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Risk analysis for acute oroantral communication: a retrospective study

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ABSTRACT

Aims: The purpose of this study was to evaluate the relationship to type of sinus pneumatization with the relationship between extracted tooth and maxillary sinus in patients who developed oroantral communication (OAC).

Methods: The patients who developed OAC after maxillary extraction and underwent OAC treatment were included in the study. The predictor variable was the type of maxillary sinus pneumatization (MSP). The primary outcome was relationship between extracted tooth and maxillary sinus. The covariates were age and sex. A Kruskal-Wallis and Pearson chi-square tests were used for the statistically analysis.

Results: The study completed with 429 patients who met inclusion criteria. There was a statistically significant difference in the mean age between the relationship type between the extracted teeth and the maxillary sinus groups in this study ($p<0.001$). The highest mean age was found in type 2 (43.17±13.99), and the lowest was found in type 4 (36.26±12.79). In this study, type C MSP had the highest rate. In 46.03% of them, 1/3 of the roots of the extracted tooth were in the maxillary sinus. After type C, the highest rate was type E. More than half of the roots of 56.96% of them was in the maxillary sinus. There was a statistically significant relationship to MSP with type of relation between the extracted teeth and maxillary sinus ($p<0.001$).

Conclusion: The risk of developing OAC during the extraction of molar increases in young patients where the maxillary sinus dropped in the entire posterior or its borders cannot be distinguished.

Keywords: Oroantral communication, oroantral fistula, maxillary sinus, molar teeth

INTRODUCTION

Maxillary posterior tooth extraction is one of the most common procedures in dentistry practice. Sometimes it can cause an oroantral communications (OAC). OAC is relationship between the oral cavity and the maxillary sinus which is unnatural. If OAC were not treated can act as a pathway for bacteria to enter the maxillary sinus, causing infections, sinusitis, or and oroantral fistula. Thus, evaluation of risk factors is important to avoid occurrence OAC. The risk factors associated with OAC was analyzed in a few studies in past. The distance between the impacted upper third molar to maxillary sinus floor (MSF) was associated the risk of OAC occurrence.[1,2] Iwata et al.[3] evaluated the role of computed tomography scan predicting development of OAC. Archer et al.[4] classified the location of the impacted upper third molar. However, the usage of this classification for determining risk of OAC occurrence is controversial. Because this was mainly based on its spatial relationship with the second molar. Hasegawa et al.[5] evaluated the risk factors associated with OAC during extraction of impacted upper third molar. The focus of the past studies has generally been the impacted third molar. But the extraction of first and second molar are most frequent in daily practice. There are limited studies evaluating the relationship between MSF and posterior maxillary tooth. Explaining the relationships between MSF and maxillary molar roots is critical in preventing complications.[6] In this study, it was aimed to evaluate the relationship between the root of the extracted tooth and different type of maxillary sinus pneumatization (MSP) in patients who developed OAC during the extraction of maxillary posterior teeth.

METHODS

The study was designed as a retrospective cohort study on patients who applied to department of oral and maxillofacial surgery between 2012 and 2023 due to maxillary canine, premolar, and molar tooth extraction. The Clinical Researches Ethics Committee of Erciyes University Faculty of Medicine (Date: 29.03.2023, Decision No: 2023-204) approved the study. This study was conducted in accordance with the 2008 Declaration of Helsinki. The patients who developed OAC after maxillary premolar and molar extraction had pre-operative panoramic radiographs and underwent OAC relationship therapy were included in the study. Patients with congenital

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syndrome and incomplete records who had previously been operated on because of a tumor or trauma were excluded from the study.

Study Variables

The primary predictor variable was the type of MSP. Root Sinus classification of Hasegawa et al.[5] was modified to classify MSP. The primary outcome was relationship between extracted tooth and maxillary sinus. The covariates were age, sex and extracted teeth.

Radiographic Evaluation

All panoramic radiographs were taken with the same device (OP200 D; Instrumentation Dental, Tuusula, Finland; 66-85 kVp, 10-16 mA, 14.1-s exposure time) as the Frankfort horizontal plane was adjusted parallel to the floor and the sagittal plane for standardization. All evaluations were carried out by the same investigator. Type of MSP was classified on the preoperative panoramic radiograph as below:

Type A: Maxillary sinus without dropping (Figure 1a).

Type B: The maxillary sinus dropped only in extracted teeth area (Figure 1b).

Type C: The maxillary sinus dropped in posterior maxillary area (Figure 1c).

Type D: MSF follows the roots (Figure 1d).

Type E: The maxillary sinus drops over the roots, but its borders are not clear (Figure 1e).

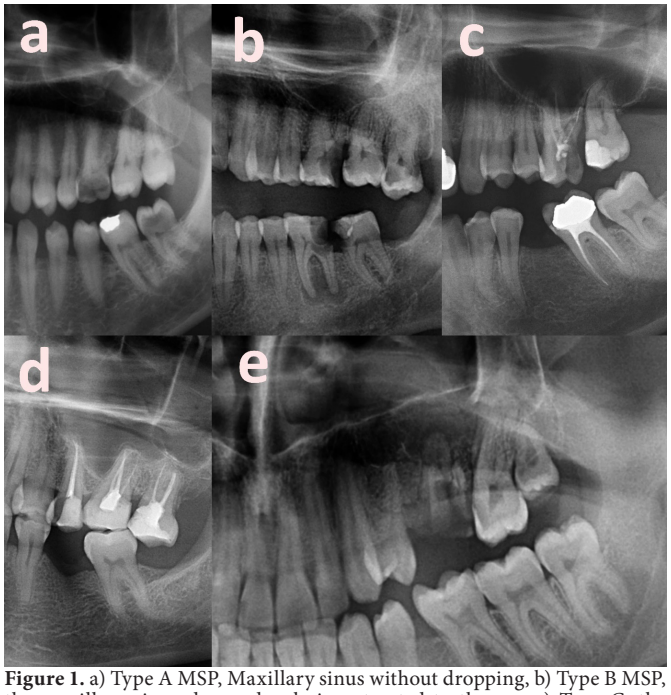

Figure 1. a) Type A MSP, Maxillary sinus without dropping, b) Type B MSP, the maxillary sinus dropped only in extracted teeth area, c) Type C, the maxillary sinus dropped in posterior maxillary area, d) Type D MSP, MSF follows the roots, e) Type E MSP, the maxillary sinus drops over the roots, but its borders are not clear

The relationship the roots of the extracted tooth with the maxillary sinus was evaluated as below:

Type 1: No contact between MSF and root of extracted tooth (Figure 2a).

Type 2: The apex of the root was in contact with the MSF (Figure 2b).

Type 3: 1/3 of the root inside of the maxillary sinus (Figure 2c).

Type 4: More than half of the root inside of the maxillary sinus (Figure 2d).

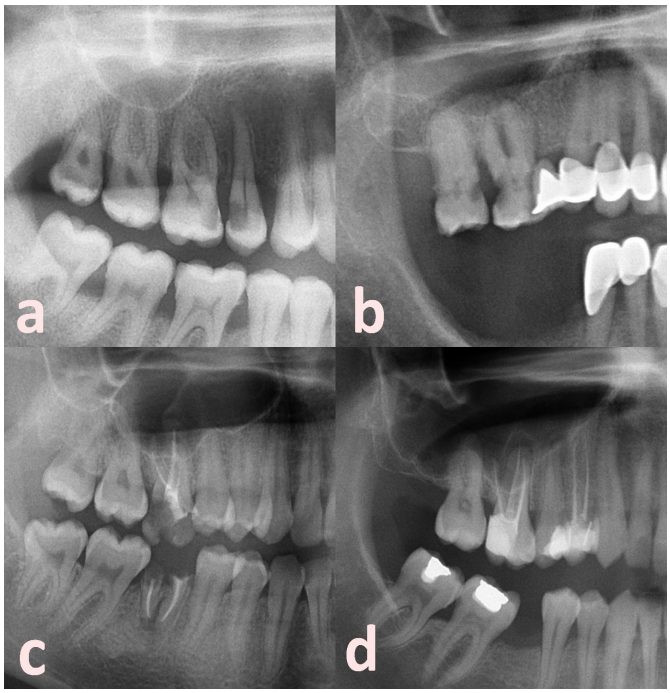

Figure 2. a) Type 1, No contact between MSF and root of extracted tooth, b) Type 2, The apex of the root was in contact with the MSF, c) Type 3, 1/3 of the root inside of the maxillary sinus, d) Type 4, More than half of the root inside of the maxillary sinus

Data Collection Method

Demographic data and the information about extracted teeth of the patients were obtained from the surgical records. The information of MSP and the relationship roots of extracted tooth to the maxillary sinus were obtained from preoperative panoramic radiographic evaluations. All data was upload excel file and the data set was created.

Statistical Analysis

Histograms, Q-Q plots, and the Shapiro-Wilk test were used to evaluate distribution of data. Descriptive statistics were calculated for each variable. The Levene's test was used homogeneity of variance. One-way ANOVA and Kruskal-Wallis tests were used for quantitative variables in more than two groups. The Pearson chi-square test was used to compare categorical data. All data analysis were done using Turcosa (Turcosa Ltd. Co., Turkiye) statistical software. Differences were considered significant at $p<0.05$.

