S. Smart respiratory monitoring: clinical development and validation of the IPI™ (Integrated Pulmonary Index) algorithm. J Clin Monit Comput. 2017; 31(2): 435–442. Published online 2016 Mar 9.

Bispectral index (BIS) monitoring was also performed to monitor the sedation level of all patients participating in the study. Before the invention, propofol (2 mg/kg-1; Polifarma, Istanbul, Turkey) 1 mg/kg i.v. and fentanyl (1 mcg/kg-1; Vem, Istanbul, Turkey) 1 µgr/kg i.v. were administered to patients admitted to the endoscopy unit. The endoscopic invention was allowed to begin at the appropriate sedation depth, and propofol 10-30 mg i.v. was administered if needed, keeping the BIS values of 60-85 until the procedure was completed. Apnea; A cessation of breathing for more than 30 seconds and $EtCO_2$=0 mmHg measured during this time was defined as RR=0. Desaturation is defined as a decrease in the initial SpO_2 value of 4% and below, and this lasted for at least 4 minutes. When apnea and desaturation were observed or IPI <6, it was planned to intervene with a verbal warning, chin-lift maneuver, and increasing oxygen flow for supporting respiration. If the apnea and desaturation times of the patients were prolonged or the SpO_2 value fell below 10% of the initial value despite the interventions, the procedure was terminated and intervention was planned to ensure airway safety and support respiration.

Processing time was defined as the endoscopic intervention time and recorded. Patients who completed the endoscopic procedure were taken to the recovery unit and HR, MAP and SpO_2 of patients were recorded till discharged at 10-minute intervals. The Fast-tracking recovery score was calculated and recorded at 10-minute intervals. Time to Fast-tracking score of 14 was recorded, and patients with two consecutive Fast-tracking scores of 14 were discharged.[6]

The patients were called 24-48 hours later invention and questioned whether they had symptoms such as abdominal distension, fever, pain at the injection site, nausea-vomiting, dizziness and weakness. At the same time, satisfaction from sedation was asked with 5 points Likert scale (1: Very dissatisfied, 2: Dissatisfied, 3: Neutral, 4: Satisfied, 5: Very satisfied).

Statistical Analysis

In order to determine the number of samples, a power analysis was performed using the G*Power (v3.1.7) program. The power of the study is expressed as 1-β (β=probability of type II error), and in general studies should have 80% power. According to Cohen's effect size coefficients; In order to determine the clinical superiority of end-tidal carbon dioxide monitoring in gastrointestinal endoscopies, the calculation made by assuming that the evaluations to be made between two independent groups will have a large effect size (d=0.80), there should be at least 26 people in the groups. Considering that there may be losses during the working process, it was decided to recruit 30 people each.

While evaluating the findings obtained in the study, IBM SPSS Statistics 22 (IBM SPSS, Turkey) program was used for statistical analysis. While evaluating the study data, the conformity of the parameters to the normal distribution was evaluated with the Shapiro Wilks Test. While evaluating the study data, in addition to descriptive statistical methods (mean, standard deviation, frequency), Student's t-test was used for comparisons of normally distributed parameters between two groups, and Mann Whitney U test was used for comparisons of non-normally distributed parameters between two groups. Paired Sample t-test was used for in-group comparisons of normally distributed quantitative data, and Wilcoxon Signed Ranks test was used for in-group comparisons of non-normally distributed parameters. Fisher's Exact test, Fisher Freeman Halton test and Continuity (Yates) Correction were used to compare qualitative data. Significance was evaluated at the p<0.05 level.

RESULTS

There was no difference in demographic data between groups. While the amount of propofol used in Group K was found to be statistically higher than in Group S (p=0.008), the processing time of the K Group was also statistically significantly longer (p<0.001). There was no statistically significant difference between the groups in terms of patient satisfaction distribution rates (Table 1).

Table 1. Demographic data and distribution of general characteristics

	Group K Median±SD1	Group S Median±SD	p
Age (year)	45.7±17.73	50.3±12.94	0.256
Weight (kilogram)	69±13.24	69.2±9.99	0.948
	n (%)	n (%)	
Sex Male Female	12 (40%) 18 (60%)	12 (40%) 18 (60%)	1.000
Mallampati I II III	8 (26.7%) 22 (73.3%) 0 (0%)	9 (30%) 20 (66.7%) 1 (3.3%)	0.779
ASA 2 I II	8 (26.7%) 22 (73.3%)	10 (33.3%) 20 (66.7%)	0.778
Initial Recovery FT3 (median)	13.1±0.8 (13)	13.07±0.78 (13)	0.800
Time FT3 is 14 (minute) (median)	3.37±3.42 (2.5)	3.43±3.44 (2.5)	0.952
Patient satisfaction (median)	4.87±0.35 (5)	4.83±0.38 (5)	0.720
Fentanil (µg)	72.17±13.88	74.5±13.09	0.506
Propofol (mg)	177±59.26	138.33±50.11	0.008*
procedure time (minute)	38.83±11.19 (35)	21.0±5.93 (20)	0.000*
	n (%)	n (%)	
Patient satisfaction 4	4 (13.3%)	5 (16.7%)	0.500
Patient satisfaction 5	26 (86.7%)	25 (83.3%)	

1Standard Deviation, 2American Society of Anesthesiologists Classification, 3 Fast-tracking recovery score., *p<0.05

There was no statistically significant difference between the groups in terms of HR. In Group K, decreases were significant at all times compared to the initial HR values (p<0.001, p=0,001, p=0,005). While the decreases observed in the 1st, 5th, 10th, 15th and 20th minute HR values in Group S were significant compared to the initial HR values (p<0.001, p=0.001, p<0.001, p=0.001, p=0.004) (Figure 2). There was no statistically significant difference in MAP measurements between the groups at all times. In both groups, it was found to be statistically significantly lower than the initial MAP values in all-time measurements (p<0.001, p=0.002, p=0.023).

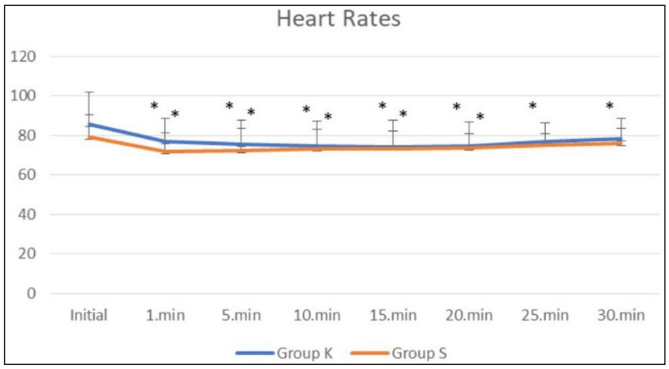

Figure 2. Heart rates of groups

When the SpO_2 values between the groups were compared, there was no statistically significant difference at all times. Compared with the baseline SpO_2 values in Group K, it was statistically significantly lower at other times (p=010, p=0.006, p<0.001, p=0.014, p=0.013). While the decreases observed in SpO_2 values at the 1st, 5th, 10th, 15th and 20th minutes were significant (p=0.006, p=0.018, p=0.038, p=0.002, p=0.031) at the baseline SpO_2 values in Group S (Figure 3). There was no statistically significant difference between the groups in terms of mean RR at all times. There was no statistically significant change in RR at all times compared to the initial RR in Group K. While there was no statistically significant change in the 25th and 30th minute RR in Group S, it was lower when compared to the baseline for other time measurements (p<0.001, p=0.001, p=0.003, p=0.012, p=0.033) (Figure 4).

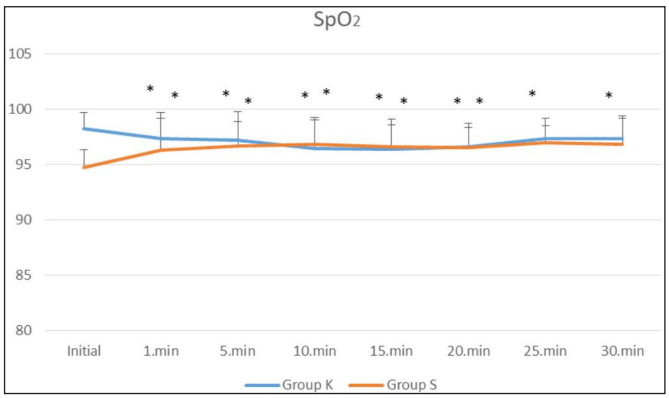

Figure 3. Peripheral oxygen saturation (SpO_2) of groups

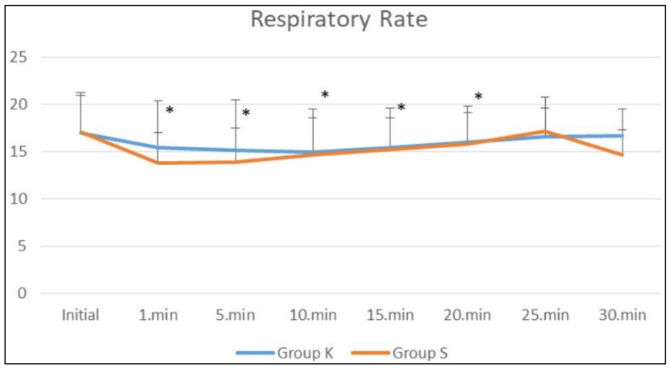

Figure 4. Respiratory rates of groups

There was no statistically significant change in $EtCO_2$ values at all times in group K. IPI values were found to be statistically low at all times compared to the baseline value (p=0.002, p=0.003, p<0.001, p=0.001, p<0.001, p=0.001, p=0.047), and measured between 7-10, they did not fall below 7 in any of the cases (**Figure 5**). There was no statistically significant difference in BIS measurements at all times, except for the 15th minute BIS values (p=0.016). No adverse respiratory events were observed in any patient during the procedure.

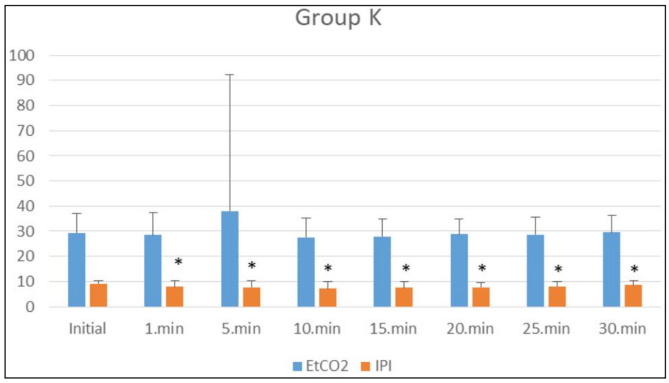

Figure 5. End-tidal carbon dioxide ($EtCO_2$) and IPI values of groups

There was no statistical difference between the groups in terms of HR, SpO_2 and MAP during the recovery period.

DISCUSSION

In gastrointestinal procedures, sedation is applied to reduce the patient's anxiety and discomfort caused by the procedure. The drugs used for sedation may differ according to the procedure, the patient and the center. Undesirable depressing effects of these different drugs on the respiratory system can be observed.[7] Propofol with rapid-onset and short-acting properties also has adverse effects on respiration.[8] Although we used fentanyl together with propofol to reduce pain during moderate sedation in our study, we did not detect any desaturation and/or apnea periods that required intervention in any of the patients. We think that because the processing time of the group monitoring for carbon dioxide was longer than the group with standard monitoring, so the amount of propofol consumed was higher.

It is necessary to monitor the vital functions of the patient in order to detect complications that may develop during sedation. Heart rate and blood pressure for hemodynamic monitoring, peripheral oxygen saturation and respiratory rate for respiratory functions are among the parameters used for this purpose.[9]

The development of capnography technology, which measures the amount of carbon dioxide in breathing air, has provided ease of use and reduced the cost. In the meta-analysis of Waugh et al.[10] they calculated that respiratory depression was detected 17.6 times more when oximetry was used together with capnography in patients who underwent deep sedation. Klare et al.[11] on the other hand, found that carbon dioxide monitoring did not reduce the incidence of hypoxemia, but was useful in detecting apnea periods. In addition, Beitz et al.[12] found that carbon dioxide monitoring in addition to respiratory rate decreased the incidence of desaturation and hypoxemia during propofol sedation applied in colonoscopy procedures. Qadeer et al.[13] showed that monitoring the respiratory activity of ERCP/EUS patients with capnography did not reduce the frequency of hypoxemia, severe hypoxemia, and apnea. There were no adverse events in our patients during our study.

IPI is a value that is used in respiratory function by calculating capnography and pulse oximetry parameters mathematically. It is thought that it can be used in the early detection of adverse respiratory events that may develop in sedated patients.[14,15] There are studies supporting that using the IPI value is beneficial in the sedation of different procedures.[16,17] However, Riphaus et al.[18] showed that the IPI value did not provide clinical benefit in addition to standard monitoring in the evaluation of the respiratory activity of sedated patients in endoscopic interventions in their study with patients who were deeply sedated.

In their study, Oba et al.[19] examined arterial blood gas samples while applying sedation to colonoscopy cases and found that the follow-up of $EtCO_2$ was compatible with $PaCO_2$ values in arterial blood gas samples. In addition, they stated that IPI monitoring did not provide clinical benefit in the early recognition of hypoventilation. In our study, IPI values were calculated above 7 in general during the procedure, and it was evaluated as a situation that is close to the normal limit but requires attention.

In our study, we applied BIS monitoring to our patients to measure the depth of sedation and adjust the drug dose and it was in the sedation range of 60-85 for all patients. It has been shown that BIS monitoring for sedation applied in endoscopy procedures reduces hypoxia, shortens the procedure time, and increases the satisfaction of the patient and the operator.[20] There was no difference in BIS values between the groups in our study.

In many studies, it has been shown that there was no difference in heart rate, arterial pressure, and peripheral oxygen saturation values between the groups with standard monitoring and the groups with standard monitoring with additional carbon dioxide monitoring.[11,12,19] Similar results were obtained in our study.

The use of propofol for sedation seems to be more advantageous than other agents as it shortens the recovery time. It is also a safe agent in terms of complications and side effects. However, close follow-up after sedation is needed and the patient should not be discharged before full recovery.[20]

In previous studies, it has not been shown that carbon dioxide monitoring during sedation has an advantageous effect on recovery time.[11,12,18] In our study, there was no difference between the groups in the discharge of the patients we followed up with the Fast-tracking recovery score. There was no difference in the hemodynamic and respiratory measurements of the patients at recovery.

When they were called and questioned later by phone to evaluate the satisfaction, it was seen that there was no difference between the groups in terms of patient satisfaction. These results are consistent with the results of the studies of Klare et al and Riphaus et al.[11,18]

There are some limitations of our study. Of these, none of the patients, the doctor performing the procedure, and the anesthetist administering the sedation were blind. Therefore, errors may occur during the observation. In addition, the number of samples used in the study may not have been sufficient to detect adverse respiratory events. We think that carbon dioxide monitoring can be effective in the early detection of respiratory complications with studies involving more patients.

CONCLUSION

In our study, the advantage of using capnography in addition to standard monitoring during sedation in the endoscopic examination of the gastrointestinal tract was not demonstrated in terms of patient safety, early recovery and patient satisfaction. At appropriate BIS levels of moderate sedation provided with propofol; we think that it does not increase the likelihood of adverse respiratory events in patients with low comorbidity.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the Health Sciences University Sureyyapasa Chest Diseases and Thoracic Surgery Training and Research Hospital Clinical Researches Ethics Committee (Date: 09.05.2019, Decision No: 053).

Informed Consent: Written consent was obtained from the patient participating in this study.

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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Original Article

MEDICINE PALLIATIVE CARE

DOI: 10.47582/jompac.1344838

J Med Palliat Care. 2023;4(5):511-515

Evaluation of endothelial dysfunction and inflammation in recovered COVID-19 patients

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Cite this article as: Doğan Y, Turunç Özdemir A. Evaluation of endothelial dysfunction and inflammation in recovered COVID-19 patients. *J Med Palliat Care*. 2023;4(5):511-515.

Received: 17.08.2023 ◆ **Accepted**: 27.09.2023 ◆ **Published**: 27.10.2023

ABSTRACT

Aims: In our study, we aimed to evaluate the endothelial functions and hemogram parameters, which are considered as inflammation markers, in young people with a history of COVID-19 infection.

Methods: This prospective study included 109 recovered COVID-19 patients and 50 healthy controls. Demographic characteristics, laboratory values and flow-mediated vasodilation test (FMD) results of the groups were compared.

Results: Demographic and biochemistry parameters of the groups were similar. The calculated FMD values were significantly lower in the recovered COVID-19 patient group compared to the control group (8.66±3.31 vs 11.69±3.01; p=0.001). While there was no difference between the groups in terms of neutrophil/lymphocyte ratio (NLR) and Platelet/Lymphocyte ratio (PLR), systemic immune-inflammation index (SII) was found to be higher in the patient group with recovered COVID-19 patients (p=0.02). In correlation analysis, there was a low moderate negative correlation between FMD and SII (r=-0.35, p=0.002).

Conclusion: FMD measurement and SII are simple, easily accessible parameters that can be useful in the early period to evaluate cardiovascular risks in the long term after COVID-19. There is a need for larger and multicenter studies on this subject.

Keywords: Endothelial dysfunction, COVID-19, inflammation.

INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), is a novel viral pneumonia that evolved into a pandemic within three months of the first confirmed cases. Although COVID-19 primarily affects the lungs, cardiovascular involvement has also been widely reported.[1] Direct myocardial cell damage, myocardial oxygen supply/demand mismatch, acute plaque ruptures leading to acute coronary syndrome as part of systemic inflammation, and catecholamine surges, and increased thrombosis have been reported as cardiac manifestations. Some of these are directly caused by the disease, while others are associated with potential side effects of drugs used in the treatment of COVID-19.[2,3]

Although endothelial dysfunction and inflammation play an important role in the initiation and progression of atherosclerotic disease, the biochemical and cellular events that initiate atherosclerosis and lead to its progression are not fully understood. During the acute phase of COVID-19 infection, a cytokine storm and subsequent endothelial damage and thrombosis are involved in the pathogenesis of cardiovascular complications.[4] However, few studies have focused on endothelial dysfunction in patients recovering from COVID-19.

Flow-mediated dilatation (FMD) is a non-invasive method that allows accurate assessment of the function of vascular endothelial cells. Decreased FMD, indicating endothelial dysfunction, is a predictive factor for major vascular complications, including cardiovascular disease.[5]

The systemic immune-inflammation index (SII), which is calculated by using platelet, neutrophil, and lymphocyte counts together, is a much more important marker of inflammation and immune response. Studies have shown that high SII values are associated with disease severity and poor prognosis in many diseases.[6,7]

Measuring endothelial function, in addition to markers of myocardial damage and pulmonary function in

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patients recovered from COVID-19, may be a possible tool for early detection of vascular sequelae after COVID-19. The aim of this study was to assess the risk of endothelial dysfunction and preatherosclerosis in young people with a history of COVID-19 infection by measuring FMD and investigating inflammation parameters.

METHODS

This prospective study was carried out with the permission of Kayseri City Hospital Clinical Researches Ethics Committee (Date: 10.02.2022, Decision No: 2022/578). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study included patients aged 18-40 years who presented to cardiology outpatient clinic of our hospital between 01.10.2022 and 05.05.2022 dates and had history of confirmed COVID-19 by laboratory data. Patients who have passed at least 3 months after COVID-19 infection were included. Healthy individuals aged 18-40 years without chronic disease and without COVID-19 infection were included as the control group. Exclusion criteria were known cardiovascular disease, hyperlipidemia, hypertension, diabetes mellitus, chronic renal failure, thyroid disease, rheumatologic disease, malignancy, obesity, active infection, smoking, and alcohol use.

Data on age, gender, body mass index (BMI), vital signs such as blood pressure (BP) and heart rate, biochemical parameters, and hemogram parameters were filled in detail in the relevant sections of the case report form. Blood samples were taken for hemogram and biochemistry parameters during admission. Venous blood draws were performed following vascular measurement. Neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) and systemic immune-inflammation index score (platelet × neutrophil/lymphocyte counts) were calculated according to laboratory results.

Flow-mediated Vasodilation Test (FMD)

FMD measurement was performed by the ultrasonographic measurement technique of the brachial artery. The systolic and diastolic blood pressures of the patients were measured after 10 minutes of rest before the FMD measurement. Patients were placed in a comfortable supine position, and the brachial artery was palpated in the longitudinal plane just above the antecubital fossa. The transducer was placed over the right brachial artery tracing, and the brachial artery was visualized longitudinally in the area where there was no tortuosity and the best view was obtained. The diameter of the brachial artery was measured three times from intima to intima, and the average of these measurements was recorded as the basal diameter (BD). These measurements from the brachial artery were taken at the end of diastole, according to ECG monitoring. The cuff of the sphygmomanometer was placed on the upper part of the right antecubital fossa to create a brachial artery flow stimulus. After baseline measurements were recorded, the cuff pressure was increased to 50 mmHg above the patient's systolic blood pressure for complete cessation of arterial flow, and the cuff was held in this position for 5 minutes after antegrade blood flow was interrupted. Antegrade blood flow was interrupted, and ischemia was created. After the cuff was lowered, 2-dimensional images of the brachial artery in the longitudinal plane were taken until 60 seconds later. The mean of three different measurements was recorded as the post-flow brachial artery lumen diameter (endothelium-dependent vasodilator response-EBVR). FMD was expressed as a percentage increase relative to baseline vessel diameter (BC). Endothelium-dependent dilatation was calculated by the equation FMD="(EBVR-BC) \BC"X100.

Statistical Analysis

The categorical variables are expressed as percent while continuous variables are expressed as mean±standard deviation. The categorical variables were compared using the Chi-square test. The normal distribution of continuous variables were tested using Kolmogorov-Smirnov test and histograms. The variables with normal distribution was assessed using Student's t test while those with skewed variables were assessed using Mann Whitney U test. Associations between FMD and SII, Hs-CRP, NLR, PLR were analyzed using Pearson or Spearman correlation. All statistical analyses were performed using SPSS version 22.0 (Statistical Package for Social Sciences; SPSS Inc., Chicago, IL). A p value<0.05 was considered as statistically significant.

RESULTS

A total of 159 people were included in the study, including 109 patients who had recovered COVID-19 in the patient group (group 1) and 50 in the control group (group 2). The mean age of the group with COVID-19 infection was 30.86±6.55 years, and %48.3 of the patients were male. The groups had similar characteristics in terms of gender and mean age, and no statistically significant difference was observed. There was no difference in BMI between the groups. There was no significant difference between the 2 groups in terms of systolic blood pressure (SBP), diastolic blood pressure (DBP), and resting heart rate (**Table 1**).

Table 1. Demographic and laboratory variables of the study population

Variables	Recovered COVID-19 (n=109)	Control group (n=50)	P
Age (years)	30.86±6.55	30.02±7.69	0.54
Male/Female (n (%))	48.3	48.6	0.97
SBP (mmHg)	110 (90-150)	110(80-140)	0.48
DBP (mmHg)	70 (50-90)	70 (50-80)	0.23
Heart rate (BPM)	76.86±8.46	77.65±9.96	0.62
BMI (kg/m²)	24.15±2.90	23.91±2.68	0.130
Fasting plasma glucose (mg/dl)	90 (58-110)	86 (62-106)	0.108
Creatinine (mg/dl)	0.70 (0.30-1.20)	0.80 (0.30-1.10)	0.53
AST	19.38±5.92	19.20±6.26	0.86
ALT	20.21±5.37	20.14±5.77	0.91
LDL	96.12±31.21	95.26±29.19	0.487
HDL	32.04±20.84	34.93±21.21	0.109
Triglyceride (mg/dl)	239.92±51.82	192.7±60.43	0.422
Total cholesterol (mg/dl)	152.28±44.98	147.14±43.23	0.184
Hs-CRP (mg/dl)	1.73 (0.69-9.17)	1.67(1.18-7.2)	0.345
FMD (%)	8.66±3.31	11.69±3.01	0.001

SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; HDL, high density lipoprotein; AST, Aspartate Aminotransferase; ALT, Alanine Aminotransferase; FMD, Flow-Mediated Dilation

There were no differences between the groups in terms of glucose, creatine, AST/ALT, and lipid profiles (Table 1). Hs-CRP values were similar between the groups. The comparison of hematologic data for both groups is shown in Table 2. Hemoglobin, white blood cell count, platelet count, and mean platelet volume were similar in both groups. In addition, neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) did not differ between the groups, while systemic immune-inflammation index (SII) was higher in the patient group with COVID-19 infection (p=0.02) (Table 2).

Table 2. Hemogram variables of the study population

Variables	Recovered COVID-19 (n=89)	Control Group (n=50)	P
WBC (×10³/µl)	7417.04±1725.48	7203.42±1035.85	0.54
Neutrophil (K/ml)	4702.27±1429.73	4360.00±985.54	0.24
Lymphocyte (K/ml)	1950 (400-3800)	2100 (900-3700)	0.55
Hemoglobin (g/dl)	14.41±1.69	13.84±1.39	0.10
Platelet (K/ml)	233.50 (113.00-501.00)	243.00 (123.00-371.00)	0.46
MPV	10.05 (8.40-12.10)	10.00 (7.90-11.70)	0.56
NLR	2.40 (0.90-9.10)	2.10 (1.10-6.70)	0.13
PLR	143.25 (50.9-485.50)	116.80 (58.50-332.20)	0.09
SII	582.25 (58.60-2834.70)	440.30 (61.80-1699.30)	0.02

MPV, mean platelet volume; NLR, neutrophil lymphocyte ratio; PLR, platelet lymphocyte ratio; SII, systemic immune- inflammation index; WBC, white blood cell

The calculated FMD values were significantly lower in the patient group with COVID-19 infection compared to the control group (8.66±3.31 vs. 11.69±3.01; p=0.001). In correlation analysis, there was a low moderate negative correlation between FMD and SII (r=-0.35, p=0.002). There was a weak negative correlation between FMD and CRP (r=-0.251, p=0.036). There was a weak negative correlation between FMD and NLR and PLR (Table 3).

Table 3. Correlation analysis between FMD and other variables in the patient group

	FMD	
Variables	r	p
SII	-0.35	0.002
Hs-CRP	- 0.251	0.036
NLR	-0.238	0.045
PLR	-0.280	0.029

NLR, neutrophil lymphocyte ratio; PLR, platelet lymphocyte ratio; SII, systemic immune- inflammation index, hs-CRP high-sensitivity C-reactive protein, FMD, Flow-Mediated Dilation.

DISCUSSION

In our study, FMD values caused by endothelium-dependent reactive hyperemia were significantly lower in patients who recovered from COVID-19 infection compared to the control group. SII, which is predicted as a marker of inflammation, was found to be higher in patients who recovered from COVID-19 infection compared to the control group, and SII values were shown to be independently associated with decreased FMD.

Myocardial damage and heart failure due to both arrhythmic and ischemic complications have been reported in COVID-19 patients.[8,9] In addition, more severe forms have been shown to be associated with a high risk of stroke and thromboembolism.[10] However, cardiovascular risk may persist beyond the acute phase. Abnormalities were found by echocardiography and cardiac MRI in patients who recovered from COVID-19 but subsequently had a high rate of arterial and venous events.[11,12] However, despite the evidence, the mechanisms underlying these acute and post-acute manifestations of COVID-19 are still under investigation.

Recent epidemiological data show that the increased risk of arterial and venous thrombotic events persists for up to 12 months after recovery, even in non-hospitalized patients.[13] Several mechanisms have been proposed in the pathogenesis of this, including immune activation, persistent SARS-CoV-2 infection, reactivation of latent viruses, prolonged inflammation, and intense cardiopulmonary deconditioning.[14-18] Approximately 2.5% of recovered COVID-19 patients reported arterial and venous thrombosis events 30 days after discharge.[19]

However, it is not unreasonable to argue that COVID-19 has been an endothelial disease since the first moments of the pandemic.

FMD has been widely accepted as an accurate and non-invasive method for the clinical assessment of endothelial function, providing important prognostic data beyond traditional cardiovascular risk factors. Each 1% absolute increase in FMD has been shown to be associated with a 12% to 13% reduction in CV events.20,21 Endothelial dysfunction is a predictor of subclinical atherosclerosis and subsequent long-term cardiovascular events.[22,23] Therefore, early detection reduces the incidence of cardiovascular events, allowing for the combating of adverse events. Endothelial dysfunction has been shown in studies with low FMD values in COVID-19 patients in the acute phase compared to controls.[24] In the study conducted by Çiftel et al.[25] impaired endothelial function was detected with FMD in children diagnosed with COVID-19. While Oliveira et al.[24] showed endothelial vascular dysfunction with FMD at the early stage of the disease in patients hospitalized due to COVID-19, Ambrosino et al.[26] found improvement in FMD after discharge with pulmonary rehabilitation in patients recovering from COVID-19. In our study, we found decreased FMD values in patients without chronic disease and recovered from COVID-19.

Increased neutrophils indicate activation of inflammation, and lymphopenia is an indicator of physiologic stress. NLR indicates the balance between neutrophil and lymphocyte counts and can be considered a measure of systemic inflammation as well as the response to stress. In addition, neutrophils can cause hypercoagulability and are associated with reperfusion injury.[27] It is clear that COVID-19 infection causes severe stress, and it is plausible that it causes a decrease in the number of lymphocytes. Platelets play an important role in hemostasis, a physiological response that occurs to prevent extravasation of blood when vascular damage occurs. They also have both an inflammatory effect and activate the immune system by releasing chemokines and cytokines.[27] Xue et al.[1] showed a positive correlation between SII and COVID-19 severity in their study. Fois et al.[2] found that SII can be used as a biomarker for increased mortality. Salman et al.[3] showed that increased SII levels led to more marked progression and increased intubation and mortality rates. As a result of our study, we concluded that SII obtained from complete blood counts of COVID-19 patients at the time of hospital admission can predict disease progression, disease severity, and mortality in accordance with the literature.

The European Society of Cardiology (ESC) recommends noninvasive procedures, including FMD, for clinical assessment of endothelial function to monitor the risk of long-term cardiovascular complications in the follow-up of recovered COVID-19 patients.[28] The limitations of our study are that it is not multicenter and the number of patients participating is not large.

In the light of the results of our study, we think that FMD, which is a reliable and cost-effective procedure, can be used for cardiovascular system evaluation after COVID-19 in accordance with this recommendation.

CONCLUSION

In our study, we showed that FMD, a marker of endothelial dysfunction, decreased as an indicator of early atherosclerosis in patients who had COVID-19 and recovered. While COVID-19 causes widespread cardiovascular involvement in the acute disease picture, evidence now suggests that patients recovering from COVID-19 also have an increased cardiovascular risk. However, the long-term consequences for healthy survivors are still unclear. Detecting changes at an early stage with easily accessible parameters and determining treatment follow-up protocols accordingly may be useful to reduce cardiovascular disease in the future. Larger-scale, long-term studies are needed for this.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kayseri City Hospital Clinical Researches Ethics Committee (Date:10.02.2022, Decision No: 2022/578).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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Original Article

MEDICINE PALLIATIVE CARE

DOI: 10.47582/jompac.1348845

J Med Palliat Care. 2023;4(5):516-523

Systemic immune inflammation indices: novel predictors for preterm premature rupture of membranes and associated complications

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Cite this article as: Küçükbaş GN, Yavuz A. Systemic immune inflammation indices: novel predictors for preterm premature rupture of membranes and associated complications. *J Med Palliat Care*. 2023;4(5):516-523.

Received: 23.08.2023 ◆ **Accepted**: 29.09.2023 ◆ **Published**: 27.10.2023

ABSTRACT

Aims: This study aimed to investigate the relationship between systemic immune inflammation (SII) and response indices (SIRI), which are new markers of systemic inflammation derived from immune cells, and preterm premature rupture of membranes (PPROM), as well as adverse pregnancy outcomes.

Methods: The retrospective study included 75 women with singleton pregnancies complicated by PPROM between the 24th and 34th gestational week and 75 healthy pregnant women who delivered at term without any additional diseases (control group). Inflammation indices were calculated based on neutrophil (N), platelet (P), lymphocyte (L), and monocyte (M) counts as follows: The neutrophil-to-lymphocyte ratio (NLR)=N/L; the platelet-to-lymphocyte ratio (PLR)=P/L; SII=(N×P)/L; and SIRI=(N×M)/L.

Results: The median NLR (4.8 vs. 3.5, p <0.001), median PLR (145.1 vs. 126.5, p<0.001), median SII (1208.6 vs. 807.4, p<0.001), and median SIRI (3.1 vs. 2.0, p<0.001) were higher in the PPROM group compared to the control group. Multiple logistic regression analysis showed that increased SIRI (OR= 7.05, p=0.010), as well as increased C-reactive protein levels were determined as independent predictors of PPROM. In the PPROM group, the SIRI was higher in the presence of combined complications compared to without complications (3.4 vs. 2.5, p<0.001). The SIRI showed superior diagnostic performance in predicting the presence and complications of PPROM compared to other inflammation indices.

Conclusion: The PPROM group had higher leukocyte-based inflammation indices compared to the control group. Due to the superior diagnostic performance of the SIRI in distinguishing both PPROM and combined complications compared to other leukocyte-based inflammation indices, it may serve as a significant screening tool for PPROM.

Keywords: Preterm premature rupture of membranes, immune inflammation index, pregnancy complications, neonatal outcomes

INTRODUCTION

Preterm premature rupture of membranes (PPROM) is defined as the rupture of the membranes prior to 37 weeks of gestation, occurring without any initiation of labor.[1] It complicates about 3% of pregnancies and heightens the risk of chorioamnionitis, placental abruption, preterm birth, and neonatal challenges such as respiratory distress syndrome, necrotizing enterocolitis, and intraventricular hemorrhage.[2] Although the exact pathophysiological mechanism of PPROM has not been clearly defined, it is widely recognized that inflammation plays a significant role in the rupture of fetal membranes.[3] This is consistent with the inclusion of antibiotic administration in the clinical management of PPROM.[4]

It has been established that PPROM can occur with intra-amniotic infection (detectable microorganisms along with high interleukin-6 (IL-6) concentrations in the amniotic fluid), sterile intra-amniotic inflammation (high IL-6 concentrations without detectable microorganisms), or without intra-amniotic inflammation (low IL-6 concentrations).[5] On the other hand, changes in enzymes such as tropoelastins, elastin cross-linking enzymes, lysyl oxidase, and lysyl oxidase-like enzymes, which are involved in the amniotic extracellular matrix and contribute to the mechanical function of the amnion, could make the membrane more prone to early rupture.[6] Additionally, the intrauterine environment undergoes redox changes during pregnancy. Imbalanced redox changes can lead to the accumulation of reactive oxygen species (ROS), and an excessive release of cytokines, chemokines, growth factors, and matrix metalloproteases (MMPs).[7] For these reasons, the inflammatory response triggered by the immune system may play a significant role in the development of PPROM.

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PPROM, characterized by infection and inflammation, can lead to an excessive release of immune cells.[8] Leukocytes and their subtypes obtained from a complete blood count serve as the first line of defense in an inflammatory milieu.[9] In this context, several studies have reported a significant relationship between various inflammatory markers and PPROM.[10-14] However, biomarkers involving more comprehensive immune cells may enhance the predictive ability of PPROM.

In the landscape of modern medicine, the search for comprehensive and reliable biomarkers to gauge individuals' overall health and prognostic potential has become increasingly important.[15,16] Within this realm, systemic immune inflammation (SII) and response (SIRI) indices have emerged as promising candidates for providing deeper insights into the functioning of the immune system and their potential implications across various medical conditions.[17,18] The SII, which is an indicator of inflammatory status, is calculated by platelet count × neutrophil count/lymphocyte count,[19] while the SIRI, which is an indicator of the balance between the inflammatory response and immune status, is calculated by neutrophil count × monocyte count/lymphocyte count.[20] These indices are reported to have significant diagnostic performance in various diseases.[17-22] However, the diagnostic performance of these indices regarding PPROM or adverse pregnancy outcomes has not yet been sufficiently investigated.

We hypothesized that there might be an association between leukocyte-based inflammatory indices and PPROM. Thus, this study aimed to investigate the relationship SII and SIRI indices, which are new markers of systemic inflammation derived from immune cells, and PPROM, as well as adverse pregnancy outcomes.

METHODS

Following the principles set forth in the Declaration of Helsinki, this retrospective study was conducted at the Kocaeli Derince Training and Reseach Hospital Gynecology Clinic between January 2022 and December 2022. The study was carried out with the permission of Kocaeli Derince Training and Reseach Hospital Clinical Researches Ethics Committee (Date: 12.01.2023, Decision No: 2023-001). The local ethics committee waived the requirement of informed consent due to the retrospective nature of the research.

Study Population

A total of 256 women with singleton pregnancies complicated by PPROM between the 24th and 34th gestational week were evaluated retrospectively. The exclusion criteria were multiple pregnancy, smoking or substance abuse, maternal infection (positive cultures of urine, blood, throat swab and cervical swab), fetal infection (positive maternal serum tests indicating acute intrauterine infection test results of toxoplasmosis, cytomegalovirus, rubella or any other microorganism such as anti- cytomegalovirus immunoglobulin-M), gestational or pregestational diabetes mellitus, all types of hypertensive diseases of pregnancy, hematologic or autoimmune diseases, malignancies, poor nutritional status (body mass index <18.5 kg/m2),[23] being on any medication except antenatal supplements, history of invasive procedure or surgery during pregnancy, insufficient cervix, and antenatal trauma. Women with pregnancies complicated with PPROM but who received any treatment of antenatal corticosteroids, magnesium, or antibiotherapy before admission were also excluded. After this exclusion process, 70 women with singleton pregnancies complicated with PPROM between the 24th and 34th gestational week were enrolled in this study. The control group was comprised of pregnant women who delivered at term without any additional diseases and were matched 1:1 in terms of gestational age with the PPROM group.

Study Protocol

PPROM was diagnosed under sterile speculum examination either with the visualization of amniotic leakage from the cervix or with the detection of an amniotic protein called insulin-like growth factor binding protein in the posterior fornix (Amni Sure, QIAGEN, Germantown, USA) complying with the guidelines.[1] After PPROM diagnosis, the pregnant women were admitted to the hospital. After the first blood sample for this study was drawn, a single course of antenatal corticosteroids and antibiotic prophlaxis were administered. Upon admission, 1 gram of azithromycin, orally, and 2 grams of ampicillin, intravenously, were administered every 6 h for the first 2 days, followed by 500 mg of amoxicillin, orally, every 8 h for an additional 5 days. This prophylaxis complied with the ACOG Guidelines.[24] Delivery was planned at the 34th week of gestational age unless chorioamnionitis, placental abruption, or fetal distress were present.[1] From hospitalization to delivery, the physical and laboratory signs and findings of chorioamnionitis, placental abruption, or fetal distress were investigated.

The demographic and clinical data, such as maternal age, gravida, parity, abortus, gestational week at amniorrhexis, number of days until delivery, delivery mode, birth weight, gender, examination findings, PPROM complications, need for neonatal intensive care unit (NICU) admission, and days of stay were extracted from the electronic records of the patients. Infants were stratified according to their birth weight into the following categories: those weighing 2500 grams or more were classified as having a normal birth weight, those below 2500 grams as low birth weight, those below 1500 grams as very low birth weight, and those under 1000 grams as extremely low

birth weight. Infants with a gestational age of 37 weeks and above were categorized as term, those between 34-37 weeks as late preterm, those between 32-34 weeks as moderate preterm, those between 28-32 weeks as very preterm, and those below 28 weeks as extremely preterm.[25] Blood samples of all patients were taken at admission. All samples were analyzed in a single laboratory using the same methodology as described below.

Laboratory Parameters

A Sysmex XN-1000 hematology analyzer (Sysmex USA, Inc. Lincolnshire, IL, USA) was used to evaluate the venous blood samples of the patients. The levels of hemoglobin (photometrically) and C-reactive protein (CRP) (immunoturbidimetric method), and the platelet count (impedance method) were determined. The urine culture test was also used to determine urinary infection diseases.

The inflammation indices were respectively calculated as follows: The neutrophil-to-lymphocyte ratio (NLR)=neutrophil count/lymphocyte count, platelet-to-lymphocyte ratio (PLR)=platelet count/lymphocyte count, SII=(platelet count × neutrophil count)/lymphocyte count, and SIRI=(neutrophil count × monocyte count)/lymphocyte count.[19,20]

Statistical Analysis

All of the data were analyzed with IBM SPSS Statistics for Windows 20.0 (IBM Corp., Armonk, NY, USA). Numerical data determined to be normally distributed based on the results of the Kolmogorov-Smirnov test were given as the mean±standard deviation (SD), while non-normally distributed variables were given as the median (25^{th}-75^{th} quartile). For the comparison of numerical data between the control and PPROM groups, data exhibiting a normal distribution was analyzed using the Student's T-test, whereas data without a normal distribution was analyzed with the Mann-Whitney U test. The SIRI levels did not exhibit a normal distribution. Therefore, for its comparisons among more than two groups, the Kruskall Wallis H test (post-hoc: Dunn test) was used. Categorical variables were given as numbers and percentages, and inter-group comparisons were conducted with the Chi-square and Fisher exact tests. Spearman correlation analyses were applied to evaluate the relationships between the numerical variables. A Spearman correlation coefficient of <0.10 was evaluated as a negligible correlation, 0.10-0.39 as a weak correlation, 0.40-0.69 as a moderate correlation, 0.70-0.89 as a strong correlation, and 0.90-1.00 as an almost perfect very strong correlation.[26] Multivariable logistic regression analysis with the backward Wald method was subsequently performed to identify any possible independent predictors of PPROM. The receiver operating characteristic (ROC) curve analysis was applied to assess diagnostic performance. Threshold values were determined using the Youden index. Comparison of the area under the curves (AUC) was performed with a nonparametric approach using the theory on generalized U-statistics to generate an estimated covariance matrix, as previously reported by DeLong et al.[27] Significance was accepted at p<0.05 (*) for all of the statistical analyses.