RESULTS

The records of 469 patients treated for closure of OAC were scanned through the hospital registry software. Forty patients were excluded the study due to incomplete records. The study completed with 429 patients. Descriptive data was shown in

Table 1. 182 were female and 247 were male. The mean age of 39.90±13.90 years. Of the extracted teeth, 209 (48.72%) were first molars, 116 (27.04%) were second molars, 74(17.25%) were third molars, and 30(6.99%) were second premolars. The maxillary sinus was drooping in the entire posterior region in 252 (58.74%) patients. In 79 (18.41%) patients, the cortical margin of the maxillary sinus could not be clearly distinguished. In 58 (13.52%) patients, the sinus was drooping only in the extracted tooth area. There was no drooping of the maxillary sinus in 25(5.83) patients. In 15 (3.50%) patients, MSF line followed roots. In 167 (38.93%) patients, 1/3 of the roots of the extracted tooth were associated with the maxillary sinus. In 149 (34.73%) patients, more than half of the roots were inside the maxillary sinus. In 105(24.48%) patients, the roots of the extracted tooth were in contact with the cortical of MSF. In 8 (1.86%) patients, the roots of the extracted tooth were not related to the MSF. Descriptive data was shown in Table 1.

Table 1. Descriptive Data of demographic variables

Variable	Total (n=429)
Age (years)	39.90±13.90
Sex	
Female	182 (42.42)
Male	247 (57.58)
Extracted teeth	
2nd premolar	30 (6.99)
1st molar	209 (48.72)
2nd molar	116 (27.04)
3rd molar	74 (17.25)
Type of sinus pneumatization	
Type A	25 (5.83)
Type B	58 (13.52)
Type C	252 (58.74)
Type D	15 (3.50)
Type E	79 (18.41)
Relationship between extracted tooth and maxillary sinus	
Type 1	8 (1.86)
Type 2	105 (24.48)
Type 3	167 (38.93)
Type 4	149 (34.73)

Data are expressed as n (%), Key: Type A: Maxillary sinus without dropping, Type B: The maxillary sinus dropped only in extracted teeth area, Type C: The maxillary sinus dropped in posterior maxillary area, Type D: The line of maxillary sinus floor follows the roots, Type E: The maxillary sinus drops over the roots, but its borders are not clear, Type 1: No contact between root and maxillary sinus floor, Type 2: The apex of the root was in contact with the cortical border of the maxillary sinus, Type 3: 1/3 of the root exceeds the maxillary sinus cortical border, Type 4: More than half of the root inside of the maxillary sinus

Table 2 shows the distribution of age, sex, and extracted teeth in the sinus pneumatization groups. The mean age was 40.6±12.09 years in in the type A MSP group, 44.28±12.04 years in the type B MSP, 39.82±13.91 years in the type C MSP, 34.8±12.23 years in the type D MSP, 37.70±15.37 years in the type E MSP. There was a statistically significant difference between type B and type A in terms of age (p=0.008). Gender distribution was statistically similar between the groups (p=0.093). In all types of MSP, OAC developed mostly due to extraction of 1st molar. This was mostly followed by 2nd and 3rd molar. The highest rate of OAC due to extraction of second premolar (9.13%) was observed in type C, the highest rate of OAC due to extraction of second molar (43%) was observed in type B, and the rate of OAC due to extraction of third molar (24%) was most observed in type A. There was a statistically significant relationship between MSP groups in terms of extracted tooth (p<0.001). This difference is between type B-type C and type C-type E. This difference is due to the high 2nd molar ratio and low 2nd premolar ratio in type B and type C. In addition, the 1st molar ratio in type C is 45.24% while type E is 64.55%.

Table 3 shows the relationship between covariates and the primary outcome variable. The mean age was 49.88±19.45 years in the type 1 group, 43.17±13.99 years in the type 2 group, 40.62±13.82 years in the type 3 group, 36.26±12.79 years in the type 4 group. There was a statistically significant difference between type 4 and other groups in terms of age (p<0.001). The gender distribution was not statistically significant different between the groups(p=0.831). More than half of the roots of 41.63% of the first molars were in the maxillary sinus, and 1/3 of the roots of 39.23% were in the maxillary sinus. 17.22% were at the cortical border of the sinus, and 1.92% were not related to the sinus. While the roots of 38.79% of the second molars were in contact with the floor of the maxillary sinus, more than half of the roots of 30.17% and 1/3 of the roots of 29.31% were in the maxillary sinus. 1/3 of the roots of 51.35% of the third molars were in the maxillary sinus, more than half of the roots of 25.68% were in the maxillary sinus, and 22.97% were in contact with the floor of the maxillary sinus. There was a statistically significant relationship with extracted tooth and relationship between extracted teeth and maxillary sinus (p<0.001).

The relationship between the predictor variable (sinus pneumatization type) and primary outcome (type of relationship between extracted teeth and maxillary sinus) was given in Table 4. When the maxillary sinus was drooping in the entire posterior region (type C), 1/3 of the roots were inside the maxillary sinus (type 3) in 46.03% of the extracted teeth. In 37.70%, more than half of the roots were inside the maxillary sinus (type 4) and in 16.27% the roots were in contact with the maxillary sinus cortical (type 2). When the maxillary sinus was drooping only in the extracted tooth region (type B), 46.55% of the extracted teeth were in contact with the cortical of the maxillary sinus (type 2), 1/3 of the roots of 39.66% were within the maxillary sinus (type 3), and more than half of the roots of 12.1% were inside the maxillary sinus (type 4). If the maxillary sinus was drooping and its borders could not be clearly distinguished (type E), more than half of the roots of 56.96% of the extracted teeth were inside the maxillary sinus (type 4), 1/3 of the roots of 26.58% were inside the maxillary sinus (type 3), and 12.66% of the roots were in the cortical of the maxillary sinus (type 2). If the line of sinus followed the roots (type D), 86.67% of the extracted teeth were in contact with the cortical of the maxillary sinus (type 2), and 1/3 of the roots were inside the maxillary sinus in 13.33% (type 3). If the maxillary sinus is not prolapsed (type A), 56% of the extracted teeth are in contact with the cortical

Table 2. Comparison of demographic variable and extracted teeth between the sinus pneumatization groups

Variable	Type of maxillary sinus pneumatization					p
	Type A (n=25)	Type B (n=58)	Type C (n=252)	Type D (n=15)	Type E (n=79)	
Age (years)	40.6±12.09[ab] 40 (32-46)	44.28±12.04[a] 44 (36.75-53)	39.82±13.91[ab] 38 (29-49.75)	34.8±12.23[ab] 36 (25-41)	37.70±15.37[b] 35 (25-48)	0.008[ŋ]
Sex						
Female	16 (8.79)	29 (15.93)	103 (56.59)	6 (3.30)	28 (15.38)	0.093[†]
Male	9 (3.64)	29 (11.74)	149 (60.32)	9 (3.64)	51 (20.65)	
Extracted teeth						
2nd premolar	2 (8)[ac]	2 (3.45)[ab]	23 (9.13)[c]	2 (13.34)[abc]	1 (1.27)[ab]	<0.001[†]
1st molar	11 (44)	28 (48.28)	114 (45.24)	5 (33.33)	51 (64.55)	
2nd molar	6 (24)	25 (43.10)	61 (24.21)	5 (33.33)	19(24.05)	
3rd molar	6 (24)	3 (5.18)	54 (21.43)	3 (20)	8(10.13)	

Different superscript letters in the same row indicate significant differences between groups. Data are expressed as mean ± standard deviation, n (%), and median (first-third quartile). Key: Type A: Maxillary sinus without dropping, Type B: The maxillary sinus dropped only in extracted teeth area, Type C: The maxillary sinus dropped in posterior maxillary area, Type D: The line of maxillary sinus floor follows the roots, Type E: The maxillary sinus drops over the roots, but its borders are not clear, ŋ: Kruskal-Wallis test, †: Fisher exact test

Table 3. Relationship between covariates and primary outcome variable

Variable	Relationship between tooth and maxillary sinus				p
	Type 1 (n=8)	Type 2 (n=105)	Type 3 (n=167)	Type 4 (n=149)	
Age (years)	49.88±19.45[a] 43.5 (38.75-67.5)	43.17±13.99[a] 42 (34.5-51)	40.62±13.82[a] 39 (30-50)	36.26±12.79[b] 33 (25.5-44)	<0.001[ŋ]
Sex					
Female	4 (2.20)	46 (25.27)	73 (40.11)	59 (32.42)	0.831[†]
Male	4 (1.62)	59 (23.89)	94 (38.06)	90 (36.44)	
Extracted teeth					
1st premolar	2 (6.67)[a]	7 (23.33)[ab]	13 (43.33)[ac]	8 (26.67)[ac]	<0.001[†]
1st molar	4 (1.92)	36 (17.22)	82 (39.23)	87 (41.63)	
2nd molar	2 (1.72)	45 (38.79)	34 (29.31)	35 (30.17)	
3rd molar	0 (0)	17 (22.97)	38 (51.35)	19 (25.68)	

Different superscript letters in the same row indicate significant differences between groups. Data are expressed as mean ± standard deviation, n (%), and median (first-third quartile). Key: Type A: Maxillary sinus without dropping, Type B: The maxillary sinus dropped only in extracted teeth area, Type C: The maxillary sinus dropped in posterior maxillary area, Type D: The line of maxillary sinus floor follows the roots, Type E: The maxillary sinus drops over the roots, but its borders are not clear, ŋ, Kruskal-Wallis test; †: Fisher exact test

Table 4. Relationship between the predictor variable and primary outcome

Variable	Relationship between tooth and maxillary sinus				p
	Type 1 (n=8)	Type 3 (n=105)	Type 3 (n=167)	Type 4 (n=149)	
Type A	4 (16)[a]	14 (56)[b]	5 (20)[c]	2 (8)[a]	<0.001[†]
Type B	1 (1.72)	27 (46.55)	23 (39.66)	7 (12.1)	
Type C	0 (0)	41 (16.27)	116 (46.03)	95 (37.70)	
Type D	0 (0)	13 (86.67)	2 (13.33)	0 (0)	
Type E	3 (3.80)	10 (12.66)	21 (26.58)	45 (56.96)	

Different superscript letters in the same row indicate significant differences between groups. Data are expressed as n (%). Key: Type A: Maxillary sinus without dropping, Type B: The maxillary sinus dropped only in extracted teeth area, Type C: The maxillary sinus dropped in posterior maxillary area, Type D: The line of maxillary sinus floor follows the roots, Type E: The maxillary sinus drops over the roots, but its borders are not clear, Type 1: No contact between root and maxillary sinus floor, Type 2: The apex of the root was in contact with the cortical border of the maxillary sinus, Type 3: 1/3 of the root exceeds the maxillary sinus cortical border, Type 4: More than half of the root inside of the maxillary sinus

of the maxillary sinus (type 2), 1/3 of the roots of 20% are inside the maxillary sinus (type 3), 16% have no relation with the maxillary sinus (type 1), and 8% more than half of its roots were in the maxillary sinus (type 4). There was a statistically relationship between type of sinus pneumatization and type of relation between the extracted teeth and maxillary sinus (p<0.001).