RESULTS

The distribution of age, gravida, parity, abortion history, and previous birth history was similar between the PPROM and the control groups. The mean gestational age at diagnosis for the PPROM group was 30.1±3.7 weeks, the median latent period was 8 days, and the rate of the amnisure test was 24.3%. In the women with PPROM, oligohydramnios was detected in 30% and anhydramnios in 20%. Their basic characteristics are shown in Table 1.

Table 1. Demographic and clinical characteristics of the patients.

Variables	Control group n=70	PPROM group n=70	p
Age, years	27.9±5.3	28.3±6.1	0.679
Gravida	3 (2-4)	3 (2-4)	0.905
Parity	1 (0-1)	1 (0-2)	0.715
Abortus	0 (0-1)	0 (0-1)	0.986
Previous birth history, n (%)			0.407
No	27 (38.6)	22 (31.4)	
Vaginal delivery	24 (34.3)	32 (45.7)	
Caesarean section	19 (27.1)	16 (22.9)	-
Gestational age at diagnosis, week	-	30.1±3.7	-
Latent period, days	-	8 (4-18)	
Cervical dilatation, n (%)			<0.001*
Yes	-	39 (55.7)	
No	70 (100)	31 (44.3)	-
Amnisure test, n (%)	-	17 (24.3)	
Amniotic fluid index, n (%)			<0.001*
Normal	70 (100)	35 (50.0)	
Oligohydramnios	-	21 (30.0)	
Anhydramnios	-	14 (20.0)	
Fetal gender, n (%)			0.854
Female	20 (28.6)	22 (31.4)	
Male	50 (71.4)	48 (68.6)	

Data are shown as mean ±SD or median (25th-75th quartile) or number and percentage (%). Abbreviations: PPROM, preterm premature rupture of membranes.

The mean hemoglobin level, mean leukocyte count, mean platelets count, mean neutrophil count, and mean monocytes count, and the median CRP level were higher in the PPROM group compared to the control group, while the median leukocyte count was lower. The median NLR (4.8 vs. 3.5, p<0.001), median PLR (145.1 vs. 126.5, p<0.001), median SII (1208.6 vs. 807.4, p<0.001), and median SIRI (3.1 vs. 2.0, p<0.001) were higher in the PPROM group compared to the control group (Table 2).

Table 2. Comparison of the laboratory findings between the control and preterm premature rupture of membranes groups.

Variables	Control group n=70	PPROM group n=70	p
Hemoglobin, g/dl	10.7±1.1	11.3±1.6	0.006*
Leukocytes, $\times10^3$/µl	9.0±2.0	11.9±3.3	<0.001*
Platelets, $\times10^3$/µl	233.4±64.4	252.2±71.2	0.103
Neutrophils, $\times10^3$/µl	6.5±1.4	8.2±1.5	<0.001*
Lymphocytes, $\times10^3$/µl	1.9 (1.6-2.1)	1.7 (1.5-1.9)	0.042*
Monocytes, $\times10^3$/µl	0.6±0.2	0.7±0.3	<0.001*
NLR	3.5 (3-4)	4.8 (3.9-5.9)	<0.001*
PLR	126.5 (108.5-145.2)	145.1 (117.3-180.8)	0.001*
SII	807.4 (636.7-956)	1208.6 (852.9-1524.1)	<0.001*
SIRI	2.0 (1.6-2.5)	3.1 (2.4-4.3)	<0.001*
PDW, %	15.5±2.7	17.2±2.9	<0.001*
RDW, %	14.4±2.2	14.9±1.8	0.158
MCV, fL	87.9±6.3	89.6±7.8	0.173
MPV, fL	8.8±1.0	9.0±0.8	0.170
CRP, mg/L	1 (0.2-3.1)	8 (3.1-24.0)	<0.001*

Data are shown as mean ±SD or median (25th-75th quartile) or number and percentage (%). Abbreviations: CRP, C-reactive protein; MCV, mean corpuscular volume; MPV, mean platelet volume; NLR, neutrophil-to-lymphocyte ratio; PDW, platelet distribution width; PLR, platelet-to-lymphocyte ratio; PPROM, preterm premature rupture of membranes; RDW, red cell distribution width; SII, systemic immune inflammation index; SIRI, systemic inflammation response index.

Among the potential confounding factors associated with PPROM, hemoglobin, SII, SIRI, platelet distribution width (PDW), and CRP were included in the multivariable logistic regression model. Leukocytes or their subtypes, NLR, and PLR were not included in the multivariable regression model because they caused multicollinearity with the SII and SIRI values. Increased SIRI and CRP levels were determined as independent predictors of PPROM. Accordingly, a 1% increase in the SIRI index increased the risk of PPROM by 7.05-fold (OR=7.05, p=0.010) (Table 3). The threshold value of the SIRI was found to be >2.7 with 81.2% sensitivity and 79.1% specificity (AUC=0.854, p<0.001). The SIRI showed superior diagnostic performance compared to the SII in predicting PPROM (Figure 1A).

Table 3. Independent predictors of preterm premature rupture of membranes.

Variables	Univariable regression analysis			Multivariable regression analysis			VIF
	OR	95% CI	p	OR	95% CI	p	
Hemoglobin	1.41	1.09-1.82	0.008*	-	-	-	1.06
SII	1.04	1.02-1.06	<0.001*	-	-	-	1.56
SIRI	4.6	2.60-8.03	<0.001*	7.05	1.69-57.22	0.010*	1.86
PDW	1.25	1.10-1.43	0.001*	-	-	-	1.14
CRP	2.76	1.34-5.24	<0.001*	1.96	1.09-23.11	0.037*	1.54

CI, confidence interval; CRP, C-reactive protein; OR, odds ratio; PDW, platelet distribution width; SII, systemic immune inflammation index; SIRI, systemic inflammation response index; VIF, variable important factor.

The mean week of delivery, rates of caesarean section, and NICU admission were higher in the PPROM group compared to the control group. The neonatal outcomes of the PPROM group are presented in detail in Table 4. In the PPROM group, there was a moderate negative correlation between the SIRI and the week of delivery (r=-0.492, p<0.001). In PPROM group, SIRI was higher in the presence with complications compared to without complications (3.4 vs. 2.5, p<0.001). In the women with PPROM who developed complications of fetal distress and placental abruption, the median SIRI values were similar However, the median SIRI value in these complication groups was higher compared to the women with PPROM who developed chorioamnionitis complications (Fetal distress: 4.0 vs. Placental abruption: 3.7, vs. Chorioamnionitis: 2.8, p<0.05). In the women with PPROM who developed chorioamnionitis complications, the median SIRI value was similar to those with PPROM without complications (2.8 vs. 2.5, p > 0.05). No significant association was found between the SIRI values and other neonatal outcomes (Table 5). The threshold value of the SIRI in predicting the combined complications of PPROM was >3.2 with 74.8% sensitivity and 76.4% specificity (AUC=0.781, p<0.001). The SIRI showed superior diagnostic performance compared to the SII in predicting the combined complications of PPROM (Figure 1B).

Table 4. Neonatal outcomes of the control and preterm premature rupture of membranes group.

Variables	Control group n=70	PPROM group n=70	p
Week of delivery	39.4±1.2	31.0±2.7	<0.001*
Mode of delivery, n (%)			0.037*
Vaginal delivery	33 (47.1)	21 (30.0)	
Caesarean section	37 (52.9)	49 (70.0)	
Prematurity, n (%)			-
Extreme preterm	-	19 (27.1)	
Very preterm	-	22 (31.4)	
Moderate preterm	-	11 (15.7)	
Late preterm	-	18 (25.7)	
Birth weight, g	3387.8±383.4	1718.1±619.3	<0.001*
Extremely low	-	13 (18.6)	
Very low	-	12 (17.1)	
Low	-	38 (54.3)	
Normal	70 (100)	7 (10.0)	
Complication, n (%)			<0.001*
None	70 (100)	45 (64.3)	
Fetal distress	-	13 (18.6)	
Placental abruption	-	8 (11.4)	
Chorioamnionitis	-	4 (5.7)	
Neonatal outcome, n (%)			<0.001*
No need for NICU	60 (85.7)	20 (28.6)	
NICU admission	10 (14.3)	40 (57.1)	
Mortality	-	2 (2.9)	
Duration of NICU stay, days	7 (5-9)	13 (10-16)	<0.001*

Data are shown as mean ±SD or median (25th-75th quartile) or number and percentage (%). NICU, neonatal intensive care unit; PPROM, preterm premature rupture of membranes.

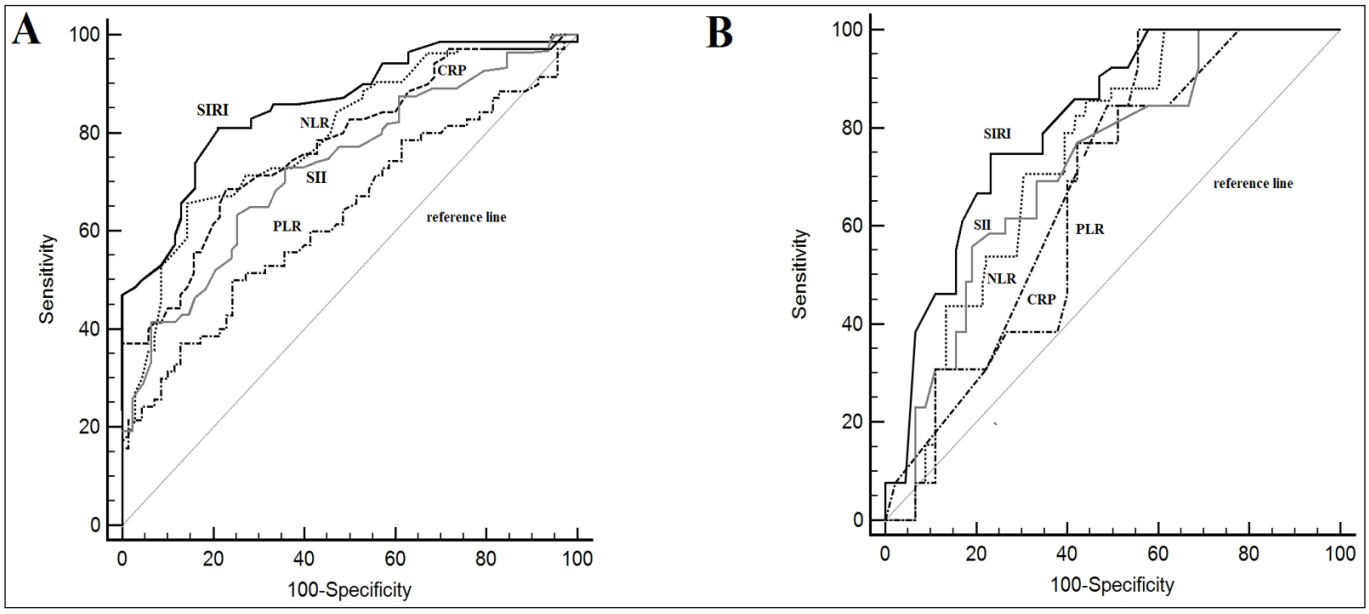

Figure 1. Diagnostic performance assessment of the leukocyte-based inflammatory indices in predicting the presence (A) and combined complications (B) of preterm premature rupture of membranes.

Table 5. Relationship between the SIRI and neonatal outcomes in the preterm premature rupture of membranes group

Variables	Median (IQR) or correlation coefficient (r)	p
Week of delivery	r=-0.492	<0.001*
Mode of delivery		0.460
Vaginal delivery	3.6 (2.4-4.3)	
Caesarean section	3.0 (2.4-4.3)	
Prematurity		0.598
Extreme preterm	3.6 (2.9-5.2)	
Very preterm	3.1 (2.3-4.2)	
Moderate preterm	3.0 (2.4-4.3)	
Late preterm	3.7 (2.3-4.5)	
Birth weight	-	0.755
Extreme	3.7 (2.9-5.2)	
Very low	3.0 (2.6-4.3)	
Low	3.1 (2.3-4.2)	
Normal	3.6 (1.6-4.5)	
Complication		0.031*
None	2.5 (2.1-3.0)	
Fetal distress	3.7 (2.8-4.5)	
Placental abruption	4.0 (3.5-5.1)	
Chorioamnionitis	2.8 (2.2-3.3)	
Neonatal outcome		0.582
No need for NICU	3.5 (2.7-4.2)	
NICU admission	3.0 (2.3-4.7)	
Mortality	4.7 (3.1-6.3)	

IQR, 25th-75th quartiles; NICU, neonatal intensive care unit; PPROM, preterm premature rupture of membranes.

DISCUSSION

To the best of our knowledge, this study is the first in the current literature to highlight the association between old and new leukocyte-based inflammatory indices with PPROM and adverse pregnancy outcomes. The levels of SII and SIRI indices were higher in the PPROM group compared to the control group. The SIRI was identified as an independent predictor of PPROM, demonstrating better diagnostic capabilities than other leukocyte-based inflammatory indices. The women with PPROM who developed complications of fetal distress and placental abruption had higher SIRI levels.

The maternal innate immune system plays a significant role in all stages of human pregnancy, including the integrity of the amniotic membrane and the labor process.[28] As gestation progresses, the fetal membranes experience a systematic collagen degradation process, adapting to the rising uterine pressure and expanding volume. The regulation of the collagenolytic process is facilitated by MMPs.[29] During preterm labor, leukocytes, especially neutrophils, from the human decidua produce multiple inflammatory substances and MMPs that disintegrate the extracellular matrix of the fetal membranes.[7] In cases of PPROM, heightened collagenolysis, reduced membrane collagen content, and increased MMPs activation have been documented.[30] On the other hand, various epidemiological and clinical factors, including maternal reproductive system infections, habits like substance abuse, smoking, and inadequate nutritional status, along with pregnancy-related challenges such as gestational bleeding, multiple gestation, and antenatal trauma, may exacerbate to inflammation and elevate the risk of PPROM.[31,32] Therefore, in this study, we omitted patients with additional risk factors to assess the impact of inflammation on PPROM more objectively.

In the PPROM group, there was a notable difference in the levels of neutrophils, lymphocytes, and monocytes among the leukocyte subtypes when compared to the

control group. Among the potential mechanisms involved in the pathogenesis of PPROM is the inflammatory response caused by redox changes. These changes lead to the release of ROS, cytokines, and MMPs, activating the immune system and resulting in neutrophil and macrophage infiltration in the fetal membranes.[7] This is also supported by high leukocyte levels shown in previous PPROM studies.[33-35] Therefore, there has been growing interest in indices derived from complete blood counts, which can be easily and inexpensively obtained in every hospital, for predicting PPROM.

Consistent with current findings, many studies have shown that the NLR is higher in the PPROM group, while there have been conflicting results regarding the PLR .[13,14,36,37] The conflicting results associated with the PLR are attributed to the PLR not changing in cases of oligohydramnios and with normal amniotic fluid volume.[13] In predicting PPROM, the diagnostic performance of the NLR varies between 70%-84% sensitivity and 58%-90% specificity,[13,38] while the diagnostic performance of the PLR ranges between 58%-63% sensitivity and 63%-74% specificity.[39,40] To the best of our knowledge, this was the first study evaluating the diagnostic performance of the SII and SIRI values in distinguishing PPROM. In the PPROM patients, the SII and SIRI values were higher. On the other hand, some inflammatory mechanisms might have contributed to identifying only CRP and SIRI as independent predictors for PPROM. While elevated levels of CRP in circulation can influence leukocyte function through the activation of the complement system,[41] neutrophils and macrophages are involved in the activation and regulation of platelets.[42] It has been shown that platelet indices such as PDW and plateletcrit exhibit a low diagnostic performance in PPROM.[43] This is also consistent with the conflicting results of platelet or PLR in the current literature.[13,14,36,37] All of these findings suggest that neutrophil-macrophage activation may be more dominant in the inflammatory response that plays a role in the pathogenesis of PPROM. Consistent with this, in distinguishing PPROM, the SIRI demonstrated superior diagnostic performance compared to other leukocyte-based inflammatory indices. Therefore, the superior diagnostic performance of the SIRI can be attributed to the activation of neutrophils and macrophages involved in the pathogenesis of PPROM.[7]

In PPROM, which complicates approximately 3% of pregnancies, maternal inflammation plays a significant role in neonatal outcomes.[44] Due to inflammation, the fetus suffers damage and can experience severe complications during the neonatal period, including intraventricular hemorrhage, respiratory distress, and even neonatal compromise.[45] The SIRI was notably linked to adverse neonatal outcomes, particularly fetal distress, and placental abruption. Fetal distress and placental abruption are urgent obstetric situations that necessitate immediate delivery. They often result in a grim prognosis for newborns due to the lack of time for antenatal corticosteroid administration, leaving preterm infants vulnerable to complications associated with prematurity. Previous studies have shown that SII, as well as the NLR and PLR, are significant predictors for forecasting sepsis or adverse neonatal outcomes in PPROM.[14,39,46] However, the SIRI was more successful in predicting composite complications than SII, the NLR, and PLR. Therefore, the SIRI, which encompasses a more comprehensive set of immune cells, could be a significant screening tool in predicting PPROM and adverse neonatal outcomes.

This study had certain limitations. Firstly, due to its retrospective nature, cytokines and chemokines that play a role in PPROM could not be assessed. Additionally, evaluating leukocyte subtypes with flow cytometry analysis might be more elucidative in the development of PPROM. Assessing these factors in large-scale prospective studies could further clarify the role of inflammation indices in PPROM cases.

CONCLUSION

The PPROM group had higher leukocyte-based inflammation indices compared to the control group. Notably, the SIRI demonstrated superior diagnostic performance in distinguishing both PPROM and combined complications compared to other leukocyte-based inflammation indices. In PPROM, composite indices encompassing a broader range of immune cells may serve as more significant screening tools.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kocaeli Derince Training and Reseach Hospital Clinical Researches Ethics Committee (Date: 12.01.2023, Decision No: 2023-001).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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Original Article

MEDICINE PALLIATIVE CARE

DOI: 10.47582/jompac.1352478

J Med Palliat Care. 2023;4(5):524-529

Evaluation of clopidogrel use on gastric precancerous lesions: does it have chemopreventive effect?

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Cite this article as: Akyol T. Evaluation of clopidogrel use on gastric precancerous lesions: does it have chemopreventive effect?. *J Med Palliat Care*. 2023;4(5):524-529.

Received: 30.08.2023 ◆ **Accepted**: 03.10.2023 ◆ **Published**: 27.10.2023

ABSTRACT

Aims: Gastric malignancies are the third most common cause of cancer-related deaths. Although aspirin and clopidogrel have been reported to reduce the risk of colorectal cancer, their effects on gastric cancer are still under investigation. In this study, we aimed to determine whether clopidogrel has an effect on the development of gastric precancerous lesions.

Methods: The study was designed as a retrospective case-control study. The study was conducted between January 2021 and April 2023 in the Gastroenterology Clinic of Samsun Training and Research Hospital. Patients who underwent upper GIS endoscopy and biopsy examination due to dyspeptic complaints were scanned from the electronic data system of the hospital and their data were recorded by forming 4 groups as clopidogrel (89 patients), low-dose aspirin (ASA) (172 patients), non-aspirin non-steroidal anti-inflammatory drug (NA-NSAID) users (110 patients) and control group without antiplatelet use (110 patients).

Results: Mean duration of drug use was 2 years for clopidogrel, 1.47 years for ASA and 0.35 years for NA-NSAID. The incidence of peptic ulcer was 7.2% in the control group, 38%, 15.1%, 49% in clopidogrel, ASA, NA-NSAID users, respectively ($p<0.001$). The frequencies of *H. pylori* infection in the groups were 61%, 53.5%, 40.1%, 46.1%, respectively. There was a significant difference between ASA and control group ($p<0.001$). Intestinal metaplasia was observed in 23.1%, 29.5%, 31.2%, 23.1%, respectively ($p=0.291$). Atrophic gastritis was seen in 16.6%, 35.2%, 19.2%, 29.3%, respectively ($p=0.003$). No difference was observed between the groups in terms of dysplasia, gastric cancer and esophageal cancer.

Conclusion: According to our results, no preventive effects of clopidogrel, ASA and NA-NSAID use on precancerous lesions or gastric cancer development were observed. However, the use of these drugs was associated with severe gastroduodenal lesions.

Keywords: Aspirin, clopidogrel, gastric cancer, gastric precancerous lesions

INTRODUCTION

Gastric cancer (GC) is the fifth most common type of cancer in the world and is the third leading cause of cancer-related deaths worldwide.[1,2] Most of the patients miss the chance of curative surgical treatment when diagnosed.

The most important risk factor for the development of GC is *Helicobacter pylori* (HP) infection.[3] HP infection causes chronic gastritis of the gastric mucosa and thus initiates the Correa cascade, progressing to atrophic gastritis (AG), gastric intestinal metaplasia (GIM), dysplasia and finally gastric cancer.[4]

Although HP eradication reduces the risk of GC and may regress precancerous gastric mucosal changes, the risk of GC development persists even after eradication.[5] The persistence of GC development after HP treatment suggests that there are different pathogenesis and therefore other methods to prevent GC development should be investigated.

Meta-analyses and some studies have reported that aspirin and NA-NSAIDs reduce the risk of both colorectal cancer (CRC) and GC through cyclooxygenase (COX-2) inhibition.[6,7] Although aspirin and NA-NSAID use may have beneficial effects in the prevention of gastric cancer, their clinical significance remains unclear. To reduce the risk of GC after HP eradication, new preventive agents such as anti-inflammatory (COX-2 inhibitors), statins and metformin continue to be investigated.[8]

Clopidogrel, an alternative antiplatelet to aspirin, acts by irreversibly inhibiting the platelet adenosine diphosphate (ADP) receptor and prevents ischemic events. A case-control study reported that the use of clopidogrel alone or in combination with low-dose aspirin reduced the risk of CRC by 20% to 30%, and it is considered that this anti-cancer effect is probably due to its antiplatelet property.[9]

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Aspirin, NA-NSAIDs and clopidogrel cause gastroduodenal lesions. In many studies, clopidogrel has been reported to cause less gastroduodenal lesions than aspirin.[10] However, not all patients receiving antiplatelet agents are at the same risk. The presence of HP infection in patients receiving antiplatelet agent therapy is one of the high-risk factors for gastroduodenal complications.[11] In subgroup comparisons of one study, it was noteworthy that the frequency of HP infection was significantly lower in patients receiving clopidogrel than in those receiving aspirin (17% and 35%, respectively. p= 0.007).[10] In addition to the mechanisms of action, the fact that HP infection, which is one of the major causes of gastroduodenal lesions, is less common in patients using clopidogrel may be one of the important reasons why clopidogrel causes gastroduodenal lesions less frequently and this issue has not been investigated in the literature before. In addition, the low incidence of HP, which is known to be associated with gastric cancer, in clopidogrel users suggests that clopidogrel may have chemoprevention effects similar to aspirin and NA-NAID. As far as we searched, we could not find any study investigating the relationship between clopidogrel and gastric premalignant lesions and GC development. We tried to clarify these issues in our study.

Our aim was to determine whether clopidogrel, aspirin and non-aspirin non-steroidal anti-inflammatory drugs have beneficial effects on reducing gastric premalign lesions and the risk of gastric cancer development

METHODS

The study was carried out with the permission of Samsun Training and Research Hospital Non-interventional Clinical Research Ethics Committee (Date: 30.10.2019, Decision No: 2019/1/9). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design and Patient Selection

The study was designed as a retrospective case-control study. Patients who underwent upper GIS endoscopy and biopsy examination due to dyspeptic complaints in the Gastroenterology Clinic of Samsun Training and Research Hospital between January 2021 and April 2023 were scanned from the electronic data system of the hospital and their data were recorded by forming 4 groups as clopidogrel, low-dose aspirin and non-aspirin non-steroidal anti-inflammatory drug users and control group (those who did not use any antiplatelet or NSAID drugs).

After analyzing the data, patients who had been using clopidogrel or low-dose aspirin for at least 1 year before the procedure and patients who started to use at least 1 non-aspirin NSAID per day at least 3 months before the procedure were included in the study. Age, gender, endoscopic diagnosis, histopathological diagnosis and HP status were recorded. Cases with hepatic and renal insufficiency, malignancy, primary immunodeficiency, immunosuppressive therapy, gastric surgery, dual antithrombotic or NSAIDs and antithrombotic drugs were excluded from the study. Moreover, a control group was formed from patients without chronic disease and drug use and who underwent upper GIS endoscopy and biopsy examination due to dyspepsia.

Histopathological examination and grading of endoscopic biopsies were evaluated by two senior pathologists according to the current Sidney classification.[27]

Statistical analysis

Statistical analysis was performed using SPSS software (Statistical Package for the Social Sciences, version 20.0, SPSS Inc., Chicago, USA). Categorical data were defined as percentage. Chi-squared test was used to evaluate statistical differences between clinical features according to treatments groups. $p<0.05$ was considered statistically significant.

RESULTS

A total of 461 patients including 110 patients in the control group (group 1), 89 patients in the clopidogrel group (group 2), 172 patients in the ASA group (group 3) and 90 patients in the NA-NSAID group (group 4) were included in the study. There was no difference between the groups in terms of gender (p=0.064). In terms of age, clopidogrel and NA-NSAID group were older than the other groups (p<0.001). The mean drug use duration was 1.47 year for ASA, 2 year for clopidogrel and 0.35 year for NA-NSAID. Demographic characteristics, endoscopic and histological findings of the groups included in the study are shown in Table 1.

Endoscopic findings

The incidence of erosive gastropathy was 10.9%, 21.3%, 18%, 22.2% in the control, clopidogrel, ASA, NA-NSAID groups, respectively. There was no significant difference between the drug groups. When compared with the control group, the incidence of erosion was significantly higher in the clopidogrel and NA-NSAID groups (p=0.043, p=0.030).

There was a significant difference between the groups in terms of peptic ulcer (7.2%, 38%, 15.1 %, 49%, respectively) (p<0.001). Peptic ulcer was observed more in all groups using drugs than in the control group and was statistically significant.

Ulcer frequency was higher in both clopidogrel and NA-NSAID groups than in ASA group and was statistically significant (p<0.001 for both). The frequency of HP infection in the groups was 61%, 53.5%, 40.1%, 46.1%, respectively. There was no statistically significant difference between the groups using drugs.

Compared with the control group, the frequency of HP infection was lower in all groups using drugs, but only the difference between the ASA group and the control group was statistically significant (p<0.001).

Histological Findings

There was no significant difference between the groups in terms of intestinal metaplasia (23.1%, 29.5%, 31.2%, 23.1%, respectively) (p=0.291). The incidence of atrophic gastritis (16.6%, 35.2%, 19.2%, 29.3%, respectively) was significantly different between the groups (p=0.003). GA was observed more in clopidogrel and NA-NSAID groups than in control and ASA groups (clopidogrel p= 0.004, 0.009, NA-NSAID p= 0.009, 0.019). No difference was observed between the groups in terms of neutrophil activity, chronic inflammation, dysplasia, gastric cancer and esophageal cancer.

Statistical analyses of all findings between groups are given in Table 2.

Table 1. Demographic characteristics, endoscopic and histological findings of the groups included in the study

		Control group 1	Clopidogrel group 2	ASA group 3	NA-NSAID group 4	All groups p
Gender	Female Male	68 42	39 50	89 83	43 47	0.064
Age	<65 years >65 years	67 43	30 59	84 86	26 64	<0.001*
Esophagitis	No Yes	65 45	58 31	120 52	82 8	<0.001*
Gastritis	No Yes	17 93	31 58	50 122	53 37	<0.001*
Peptic ulcer	No Yes	102 8	55 34	146 26	44 46	<0.001*
Erosive gastropathy	No Yes	98 12	70 19	141 31	70 20	0.136
Duodenitis	No Yes	102 8	84 5	169 3	88 2	0.077
H. pylori	No Yes	42 66	33 38	95 66	35 30	0.011*
Intestinal metaplasia	No Yes	83 25	50 21	108 52	50 15	0.291
Atrophic gastritis	No Yes	90 18	46 25	130 31	43 22	0.003*
Neutrophil activity	No Yes	36 72	33 38	70 91	21 44	0.131
Chronic inflammation	No Yes	6 102	5 66	6 155	1 64	0.403
Dysplasia	No Yes	107 1	69 2	160 1	65 0	0.347
Gastric cancer	No Yes	109 1	83 4	168 4	88 2	0.414
Esophageal cancer	No Yes	110 0	86 1	170 2	90 0	0.506

*p<0.05 was considered statistically significant.

Table 2. Statistical analysis of findings between groups

	Group 1-2 p	Group 1-3 p	Group 1-4 p	Group 2-3 p	Group 2-4 p	Group 3-4 p
Gender	0.011*	0.097	0.047*	0.225	0.595	0.542
Age	<0.001*	0.059	<0.001*	0.016*	0.487	0.001*
Esophagitis	0.380	0.066	<0.001*	0.449	<0.001*	<0.001*
Gastritis	0.001*	0.009*	<0.001*	0.340	0.001*	<0.001*
Duodenal ulcer				0.001*	0.015*	<0.001*
Gastric ulcer				0.003*	0.055	<0.001*
Peptic ulcer	<0.001*	0.048	<0.001*	<0.001*	0.082	<0.001*
Erosive gastropathy	0.043	0.105	0.030*	0.518	0.887	0.415
Duodenitis	0.639	0.019*	0.103	0.085	0.241	0.788
H. pylori	0.314	0.001*	0.055	0.077	0.391	0.477
Intestinal metaplasia	0.336	0.097	0.991	0.659	0.391	0.161
Atrophic gastritis	0.004*	0.590	0.009*	0.009*	0.867	0.019*
Neutrophil activity	0.077	0.095	0.889	0.672	0.092	0.121
Chronic inflammation	0.685	0.476	0.194	0.273	0.118	0.390
Dysplasia	0.335	0.775	0.437	0.172	0.173	0.524
Gastric cancer	0.102	0.379	0.447	0.318	0.383	0.958
Esophageal cancer	0.260	0.256		0.992	0.308	0.304

*p<0.05 was considered statistically significant. **Group 1; Control, Group 2; Clopidogrel, Group 3; ASA, Group 4; NA-NSAID.

DISCUSSION

To the best of our knowledge, whether clopidogrel has chemoprevention activity for GC was investigated for the first time in our study. We compared the endoscopic and histological findings of patients using clopidogrel for a mean of 2 years with those using low-dose aspirin and NA-NSAIDs, which have been suggested to be chemopreventive for GC, and with the control group not using any drug and tried to reveal the relationship with gastric lesions.

In our study, both gastric erosions and ulcers were more common in the drug users compared to the control group. While there was no difference between the drug groups in terms of erosions, more ulcers were observed in the clopidogrel and NA-NSAID groups than in the aspirin group, which was statistically significant. These results clearly show that clopidogrel, ASA and NA-NSAID drugs all cause gastric lesions. The group with the highest number of gastric lesions was symptomatic NA-NSAID users. Although ASA causes gastric damage essentially through the same mechanism as aspirin (COX-1 inhibition), gastrointestinal damage varies in a dose-dependent manner.[12]

Although clopidogrel is safer than aspirin in terms of the risk of gastrointestinal (GI) bleeding, the frequency of GI lesions in studies conducted with symptomatic patients in general was compatible with our results.[10,13] When compared with the control group, the frequency of HP infection was lower in all groups using drugs, but the difference between the ASA group (40.1%) and the control group (61%) was statistically significant ($p<0.001$). The fact that HP infection, which is the most important risk factor for the development of GC, is lower in aspirin users may be related with the lower incidence of gastric cancer in long-term low-dose aspirin users.

In this current study, the presence of HP was evaluated by histological examination, which is considered to be one of the gold standard methods.[14] Although the prevalence of HP infection in the clopidogrel group was lower than in the control group, it was not statistically significant, which can be clarified with larger studies.

Despite advances in endoscopy and HP eradication, gastric cancer remains the third leading cause of cancer-related death.[1] Preventive research is ongoing, including the search for GC preventive drugs such as NSAIDs, statins and metformin, and screening programs to identify patients at risk.

There have been various studies suggesting that aspirin and other NSAIDs may prevent gastric cancer and bowel cancers. Although NSAIDs cause gastrointestinal damage, their long-term use may be associated with a reduced risk of gastric cancer. This effect is thought to be due to COX-2 inhibition.[15,16] However, a meta-analysis has suggested that aspirin use has no evidence-based beneficial effect on gastric cancer.[8] Although general opinion and evidence suggest that NSAIDs have a beneficial effect, it has not been proven and the actual clinical effect is uncertain.[17]

Gastric intestinal metaplasia (GIM) is a premalignant lesion that progresses to dysplasia and intestinal-type gastric cancer.[18] The prevalence of GIM varies between 3.4% and 29.6% according to ethnicity.[19,20] In a study conducted by Ozdil et al.[21] among 3031 adult dyspeptic patients in Turkey, GIM and HP were found to be 17.8% and 71.3%, respectively. In that study, it was reported that the prevalence of intestinal metaplasia increased inversely proportionally while the intensity of HP infection decreased. In addition, it has been shown that HP colonization density may be important in the development of other diseases.[22] In our results, the prevalence of GIM (31.2%, 23.1%) was high in the group with low prevalence of HP (40%, 61%). The prevalence of GIM was 23.1% in the control group, 29.5% in the clopidogrel group, 31.2% in the aspirin group and 23.1% in the NA-NSAID group. No significant difference was found between the groups.

In the study by Nagata et al.[23] comparing the rate of gastric cancer, intestinal metaplasia and neutrophil infiltration in ASA, NA-NSAID users and non-users, no difference was observed between the groups in terms of GIM. However, it was suggested that long-term (>2 years) aspirin use had no preventive effect on the development of intestinal type gastric cancer developing through the Correa cascade, but was associated with a decrease in the development of diffuse type gastric cancer, suggesting that the chemopreventive effects of aspirin may be specific to this type of histological cancer.[23] In this current study, no difference was observed between ASA, NA-NSAID and control group. Moreover, although not statistically significant, the fact that GIM was higher in the aspirin group compared to the control group supported that it had no preventive effect on the Correa cascade. We did not encounter any other study on clopidogrel in this regard. The results of our study suggest that clopidogrel has no favorable effect on GIM in patients using clopidogrel for an average of 2 years.

In our study, the incidence of atrophic gastritis was 16.6%, 35.2%, 19.2%, 29.3% in the control, clopidogrel, aspirin and NA-NSAD groups, respectively. The incidence of AG was higher in the drug groups compared to the control group. The presence of AG was significantly different between the groups ($p=0.003$). AG was observed more in clopidogrel and NA-NSAID groups than in control and ASA groups (clopidogrel; $p=0.004$, $p=0.009$, NA-NSAID; $p=0.009$, $p=0.019$). AG is more common in the elderly and may occur as a long-term consequence of HP infection or as a result of autoimmune gastritis.

Since clopidogrel and NA-NSAID groups were older than the other groups in our study population, AG may have been observed more in these groups. Nevertheless, AG is associated with an increased risk of gastric cancer.[24] On the other hand, patients using clopidogrel and NA-NSAIDs may be selected for endoscopic follow-up according to the intragastric distribution of gastric atrophy and other risk factors.[25] No difference was observed between the groups in terms of neutrophil activity, chronic inflammation, dysplasia, gastric cancer and esophageal cancer.

The total incidence of gastric cancer was 0.9%, 5.7%, 3.5%, 2.2% in the control, clopidogrel, ASA, NA-NSAID groups, respectively, and there was no statistically significant difference between the groups. However, more cancer was observed in the drug group compared to the control group. Important point for this may be related to the discovery of anticoagulant-induced GI bleeding or anemia and pre-existing malignancies.[26]

There are some limitations in this current study. We could not standardize the groups in terms of other cancer related factors (Epstein-Barr virus infection, genetic susceptibility, dietary habits, alcohol and smoking) that increase the risk of GC other than HP. In addition, especially elderly patients may have used more NSAIDs outside the hospital records because they can easily access and use non-prescription NSAIDs. Moreover, relatively small study population, the retrospective design, low drug duration, being an single centered study and not to excluding patients with gastrointestinal bleeding are other limitations of the study.

CONCLUSION

In our study, no preventive effects of clopidogrel, aspirin and other nonsteroidal anti-inflammatory drugs on gastric premalign lesions were observed. In addition, all these drugs were associated with severe gastric lesions. Considering these gastrointestinal side effects, new evidence is needed for the use of these drugs as gastric cancer preventive agents in well-standardized studies with larger numbers and longer duration of observation.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Samsun Training and Research Hospital Non-interventional Clinical Research Ethics Committee (Date: 30.10.2019, Decision No: 2019/1/9).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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Original Article

MEDICINE PALLIATIVE CARE

DOI: 10.47582/jompac.1358089

J Med Palliat Care. 2023;4(5):530-534

Prenatal diagnosis and clinical outcomes of isolated interruption of the inferior vena cava: an analysis of 12 cases

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Cite this article as: Acar Z, Turan Bakırcı I, Acar DK, Bornaun H. Prenatal diagnosis and clinical outcomes of isolated interruption of the inferior vena cava: an analysis of 12 cases. *J Med Palliat Care*. 2023;4(5):530-534.

Received: 10.09.2023 • **Accepted**: 03.10.2023 • **Published**: 27.10.2023

ABSTRACT

Aims: This study aimed to thoroughly examine the clinical presentations and outcomes associated with prenatally detected isolated interrupted inferior vena cava (IIVC) with azygos continuation. The intention was to provide further insight into the importance of prenatal diagnosis for this particular condition.

Methods: A longitudinal study was conducted on a cohort of 12 fetuses who had been diagnosed prenatally with inferior vena cava interruption and azygos vein continuation. Comprehensive fetal anomaly scans and echocardiography were performed, and pediatric cardiologists further validated postnatal diagnoses. In addition, genetic testing and comprehensive follow-up procedures were implemented.

Results: The research findings substantiated the considerable diagnostic precision of prenatal identification, as evidenced by the 100% confirmation rate in postnatal assessments. Most patients demonstrated positive outcomes, underscoring the significance of prenatal diagnosis. Genetic testing results indicated that all the studied cases exhibited normal chromosomal configurations.

Conclusion: This study contributes to understanding this rare vascular anomaly and its implications in clinical practice. Additionally, our findings emphasize the importance of regular prenatal screenings and the need for healthcare providers to be knowledgeable about isolated IIVC cases. By increasing awareness and understanding of this vascular anomaly, healthcare professionals can provide better care and support for affected patients and their families. Furthermore, future research should investigate the potential genetic factors contributing to the development of isolated IIVC, which could further enhance our understanding of this condition.

Keywords: Isolated interruption inferior vena cava, azygos continuation, prenatal diagnosis, echocardiography

INTRODUCTION

Vascular anomalies known as interrupted inferior vena cava (IIVC) with azygos continuation have yet to receive considerable attention. However, their clinical significance should be considered. The inferior vena cava (IVC) forms during embryonic development when the cardinal, subcardinal, and supracardinal veins join. Any deviation or stoppage in this physiological process, namely inside the right subcardinal vein, can result in an alternative pathway that redirects blood flow through azygos continuation, bypassing the hepatic segment.[1]

According to available reports, evidence suggests a higher occurrence of this uncommon vascular variant, affecting an estimated 0.2-3% of the overall population, in persons with congenital cardiac anomalies, specifically left isomerism and atrial septal defects.[1-4] In individuals who do not experience any physiological abnormalities, solitary occurrences of IIVC constitute a significant fraction, with an estimated prevalence of approximately one in 5,000 individuals.[5] The prognosis for these isolated variants, especially those with a normal karyotype, is typically favorable, although there may be significant variability. The overall prognosis for isolated variants, particularly those with a normal karyotype, tends to be favorable; however, there can be large variations.[5,7]

Prenatal detection of the IIVC is becoming increasingly common in medical practice. This vascular aberration has many clinical ramifications, including venous thromboembolic diseases and abnormal spleen function.[5]

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This study aimed to conduct a thorough analysis of the clinical presentations of IIVC at different stages of life, focusing on the importance of prenatal diagnosis for making therapeutic intervention more effective. In light of the complex characteristics of IIVC and the little scholarly discussion around this phenomenon, the present work aims to make a valuable contribution towards enhancing the comprehension of this anomaly.

METHODS

The study was carried out with the permission of Kanuni Sultan Süleyman Training and Research Hospital Clinical Researches Ethics Committee (Date: 2019, Decision No: KAEK/2019.06.144). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The current study employed longitudinal research involving 12 fetuses diagnosed with IIVC with azygos continuation during the prenatal period. All participating families provided informed consent, and the Institutional Ethics Board approved the study. Echocardiographic and sonographic examinations were conducted using Voluson E6 Expert ultrasound equipment manufactured by GE Healthcare, Milwaukee, WI, USA. Pulsed-wave and color Doppler techniques were employed. All imaging techniques were performed by highly skilled professionals in both perinatology and cardiology, demonstrating proficiency in fetal heart imaging. All enrolled fetuses underwent a thorough examination consisting of a comprehensive fetal abnormality scan and echocardiography. Several crucial diagnostic characteristics were identified in the study. The "double vessel sign"[7,8] is distinguished by the concurrent existence of the aorta and another vein of comparable dimensions on the right side of the spinal column or posterior to the heart (**Figure 1**).

The present investigation involved the identification of a dilated azygous vein that traversed the diaphragm and drained into the superior vena cava (SVC). The sagittal plane image of the fetal abdomen revealed the absence of a hepatic section of the inferior vena cava. A dilated vessel running parallel to the aorta was observed in the longitudinal view. This image suggested the presence of an inferior vena cava with azygos continuation (**Figure 2**). Color Doppler imaging confirmed that the flow direction within the azygous vein was in direct opposition to that observed within the descending aorta. Postnatal diagnoses were confirmed using neonatal echocardiography, which a specialist in pediatric cardiology conducted. Supplementary examinations were performed to evaluate cardiac rhythm and anatomical positioning of the visceral organs, including electrocardiography (ECG), Holter ECG, abdominal ultrasonography, and chest radiography. Longitudinal sonographic follow-up was conducted on all fetuses throughout pregnancy and postpartum to observe and assess any potential problems or related conditions.

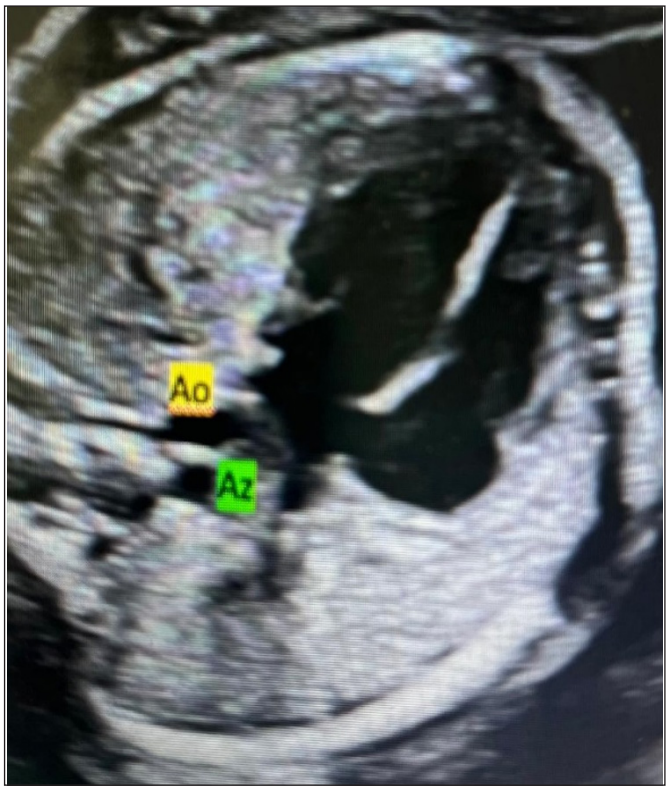

Figure 1. An axial view reveals the aorta (Ao) and the dilated paraspinal azygous vein (Az) situated posteriorly to the heart, indicating the presence of the 'double-vessels' sign.

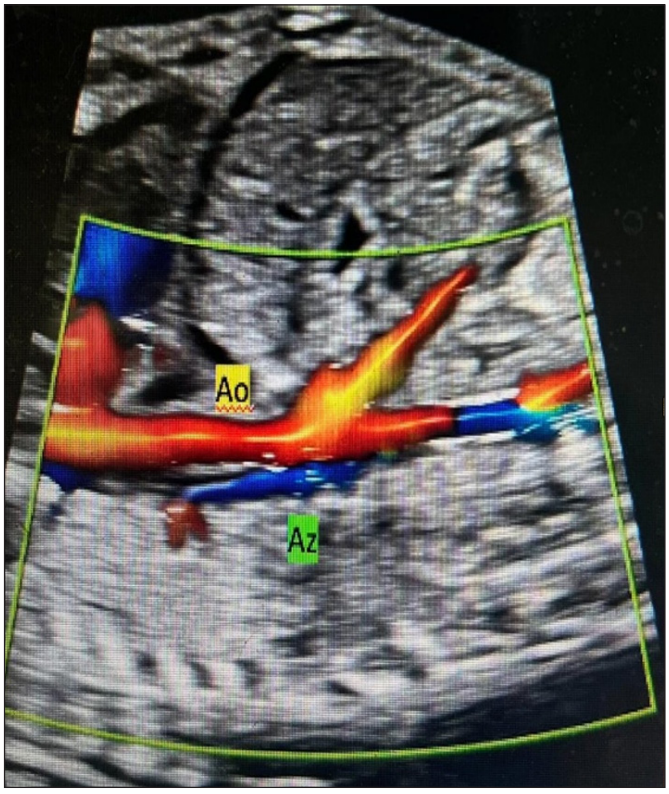

Figure 2. The azygous vein is positioned parallel to and behind the descending thoracic and abdominal aorta in sagittal view (Ao, aorta; Az, azygous)

Statistical Analysis

This study employed a sample size of 12 instances, and descriptive statistics were utilized to characterize the obtained results succinctly. Owing to the limited quantity of our dataset, we opted for a simplistic methodology whereby we computed the medians and ranges for continuous variables, including maternal age, diagnosis week, delivery week, and birth weight. It is essential to highlight that we abstained from performing more sophisticated statistical analyses due to the restricted sample size. The limited sample size, which made it impossible to conduct complex statistical analysis, was the driving force behind the decision to prioritize descriptive statistics.

RESULTS

This study examined 12 cases of isolated IIVC during fetal development. Each case was meticulously investigated, and the accuracy of the diagnosis was subsequently validated by a pediatric cardiologist, resulting in a diagnostic accuracy rate of 100%. The findings of this study provide robust evidence supporting the reliability of prenatal diagnostics in detecting this infrequent, although medically relevant, vascular abnormality. The clinical outcomes observed in this study were predominantly positive (Table 1). The median gestational age at diagnosis was 22 weeks (range 21-31 weeks). The median gestational age at birth was 39 weeks, and the median birth weight was 3485 g. The predominant mode of delivery observed in the study population was normal spontaneous delivery (NSD), which is frequently associated with favorable Apgar scores. Three instances were observed wherein newborn problems were observed in the context of preterm deliveries. Owing to the significant implications associated with preterm birth, it is imperative to evaluate this aspect of clinical therapy carefully. In genetics, it is worth mentioning that a significant proportion of families opted to undergo prenatal genetic testing. However, the four remaining individuals who underwent karyotyping exhibited typical chromosomal configurations, highlighting the potential occurrence of isolated inferior vena cava interruption without any accompanying genetic disorders. None of the newborns that were not subjected to testing had observable indications of aneuploidy. No fetal arrhythmia or intrauterine growth restriction was observed during prenatal monitoring of the 12 fetuses with isolated IIVC. In addition, postnatal

Table 1. Prenatal and postnatal findings of cases

Case no	Gestational age at diagnosis (wk)	Prenatal findings	Postnatal diagnosis	Mode of delivery	Gestational age at delivery (wk)	Birth weight (grams)	1-minute Apgar score	5-minute Apgar score	Neonatal complications
1	23	Interruption of the inferior vena cava (IVC) with azygos continuation	Similar	Vaginal delivery	38	3205	7	8	
2	21	Interruption of the inferior vena cava (IVC) with azygos continuation	Similar	Vaginal delivery	35	2709	5	10	Respiratory distress syndrome
3	24	Interruption of the inferior vena cava (IVC) with azygos continuation	Similar	Vaginal delivery	39	3300	7	10	
4	22	Interruption of the inferior vena cava (IVC) with azygos continuation	Similar	Cesarean section	28	980	6	8	Respiratory distress syndrome
5	29	I Interruption of the inferior vena cava (IVC) with azygos continuation	Similar	Vaginal delivery	36	2578	8	10	
6	31	Interruption of the inferior vena cava (IVC) with azygos continuation	Similar	Vaginal delivery	39	3980	7	10	
7	21	Interruption of the inferior vena cava (IVC) with azygos continuation	Similar	Vaginal delivery	40	3780	8	10	
8	25	Interruption of the inferior vena cava (IVC) with azygos continuation	Similar	Cesarean section	39	3980	6	10	
9	22	Interruption of the inferior vena cava (IVC) with azygos continuation	Similar	cesarean section	40	4100	8	10	
10	22	Interruption of the inferior vena cava (IVC) with azygos continuation	Similar	Vaginal delivery	34	2370	8	10	Sepsis
11	22	Interruption of the inferior vena cava (IVC) with azygos continuation	Similar	Vaginal delivery	39	3670	8	10	
12	22	Interruption of the inferior vena cava (IVC) with azygos continuation	Similar	Cesarean section	40	4200	10	10	

abdominal ultrasonography findings indicated that the anatomical locations of the stomach, spleen, and liver were within the expected range in all neonates. Furthermore, it was observed that none of the 12 fetuses exhibited any postnatal arrhythmia as determined by electrocardiogram (ECG) or Holter investigations.

DISCUSSION

Interrupted inferior vena cava, also called azygos continuation of the inferior vena cava, is a congenital anomaly in the blood vessels that occurs when the link between the right subcardinal vein and the right vitelline vein does not form fully during embryonic development. When this happens, venous blood from the lower limbs is redirected to the heart through the azygos vein and superior vena cava instead of the usual route through the inferior vena cava. The prevalence of this particular illness is considered low, with an estimated occurrence rate ranging from one in every 20,000 to 40,000 live births, as reported in various studies.[1-4] Prenatal screening techniques frequently detect IIVC, a significant congenital anomaly that is relatively uncommon. This study contributes significantly to the current knowledge base by focusing solely on cases with isolated IIVC, in contrast to earlier studies that mostly associated inferior vena cava interruption with isomerism and other complex illnesses.[5-8] IIVC has been recognized as a noteworthy diagnostic indicator for some medical conditions, such as atrial heterotaxy and polysplenia syndrome.[1,9,10] Nevertheless, our findings suggest that IIVC can present as a distinct illness without concomitant abnormalities.

Xu[6] examined a sample of 21 fetuses with interrupted inferior vena cava with azygous continuation. This study provides significant insights into the clinical outcomes of this uncommon vascular defect. The results indicate that the outlook for patients with a solitary interrupted inferior vena cava is typically positive, especially when the fetal karyotype is normal.[6] A similar study conducted by Babaoğlu et al.[11] also suggests that the prognosis for isolated instances was generally favorable unless there were concurrent cardiac or chromosomal problems. The work conducted by Celentano[3] offers valuable insights into identifying isolated IIVC with azygos continuation during regular prenatal imaging. This study emphasized that this vascular abnormality generally does not have identifiable disease effects and tends to result in positive outcomes.[3] Our study aligns with these findings and highlights the limited occurrence of serious clinical consequences in individual instances.

The absence of an inferior vena cava has substantial implications for medical treatments that use the venous system. For instance, in certain cases, other techniques may be required for venous angiography or treatment of portal hypertension. One strategy is ligation of the azygos vein, associated with potentially catastrophic outcomes.[5,12] This situation underscores the significance of employing specialized surgical planning and adopting a multidisciplinary approach, mainly when performing procedures that have the potential to damage the azygos vein unintentionally. While IIVC typically does not exhibit symptoms, it has the potential to introduce complexities within the therapeutic context.[13] Instances of fortuitous venous thromboembolism (VTE) have been recorded, highlighting the potential prothrombotic hazards linked to this vascular anomaly.[14-20]

A study by Bronshtein[5] emphasizes the significance of isolated cases of interrupted inferior vena cava, which frequently result in favorable outcomes and are typically not associated with additional fetal abnormalities. Nevertheless, this observation brings attention to the fact that in certain instances, an atypical spleen functioning may be identified following delivery, necessitating the administration of pneumococcal immunization after birth. The idea behind this study is that having an isolated inferior vena cava interruption might affect how the spleen works, which is why new ways of immunizing women after giving birth are needed.

Limitations of the Study

Although our research provides vital insights, it is essential to acknowledge its limitations. Our study's limited number of participants hinders our ability to apply our findings to a broader population. Furthermore, the lack of comprehensive long-term follow-up data makes it challenging to thoroughly understand the potential difficulties that could manifest in the later stages of life. Hence, it is advisable to conduct additional studies using a larger sample size and an extended duration of follow-up to validate our findings.

CONCLUSION

Our research and accompanying studies highlight the importance of understanding and effectively managing instances of prenatally detected isolated interrupted inferior vena cava. This is particularly relevant because of the generally positive outlook associated with this condition. Furthermore, our findings underscore the crucial role of prenatal diagnosis in ensuring optimal future outcomes.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kanuni Sultan Süleyman Training and Research Hospital Clinical Researches Ethics Committee (Date: 2019, Decision No: KAEK/2019.06.144).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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Original Article

MEDICINE PALLIATIVE CARE

DOI: 10.47582/jompac.1341805

J Med Palliat Care. 2023;4(5):535-541

Upper gastrointestinal bleeding in octogenarians: a prospective comparative study on clinical, endoscopic findings and outcomes with younger patients

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Cite this article as: Durak MB, Şimşek C, Çağır Y, Yüksel İ. Upper gastrointestinal bleeding in octogenarians: a prospective comparative study on clinical, endoscopic findings and outcomes with younger patients. *J Med Palliat Care*. 2023;4(5):535-541.

Received: 12.08.2023 ◆ **Accepted**: 03.10.2023 ◆ **Published**: 27.10.2023

ABSTRACT

Aims: Acute upper gastrointestinal bleeding (UGIB) is a critical medical emergency that becomes more prevalent with advancing age. This study aimed to compare clinical and endoscopic features, as well as clinical outcomes, between patients below 80 years of age and octogenarians (≥80 years of age) presenting with UGIB.

Methods: Data related to past medical history, physical examination, laboratory, and endoscopic findings were collected prospectively. The clinical outcomes evaluated in both octogenarian and younger groups included: (1) necessity for endoscopic intervention; (2) transfusion requirement; (3) hospital stay duration; (4) rebleeding events; and (5) 30-day mortality rate.

Results: The study revealed that comorbidities such as cardiovascular diseases, chronic renal failure, and hypertension were statistically more prevalent in octogenarians. Furthermore, octogenarians had lower serum albumin and hemoglobin levels, and higher INR and BUN levels. High-risk categorization according to risk scoring systems was significantly more prevalent among octogenarians. Upon evaluating clinical outcomes, octogenarians demonstrated a longer hospital stay, higher transfusion needs, and a higher 30-day mortality rate. Peptic ulcer was identified as the most common cause of bleeding in both groups, but gastric ulcers were statistically more common in octogenarians.

Conclusion: The severity of UGIB is notably increased in octogenarians than younger because of more comorbid disease, lower serum albumin hemoglobin levels, and higher INR BUN and also High-risk scoring systems. Gastric ulcers were statistically more common in octogenarians.

Keywords: Nonvariceal upper gastrointestinal bleeding, octogenarian, rebleeding, 30-day mortality.

INTRODUCTION

Acute upper gastrointestinal bleeding (UGIB) represents a significant emergency, with life-threatening implications that disproportionately affect elderly populations.[1-3] In these individuals, UGIB results in extended hospital stays and presents higher morbidity and mortality rates compared to their younger counterparts, despite advancements in endoscopic hemostasis and diagnostic and therapeutic modalities.[4,5]

The relationship between advancing age and escalating mortality rates in UGIB cases has been consistently observed. However, discrepancies in the definition of 'elderly' across various studies have led to variable reported mortality rates associated with acute UGIB, reaching upwards of 44% in certain studies.[3,6-8] Compared to younger demographics, the elderly population experiences a notably higher incidence of UGIB[5,9] with mortality rates spanning from 12 to 25% for individuals aged over 60 and falling below 10% for those under 60.[10]

Factors such as the patient's demographic characteristics, the etiology of the bleeding, and the timeliness of treatment substantially influence the mortality and morbidity outcomes associated with UGIB. It is reported that 35-45% of UGIB presentations involve individuals aged over 60.[11,12] This population is more susceptible to UGIB complications, likely due to a higher prevalence of comorbid conditions and the common use of nonsteroidal anti-inflammatory drugs (NSAIDs) or antiplatelets.[13]

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Several studies have compared the presentation of acute UGIB in elderly populations to younger ones, albeit with inconsistent age classifications for the elderly group.[4,6,7,11] Our study aims to address this inconsistency by examining individuals aged under 80 and octogenarians (those aged 80 or above). The comparison will focus on their clinical and endoscopic profiles as well as clinical outcomes in the context of UGIB.

METHODS

The study was carried out with the permission of Ankara City Hospital Scientific Researches Ethics Committee (Date: 05.10.2022, Decision No: E1/22/2951). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Population

This investigation included participants aged 18 years and above who were diagnosed with non-variceal upper gastrointestinal bleeding (NVUGIB) from February 2019 to February 2020. All NVUGIB diagnoses were confirmed via endoscopy. Patients over the age of 80 were classified as octagenerian, and those between the ages of 18-80 were classified as younger. Exclusions encompassed patients with variceal bleeding and those unable or unwilling to undergo endoscopy due to unfavorable clinical conditions.

Patient Management

Upon arrival at the emergency room, NVUGIB patients were assessed by a gastroenterologist. Initial diagnoses were based on symptoms such as hematemesis, melena, or the presence of blood in nasogastric aspirate. Treatment with pantoprazole (8 mg/h following an 80 mg bolus) was initiated immediately for all NVUGIB patients. Erythrocyte suspension (ES) transfusions were administered to those with hemoglobin levels under 9.0 g/dl.

Endoscopy was performed within the first 12 hours for patients presenting with unstable hemodynamic conditions, signs of ongoing bleeding, or reduced hematocrit despite transfusion. Patients deemed clinically stable and showing no signs of severe bleeding underwent endoscopy within the first 24 or 48 hours. The timing of endoscopy was determined relative to the patient's arrival at the emergency department. If endoscopic treatment proved unsuccessful, patients were referred to interventional radiology or surgery. The decision to admit or discharge a patient was based on initial evaluations, clinical status, and endoscopic findings. All patients were monitored for 30 days.

Clinical Outcomes

Clinical outcomes under evaluation included: (1) necessity for endoscopic intervention; (2) need for transfusion; (3) duration of hospital stay; (4) rebleeding occurrences; and (5) 30-day mortality. Endoscopic treatment could involve mechanical (hemoclips), heater therapy, or adrenaline injections. However, adrenaline injection alone was not deemed as endoscopic treatment. Besides bleeding symptoms, a hemoglobin drops of more than 2.0 g/dl indicated rebleeding. Rebleeding was confirmed via a second-look endoscopy (also termed as active bleeding or SRH). Mortality was any death occurring within 30 days of bleeding.

Data Collection

Prospective data collected encompassed evidence of bleeding (including hematemesis, melena, and syncope), prior medical conditions, physical examination results, and laboratory and endoscopic findings. Upon identification of high-risk stigmata of recent hemorrhage (SRH), such as fresh bleeding (spurting/oozing) or non-bleeding visible vessels, endoscopic therapy was initiated. Endoscopic data, including the type of procedures employed, the bleeding source, ulcer presence, its location, number, size, and Forrest classification were recorded. Hospitalization details, blood transfusions, endoscopic interventions, length of hospital stay, rebleeding instances, and 30-day mortality were logged using the hospital's computerized civil medical registration system. At the time of admission, the Glasgow Blatchford Score (GBS), Clinical Rockall Score (CCRS), and AIMS65 score were calculated by gastroenterologists. The Complete Rockall Score (CRS) was computed post-endoscopy. Patients not requiring hospitalization were re-evaluated at the 1st and 4th week follow-ups.

Statistics

The Kolmogorov-Smirnov test assessed the normality of the continuous variables' distribution. Normally distributed continuous variables were expressed as mean ± standard deviation (SD), compared via the student's t-test. Non-normally distributed continuous variables were conveyed as median (interquartile range [IQR]), and compared using the Mann-Whitney U test. Categorical variables were reported as frequency (percentage) and compared through the Chi-Square test or Fisher's Exact test, as deemed appropriate. IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, N.Y., USA) was employed for statistical analyses. A p-value <0.05 was considered statistically significant.

RESULTS

Patient Characteristics

The study encompassed 467 patients with a median age of 67 (ranging from 46-89) years. Of these, 106 patients (22.7%) were octogenarians and 361 (77.3%) patients were in the under 80 age group. Within the octogenarian group, 58 (54.7%) were male, compared to 256 (70.9%) male patients in the under 80 age group. This difference between the groups was statistically significant (p=0.002). On comparing comorbidities, cardiovascular diseases, chronic renal failure, and hypertension were significantly more prevalent in the octogenarian group (p0.001 for all parameters). Use of proton pump inhibitors (PPI), acetylsalicylic acid (ASA), and Novel oral anticoagulant drugs (NOAC) were significantly higher in octogenarians (p=0.026, p=0.011, and p<0.001, respectively). However, the usage of nonsteroidal anti-inflammatory drugs (NSAID) was significantly higher in the under 80 age group (p=0.040) (Table 1).

Table 1. Patient characteristics, clinical and laboratory data of the study group and subgroups by age[x]

	Study group (n=467)	Aged <80 years (n=361)	Aged ≥80 years (n=106)	P
Age, years	67 (46-89)	61 (46-78)	86 (82-89)	**<0.001**
Gender, male, n (%)	314 (67.2)	256 (70.9)	58 (54.7)	**0.002**
Presenting symptoms, n (%)				
Hematemesis	238 (51)	178 (49.3)	60 (56.6)	0.186
Melena	318 (68.1)	248 (68.7)	70 (66)	0.605
Hematochezia	39 (8.4)	32 (8.9)	7 (6.6)	0.460
Hematemesis/Melena	427 (91.4)	329 (91.1)	98 (92.5)	0.670
Comorbidities, n (%)				
Cardiovascular diseases (AF, CAD, CHF)	200 (42.8)	133 (36.8)	67 (63.2)	**<0.001**
CVD	39 (8.4)	26 (7.2)	13 (12.3)	0.098
CRF	51 (10.9)	28 (7.8)	23 (21.7)	**<0.001**
HT	208 (44.5)	141 (39.1)	67 (63.2)	**<0.001**
CLD	10 (2.1)	7 (1.9)	3 (2.8)	0.577
DM	99 (21.2)	77 (21.3)	22 (20.8)	0.899
PPI usage, n (%)	112 (24)	78 (21.6)	34 (32.1)	**0.026**
Previous episode of UGIB, n (%)	100 (21.4)	83 (23)	17 (16)	0.125
Previous GIS surgery, n (%)	16 (3.4)	15 (4.2)	1 (0.9)	0.136
Medication, n (%)				
NSAIDs	74 (15.8)	64 (17.7)	10 (9.4)	**0.040**
Antithrombotic Agents				
Aspirin	123 (26.3)	85 (23.5)	38 (35.8)	**0.011**
DAPT	13 (2.8)	11 (3)	2 (1.9)	0.742
Anticoagulants				
Warfarin	41 (8.8)	34 (9.4)	7 (6.6)	0.368
NOAC	31 (6.6)	12 (3.3)	19 (17.9)	**<0.001**
Pulse, > 100 beats/min, n (%)	198 (42.4)	145 (40.2)	53 (50)	0.072
Systolic blood pressure, < 90 mmHg, n (%)	34 (7.3)	30 (8.3)	4 (3.8)	0.114
Hemoglobin level on admission (g/dl)	9.91 ± 2.92	10.08 ± 2.92	9.33 ± 2.84	**0.019**
BUN level on admission (mg/dl)	33.13 (21.93-52.73)	29.87 (20.07-43.87)	49 (29.87-74.09)	**<0.001**
INR on admission	1.13 (1.05-1.27)	1.11 (1.04-1.24)	1.2 (1.09-1.34)	**<0.001**
Serum albumin level on admission (g/L)	36 (32-40)	37 (32-41)	34 (31-37)	**<0.001**
Serum platelet level on admission (10^9/L)	254 (201-333)	250 (202.5-329.5)	273 (198-355.25)	0.258
Endoscopy time, n (%)				0.073
<12 hours	329 (70.4)	260 (72)	69 (65.1)	
12-24 hours	94 (20.1)	73 (20.2)	21 (19.8)	
24-48 hours	44 (9.4)	28 (7.8)	16 (15.1)	
GBS ≤ 1*	26 (5.6)	25 (6.9)	1 (0.9)	**0.018**
GBS ≥ 7**	336 (71.9)	248 (68.7)	88 (83)	**0.004**
AIMS65 score = 0*	181 (38.8)	181 (50.1)	-	**<0.001**
AIMS65 score ≥ 2**	135 (28.9)	81 (22.4)	54 (50.9)	**<0.001**
CCRS = 0*	83 (17.8)	83 (23)	-	**<0.001**
CCRS ≥ 3**	290 (62.1)	197 (54.6)	93 (87.7)	**<0.001**
CRS ≤ 2*	83 (17.8)	83 (23)	-	**<0.001**
CRS ≥ 8**	49 (10.5)	33 (9.1)	16 (15.1)	0.079

x Results are expressed as: mean ± standard deviation, median (interquartile range), or frequency (%).
*: Patients classified as low risk
**: Patients classified as high risk
Significant P values are in bold.
AF: Atrial fibrillation, CAD: Coronary artery disease, CHF: Congestive heart failure, CVD: Cerebrovascular disease, CRF: Chronic renal failure, HT: Hypertension, CLD: Chronic liver disease, DM: Diabetes mellitus, PPI: Proton Pump Inhibitors, UGIB: Upper gastrointestinal bleeding, GIS: Gastrointestinal system, NSAIDs: Non-steroidal anti-inflammatory drugs, DAPT: Dual antiplatelet therapy, NOAC: Novel oral anticoagulant drugs, BUN: Blood urea nitrogen, INR: International normalized ratio, GBS: Glasgow-Blatchford score, CCRS: Clinical Rockall score, CRS: Complete Rockall score,

Initial Presentation

At admission, octogenarians had significantly higher blood urea nitrogen (BUN) and international normalized ratio (INR) levels (p0.001 for both). On the other hand, the under 80 age group had significantly higher hemoglobin and serum albumin levels (p=0.019 and p0.001, respectively). Moreover, they were significantly more likely to have low-risk Glasgow Blatchford Score (GBS) ≤1, AIMS65 score =0, Clinical Rockall Score (CCRS) =0, and Complete Rockall Score (CRS) ≤2 (p=0.018, p0.001, p0.001, and p0.001, respectively). In contrast, octogenarians had significantly higher numbers of patients with high-risk GBS ≥7, AIMS65 score ≥2, and CCRS ≥3 (p=0.004, p0.001, and p0.001, respectively). The remaining investigated factors showed no significant difference (p>0.05 for all parameters) (Table 2).

Endoscopic Findings Clinical Outcomes

Peptic ulcers were the most common cause of UGIB across the entire study group and the age-based subgroups, with the majority being duodenal and single ulcers. Most ulcers were less than 10 mm in size. Subgroup analyses revealed that the octogenarians had significantly more gastric ulcers, whereas the under 80 age group had significantly more esophageal ulcers (p=0.031 and p=0.043, respectively) (Table 3).

Octogenarians had a statistically significantly longer hospital stay (5 (0-12) days) than the under 80 age group (4 (0-8) days; p=0.025). They also had a significantly higher need for transfusion and 30-day mortality rate (p=0.001 and p=0.006, respectively). The other parameters examined did not reveal any statistically significant difference (p>0.05 for all parameters).

Table 2. Results and comparisons of clinical outcomes[x]

	Study group (n=467)	Aged <80 years (n=361)	Aged ≥80 years (n=106)	P
Discharged within 24 hours, n (%)	132 (28.3)	105 (29.1)	27 (25.5)	0.468
Hospitalization, n (%)	335 (71.7)	256 (70.9)	79 (74.5)	0.468
Length of hospital stay, days	4 (0-8)	4 (0-8)	5 (0-12)	**0.025**
Need for endoscopic intervention, n (%)	136 (29.1)	106 (29.4)	30 (28.3)	0.833
Need for surgical/radiological intervention, n (%)	8 (1.7)	5 (1.4)	3 (2.8)	0.389
Need for transfusion, n (%)	254 (54.4)	182 (50.4)	72 (67.9)	**0.001**
Rebleeding (during hospital stay), n (%)	36 (7.7)	26 (7.2)	10 (9.4)	0.449
30-day mortality, n (%)	50 (10.7)	31 (8.6)	19 (17.9)	**0.006**

x Results are expressed as: median (interquartile range), or frequency (%). Significant P values are in bold.

Table 3. Comparisons of endoscopic findings[x]

	Study group (n=467)	Aged <80 years (n=361)	Aged ≥80 years (n=106)	P
Peptic ulcer, n (%)	235 (50.3)	180 (49.9)	55 (51.9)	0.714
Gastric ulcer, n (%)	78 (16.7)	53 (14.7)	25 (23.6)	**0.031**
Duodenal ulcer, n (%)	157 (33.6)	127 (35.2)	30 (28.3)	0.188
Number of ulcers, n (%)				
Single	238 (51)	186 (51.5)	52 (49.1)	0.655
Multiple	48 (10.3)	36 (10)	12 (11.3)	0.688
Size of ulcer, n (%)				
<10 mm	159 (34)	126 (34.9)	33 (31.1)	0.471
10-20 mm	87 (18.6)	67 (18.6)	20 (18.9)	0.943
>20 mm	41 (8.8)	30 (8.3)	11 (10.4)	0.508
Forrest classification of UGIB, n (%)				
Ia, Ib, IIa, IIb	105 (22.5)	81 (22.4)	24 (22.6)	0.965
IIc, III	180 (38.5)	141 (39.1)	39 (36.8)	0.673
Erosive esophagitis, n (%)	17 (3.6)	11 (3)	6 (5.7)	0.237
Esophageal ulcer, n (%)	28 (6)	26 (7.2)	2 (1.9)	**0.043**
Upper GIS malignancy, n (%)	42 (9)	34 (9.4)	8 (7.5)	0.554
Erosive/hemorrhagic gastropathy/duodenopathy, n (%)	73 (15.6)	53 (14.7)	20 (18.9)	0.297
Angioectasia, n (%)	17 (3.6)	11 (3)	6 (5.7)	0.237
Dieulafoy lesion, n (%)	5 (1.1)	4 (1.1)	1 (0.9)	1
Cameroon lesion, n (%)	5 (1.1)	4 (1.1)	1 (0.9)	1
Lesion not visualized, n (%)	20 (4.3)	16 (4.4)	4 (3.8)	1

x Results are expressed as: frequency (%). Significant P values are in bold. UGIB: Upper gastrointestinal bleeding, GIS: Gastrointestinal system

DISCUSSION

The mortality rate is persistently increasing among the elderly, despite significant advances in the diagnosis and management of upper gastrointestinal bleeding (UGIB). This could be attributed to heightened vulnerability, diminished ability in the elderly to withstand hemodynamic changes during acute bleeding episodes, presence of underlying co-morbidities, and concurrent use of multiple medications.[5,10,13,14]

Previous research conducted by Laine et al.[2] in the US identified that the incidence of UGIB was 31.7 per 100,000 in the patient group under 65 years of age, and significantly higher at 425.2 per 100,000 in the population over 75 years 2. In the USA, the incidence of UGIB was found to be 31.7/100.00 in the patient group under 65 years of age, while this rate was found to be 425.2/100.000 in the population over 75 years of age. UGIB, the incidence and mortality of which increase with aging, poses a concern and challenge for healthcare providers. Key strategies for reducing poor clinical outcomes in the elderly presenting with UGIB include close monitoring, risk stratification, and effective endoscopic and medical treatment. Another important distinction between older and younger patients presenting with UGIB is the cause of bleeding. Peptic ulcers, malignancies, and variceal bleeding are more prevalent in elderly patients.[13,15]

Our study revealed that cardiovascular diseases, chronic renal failure, and hypertension were more common among octogenarians, as were ASA and NOAC use. In contrast, NSAID use was higher in the under-80 group. Laboratory findings showed lower serum albumin and hemoglobin levels, but higher INR and BUN levels in octogenarians. These patients were also more frequently identified as high-risk by risk scoring systems. Poor clinical outcomes such as longer hospital stays, increased need for transfusion, and higher 30-day mortality were more prevalent among octogenarians. Peptic ulcer was the leading cause of bleeding in both groups, though gastric ulcers were more common in octogenarians and esophageal ulcers were more common in the younger population.

Contradictory results are evident in previous studies regarding acute upper GI hemorrhage mortality between elderly and younger individuals.[3,7,8,10] For instance, Elsabaey and colleagues 1 reported a rebleeding rate of 6.4% and an in-hospital mortality rate of 4.8% in NVUGIB patients over 60 years, with a median age of 68.5. Our study, however, noted a rebleeding rate of 9.4% and a 30-day mortality rate of 17.9% in octogenarians. The higher rebleeding and mortality rates could be attributed to the older age of our patient population and our 30-day evaluation of mortality. In fact, Emektar et al.[16] study on 30-day mortality in patients over 65 years of age reported a 14.1% mortality rate.

In their study on upper gastrointestinal tract bleeding in patients over 85 years of age, Koziel et al.[17] found the rebleeding rate to be 11.9% and the mortality rate as high as 20.24%. Similar studies conducted in elderly patients also supported these data.[18,19] The increase in comorbid diseases with aging, Use of NSAIDs, antiplatelet agents and anticoagulants were common risk factors. Increased oxidative stress with aging, mitochondrial dysfunction, impaired resistance to molecular stressors, and endothelial dysfunction due to chronic low-grade inflammation may explain the severity of bleeding in older patients.[20,21]

Developing a geriatric assessment methodology for elderly patients presenting with NVUGIB could be beneficial, given the increase in comorbidities with age, multiple drug use, and various age-related disorders which contribute to morbidity and mortality.[9,22,23]

Risk scoring systems like GBS, CCRS, CRS, and AIMS65 scores are advised for patients presenting with NVUGIB 24-28. Although no optimal scoring system specific to the elderly has been designed yet, our study found that octogenarians were more frequently identified as high-risk according to current scoring systems: 83% of octogenarians had GBS ≥7, 50.9% had AIMS65 score ≥2 and 87.7% had CCRS ≥3. In contrast, low-risk patients were more prevalent in the under-80 group.

The most common cause of acute UGIB in older adults is peptic ulcer disease.[11,29,30] Similarly in our study, peptic ulcer was the most common cause in both groups. However, gastric ulcer was more common in octogenarians. The explanation for this may be the high use of ASA and NOAC in the octogenarian group and the higher rate of concomitant chronicle kidney disease. Both conditions increase the incidence of gastric ulcers.[31-33] In our study, the incidence of esophageal ulcer was lower in octogenarians and we could not explain the reason for this, which may be explained by the relatively low number of patients with esophageal ulcer.

Limitations of our study include its single-center design and a possible bias towards higher acceptance of high-risk patients, which could have influenced our results. Also, we could not detect *Helicobacter pylori* (HP) status in all patients. Although the incidence of drug-related bleeding increases with advancing age, HP-associated peptic ulcer remains important.[31,34] The strengths of the study include its prospective and comparative design, performance of endoscopy on all patients, and data collection by gastroenterologists.

CONCLUSION

The clinical outcomes of NVUGIB are significantly poorer in the elderly population because of more common comorbid disease, lower serum albumin, hemoglobin levels, and higher INR, BUN and also High-risk scoring systems. Gastric ulcers were statistically more common in octogenarians. It is crucial, therefore, to develop an optimal assessment and management methodology specifically for these patients, which could help improve their clinical outcomes and overall prognosis.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara City Hospital Scientific Researches Ethics Committee (Date: 05.10.2022, Decision No: E1/22/2951).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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Original Article

MEDICINE PALLIATIVE CARE

DOI: 10.47582/jompac.1349803

J Med Palliat Care. 2023;4(5):542-546

The role of the systemic inflammatory response index (SIRI) in the prediction of chronic total occlusion: useful or not?

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Cite this article as: Ergün G, Doğan Y. The role of the systemic inflammatory response index (SIRI) in the prediction of chronic total occlusion: useful or not?. *J Med Palliat Care*. 2023;4(5):542-546.

Received: 25.08.2023 ◆ **Accepted**: 07.10.2023 ◆ **Published**: 27.10.2023

ABSTRACT

Aims: Inflammation is very important in the pathogenesis of atherosclerosis and coronary artery disease (CAD). Chronic total occlusion (CTO) is a chronic form of CAD and is common in patients with severe CAD. The aim of this study was to determine the association of the systemic inflammatory response index (SIRI), a marker of inflammation, with CTO.

Methods: Our study was retrospective and included 100 CAD patients with CTO and 100 CAD patients without CTO. SIRI was compared between the two groups.

Results: Among the basic clinical and laboratory characteristics of the patients, age, white blood cell, and neutrophil counts were statistically higher in the CTO group (p=0.044, p=0.044, p=0.036, respectively). SIRI parameters were similar between the groups, and no statistical difference was observed (p=0.111). According to the ROC analysis, the optimum cut-off value for SIRI was >1040 (sensitivity 70.0% and specificity 44.0%).

Conclusion: SIRI is not a useful predictor for the detection of CTO.

Keywords: Systemic inflammatory response index, chronic total occlusion, coronary artery disease

INTRODUCTION

Cardiovascular diseases (CVD) are the major cause of death worldwide in 2020.[1] Therefore, early detection of coronary artery disease (CAD) is important, and coronary angiography is the main diagnostic modality. Chronic total obstruction (CTO) is a common finding on coronary angiography and refers to total occlusion of at least one epicardial artery for more than 3 months and the absence of blood flow in the distal part of the vessel.[2] In one study, approximately 1/3 of patients undergoing coronary angiography (CAG) had CTO.[3] In a study by Christofferson et al.[4] 52% of patients with severe CAD had one CTO, and 12% had more than one CTO. Intervention in vessels with CTO requires an experienced and trained operator, along with the variety and adequacy of the materials used for successful revascularization. Therefore, pre-procedural planning becomes important. The ACC/AHA guideline recommends intervention for CTO in patients with persistent angina despite revascularization of all other non-CTO vessels and optimal medical therapy if the coronary anatomy is suitable for revascularization (class 2b).[5] Therefore, it becomes very important to find predictive markers for CTOs with limited indications for intervention and difficult revascularization compared to other vessels. One study emphasized the importance of evaluating the inflammatory status in selecting low-risk CTO patients for intervention.[6]

In recent years, many studies have shown the relationship between atherosclerosis and inflammation. For example, neutrophil-to-lymphocyte ratio (NLR), erythrocyte distribution width (RDW), and systemic inflammatory index (SII) parameters, which are indicators of inflammation, have been associated with CAD,[7-10] and a significant association with CTO has also been shown.[11-14] Another inflammatory marker, the systemic inflammatory response index (SIRI), is also associated with CAD, and its elevation has been associated with three-vessel disease.[10]

Considering that CTO is more common in patients with chronic-severe CAD and the association of other inflammatory parameters with CTO, it is not far from the mind that SIRI may be associated with CTO. In addition, we did not find any studies in the literature on the relationship between SIRI and CTO. Therefore, we planned this study with the hypothesis that SIRI may be a good predictor of CTO.

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METHODS

The study was carried out with the permission of Kayseri City Training and Research Hospital Clinical Researches Ethics Committee (Date: 17.01.23, Decision No: 780). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Our study was retrospective and included all patients over the age of 18 years who were admitted to the cardiology outpatient clinic between 1/2022 and 12/2022 with stable angina pectoris and who underwent coronary angiography. Patients under 18 years of age, history of acute coronary syndrome, history of previous by-pass operation, history of chronic renal and hepatic failure, history of known inflammatory and rheumatologic diseases, history of known malignancy, history of known anemia (Hb <13 g/dl (male), Hb <12 g/dl (female)), blood transfusion in the last three months, and active infection were excluded.

A total of 200 patients with coronary artery disease who met the inclusion criteria were included in the study. For the CTO group, 100 consecutive patients with 100% stenosis in at least one epicardial artery and for the control group, 100 consecutive patients with coronary artery disease but without 100% occlusion in any epicardial artery were selected.

In all patients, CAG was performed using the Judkins technique with multiple projections using 6 or 7 French (F) catheters through the right or left femoral approach. Iopromide (Ultravist-370®) or Iohexol (Omnipaque® 350 mg/mL) were used as opaque agents. CTO was defined as 100% occlusion of at least one epicardial artery for more than 3 months and the absence of blood flow distal to the vessel.[2] The results of all patients' CAGs were evaluated by two experienced cardiologists.

Blood samples for laboratory examination were collected from the antecubital vein before angiography and after a 12-hour fasting period between 08.00-10.00 hours. A comprehensive metabolic panel and complete blood count (neutrophils, lymphocytes, monocytes, platelets, hemoglobulin, RDW, low-density lipoprotein, high-density lipoprotein cholesterol, and triglycerides) were evaluated. With these results, SII was calculated by multiplying the number of platelets by the number of neutrophils and dividing by the number of lymphocytes, and SIRI was calculated by multiplying the number of monocytes by the number of neutrophils and dividing by the number of lymphocytes.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics Standard Concurrent User V 26 (IBM Corp., Armonk, New York, USA) and MedCalc® Statistical Software version 19.6 (MedCalc Software Ltd., Ostend, Belgium). Descriptive statistics were given as the number of units (n), percentage (%), mean, and standard error. Pearson chi-square analysis was used to compare categorical variables. Homogeneity of variances, one of the prerequisites of parametric tests, was checked by the "Levene" test. The normality assumption was checked with the "Shapiro-Wilk" test. When the differences between the two groups were to be evaluated, the "Student's t Test" was used when the parametric test preconditions were met, and the "Mann Whitney-U test" was used when they were not met. The performance of RDW, SII, and SIRI parameters in predicting CTO was evaluated by Receiver Operating Characteristic (ROC) curve analysis. $p<0.05$ was considered statistically significant.

RESULTS

In the CTO group, the number of patients with CTO in 1 vessel was 87, while the number of patients with CTO in more than 2 vessels was 13. CTOs were most frequently observed in the right coronary artery, with 52 CTOs. This was followed by the left coronary artery with 32 and the circumflex artery with 31.

Basic clinical and laboratory characteristics of the patients are presented in Table 1. Patients in the CTO group were found to be older (p=0.044). White blood cell and neutrophil counts were also statistically higher in the CTO group (p=0.044, p=0.036, respectively).

Table 1. Baseline clinical and demographic characteristics and laboratory values

	Non-CTO group n=100	CTO group n=100	p
Age	60±8.56	62.41±9.19	0.044
Sex (F/M) n (%)	25 (58.1)/75 (47.8)	18 (41.9)/82 (52.2)	0.228
Body mass index	29.64±4.2	29.64±3.68	0.892
Hypertension, n (%)	48 (48.5)	51 (51.5)	0.671
Diabetus mellitus, n (%)	40 (50.0)	40 (50.0)	0.999
Hyperlipidemia, n (%)	41 (50.6)	40 (49.4)	0.885
Coronary artery disease, n (%)	32 (46.4)	37 (53.6)	0.457
Glucose	154.34±74.4	143.43±64.47	0.324
GFR	88.48±13.84	84.64±15.31	0.109
LDL	120.57±34.1	127.28±40.46	0.256
TG	208.74±86.98	216.09±111.84	0.832
HDL	40.76±10.18	39.66±12.1	0.426
WBC	7628.7±1831.26	8157±1859.12	0.044
Hb	14.97±1.37	15.08±1.28	0.568
Platelets	260.97±65.49	255.44±62.9	0.543
Neutrophil	4554.5±1402.21	4991.8±1475.48	0.036
Lymphocyte	2249.3±728.26	2308.4±775.5	0.741
Monocyte	584.7±175.81	625.7±206.63	0.166

GFR: Glomerular filtration rate, Hb: Hemoglobin, HDL: High-density lipoprotein cholesterol, LDL: Low-density lipoprotein cholesterol, TG: Triglycerides, WBC: White blood count.