DISCUSSION

The close relationship of the MSF and the upper molar roots can lead to OAC, odontogenic sinusitis, or displacement of the root inside of the maxillary sinus during maxillary molar extraction.[7] Therefore, diffuse MSP can cause complication such as OAC, odontogenic sinusitis or oroantral fistula that

can profoundly affect people's quality of life.[8] In this study, the relationship between the root of the extracted tooth and different type of MSP in patients who developed OAC during the extraction of maxillary posterior teeth was evaluated. There was a statistically relationship between type of MSP and type of relation between the extracted teeth and maxillary sinus.

Wu et al.[8] reported that the MSP was significantly associated with age. Especially, it increases in 18-34 years old group. In addition, they suggested that the determinig degree of MSP could be important before treatment of the upper molar, especially young patients. In this study there was a statistically significant difference between type of MSP in terms of age (p=0.008). In consistent with the literature, the highest mean age was in the type B (dropped only in extracted teeth area) pneumatization, while the lowest mean age was in the Type E (drops over the roots, but its borders are not clear). Diffuse MSP in young patients can increases the risk of teeth protrusion into the sinus by decreasing the distance between apex of the root and maxillary sinus[8] and, additionally, Pei et al.[6] reported that the distance between molars and MSF increases with age. This confirms that the risk of complications during molar tooth extraction, endodontic treatment or implantation is relatively higher in young patients.[6] In consistent with the literature, there was a statistically significant difference in the mean age between different type of the relation between extracted teeth and the MSF groups in this study. (p<0.001). The highest mean age was found in type 2 (contact maxillary sinus), and the lowest was found in type 4 (more than half of the roots are in the maxillary sinus). These results show that there is a close relationship between the maxillary sinus and molar teeth in young patients and may increase the risk of OAC after extraction.

Bornstein et al.,[9] Luz et al.[10] and Cavalcanti et al.[11] reported that there was a statistically difference between male and female in terms of MSP. Further analysis showed that the difference may be due to larger skulls and body proportions in males and a higher MSP rating. However, Pei et al.[6] showed that female molars were closer to the maxillary sinus than males, but these differences were not statistically significant. In this study, the proportion of men (57.58%) was higher than women (42.42%). MSP was extensive in men than in women, but the relationship was not statistically significant (p<0.005). Takahashi et al.[12] stated that although maxillary sinus volume decreases with age, there is no significant difference between male and female, which can be explained by the decrease in female gender in the study group. The sex distribution was similar in the types of relationship between the extracted tooth and the maxillary sinus groups in this study (p>0.005).

The maxillary molar roots are very close to MSF. Previous studies have reported that in approximately 50% of patients, the maxillary sinus prolapses towards the alveolar bone, which may extend between roots of the teeth.[13] In addition, Sharan and Madjar[14] suggested that maxillary molar extraction could lead to MSP. It can cause if the apex of the root close to the maxillary sinus. In this study, 96.5% of the extracted teeth were in contact or inside to the maxillary sinus. Only 3.5% were distant from the MSF. OAC was most often seen after the extraction of the first molar, followed by the second molar. Purmal et al.[15] found that the MSF was most inferior location between the right molars. In addition, the highest location was between the left premolars. The buccal roots of the upper second molar were nearest to the MSF.[14,16,17] However, Themkumkwun et al.[18] analyzed 354 upper molar roots on CBCT. They found that extending of the molar roots into the maxillary sinus were common. Zhang et al.[19] reported that that half of the molar roots were inside of the maxillary sinus or in contact with MSF. Jung et al.[20] also found that the most common type of molar buccal root is entering the maxillary sinus. In contrast to literature, more than half of the roots of 41.63% of the first molars were in the maxillary sinus, and 1/3 of the roots of 39.23% were in the maxillary sinus. 17.22% were at the cortical border of the sinus, and 1.92% were not related to the sinus. While the roots of 38.79% of the second molars were in contact with the MSF, more than half of the roots of 30.17% and 1/3 of the roots of 29.31% were in the maxillary sinus. There was a statistically significant relationship with extracted tooth and relationship between extracted teeth and maxillary sinus in this study (p<0.001).

The previous studies evaluated the relationship of molar teeth to the maxillary sinus on CBCT. However, this study was the first to evaluate both the types of MSP and the relationship between the extracted tooth and the maxillary sinus in patients who developed OAC after extraction of maxillary molars. In this study, type C MSP (pneumatization in the entire posterior region of the maxillary sinus) had the highest rate. In 46.03% of them, 1/3 of the roots of the extracted tooth were in the maxillary sinus, and in 37.70%, more than half of the roots of the extracted tooth were in the maxillary sinus. After type C, the highest rate was type E. More than half of the roots of 56.96% of them, and 1/3 of the roots of 26.58% were in the maxillary sinus. These results indicate that the risk of developing OAC during the extraction of maxillary molar teeth increases in patients where the maxillary sinus sags in the entire posterior or its borders cannot be distinguished. The periapical or panoramic x-ray don't allow 3D evaluation of the relationship when molar roots superposed to the MSF.[21] A CBCT images provides 3D evaluation of the relationship between MSF and molar roots. The 3D evaluation provided on CBCT allow for rationalization of surgical plans to avoid risk for oroantral perforation.[22] However, in this study, evaluation was made on preoperative panoramic radiographs due to its retrospective natures. In addition, taking a CBCT image before the tooth extraction is not a routine procedure. But it may have caused limitations in determining the relationship between the maxillary sinus and the teeth. The difference mentioned above may have arisen for this reason or due to different racial and genetic origins.

CONCLUSION

The risk of developing OAC during the extraction of maxillary molar teeth increases in young patients where the maxillary sinus dropped in the entire posterior region or its borders cannot be distinguished. A compherensive analysis should be performed on CBCT in patients with high risk of OAC development during the interventions to the maxillary posterior region.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Clinical Researches Ethics Committee of Erciyes University Faculty of Medicine (Date: 29.03.2023, Decision No: 2023-204)

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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The prognostic impact of the pan-immune-inflammation value (PIV) on the efficacy of treatment and clinical outcomes in patients with extensive-stage small cell lung cancer (ES-SCLC)

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ABSTRACT

Aims: This study aimed to assess the prognostic and predictive implications of pre-treatment pan-immune-inflammation value (PIV) on treatment efficacy and clinical outcomes in patients with extensive-stage small-cell lung cancer (ES-SCLC), comparing it with established indices such as the systemic immune-inflammation index (SII) and neutrophil to lymphocyte ratio (NLR).

Methods: A retrospective cohort study included 70 patients diagnosed with ES-SCLC treated with standard chemotherapy with or without immune checkpoint inhibitors. PIV was calculated as PIV=(neutrophils×platelets×monocytes)÷lymphocytes. Patients were categorized into low PIV (<825) and high PIV (≥825) groups. The primary endpoint was overall survival (OS).

Results: Patients with low PIV exhibited significantly longer OS compared to those with high PIV (p=0.047). Although progression-free survival in the low-PIV group was longer than the high-PIV group, the difference was not statistically significant (p=0.081). The highest area under the receiver operating characteristic (ROC) curve AUC values were found for PIV at 0.83 (95% CI: 0.65-1.0), SII at 0.90 (95% CI: 0.81-0.99), and NLR at 0.81 (95% CI: 0.67-0.95). Univariate and multivariate analyses revealed that PIV's impact on clinical outcomes in ES-SCLC was less pronounced compared to SII. Elevated values of the SII (≥829.5) and the NLR (≥5.5) demonstrated superior predictive performance for adverse PFS and OS outcomes, albeit the study's limited sample size might have influenced these findings. Moreover, independent predictors of poorer prognosis included liver metastasis and elevated SII, underscoring the importance of systemic inflammation and disease burden in treatment decisions.

Conclusion: This study provides valuable insights into the value of PIV as a prognostic biomarker for survival outcomes in ES-SCLC patients. It suggests potential for PIV to aid in personalized treatment strategies for this aggressive lung cancer subtype. Despite limitations, such as the study's retrospective nature and relatively small sample size, future research with larger cohorts is essential to validate these findings and support the routine clinical integration of PIV in ES-SCLC management.

Keywords: Extensive-stage small-cell lung cancer, survival, prognosis, pan-immune-inflammation, biomarker

INTRODUCTION

Lung cancer, the second most common cause of cancer-related mortality,[1] encompasses various subtypes, including small-cell lung cancer (SCLC), constituting approximately 15 percent of all cases. SCLC, predominantly occurring in smokers, is characterized by its neuroendocrine nature and aggressive behavior, quick doubling time, and early metastatic dissemination, setting it apart clinically from most non-small cell lung cancers (NSCLC).[2,3]

Chronic inflammation promotes cancer pathogenesis by causing DNA damage, genetic mutations, and dysregulated cell proliferation due to sustained cell renewal and prolonged presence of immune cells.[4] Platelets, neutrophils, monocytes, and lymphocytes, which play critical roles in the inflammatory response, possess distinct characteristics that affect the immune system. These cells constitute the main components of peripheral blood elements in this process. There is a growing interest in identifying prognostic indices formulated from these different components, which can aid in the treatment decision-making process and improve patient outcomes. Peripheral blood-derived inflammatory indices have been extensively studied in lung cancer prognosis and found to be associated.[5-8] They are easily and quickly calculable biomarkers that facilitate clinicians' treatment approaches owing to their ease of use and low cost. One such biomarker is the pan-immune inflammation value (PIV), which integrates various immune and inflammatory cell counts derived from routine blood tests. The prognostic utility of PIV has been extensively investigated across various cancer types including colon cancer (CC),[9] esophageal cancer,[10] melanoma,[11] kidney cancer,[12] breast cancer,[13] Merkel cell carcinoma,[14] prostate

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cancer,[15] and nasopharyngeal carcinoma.[16] Studies have demonstrated that PIV is linked to clinical outcomes and prognosis in these cancer types, and it may serve as a valuable biomarker for predicting survival and treatment efficacy. PIV has also been compared with other inflammatory markers and shown to be independently associated with disease recurrence and survival outcomes.[17] These findings suggest that PIV could be a promising tool for guiding personalized treatment strategies and improving the prognosis of patients with cancer.[18]

This study aimed to comprehensively investigate the relationships between clinical-pathological features and PIV, as well as its associations with other established prognostic indices such as SII and NLR. Furthermore, a detailed comparative power analysis was conducted between PIV and the others. Understanding the role of PIV and other inflammatory markers in extensive-stage small-cell lung cancer (ES-SCLC) could enhance risk stratification and treatment decisions, ultimately improving care and prognosis for these patients. In light of the existing literature to date, this study stands out as the first to investigate the sole prognostic significance of PIV in ES-SCLC treated with conventional chemotherapy.

METHODS

Study Design & Patient Selection & Collection of the Data

The present study followed the principles set forth in the Declaration of Helsinki, and approved by the University of Health Sciences Antalya Training and Research Hospital Clinical Researches Ethics Committee (Date: 14.12.2023, Decision No: 17/4).

This retrospective study includes patients followed at the Oncology Department of University of Health Sciences Antalya Training and Research Hospital (HSUAERH) between January 2013 and June 2023. The data were collected from 91 patients with pathologically confirmed ES-SCLC. 7-10 days before treatment, comprehensive biochemical tests including complete blood count, uric acid, lactate dehydrogenase (LDH), albumin, and C-reactive protein (CRP) were conducted. Patients with chronic immune or inflammatory diseases, active acute infections, documented within the past month, a history of medications (such as steroids or antibiotics) that could affect immune and inflammatory responses, or those who underwent blood transfusion in the last three months were excluded from the study. The final analysis included 70 patients with complete clinical and laboratory data.

After reviewing the clinical, laboratory, and radiological records of the patients, the following data were collected: age, gender, Eastern Cooperative Oncology Group performance status (ECOG PS), body-mass index (BMI), smoking habits, presence of comorbidities, presence of brain metastases at diagnosis, disease stage at diagnosis, tumor localization, treatment history, treatment response, progression-free survival (PFS), second-line treatments administered upon progression, and overall survival (OS).

PIV was calculated using the formula proposed by Fuca et al.,[19] defined as follows: PIV = (neutrophils × platelets × monocytes) ÷ lymphocytes. Additionally, NLR was calculated as neutrophils ÷ lymphocytes,[6] SII as NLR × platelets.[20]

Treatment Details and Response Evaluation

Diagnostic imaging, which includes computed tomography (CT), 18F-fluorodeoxyglucose positron emission CT (PET-CT), and brain magnetic resonance imaging (MRI) scans, were conducted for disease staging. The disease was classified as ES-SCLC (Stage IV: T any, N any, M 1a/b/c), or T3-4, due to either extensive multiple lung nodules or tumor/nodal volume exceeding the capacity of a tolerable radiation plan according to the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, eighth edition. Following the initial clinical evaluation, all patients received the standard treatment protocol including platinum and etoposide with or without immune checkpoint inhibitors (ICIs) in accordance with the National Comprehensive Cancer Network (NCCN) recommendations. Clinical responses were assessed and categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD), according to the revised Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1). PFS was defined as the time elapsed from the date of pathological diagnosis to the date of progression or death from any cause. OS was calculated as the time elapsed from the date of pathological diagnosis to the date of death from any cause or last visit. The primary endpoint of the study was OS.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) for Windows 27 (IBM SPSS Inc., Chicago, IL). Normal distribution of the data was evaluated using the Kolmogorov-Smirnov test. For numerical variables exhibiting normal distribution, mean ± standard deviation was presented, while for those not exhibiting normal distribution, the median (min-max) was presented. The diagnostic performance of PIV, SII, and NLR for mortality was assessed using ROC Curve analysis. The cutoff values for PIV, SII, and NLR ratios were determined using the Youden index method. The relationship between PIV and clinical/laboratory markers was determined using the chi-square, Mann-Whitney U, and Kruskal-Wallis tests. PFS and OS were estimated using the Kaplan-Meier method and compared using the log-rank test. The association between variables and survival was further analyzed in detail using univariate and multivariate Cox regression models. Differences were considered statistically significant at $p<0.05$.

RESULTS

In this retrospectively designed study, out of the initial 91 patients diagnosed with ES-SCLC who were screened, 3 patients who underwent cranial radiotherapy along with steroid treatment, 10 patients using chronic immunosuppressive drugs or antibiotics, and 8 patients with incomplete clinical and laboratory data during follow-up were excluded from the study. Therefore, a total of 70 patients who fulfilled all criteria were included in the final analysis. The standard treatment regimen for all patients included chemotherapy with platinum

and etoposide. Among these patients, 10 received an ICI in conjunction with chemotherapy: 8 patients were treated with atezolizumab, while 2 patients received durvalumab.

The median age of the cohort was 63 years, ranging from 42 to 80. Of the patients included in the study, 59 (84.3%) were male, and 44 (62.9%) were current or former smokers. The most common tumor location was the left upper lobe (31.4%), whereas the least common was the right lower lobe (10%). At the time of diagnosis, brain metastases were present in 19 out of 70 patients (27.1%), while bone metastases were present in 30 out of 70 patients (42.9%). The clinical and demographic data of the patients are summarized in Table 1.

Table 1. Basic sociodemographic and clinicopathological characteristics of patients with extensive-stage lung cancer

Variable	All patients, (n=70)	
Age (year), n (%)	<65	36 (51.4)
	≥65	34 (48.6)
Sex, n (%)	Male	59 (84.3)
	Female	11 (15.7)
ECOG PS, n (%)	0-1	49 (70.0)
	2	21 (30.0)
Smoking status, n (%)	Non-smoker	26 (37.1)
	Smoker	44 (62.9)
Comorbidity, n (%)	None	34 (48.6)
	Present	36 (51.4)
Tumor location, n (%)	Left	34 (48.6)
	Right	36 (51.4)
Brain metastasis, n (%)	None	51 (72.9)
	Present	19 (27.1)
Bone metastasis, n (%)	None	40 (57.1)
	Present	30 (42.9)
Mortality, n (%)	None	13 (18.6)
	Present	57 (81.4)
PIV, n (%)	<825	35 (50.0)
	≥825	35 (50.0)
SII, n (%)	<829.5	21 (30.0)
	≥829.5	49 (70.0)
NLR, n (%)	<5.5	45 (64.3)
	≥5.5	25 (35.7)

ECOG PS: Eastern Cooperative Oncology Group performance status, PIV: Pan-immune-inflammation value, SII: Systemic inflammation index, NLR: Neutrophil to lymphocyte ratio

Cut-Off Values of the Laboratory Parameters

The PIV, SII, and NLR indices were assessed for their predictive efficacy with respect to mortality using ROC curve analysis (Figure 1). The highest area under the ROC curve (AUC) values were found for PIV at 0.83 (95% CI: 0.65-1.0), SII at 0.90 (95% CI: 0.81-0.99), and NLR at 0.81 (95% CI: 0.67-0.95). Optimal cutoff values, determined using the maximum Youden index, were 825 for PIV, 829.5 for SII, and 5.5 for NLR. Clinicopathological features and laboratory parameters, including prognostic indices, were compared between the low- and high-PIV cohorts (Table 2). Statistically significant associations were observed between PIV and mortality, SII, and NLR; however, no significant associations were found with other variables.