Table 2 shows the comparison of SIRI, SII, and RDW parameters of these groups, and no statistical difference was observed (p=0,111, p=0,404, p=0,507 respectively).

Table 2. Comparison of inflammatory parameters

	Non-CTO group n=100	CTO group n=100	p
SIRI	1355.7±933.04	1529.57±1024.94	0.111
SII	590.22±343.21	607.83±305.55	0.404
RDW	13.18±1.09	16.74±1.97	0.507

RDW: Red cell distribution width, SII: Systemic Inflammatory Index, SIRI: Systemic Inflammatory Response Index.

Table 3 shows the performance of these parameters in predicting CTO. The optimum cut-off value for SIRI was >1040 (sensitivity 70.0% and specificity 44.0%), the optimum cut-off value for SII was >483 (sensitivity 65.0% and specificity 47.0%), and the optimum cut-off value for RDW was >13.3, (sensitivity 25.0% and specificity 85.0%).

Table 3. Evaluation of the Performance of SIRI, SII and RDW Variables in Predicting CTO Groups by ROC Curve Analysis

	AUC (95.0% CI)	p	Cutoff	Sensitivity (95.0% CI)	Specificity (95.0% CI)
SIRI	0.565 (0.493-0.635)	0.109	>1040	70.0 (60.0-78.8)	44.0 (34.1-54.3)
SII	0.534 (0.462-0.605)	0.406	>483	65.0 (54.8-74.3)	47.0 (36.9-57.2)
RDW	0.527 (0.455-0.598)	0.508	>13.3	25.0 (16.9-34.7)	85.0 (76.5-91.4)

RDW: Red cell distribution width, SII: Systemic Inflammatory Index, SIRI: Systemic Inflammatory Response Index.

DISCUSSION

The main conclusion of our study is that SIRI is useless as a predictor of CTO in patients with stable CAD.

The underlying mechanism of CAD is atherosclerosis. Atherosclerosis has a very complex and incompletely elucidated pathophysiology. Clinical and experimental studies have shown that inflammation plays a critical role in atherosclerosis and CAD.[15] The inflammation that causes atherosclerosis involves various mediators, particularly monocytes and cholesterol particles. During the development of atherosclerotic plaque, monocytes expressed in damaged endothelium are activated by binding to adhesion molecules.[16] The activated monocytes then migrate to the arterial intima, where they differentiate into macrophages and form foam cells characteristic of atherosclerosis by phagocytosis of modified lipoproteins and lipid loading.[17]

Neutrophils and lymphocytes, other elements of the immune system, are also active in atherosclerosis. Neutrophils mediate the inflammatory reaction by releasing numerous bioactive substances, such as arachidonic acid metabolites and platelet-inhibiting factors,[18] leading to the progressive development and fragility of the plaque.[19] On the other hand, lymphocytes have also been shown to be important for the development of atherosclerosis. [20,21] Therefore, the monocytes, neutrophils, and lymphocytes used to calculate the SIRI are important components of the inflammatory and atherosclerotic processes.

SIRI is a relatively new parameter and is considered an indicator of inflammation. This parameter was first used in cancer patients, and it was demonstrated that it could be used to predict the survival of patients with pancreatic adenocarcinoma receiving chemotherapy.[22] In the following years, its relationship with CAD was also investigated. In one study, SIRI was found to be significantly elevated in patients with severe CAD.[10] In another study, SIRI elevation was found to be associated with single-vessel and complex coronary artery disease.[23] Inflammatory markers, such as SII and RDW, have been the subject of interest in CAD-related studies. Different studies have found a significant association between elevated SII and CAD severity.[9,24,25] RDW have also been found to be associated with the presence of CAD and CAD severity in patients with stable angina pectoris.[8]

CTO is a chronic-advanced form of CAD and occurs against a background of atherosclerosis. Since inflammation plays an important role in the pathogenesis of atherosclerosis, the association of inflammatory parameters such as SII and RDW with CTO has also been investigated. SII has been shown to be an easy and practical indicator for identifying high-risk CTO patients.14 RDW has been shown to be associated with infarct-related artery (IRA)-CTO12 and non-IRA-CTO13 in patients with acute coronary syndrome (ACS) and has also been independently correlated with inadequate coronary collateral circulation in patients with stable CAD.[26]

Based on previous studies, it is possible to conclude that SII and RDW have a close relationship between CAD and CTO. In our study, we predicted that SIRI, which has been correlated with the presence and severity of CAD, would also show a positive correlation with CTO. According to the data we obtained, SIRI was higher in the group with CTO compared to the group without CTO. However, this elevation was not statistically different. Moreover, not only SIRI but also SII and RDW did not reach statistical significance in CTO patients compared to non-CTO patients.

In contrast to previous studies, the lack of a significant association between RDW and CTO may be due to the difference in the study population. The patient group selected in our study was stable CAD, while previous studies showing the relationship between RDW and CTO were performed in patients with acute coronary syndromes.[12,13] Therefore, a significant relationship between CTO and RDW may have been found due to the physiopathological process of ACS. Similarly, in the study with SII and CTO, the study group was different from our study.[14] The patient group selected for CTO was highly heterogeneous and included patients with ACS, stable CAD and previous bypass surgery. In addition, this study emphasized the relationship between SII and high-risk CTO rather than the relationship between CTO and SII.

The failure of SIRI and other parameters to detect CTO in our study suggests that the level of inflammation in CTO patients may not be higher than in non-CTO patients. In a previously published study, it was reported that the main pathophysiological basis of CTO is soft plaque rupture, followed by thrombotic coronary occlusion and organization of thrombotic material, and to a lesser extent, progression of partial atheroma plaque.[27] Therefore, although CTO develops in the background of atherosclerosis, the basic physiopathologic process may not be inflammation. We think that this is the reason why SIRI and other parameters were not found to be predictors of CTO in our study.

Limitations

This study has some limitations that should be considered. First of all, the most important limitation was that it was a retrospective study conducted at a single center. In addition, due to the retrospective design of the study, although broad exclusion criteria were used, all other factors that may affect these parameters may not have been revealed. Finally, high-sensitivity C-reactive protein (hsCRP), an inflammatory marker that provides prognostic information in predicting cardiovascular events, was not included in the study.[28] A clearer result could have been obtained by correlating hsCRP values with other inflammatory parameters, especially SIRI. We think that prospective studies, including hsCRP along with all inflammatory parameters and with a larger number of patients, are needed.

CONCLUSION

Although SIRI is valuable in predicting the severity of CAD, the same is not true for CTO. The main conclusion from our study is that SIRI is an inflammatory predictor that is not useful in the detection of CTO.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kayseri City Training and Research Hospital Clinical Researches Ethics Committee (Date: 17.01.23, Decision No: 780).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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Original Article

MEDICINE PALLIATIVE CARE

DOI: 10.47582/jompac.1357295

J Med Palliat Care. 2023;4(5):547-554

Knowledge levels of graduate and trainee dentists on antibiotic use in endodontics

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Cite this article as: Topbaş C, Keskin Tunç S, Güdücüoğlu H. Knowledge levels of graduate and trainee dentists on antibiotic use in endodontics. *J Med Palliat Care*. 2023;4(5):547-554.

Received: 08.09.2023 ◆ **Accepted**: 07.10.2023 ◆ **Published**: 27.10.2023

ABSTRACT

Aims: The aim of this study was to compare and evaluate the level of knowledge of dentists and dental students about the rational use of antibiotics (RUA), their clinical approaches when prescribing antibiotics, and student and graduate dentists. Rational use of medicines means that patients take their medicines according to their clinical needs, in appropriate doses, for sufficient time, and at the lowest cost to themselves and society. The RUA is very important in the treatment and prevention of bacterial infections.

Methods: The questionnaire, which was prepared on Google Forms for all graduate and trainee dentists in Turkey that we could reach and included questions about RUA and antibiotic use in dentists, was distributed to approximately 400 people, and 331 people returned the questionnaire.

Results: Of the respondents, 52.3% were dental students, and the remaining 47.7% were dental graduates. 94.8% of the participants reported that they received information about RUA from the faculty, followed by scientific publications, the internet and social media, the Ministry of Health, relatives, spouses, and friends, professional associations, and newspapers. The majority of participants, 303 people, answered the question, 'Can inappropriate use of antibiotics increase antimicrobial resistance? The majority of participants answered yes, while the remaining 18 answered no. The majority of participants, 62.1%, thought that antibiotics were prescribed more than necessary. Only 35% of participants (110 people) correctly answered the question about antibiotics that are not suitable for use during pregnancy and breastfeeding.

Conclusion: According to the results of our study, dentists have an important role to play in ensuring the RUA. Dentists should be regularly trained with updated curricula.

Keywords: Rational antibiotic use, dentistry, dental trainees

INTRODUCTION

Rational use of antibiotics (RUA) means prescribing drugs in accordance with the clinical needs of patients, in appropriate doses, for an adequate duration, and at the lowest cost to themselves and society.[1,2] RUA has a very important place in the treatment and prevention of bacterial infections.[3,4] RUA is necessary to prevent important problems such as the development of antibiotic resistance. Antibiotic resistance has become one of the biggest obstacles to the successful treatment of infections. WHO (World Health Organization) and various national and international organizations have made emergency action plans to prevent the development of resistant bacterial strains and limit their spread.[5,6] There are various reasons for this increasing problem, but the most important is the misuse or overuse of antibiotics in both human and veterinary medicine and animal husbandry.[7] Awareness-raising trainings should be organized for both prescribing physicians and the public in order to limit and improve the unnecessary use or misuse of this group of drugs. Antibiotics, which are also widely used in dental practices, are among the most commonly used drugs in Turkey.[8-10] As a result of the misuse of antibiotics, both adverse effects on patients and harmful effects, such as the emergence of harmful and resistant bacterial strains in the environment, occur.

The more they are used, the more resistance develops and spreads. As with medical and veterinary practitioners, new initiatives have increased in dentistry, a field of serious importance for rational antibiotic use. Dentists constitute a significant portion of physicians prescribing antibiotics, but it has been shown that the therapeutic decisions of dentists

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when prescribing antibiotics are not always correct.[11,12] It is known that there are more than 700 microorganisms in our oral microflora.[13,14] This flora consists of viruses, gram-positive and gram-negative aerobic and anaerobic bacteria, and a small number of yeast fungi. These flora members are mostly non-pathogenic, but pathogenic species may increase and lead to dental infections due to reasons such as poor oral hygiene, nutrition, host immune response, and aging.[15-17] Although antibiotics are widely used in the treatment of dental infections, they actually have a limited indication for use.[18] Instead of using antibiotics, dental infections are mostly treated with root canal treatments, tooth extraction, surgical drainage, and scaling or smoothing of the tooth root surface. Systemic antibiotic use is required only in cases where prophylaxis is required, abscesses cannot be drained, the effect of local anesthesia is insufficient, fever, trismus, cellulitis, osteomyelitis, and lymphadenopathy.[15] When indicated, RUA includes selecting the right antibiotic at the appropriate dose and duration, considering the cost of treatment, prescribing it in the right format, providing adequate and understandable information to the patient, using the antibiotic correctly, and evaluating the results of treatment. Physicians have a very important role in this process. They should diagnose the patient correctly and make sure that the above-mentioned requirements for antibiotic use are met. Irrational use of antibiotics (IUA) leads to many irreparable problems, such as increased bacterial resistance and low treatment success rates. Antibiotics are medicines that need to be used with caution due to increasing bacterial resistance, high costs, and the decline in new antibiotic discoveries. RUA means using the appropriate antibiotic at the appropriate time and dose at the lowest cost. Dentists frequently encounter situations such as dental-gingival infections and endocarditis prophylaxis. Therefore, they work in a field where antibiotics are frequently used. The aim of this study was to compare and evaluate the level of knowledge of dentists and dental students about RUA, their clinical approaches when prescribing antibiotics, their tendency to prescribe antibiotics in pulpal infections for which antibiotics are not indicated, and student and graduate dentists.

METHODS

The study was carried out with the permission of Van Yüzüncüyıl University Clinical Researches Ethics Committee (Date: 01.09.2022, Decision No: 01). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The questionnaire, which was prepared via Google Forms for all accessible graduate and trainee dentists in Turkey and included questions about RUA and the use of antibiotics in dentists, was distributed to approximately 400 people, and 331 people returned the questionnaire. Only participants who read the consent form and selected the "I agree to participate in the study" tab were included in the study. The questions do not include personal information. Some of the questions included demographic data, some included data on the issues to be considered when prescribing antibiotics, and the questionnaire also included questions to assess the participant's level of knowledge and interest in RUA. The responses of graduate and trainee participants were compared and evaluated.

Inclusion Criteria

Students in their 4th or 5th year of internship at a university in Turkey, dentists who graduated from the faculty of dentistry, and those who agreed to fill out the online survey.

Exclusion Criteria

No other occupational group is included, and those who did not complete the questionnaire completely are not included.

Obtaining Data

In our study, all data was available in the Excel system in Google Forms. All data were statistically evaluated.

Statistical Evaluation Methods

NCSS (Number Cruncher Statistical System) 2020 Statistical Software (NCSS LLC, Kaysville, Utah, USA) was used for statistical analyses while evaluating the findings obtained in the study. While evaluating the study data, quantitative variables were shown with mean, standard deviation, median, min, and max values, and qualitative variables were shown with descriptive statistical methods such as frequency and percentage. Shapiro-Wilks test and box plot graphs were used to evaluate the conformity of the data to the normal distribution. Chi-Square test, Fisher's exact test, and Fisher Freeman Halton test were used to compare qualitative data. The results were evaluated at the 95% confidence interval, and significance was evaluated at the p 0.05 level.

RESULTS

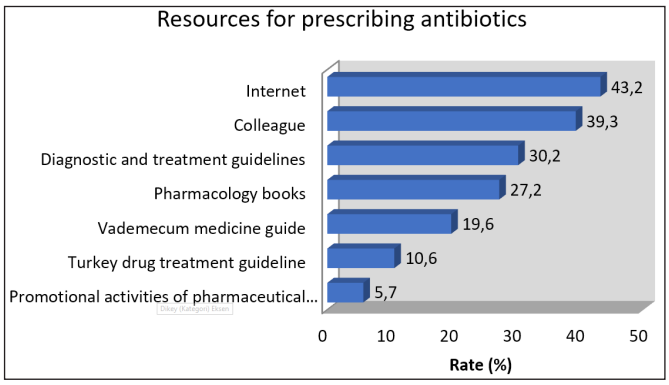
The questionnaire was distributed to a total of 400 people via the WhatsApp application, e-mail groups, and professional organizations' chambers. The questionnaire was completed by 331 volunteers. It was observed that almost every geographical region of our country participated in the study (Table 1). Part of the questionnaire consisted of general and demographic questions; part of the questionnaire consisted of questions about RUA; and part of the questionnaire consisted of questions evaluating information about endodontic infections, which are the most common reason for antibiotic use in dentistry and one of the most common reasons for antibiotic prescription. Of the participants, 52.3% were trainee

dentists, and the remaining 47.7% were graduate dentists. The numerical distribution of graduated dentists was close to each other. Table 1 also shows the specialty, type of workplace, professional status, and average age.

Table 1. Distribution of descriptive characteristics

	n (%)
Gender	
Female	174 (52.6)
Male	157 (47.4)
Age	
<25 years	174 (52.6)
25-30 years	61 (18.4)
30-45 years	87 (26.3)
>45 years	9 (2.7)
Professional status	
Academician	41 (12.4)
Dental resident	33 (10.0)
Dentist	50 (15.1)
Graduate specialist/PhD dentist	34 (10.3)
Trainee	173 (52.3)
Specialization	
Oral, and maxillofacial surgery	21 (6.5)
Endodontics	46 (14.3)
General dentist	49 (15.3)
Oral pathologist	1 (0.3)
Orthodontist	2 (0.6)
Pedodontics	7 (2.2)
Periodontology	8 (2.5)
Prosthetic dentist	8 (2.5)
Restorative	6 (1.9)
Number of years of practice	
<5 years	46 (29.9)
5-10 years	34 (22.1)
10-20 years	63 (40.9)
>20 years	11 (7.1)
Region of residence	
Mediterranean Region	22 (6.6)
Eastern Anatolia	39 (11.8)
Aegean Region	12 (3.6)
Southeastern Anatolia	53 (16)
Central Anatolia Region	19 (5.7)
Black Sea Region	11 (3.3)
Marmara Region	175 (52.9)
What type of workplace he/she works in	
State Hospital	32 (16.5)
Private practice	25 (12.9)
Policlinic	40 (20.6)
University	97 (50)

When question 2 of the questionnaire, which inquired about their specialty, was examined, it was observed that general dentists and endodontists participated more intensively in the survey (Table 1). Gender distribution was homogeneous, with 52.6% female and 47.4% male. Among the trainee participants, 87 were female and 86 were male, while 87 were female and 71 were male among the graduates. Statistically, there is no significant difference between the graduate and trainee groups (Table 1). However, there was no statistically significant difference between the genders of the participants according to the graduate and trainee groups ($p > 0.05$). The sources used for prescribing antibiotics show the increasing use of the internet, although other methods are also frequently used (Graph 1).



Graph 1. Distribution of sources used for prescribing antibiotics

The majority of the participants, 303 people, answered yes to the question, 'Can inappropriate antibiotic use increase antimicrobial resistance? Yes, while the remaining 18 answered no. The majority of the participants, 62.1%, thought that antibiotics were prescribed more than necessary, followed by 19.1% who thought that antibiotics were prescribed as needed, and 18.8% had no idea. When asked which antibiotic you would use as the first choice in the treatment of dentoalveolar abscesses, 86.4% (280 people) answered amoxicillin, 6.8% (22 people) clindamycin, 5.9% (19 people) metronidazole, and the remaining 0.19% (3 people) erythromycin.

When asked, 'In which of the following cases is antibiotic prophylaxis not necessary? ', the vast majority of respondents, 96.6% (317 people), selected the correct answer, 'In the absence of heart defects', while the other answers were: 4% (13 people) congenital heart defects involving abnormal leakage or a shunt between the systemic and pulmonary circulation'; 1.8% (6 people) surgical repair of congenital heart defects (if performed less than 6 months before dental treatment)'; 1.2% (4 people) in patients with artificial heart valves Only 2 people checked in patients with a history of infective endocarditis'. When asked which antibiotics can be prescribed to a breastfeeding patient, only 13.9% of the participants gave the correct answer: "Amoxicillin-clavulanic acid, erythromycin, and cefuroxime axetil". To the question "Which of the following cephalosporins is appropriate to use in a patient with an antibiotic allergy who can use oral medication?", the majority of the participants gave the correct answer "Cephalexin".

When the answers given to the questions about antibiotic use in endodontic treatments, one of the most frequently performed procedures in dentistry, were evaluated, it was observed that the majority of the participants gave the correct answer (Table 2). In the case of congenital heart defects involving abnormal leakage or a shunt between the systemic and pulmonary circulation, 4% (n=13) and 1.8% (n=6) stated that prophylaxis was not necessary in patients with a history of infective endocarditis, 96.6% (n=317) in patients without heart defects, and 1.2% (n=4) in patients with artificial heart valves. When asked which of the following cephalosporins is appropriate to use in a patient with an antibiotic allergy who can use oral medication, 56.2% (n=173) of the participants answered Cephalexin, 4.5% (n=14) Cephalothin, 4.9% (n=15) Cefapirin, 32.8% (n=101) Cefazolin, and 15.9% (n=49) Ceftriaxone. In endodontic infections, 11% (n=36) preferred antibiotics for fistulized chronic apical abscess, 77.3% (n=252) for non-localized infection with widespread distribution in soft tissue, 25.5% (n=83) for localized swelling, 21.2% (n=69) for symptomatic apical periodontitis, and 9.2% (n=30) for symptomatic pulpitis.

Table 2. Distribution of questions related to endodontics

	n (%)
First choice for first-line treatment of dentoalveolar abscesses	
Amoxicillin*	280 (86.4) *
Erythromycin	3 (0.9)
Clindamycin	22 (6.8)
Metronidazole	19 (5.9)
In which cases there is no need for prophylaxis	
Congenital heart defects involving abnormal leakage or a shunt between the systemic and pulmonary circulation.	13 (4.0)
Surgical repair of congenital heart defects (if performed less than 6 months before dental treatment)	6 (1.8)
In patients with a history of infective endocarditis	2 (0.6)
Those without heart defects *	317 (96.6)*
In patients with artificial heart valves	4 (1.2)
Which of the following cephalosporins is appropriate to use in a patient with antibiotic allergy who can use oral medication	
Cephalexin*	173 (56.2)*
Cephalothin	14 (4.5)
Cefapirin	15 (4.9)
Cefazolin	101 (32.8)
Ceftriaxone	49 (15.9)
In which case the patient prefers to use antibiotics in endodontic infections	
Chronic apical abscess with sinus tract	36 (11.0)
Non-localized infection with widespread distribution in soft tissue *	252 (77.3)*
Localized swelling	83 (25.5)
Symptomatic apical periodontitis	69 (21.2)
Symptomatic pulpitis	30 (9.2)
In which of the following should antibiotics be prescribed as supportive therapy after endodontic intervention?	
Chronic apical abscess	42 (13.1)
Chronic apical periodontitis	24 (7.5)
Necrotic pulp	13 (4.0)
Cellulitis*	266 (82.9)*
Symptomatic irreversible pulpitis	40 (12.5)
Which antibiotic would be your most appropriate choice for persistent endodontic infections?	
4th Generation Cephalosporin	28 (8.7)
Empirical antibiotic treatment	15 (4.7)*
Broad-spectrum antibiotics	118 (36.8)
Culture-assisted antibiotic treatment*	149 (46.4)*
Penicillin group	61 (19.0)
I. Amoxicillin II. Beta-lactamase inhibitors III. Doxycycline IV. Clindamycin V. Erythromycin Which or which of the above antibiotics is not suitable for use in pregnancy and lactation?	
I, II and IV	27 (8.6)
I, II and V	19 (6.1)
III and V*	110 (35)*
Only II	34 (10.8)
Only III	124 (39.5)
Which of the following antibiotics is not used in endodontic infections	
Amoxicillin	3 (1.0)
Azithromycin	42 (13.9)
Metronidazole group	38 (12.6)
Penicillin V	35 (11.6)
Rifampicin*	206 (68.2)*
I. Cephalexin II. Cefazolin III. Ceftriaxone IV. Azithromycin V. Doxycycline According to the AHA guidelines for prophylaxis in dental treatment, which or which of the above antibiotics can now be used in patients with penicillin allergy?	
I, II and IV	125 (41.7)
I, II and V	33 (11.0)
I, IV and V*	42 (14.0)*
All	78 (26.0)
None	22 (7.3)
Which is not one of the conditions for which prophylaxis is recommended for the risk of bacterial endocarditis?	
Patients who have had a myocardial infarction within the previous year*	244 (76.5)*
Patients with a history of infective endocarditis	16 (5.0)
Those with heart valve prosthesis	16 (5.0)
Cardiac transplant patients with cardiac valvulopathy	25 (7.8)
Congenital heart disease	52 (16.3)

More than one option is marked. *indicates the correct answer.

In which case antibiotics should be prescribed as supportive treatment after endodontic intervention, 13.1% (n=42) responded to chronic apical abscess, 7.5% (n=24) to chronic apical periodontitis, 4% (n=13) to necrotic pulp, 82.9% (n=266) to cellulitis, and 19% (n=61) to the penicillin group. Which is not one of the conditions for which prophylaxis is recommended to reduce the risk of bacterial endocarditis? To this question, 76.5% (n=244)

of the study participants answered: patients who had myocardial infarction one year ago; 5% (n=16) patients with a history of infective endocarditis; 5% (n=16) patients with a heart valve prosthesis; 7.8% (n=25) heart transplant patients with cardiac valvulopathy; 16.3% (n=52) congenital heart disease. When asked about antibiotics that are not suitable for use in pregnancy and lactation, only 35% (110 respondents) answered correctly, and 39.5% answered "Doxycycline only". According to the most recent AHA (American Heart Association) guidelines for prophylaxis in dental treatment (19), which of the above antibiotics can be used instead of clindamycin, which is no longer recommended for patients with penicillin allergies? When we analyze the answers to the question, we see in **Table 2** that only 42 people (14%) gave the correct answers of Cephalexin, Azithromycin, and Doxycycline.

In **Table 3**, the responses of interns and graduated dentists to general RUA questions are evaluated. The proportion of interns who thought that dentists were over-prescribed in terms of RUA was found to be statistically significantly lower than that of graduates (p=0.001; p 0.01). The rate of the interns' first choice of Clindamycin in the first-line treatment of dentoalveolar abscesses was statistically significantly higher than that of the graduates (p=0.001; p 0.01). Interns had a higher rate of thinking that the use of Cephalexin was appropriate in a patient with an antibiotic allergy who could use oral medication (p=0.001; p 0.01), while the rates of using Cefapirin, Cefazolin, and Ceftriaxone were lower (p=0.042; p=0.009; p=0.039; p 0.05).

In **Table 4**, the evaluation of the questions related to endodontic treatment and antibiotics was compared according to the groups. The preference rate of the interns for antibiotic use in cases of non-localized infection with widespread distribution in soft tissue was statistically significantly lower than that of the graduates (p=0.001; p 0.01). The correct answer to this question was lower than that of the graduates. However, when the other response rates given by the interns are examined (even if there is an incorrect answer), the interns are statistically significantly more likely than graduates to prefer the use of antibiotics in the case of fistulized chronic apical abscess, in the case of symptomatic apical periodontitis, and in the case of symptomatic pulpitis (p=0.001; p 0.01). In which of the following cases should antibiotics be prescribed as supportive treatment after endodontic intervention? In both groups, the correct answer to the question was cellulitis, and no significant difference was observed between the groups. However, the rate of prescribing antibiotics as supportive treatment after endodontic intervention in chronic apical abscess, chronic apical periodontitis, and symptomatic irreversible pulpitis was statistically significantly higher in interns than in graduates (p=0.004; p 0.01).

Table 3. Evaluation of 'rational use of antibiotics related questions by groups

	Group		p
	Trainee dentist	Others	
What he/she thinks about the attitude of dentists regarding RUA			
No opinion	44 (25.4)	18 (11.5)	[c]0.001**
I think it is prescribed more than necessary.	82 (47.4)	123 (78.3)	
I think it is prescribed as needed.	47 (27.2)	16 (10.2)	
First choice for first-line treatment of dentoalveolar abscesses			
Amoxicillin	134 (79.3)	146 (94.2)	[c]0.001**
Erythromycin	2 (1.2)	1 (0.6)	
Clindamycin	19 (11.2)	3 (1.9)	
Metronidazole	14 (8.3)	5 (3.2)	
In which cases is there no need for prophylaxis?			
Congenital heart defects involving abnormal leakage or a shunt between the systemic and pulmonary circulation.	3 (1.8)	10 (6.4)	[a]0.032*
Surgical repair of congenital heart defects	4 (2.3)	2 (1.3)	[b]0.686
In patients with a history of infective endocarditis	1 (0.6)	1 (0.6)	[b]1.000
In those without heart defects	164 (95.9)	153 (97.5)	[a]0.437
In patients with artificial heart valves	3 (1.8)	1 (0.6)	[b]0.357
Which of the following cephalosporins is appropriate to use in a patient with antibiotic allergy who can use oral medication			
Cefalexin	111 (68.9)	62 (42.2)	[a]0.001**
Cephalothin	4 (2.5)	10 (6.8)	[a]0.069
Cefapirin	4 (2.5)	11 (7.5)	[a]0.042*
Cefazolin	42 (26.1)	59 (40.1)	[a]0.009**
Ceftriaxone	19 (11.8)	30 (20.4)	[a]0.039*

aPearson Chi-Square Test, bFisher's Exact Test, cFisher Freeman Halton Test, *p<0,05, **p<0,01

According to the most recent AHA (American Heart Association) guidelines for prophylaxis in dental treatment, which of the above antibiotics can be used instead of clindamycin, which is no longer recommended? The question was mostly answered incorrectly in both groups. There was no statistically significant relationship between the answers in both groups. To the question "Which or which of the antibiotics is not used in endodontic infections?" both groups gave the correct answer in the majority. Trainees were statistically significantly less likely than graduates not to use the antibiotic Rifampicin in endodontic infections (p=0.026; p 0.05). According to the groups, the most appropriate antibiotic selection of the participants in persistent endodontic infections did not show a statistically significant difference (p > 0.05).

Table 4. Evaluation of 'endodontic treatment and antibiotic' related questions by groups

	Profession		p
	Trainee Dentist	Graduate	
In which case the dentist prefers to use antibiotics in endodontic infections			
Chronic apical abscess with a sinus tract	29 (16,9)	7 (4,5)	[a]0,001**
Non-localized, widespread soft tissue infection^	119 (69,2)	133 (86,4)	[a]0,001**
Localized swelling	48 (27,9)	35 (22,7)	[a]0,284
Symptomatic apical periodontitis	50 (29,1)	19 (12,3)	[a]0,001**
Symptomatic pulpitis	23 (13,4)	7 (4,5)	[a]0,006**
In which of the following cases should antibiotics be prescribed as supportive treatment after endodontic intervention?			
Chronic apical abscess	31 (18,2)	11 (7,3)	[a]0,004**
Chronic apical periodontitis	19 (11,2)	5 (3,3)	[b]0,010*
Necrotic pulp	4 (2,4)	9 (6,0)	[b]0,155
Cellulitis^	137 (80,6)	129 (85,4)	[a]0,250
Symptomatic irreversible pulpitis	30 (17,6)	10 (6,6)	[a]0,003**
Which antibiotic would be your most appropriate choice for persistent endodontic infections?			
4th Generation Cephalosporin	18 (10,8)	10 (6,5)	[b]0,235
Empirical antibiotic treatment	11 (6,6)	4 (2,6)	[b]0,114
Broad-spectrum antibiotic	57 (34,1)	61 (39,6)	[a]0,309
Culture-assisted antibiotic therapy^	74 (44,3)	75 (48,7)	[a]0,431
Penicillin group	32 (19,2)	29 (18,8)	[a]0,940
Which of the following antibiotics is not used in endodontic infections?			
Amoxicillin	1 (0,6)	2 (1,4)	[b]0,607
Azithromycin	12 (7,6)	30 (20,8)	[a]0,001**
Metronidazole group	18 (11,4)	20 (13,9)	[a]0,603
Penicillin V	18 (11,4)	17 (11,8)	[a]1,000
Rifampicin^	117 (74,1)	89 (61,8)	[a]0,026*
I. Cephalexin II. Cefazolin III. Ceftriaxone IV. Azithromycin V. Doxycycline According to the AHA (American Heart Association) guidelines for prophylaxis in dental treatment, which or which of the above antibiotics can be used for patients with penicillin allergy?			
I, II and IV	67 (43,2)	58 (40)	[c]0,872
I, II and V	19 (12,3)	14 (9,7)	
I, IV and V^	21 (13,5)	21 (14,5)	
All	37 (23,9)	41 (28,3)	
None	11 (7,1)	11 (7,6)	
Which is not one of the conditions for which prophylaxis is recommended for the risk of bacterial endocarditis?			
Patients who had a myocardial infarction one year ago^	123 (74,5)	121 (78,6)	[a]0,397
Patient with a history of infective endocarditis	11 (6,7)	5 (3,2)	[b]0,203
Heart valve prosthesis	8 (4,8)	8 (5,2)	[b]1,000
Heart transplant patients with cardiac valvulopathy	19 (11,5)	6 (3,9)	[b]0,012*
Congenital heart disease	17 (10,3)	35 (22,7)	[a]0,003**

aPearson Chi-Square Test, bFisher's Exact Test, cFisher Freeman Halton Test, *p<0,05, **p<0,01, ^ Indicates the correct answer.

There was no statistically significant difference (p > 0.05) between the groups in which antibiotics the participants used instead of clindamycin, which is no longer recommended for patients with penicillin allergies according to the most recent AHA (American Heart Association) guidelines for prophylaxis in dental treatment. In both groups, the wrong answer was mostly marked. It can be said that physicians have deficiencies in following current information. Which is not one of the situations in which prophylaxis is recommended in terms of bacterial endocarditis risk? Both groups gave mostly correct answers to the question. However, the rate of trainees not considering heart transplantation patients with cardiac valvulopathy as a recommended condition for prophylaxis in terms of bacterial endocarditis risk was statistically significantly higher than that of graduates (p=0.012; p 0.05).

The rate of graduates who did not consider congenital heart disease as a condition for which prophylaxis is recommended in terms of bacterial endocarditis risk was statistically significantly higher than that of interns (p=0.003; p 0.01). According to the groups, there was no statistically significant difference in the rate of participants not considering patients who had myocardial infarction one year ago, patients with a history of infective endocarditis, and patients with heart valve prostheses as recommended prophylaxis in terms of bacterial endocarditis risk (p > 0.05).

DISCUSSION

Today, IUA has become quite common. Various activities aimed at limiting and correcting the misuse of this extremely valuable group of drugs are becoming more important. The prescribing physician group has a very important role not only in the emergence and spread of antibiotic resistance but also in its prevention. Therefore, physicians' knowledge of the rational and appropriate use of antibiotics is very important in the fight against microbial resistance. A prescription is an official document that carries the physician's information and signature and imposes legal liability on physicians. According to Turkish legislation, physicians, dentists, and veterinarians are authorized to write prescriptions. Authorization also means liability. Problems that may arise as a result of the negligence or fault of the physician are also the responsibility of the physician. For this reason, the main goal of physicians when prescribing should be rational treatment, i.e., choosing appropriate, safe, effective, and inexpensive medicines and keeping in mind the principles of evidence-based medicine (carefully examining the data related to the disease and the patient and making the treatment plan accordingly). Various studies have shown that 8% to 10% of all first-line prescriptions are written by dentists.[11,20] Some studies have shown that not only physicians but also dentists overprescribe antibiotics. For example, a survey in the

USA showed that 70% of dentists prescribed inappropriate antibiotics prophylactically before dental procedures.[21] A similar study conducted among general practitioner dentists in the UK showed that only 19% of dentists prescribed appropriate antibiotics as specified in the guidelines.[22] Trainee dentists receive extensive information on rational antibiotic use in their university courses as part of their education. After graduation, they improve their knowledge through the trainings of the Ministry of Health, professional chambers, scientific publications, and various media, such as the internet. This information is of utmost importance for their dental procedures to be more accurate and precise. For this reason, our questionnaire distributed to trainees and graduates included both general information and information on RUA.

It was observed that the respondents generally gave satisfactory answers and were generally well educated. When asked whether inappropriate antibiotic use would increase antibiotic resistance, the majority (91.8%) answered correctly that it would. In our study, graduating physicians and dental students understood that antibiotic resistance is an important problem and that dentists prescribe more antibiotics than necessary for viral infections. This view was also expressed by physicians and the public in other studies.[23,24] Not all conditions associated with an infection in dentistry require antibiotic treatment. Antibiotics do not need to be used in routine dental procedures such as pulpitis, fillings, root canal treatment, apical periodontitis, and drainage of localized dentoalveolar abscesses without systemic symptoms, which do not show signs of systemic involvement, such as fever, malaise, chills, and spread to surrounding tissues such as trismus or cellulitis. Unfortunately, dentists still prescribe antibiotics before treatment, even in these cases.[25] The first step in the treatment of a dentoalveolar abscess should often include surgical debridement, and an antibiotic is only given when medically necessary and general symptoms are apparent.[26] When asked which antibiotic would be preferred, when necessary, the majority of dentists and students (86.4%-280 people) gave the correct answer of amoxicillin. It was observed that the results overlapped with another study conducted on this subject.[27] However, clindamycin was the first choice in a study conducted in Poland.[28] Attention should be paid to safe antibiotic use in breastfeeding or pregnant patients. It was observed that the level of knowledge of the respondents on this subject was insufficient (13.9% correct answer) and needed to be improved with education. Appropriate treatment for a patient allergic to 'penicillin', which is usually one of the first-line drugs in dentistry, was also addressed in our study. In 2021, after the American Heart Association published an update on the prevention of infective endocarditis caused by viridans group streptococci, the prophylaxis guideline for dental treatments was also updated. Accordingly, clindamycin is no longer recommended in patients with penicillin allergies.[19] According to this publication, the use of cephalexin, azithromycin, clarithromycin, or doxycycline is recommended in cases of oral drug intake in patients with penicillin allergy, and cefazolin or ceftriaxone is recommended in cases of non-oral drug intake. Current dental prophylaxis knowledge was also questioned in our study.

Only 7.7% of the respondents gave the correct answer. Thus, in addition to revealing the lack of physicians following the current literature, the importance of following the current literature has once again emerged. In a study, the knowledge, and behaviors of parents of patients admitted to the pediatric outpatient clinic on antibiotic use were measured. While the rate of antibiotic initiation without visiting a doctor was found to be lower in fathers (31.8%) than in mothers (42.9%), the rate of antibiotic initiation without visiting a doctor was found to be statistically significantly higher in those with 8 years of education than in those with >8 years of education.[29] There is a need to increase the level of knowledge and awareness with educational programs on this subject.

In a study conducted in India in 2017, the knowledge levels and practices of trainee and graduate dentists in prescribing antibiotics and analgesics were compared. In the study with 870 participants, it was shown that the knowledge level of trainee dentists was lower than that of graduate dentists.[30] In our study, 94.2% of the graduate dentists and 79.3% of the trainee dentists gave the correct answer "amoxicillin" to the question of which antibiotic you would prefer in the first-line treatment of dentoalveolar abscesses. There is a statistically significant (p=0.001) difference between them. In line with the study of Doshi et al.[30] and in a way that can be explained by professional experience, the knowledge level of the trainee dentists was lower than that of the graduate dentists (**Table 3**). Again, in our study, 86.4% of the graduate dentists and 69.2% of the trainee dentists marked the correct answer "non-localized infection with widespread distribution in soft tissues" when asked which antibiotic should be used in endodontic infections. There was a statistically significant difference between them (p=0.001).

CONCLUSION

According to the results of our study, dentists play a major role in ensuring rational antibiotic use. In the study, the general situation of the trainees who are still learning to treat with new information and the experienced graduate dentists on antibiotic use was evaluated. We can say that graduates and interns do not differ significantly on this important issue. We can say that dentists should be regularly trained with updated curricula after graduation.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Van Yüzüncüyıl University Clinical Researches Ethics Committee (Date: 01.09.2022, Decision No: 01).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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Original Article

MEDICINE PALLIATIVE CARE

DOI: 10.47582/jompac.1343562

J Med Palliat Care. 2023;4(5):555-560

Evaluation of attitudes, behaviors and knowledge levels of students of functional foods

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Cite this article as: Arslan N, Alataş H. Evaluation of attitudes, behaviors and knowledge levels of students of functional foods. *J Med Palliat Care*. 2023;4(5):555-560.

Received: 08.09.2023 ◆ **Accepted**: 07.10.2023 ◆ **Published**: 27.10.2023

ABSTRACT

Aims: This study aimed to determine the knowledge level of students studying functional foods at a public university in Malatya and to evaluate the factors affecting their attitudes and behaviors.

Methods: A total of 618 individuals (363 female and 255 male) studying at universities in Malatya were included in this study. Data were collected using a face-to-face survey. The questionnaire consisted of questions about demographic characteristics, eating habits, general health, anthropometric measurements (body weight and height), functional food knowledge level, and food preference scale sections. The data were analyzed using SPSS.

Results: The mean age of the participants was 24.45±2.18 years. It was determined that 65.04% of the individuals had heard of the term functional food. The YETBID-Basic Nutritional Knowledge Scores were higher in females (54.66±8.85) than males (51.14±8.22) (p=0.031). Individuals' knowledge attitude scale confidence subheading score for functional foods was higher in female (3.95±1.04) than in male (3.15±1.04) (p=0.044). It was observed that as the basic nutrition score increased in both female and male, the score on the attitude scale towards functional foods also increased. In the multiple regression analysis, it was determined that the total score of the attitude scale towards functional foods was significantly affected by the variables of female (sex), duration of education, basic nutrition score, and food preference score (p<0.05).

Conclusion: It was determined that as the education level of the individuals increased, their level of basic nutrition knowledge increased, which affected their attitude towards functional foods. It has been determined that female have higher nutritional knowledge levels than male, find functional foods more reliable, and are more inclined to consume them.

Keywords: Nutrition, knowledge level, functional foods

INTRODUCTION

Over the years, functional foods have been the focus of numerous studies, particularly in the fields of technology and better nutritional health.[1] No single definition of functional foods exists.[2] More than 100 experts in nutrition and related fields came to an agreement on the definition of functional nutrients between 1995 and 1998 as part of the European Commission's coordinated action on functional nutritional science, coordinated by the International Life Sciences Institute.[2] A nutrient can be deemed functional if, in addition to the benefits of adequate nutrition, it has been satisfactorily demonstrated to positively affect one or more target bodily functions, either by enhancing health or well-being and/or lowering the risk of disease. In earlier studies, it was the definition of a functional nutrient that was most frequently cited.[3]

People are becoming more and more aware of the nutritional value and health advantages of various foods as functional foods gain popularity.[4] As a result, there has been a significant rise in both consumer interest in and demand for healthy food products. To satisfy these demands, it is necessary to create new functional foods.[5] However, the creation of functional foods is not only a time-consuming, expensive, and uncertain process that depends on a variety of factors for consumer acceptance of foods. New functional foods may not be well-received by consumers due to their skepticism and uncertainty. Understanding consumer reactions to functional foods is crucial because it influences their consumability.[6]

The factors that can predict consumer acceptance of functional foods have been the subject of numerous studies, and a wide range of significant factors have been identified.[7,8] However, it has proven challenging to clearly and completely understand the factors influencing consumer acceptance due to studies carried out in various contexts. It is challenging to pinpoint broad trends

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that will aid researchers and functional food producers when creating and introducing functional foods due to the complexity of the interrelationships between the various factors and their diversity.[9] The functional foods industry's communication and marketing professionals are working with a wide range of influencing factors to develop precise communication strategies that will increase consumer acceptance of functional foods.[10]

The purpose of this study was to ascertain the functional food knowledge levels of students attending a public university in Malatya and to assess the variables influencing their attitudes and behaviors.