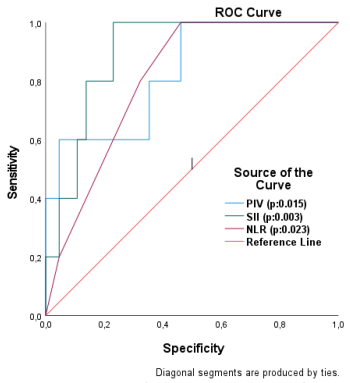

Figure 1. Comparison of the capability of PIV, SII, and NLR to predict mortality in extensive-stage lung cancer using ROC curve analysis

PIV: Pan-immune-inflammation value, SII: Systemic inflammation index, NLR: Neutrophil to lymphocyte ratio, ROC: Receiver operating characteristic

Table 2. The relationship between PIV groups and patient clinicopathological characteristics

Variables		PIV		
		Low <825	High ≥825	p*
Age (year), n (%)	<65	17 (48.6)	19 (54.3)	0.406
	≥65	18 (51.4)	16 (45.7)	
Sex, n (%)	Male	27 (77.1)	32 (91.4)	0.094
	Female	8 (22.9)	3 (8.6)	
ECOG PS, n (%)	0-1	23 (65.7)	26 (74.3)	0.301
	2	12 (34.3)	9 (25.7)	
Smoking Status, n (%)	Non-smoker	11 (31.4)	15 (42.9)	0.267
	Smoker	24 (68.6)	20 (57.1)	
Comorbidity, n (%)	None	18 (51.4)	16 (45.7)	0.406
	Present	17 (48.6)	19 (54.3)	
Tumor location, n (%)	Left	18 (51.4)	16 (45.7)	0.406
	Right	17 (48.6)	19 (54.3)	
Brain metastasis, n (%)	None	24 (68.6)	27 (77.1)	0.296
	Present	11 (31.4)	8 (22.9)	
Liver metastasis, n (%)	None	20 (57.1)	20 (57.1)	0.595
	Present	15 (42.9)	15 (42.9)	
Mortality, n (%)	None	10 (28.6)	3 (8.6)	0.018
	Present	25 (71.4)	32 (91.4)	
SII, n (%)	<829.5	21 (60.0)	0 (0.0)	<0.001
	≥829.5	14 (40.0)	35 (100.0)	
NLR, n (%)	<5.5	29 (82.9)	16 (45.7)	<0.001
	≥5.5	6 (17.1)	19 (54.3)	

PIV: Pan-immune-inflammation value, ECOG PS: Eastern Cooperative Oncology Group performance status, SII: Systemic inflammation index, NLR: Neutrophil to lymphocyte ratio, *statistical significance, (p<0.05)

Survival Analysis

In an average follow-up duration of 13.2 months (95% CI: 2.1-51.0), progression occurred in 65 patients (92.8%), and 57 patients (81.4%) died. The median OS of the study cohort was found to be 17 months. OS was 18.0 months (95% CI:

11.45-24.68) in patients with low PIV and 10.5 months (95% CI: 8.44-12.58) in patients with high PIV. Patients with low PIV exhibited significantly longer OS than those with high PIV (p=0.047). The median PFS of the patients was found to be 8.4 months. PFS was 12.0 months (95% CI: 6.30-17.96) in patients with low PIV and 6.7 months (95% CI: 5.36-7.96) in patients with high PIV. Although PFS in the low-PIV group was longer than that in the high-PIV group, no statistically significant relationship was observed (p=0.081). The Kaplan-Meier survival curves for OS and PFS stratified by low and high PIV groups are shown in Figures 2 and 3, respectively.

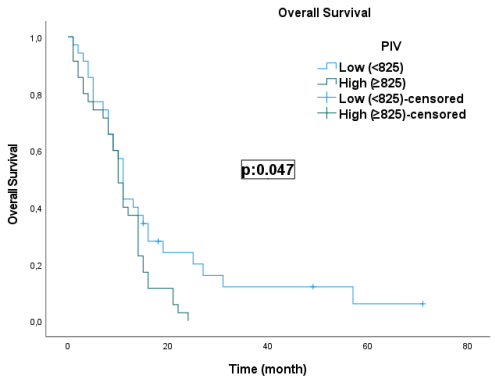

Figure 2. Kaplan-Meier curve illustrating the OS for low and high PIV groups

OS: Overall survival, PIV: Pan-immune-inflammation value

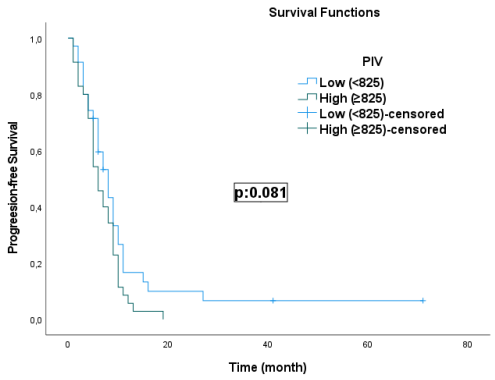

Figure 3. Kaplan-Meier curve illustrating the PFS for low and high PIV groups

PFS: Progression-free survival, PIV: Pan-immune-inflammation value

The clinical and laboratory parameters affecting OS in patients with ES-SCLC were investigated using a univariate Cox proportional hazards model (Table 3). In univariate analysis, liver metastasis, SII, and NLR were significantly associated with OS (p<0.05). In multivariate analysis, the presence of liver metastasis and SIRI remained significantly associated with OS (p<0.05). Consequently, both the presence of liver metastasis and high SII were identified as poor prognostic factors associated with a lower OS.

The clinical and laboratory parameters affecting PFS in patients with ES-SCLC were investigated using a univariate Cox proportional hazards model (Table 4). In the univariate analysis, both SII and NLR were significantly associated with PFS (p<0.05). However, in the multivariate analysis, no significant relationship was observed (Table 4).

Table 3. Cox regression model of overall survival in patients with ES-SCLC

	Overall survival							
	Univariate				Multivariate			
	HR (95% CI for HR)			p*	HR (95% CI for HR)			p*
Age	0.924	0.565	1.513	0.754	1.229	0.688	2.197	0.486
Sex	1.024	0.533	1.970	0.943	0.912	0.417	1.995	0.817
Comorbidity	0..870	0.534	1.415	0.574	0.876	0.434	1.867	0.386
Smoking status	1.386	0.399	4.817	0.607	0.259	0.061	1.096	0.066
Tumor location	0.803	0.489	1.321	0.388	1.124	0.441	2.863	0.807
ECOG PS	1.282	0.607	2.706	0.515	1.553	0.951	2.537	0.078
Brain metastasis	1.163	0.105	12.858	0.902	1.456	0.675	7.230	0.320
Liver metastasis	1.917	1.000	3.675	0.049	4.473	1.548	12.924	0.006
PIV	1.630	0.976	2.721	0.062	0.783	0.379	1.617	0.509
SII	3.008	1.569	5.767	<0.001	3.106	1.159	8.323	0.024
NLR	2.596	1.531	4.400	0.001	1.641	0.848	3.177	0.142

ES-SCLC: Extensive-stage small-cell lung cancer, ECOG PS: Eastern Cooperative Oncology Group performance status, PIV: Pan-immune-inflammation value, SII: Systemic inflammation index, NLR: Neutrophil to lymphocyte ratio, HR: Hazard ratio, CI: Confidence interval, *statistical significance, (p<0.05)

Table 4. Cox regression model of progression-free survival in patients with ES-SCLC

	Progression-free Survival							
	Univariate				Munivariate			
	HR (95% CI for HR)			p*	HR (95% CI for HR)			p*
Age	0.945	0.580	1.541	0.821	0.782	0.439	1.394	0.404
Sex	0.885	0.462	1.696	0.712	1.069	0.491	2.327	0.867
Comorbidity	1.092	0.670	1.781	0.723	1.071	0.613	1.871	0.809
Smoking status	2.207	0.646	7.540	0.207	0.973	0.214	4.433	0.972
Tumor location	0.878	0.536	1.437	0.604	0.940	0.356	2.484	0.901
ECOG PS	1.222	0.585	2.553	0.593	1.179	0.736	1.888	1.179
Brain metastasis	1.855	0.986	3.489	0.055	2.606	0.930	7.306	0.069
Liver metastasis	1.065	0.652	1.740	0.800	2.173	0.548	7.122	0.326
PIV	1.505	0.915	2.476	0.108	0.847	0.418	1.714	0.644
SII	2.165	1.186	3.951	0.012	2.085	0.861	5.052	0.104
NLR	2.041	1.207	3.451	0.008	1.723	0.908	3.267	0.096

ES-SCLC: Extensive-stage small-cell lung cancer, ECOG PS: Eastern Cooperative Oncology Group performance status, PIV: Pan-immune-inflammation value, SII: Systemic inflammation index, NLR: Neutrophil to lymphocyte ratio, HR: Hazard ratio, CI: Confidence interval, *statistical significance, (p<0.05)

DISCUSSION

In early-stage SCLC, effective treatment options such as surgery or curative radiotherapy remain standard; however, in advanced stages, despite the clinical outcomes improved with ICIs, survival remains limited. Despite the development of ICIs and targeted therapies identified in recent clinical trials for advanced-line treatment, OS remains unfortunately limited to approximately 12-15 months. As treatment progresses, tolerability diminishes due to side effects, accompanied by nutritional deficiencies and reduced quality of life, leading to parallel declines in treatment responses.

Given the aggressive clinical course of this disease, there is an essential need for predictive markers capable of anticipating treatment responses and clinical outcomes.

Examining the evolution of cancer and prognostic biomarker research over the past decade, initially, the field focused on designing marker combinations based on immune-inflammation to enhance cancer prognosis, such as NLR, PLR, and MLR. Subsequently, this phase was followed by the development of indices that utilize multiple parameters to further refine prognostic assessments such as SII and PIV. In a study conducted by Kucuk et al.,[21] the prognostic significance of PIV was assessed in patients with limited-stage SCLC before concurrent chemoradiotherapy (C-CRT) and prophylactic cranial irradiation (PCI). The results revealed that patients with PIV <417 exhibited significantly longer PFS and OS than those with PIV ≥417, highlighting the potential of PIV as an independent prognostic biomarker in patients with LS-SCLC undergoing C-CRT and PCI. In a study conducted by Topkan et al.,[22] the prognostic significance of PIV was investigated in patients with stage IIIB/C NSCLC undergoing C-CRT. The results revealed that patients with high PIV had significantly shorter median PFS and OS than those with low PIV, indicating the potential of PIV as an independent predictor of outcomes in stage IIIB/C NSCLC patients undergoing C-CRT. In a study conducted by Zhai et al.,[23] the predictive value of PIV was investigated in patients undergoing neoadjuvant immunotherapy for NSCLC. The results revealed that patients with pathological complete response (pCR) had a significantly longer disease-free survival (DFS) than those without pCR. As a result of the statistical analyses, it was demonstrated that PIV may have a strong predictive performance regarding the efficacy of neoadjuvant immunotherapy and pCR for NSCLC. The PIV also studied and has been found to be prognostic in patients with NSCLC undergoing ICI and in those with ALK-positive NSCLC.[24,25]

Numerous studies have explored the impact of SII on clinical outcomes in lung cancer. In a meta-analysis encompassing nine studies and a total of 2,441 patients, pretreatment SII was found to be significantly associated with poorer OS, DFS, PFS, and cancer-specific survival in NSCLC patients.[26] Additionally, the prognostic significance of SII has been found in NSCLC patients treated with nivolumab,[5] resected NSCLC patients,[20,27] NSCLC patients receiving neoadjuvant chemotherapy,[28] and NSCLC patients treated with C-CRT.[29]

The findings of this study support the notion that high PIV values are statistically significantly associated with poorer OS outcomes in patients with ES-SCLC, highlighting the potential use of PIV as a prognostic biomarker in ES-SCLC. For PFS, the results, although clinically significant, did not reach statistical significance. Statistically significant relationships were observed between PIV and mortality, SII, and NLR, once again underscoring the interaction between inflammation and cancer progression in ES-SCLC patients. According to ROC curve analysis, when examining the predictive capacity for mortality in ES-SCLC, SII was found to be superior to both PIV and NLR. Univariate and multivariate analyses demonstrated that the impact of PIV on clinical outcomes in ES-SCLC was not as strong as that of SII. It was found that both the SII and the NLR have significant associations with PFS and OS. However, the relatively small size of the study cohort may affect the generalizability of these results. Additionally, the presence of liver metastasis and high SII were identified as independent poor prognostic factors associated with lower OS, emphasizing the importance of considering both systemic inflammation and disease burden when making treatment decisions. The findings of this study are consistent with previous research on the relationship between PIV and lung cancer prognosis.[18] The ease of calculating PIV using routine blood tests makes it an attractive option for integration into clinical practice, which can aid clinicians in risk stratification and treatment selection for ES-SCLC patients.

Limitations

There were some limitations in the current study. Its retrospective design and single-center nature could affect the balanced distribution of cases, the application of more detailed statistical analyses, and the generalizability of the results. This index, based on a multivariate formula, includes markers that may indirectly influence each other. Additionally, some of these markers may activate intrinsic chemokines or cytokines in the body, potentially affecting immune responses and the clinical course of cancer through different mechanisms. The lack of internationally accepted standard cut-off values for each marker can also be considered a limitation. Furthermore, certain issues may have been overlooked, such as mild infections without clinical symptoms at the time of parameter measurements, individual differences in immune system changes, variable transient fluctuations in marker levels, and the absence of an internal validation group. The possibility of bias in PIV groups due to differences in advanced-line treatment options should also be considered. In the future, designing studies based on larger cohorts and including an internal validation group may provide more accurate and convincing information regarding the prognostic significance and predictive capacity of PIV.

CONCLUSION

This study provides evidence supporting the prognostic significance of PIV in patients with ES-SCLC who received standard chemotherapy with or without ICIs. PIV, along with other inflammatory markers, holds promise as a valuable tool for predicting clinical outcomes and guiding personalized treatment approaches for this aggressive form of lung cancer. Further research is warranted to validate these findings and to explore the potential integration of PIV into routine clinical practice for the management of ES-SCLC.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the University of Health Sciences Antalya Training and Research Hospital Clinical Researches Ethics Committee (Date: 14.12.2023, Decision No: 17/4).

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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Subjective outcomes of female genital cosmetic procedures: a prospective study with a median follow-up of 18 months

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ABSTRACT

Aims: To investigate the affects of labiaplasty and/or vaginoplasty on sexual function and satisfaction, as well as the potential to improve body image and genital self-image.

Methods: A total of 131 heterosexual sexually active women receiving either a vaginoplasty and/or labioplasty were included in the study population. Patients were subsequently divided into three groups: labioplasty (LP) (n=44), vaginoplasty (VP) (n=44), and labioplasty-vaginoplasty (LVP) (n=43) for statistical evaluation. All participants were administered preoperatively and postoperatively validated questionnaires including Body Image Scale (BIS); Female Sexual Function Index (FSFI), Sexual Quality of Life Questionnaire-Female (SQOL-F), Female Sexual Distress Scale (FSDS), Female Genital Self-Image Scale (FGSIS), and Quality of Sexual Experience Scale (QSES).

Results: The median follow-up was 18 months after the female genital cosmetic procedure (FGCP). FGSIS, BIS, SQOL-F, QSES, and FSDS postoperative questionnaires total scores improved significantly in the LP, VP, and LVP groups. FSFI postoperative total scores improved among all groups, but no statistically significant difference was detected in the LP group, unlike the VP and LVP groups. No intraoperative complications occurred. Postoperative complications were detected in 2 (4.5%) women in the LP group and 1 (2.3%) woman in the LVP group. These complications were wound dehiscence (<1 cm) in the labiaplasty line and no reoperation was required.

Conclusion: This prospective study determined the curative effect of FGCP on body image, sexual quality, sexual distress, genital image, and sexual function.

Keywords: Female genital cosmetic procedure, female genital cosmetic surgery, labioplasty, sexual function, vaginoplasty

INTRODUCTION

The popularity of female genital cosmetic procedures (FGCPs) for aesthetic (diminishment of perceived large, irregular, etc.) and/or functional (labial irritation with physical activities, dyspareunia etc.) concerns is increasing. Labia minora reduction or labioplasty (LP), clitoral hood reduction, labia majora enlargement or reduction, vaginoplasty (VP), and perineoplasty (PP) are some of the commonly conducted FGCPs. FGCPs are thought to enhance sexual satisfaction by increasing penile pressure on the clitoral complex and increase self-esteem by amending the appearance of the external genitalia. Despite the increasing number of FGCPs, the precise outcomes for women are limited and debated.[1]

Self-esteem is a person's whole belief in their own value or worth.[1] It's commonly assumed that performing cosmetic surgery for improving an individual's seems may improve a patient's self-esteem.[1] One of the most often reported motivations for why patients seek out various cosmetic operations is the desire to improve their self-esteem.[1,2] A recent review of FGCP outcomes across a variety of procedures revealed a beneficial effect on self-esteem.[3]

The intricate physiological process of female sexual function is influenced by biological, societal, and psychological variables. Female sexual function is affected negatively by relationship problems, stress, discomfort with vulvar appearances poor physical health and mental health.[4] Some studies identify a direct relationship between a woman's genital self-image and cosmetic functional improvement in women, but the literature is mostly retrospective.[5,6] In addition FGCPs appear to contribute to cosmetic and functional improvement in women, but the literature is mostly retrospective.[7] More prospective studies and standardized measurements should be performed for definitive and long-term results.

This prospective study aimed to determine the effects of FGCPs on body image, genital self-image, sexual distress, and sexual function and quality.

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METHODS

We conducted this prospective questionnaire study at a private clinic. Patient inclusion in the study started on 1 January 2022. The last patient was included on 1 November 2022. The questionnaires were administered preoperatively and postoperatively last follow-up. The Kartal Dr. Lütfi Kırdar City Hospital Clinical Researches Ethics Committee approved the study (Date: 03.01.2022, Decision No: 2022/514/240/7). All participants gave written informed consent. It was performed following the ethical standards described in the Declaration of Helsinki.

In the study, three groups were planned according to the cosmetic procedure performed: only the linear resection technique LP group, only the VP group, and the LVP combined group. All procedures were performed by a surgeon (OD) with adequate experience in cosmetic gynecology. The primary outcome was determined as the effect on the FSFI score after the FGCP including LP, VP, or LVP. In this study, the effect of the FGCP on genital self-image, body image, sexual quality, and female sexual distress were defined as secondary outcomes. The sample size was calculated with the G power 3.1 program based on the FSFI questionnaire data in the prospective study of Goodman et al.[6] The sample size determined for each group was 39 women. Since it was predicted that there might be a loss in postoperative follow-up, the patient collection continued until 45 women were included in the study for each group.

Body dysmorphic disease was excluded preoperatively in all patients. Criteria for inclusion were: 18-65 years old heterosexual woman and being a sexually active. Exclusion criteria were: women who had techniques other than linear resection technique labiaplasty, had a psychiatric disease, were pregnant, and with an inability to comprehend the research or the questionnaire forms.

A total of 131 patients who underwent LP (n=44), VP (n=44), and LVP (n=43) were included in the analysis. No response was obtained from 4 women in the postoperative follow-up. Validated questionnaires to measure body image, genital self-image, sexual dysfunction, sexual quality, and sexual distress were performed preoperatively and postoperatively.[8-12] 7-10 days before surgery and the last postoperative follow-up, participants were given the questionnaire pack to complete alone. In addition to the questionnaire forms, we extracted the following information from medical records and by asking face to face: patient's demographic and clinical data (including age, menopausal status, parity and comorbidities), socioeconomic data (including education, income more/equal/less than expenses, number of partners, first sexual intercourse age, and marital status), and intraoperative - postoperative complications.