METHODS

The study was carried out with the permission of Malatya Turgut Özal University, Non-interventional Clinical Researches Ethics Committee (Date: 12.01.2022, Decision No: 2022/15-24). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Individuals And Ethical Procedures

This case study was cross-sectional in nature. Prior to gathering data, the non-interventional research ethics committee granted its approval. A face-to-face questionnaire was used to gather research data. The participants were informed of the study's goals and specifics prior to the survey, and their written consent was obtained. In this study, research was done from March to May 2022.

Sample Of The Study

Using G-Power 2.19, the power analysis for this study was carried out. According to the power analysis, 578 people should be included in the study because the 'critical F' value was calculated to be 2.63 with 90% power, an effect size of 0.3, and a margin of error of 0.05.

Participants in this study were undergraduate students at two universities in southern Turkey. The study included university students who were between the ages of 18 and 65 and did not have any communication issues.

Data Collection Tool

The information collection form used in the research included questions about demographic characteristics, nutritional habits, general health status, anthropometric measurements (body weight and height), functional food knowledge level, and food preference scales.

Anthropometric Measurements

Body weight and height measurements of all individuals participating in the study were obtained by the researchers. Body weight of the individuals was measured with a portable scale (Tanita-HA-622) sensitive to 1 kg, in light clothing and without shoes, in accordance with the method. The distance was measured in centimeters (cm) with a non-stretchable measuring tape.

Body mass index: Body mass index (BMI) was determined by dividing the individual's body weight in kilograms by the square of the individual's height in meters. BMI classifications include underweight if an individual's BMI is less than 18.5 kg/m², normal weight if between 18.5 and 24.9 kg/m², overweight if BMI is between 25.0 and 29.9 kg/m², and. If BMI is more than 30.0 kg/m², it is considered as obese.[11]

Functional Foods Knowledge Level and Food Preference Scales

The research data were collected through face-to-face interviews with volunteers using an information collection form. In addition, the Functional Food Attitude Scale, which was developed by Urala and Lahteenmaki (2007) and adapted in Turkish by Hacıoğlu and Kurt[12] (2015), was used to measure the attitudes of the individuals participating in the study towards functional foods. This scale consists of 25 items in total and includes variables such as benefit, necessity, trust, and security. The statements on the scale were evaluated using a five-point Likert 5-point scale.

In 2018, Batmaz[13] established the accuracy and reliability of this scale. The adult nutrition knowledge level (YETBID)'s "Basic nutrition" section had a Cronbach's Alpha reliability coefficient of 0.81 while the "Nutrition preference" section had a Cronbach's Alpha reliability coefficient of 0.78. Following a visual analog scale (VAS) that rates the relationship between nutrition and health, the scale's first section contains 20 propositions on a 5-point Likert scale that probe participants' fundamental understanding of nutrition and the connection between food and health. The basic nutrition section earned the highest score of 80 points, and the food preference section earned the second-highest score of 48 points. Table 1 lists the food preference scale's evaluation standards.

Table 1. Evaluation criteria of the basic nutrition and food preference scale

Point range	Classification
Basic Nutrition Score	
<45 points	Bad
46-55 points	Middle
56-65 points	Good
>66 points	Very good
Food Preference Score	
<30 points 'bad' knowledge	Bad food preference
30-36 points 'middle' knowledge	Middle food preference
37-42 points 'intermediate' knowledge	Good food preference
>42 points 'very good' knowledge	Very good food preference

Statistical Analysis

IBM SPSS 22.0 package program was used for data analysis. Continuous variables were evaluated using mean and standard deviation. The χ^2 test was used to compare the means of more than two groups, the Mann-Whitney U test was used to compare the means of independent variables belonging to two groups, and the Wilcoxon signed-rank test was used to compare the means of dependent variables within the group. Spearman's correlation analysis was performed to describe the relationships between variables.

RESULTS

The demographic characteristics of the participants are presented in Table 2. A total of 618 students, aged between 18 and 48 years, were included in the study. Of the individuals, 35.76% were associate degree students, 35.92% lived in dormitories, 18.12% had an active working life, 39.16% smoked, 89.64% did not have any disease, and most earned a minimum wage and monthly income. It was stated that 69.90% of the individuals did not engage in any physical activity regularly. Within the scope of the study, 65.04% of the individuals declared that they had heard of the term Functional Nutrient.

The average YETBID scores of individuals by gender are shown in Table 3. According to the sub-headings of the individuals' knowledge attitude scale for functional foods, the highest sub-heading score of male individuals was in the "benefit" subheading (3.16±1.01), while the female were in the "confidence" subheading (3.95±1.04). When the differences between the averages between male and female were examined, it was observed that the difference in scores between the "confidence" subheading was statistically significant (p=0.044). According to the YETBID-Basic Nutrition Knowledge Score, female had higher mean scores than male, and this difference was statistically significant (p =0.013).

A comparison of the mean scores of the attitude scale towards functional foods according to the eating attitude scale score according to gender is given in Table 4. It was observed that as the basic nutrition score increased in both female and male, the score of the attitude scale towards functional foods also increased. It was determined that individuals with good basic nutrition scores had different attitudes towards functional foods according to sex, and this difference was statistically significant (p=0.035). An increase in the basic nutrition score in female increased the attitude score towards functional foods. The value which was 3.89±1.01 points in female was found as 3.04±0.23 in male. According to food preference scores, there was no difference between the scores of individuals whose attitudes towards functional foods were examined according to gender. In general, an increase in the food preference score in both gender also increased the taste score for functional foods.

Table 2. Demographic characteristics of the participants

	n=618	%
Age(mean±SD)(Years)	24.45±2.18	
Gender		
Female	363	58.74
Male	255	41.26
Education Degree		
Associate degree (2 years and below)	221	35.76
Undergraduate (4 years and below)	240	38.83
Master	102	16.50
Doctorate	55	8.90
Where and with he/she lives?		
At home with his family	210	33.98
At home with friends	186	30.10
In the dormitory	222	35.92
Working status		
Yes	112	18.12
No	506	81.88
Smoking		
Yes	242	39.16
No	376	60.84
Monthly income		
1/3 of the minimum wage	312	50.49
½ of the minimum wage	245	39.64
Minimum wage	31	5.02
Above minimum wage	30	4.85
Physical activity habit		
Yes	186	30.10
No	432	69.90
Physical frequency per week		
2 Days a Week	64	10.36
3 Days a Week	55	8.90
3 Days A Week And More	67	10.84
Have you heard the term functional food before?		
Yes	402	65.04
No	216	34.96

**More than one answer was received.

Table 3. Comparison of individuals' attitude scale towards functional foods and YETBID scale Means according to gender

	Male	Female	p*
	$\bar{x}$±SD	$\bar{x}$±SD	
Attitude scale towards functional foods			
Use	3.16±1.01	3.36±1.03	0.309
Necessity	2.19±0.64	2.09±0.68	0.204
Trust	3.15±1.04	3.95±1.04	0.044
Security	2.94±0.68	2.25±0.67	0.103
Total	3.11±0.59	3.01±0.52	0.905
YETBID-Basic nutrition knowledge score	51.14±8.22	54.66±8.85	0.031
YETBID-Nutrition and health relationship VAS scale score	8.03±2.09	8.99±6.04	0.667
YETBID- Food preference score	35.06±5.70	36.24±6.09	0.119
YETBID-Food preference VAS scale score	6.26±2.24	6.56±1.830	0.702

*Mann Whitney U Test

Table 4. Comparison of the mean scores of the attitude scale towards functional foods according to the eating attitude scale score

	Attitude scale score towards functional foods		p*
Basic Nutrition Score	**Male** $\bar{x}$±SD	**Female** $\bar{x}$±SD	
<45 points	2.14±1.01	2.66±0.66	0.201
46-55 points	2.56±0.65	2.55±0.99	0.398
56-65 points	3.04±0.23	3.89±1.01	0.035
>66 points	3.15±0.94	3.21±1.06	0.417
Food Preference Score			
<30 points 'bad' knowledge	2.99±0.86	2.88±0.55	0.310
30-36 points 'middle' knowledge	2.85±.0.81	2.91±0.85	0.701
37-42 points 'intermediate' knowledge	3.55±1.21	3.11±1.01	0.205
>42 points 'very good' knowledge	3.01±1.09	2.99±1.04	0.201

*Mann Whitney U Test

Multiple linear regression analysis was performed to estimate the total scale score based on sex, educational status (based on education period), basic nutrition score, and food preference score (F=29,509, p<0.001). All the variables together explained 46% of the variance in the total score. Gender, education level (according to education period), basic nutrition score, and food preference score affected the total score of the scale (p<0.05).

DISCUSSION

Functional foods have been shown to protect against many diseases, such as cardiovascular diseases, diseases related to the gastrointestinal system, diabetes, and cancer, and can be used in the treatment of diseases.[14,15]It has been reported that the demand for functional foods has increased in recent years. The reason for this situation stems from individuals' perceptions, attitudes and behaviors towards functional food.[16,17]

College years are a crucial time to prepare young people for adulthood. During this period, it is important to increase awareness of healthy nutrition in young people and to gain life skills to prevent diseases. This study aimed to evaluate the knowledge, attitudes, and behaviors of university students regarding functional foods.

The education level of the students and the social environment they stay in significantly affects their eating habits. In this study, it was observed that the majority of students received education at the associate degree level and stayed in the dormitory. It is known that there is a relationship between individuals' incomes and eating behaviors. There is a linear relationship between personal disposable income and nutrition.[18] It is seen that the majority of the individuals participating in this study have an income equal to half of the minimum wage. The fact that university students left home during this period changed their eating habits. In particular, poor eating habits, such as skipping meals, eating out more often, snacking, and getting most of their nutrition from fast food, are observed.[19,20] It was determined that the individuals participating in this study had two main meals a day and skipped lunch the most often. In addition, the majority of individuals do not have a smoking habit. The majority of individuals participating in the study did not have a chronic disease that would affect their nutritional status. Physical activity plays an important role in the prevention of chronic diseases and the development of physical and mental health. In this study, the majority of the students reported that they engaged in physical activity two or three days a week.

Studies show that people who understand the concept of functional food and have knowledge of it consume these nutrients at a higher rate.[21,22] However, individuals' views on functional foods are not greatly affected by vocabulary.[23] The majority (64%) of the individuals participating in this study were university students who had heard of functional foods before. Another study conducted with university students showed that knowing functional foods, their previous use and monthly income affect attitudes towards these foods.[24] A study conducted in Italy showed that people do not have sufficient knowledge about functional foods, 20% of the participants mix functional foods with diet and light products, 24% cannot define functional foods, and 16% incorrectly associate foods with health.[25] In a study conducted with 1039 individuals aged between 14 and 30 years in Croatia, it was reported that 66.60% of the youth were not familiar with the concept of functional foods.[26]

Table 5. Multiple regression analysis of gender, education level, BMI, basic nutrition score and food preference score factors affecting the total score of the attitude scale towards functional foods

Model	B	Beta	Standart error	p<0.05	95.0% CI		F	R	R^2
					Lower bound	Upper bound			
Constantly	104.214		24.327	.000	90.489	106.940			
Gender(ref. Male)	1.781	-.239	0.181	.000	1.252	3.311			
Educational status (according to education period)	2.279	-.165	0.572	.000	1.545	3.014	29.509	0.678	0.461
Basic Nutrition Score	2.152	.174	1.058	.002	1.129	5.175			
Food Preference Score	1.377	.066	0.164	.031	0.533	2.222			

CI: Confidence Interval, Ref.:reference

Consumption and awareness of functional foods are affected by education level.[24] Similarly, in this study, it was determined that the increase in the education period of individuals affected the total score of the attitude scale towards functional foods ($p<0.05$).

In studies examining attitudes towards functional foods; In a study conducted with Swedish consumers on the necessity of functional foods, the participants defined functional foods as unnatural foods, therefore they stated that they did not need functional foods. However, they stated that these nutrients can be used if a healthy lifestyle is insufficient to improve health status.[27] In another study, it was determined that people's attitudes towards functional foods, because they find these foods unnecessary, and their beliefs cause distrust towards these foods.[26] In a study conducted with students studying health sciences in Turkey, it was claimed that female found functional nutrients more reliable and important than men.[28] Similarly, in another study, it was determined that female were more agreeable than male about the utility and necessity of functional nutrients.[29] In this study, it was seen that the highest sub-heading score of the attitude scale score towards functional foods was in the sub-title of benefit for male, and the sub-title of confidence for female. It has been shown that female find functional foods more beneficial for health than male, and female consume functional foods at a higher rate.[29] According to a study on female, improving physical health and reducing fatigue are the main reasons for consuming functional foods.[30] In another study, individuals stated that they consumed functional foods because they thought they were delicious, of good quality, and beneficial to health.[31] In this study, it was observed that as the basic nutrition score increased in both female and male, the score of the attitude scale towards functional foods also increased. The basic nutrition score increased the attitude scale score towards functional foods 2.152 times. On the other hand, the basic nutrition score of female was higher than that of male, and the scores of the attitude scale towards functional foods of female with good nutrition scores were significantly higher than those of male ($p=0.035$). Female's attitudes towards functional foods were 1.781 times higher than male's. In addition, it was observed that the increase in the food preferences of individuals affected the attitude scale score towards functional foods by 1.377 times.

Limitations of the study

The fact that this study was conducted only with university students in the province of Malatya creates a limitation in terms of the generalization of the results. To determine the general situation, it is recommended to conduct multicenter studies with larger sample sizes and to plan training for this.

CONCLUSION

As a result, in this study, it was determined that as the education level of the individuals increased, the level of basic nutrition knowledge increased, which affected their attitude towards functional foods. In addition, it was determined that female's nutritional knowledge levels were higher than those of male, and they were more inclined to consume functional foods. Functional foods have many beneficial health effects. Therefore, it should be ensured that the right information about functional foods is delivered from the right sources. Society should be informed more about functional foods, and strategies should be created to encourage male to understand and consume these foods, especially regarding gender. Healthy nutrition should be evaluated as a whole, the tendency towards a single food group should be prevented, and the importance of appropriate and balanced nutrition from all food groups should be emphasized in order to increase social awareness about functional foods.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Malatya Turgut Özal University, Non-interventional Clinical Researches Ethics Committee (Date: 12.01.2022, Decision No: 2022/15-24).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

Acknowledgments: We thank all the study participants.

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Original Article

MEDICINE PALLIATIVE CARE

DOI: 10.47582/jompac.1359372

J Med Palliat Care. 2023;4(5):561-565

Efficacy of vitamins B9, C, and E on fat graft viability

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Cite this article as: Okyay MF. Efficacy of vitamins B9, C, and E on fat graft viability. *J Med Palliat Care*. 2023;4(5):561-565.

Received: 13.09.2023 ◆ **Accepted**: 13.10.2023 ◆ **Published**: 27.10.2023

ABSTRACT

Aims: This study aims to investigate the potential of folic acid (vitamin B9), ascorbic acid (vitamin C), and α-tocopherol (vitamin E) in enhancing the survival of fat grafts.

Methods: We divided the dorsal regions of ten Sprague-Dawley rats into four quadrants, serving as recipient sites for inguinal fat grafts. Fat grafts were placed in these sites after incubation, with different sites receiving 0.9% NaCl (left cranial), vitamin B9 (right cranial), vitamin C (left caudal), and vitamin E (right caudal). After three months, we harvested the fat grafts and evaluated their viability using perilipin immunohistochemistry.

Results: Folic acid, vitamin C, and vitamin E all significantly improved fat graft survival rates when compared with control ($p<0.001$ for each).

Conclusion: Folic acid (vitamin B9) promotes angiogenesis and collagen synthesis, vitamin C's antioxidant properties support collagen synthesis, and vitamin E's potent antioxidant capacity protects grafted adipose tissue from oxidative stress and inflammation, facilitating graft vascularization and integration. These findings suggest that these readily available and cost-effective vitamins, B9, C, and E, enhance fat graft survival immunohistochemically. The improved graft viability presented here could inspire further clinical studies and applications.

Keywords: Adipogenesis, ascorbic acid, fat graft survival, folic acid, vitamin C, vitamin E

INTRODUCTION

The realm of plastic and reconstructive surgery has witnessed significant transformation with the emergence of fat grafting, a technique renowned for its ability to restore tissue volume and shape, achieving natural-looking results. Nevertheless, challenges persist in maintaining consistent and dependable fat graft survival, driving ongoing efforts to refine methods and introduce complementary strategies.[1] This investigation focuses on the intriguing roles of vitamin B9 (folic acid), vitamin C (ascorbic acid), and vitamin E (α-tocopherol) in influencing fat graft survival outcomes. The utilization of these vitamins, each celebrated for its unique biological properties, offers a new avenue to address the longstanding issue of graft retention variability.

Folic acid, an essential B vitamin vital for cell division and tissue development, has garnered attention for its potential to stimulate angiogenesis and collagen synthesis. These mechanisms suggest a capacity to facilitate graft integration and vascularization, factors critical for graft survival.[2] Vitamin C, known for its antioxidant potential and its role as a cofactor in collagen synthesis, presents an enticing prospect for enhancing fat graft survival. By mitigating oxidative stress and supporting tissue repair mechanisms, vitamin C could contribute to graft integrity and function preservation.[3] Similarly, vitamin E, another potent antioxidant, may offer protection against oxidative damage and inflammation, potentially safeguarding grafted adipose tissue from early resorption.[4] With these promising attributes, this study delves into the existing literature regarding the effects of folic acid, ascorbic acid, and α-tocopherol on fat graft survival, aiming to bridge the gap between theoretical advantages and practical clinical application.

In summary, the integration of vitamin B9, vitamin C, and vitamin E into fat grafting procedures opens up new horizons for enhancing graft survival and overall surgical outcomes.

METHODS

The study was carried out with the permission of Hatay Mustafa Kemal University Animal Experimental Researches Ethics Committee (Date: 21.09.2020, Decision No: 2020/06-6). All relevant institutional and national guidelines for animal care and use were strictly adhered to.

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Surgical Procedure

We divided the dorsal regions of ten male Sprague-Dawley rats, aged between 8-9 weeks and weighing 300±10 grams, into four separate quadrants: left cranial, right cranial, left caudal, and right cranial (Figure 1a). These quadrants served as recipient sites for fat grafts (serum, vitamin B9, vitamin C, and vitamin E groups, respectively).[5] Under general anesthesia, with surgical antibiotic prophylaxis and local antisepsis, inguinal fat was harvested, and approximately four pieces of 0.2-gram fat grafts were obtained. During the surgery, fat grafts, harvested in a sterile environment, were immersed in separate 5 ml solutions, sequentially containing 0.9% sodium chloride, 20 mg/2 ml Vitamin B9 (Folsaure forte-Hevert 20 mg/2 ml Ampoule, Hevert-Arzneimittel GmbH & Co. KG, Nussbaum, Germany), 500 mg/5 ml Vitamin C (Redox-C® Ampul 500 mg/5 ml, Bayer Türk Kimya San. Ltd. Şti., Istanbul, Türkiye), and 100 mg/2 ml Vitamin E (Evicap 100 mg/2 ml Ampul, Koçak Farma İlaç ve Kimya San. A.Ş., Istanbul, Türkiye) (Figure 1b) at 37 degrees Celsius to mimic the body temperature of male Sprague-Dawley rats. Four one-centimeter incisions were made on the back regions, and fat grafts were placed beneath the subcutaneous tissue overlying the muscle fascia (Figure 1c). The incisions in the donor and recipient areas were closed with non-absorbable sutures. The rats were housed individually in cages maintained at standard room temperature and were provided with ad libitum food.

After a three-month period, the rats were euthanized, and the fat grafts, along with the surrounding transition area, were excised (Figure 1d) and evaluated immunohistochemically.

Immunohistochemical Evaluation

Pathological examination service was procured from Merter Medical Company, with the pathologists employed by the company waiving their right to publish. The samples underwent standard processing and were embedded in paraffin blocks. Longitudinal slices of 5 µm thickness were cut from the widest areas of the samples. After routine processing and immunohistochemical staining, the slices were stained with perilipin (PP) to assess adipocyte viability rate (Figure 2). Quantitative results were obtained using Fiji software (ImageJ version 2.1.0, National Institutes of Health, Bethesda, MD, USA), and the data were presented as optic density ± standard deviation.[6]

Statistical Analysis

We performed a power analysis using G*Power 3.1 to determine the required sample size for a one-way analysis of variance. The analysis indicated that at least six rats in each group would be required to achieve 80% power, with a significant P-value of 0.05 and a Cohen effect (f) of 0.6. Statistical analysis of the study was conducted using GraphPad software (Graph Pad Prism, San Diego, CA, USA). The mean values of the groups were evaluated with the One-Way ANOVA test. Values were reported as mean ± standard deviation (SD) and standard error of the mean (SEM). Post-hoc analysis was performed using Tukey's multiple comparison test, with statistical significance accepted at $p<0.05$.[7]

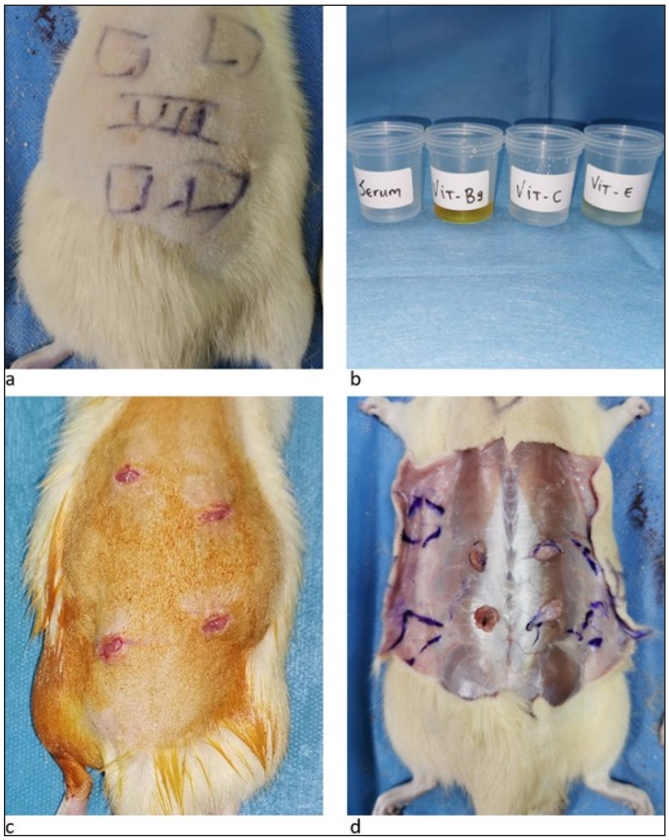

Figure 1: Visual representation of the surgical procedure (subfigures; a: four distinct quadrants in the dorsal region of the rats, b: preparation during incubation, c: placement of grafts, d: harvesting of grafts).

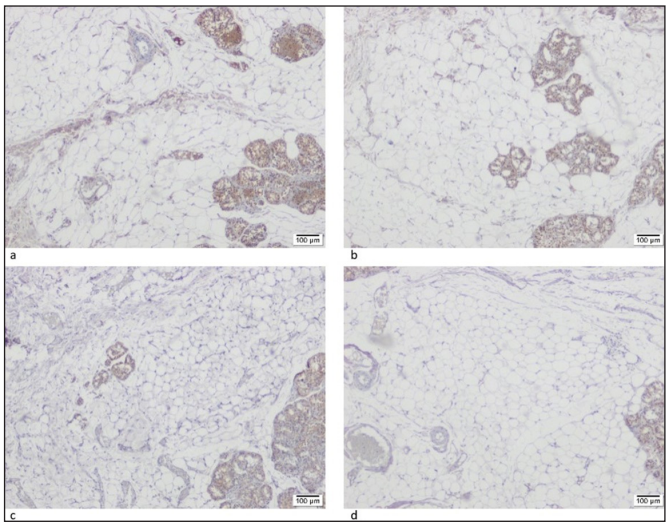

Figure 2: Perilipin staining for assessment (subfigures; a: control group, b: vitamin B9 group, c: vitamin C group, d: vitamin E group, scale 100 µm).

RESULTS

The results showed a statistically significant difference in the survival and integration of fat grafts among the vitamin B9, C, and E groups when compared with the control group ($p<0.001$ for each). While the vitamin E group exhibited a higher perilipin rate compared to other experimental groups (**Table 1**), these differences were considered statistically insignificant ($p>0.05$ for each) (**Table 2**).

Table 1. Results of Perilipin staining

Groups	N	Mean	SD	SEM
Control	10	0.08034	0.006592	0.002084
Vitamin B9	10	0.1176	0.01606	0.005077
Vitamin C	10	0.1197	0.02383	0.007536
Vitamin E	10	0.1332	0.01045	0.003303

Table 2. Statistical results in detail of two groups comparison

Groups Comparison	Difference	q value	p value
S vs B9	-0.03731	7.545	p<0.001
S vs C	-0.03935	7.958	p<0.001
S vs E	-0.05283	10.683	p<0.001
B9 vs C	-0.002042	0.4128	p>0.05
B9 vs E	-0.01552	3.138	p>0.05
C vs E	-0.01348	2.725	p>0.05

S: serum group, B9: vitamin B9 group, C: vitamin C group, E: vitamin E group, vs: versus

DISCUSSION

In recent decades, the utilization of autologous fat grafting procedures has experienced a remarkable proliferation within the domain of aesthetic and plastic surgery. This upsurge has, in turn, accentuated the importance of preserving the viability of transplanted fat, a matter of significant concern as these procedures continue to see extended application in clinical practice.[1] The endeavor to amplify the persistence and vitality of grafted fat has led to an exploration of the potential advantages associated with the incorporation of bioactive agents into fat grafting protocols.[2]

The affirmative outcomes observed in this study concerning vitamin B9 (Folic Acid) align with earlier research, underscoring its role in the stimulation of angiogenesis and collagen synthesis. These mechanisms could engender an environment conducive to graft vascularization and integration, thereby contributing to heightened graft survival.[2] Similarly, the antioxidative properties of Vitamin C (ascorbic acid), coupled with its participation in collagen synthesis, likely played a pivotal role in tissue repair, attenuating oxidative stress, and consequently supporting graft viability.[3] In a comparable vein, the pronounced antioxidative capacity of vitamin E (α-tocopherol) appeared to confer a protective shield against oxidative damage and inflammation, both recognized factors with the potential to curtail graft longevity.[4]

This present study embarked on the task of unraveling the potential benefits offered by folic acid, ascorbic acid, and α-tocopherol in enhancing the survival and viability of fat grafts. It's noteworthy that in our study, each rat was included in all experimental groups within a 'four quadrants' model.[5] This meticulous design served to minimize inter-rat variations in genetic, metabolic, and physiological factors. Consequently, the groups were rendered more homogenous, and the total number of experimental animals was kept at a minimum.

Through this rigorously devised rat model, the study scrutinized the impact of these vitamins on the aspects of fat graft integration, retention, and overall survival, thereby shedding light on their prospective roles as adjunctive agents to augment the efficacy of fat grafting procedures. The study findings revealed that the supplementation of vitamin B9, vitamin C, and vitamin E significantly influenced the survival and viability of fat grafts, findings that align harmoniously with existing literature.[8,9] A recent study, for instance, alluded to improved fat graft retention stemming from an elevation in the total antioxidant capacity in rats supplemented with vitamin C and E.[10] Notably, our experimental groups, those treated with these vitamins, exhibited substantially larger proportions of living fat cells in comparison to the control group (**Figure 3**). These results conspicuously allude to the favorable impact of vitamin B9, Vitamin C, and Vitamin E on the enhancement of graft integration, reduction of resorption, and an overall boost in viability. Collectively, these outcomes lend credence to the proposition that the incorporation of these vitamins can serve as valuable adjuncts in fortifying the effectiveness of fat grafting procedures, with the potential to elevate clinical outcomes within the realms of plastic and reconstructive surgery. It's paramount to emphasize, however, that while this study showcases promising results, the need for further research is unmistakable. This imperative is rooted in the necessity to fully elucidate the precise mechanisms underpinning the observed effects and to optimize the dosage and administration protocols of these vitamins within the context of fat grafting procedures.

In summation, this study provides robust evidence that vitamin B9, vitamin C, and vitamin E confer a constructive impact on the survival and viability of fat grafts. The implications of these observations have the potential to revolutionize fat grafting techniques, by presenting surgeons with additional tools to bolster graft retention and

to amplify overall procedural success. As the field of plastic and reconstructive surgery continues its evolution,[11-13] the integration of vitamin supplementation introduces an exciting avenue to enhance the reliability and durability of fat grafting procedures.[14] This, in turn, serves to benefit both the aesthetic and reconstructive aspects of patient care.[15-18]

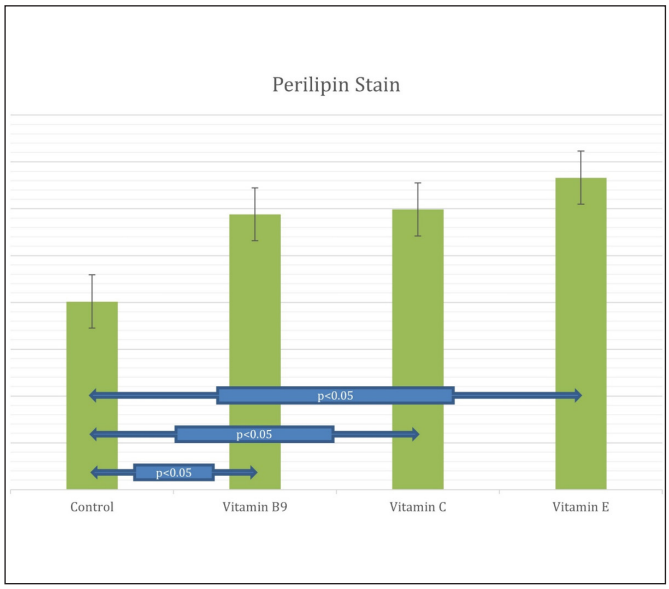

Figure 3: Comparative analysis of Perilipin staining rates.

Limitations

It's crucial to recognize that this study, being experimental in nature, inherits the inherent limitations associated with animal-based investigations. Furthermore, the study's reliance on a rat model necessitates caution when extrapolating these findings to human clinical scenarios.[19,20] The implantation model used in this study, while offering insights, may diverge from the cannula injection model more typical of clinical practice.

CONCLUSION

To summarize, the inquiry into the effects of vitamin B9 (folic acid), vitamin C, and vitamin E on fat graft survival has yielded promising findings. The study has compellingly demonstrated that these vitamins can exert a positive influence on graft viability, integration, and retention within a rat model. However, it remains imperative to delve deeper into factors such as dosage, administration methodologies, and the potential synergistic effects that might arise from the concurrent use of these vitamins. Future investigations could further explore the molecular pathways influenced by these vitamins, potentially unraveling the intricate interplay between angiogenesis, collagen synthesis, oxidative stress, and graft survival.

The notable enhancements in fat graft survival observed here underscore the potential value of these vitamins as valuable adjuncts for fortifying fat grafting procedures. Nevertheless, it is abundantly clear that further research is necessary to fully comprehend the underlying mechanisms, optimize dosages, and validate these findings in clinical settings. In this regard, clinical trials involving human subjects are indispensable to affirm the applicability of vitamin supplementation in the context of clinical fat grafting procedures. The findings of this study contribute to the expanding body of knowledge within the realm of plastic and reconstructive surgery, signifying a promising pathway toward improving the outcomes of fat grafting techniques and advancing patient care.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Hatay Mustafa Kemal University Animal Experimental Researches Ethics Committee (Date: 21.09.2020, Decision No: 2020/06-6).

Informed Consent: Since this study was an animal experiment conducted in a laboratory, informed consent was not obtained.

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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Original Article

MEDICINE PALLIATIVE CARE

DOI: 10.47582/jompac.1367086

J Med Palliat Care. 2023;4(5):566-571

Analysis of occupational accident reports of hospital employees applying to the emergency department

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Cite this article as: Biberoğlu S, Özkan S. Analysis of occupational accident reports of hospital employees applying to the emergency department. *J Med Palliat Care*. 2023;4(5):566-571.

Received: 27.09.2023 ◆ **Accepted**: 13.10.2023 ◆ **Published**: 27.10.2023

ABSTRACT

Aims: The purpose of this study is to analyze the occupational accidents experienced by all employees working in a university hospital in Turkey. In addition to demographic data, we aimed to analyze according to their titles, professions, type of accident, location of the accident in the hospital, accident day, and time periods.

Methods: In this descriptive research, 'Occupational Accident Forms' of work accidents that occurred within the hospital between 15 August 2022 and 15 August 2023 were analyzed retrospectively. Applications from all hospital staff (both healthcare workers and non-healthcare workers) were included. Categorical variables in the study were shown as frequency (n) and percentage values (%).

Results: The number of work accidents is equal to the number of hospital employees exposed to an occupational accident. According to gender in the study; 51.8% (n=59) were female and 48.2% (n=55) were male. The frequency of singles according to marital status was 57%,(n=65). According to their occupations, nurses came first with 25.4% (n=29), cleaning staff came second with 23.7% (n=27), and doctors came third with 17.5.4% (n=20). The most common days spent on occupational accidents are Friday with 22.8% (n=26). The most common hours were between 08:00 and 16:00 with 64.9% (n=74). According to the units where employees work, Internal medicines first with 32.5% (n=37). The types of injuries; needle and sharp injuries were in the first place with 59.6% (n=68). The most frequently injured part of the body is the upper extremity with 74.6% (n=85) No fatal accident was detected in this retrospective study.

Conclusion: In conclusion, nurses and cleaning staff were most frequently exposed to work accidents, and they were most frequently detected in areas affiliated with internal medicine units. Work accidents occur most frequently on Fridays and in the period between 8.00-16.00, and they were most frequently seen during patient treatment. Occupational health and safety training for its employees is mandatory in every institution. It can be aimed to protect hospital employees from occupational accidents by determining each unit's own risks, accident causes and precautions according to time periods, and providing more specific training.

Keywords: Occupational accidents, hospital employees, emergency department, needlestick and sharp injuries

INTRODUCTION

The International Labour Organization (ILO) estimates that approximately 2.3 million people worldwide suffer work-related accidents or illnesses annually; That's more than 6,000 deaths every day. It also reports that approximately 340 million work accidents and 160 million work-related diseases occur every year worldwide and is constantly updated by the ILO.[1]

Occupational Health and Safety Implementation Guide in Hospitals,[2] The topics in the guide were prepared as recommendations by the General Directorate of Occupational Health and Safety of the Ministry of Family, Labor, and Social Services of Turkey. It was published in June 2020.[2] In Turkey, a work accident is legally accepted as 'an event that occurs in the workplace or due to the execution of work, causing death or causing physical or mental disability.[3]

Hospitals; Article 56 of the Constitution states that "Everyone has the right to live in a healthy and balanced environment. It is the State and citizens' duty to improve the environment, protect environmental health, and prevent environmental pollution. The state protects everyone's life, physical and mental health to ensure that it continues within; It organizes health institutions to plan and provide services from a single source to achieve cooperation by increasing savings and efficiency in human and material resources. The state fulfills this duty by utilizing and supervising health and social institutions in the public and private sectors. It was established by the provision that "General health insurance may be established by law to provide health services widely." by the public.[4] There are hospitals affiliated with the Ministry of Health and universities, as well as hospitals belonging to private individuals, organizations, and foundations/associations. Due to the different types of organization in each hospital

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structure, difficulties are experienced in the practices to be carried out by the Occupational Health and Safety Law No. 6331, and differences arise between hospitals.[3]

The risks of occupational accidents in hospitals for health professionals and practices in middle-income[5-8] and high-income countries[9-11] have been reported. But, the situation for health professionals in southeastern European countries is reportedly inadequately documented.[12-14]

Healthcare professionals are at serious risk due to the occupational accidents that may occur as a result of percutaneous injuries (needle stick or other sharps injuries), blood or other body fluids splashing into the eyes, nose or mouth.[15]

In the literature, studies on occupational accidents regarding healthcare workers frequently appear and maintain their importance.[16,17] We thought that our study would bring a different perspective because it included both healthcare workers and all non-healthcare workers working in the hospital. As a university hospital with a large campus, it is aimed to shed light on occupational health and safety studies within the framework of Health Quality Standards in the hospital by analyzing the work accidents of hospital employees who apply to our Department of Emergency Medicine.

According to the university's OHS coordinator directive;[18] The Obligation of Staff and Students is emphasized in Article,[14] according to which 'Staff and students' must comply with the rules, prohibitions, decisions, and measures taken by occupational health and safety boards to protect and improve health and safety. Staff and students cooperate with the committees in determining and implementing Occupational Health and Safety measures in the workplace and complying with the measures taken. Staff and students inform the board through their representatives about the decisions taken by the boards or the difficulties they encounter in implementation.

METHODS

The study was carried out with the permission of İstanbul University Cerrahpaşa Clinical Researches Ethics Committee (Date: 19.09.2023, Decision No: 2023/128). All procedures followed were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The purpose of this study is to analyze the occupational accidents experienced by all employees working in a university hospital in Turkey. In addition to the demographic data of the cases, they were grouped according to their titles, professions, accident type and, the accident locations in the hospital. The accident days and time periods were analyzed.

The data of this descriptive research, is collected from all staff (both healthcare workers and non-healthcare workers) of the university hospital, which provides tertiary healthcare services, who applied to the emergency department (ED) due to an occupational accident, were registered between 15 August 2022 and 15 August 2023 and completed the 'Occupational Accident Form' (OAF). Patients who filled out the OAF completely were included. According to the data in the OAF, it was analyzed according to gender, marital status, days in which the patient had an accident, and the time periods in which the accident occurred (08:00-16:00, 16:00-24:00, 24:00-08:00). Occupations at the time of the OA; they were divided into 9 groups as; nurses, cleaning personnel, caregivers, health technicians, physicians, intern doctors, security guards, intern nurses, and technicians. The units they work in are Internal departments, Surgical departments, operating rooms, intensive care units, emergency services, technical workshops/pharmacies, and administrative and educational areas. During the OA their duties were; patient treatment, patient examination/care, treatment preparation and material preparation, blood collection/vascular access, interventional procedures (venous/arterial catheterization, bladder irrigation, suturing, removal of foreign objects from the cornea, paracentesis), building maintenance, repair and installation, resting, security, carrying/storage/placement, cleaning and walking outdoors/stairs. The types of occupational accidents are divided into 8 groups; needlestick and sharp injuries, blunt trauma, strain-sprain, crushing, burn/electric shock, body fluid/drug splash (blood, urine, drug splash), verbal and physical violence (to be beaten and bitten) and fall. Accident Locations are divided into eight groups; Internal Services, Surgical Services, Operating Room, ICU, outdoor, Administrative units, Emergency Service, and warehouse.

The forms of all patients who applied to the ED and were registered between January 1, 2022, and August 15, 2023, and whose 'Occupational Accident Form' (OAF) was found to be complete were examined and analyzed retrospectivel.

Statistical Analysis

An analysis was made by transferring the demographic data of hospital employees who had work accidents, their time zones at the time of the accident, their duties and units, injury incident types and environments to the IBM SPSS 29 program.

Categorical variables in the study were shown with frequency (n) and percentage values. Numerical variables were shown with arithmetic mean, standard deviation, and median value. Statistical analysis of categorical variables was evaluated with Pearson Chi-square and Fisher Chi-square tests. All statistical analyses were performed by taking the p-value as a threshold value of 0.05 within the 95% confidence interval.

RESULTS

According to the accident reporting forms examined in the study; there were no recurrent applications. The number of work accidents is equal to the number of hospital employees exposed to occupational accidents. Of those who had OA, 51.8% (n=59) were female and 48.2% (n=55) were male. According to their marital status, 57% (n=65) were found to be single, and 43% (n=49) were married (Table 1). The most common days spent on OA are Friday with 22.8% (n=26), followed by Tuesday (n=25, 22%), Monday (n=16, 14.0%) and Thursday (n=15, 13.2%). When OA was analyzed according to the time periods in which the accident occurred; 64.9% (n=74) were most frequently in the working hours between 08:00-16:00, 26.3% (n=30) between 16:00-24:00, and the second most frequent and last period was 24:00-08:00. It was found to be in the third place with 8.8% (n=10).

Table 1. Demographic characteristics of hospital employees and occupations, time periods of accidents

	n	%
Gender		
Female	59	51.8
Male	55	48.2
Martial Status		
Single	65	57.0
Married	49	43.0
Occupation		
Nurse	29	25.4
Cleaning staff	27	23.7
Caregiver	14	12.3
Health technician	4	3.5
Physicians	20	17.5
Intern Doctor	10	8.8
Security	3	2.6
Intern Nurse	2	1.8
Technician	5	4.4
Days of Accidents		
Monday	16	14.0
Tuesday	25	22.0
Wednesday	21	18.4
Thursday	15	13.2
Friday	26	22.8
Saturday	8	7.0
Sunday	3	2.6
Time Period (Hour)		
08:00-16:00	74	64.9
16:00-24:00	30	26.3
24:00-08:00	10	8.8

When those who underwent OA were analyzed according to their occupations, nurses came first with 25.4% (n=29), cleaning staff came second with 23.7% (n=27), and doctors came third with 17.5.4% (n=20). Then respectively; It was determined that there were caregivers, intern doctors, technicians, health technicians, security guards, and intern nurses (Table 1). When evaluated according to the units they work in; Internal medicines came first with 32.5% (n=37), followed by Surgery clinics with 27.2% (n=31). In third place is the Emergency Department with 18.4% (n=21).