Standardized Measures (Questionnaires)

BIS or Body Cathexis Scale (BCS): It is a 5-point Likert-type scale survey consisting of 40 questions adapted to Turkish by Hovardaoğlu (1993). It is scored between 40 and 200 points, and higher scores are associated with better body image perception. As the fortieth question measures the view of the genital organ, it was also analyzed separately in the study.

FSFI is a questionnaire with 6 subparameters (desire, arousal, lubrication, pain associated with vaginal penetration, satisfaction, and orgasm) measuring sexual function in women in the last 4 weeks. A score ranging from 0 to 36 is determined to measure sexual function; higher values indicate greater sexual function. The threshold for sexual dysfunction is set at a score below 26.55.[13]

SQOL-F is used to assess the impact of sexual dysfunction on quality of life in women. It is a Likert-type scale consisting of 18 items with answers ranging from 1 = "Strongly disagree" to 4 = "Strongly agree"; higher scores are indicative of a better quality of sexual life.[11]

The FSDS assesses different parameters of distress related to sexual activity in women (13 items, range of 0-52 points). Lower scores indicate less sexual distress.[10]

The FGSIS is a seven-item questionnaire intended for analyzing women's opinions and views regarding their genitalia. It is a survey with 4 answer options (strongly agree, agree, disagree, and strongly disagree), with a minimum of 7 and a maximum of 28 points calculated; higher scores indicate a more positive genital self-image.[14]

QSES: The QSES (7 items, the total score ranging from 7 to 49) was used to assess the quality of sexual experiences. Higher scores correspond to better sexual quality.[15]

Statistical Analysis

The data collected through the questionnaires were analyzed using IBM SPSS Statistics (version 25; IBM Corporation, Armonk, NY). Demographic variables and specific scale measures were given with the mean, standard deviation, standard error of the mean, median, interquartile range, and frequency for the relevant items. The subjective scale scores were compared using the samples t-test for parametric variables. Statistical significance was defined as $p<0.05$.

RESULTS

A total of 131 heterosexual sexually active women who either had a vaginoplasty and/or labioplasty were included in the study population. Patients were subsequently divided into three groups: LP (n=44), VP (n=44), and LVP (n=43) for statistical evaluation. All demographic data including age, body-mass index, parity, menopausal status, and comorbidities are summarized in Table 1. First sexual intercourse age was determined as 22.55±4.3, 23.41±3.9, and 22.83±4.6 in the LP, VP, and LVP groups, respectively (p=0.803). Social and economic data are summarized in Table 2.

Table 1. Demographic data

	LP (n=44)	VP (n=44)	LVP (n=43)	p-value
Age (year), mean±SD	30.4±7.7	38.3±8.5	38.8±7	<0.001*
BMI (kg/m^2), mean±SD	21.6±2.9	26.1±3.1	24.5±4.1	<0.001*
Parity, median±IQR (min-max)	0±0 (0-3)	2±1.5 (0-3)	2±1.25 (0-7)	<0.001*
Post-menopausal, n (%)	4 (9)	5 (11.3)	8 (18.6)	0.063
Comorbidities, n (%)	2 (4.5)	4 (9)	5 (11.6)	0.175
Smoker, n (%)	18 (40.9)	9 (20.4)	17 (39.5)	0.633

LP: Labioplasty, VP: Vaginoplasty, LVP: Labioplasty-vaginoplasty, SD: Standard deviation, BMI: Body-mass index, IQR: Inter quantile range

Table 2. Social/economic data*

	LP (n=44)	VP (n=44)	LVP (n=43)
Marital status, n (%)			
Single/divorced/widow	13 (29.5)	10 (22.7)	11 (25.6)
Married	31 (70.4)	34 (77.3)	32 (74.4)
Education, n (%)			
Primary and secondary school	8 (18.1)	6 (13.6)	9 (20.9)
High school and more	36 (81.9)	38 (86.4)	34 (79.1)
Occupation, n (%)			
Housewife	16 (36.3)	18 (40.9)	16 (37.2)
Civil servant	20 (45.5)	18 (40.9)	18 (41.9)
Self-employed	8 (18.2)	8 (18.2)	9 (20.9)
Number of partners, n (%)			
Single partner	38 (86.4)	40 (91)	38 (88.4)
Multiple partners	6 (13.6)	4 (9)	5 (11.6)
Economic status, n (%)			
Intake < expense	2 (4.5)	3 (6.8)	5 (11.6)
Intake = expense	32 (72.7)	30 (68.2)	29 (67.5)
Intake > expense	10 (22.7)	11 (25)	9 (20.9)
Family type, n (%)			
Small family	40 (91)	37 (84.1)	38 (88.4)
Large family	4 (9)	7 (15.9)	5 (11.6)

*No significant difference was found between groups for social/economic data (p>0.005), LP: Labioplasty, VP: Vaginoplasty, LVP: Labioplasty-vaginoplasty

Autologous fat lipofilling to the labia majora was performed for 10 (22.7%), 12 (27.2%), and 36 (83.7%) women in the LP, VP, and LVP groups, respectively. A clitoral hood reduction was performed for 40 (90.9%), 16 (36.3%), and 35 (81.3%) women in the LP, VP, and LVP groups, respectively. No intraoperative complications were found in any group. Postoperative complications were detected in 2 (4.5%) women in the LP group and 1 (2.3%) woman in the LVP group. These complications were minimal dehiscence (<1 cm) in the labiaplasty line and no reoperation was required. No postoperative complications were detected in the VP group. No significant difference was detected between the groups in terms of postoperative complication rates (p=0.368).

Preoperative and postoperative questionnaire scores are given in Table 3. The median follow-up was 18 months with a range of 13-26 months (interquartile range=6.5; median follow-up between groups was similar, p=0.984).

FGSIS, BIS, SQOL-F, QSES, and FSDS postoperative questionnaire total scores improved significantly in the LP, VP, and LVP groups. FSFI postoperative total scores improved among all groups, although no statistically significant difference was detected in the LP group, unlike the VP and LVP groups. The comparison of the pre- and postoperative scales is given in Table 3.

There was no significant difference in total scores of preoperative and postoperative FGSIS (p=0.493/0.208), BIS (p=0.078/0.972), FSFI (p=0.635/0.860), and FSDS (p=0.138/0.573) questionnaires between the LP, VP, and LVP groups. The *p*-values of the differences between the preoperative LP, VP, and LVP groups of the SQOL-F and QSES questionnaires were <0.001 and 0.001. p-values of postoperative differences were 0.004 and 0.032, respectively.

Table 3. Comparison of pre-and postoperative scale scores

		Preoperative		Postoperative		
		Mean±SD	min-max	Mean±SD	min-max	p (z)
Labioplasty group	**BIS**					
	Genital score[a]	4.45±0.74	2-5	1.89±0.58	1-4	<0.001 (-4.18)
	Total score	88.9±7.58	82-120	83.26±2.5	78-88	<0.001 (-3.61)
	FSFI					
	Desire	2.69±1.32	1.2-5.4	3.17±0.91	1.2-6	0.143 (-1.46)
	Arousal	3.14±0.92	0-3.9	3.32±0.84	0-5.7	0.406 (-0.83)
	Lubrication	3.13±0.92	0-3.9	3.33±0.84	0-6	0.405 (-0.83)
	Orgasm	3.05±1.06	0-4.4	3.42±0.80	0.4-6	0.135 (-1.49)
	Satisfaction	3.16±0.94	0-4.8	3.52±1.42	0-6	0.212 (-1.25)
	Pain	3.36±0.91	1.2-5.2	3.42±1.12	0-6	0.575 (-0.56)
	Total score	18.9±5.54	1.2-21.6	23.93±8.46	0-34.6	0.055 (-1.54)
	QSES total score	18.26±12.44	0-28	32.04±26.79	0-115	0.003 (-2.94)
	SQOL-F total score	40.13±27.68	0-69	50.04±33.81	0-83	<0.001 (-3.58)
	FGSIS total score	11.3±3.46	10-21	21.65±2.84	13-28	<0.001 (-4.13)
	FSDS total score	11.48±11.95	0-35	10.39±4.32	0-13	0.001 (-3.23)
Vaginoplasty group	**BIS**					
	Genital score[a]	4.5±0.52	4-5	2±0.73	1-4	<0.001 (-5.54)
	Total score	88.71±7.89	83-115	83.31±2.02	80-86	0.001 (-3.27)
	FSFI					
	Desire	3.41±1.08	1.2-5.4	3.2±0.54	2.4-6	0.439 (-0.77)
	Arousal	2.95±1.22	0-3.9	3.42±0.48	0-5.7	0.326 (-0.98)
	Lubrication	3.02±1.29	0-4.8	3.43±0.47	0-6	0.514 (-0.65)
	Orgasm	3.07±1.33	0-4.4	4.02±0.90	0-6	0.048 (-2.11)
	Satisfaction	3.19±1.47	0-5.2	4.17±0.91	1.2-5.6	0.035 (-2.05)
	Pain	3.23±1.34	0-5.2	4.01±0.90	0-6	0.075 (-1.82)
	Total score	16.94±8.59	1.2-26.4	24.96±5.88	7.2-34.9	0.012 (-2.51)
	QSES total score	27±8.32	0-42	39.56±12.24	0-49	0.001 (-3.22)
	SQOL-F total score	58.31±19.36	0-88	67.93±20.38	0-86	0.004 (-2.86)
	FGSIS total score	12.12±3.7	10-21	21.44±2.88	14-28	<0.001 (-3.52)
	FSDS total score	23.56±15.46	0-71	9.8±4.75	2-13	0.001 (-3.34)
Labio-vaginoplasty group	**BIS**					
	Genital score[a]	4.16±0.68	3-5	1.95±0.62	1-4	<0.001 (-5.54)
	Total score	85.55±3.47	81-98	83.26±2.09	80-87	0.001 (-3.27)
	FSFI					
	Desire	3.11±1.18	1.2-5.4	3.36±0.81	0-6	0.311 (-1.01)
	Arousal	2.97±1.08	0-3.9	3.49±0.76	0-6	0.012 (-2.51)
	Lubrication	3.12±1.04	0-4.8	3.49±0.75	0-6	0.039 (-2.07)
	Orgasm	3.05±1.15	0-4.4	3.7±0.86	0-6	0.006 (-2.74)
	Satisfaction	3.14±1.29	0-5.2	3.6±0.87	0-6	0.017 (-2.40)
	Pain	3±1.13	0-5.2	3.7±0.85	0-6	0.003 (-2.93)
	Total score	17.75±7.29	1.2-26.2	23.64±6.53	6.4-34.6	0.001 (-3.31)
	QSES total score	26.47±6.7	0-42	41.77±13.54	0-98	<0.001 (-5.11)
	SQOL-F total score	59.07±7.76	49-86	69.3±16.04	0-86	<0.001 (-2)
	FGSIS total score	10.85±21.8	10-17	20.55±3.03	12-28	<0.001 (-5.53)
	FSDS total score	21.22±6.94	2-38	11.51±6.9	0-45	<0.001 (-5.09)