During the OA they were doing; the most common one was 'patient treatment' with 24.6% (n=28), followed by 'cleaning' with 16.7% (n=19), and third with ' opening a vascular line and blood ' with 14.0% (n=16) (Table 2). When OA injury incident types are examined; needlestick and sharp injuries comes first with 59.6% (n=68), blunt trauma comes second with 16.7% (n=19), and verbal and physical violence comes third with 6.1% (Table 2). The most frequently injured part of the body was the upper extremity with 74.6% (n=85) (Table 2).

No fatal accident was detected in this retrospective study. It was determined that physical and verbal violence occurred in the Department of Dermatology.

Table 2. Characteristics of occupational accidents of hospital employees

	n	%
Duty During the Accident		
Patients' treatments	28	24.6
Medical exam	6	5.3
Preparing treatment/materials	10	8.8
While opening a vascular line and blood	16	14.0
Interventional procedures	8	7.0
Building maintenance and repair	5	4.4
Resting	3	2.6
Security	3	2.6
Carrying/storage/placement	13	11.4
Cleaning	19	16.7
Walking outdoors/stairs	3	2.6
Accident Locations		
Internal Medicine	34	29.8
Surgery Department	25	21.9
Operating Rooms	13	11.4
Intensive Care Unit	9	7.9
Outdoor	6	5.3
Hospital Management	5	4.4
Emergency Department	21	18.4
Storage	1	0.9
Injury Localization		
Head and neck	11	9.6
Face	1	0.9
Thorax	1	0.9
Abdomen/lumbar	1	0.9
Upper extremity	85	74.6
Lower extremity	1	0.9
Vertebrae	12	10.4
Verbal violence	2	1.8
Types of Occupational Accidents		
Needlestick and sharp injuries	68	59.6
Blunt trauma	19	16.7
Sprains and strains	4	3.5
Crush	5	4.4
Burns/Elektrical shock	5	4.4
Bodily fluids exposure/medication splashing	4	3.5
Verbal and physical violence	7	6.1
Fall	2	1.8

DISCUSSION

World Health Organization defines employee safety as "maximizing the physical, mental and social condition of working individuals, taking and implementing protective measures to minimize the risks that may occur to the health of the employee, and suiting the employee's job and the job to the employee".[16]

In Turkey, a work accident is legally accepted as 'an event that occurs in the workplace or due to the execution of work, causing death or causing physical or mental disability'.[3] As a university hospital with a large campus and approximately 5 thousand employees, it was aimed to shed light on occupational health and safety studies within the framework of Health Quality Standards by analyzing occupational accidents in the hospital.

It is reported that the most common occupational accidents for healthcare personnel are needlestick and sharp injuries, exposure to blood and body fluids, musculoskeletal injuries, stress, and violence.[17,19] In particular, sharp object injuries rank first among work accidents occurring in hospitals.[17,19-21]

In a study reaching 1047 healthcare workers, evaluating the occupational accidents reported by healthcare personnel working in a university hospital, 64.4% of the healthcare workers stated that they had experienced a needlestick and sharp injury at least once in their professional life, and 64.4% reported blood/stab injury. They found that they stated that they were exposed to body fluids.[22] In our study, although all hospital employees were involved, the most common OA was found to be needlestick and sharp injuries. Occupational health and safety training for hospital employees is mandatory in every institution. Perhaps we can protect ourselves from work accidents by increasing the frequency of these trainings or by determining the risks of each unit individually and providing training.

Consistent with the analysis made according to the injury areas in our study, the most common upper extremity (n=85, 74.6%) injury was found. Since in our study, all upper extremity regions such as 'hand, arm, finger' were grouped as a single injury localization. İnci et al.'s[23] study carried out as a result of a work accident, 19% of the personnel suffered injuries in the foot-leg region, 47% in the hand-arm region, 8% in the finger region, and 8% in the eye area. They found that they were injured in the face and face area, and 17% were injured in various parts of the body (back, waist, shoulder, ear, whole body, ribs, chest). These results suggest that the importance of correct and regular use of personal protective equipment increases. And also, increased inspections may be required along with occupational health and safety training.

In a study by Monteiro et al.[24] based on the Occupational Accident Reports (OAR) of 3 hospitals in Brazil, it was determined that 251 workers out of a total of 1,117 workers were injured in work accidents between 2000 and 2005. The injured workers worked in healthcare, nursing, and support services (kitchen, laundry, cleaning, and maintenance). According to days, it is most common on Tuesday, and according to work shifts, it is most common between 07:00-19:00. In our study, although we found it to be most common on Friday (22.8%), it was followed by Tuesday (22.0%). Additionally, in our study, we determined that the most common time period was 08:00-16:00. There may be a decrease in attention as it is the last day of the business days of the week. Weekdays and first shifts of the day are always busier in hospitals.[24] Both the patient crowd and the number of outpatient clinics and surgeries are higher. This may explain the fact that in our study, the majority of occupational accidents occurred on weekdays and during the 8.00-16.00 period.

Appiagyei et al.[25] In the study, in the analysis of OA according to professional groups, it was determined that nurses ranked first (78%), followed by doctors (9.4%), laboratory technicians (5.7%) and finally non-medical personnel (6.9%). Many studies[17,26,27] have shown literature showing that the majority of healthcare workers exposed to work accidents are nurses. In our study, nurses were found to be in the first place (25.4%), but unlike other professional groups, no significant difference was observed. We can attribute this to the fact that nursing services in our country/hospital keep their work shifts short and carry out in-house training meticulously.

In a study of a public hospital by Diker et al.[17] although the units collected under the heading of other units were found more frequently in total, where 57% were women, the majority of them were nurses, when examined separately, the most common cases were in intensive care units, followed by emergency departments. and operating rooms were observed. In the same study, a needlestick and sharp injuries rate of 81% was detected. According to time periods, work accidents were most frequently found during day shifts, consistent with our study. In this study,[21] OA (18.4% according to accident locations groups) occurred in the emergency department. If we discuss occupational accident exposures within the emergency department itself; It was determined that there were 14 doctors, 4 nurses, 2 cleaning staff, and 1 security guard. Only one of the 21 people was married and that was the cleaning staff. It was determined that work accidents occurred most frequently during patient treatment and the

most common was needlesticking. In the survey study conducted by Serinken et al.[6] on emergency service workers, they found the frequency of needlestick and harps injuries in the emergency department to be 86.3%. The most common cause was found to be a syringe needle. The most common accident location in the emergency department was reported as the resuscitation room. Since the emergency department has a separate dynamic and cycle within itself, we can conclude that healthcare professionals do not act in accordance with occupational safety during rapid interventions on patients in acute situations. And also we should not forget the patient crowd and stress factor in the emergency department.

The most important limitation of this study is that it was in only one center. Due to this being a retrospective study, patients could not be interviewed one-on-one while filling out the OAF.

CONCLUSION

The findings of this study; nurses and cleaning staff were most frequently exposed to work accidents, and they were most frequently detected in areas affiliated with internal medicine units. Work accidents occur most frequently on Fridays and in the period between 8.00-16.00, and they were most frequently seen during patient treatment. Occupational health and safety training for its employees is mandatory in every institution. It can be aimed to protect hospital employees from work accidents by increasing the frequency of these trainings and by determining the risks of each unit separately and providing training.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of İstanbul University Cerrahpaşa Clinical Research Ethics Committee (Date: 19.09.2023, Decision No: 2023/128).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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Original Article

MEDICINE PALLIATIVE CARE

DOI: 10.47582/jompac.1346978

J Med Palliat Care. 2023;4(5):572-578

Intensive care unit: mortality score in early prediction of mortality in critical COVID-19 patients

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Cite this article as: Sağlam E, Savaş A, Oke D, Özlü C, Koçar B, Erkalp K. Intensive care unit: mortality score in early prediction of mortality in critical COVID-19 patients. *J Med Palliat Care*. 2023;4(5):572-578.

Received: 21.08.2023 ◆ **Accepted**: 14.10.2023 ◆ **Published**: 27.10.2023

ABSTRACT

Aims: The mortality data available in the literature with regard to patients with SARS-COV-2, thus requiring hospitalization in the intensive care unit (ICU) are not sufficient. This research aims to compare the correlation between COVID-19 mortality ratios (CMR), AST/ALT and neutrophil/lymphocyte (N/L) ratios of non-smoker COVID-19 patients hospitalized in the ICU and their mortality rates.

Methods: This cross-sectional study was conducted on 77 patients hospitalized in the ICU. Female participants constituted 64.9% (n=50) of the study group while male made up 35.1% (n=27); the mean age was 61.3±14.3 and 66.2% (n=51) of the patients died. To exclude the adverse effect of smoking on mortality, patients were confirmed to be non-smokers by analyzing the cotinine levels in urine samples. For this purpose, patients' age, gender, comorbidities, fever, pulse, blood pressure, saturation values, APACHE scores and biochemical parameters were evaluated.

Results: In the study, 66.2% (n=51) of the patients died during follow-up. Age, urea, creatinine, AST/ALT, N/L ratio and CMR values of the nonsurvivors were significantly higher than those of the survivors. The systolic blood pressure and lymphocyte values of non-survivors were lower than survivors.

Conclusions: The conclusion of the study revealed that CMR scores, AST/ALT levels and the N/L ratio can effectively be utilized in early period to project the mortality rates of non (active) smoking patients with critical COVID-19 infection hospitalized in the ICU.

Keywords: SARS-COV-2; intensive care unit; COVID-19 mortality ratio; cotinine; smokers and non-smokers

INTRODUCTION

Patients in intensive care unit (ICU) due to infectious diseases such as COVID-19 have high mortality rates. It is vital to predict the mortality of patients in the earliest term, prevent mortality, and initiate early aggressive treatment. Smoking is one of the leading factors of increased mortality rates and is the subject of many studies; however, the correlation between smoking, COVID-19, and mortality has not yet been fully elucidated, although different mechanisms have been suggested.[1]

The manifestation of COVID-19 cases ranges from asymptomatic cases having a significant part in the spread of the virus to the severe cases requiring ventilation support, depending on the spectrum of severity.[2,3] Although estimation methods related to COVID-19 have been incorporated into literature, a limited number of studies report on risk factor estimation and mortality analysis of the COVID-19 patients.

The estimation methods include models to estimate high-risk groups[4] diagnostic models to detect COVID-19,[5] and models to estimate mortality rates and severe disease development.[6] However, studies are not sufficiently reliable for various reasons, such as the low number of cases or the variability of results depending on ethnicity. COVID-19 mortality ratio (CMR), through a personalized death risk score, enables to improve triage process, even in systems lacking main resources. CMR is the first risk score verified in a cohort of COVID-19 patients from Europe and the USA.[7]

The CMR model synthesizes multiple clinical data items, such as demographics, laboratory test statistics, symptoms, and comorbidities. A machine learning

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system, the XGBoost algorithm,[8] is used to estimate mortality rates. The score can pick up non-linear features in risk factors and provides an advanced estimation under the "out-of-sample area" under the ROC Curves (AUCs) of 0.90 (95% CI, 0.87-0.94). It discerns new insights confirming acknowledged risk factors including age and oxygen saturation.[7]

The death rate for COVID-19 was observed as 2.8% in men and 1.7% in women in a report from China with 44,672 cases.[9] The smoking rate in China is 52.1% for men and 2.7% for women; therefore, it is suggested that habitual smoking might be associated with a higher prevalence of comorbidity in male.[10]

The role of tobacco use in the etiology of lung cancer and chronic obstructive pulmonary disease (COPD) has been proven. These relationships have been revealed by reporting decades of multi-centre and diverse epidemiologic data.[11] A meta-analysis investigating the severe COVID-19 risk in COPD patients with a history of pre-existing and ongoing smoking reported that habitual smoking exacerbates the progression of COVID-19 causing worse outcomes.[12] Concerning relation between COVID-19 and smoking, analyses in the existing studies revealed that the likelihood of patients with a smoking history developing severe symptoms of COVID-19 is higher than non-smokers. Considering smoking affects the mortality rate in COVID-19 patients, it is suggested that the CMR score can enable to project the probability of mortality of non-smoking patients with critical COVID-19.

We aimed to estimate the risk of mortality in hospitalized COVID-19 patients using a new machine learning (ML) model: the COVID-19 Risk of Mortality (CMR) calculation. Hence, the effect on mortality of CMR, aspartate transaminase/alanine transaminase (AST/ALT) levels, and neutrophil/lymphocyte (N/L) ratios (NLR) of non (active) smokers with COVID-19 in the ICU was investigated.

Our hypothesis in this study; it is to show that the CMR model is a good tool for monitoring surveillance in non-smoking COVID-19 patients in ICU.

METHODS

This cross-sectional study was carried out with the permission of University of Healthy Science, Bağcılar Training and Research Hospital Clinical Researches Ethics Committee (Date: 29.05.2020, Decision No: 2020.05.2.02.058). Written informed consent was provided from all participants. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design and Participants

Seventy seven non-active smokers with COVID-19 were selected. The primary author personally invited the participants, and the data were collected via face-to-face interviews. 183 patients were treated for three weeks (10-30 May 2021) in the ICU, 137 of whom had COVID-19. While 109 of the patients agreed to participate, 32 participants having smoked in the last two weeks were excluded (**Figure 1**). Written informed consent was provided from all participants.

To prevent selection bias, all COVID-19 patients were included in the research. Additionally, the same investigator collected the data, and the data analysis was done independently.

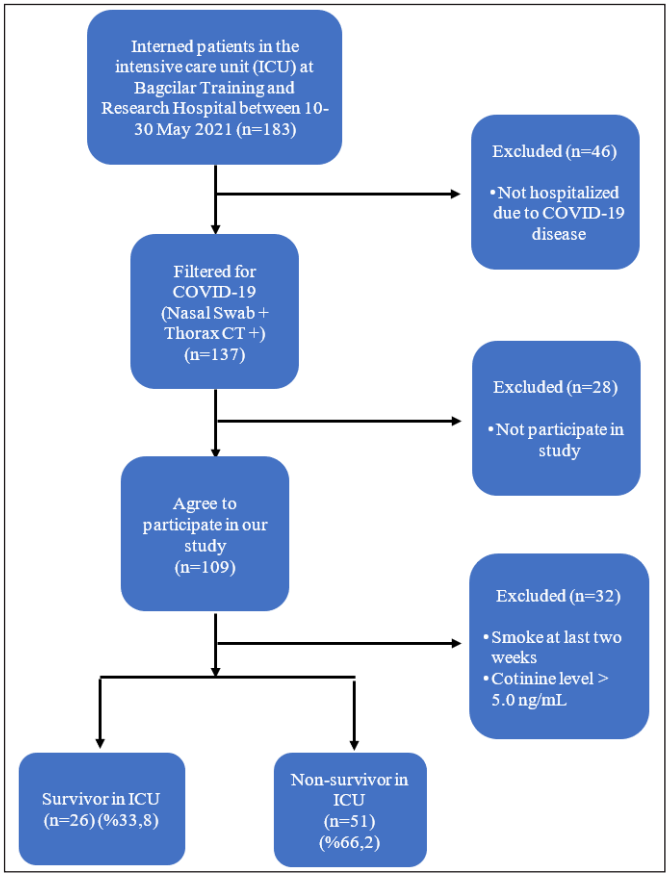

Figure 1. The figure shows the patients selection

Biochemical Analysis

The primary outcome of the study was the mortality ratio from COVID-19. Additionally, demographic features were recorded and urine cotinine levels were tested. With a 2-hour elimination half-life, nicotine is quickly metabolized in the liver into cotinine. Having a 15-hour half-life, cotinine accumulates in urine in proportion to dosage and hepatic metabolism; tobacco users usually excrete cotinine ranging from 1,000 to 8,000 ng/ml. Heavy tobacco users avoiding tobacco for a fortnight exhibit urine cotinine <50 ng/ml. Cotinine concentrations, at 1,000 to 8,000 ng/ml when using a tobacco product, <50

ng/ml after 2 weeks of complete abstinence for a tobacco user, <20 ng/ml for a passively exposed non-tobacco user and measured at <5.0 ng/ml for the non-user.

Since the impact of smoking on COVID-19 prognosis and mortality is not conclusive, the research patients proved not to have been exposed to active or passive smoking in the last two weeks. Thus, impact of smoking was excluded from the study.

Eighteen features -disease severity, age, temperature, gender, oxygen saturation, ALT, AST, urea, creatinine, sodium, potassium, blood glucose, hemoglobin, leukocytes, CRP, mean corpuscular volume, platelets, prothrombin time and comorbidities parameters- were selected for CMR calculation in COVID-19 mortality.[13]

Our secondary outcome in this study is to evaluate the surveillance of COVID-19 disease in non-smoking COVID-19 patients.

Statistical Methods

The NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) was utilized for statistical analysis. Research data were analyzed using descriptive statistical methods and the distribution of data was evaluated with the Shapiro-Wilk Test. The Mann-Whitney test was preferred to compare the quantitative data between two groups without a normal distribution. The Student's t-test was utilized for comparing quantitative data between two groups with a normal distribution. The chi-square test was used to compare the qualitative data between the two groups. The significance was evaluated at $p<0.05$.

Power analysis was performed using the G*Power program to determine the number of samples. The power of the study is expressed as 1-β (β=probability of type II error) and in general studies should have 80% power. According to Cohen's effect size coefficients; it was decided to take 77 people totally, considering that at the level of $\alpha=0.05$.

RESULTS

In the study, 64.9% of the participants (n=50) were female while 35.1% (n=27) were male; the mean age was 61.3±14.3 and 66.2% (n=51) of the patients died. The study showed that, 11 non-survivors died as a result of complications related to underlying chronic diseases (3 patients with coronary artery disease, 3 patients with COPD, 2 patients with CHF, 2 patients with CVA and 1 patient with malignancy) and the other 40 patients died as a result of reasons related to COVID-19 and its complications. The mean number of days the participants were hospitalized in the ICU was 12.5±8.06.

Non-survivors were significantly older with a lower systolic blood pressure values than survivors (p=0.002) (Table 1). No statistically significant difference of mortality risk was found when evaluated based on gender, total hospitalization days, diastolic blood pressure, heart rate, fever, and saturation value (p=0.485, p=0.398, p=0.804, p=0.583, p=0.336 and p=0.815; respectively) (Table 1).

Compared to survivors, non-survivors had higher urea, creatinine, direct bilirubin, and pro-BNP values and lower total protein and lymphocyte values (p=0.035, p=0.023, p=0.018, p=0.012, p=0.031 and p=0.002; respectively).

The difference between survivors and non-survivors with regard to mean glucose, uric acid, AST, ALT, alkaline phosphatase (ALP), GGT, total bilirubin, albumin, LDH, TSH, FT4, FT3, CRP, sedimentation, procalsitonine, IL-6, D-dimer, ferritin, Na, K, Cl, Ca, PT, INR, APTT and hemogram parameters like leukocyte, RBC, hemoglobin, platelet, MCV, MCH, MCHC, RDW, PCT, MPV, PDW, neutrophil, monocyte, eosinophil, and basophil values on mortality rates were not significantly different. Non-survivor group had higher AST/ALT and neutrophil/lymphocyte (NLR) ratios than the other group (p=0.008 and p=0.001; respectively). No statistically significant difference of mortality risk was identified when evaluated based on MPV/PLT and neutrophil/albumin ratios (p=0.836 and p=0.119; respectively) (Table 2).

Table 1. Comparison of mortality risk with regard to scales

Variables		n	Mean±SD	Min-Max (Median)	p
Age (year)	Survivor Nonsurvivor	26 51	53.5±11.2 65.2±14.2	32-81 (52.5) 37-102 (64)	**0.001**[a]
Total hospitalization days	Survivor Nonsurvivor	26 51	11.4±9.7 13.0±7.1	2-38 (8.5) 1-35 (12)	0.398[a]
Systolic blood pressure (mmHg)	Survivor Nonsurvivor	26 51	134.5±18.1 120.4±17.7	100-180 (132.5) 80-160 (120)	**0.002**[a]
Diastolic blood pressure (mmHg)	Survivor Nonsurvivor	26 51	71.4±19.5 68.0±11.7	43-150 (70) 36-90 (70)	0.804[b]
Pulse per minute	Survivor Nonsurvivor	26 51	87.2±13.6 89.2±15.7	65-120 (85.5) 59-129 (88)	0.583[b]
Temperature (°C)	Survivor Nonsurvivor	26 51	36.8±0.5 36.7±0.5	36-38.8 (36.95) 36-38.2 (36.8)	0.336[a]
Saturation (%)	Survivor Nonsurvivor	26 51	92.73±4.25 93±4.98	85-100 (92.5) 78-100 (93)	0.815[a]

a Student t-test (Mean±SD), b Mann Whitney Test (Min-Max/Median). All the p values that were considered statistically significant (<0.05) are identified in bold.

Table 2. Comparison of mortality risk with regard to biochemical parameters

Variables		n	Mean±SD	Min-Max (Median)	p
AST/ALT ratio	Survivor	26	1.54±0.87	0.44-5.13 (1.46)	**0.008**[b]
	Nonsurvivor	51	1.97±0.82	0-4.1 (1.98)	
MPV/PLT ratio	Survivor	26	0.04±0.02	0.01-0.09 (0.04)	0.836[b]
	Nonsurvivor	51	0.04±0.02	0.02-0.12 (0.04)	
Neutrophil/Lymphocyte ratio	Survivor	26	9.51±7.05	2.70-32.67 (8.04)	**0.001**[b]
	Nonsurvivor	51	17.21±13.26	3.73-64.73 (13.7)	
Neutrophil/Albumin ratio	Survivor	26	2.6±1.25	0-5.18 (2.51)	0.119[b]
	Nonsurvivor	51	3.67±2.39	1.15-12.98 (2.91)	

a Student t-test (Mean±SD), b Mann Whitney Test (Min-Max/Median). All the p values that were considered statistically significant (<0.05) are identified in bold. AST:Aspartate Aminotransferase, ALT:Alanine Aminotransferase, MPV:Mean platelet volume, PLT:Platelet count ratio.

No statistically significant relationship could be established between mortality rates and the presence of comorbidities such as diabetes mellitus, hypertension, asthma, COPD, malignancy, chronic renal failure (CRF), congestive heart failure (CHF), cerebrovascular accident (CVA), rheumatism, Alzheimer's, coronary artery disease and complaints of admission to hospital such as cough, shortness of breath, fever, myalgia, loss of appetite, syncope, diarrhea, and abdominal pain (p=0.568, p=0.999, p=0.073, p=0.568, p=0. 623, p=0.099, p=0.594, p=0.069, p=0. 472, p=0.472, p=0.703, p=0.847, p =0.594, p=0.371, p=0.356, p=0.219, p=0.472, p=0.472 and p=0.159; respectively).

As expected non-survivors had higher CMR values (p=0.001). No statistically significant correlation was relieved between mortality rates and APACHE scores (p=0.453) (**Table 3**).

Table 3. Comparison of mortality risk with regard to CMR and APACHE scores

Variables		n	Min-Max (Median)	p
CMR score	Survivor	26	2-61 (13)	**0.001**
	Nonsurvivor	51	5-82 (28)	
APACHE score	Survivor	26	16-41 (28)	0.453
	Nonsurvivor	51	18-40 (28)	

Mann Whitney Test. All the p values that were considered statistically significant (<0.05) are identified in bold. CMR:COVID-19 Mortality Ratios

DISCUSSION

The results of the research indicated that the CMR score, AST/ALT values and N/L ratios of non (active) smoking (ex-smoker) critical COVID-19 patients in ICU provided beneficial data in early prediction of mortality rates.

Contrary to the common belief that smoking deteriorates the consequences associated with COVID-19, studies conducted before 2020 praised the positive impact of smoking on the course of the disease.[14-16] Within this context, to exclude the effect of smoking and to reveal the other factors affecting the mortality rates of non-smoking COVID-19 patients, we focused on the non-smoking patients only.

Factors affecting mortality risk in the ICU patients were reviewed to examine the risk factors related to COVID-19 contributing to the purpose of the study. There is a wealth of complex information evaluating the clinical pattern and mortality risks of COVID-19 patients, but regardless of their smoking habits. Likewise, data from previous researches confirm the presence of a complicated correlation between habitual smoking and disease severity. Some studies conducted during the pandemic suggested a low prevalence of active smoking COVID-19 patients in the general population. Another study with a sample size of 8.28 million in the UK concluded that smoking was associated with milder risks of COVID-19.[14] Although prior tobacco use was related to a higher risk of serious consequences of COVID-19, another study covering 645 cases examining the relationship between the smoking habits of hospitalized patients and the severity of the disease demonstrated that active smoking may have a protective but insignificant effect. Prior smoking habits proved to be related to the exacerbation of severe consequences of COVID-19 in hospitalized patients.[15]

A UK-based study investigating the correlation between smoking habits and COVID-19-related outcomes on 53.002 adults correlated current habitual smoking with COVID-19.[16] A meta-analysis examining 11.590 COVID-19 patients, in which 2.133 (18.4%) had severe COVID-19 and 731 (6.3%) had a history of smoking, revealed that the pattern of the disease was exacerbated in 218 patients (29.8%) with a smoking history whereas the rate was as low as 17.6% in the non-smokers. Thus, the meta-analysis indicated a statistically significant relationship between habitual smoking and the development of COVID-19.[17] Generally, the concordance of the observational analyses demonstrating the relationship between recent smoking behavior and COVID-19 together with the Mendelian Randomisation (MR) analyses demonstrating the correlation with lifetime smoking predisposition and the frequency of smoking support the causal impact of smoking on the severe course of the disease.[18] The results of this research, like those of the prior studies, suggested that habitual smoking is a risk factor affecting the development of COVID-19 and that smokers have a greater risk of exacerbation of COVID-19 compared to

patients who have never smoked. At the same time, a recent cohort study examining the relationship between smoking status and death from COVID-19 found that non-smokers are more likely to survive COVID-19 disease.[19]

A meta-analysis covering 109 articles examining a total of 517.020 COVID-19 patients suggested a statistically significant correlation between habitual smoking and the severity of COVID-19. Accordingly, habitual smoking and the presence of comorbidities (diabetes, hypertension and COPD) have proved to be correlated with the possibility of hospitalization in the ICU, increasing mortality rates.[20] 2023 data also supports that these comorbidities are likely to mediate the effect of smoking on mortality from COVID-19.[21]

In a research on 473.550 patients utilizing the UK Biobank cohort investigating risk factors causing death in COVID-19 cases, the main contributing factors were found to be age, male gender, and black ethnicity. Specifically, black ethnicity, oral steroid use, and hypertension proved to be closely associated with COVID-19.[22] Age was also found to be a notable cause of mortality risk, however, no significant relationship was determined between gender and mortality. Considering comorbidities, although no significant difference was found between hypertension and mortality in accordance with the information obtained herein, low systolic blood pressure proved to be significantly correlated with mortality. Sun et al.'s study, just like ours, supports that low blood pressure may be associated with COVID-19 mortality and may worsen the condition of critical COVID-19 patients.[23]

A cohort study of 521 patients demonstrated that the prevalence of COPD was not high in smoking COVID-19 patients, thus suggested that COPD patients are not under a higher risk of the disease. However, when the SARS-CoV-2 infection first appeared, COPD patients and former smokers were reported to be under the highest risk of mortality. Accordingly, the study suggested that the risk of morbidity was not directly related to COPD and smoking habits, but rather to the presence of comorbidities.[24]

A single-center study investigating whether there is an independent correlation between elevated liver enzyme values and risk of mortality as well as hospitalization of COVID-19 patients in the ICU argued that the three are significantly correlated.[25] Likewise, a multi-center retrospective cohort research examining 5,771 adults with COVID-19 demonstrated that initially AST values and then ALT values of severe COVID-19 patients tend to elevate throughout the course of the disease. Additionally, the abnormality in AST levels was related to the highest risk of mortality compared with other indicators of liver failure experienced during hospitalization.[26] As can be seen in literature, the AST/ALT ratio used in the evaluation of liver enzymes during the course of COVID-19 was correlated with mortality, although the reason for the elevation in liver enzymes is probably multi-factorial.

A study suggested that a dynamic change in neutrophil/lymphocyte ratio (NLR) and D-dimer level can distinguish severe cases of COVID-19 from mild/moderate cases. The NLR ratio was found to be 6.29±3.72 and 2.33±1.22 in the groups with severe and mild/moderate COVID-19 respectively.[27,28] In the current research, the N/L ratio was found as a minimum of 3.73 and a maximum of 64.73 in the hemogram findings of non-surviving patients. In this respect, NLR is suggested for consideration as a significant indicator of mortality and disease severity.

A research on high-risk patients in the ICU diagnosed with COVID-19 may provide further information about disease control strategies. A retrospective study involving 114 adult inpatients with COVID-19 pneumonia, comprising of 19 active smokers (15.9%), 23 ex-smokers (20.1%), and 72 non-smokers (63.1%), concluded that habitual smoking did not have a statistically significant effect on the course of the disease, the duration of hospitalization, the need for non-invasive mechanical ventilation (NIMV), the need for follow-ups in the ICU, and mortality. The study argued that the active smoking rate of hospitalized COVID-19 patients is lower than the population average. Accordingly, it was observed that habitual smoking is not correlated with disease progression, or with prognostic indicators and mortality.[29]

In a meta-analysis of COVID-19 patients, while age, pre-existing comorbidities, severity of the disease based on validated scoring systems and patients' response to disease were correlated with mortality, male gender and increased BMI were not. Therein, related factors were found to have prognostic significance for ICU patients with COVID-19 diagnosis.[30]

As the term "habitual smoking" alone does not specify the number of cigarettes smoked or the duration of smoking, it may be considered as an 'imperfect' measure for evaluating the correlation with severe COVID-19 outcomes. Based on a retrospective cross-sectional study involving 4.611 patients that evaluated whether smoking status, smoking intensity, duration of smoking, and pack/year smoking were related to serious consequences among adult COVID-19 patients, it was concluded that the smoking status, pack/year smoking and smoking intensity of COVID-19 patients correlated with

hospitalization, and smoking intensity also correlated with admission to the ICU.[31] A meta-analysis including 47 researches examining 32.849 hospitalized COVID-19 cases, 8.417 (25.6%) of which had a smoking history, 1.501 current smokers, 5.676 ex-smokers and 1.240 smokers with an unspecified frequency, concluded that smoking history is related to severe COVID-19, mortality, need for mechanical ventilation, and disease progression.[32]

Within this context, our research examined the correlation between mortality and the CMR scoring system, AST/ALT and the N/L ratio in non-smoking COVID-19 patients in the ICU. Cotinine levels were tested from participants' urine samples and the sample structure was specified by excluding individuals who had smoked in the previous two weeks, including passive smokers. Including only the smoking-free patients allowed us to exclude the effect of active and passive smoking on the outcomes of COVID-19. Another strength of our study is that the data were gathered simultaneously at the peak of the pandemic. The data was collected retrospectively and the study was carried out prospectively, thus minimizing the risk of using incomplete data.

Study Limitations

One limitation is that the study provides information from a specific hospital in Turkey. The overall outcome of COVID-19 may differ from the morbidity and mortality figures outside the ICU or in different institutions. During this study, there were higher or lower rates of COVID-19 cases in several countries. The CMR was examined, including the distribution of products with negative cotinine concentration. CMR correlation could be examined in people with high urine cotinine levels. Another limitation of the study is that COVID-19 patients who do not smoke or have low cotinine levels may have further racial and social differences. Additionally, the characteristics of the sample may vary according to different demographic profiles and population characteristics. Final limitation is that data collected throughout a three-week period will not be sufficient for statistical generalizations of the entire year.

CONCLUSION

Consequently, significant findings were identified between COVID-19 and the mortality rates in patients proven to be non-smokers by testing cotinine levels in urine samples. This study is significant as it provides the first data investigating COVID-19-related mortality in non-smoking patients with critical COVID-19 in the ICU. We hereby suggest the extension of our findings in the context of correlation with mortality due to COVID-19 and the submission of further studies in conjunction with future COVID-19 mortality data as they will aid early diagnosis in detecting the long-term sequelae and mortality of COVID-19.

Our research provides data by examining mortality rates of actively non-smoking patients with critical COVID-19. Further research with larger sample size is required to better demonstrate the correlation between smoking and COVID-19, the effects of smoking on COVID-19, and to understand the mechanisms thereof.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of University of Healthy Science, Bağcılar Training and Research Hospital Clinical Researches Ethics Committee (Date: 29.05.2020, Decision No: 2020.05.2.02.058).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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Original Article

MEDICINE PALLIATIVE CARE

DOI: 10.47582/jompac.1344338

J Med Palliat Care. 2023;4(5):579-584

Detailed analysis of elastofibroma dorsi cases detected incidentally on thorax CT

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Cite this article as: Köksal A, Tuğtağ Demir B, Çankal F. Detailed analysis of elastofibroma dorsi cases detected incidentally on thorax CT. *J Med Palliat Care*. 2023;4(5):579-584.

Received: 16.08.2023 • **Accepted**: 15.10.2023 • **Published**: 27.10.2023

ABSTRACT

Aims: Elastofibroma dorsi (ED) is a benign pseudotumor detected by Computed Tomography and/or Magnetic resonance imaging due to the penetration of fibrous and fatty tissues between the muscle structures and is more common in elderly people, especially in women, with subscapular topography. This study investigated the prevalence of elastofibroma dorsi in large series and CT findings.

Methods: A total of 469 patients (212 females, 257 males) who underwent thoracic computed tomography for various reasons were included in this study. The presence, dimensions, contour and density of ED were investigated in these patients.

Results: The mean age of 469 patients was 54.51±17.42 (18-88 years). Elastofibroma was detected in 15.5% (n=73) of these patients. It was determined that 69.9% (n=51) of the patients with ED were female, and the mean age of these patients was 63.21±15.72. ED was usually isodense in both genders. Again, in both genders, ED was more regularly contoured, and the fat planes between adjacent muscle structures were usually closed.

Conclusion: Additional studies are not required when the lesion is typical and asymptomatic on CT scans. However, surgical treatment may be recommended if the lesion is symptomatic or if doubt remains regarding the benign nature of the lesion.

Keywords: Elastofibroma dorsi, computed tomography, prevalence

INTRODUCTION

Elastofibroma dorsi (ED) is often located in the lower subscapular region between the thorax wall and the scapula.[1] Originating from fibrous tissue, ED is actually a benign soft tissue tumor that tends to grow slowly.[2] The lesion was named elastofibroma dorsi because of its characteristic subscapular-infrascapular location.[3] In 99% of cases, it is located in the lower corner of the scapula between the musculus latissimus dorsi and the serratus anterior, adherent to the periosteum of the thoracic wall. Although ED is a benign tumor, it can mimic soft tissue tumors such as sarcoma or fibromatosis.

ED was defined by the World Health Organization in 2002 as a benign fibroblastic/myofibroblastic tumor in the classification of soft tissue tumors.[4] Although it is thought that the etiology of ED may be a reactive lesion as a result of abnormal degeneration of elastic fibers due to the friction of the scapula against the thoracic fascia, its pathogenesis is still not entirely determined.[5] However, it has been reported that microtrauma, genetic factors, gender, fibroelastic tissue changes and age may play a role in the etiology.[6,7] Although the fact that ED is more common in people who do heavy work, especially using their hands, supports this view, ED can also be seen in people who have not worked in heavy-duty jobs throughout their lives and in different settlements.[8] Due to its rarity, the diagnosis and treatment algorithm is unclear. Although considered a rare soft tissue mass, small and subclinical elastofibromas were detected in 24% of women and 11% of men in autopsy series over 55 years of age.[9] Its incidence in autopsy studies is 13-17%.[10] Although it is mainly detected unilaterally in female patients over 50 years of age, it can be seen on both sides at a rate of 10% and is very rare in children.[11,12]

ED may not cause clinical complaints in half of the patients, and it is asymptomatic because it does not cause symptoms before reaching a certain size.

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However, painful swellings larger than five centimeters may raise suspicion of malignancy.[2] It is generally described as an ill-defined mass with symptoms such as back and shoulder pain, a popping sound in the back, swelling at the lower pole of the scapula, discomfort, cracking, stiffness, and occasional pain.[13,14] In a patient who presents with these complaints, even if no pathology is detected in the physical examination, a computed tomography (CT) examination should be performed.[8] CT is a reliable and noninvasive technique that can show the characteristic fibrous and fat components of the mass. It is typically seen as a solitary, heterogeneous and irregularly circumscribed soft tissue mass on CT, and diagnosis with CT is important in preventing radical surgery. This study investigated the prevalence of ED in large series and CT findings.

METHODS

The study was carried out with the permission of Ankara Bayındır Private Hospital Ethics Committee (Date: 24.03.2023, Decision No: BTEDK-2023/8). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Research Design

Four hundred sixty-nine patients (212 females, 257 males) with adequate image quality were included in the study. After excluding the examinations with technical problems due to respiratory artifact and movement, out of 492 patients who underwent thorax Computed Tomography (CT) between 01.2021 and 04.2023 in hospital. The mean age of the patients included in the study was 54.51±17.42 (18-88 years).

Research Parameters

In this study, which was carried out to determine the radioanatomical features of ED, the parameters as the presence of ED, the density of the ED according to the adjacent muscular structure (isodense, hypodense or hyperdense), regular or irregular ED contour, and open or closed fat plane between the ED and adjacent muscular structures were examined (Figure 1).

CT Protocol

CT examinations were performed in the supine position with a multislice computed tomography device (MSCT) (General Electric IQ™ 32-Detector Spiral MSCT). The acquisition parameters are 200-320 mAS, 120 kV, an average 350 mm field of view (FOV), and 1.25 mm slice thickness. Images were evaluated axially, coronally, and sagittally in the bone and soft tissue windows. RadiAnt DICOM Viewer 2022.1 program was used for evaluation processes. All measurements were conducted by two radiologists together.

Statistical Analysis

All the measurements were performed on the osseous surfaces. Length measurements are in millimeters (mm). Statistical analyses were carried out using SPSS for Windows statistical package (version 21.0; SPSS, Chicago, Illinois), and a p-value <.05 was considered statistically significant.

RESULTS

As a result of the analysis, elastofibroma was detected in 15.5% (n=73) of 469 patients, while elastofibroma was not present in 84.6% (n=397). A bilateral tumor was observed in 2 of 73 patients with ED, and a unilateral tumor was observed in the others (Figure 2).

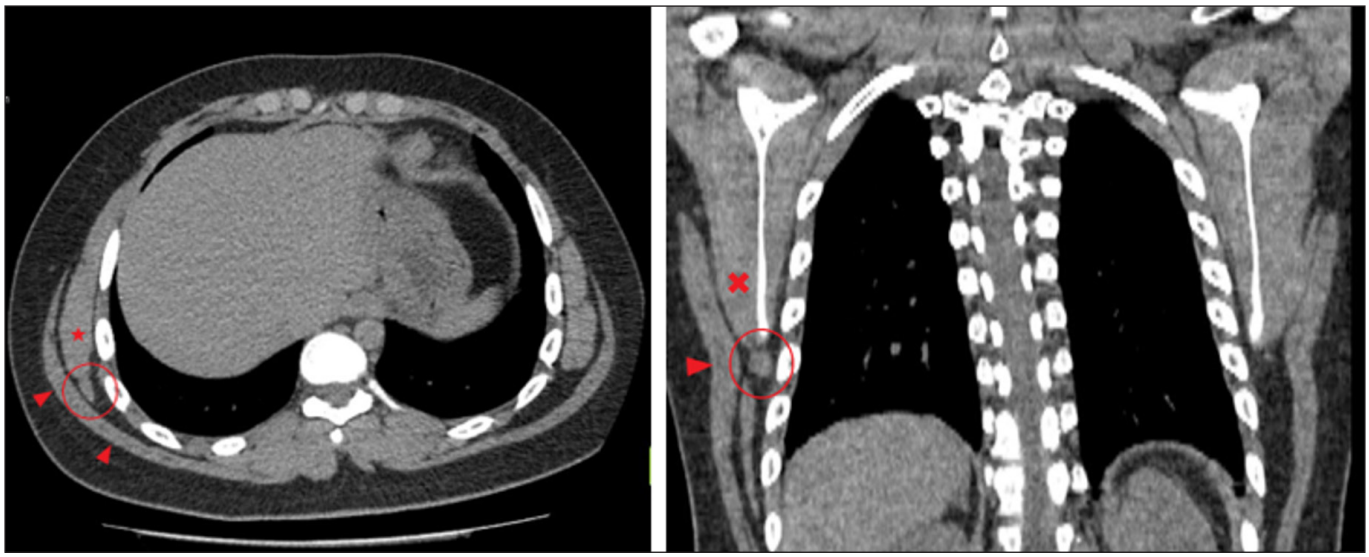

Figure 1: (a) Axial non-contrast CT images of a 19-year-old male patient show an ED mass (in-circle), well-contoured, hypodense, and a clear fat plane between the muscle (b) coronal reformat image of the same patient, star (*): musculus serratus anterior, arrowhead: musculus latissimus dorsi, x: musculus infraspinatus.

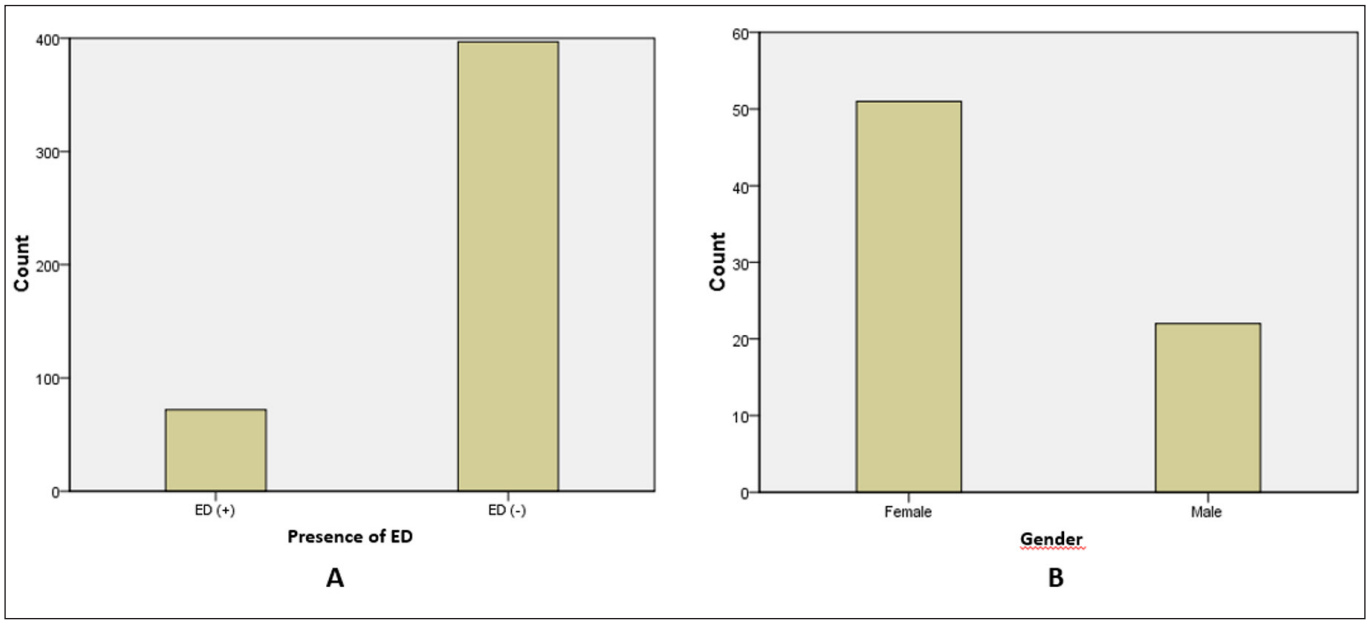

Figure 2: A: Presence of ED, B: Distribution of patients with ED by gender

Elastofibroma was seen in 69.9% (n=51) females and 30.1% (n=22) males (Figure 2). While ED was observed on the right side in 53.4% (n=39) of the patients, it was observed on the left side in 46.6% (n=34).

The mean age of the patients diagnosed with elastofibroma was 63.21±15.72 years. Considering the rates of elastofibroma in people younger than 60 years old and over, it was determined that 24.7% (n=18) of those with ED (+) were under 60 years old, and 75.3% (n=55) were individuals over 60 years old. In the distribution of age by gender, it was determined that 74.5% of the women were >60 years old (Figure 3).

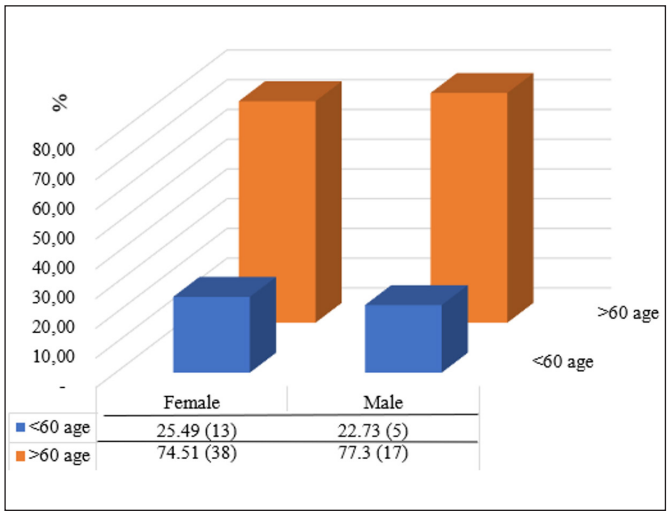

Figure 3: Distribution of ED presence by age and gender (%(n))

The ED density was 12.3% (n=9) hyperdense, 53.4% (n=39) isodense, 34.2% (n=25) hypodense, and the ED contour was found regular in 87.7% (n=64) of the patients and irregular in 12.3% (n=9). It was found that the fat plane between the ED and the adjacent muscle was open in 16.4% (n=12) of the patients and closed in 83.6% (n=61) (Figure 3). The distribution between the sides is summarized in Table 1.

Table 1. Distribution of ED morphology by sides

	Total		Right		Left	
	N	%	N	%	N	%
ED density						
Hyperdense	9	12,3	5	12,8	4	11,8
Isodense	39	53,4	20	51,3	19	55,9
Hypodense	25	34,2	14	35,9	11	32,4
ED contour						
Regular	64	87,7	34	87,2	30	88,2
Irregular	9	12,3	5	12,8	4	11,8
ED fat plane						
Open	12	16,4	6	15,4	6	17,6
Closed	61	83,6	33	84,6	28	82,4

While the mean elastofibroma size was 31×25×17 mm on the right side, it was determined as 32×24×16 mm on the left side. It was determined that there was statistical significance between them, and the masses on the right side were generally larger than on the left side ($p<0.05$). It was determined that the tumors were at least 5×4×2 mm in size and at most 94×88×60 mm.

It was determined that ED was found on the right side in 54.9% of women and equally on the right and left sides of men. ED was usually isodense in both genders. In both sexes, ED was more regularly contoured, and the fat planes between adjacent muscle structures were usually closed (Table 2).

Table 2. Distribution of ED morphology by gender

		Gender		Total
		Female	Male	
Side				
Right	N	28[a]	11[a]	39
	%	54,9%	50,0%	53,4%
Left	N	23[a]	11[a]	34
	%	45,1%	50,0%	46,6%
Total	N	51	22	73
	%	100,0%	100,0%	100,0%
ED Density				
Hyperdense	N	8[a]	1[a]	9
	%	15,7%	4,5%	12,3%
Isodense	N	23[a]	16[a]	39
	%	45,1%	72,7%	53,4%
Hypodense	N	20[a]	5[a]	25
	%	39,2%	22,7%	34,2%
Total	N	51	22	73
	%	100,0%	100,0%	100,0%
ED Contour				
Regular	N	46[a]	18[a]	64
	%	90,2%	81,8%	87,7%
Irregular	N	5[a]	4[a]	9
	%	9,8%	18,2%	12,3%
Total	N	51	22	73
	%	100,0%	100,0%	100,0%
ED fat plane				
Open	N	8[a]	4[a]	12
	%	15,7%	18,2%	16,4%
Closed	N	43[a]	18[a]	61
	%	84,3%	81,8%	83,6%
Total	N	51	22	73
	%	100,0%	100,0%	100,0%

DISCUSSION

Elastofibroma dorsi is a rare lesion that should be known, diagnosed and treated in a patient who presents with functional disturbance in scapula movement. Repetitive micro-injuries between the chest wall and scapula, the source of collagen degeneration, and excessive elastin production may play a pathophysiological role in this rare lesion.[15,16] Hisaoka et al.[17] suggested that ED may not be a simple reactive fibroblastic pseudotumor but rather a monoclonal neoplastic process with genomic instability. Nishio et al.[18] emphasize that recurrent 1p and Xq abnormalities are evident in elastofibroma dorsi, and further studies are needed to determine the biological consequences of these genomic changes in elastofibroma dorsi.[18] However, first of all, radiological evaluation should be done very well. Based on these data, there are generally case reports and review studies on ED in the literature.[2,11,19,20] and radiological studies on large sample groups are very limited. Therefore, this study was conducted to investigate the prevalence of ED in large series and CT findings.

The most important assessment for elastofibroma dorsi is undoubtedly CT, as Alouni et al.[21] suggested. CT reveals characteristic findings that may lead to a presumptive diagnosis of elastofibroma. In all patients, CT can clearly show the changing fibrous tissue and adipose tissue pattern, as well as the highly characteristic location of the tumor. Boundaries may be indistinct, and the tumor may be heterogeneous.[22] In the most typical pattern, fatty tissue lines alternate with fibrous tissue filaments to form straight or curved lines roughly parallel to the chest wall. All of the positive patients in our study had these typical patterns; thus, a possible diagnosis of elastofibroma dorsi was obtained. Some other diagnoses must be ruled out if features are atypical, including lipoma, differentiated liposarcoma, and hemangioma.

Elastofibromas are traditionally considered rare, but their exact prevalence is unknown. In a study conducted with CT, it was stated that 2% of adults over the age of 60 have incidental lesions.[23] Jarvi and Lansimies reported that they detected elastofibroma in the subscapular thoracic fascia in 24.4% of females and 11.2% of males in a postmortem series in which they examined 235 cases older than 55 years.[24] Blumenkrantz reported to detect ED in 1.66% of 1751 patients who underwent PET/CT.[25] The inconsistency in incidence is likely related to the large variability in tumor size. Larger studies of elastofibromas report that ED predominates in females over 50.[26-28] In their study with 14 patients with ED, Sarıçam et al.[29] reported that 72.5% were females, and the median age was 54.2. In our series, 15.5% (n=73) of 469 patients had elastofibroma, while 69.9% (n=51) of these patients were female, and 75.3% (n=55) were patients over 60 years of age, and ED was present unilaterally in all patients except 2 patients.

According to our research results, the average size of elastofibroma was 9×8×6 mm on the right side and 6×5×2 mm on the left side. It was determined that there was statistical significance between them, and the masses on the right side were generally larger than on the left side. There are no results in the literature on tumor size between the right and left sides.[9,30] It has been reported that surgical treatment can usually be performed for masses larger than ≥5 cm and due to aesthetic concerns.[5] Although the subscapular region is a richly vascularized anatomical region, often at risk of hematoma, complete excision can be easily achieved with healthy surgical margins. However, since the elastofibromas detected in this study are small in size and determined by screening and are probably asymptomatic, it is thought that surgical treatment is not required.

The typical feature on CT is an unencapsulated, lenticular-shaped mass with the largest dimension craniocaudal, with a density of adipose tissue in

the form of isodense, hypodense lines compared to adjacent musculature. The absence of bone structures in ED masses is one of the characteristic features of ED.[21] Tumors can often be distinguished by weak differentiation from the margins of the surrounding muscles on CT and give the impression of being part of the intercostal muscles.[31] Radouane et al.[32] reported that the borders of elastofibromas are clearly and distinctly visible on CT.[32] Our results determined that elastofibroma was seen as isodense in 53.4% of the patients, regular contour in 87.7% and enclosed fat plane in 83.6%. There was no statistically significant difference between the radiological appearances of ED in male or females. Fibrolipoma, a rare variant of lipoma, has a prominent fibrous tissue component and may have imaging findings that overlap with elastofibroma dorsi if these structures have a prominent hypointense signal.[18] In the presence of typical CT findings found in most of our patients, the diagnosis of elastofibroma dorsi can be easily considered. In the presence of atypical findings on CT, it is thought that the typical localization of the lesion, its bilateral nature, and the fact that the patient is elderly and female will support the diagnosis of elastofibroma dorsi.

Finally, the prevalence of ED in the elderly, especially in females, its subscapular topography, bilateral/unilateral nature, and findings on cross-sectional imaging (CT and/or MRI) are sufficient for a positive diagnosis, thus avoiding systematic biopsies and unnecessary surgical resection. Therefore, it is thought that the radiological findings of ED should be analyzed accurately and well.

CONCLUSION

ED is a benign tumor that mainly affects people over the age of 50 and predominantly females. It typically presents as a soft, mobile mass located in the subscapular region, causing swelling and pain on movement. Considering its possible location, the diagnosis should be confirmed by both careful physical examination and radiological studies.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara Bayındır Private Hospital Noninvasive Clinical Researches Ethics Committee (Date: 24.03.2023, Decision No: BTEDK-2023/8).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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Original Article

MEDICINE PALLIATIVE CARE

DOI: 10.47582/jompac.1352325

J Med Palliat Care. 2023;4(5):585-590

Can surgical embolectomy or bypass surgery be the first treatment option in ischemic cerebrovascular pathologies?

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Cite this article as: Çakın H, Gediz T. Can surgical embolectomy or bypass surgery be the first treatment option in ischemic cerebrovascular pathologies?. *J Med Palliat Care*. 2023;4(5):585-590.

Received: 30.08.2023 ◆ **Accepted**: 15.10.2023 ◆ **Published**: 27.10.2023

ABSTRACT

Aims: Well-established treatment methods have been utilized for intracerebral vascular occlusion, including medical thrombolytic treatments, endovascular interventions, and surgical procedures. We aimed with this study to show rapid and first-line surgical treatment is good option for recanalization.

Methods: This study focused on surgical recanalization techniques, illustrating them through seven patients. In emergency scenarios at our hospital, late term thromboembolectomy was performed on three patients who had experienced thromboembolic events. The other two patients were treated not in emergency conditions, but with by-pass surgery in the following week. Last two patients were in the group of patients who had reperfusion with recanalization surgery due to chronic ischemic intracerebral processes with clinical symptoms. This study was done retrospectively.

Results: One of the patient underwent emergency surgery for total infarction of the internal carotid artery (ICA), which remained unresponsive to other therapeutic approaches. Similarly, the second patient, who had undergone heart transplantation, required surgery due to unyielding small atheroma plaques originating from the main arteries after failed thrombolytic treatments. Similarly, after cardiac surgery, the patient who had a complete blockage at the bifurcation point of the right anal artery with an atheroma plaque was taken into emergency surgery. Successful recanalization procedures were achieved in three cases. Among the other patients who underwent semi-emergency surgery, one patient with internal carotid artery insufficiency after a traumatic process, another patient with left hemisphere vascular insufficiency after vascular disease, and another two patients who had vascular insufficiency due to occlusion of the main vascular structure by an aneurysm thrombus were operated on.

Conclusion: Our findings suggest that surgical intervention could be considered as the primary treatment option in selected cases for managing acute stroke or vascular insufficiency. In selected patients, rapid and first-line surgical treatment is satisfactory. This approach aligns with the need for more comprehensive investigations to determine the optimal approach in different scenarios of intracerebral vascular occlusion.

Keywords: Intracranial bypass, neurosurgery, recanalization surgery, stroke

INTRODUCTION

Intracerebral vascular occlusion necessitates well-established treatment strategies that have been in practice for an extended period. These interventions encompass medical thrombolytic treatments, intra-arterial thrombolytic, endovascular therapies, surgical embolectomy, and recanalization/bypass alternatives.[1,2] Among these, medical thrombolytic treatments, including tissue plasminogen activator (tPA), are the most common and easily accessible options. However, their success rates are modest. In contrast, endovascular methods have garnered favor due to their comparatively higher rates of treatment success and reduced invasiveness.

Surgical embolectomy and bypass procedures were historically recognized approaches in this context, preceding the advent of contemporary methods. Nonetheless, their popularity has waned due to their invasive nature and the requisite expertise. Earlier literature suggests limited efficacy in terms of clinical improvement associated with these approaches. However, recent studies conducted by Tetsuyoshi and Tomohiro present results that challenge this perspective, particularly in carefully selected patient populations.[1,2]

As a response to these evolving dynamics, our study aims to reevaluate the role of surgical procedures, with an emphasis on their efficacy in clinical practice. We seek to contribute to a more nuanced understanding of the optimal treatment strategies for intracerebral vascular occlusion.

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METHODS

The study was carried out with the permission of Akdeniz University Faculty of Medicine Clinical Researches Ethics Committee (Date: 23.08.2023, Decision No: KAEK-684). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design and Participants

This study involved the retrospective analysis of seven patients who underwent late-term thromboembolectomy with or without by- pass as part of emergency surgical interventions for thromboembolic or vascular events at our hospital. This study was done retrospectively.

Patient 1: A 72-year-old male patient presented to the emergency department with acute aphasia, right hemiplegia, and syncope. Neurological examination prompted Computed Tomography (CT) and CT angiography assessments. CT angiography revealed complete occlusion of the left Internal carotid artery (ICA), left anterior cerebral artery (ACA), and middle cerebral artery (MCA). Given the high risk of bleeding due to extensive infarct area, medical thrombolytic treatment was excluded as an option The endovascular treatment failed to remove thrombus. The patient was subjected to emergency decompressive surgery involving thrombectomy and a superior temporal artery (STA)-MCA bypass procedure. A left frontotemporoparietal decompressive craniotomy was executed, followed by extensive Dural opening. Microsurgical Sylvain dissection facilitated access to the left MCA bifurcation. Utilizing the left STA, an end-to-side bypass was established between the STA and MCA M2 superior division. Intraoperative doppler ultrasound verified vascular anastomosis viability and distal MCA segment blood flow after bypass (Figure 1). Postoperatively, the patient exhibited improved aphasia and reduced hemiplegia to 3/5 strength. A follow-up CT angiography, conducted 24 hours' post-surgery, confirmed functional vascular anastomosis and blood flow in the left MCA feeding region.

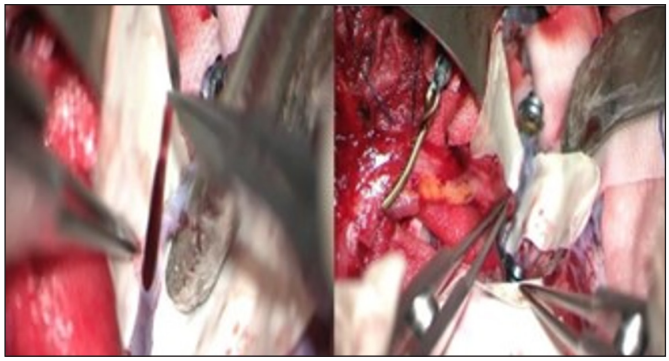

Figure 1. Intraoperative picture of thrombectomy and bypass procedure.

Patient 2: A 38-year-old male patient presented with left hemiplegia six hours after heart transplantation. Brain CT revealed extensive infarction, edema, and midline shift in the right hemisphere. CT angiography indicated absent vascular flow in the right MCA bifurcation, the right distal Anterior cerebral artery's A3 segment, and the right posterior cerebral artery's (PCA) P3 segment, attributed to micro emboli. Emergency a right frontotemporoparietal decompressive craniectomy and embolectomy were performed, and dura was widely opened. During surgery, intervention focused on the MCA artery occlusion, facilitated by the accessible edematous brain tissue. A vertical incision was made on the MCA to remove the plaque causing the obstruction. Restoration of flow obviated the need for bypass, and the vessel was closed with a primary suture. Due to the limited feasibility of other vessels, the procedure concluded with duraplasty and cranial bone retention for decompression (Figure 2). A subsequent CT angiography, conducted 24 hours after surgery, indicated restored blood flow in the right MCA feeding area. However, the extensive infarct area in the feeding territories of the right ACA and PCA persisted.

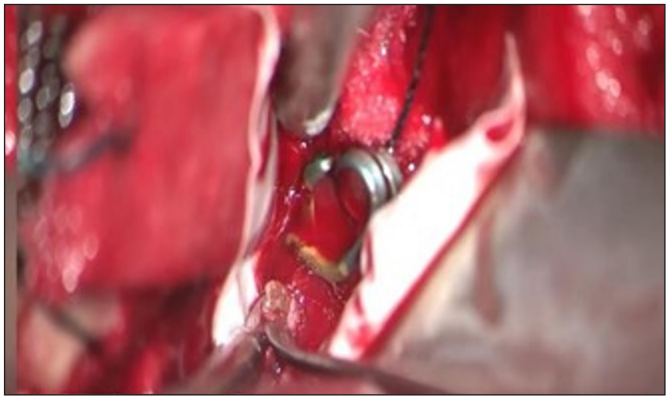

Figure 2. Intraoperative picture of embolectomy.

Over two months, the patient's hemiplegia gradually improved to 3/5 strength.

Patient 3: A-24 years old male patient presented with post-traumatic right-sided hemiparesis. CT angiography was performed after Subarachnoid hemorrhage was seen on computed tomography. The patient had right posterior communicating artery aneurysm and also vascular insufficiency due to dissection of the left internal carotid artery. (Figure 3) Because of the patient's left anterior cerebral artery was hypoplastic, all feeding area on the left side was via the left carotid artery and the flow in this artery did not provide adequate cerebral nutrition. The urgent by-pass surgery procedure performed to patient. After the surgery, clinical hemiparesis improved 3/5 to 5/5 strength.

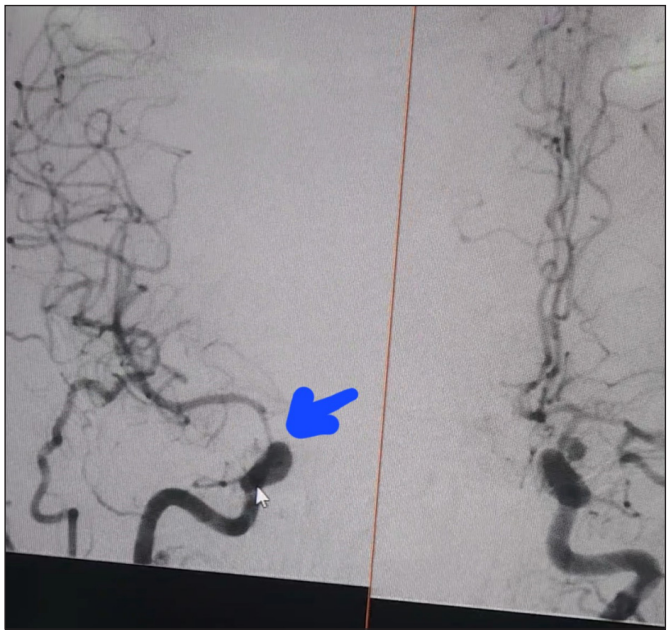

Figure 3. Selective Cerebral angiography of stenotic internal cerebral artery and successful bypass

Patient 4: A 64-year-old male patient was admitted to the emergency department due to a giant aneurysm in the left middle cerebral artery that caused thrombus. The patient had right hemiplegia and speech disorder due to insufficiency in the middle cerebral artery irrigation area. Surgery was performed on the patient under urgent conditions. The aneurysm was excised. The thrombus obstructing the middle cerebral artery was removed. (Figure 4) Recanization was achieved. In the first month after the operation, the patient improved to 3/5 hemiparesis. But speech disorder did not improve.

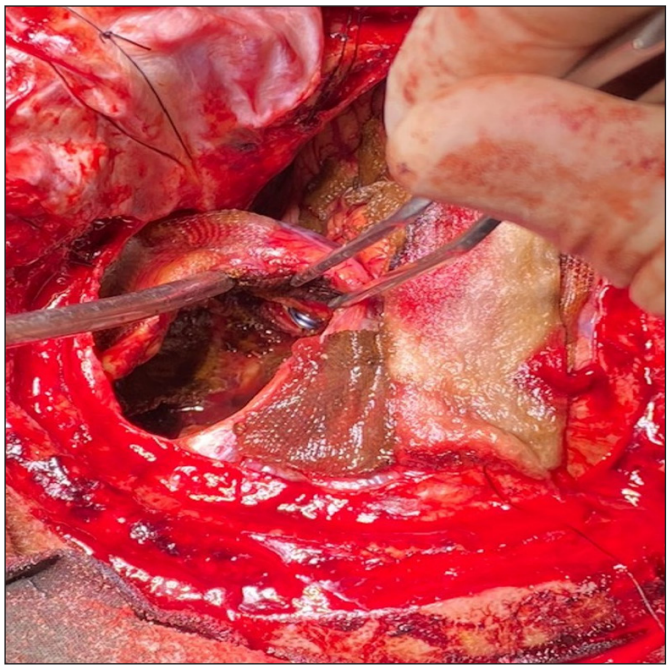

Figure 4. Intraoperative picture of thrombus in aneurysm

Patient 5: 35 years old female patient presented severe headache and right hemiparesis and seizure. The CT Angio and selective cerebral angiography demonstrated, left internal cerebral artery severe stenosis. Surgery was performed on the patient under urgent conditions. Cerebral By-pass procedure was performed. Superior temporal artery harvested with two branches and anastomosed to middle cerebral artery M2 and M4 segments. The cerebral blood flow has been adequately restored. (Figure 5) After the surgery, clinical hemiparesis improved 3/5 to 5/5 and headache resolved. In the follow-up, the patient has not had a seizure for 9 months.

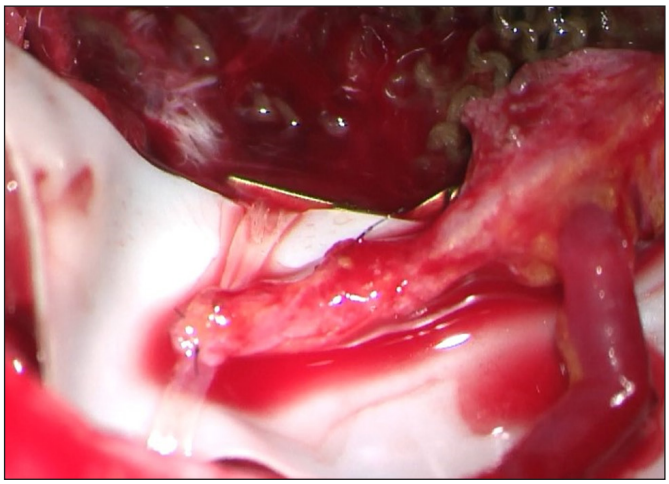

Figure 5. Intraoperative picture of double bypass procedure.

Patient 6: A 46-year-old female patient applied to the external center emergency service with numbness and syncope in the left half of her body, which has been 20-25 days. Upon detection of a 2 cm diameter hyperdense lesion adjacent to the right sphenoid bone ala major in Brain CT, we were referred to us. CT angiography was performed. Saccular aneurysmatic dilatation, 2.5 cm of which was thrombosed and 6 mm in diameter, was observed in the distal right middle cerebral artery M1 segment. Surgery was performed on the patient under urgent conditions. During surgery, it was observed that there was weak flow in the middle cerebral artery M2 segment in the distal of the aneurysm with Doppler USG and it was occluded by thrombus. First, the aneurysm was clipped and the thrombus within the aneurysm dome was excised. Then, the M2 segmental thrombus was removed by thrombectomy, and flow was restored (Figure 6).

Patient 7: A 65-year-old male patient presented with left hemiplegia eigth hours after heart bypass surgery. Brain CT revealed extensive infarction, and midline shift in the right hemisphere. CT angiography indicated absent vascular flow in the right MCA bifurcation. A right frontotemporoparietal decompressive craniectomy

and embolectomy were performed to patient. A vertical incision was made on the MCA. The plaque removed who causing the obstruction. Restoration of flow preserved, and the vessel was closed with a primary suture. A subsequent CT angiography, conducted 24 hours after surgery, indicated restored blood flow in the right MCA feeding area (Figure 7)

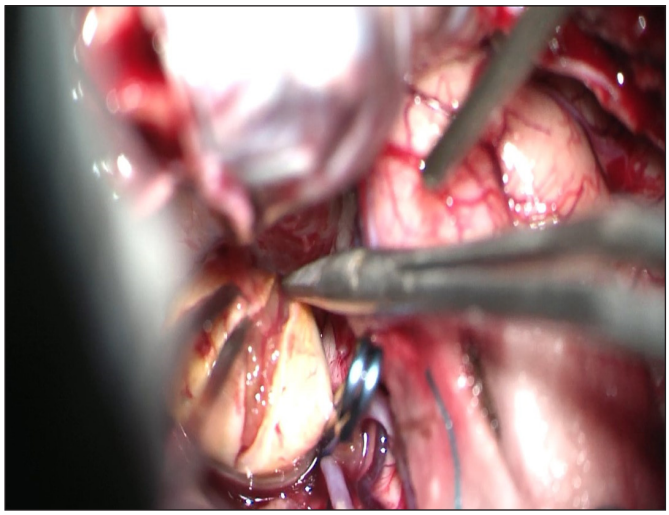

Figure 6. Intraoperative picture of removing the thrombus in aneurysm

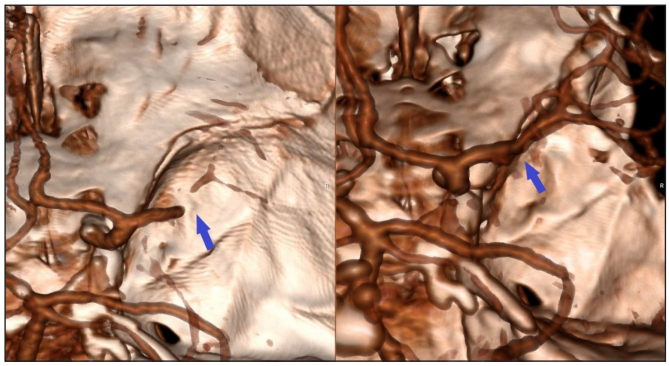

Figure 7. Preoperative and postoperative 3 D CT Angio of MCA embolectomy and recanalization area (blue arrows)

RESULTS

Surgical intervention was deemed necessary for the first patient due to an ICA total infarction that remained refractory to alternative treatments. The same applied to the second patient, where small atheroma plaques ruptured from main arteries during heart transplantation, and conventional thrombolytic treatments yielded no response. In all cases, thromboembolic drugs and endovascular methods are insufficient to restore flow. The reason for this is that the causes that prevent vascular flow are not only thrombus, but also atheroma plaques and mechanical causes.

In all cases, surgical procedures emerged as the primary and optimal approach. Decompression of brain parenchyma and restoration of arterial flow were the primary outcomes of these surgeries.

For the first patient, successful vascular anastomosis facilitated robust blood flow, effectively nourishing the MCA feeding area (Figure 8). As a result of this early intervention, neurological deficits exhibited rapid improvement. Notably, aphasia resolved, and hemiplegia transitioned to hemiparesis (3/5).

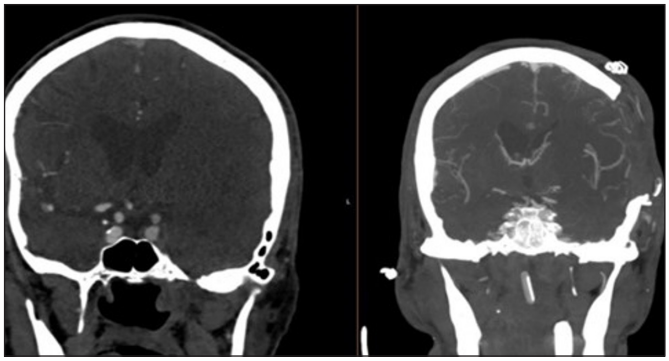

Figure 8. Preoperative and post operative CT Angio of Bypass procedure.

The second patient's case posed greater challenges. Neurological deficits remained undetected until the patient regained consciousness after the transplant surgery. Furthermore, extensive brain parenchymal areas suffered due to multiple occlusions of small-sized vessels. The objective of the surgery was to alleviate the affected brain parenchyma through decompression and to restore accessible vessel blood flow. Given its accessibility and significance in supplying crucial brain regions, the right MCA emerged as the most suitable option. Subsequent CT angiography confirmed restored blood flow in the right MCA feeding area. However, due to other concurrent vascular occlusions, the patient's neurological condition experienced gradual and partial improvement (Figure 9).

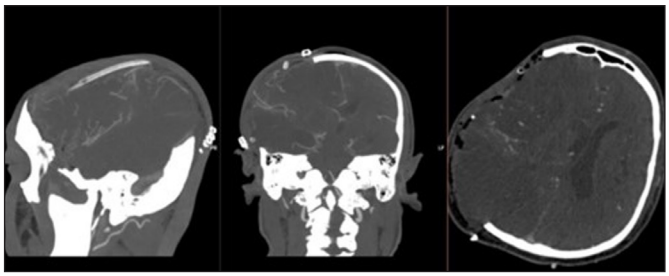

Figure 9. Post operative CT Angio of embolectomy procedure.

All patients benefited from urgent surgery. Their neurological deficits improved and quality of life improved.

The study outcomes underscore the efficacy of surgical procedures in addressing complex cases of thromboembolic events, particularly when other treatment avenues prove inadequate.

DISCUSSION

In the current healthcare landscape, cases of infarction resulting from cerebrovascular occlusions are commonly managed by neurologists employing medical therapy and antithrombotic agents. In specialized centers with proficient endovascular teams and technical capabilities, endovascular treatment methods have proven effective. However, the documented success rate of surgical embolectomy/thrombectomy, bypass procedures, and recanalization surpasses these approaches. This heightened success, however, hinges on the presence of an experienced medical team and appropriate patient selection for revascularization, highlighting the critical role of expertise in this context. Differing opinions concerning the timing of surgical intervention and patient selection further complicate this landscape.

Central to the acute stroke treatment are the principles of recanalization of occluded arteries, tissue reperfusion, optimization of collateral flow, and prevention of secondary injuries.[3] Indeed, the reopening of a partially occluded artery that causes hypoperfusion without infarction holds significant importance. Within the affected region, there is a critical area called the "penumbra," which surrounds the core infarct zone. Collateral circulation sustains this penumbra area, providing sufficient blood flow to prevent critical ischemia or infarction. However, it is inadequate to maintain normal cellular function. This explains why neurological damage improves after recanalization. Without recanalization, the penumbra transforms into an infarction.[3-16]

The utilization of intravenous tPA was initially endorsed for the treatment of acute ischemic stroke within the first 3 hours, a milestone established in 1996. The European Cooperative Acute Stroke Trial II (ECASS II) findings later extended the therapeutic window for tPA to 4.5 hours. Additionally, the time frame for intra-arterial mechanical thromboembolectomy was expanded to 6 hours in 2018. The American Stroke Association (ASA) subsequently asserted that mechanical thrombectomy remained effective within 24 hours of symptom onset. Substantiating this, studies such as DAWN and DEFUSE underscored the advantages of mechanical thrombectomy within the 24-hour window.[4,5,20]

The American Heart Association Guideline outlines the indications and contraindications for tPA treatment. Indications encompass diagnosed ischemic stroke with neurological deficits within 4.5 hours of symptom onset, as well as wake-up stroke cases exhibiting MRI mismatches and age exceeding 18 years. Conversely, contraindications encompass severe head trauma within three months, previous ischemic strokes within the same time frame, recent intracranial hemorrhage, suspected subarachnoid hemorrhage, infected endocarditis, aortic arch dissection, intracranial neoplasms, gastrointestinal or malignancy, bleeding diathesis, active internal bleeding, high blood pressure (systolic >180 mmHg or diastolic >110 mmHg), platelet count below 100,000/mm^2, acute hemorrhage on CT scan, and INR >1.7.3 The potentially more effective thrombolytics is still tenecteplase but some of the other thrombolytics, such as desmoteplase, have been unsuccessful in clinical trials.[10]

Endovascular Stroke Therapy (EST) becomes the viable alternative when contraindications to tPA treatment are present.[6,18,19] Optimal candidates for EST are individuals aged >18 years with National Institutes of Health Stroke Scale (NIHSS) scores >6, good prestroke functional status, intracranial artery occlusion, and symptom onset within 24 hours. As an invasive treatment, this method is associated with various complications.[7] A few numbers of published trials established the superiority of endovascular thrombectomy over medical trombectomy for the treatment of anterior circulation large vessel occlusion.[9,11-14]

As soon as possible after symptom onset, thrombectomy should be performed. Mechanical thrombectomy is recommended in acute ischemic stroke patients especially if intravenous thrombolysis is contraindicated.[8]

Surgical thrombectomy emerges as a definitive approach to recanalization. When intravenous tPA and endovascular recanalization are unfeasible due to contraindications or unavailability, surgical intervention becomes the primary choice. Furthermore, when surgical procedures like decompression or hematoma evacuation are warranted, simultaneous recanalization surgery can be executed.

The physiotherapy given after stroke has also been shown to benefit survival.[15-17]

In our reported cases, patients underwent recanalization concurrent with decompression surgery due to acute stroke and thromboembolic events. The first case exhibited large vessel occlusion with thrombus, while the second manifested occlusion in smaller-caliber vessels due to atheroma plaques. In other cases, the cause was not only thromboembolism, there were also accompanying pathologies such as aneurysm. Therefore, it was easier to decide on surgery. Notably, tPA and endovascular treatments failed to reopen occluded vessels in both cases, further emphasizing the primacy and efficacy of surgical intervention in such scenarios.

CONCLUSION

While tPA and endovascular treatments have gained significant popularity in recent times, surgical intervention remains a superior choice, particularly when other options are contraindicated, and especially for cases where atheromatous plaques prove challenging to eliminate through non-surgical means. Moreover, the window for surgical intervention can be extended to encompass up to 24 hours following the onset of symptoms. In selected patients, rapid and first-line surgical treatment is satisfactory.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Akdeniz University Faculty of Medicine Clinical Researches Ethics Committee (Date: 23.08.2023, Decision No: KAEK-684).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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Original Article

MEDICINE PALLIATIVE CARE

DOI: 10.47582/jompac.1360185

J Med Palliat Care. 2023;4(5):591-595

Comparison of sevoflurane insufflation and intravenous ketamine use in terms of failure rate in consecutive paediatric radiotherapy sessions: a cross-over study

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Cite this article as: Güven Aytaç B. Comparison of sevoflurane insufflation and intravenous ketamine use in terms of failure rate in consecutive paediatric radiotherapy sessions: a cross-over study. *J Med Palliat Care*. 2023;4(5):591-595.

Received: 14.09.2023 ◆ **Accepted**: 15.10.2023 ◆ **Published**: 27.10.2023

ABSTRACT

Aims: Childhood cancers are often treated with radiotherapy. During radiation therapy, sedation is often required for immobilization, especially for young children and patients with mental disabilities. Our study aimed to compare the efficacy of sevoflurane insufflation and intravenous ketamine for sedation during pediatric radiotherapy.

Methods: This prospective, randomized, cross-over study was conducted between August and December 2020 on pediatric patients (1 month to 18 years) requiring sedation or general anesthesia for radiotherapy. Three hundred fifty-two repeated sessions were conducted in the study involving 18 participating patients. Two groups were categorized by session: ketamine (Group K) or sevoflurane (Group S).

Results: The study included the evaluation of 352 sessions for 18 patients. Although there was no significant difference in procedure times between Group S and Group K during the sessions ($p>0.05$), Group K showed a significantly longer discharge time, higher failure rate, and higher score sedation scale in comparison to Group S ($p<0.001$).

Discussion: During radiotherapy sessions conducted outside of the operating room for children, the use of sevoflurane sedation was found to have a lower failure rate compared to intravenous sedation.

Keywords: Nonoperating room sedation, sevoflurane, ketamine, radiotherapy, childhood malignancies

INTRODUCTION

Radiotherapy (RT) is a frequently used treatment for childhood cancers. During radiation therapy, it is necessary to immobilize children to protect healthy tissues and ensure accurate radiation targeting of pathological tissues. Immobilization during radiation therapy often requires either superficial or deep sedation, particularly for children aged 0-5 and patients with mental disabilities.

Patients undergoing RT receive sedation during daily sessions lasting one to six weeks.[1] Due to high-energy radiation, the patient must be left alone in the treatment room during RT applications. However, the anesthesia team monitors patients through cameras from outside the room to ensure their safety. When a patient wakes up during a procedure, experiences apnea due to sedation, or if there is a problem with the device or position, it takes around 30 seconds to open the door of the RT room and provide urgent intervention.[2] These reasons may cause interruptions in the procedure, leading to longer procedure times and extended sedation periods.

An ideal method for pediatric sedation should be reliable, provide an amnesic effect, reduce anxiety, and offer immobility and analgesia.[3,4] While producing these effects, it must not depress respiratory and cardiovascular reflexes. The drugs should have a short onset and duration time, and their dosage should be adjusted based on the patient's response. Side effects should be minimized.[5]

During radiation therapy, it is essential to ensure that the patient is sedated to a level where they cannot move during the procedure. This is necessary for the treatment to be effective, but ensuring that the patient's spontaneous breathing is not suppressed is also essential. Administering additional anesthetic agents during RT interruption can decrease treatment effectiveness. In addition to the RT session, early patient recovery and discharge are important considerations. Proper dose titration of anesthetic agents can be extremely challenging under such conditions, especially during lengthy procedures.[6] Different centers utilize various

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sedation and anesthesia techniques during radiation therapy for children under 4 years old.[7,8] Sedation is often achieved through the use of propofol, midazolam, remifentanil, fentanyl, and ketamine.[9,10]

Our study aimed to compare the effectiveness of two sedation methods, sevoflurane insufflation, and intravenous ketamine, during RT sessions for pediatric patients, in terms of failure rate, discharge time and acquiring an airway with assistance. The study evaluated the occurrence of adverse events such as desaturation, hypoventilation, airway spasm, bradycardia, and tachycardia in relation to the continuous completion of the RT session with immobilization. Our study secondly aimed to investigate anesthesia complications in RT patients and identify associated factors.

METHODS

The study was carried out with the permission of Ankara City Hospital Clinical Researches Ethics Committee (Date: 02.07.2020 Decision No: E1-20-884). From August to December 2020, a study was carried out at our hospital. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.[11]

Study Population

We included all children between 1 month and 18 years who require sedation or general anesthesia for radiotherapy at Ankara City Hospital Radiotherapy Unit during August to December 2020. The study included 18 patients who participated in 352 repeated sessions. Patient data was collected during each session.

Children with certain medical conditions were excluded from the study, including symptomatic increased intracranial pressure, chronic nausea and vomiting, respiratory tract infections or diseases, cardiac disease, kidney or liver failure, and neurological or muscular diseases. All parents provided written informed consent.

Study Design

The study was prospective and randomized, with a cross-over design. Groups were categorized based on their session: IV ketamine (0.5 mg/kg) or sevoflurane (3%). The order in which the two different methods were applied to the 18 children in the daily sessions was determined using the closed envelope method in the first session. For the following sessions, the technique used was switched daily. Therefore, both groups consisted of 18 identical children who received either ketamine or sevoflurane sedation during sessions.

Anesthetic Management

All children received pre-anesthetic assessments and were classified based on ASA physical status classification a few days before the procedure at the hospital.

Per standard fasting guidelines, all children were kept nil per os (NPO) pre-operatively and received intravenous fluids after fasting.[12] Before being taken to the radiotherapy room, all children were administered 0,05 mg/kg of midazolam. Each child received standard intraoperative monitoring (non-invasive arterial blood pressure, heart rate, pulse oximetry, and end-tidal CO_2), and all intra-operative and postoperative events were recorded on an anesthetic record form until the patient achieved full recovery. The Pediatric Sedation Status Scale[13] was used to adjust the sedation depth to stage 2.

Group S: Sevoflurane insufflation at 8% concentration in oxygen 6lt/min began using an oxygen mask with sealed holes to prevent leakage. After loss of consciousness, we immediately reduced sevoflurane concentration to 2-3%.

Group K: The children were given a dose of 0.5 mg/kg of ketamine and oxygen 6lt/min using an oxygen mask when positioned on the radiotherapy table. After securing the child on the table, additional boluses of 0.025 mg/kg ketamine were administered if the child responded to stimulation.

Data Recorded

The patient's age, body weight, body mass index (BMI), body surface area (BSA), American Society of Anesthesiologists (ASA) physical status, and fasting time were recorded prior to RT. The duration of anesthesia, any interruptions during the procedure, use of an auxiliary airway, and incidents of nausea and vomiting were all documented and noted. Recorded complications included respiratory (apnea, airway obstruction, cough, desaturation) and cardiac (bradycardia, tachycardia, hypotension, hypertension, arrhythmia). Apnea is defined as a period of breathing interruption that lasts for more than 10 seconds or a reduction in the level of $ETCO_2$. Desaturation is defined as the level of SpO_2 below 92%, while bradycardia/hypotension and tachycardia/hypertension are defined as below and 30% above the baseline, respectively.

Any interruption during RT caused by hypotension, hypoventilation, bradycardia, desaturation, or movement was defined as a failure rate. The main objective was to compare the failure rate between the groups that received sevoflurane insufflation and ketamine. The secondary outcomes included the use of an auxiliary airway, respiratory and cardiac complications, and incidents of nausea and vomiting between the groups.

After the procedure, the patient was closely monitored in the recovery room until their Modified Steward score reached a minimum of 8.[14] The duration between the end of radiotherapy and the patient's recovery to a modified Stewart scale of 8 was noted as the "discharge time."

Sample Size Estimation

The study titled "Does sevoflurane add to outpatient procedural sedation in children? A randomized clinical trial" aimed to determine the number of patients needed for the study based on the Houpt crying scores as a reference. The required sample size is at least 18 patients with a d=0.71 effect size of 80% power and an error level of 0.05, or a total of 92 sessions with at least 46 sessions for each group.[15]

The calculation was performed using the "GPower 3.1.9.2" software package.

Statistical Analysis

Descriptive statistics provided Mean, Standard Deviation, Median, and IQR values for continuous data and number and percentage values for discrete data. The Shapiro-Wilk test was utilized to assess whether the continuous data adheres to a normal distribution. For comparing continuous data, the Mann-Whitney U test was utilized. Chi-square and Fisher's exact tests were used to compare nominal variables between groups using cross tables. The statistical software IBM SPSS version 20 from Chicago, IL, USA, was used for analysis. A significance level of $p<0.05$ was considered.

RESULTS

The study included the evaluation of 352 sessions for 18 patients. The patients' mean age was 42.17±25.09 months, ranging from 21 to 108 months old. The patients' average body surface area (BSA) was 0.63±0.15 m². Out of the total number of patients, 38.9% (7 patients) were girls, while 61.1% (11 patients) were boys (Table 1, 2).

Table 1. Characteristics of the children

n=18	Mean±SD Median (Min-Max); IQR	
Age (months)	42.17±25.09 36 (21-108); (24-51)	
Height(cm)	98.83±17.77 97 (65-145); (90-105)	
Weight (kg)	15.07±5.35 15 (8-31); (11-17)	
BSA (m²)	0.63±0.15 0.60 (0.42-1.04); (0.53-0.69)	
	n	%
Gender		
Girl	7	38.9
Boy	11	61.1

SD: Standart Deviation, IQR: Interquartile Range, BSA: Body Surface Area

Table 2. Descriptive values of sessions received by patients

n=18	Mean±SD	Median (Min-Max); (IQR)
Total number of sessions	19.56±9.75	17.5 (6-32); (11-30)

SD: Standart Deviation, IQR: Interquartile Range

There was no significant difference in processing times between Group S and Group K during the sessions ($p>0.05$).

In the comparison of groups, it was found that discharge time for Group K was significantly longer during sessions ($p<0.001$). In comparing the two groups, the failure rate in Group K was significantly higher than in Group S ($p<0.001$).

During the sessions, there was no statistically significant difference between Group S and Group K in terms of acquiring an airway with assistance ($p>0.05$). During the sessions, it was observed that there was a significant difference in the Sedation scale between Group S and Group K. The Sedation scale of Group K was significantly higher than that of Group S ($p<0.001$). In the comparison between the two groups, Group K had a significantly higher rate of nausea and vomiting after sessions than Group S ($p<0.05$) (Table 3).

Table 3. Intergroup comparison of sessions

Number of sessions, n (%)	Group S 176 (50%)		Group K 176 (50%)		p value
	Mean±SD; median (IQR)		Mean±SD; median (IQR)		
Processing Time (min)	9.16±5.91; 6 (5-13)		8.51±5.17; 7 (5-12)		0.565[b]
Discharge Time (min)	6.23±1.93; 6 (5-7)		8.04±1.98; 8 (7-9)		<0.001[b]
	n	%	n	%	
Failure rate					<0.001[c]
0	173	98.3	144	81.8	
>0	3	1.7	32	18.2	
Acquiring an airway with assistance					0.138[c]
No	164	93.2	156	88.6	
Yes	12	6.8	20	11.4	
Sedation scale					<0.001[c]
2	171	97.2	84	47.7	
3	4	2.3	65	36.9	
4	1	0.6	27	15.3	
Nause and vomiting					0.030[c]
No	176	100	170	96.6	
Yes	0	0	6	3.4	

SD: Standart deviation, IQR: Interquartile range, b: Mann Whitney U test, c: Chi-square test/Fisher's Exact Test

DISCUSSION

Our study involved 352 sessions where 18 children were sedated using crossover sevoflurane and ketamine. Sevoflurane sedation resulted in significantly lower failure rates, discharge duration, and sedation scales during the procedure.

Şimşek et al.[16] demonstrated successful use of sevoflurane sedation for non-operating room anesthesia in 187 pediatric patients while maintaining hemodynamic stability.

Choopong et al.[17] reported a significantly higher success rate in MRI with sevoflurane insufflation compared to propofol infusion.

In their study, Briggs et al.[18] compared the adverse effects of sevoflurane sedation on neonates undergoing MRI imaging. Based on their findings, they concluded that sevoflurane is an excellent sedative for both neonates and infants because of its fast induction, effective maintenance, quick recovery, and low incidence of complications.

In a study conducted by Ogurlu et al.[19] the effectiveness of different concentrations of sevoflurane for sedation during MRI imaging was compared. The results showed that administering a 1% concentration of sevoflurane through a face mask while allowing children to breathe normally is a safe and effective method of providing anesthesia without any impact on their spontaneous breathing.

In a study conducted by Montes et al.[20] sedation with sevoflurane was found to have a significantly lower total time to awakening, discharge, and including induction and procedure when compared to propofol and midazolam+ketamine during endoscopy in children. The study also found that sevoflurane had a lower complication rate than midazolam-fentanyl-ketamine and propofol.

Gomes et al.[15] compared the side effects of adding inhaled sevoflurane to a mixture of oral midazolam and ketamine in young children's dental treatment. According to the research, children who were given sevoflurane exhibited reduced levels of crying and movement in comparison to those who were given oxygen. Moreover, the study found that there was no increase in the occurrence of adverse events with sevoflurane supplementation.

As mentioned above, various non-operating room applications have compared IV anesthetic drugs and sevoflurane. The study focuses on the impact of treatment failure on the interruption of the procedure. The comparison made in the study pertains to this specific aspect of the process. In this study, consistent with previous research, it was found that sevoflurane sedation resulted in a significantly lower failure rate compared to ketamine sedation. It was found that no significant differences in cardiac and respiratory complications, as well as nausea and vomiting, between the two groups of children. Children receiving sevoflurane experienced faster recovery and shorter discharge times than the other group.

This study has a strong point that both sedation methods were used in consecutive sessions of the same patients, ensuring that there were no demographic data differences between the two groups.

Limitations

Due to the small number of patients, our study was limited in its evaluation of patients with different cancer types and frailties. As a result, we did not analyze the factors that could affect the failure rate through multivariate analysis.

CONCLUSION

We found that using sevoflurane sedation resulted in a lower failure rate compared to IV sedation in children undergoing RT sessions outside of the operating room. Sevoflurane sedation can be safely used for sedation outside of the operating room, allowing for spontaneous respiration to continue. This method has been shown to be well-tolerated by children, even those who may have a lower rate of failure during RT sessions. Additionally, this sedation method does not result in adverse side effects and leads to shorter recovery and discharge times.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara City Hospital Clinical Researches Ethics Committee (Date: 02.07.2020 Decision No: E1-20-884).

Informed Consent: Written consent was obtained from the patient participating in this study.

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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Original Article

MEDICINE PALLIATIVE CARE

DOI: 10.47582/jompac.1360185

J Med Palliat Care. 2023;4(5):596-600

An evaluation of risk factors for overall complications after curative gastrectomy in gastric cancer patients aged 65 or over

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Cite this article as: Şenol S, Kuşak M, Sarı AC, Kara ME. An evaluation of risk factors for overall complications after curative gastrectomy in gastric cancer patients aged 65 or over. *J Med Palliat Care*. 2023;4(5):596-600.

Received: 24.08.2023 ◆ **Accepted**: 18.10.2023 ◆ **Published**: 27.10.2023

ABSTRACT

Aims: The purpose of this study was to identify risk factors for postoperative complications in patients with gastric cancer aged 65 or over.

Methods: Data from medical records in our database were reviewed and analyzed retrospectively. Two hundred twenty-nine patients with histologically confirmed gastric cancer underwent curative gastrectomy in our clinic between January 2017 and December 2021. Eighty-eight patients younger than 65 and 21 with previous histories of abdominal surgery, multi-visceral resection, emergency surgery due to perforation, bleeding, or obstruction, 18 with preoperative radiotherapy or chemotherapy were excluded. The remaining 102 patients, aged 65 years or over, were included in the study. Patient characteristics, intraoperative findings, and postoperative complications were evaluated.

Results: Postoperative complications with Clavien–Dindo grade ≥ II were observed in 29 patients (28.4%). Univariate analysis showed that the prognostic nutritional index (<45) (odds ratio 0.91; 95% confidence interval, 0.86-0.97; p = 0.004), controlling nutritional status score (≥5) (odds ratio 1.27; 95% confidence interval, 1.09-1.49; p = 0.002), and body mass index (BMI) (≥25 kg/m²) (odds ratio 1.97; 95% confidence interval, 1.00-1.26; p = 0.042) significantly predicted postoperative complications. Multivariate analysis showed that BMI (≥25 kg/m²) (odds ratio 1.18; 95% confidence interval, 1.03-1.34; p = 0.011) significantly predicted postoperative complications.

Conclusion: The overall postoperative complication risk among older individuals with gastric cancer who underwent curative gastrectomy was significantly higher among high-BMI patients. Perioperative management with a focus on BMI is important in older patients undergoing elective curative gastrectomy.

Keywords: Gastric cancer, older patients, postoperative complication, risk factor

INTRODUCTION

The number of individuals aged 65 years or older in Turkey has increased rapidly in recent years. In 2016, older individuals accounted for 8.3% of the Turkish population. Five years later, by 2021, this had increased by 24.0% to 9.7% of the population. Projections predicted that the elderly would represent 11.0% of the population by 2025.1 This increase reflects the aging of Turkish society. Due to the aging population, the numbers and mean ages of patients diagnosed with various cancers, including gastric cancer, have also risen.2 Older patients have a higher incidence of postoperative complications caused by decreased physiological function. Additionally, rates of underlying diseases are higher in this age group, meaning that complications tend to be more severe.2-4 Although some studies have described age as a significant predictive factor for postoperative morbidity after gastric cancer surgery, no significant predictive factor postoperative complications among older individuals has yet been identified.5-7 Due to the increasing rates of gastrectomy procedures among older gastric cancer patients, clinical factors capable of predicting postoperative complications are of significant interest in terms of making adjustments to the surgical strategy. This single-center, retrospective study is planned from that perspective. In the light of the previous literature, potential predictive factors were prioritized based on their simplicity, objectivity, and preoperative availability. Analysis was then performed to identify whether any of these factors were significantly correlated with overall complications after curative gastrectomy in patients aged 65 years or older.

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METHODS

The study was carried out with the permission of Samsun University Medical Faculty Clinical Researches Ethics Committee (Date: 21.10.2021, Decision No: GOKA/2021/21/10). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This study retrospectively reviewed and analyzed data from medical records stored in our database. Two hundred twenty-nine patients with histologically confirmed gastric cancer underwent curative gastrectomy in our clinic between January 2017 and December 2021. Eighty-eight patients younger than 65, and 21 with previous histories of gastric surgery, multi-visceral resection, emergency surgery due to perforation, bleeding, or obstruction, 18 with preoperative radiotherapy or chemotherapy were excluded. The remaining 102 patients aged 65 or over were included in the study.

The preoperative index involved age, sex, body mass index (BMI), American Society of Anesthesiologists (ASA) grade, comorbidities (diabetes mellitus, hypertension, chronic obstructive pulmonary disease, cerebral infarction, and ischemic heart disease) and laboratory data obtained from baseline investigation performed within one month prior to surgery (neutrophil count, lymphocyte count, serum albumin, and total cholesterol). Perioperative data were noted, including the extent of resection, combined resection, operative time, and surgical procedure. Postoperative characteristics included tumor depth, nodal satus, and short-term complications. Postoperative short-term complications were defined as morbidity and mortality occurring during hospitalization or within 30 days after surgery. The complications were classified using the Clavien-Dindo (CD) system.8 Patient staging was adjusted according to the 8th edition of the American Joint Cancer Committee staging system after pathological examination.9

Nutrition is a well defined risk factor for postoperative morbidity and mortality.10,11 Nutrition assessment tools incorporating inflammatory factors, such as the prognostic nutritional index (PNI) and controlling nutritional status (CONUT) score, and the neutrophil to lymphocyte ratio (NLR) as an inflammatory marker, have been developed to predict postoperative morbidity and mortality in various cancers after radical surgeries.12-15 NLR was calculated by dividing the neutrophil count by the lymphocyte count. NLR <2.5 was defined as low and NLR ≥ 2.5 as high.16 PNI was calculated using the equation (10 x serum albumin (g/ dL) + (0.005 x total lymphocyte count). PNI scores <45 were defined as low and scores ≥ 45 as high.17 The CONUT score was calculated using the method shown in **Table 1**. CONUT scores <5 were defined as low and scores ≥ 5 as high.18 One of the simplest indicators of physical constitution, body mass index (BMI) was calculated as body weight (kilograms) divided by height (meters) squared. Values higher than 18.5 kg/m² and lower than 25.0 kg/m² were regarded as normal BMI, and values below 18.5 kg/m² as low BMI.

Statistical Analysis

Univariate and multivariate logistic regression models were used to determine the factors associated with postoperative complications following gastrectomy. Variables with p values <0.05 identified at univariate analysis were fitted into the multivariate model and analyzed after adjusting for potential confounders using the forced-entry method. Statistical significance was set at p <0.05. All statistical analyses were performed on Statistical Package for the Social Sciences (SPSS) software (SPSS Inc., Chicago, IL, USA).

RESULTS

The median age of the study population was 72 years (range, 65 – 92), and 72.5% were male. More than 90% of patients exhibited ASA prognostic stage ≥2, and 86.2% had at least one comorbidity such as diabetes mellitus or hypertension that required treatment with medication. The median BMI was 25 kg/m² (range, 16-35). Sixty percent of the study population had BMIs exceeding 25 kg/m². The median PNI, CONUT scores and NLR were 41.2 (range, 15-60.5), 3 (range, 0-12), 4 (range, 1.2-22.6), respectively. In terms of surgical outcomes, distal and total gastrectomies were performed on 28.5% and 71.5% of patients, respectively, and laparoscopic surgery on 26.5%. The median operative time and intraoperative bleeding were 175 minute (range, 100-360 minute), 60 ml (range, 20-300 ml), respectively. Clavien-Dindo complications ≥Grade II complications were observed in 29 (28.4%) patients; Grade II in 18 (17.64%) patients, Grade IV in 3 (2.94%), Grade V in 8 (7.84%). Ileus occurred in two patients (1.96%), surgical site infection in eight (7.84%), atelectasis in six (5.88%), pneumonia in five (4.9%), acute myocardial infarction in five (4.9%), acute cerebrovascular event in two (1.86%), and pulmonary embolism in one (0.98%). Pathological stage I, II, III accounted for 9.8%, 16.6%, and 73.6% of patients, respectively. In terms of the correlation between clinical factors and the overall complications (**Table 2**), univariate analysis identified BMI (p=0.039), PNI (p=0.004), CONUT score (p=0.002) as significantly correlated with the occurrence of overall complications. Multivariate analysis including these factors revealed that BMI 25 kg/m² or higher was the only factor significantly correlated with the occurrence of overall complications (p=0.011).

Table 1. Scoring system for the controlling nutritional status (CONUT)

Degree of undernutrition	CONUT score	Serum albumin (g/dl)	Total lymphocyte(/mm3)	Total cholesterol (mg/dl)
Normal	0-1	≥3.50 (0)	≥1,600 (0)	≥180 (0)
Mild	2-4	3.00-3.49 (2)	1,200-1,599 (1)	140-179 (1)
Moderate	5-8	2.50-2.99 (4)	8.00-1,199 (2)	100-139 (2)
Severe	9-12	<2.5 (6)	<800 (3)	<100 (3)

CONUT score =Serum albumin score + total lymphocyte score + total cholesterol score

Table 2. Univariate and multivariate analyses to identify risk factors for the occurrence of overall complication

	Univariate analysis OR (95% CI)	p value	Multivariate analysis OR (95% CI)	p value
Sex (Female)	0.99 (0.37-2.59)	0.985		
Age	1.04 (0.98-1.11)	0.183		
BMI≥25 kg/m²	1.12 (1.00-1.26)	0.039	1.18 (1.03-1.34)	0.011
ASA-PS (≥2)	0.56 (0.09-3.65)	0.561		
DM	2.36 (0.92-6.05)	0.073		
HT	1.44 (0.54-3.86)	0.463		
IHD	2.14 (0.89-5.15)	0.087		
COPD	1.27 (0.22-7.38)	0.784		
CI	2.57 (0.15-42.53)	0.509		
NLR≥2.5	1.08 (0.99-1.19)	0.071		
PNI<45	0.91 (0.86-0.97)	0.004	0.96(0.84-1.09)	0.590
CONUT≥5	1.27 (1.09-1.49)	0.002	1.22(0.85-1.74)	0.264
Bleeding	0.99 (0.98-1.00)	0.095		
Operative time	1.00 (0.99-1.01)	0.371		
Surgical procedure	0.83 (0.32-2.14)	0.714		
Surgical approach	0.64 (0.23-1.81)	0.406		
Stage 2-3	1.66 (0.33-8.33)	0.537		

CI: confidence interval; OR: odds ratio; ASA-PS: American Society of Anesthesiologists Physical Status; BMI: body mass index; DM: diabetes mellitus; HT: hypertension; IHD: ischemic heart disease; COPD: chronic obstructive pulmonary disease; CI: cerebral infarction; PNI: prognostic nutritional index; CONUT: controlling nutritional status score, NLR: neutrophil to lymphocyte ratio

DISCUSSION

Life expectancy and average age are both steadily rising in Turkey. The increase in the average age is also accompanied by a higher prevalence of various types of cancers, one of those affecting the older population being gastric cancer. As the rate of gastrectomy procedures in older patients is rising, clinical factors capable of predicting postoperative complications are of particular interest in terms of making adjustments in surgical strategies for older patients.

High BMI emerged as a significant predictive factor for overall complications (28.4%) after gastrectomy in older gastric cancer patients in the present study. The greater overall morbidity among the overwieght and obese patients resulted primarily from the high incidence of wound infections, corresponding to almost 27.5% of the patients with complications. Despite the surgical complexity caused by excessive subcutaneous fat, patients with high BMI are more likely to exhibit insulin resistance and poor glycemic control, both of which have been confirmed as risk factors for slow wound recovery.19-21 The metabolic states of high BMI patients may also alter the volume of distribution and clearance of drugs, thus impairing the effectiveness of standard antibiotic agents, which may also contribute to the relationship between high BMI and wound infection.22 The high incidence of wound infections and overall complication rates have been confirmed by the majority of previous reports.23-25 Consistent with the results of the present research, various studies have also shown that obesity affects the occurrence of postoperative complications due to cardiac complications and pulmonary embolism, in addition to wound infections.26-30 Although no anastomotic leak was present in any of the patients in this study, previous authors have reported that massive abdominal adipose tissue may result in a thick mesenterium and increased anastomotic tension.31

Nutrition assessment tools that incorporate inflammatory factors, such as the PNI and CONUT scores, have been developed to predict the postoperative morbidity and mortality of various cancers following radical surgeries.12-14 PNI and CONUT scores are attractive tools since both are based on mathematical equations, can be measured from single blood collections, are judged objectively, and can be safely applied in the clinical setting. The PNI and the CONUT score have both been assessed as predictors of perioperative morbidity for gastric cancer.32-35 A higher overall incidence of clinically significant postoperative complications

has been observed in patients with low PNI and high CONUT scores. In the present study, although these were significantly correlated with the occurrence of overall complications at univariate analysis, neither was significantly correlated at multivariate analysis.

Limitations

This study has several limitations. In particular, it involved the experience of a single center, and the sample size was limited. The study was also non-randomized, and we only analyzed prioritized potential predictive factors, based on their simplicity, objectivity, and preoperative availability, for overall complications after curative gastrectomy in patients aged 65 or over.

CONCLUSION

The overall postoperative complication risk was significantly higher in patients with high BMI among older individuals with gastric cancer who underwent curative gastrectomy. Older patients with high BMI were more likely to experience wound infections, cardiac and vascular complications. Perioperative management with a focus on BMI is important in older patients undergoing elective curative gastrectomy.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Samsun University Medical Faculty Clinical Researches Ethics Committee (Date: 21.10.2021, Decision No: GOKA/2021/21/10).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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Original Article

MEDICINE PALLIATIVE CARE

DOI: 10.47582/jompac.1367036

J Med Palliat Care. 2023;4(5):601-606

Youtube as an information source on bipolar disorder: evaluation of the Turkish and English content

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Cite this article as: Altunsoy N. Youtube as an information source on bipolar disorder: evaluation of the Turkish and English content. *J Med Palliat Care*. 2023;4(5):601-606.

Received: 27.09.2023 ◆ **Accepted**: 23.10.2023 ◆ **Published**: 27.10.2023

ABSTRACT

Aims: Assess and compare the qualities and reliabilities of Turkish and English YouTube videos providing information about Bipolar Disorder and how beneficial they are for viewers in our study.

Methods: In our study, a total of 120 videos were evaluated, with 60 in Turkish and 60 in English, which appeared on the first three pages of search results. Videos that were entirely or partially quoted and repeated were not rated, but videos with an earlier publication date were included. A total of 80 videos were included in the study. Videos published in Turkish and English were watched and rated by a psychiatrist.

Results: Significant portion of the videos were uploaded by healthcare institutions (29.3%) or a professional (psychiatrist/psychologist) (28%). When all videos were evaluated, the median Modified DISCERN score was 3.48 (IQR: 1), the median GQS (Global Quality Scale) score was 3.67 (IQR: 1), the median total video content score was 4.00 (IQR: 2), and the median VPI (Video Power Index) score was 67.14 (IQR: 207).When comparing the scales used to assess the quality of videos, it was found that the VPI score ($p<0.001$) was significantly higher in English-language videos compared to Turkish-language videos, while the GQS score ($p=0.116$) and the modified DISCERN scale score ($p=0.594$) were similar

Conclusion: It was observed that the examined videos reached an average of 70,000 views, with the highest reaching approximately 13.5 million views. These data demonstrate the significant role of the internet and YouTube in providing access to health information for patients. In this study, it was determined that YouTube videos related to Bipolar Disorder have an average to good quality and reliability.

Keywords: Bipolar disorder, mental disorder, internet, YouTube, patient education

INTRODUCTION

Bipolar disorder is a chronic and incapacitating mental disorder that typically begins during adolescence or early adulthood. BD is distinguished by repetitive mood episodes that vary from severe depressive states to manic episodes.[1] Because of the diverse factors contributing to its origins, comprehensive findings from studies involving biology, neurochemistry, and neuroimaging have not yielded definitive evidence for a specific causative theory regarding bipolar disorder.[2] The lifetime prevalence rate is reported to be 2.4%, while the annual incidence rate is 1.4%.[3] There is an extensive literature on Bipolar Disorder. However, it is not known to what extent these data are included in the continuously growing internet sources. Access to high-quality, reliable information on the epidemiology, etiology, symptoms, and treatment of the disease on the internet can be beneficial for individuals with Bipolar Disorder, both in understanding their condition and complying with their treatment processes.

It has been announced that 4.95 billion people worldwide use the internet, and YouTube is the most common video viewing platform globally.[4] While the primary purpose of YouTube is to watch entertaining videos, it is now also seen as a valuable educational resource. It is increasingly observed that YouTube is being used as a source of health-related information.[5,6] In the coming years, it is predicted that YouTube will be widely used for the flow of health information among healthcare professionals and patients, the development of supportive communication among patients, and the enhancement of public health surveillance.[7] Health information videos on YouTube are obtained from various sources, including doctors, healthcare institutions, universities, medical faculties, patients, and advertisers. However, regardless of the source of the content, YouTube's terms of service state that "the content is the responsibility of the person or organization providing the service".[8] In other words, there is no mechanism on YouTube that monitors the quality and accuracy of video content.

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YouTube's search results are based more on popularity, relevance, and viewing history rather than content quality. This leads to unverified and partially misleading content, particularly causing issues in the field of healthcare.[9] When considering the literature, it can be observed that many studies have addressed the issue of content quality in health-related videos on YouTube.[10-12] While there are studies on the role of YouTube videos in disseminating psychoeducation for conditions such as dementia, schizophrenia, and narcolepsy, there is still an insufficient number of studies regarding the quality of videos related to bipolar disorder.[13-16] The scarcity of studies evaluating the quality of YouTube videos containing information related to Bipolar Disorder in the literature, as well as the absence of such studies in Turkey, led us to aim to assess and compare the qualities of Turkish and English YouTube videos providing information about Bipolar Disorder and how beneficial they are for viewers in our study.

METHODS

In accordance with the aim of the study, the search history was cleared on August 15, 2023, and the search field of the YouTube page was used to search for Turkish videos with "Bipolar Bozukluk" and "Bipolar Bozukluk Tedavi", and for English videos with "Bipolar Disorder" and "Bipolar Disorder Treatment." Research on internet search engines indicates that a significant portion of users rates the top three pages as search results.[17] Therefore, in our study, a total of 120 videos were evaluated, with 60 in Turkish and 60 in English, which appeared on the first three pages of search results. Videos that were entirely or partially quoted and repeated were not rated, but videos with an earlier publication date were included. A total of 80 videos were included in the study. Videos published in Turkish and English were watched and rated by a psychiatrist who was proficient enough to evaluate English videos. In our study preliminary assessments were made in several videos (%10 of all videos) with two assesors, and since there was a high intraclass correlation (r=0.96), we chose a single assessor for our study.

The upload date, duration, number of views, likes, and dislikes, as well as the video uploader (1. Psychiatrist/ Psychologist, 2. Hospital, 3. Patient, 4. Educational channel, 5. Association, 6. News channel), and the number of comments were recorded. The like rate (Likes x 100 / (Likes + Dislikes)), view rate ((Views / Days)), and, consequently, the Video Power Index (VPI) value ((Like rate x View rate) / 100) were calculated.[18] The quality of the video was evaluated using the modified DISCERN scale and the Global Quality Scale (GQS). In the video's content, the presence of certain important subheadings and features which were previously explored in a research about bipolar disorder and youtube (1. Impact of the disease on daily life, 2. Symptoms of the disease, 3. Personal history, 4. Bipolar disorder type 1-2 differentiation, 5. Treatment and outcomes, 6. Discussion on prognosis, 7. Animation, 8. Graphics, 9. Pathomechanism of the disease, 10. Doctor as a speaker, 11. Patient experience) was individually assessed, and content density was measured.[16]

DISCERN Scale's aim is to assist individuals and information producers in evaluating the quality of written information regarding treatment options for any health issue. Discern instrument is a measure of the reliability of health-related information presented. Although it does not require professional knowledge, being a professional does not disadvantage the use of the scale. It has become nearly a gold standard in measuring the reliability of health-related publications-videos in studies conducted worldwide. Therefore, this scale has been chosen for this study. A modified DISCERN scale consisting of five questions is used to assess visual media and information.[17] All videos were evaluated using the modified DISCERN scale in terms of the reliability and completeness of the information contained in the content (**Table 1**).[19] The reliability of the information contained in the video was rated on a scale of 1 to 5. The Global Quality Scale (GQS) is used to assess the quality of the videos, with scores ranging from 1 to 5. Scores of 1 to 2 indicate low quality, 3 indicates average quality, and scores of 4 to 5 indicate high video quality (**Table 2**).[17,19]

Table 1. The modified DISCERN score (1 point for every yes, 0 points for no)

Item	Questions
1	Are the aims clear and achieved?
2	Are reliable sources of information used? (i.e., publication cited, speaker is a specialist)
3	Is the information presented both balanced and unbiased?
4	Are additional sources of information listed for patient reference?
5	Are areas of uncertainity mentioned?

Table 2. Global quality scale

Score	Global Score Description
1	Poor quality, poor flow of the site, most information missing, not at all useful for patients
2	Generally poor quality and poor flow, some information listed but many important topics missing, of very limited use to patients
3	Moderate quality, suboptimal flow, some important information is adequately discussed but others poorly discussed, somewhat useful for patients
4	Good quality and generally good flow, most of the relevant information is listed, but some topics not covered, useful for patients
5	Excellent quality and excellent flow, very useful for patients

Since the study did not use human or animal data and utilized publicly available videos on YouTube, as in other similar studies, an ethics committee application was not made.[20-22]

Statistical Analysis

The SPSS 17.0 software package was used for data analysis. Kolmogorov Smirnov test was used to check the compliance of variables to normal distribution. All variables were non-normally distributed as a result of this, continuous variables were expressed as median (interquartile range(IQR)), while categorical variables were presented as numbers and percentages. To assess the significance of the difference between group means for continuous variables, the Mann-Whitney U test was used for non-normally distributed groups. Values with a p-value below 0.05 were considered statistically significant.

RESULTS

Video Content

Looking at the distribution of video content subheadings, almost all videos included the impact of the disease on daily life (93.3%) and the symptoms of the disease (96%). Videos featuring a psychiatrist/psychologist as the speaker were present in 58.7% of the videos, while treatment and treatment outcome videos were found in 41.3% of them. Differentiating between Bipolar Disorder type 1 and 2 was covered in 34.7% of the videos, discussions on prognosis in 29.3%, personal stories from patients and their families in 28%, patient experience in 26.7%, the pathomechanism of the disease in 18.7%, animation in 18.7%, and graphics in 9.3% of the videos.

Video Uploading Source

The distribution of video sources was as follows: a significant portion of the videos were uploaded by healthcare institutions (29.3%) or a professional (psychiatrist/psychologist) (28%). 16% of the videos were from educational channels, 12% from news channels, 12% from associations related to bipolar disorder, and 2.7% were uploaded by patients. It was observed that the majority of Turkish-language videos (70%) and a relatively smaller portion of English-language videos (42.9%) were uploaded by healthcare institutions and professionals.

Video Statistics

Looking at the general characteristics of the videos, the average number of days since their publication was 1414 days (IQR: 1017), the median duration of videos in seconds was 310 (IQR: 466), the median number of views was 72,846 (IQR: 278,821), the median number of likes was 645 (IQR: 1002), the median number of comments was 53 (IQR: 417), the like rate was 97.3 (IQR: 3.45), and the view rate had a median of 64.89 (IQR: 201).

The average number of days since publication (p=0.464) and the average video duration (p=0.260) were similar for videos published in Turkish and English. However, the number of views (p<0.001), the number of comments (p=0.032), view rates (p<0.001), and like rates (p<0.001) of videos published in Turkish were statistically significantly lower compared to English videos (**Table 3**).

Looking at the number of views, it was determined that videos featuring healthcare professionals (median (+): 108178, median (-): 58514 p=0.035), animations (median (+): 102884, median (-): 63236 p=0.045), and patient/patient relative experiences (median (+): 112320, median (-): 59653 p=0.030) were more widely viewed.

Video Quality Assessment

When all videos were evaluated, the median Modified DISCERN score was 3.48 (IQR: 1), the median GQS (Global Quality Scale) score was 3.67 (IQR: 1), the median total video content score was 4.00 (IQR: 2), and the median VPI (Video Power Index) score was 67.14 (IQR: 207).

When comparing the scales used to assess the quality of videos, it was found that the VPI score (p<0.001) was significantly higher in English-language videos compared to Turkish-language videos, while the GQS score (p=0.116) and the modified DISCERN scale score (p=0.594) were similar (**Table 3**).

Table 3. Comparison of videos that were published as Turkish and English

	English	Turkish	p
Time (second)	357 (IQR:511)	209.5 (IQR:483)	0.260
Days since published	1161(IQR:1505)	1388.5 (IQR:1657)	0.464
Views	273240 (IQR:593713)	45069 (IQR:95802)	<0.001
Likes	2300 (IQR:17647)	405(IQR:1353)	<0.001
Comments	225 (IQR:1751)	42 (IQR:246)	0.032
Like ratio	98.58 (IQR:2.45)	95.98 (IQR:3.62)	0.562
View ratio	131.28 (IQR:970)	32.09 (IQR:61.22)	<0.001
VPI	164.72 (IQR:965)	33.31 (IQR:60.5)	<0.001
GQS	4 (IQR:1)	3.5 (IQR:1)	0.116
Modified discern	4(IQR:1)	3(IQR:1)	0.594
Total video content	4 (IQR:2)	4 (IQR:2)	0.054

*Mann Whitney U test

Regarding the content of the videos, a significant difference was observed in that approximately 70% of Turkish-language videos had at least one professional (psychiatrist/psychologist) speaker, while this percentage was limited to 40% in English-language videos (p=0.002).

In terms of content, it was found that animation was used more frequently in English-language videos (English: 28.6%, Turkish: 10%, p=0.039). There was no significant difference between English and Turkish-language videos in terms of the presence of other content subheadings such as the impact of the disease on daily life (English: 100%, Turkish: 87.5%, p=0.057), symptoms of the disease (English: 100%, Turkish: 92.5%, p=0.098), personal stories (English: 37.1%, Turkish: 20%, p=0.099), differentiation between Bipolar Disorder type 1 and 2 (English: 42.9%, Turkish: 27.5%, p=0.163), treatment and outcomes (English: 45.7%, Turkish: 37.5%, p=0.471), prognosis discussion (English: 25.7%, Turkish: 32.5%, p=0.520), diagrams (English: 8.6%, Turkish: 10%, p=0.039), pathomechanism of the disease (English: 25.7%, Turkish: 12.5%, p=0.039), and patient experience. (English: 37.1%, Turkish: 17.5%, p=0.039).

Video Quality Correlation

In the conducted correlation analysis, a high level of significant relationship was found between the Modified DISCERN and GQS (Global Quality Scale) data (r=0.775, p<0.001). There was also a significant moderate-level relationship between the total video content average (indicating how many of the 11 content subheadings were included) and GQS (r=0.595) as well as Modified DISCERN (r=0.447). No significant relationship was found between VPI (Video Power Index) and the three quality scales. In the correlation analysis, video duration was found to have a significant relationship with Modified DISCERN (r=0.313), GQS (r=0.310) and total video content (r=0.295) (Table 4).

Table 4. Video quality correlation

	Modified discern	GQS	Duration	Total video Content	VPI
Modified discern	1	r=0.775 p<0.001	r=0.313 p=0.006	r=0.447 p<0.001	r=0.097 p=0.408
GQS	r=0.775 p<0.001	1	r=0.308 p=0.007	r=0.595 P<0.001	r=0.212 p=0.068
Duration	r=0.313 p=0.006	r=0.308 p=0.007	1	r=0.295 p=0.010	r=0.076 p=0.517
Total video content	r=0.447 p<0.001	r=0.595 P<0.001	r=0.295 p=0.010	1	r=0.215 p=0.063
VPI	r=0.097 p=0.408	r=0.212 p=0.068	r=0.076 p=0.517	r=0.215 p=0.063	1

GQS: Global quality scale; VPI: Video power index

In the analysis of video content, it was observed that some content items were associated with video quality criteria. When comparing videos with and without patient experience criteria, videos with patient experience had a significantly lower median Modified DISCERN score (Median(-)=4.00, Median(+)=3.00, p=0.008).

When examining the criterion of having a professional speaker in the video content, videos with professional speakers had significantly higher median GQS (Global Quality Scale) scores (Median0: 3.00, Median1: 4.00, p=0.037) and median Modified DISCERN scores (Median(-): 3.00, Median(+): 4.00, p<0.001).

In the comparison of videos based on the criterion of explaining the pathomechanism in the video content, videos with an explanation of the pathomechanism had significantly higher VPI (Video Power Index) scores (Median (-): 47.42, Median (+): 122.66, p=0.017), view rates (Median (-): 45.36, Median (+): 122.66, p=0.011), total video content scores (Median (-): 4.00, Median (+): 7.00, p<0.001), GQS scores (Median (-): 3.00, Median (+): 4.50, p=0.001), Modified DISCERN scores (Median (-): 3.00, Median (+): 4.00, p=0.009), and median likes (Median (-): 545, Median (+): 2600, p=0.038).

Videos that met the criterion of discussing treatment and outcomes in the video content had significantly higher median VPI (Video Power Index) scores (Median(-): 43.98, Median(+): 104.90, p=0.042), view rates (Median(-): 43.98, Median(+): 95.76, p=0.049), total video content scores (Median(-): 4, Median(+): 6, p<0.001), GQS (Global Quality Scale) scores (Median(-): 3, Median(+): 4, p<0.001), Modified DISCERN scores (Median(-): 3.00, Median(+): 4.00, p=0.004), and median video duration (Median(-): 223.5, Median(+): 414, p=0.12).

In videos where there was a discussion about prognosis in the video content, total video content scores (Median(-): 4, Median(+): 6.50, p<0.001), GQS scores (Median(-): 4.00, Median(+): 4.00, p=0.007), and Modified DISCERN scores (Median(-): 3.00, Median(+): 4.00, p=0.011) were significantly higher.

DISCUSSION

To our knowledge our study is the first publication to investigate the quality and reliability of YouTube videos related to Bipolar Disorder in Turkey. It was observed that the examined videos reached an average of 70,000 views, with the highest reaching approximately 13.5 million views. These data demonstrate the significant role of the internet and YouTube in providing access to health information for patients. In this study, it was determined that YouTube videos related to Bipolar Disorder have an average to good quality and reliability. When we look at the literature, a recent study conducted in Poland examined only English-language videos related to bipolar disorder, and the quality assessment using the DISCERN scale (median 4.1) concluded it as good.[16]

Our study demonstrates that many of the YouTube videos about Bipolar Disorder are published by healthcare institutions and professionals, and it is believed that the high quality results are related to this fact. It was found that there was no significant difference in terms of content richness and quality scores between Turkish and English videos. Although English videos had higher view rates, like rates, and VPI due to their appeal to a much larger audience, the frequent participation of professionals as speakers in Turkish videos may have played a role in achieving similar video quality.

Our study showed that videos added by healthcare professionals were of higher quality (as determined by the Discern and GQS scales) compared to videos added by independent users. This highlights the importance of the source of medical information in YouTube videos.[23] However, in our study, it was also found that the VPI value calculated based on view and like rates did not parallel the quality scales. In previous research, it has been found that non-profit organizations and academic sources have the highest ratings for informative content, which is consistent with our findings. However, these videos accounted for only 12.7% of the total, with a 13.4% share of the total viewership. It is also observed that misleading or insufficient information videos, similar to those described as useful, can receive high likes.[17] There are also studies that show that a significant portion of those who watch health-related videos on the internet are not interested in the source of the video.[24]

In our study, we found that the YouTube videos we evaluated covered a wide range of topics related to Bipolar Disorder, including its symptoms, its impact on daily life, the distinction between Bipolar Disorder 1 and 2, treatment and outcomes, prognosis, the pathomechanism of the disease, the patient's quality of life, and family support. Additionally, the videos also discussed features such as disease risk factors and protective factors. In terms of content, it was shown that videos providing information on pathomechanism, prognosis, treatment, and outcomes had higher quality scores. When we look at the view numbers, it was determined that videos featuring healthcare professionals, animations, and patient/patient relative experiences were more widely viewed. In our study, videos that shared personal experiences had high view rates, but their content quality was found to be low. Studies in the literature also mention that videos where patients and their families share their experiences are preferred, so it is argued that healthcare professionals should prepare health information videos in a way that conveys these experiences.[16,25,26] Therefore, public and academic institutions that provide healthcare services need to provide more guidance and oversight on the content and quality of YouTube videos.[11]

This study has limitations. The search outcomes may vary depending on the researcher's geographical location, and they can also fluctuate based on the timing of the search due to the constant and substantial influx of new video uploads. One may argue that one assessor is not enough for evaluation. Many publications have been conducted with a single assessor on YouTube, and they have also worked on health-related projects, including mental health among them.[27-31] In a systematic review about the reliability of youtube as a health-related information source, it was shown that even most of the videos had two assessors, an important portion of the videos had a single assessor.[32] In order to avoid any bias we have conducted preliminary assessments for several videos with two assessors, as there was a high intraclass correlation, we have chosen a single assessor for our study.

Given that this paper constitutes a cross-sectional assessment, we suggest its repetition in the coming years to track changes in the quality of video content.

CONCLUSION

YouTube serves as a moderate to good source of basic information for informing patients about Bipolar Disorder. YouTube's unregulated structure implies that videos may not meet a higher standard for conveying medical information. Therefore, healthcare professionals should strive to provide reliable online information. Informative videos about Bipolar Disorder that are publicly available in Turkish on the internet should be of high quality, meet the expectations of the target audience, contain accurate and precise information, and be prepared by expert physicians as well as academic institutions to meet the expectations of the community, especially by including the experiences of patients and their families, and the use of animation could be more beneficial.

ETHICAL DECLARATIONS

Ethics Committee Approval: Since the study did not use human or animal data and utilized publicly available videos on YouTube, as in other similar studies, an ethics committee application was not made.

Informed Consent: Not required for this study.

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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