SD: Standard deviation, min: Minimum, max: Maximum, BIS: Body Image Scale, FSFI: Female sexual function index, QSES: Quality of Sexual Experience Scale, SQOL-F: Sexual quality of life questionnaire-female, FGSIS: Female Genital Self-Image Scale, FSDS: Female Sexual Distress Scale, a: BIS question 40 - Genital organ score

DISCUSSION

A variety of surgical procedures including LP, perineoplasty, VP, and vaginal rejuvenation are conducted alone or in combination to improve genital appearance and/or sexual performance. However, benefits have not been proven by systematic reviews or randomized controlled studies to date using current guidelines.[16] This prospective study explored the relationship between body image, genital self-image, sexual distress, and sexual satisfaction in women seeking LP and/or VP. The FGSIS, BIS, SQOL-F, QSES, and FSDS postoperative questionnaire total scores improved significantly in the LP, VP, and LVP groups. However, although FSFI postoperative total scores improved among all groups, no statistically significant difference was detected in the LP group, unlike the VP and LVP groups.

The main motivations for an FGCP are improvement in appearance and better self-esteem and sexual life. Doğan et al.[17] reported that about half of patients stated they were affected by the media and advertisements. Social media, in addition to print publications and ads, play a major role in spreading awareness about cosmetic surgery.[18] As demonstrated in the review and meta-analysis, an FGCP can have a positive effect on women's self-esteem, although inconsistencies in study measurements and methods limit their results [1]. However, the general opinion regarding the guidelines is that there is inadequate evidence to support FGCPs as a way to improve sexual satisfaction and/or self-image. In addition, proof of both the safety and efficacy of these procedures is lacking.[16] As authors, we think that women should not be given information about possible effect of sexual function or self-image by the preoperative surgeon. In this study, the questionnaire preoperative and postoperative mean scores did not change for a small number of participants in all three groups.

Recently, a large number of studies have reported different results regarding the safety and complication rates of different FGCPs.[7,19] In the study of Köle et al.,[7] complication rates were reported as 1.2% after the composite labiaplasty technique, 3% in W-shaped resection, and 0.8% in Z-plasty. Women should be informed and counseled about potential complications in FGCPs, including scarring, infection, hypersensitivity or loss of sensation, wound dehiscence, and dyspareunia.[20] In this study, minimal dehiscence of the labioplasty line was detected in 3 of 131 women, but reoperation was not required. We think that the reason why this complication rate is low is due to the fact that it was performed by the same person who is experienced in cosmetic genital surgery.

Standard Measurement Outcomes

Chappel et al.[4] showed that self-perceived vulvar appearance ratings were associated with FSFI scores and women who were uncomfortable with their vulvar appearance had lower FSFI scores than those satisfied with their vulvar appearance. In the study of Goodman et al.,[6] in which the pre- and postoperative FSFI scores of 33 women who underwent vulvovaginal aesthetic surgery were compared, FSFI satisfaction scores increased significantly after surgery and there was a 3.5-point improvement in the FSFI total score (p=0.03). The FSFI questionnaire findings showed an improvement of at least 5 points in all three groups. However, this improvement was statistically significant only in the VP and LVP groups. The reason why the improvement in the FSFI score was not significant in the LP group may be due to the small number of samples or the fact that only a labiaplasty did not increase the penile pressure on the clitoral complex.

Research investigating the relationship between genital self-image and female sexual dysfunction (FSD) found a negative correlation between the degree of sexual distress and a positive genital self-image.[21] Benabe et al.[22] reported that the FSDS score reduced by 1.24 units for every unit rise in the FGSIS score, suggesting that a higher genital self-image perception may reduce levels of sexual distress. Hailparn et al.[23] in their study using the FGSIS questionnaire before and after LP surgery, they found that postoperative scores were statistically higher (10 points higher). They found that LP had a positive impact on their perception of their genitals and improved their quality of life. These findings correlate with the present study, in which an inverse relationship between female genital self-image and sexual distress was observed. The FGSIS total score increased by approximately 10 points in all groups, while the FSDS total scores decreased between 2 and 14 points in this study.

In a comparative study conducted in Iran (FSFI, FGSIS, and SQOL-F questionnaires were administered to the participants only preoperatively) worse questionnaire scores were obtained in those who requested FGCPs. In addition, the findings suggest that there is a relationship between the search for aesthetic genital surgery and female sexual function, body image, and female sexual quality of life.[24] Although the preoperative FGSIS scores (range of 10.8-12.1) and SQOL-F scores (range of 40-59) in our patients who underwent FGCPs were lower than the study in Iran, the postoperative effect was examined in the present study and the positive effect of FCGS was statistically significant. In addition, this study determined BIS total score, BIS genital score, and QSES total scores improved significantly. We found, in concordance with both Şahin et al.[26] and Doğan et al.,[25] that the body, genital, and sexual dissatisfaction shown in women who received FGCPs at baseline normalized with time following the FGCP.

In this study, we used validated questionnaires because there were no standard measurement questionnaires in the literature, which limited the comparison of the present study results with the literature. In addition, although there were patients who underwent autologous fat lipofilling and clitoral hood reduction in the study, these procedures were not included in the analysis. In future studies, studies with larger sample sizes can be conducted in which the effect of additional surgical procedures can be investigated.

This study contributes to the literature on the FGCP effect and is a prospective study with a median follow-up of 18 months. A total of 131 women were included in the study and the effects of the FGCPs were analyzed separately for LP, VP, and LVP. Although this prospective study determined the curative effect of FGCP on body image, sexual quality, sexual distress, genital image, and sexual function, it is clear that more studies are needed on this subject.

CONCLUSION

The popularity of FGCP for aesthetic and/or functional concerns is increasing.[1] This prospective study determined the curative effect of FGCP on body image, sexual quality, sexual distress, genital image, and sexual function. However, the general opinion about the guidelines is that there is insufficient evidence to support that FGCPs improve self-image and/or sexual satisfaction.[16]

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Kartal Dr. Lütfi Kırdar City Hospital Clinical Researches Ethics Committee (Date: 03.01.2022, Decision No: 2022/514/240/7).

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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The relationship between uric acid albumin ratio (UAR) and prognosis in patients with atrial fibrillation hospitalized in intensive care unit

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ABSTRACT

Aims: Recent studies have demonstrated an association between uric acid (UA) albumin ratio (UAR), and newly developing atrial fibrillation (AF) and also AF recurrence. We conducted a study to examine the prognostic value of UAR in critically ill patients with AF.

Methods: A retrospective examination was conducted on patients diagnosed with AF based on electrocardiography, who admitted to the intensive care unit (ICU) from the emergency department during the period from January 1st to May 1st, 2024. UAR levels were calculated by dividing the amount of UA by the amount of albumin. Based on the cut-off value, UAR levels were categorized into two groups: low UAR and high UAR. A comprehensive comparison was conducted on all the data between these two groups.

Results: The high UAR (UAR>0.231) group exhibited significantly higher UA, vasopressor requirement, mechanical ventilation support, length of stay in ICU, and in-hospital mortality rate compared to the low UAR (UAR≤0.231) group. Conversely, albumin levels were significantly lower ($p<0.001$ for all). The UAR cut-off value was 0.231, with a sensitivity of 97.3% and a specificity of 96.7% (The area under the curve (AUC):0.995, $p<0.001$). The mortality prediction ability of UAR was superior to that of albumin and UA alone (AUC: 0.995, 0.956, 0.981, respectively).

Conclusion: UAR is a cost-effective, easily accessible, useful marker for assessing the prognosis of critically ill patients with AF in ICU.

Keywords: Uric acid albumin ratio, atrial fibrillation, intensive care unit, prognosis, mortality

INTRODUCTION

Atrial fibrillation (AF) is the most common form of arrhythmia observed in one out of every six patients hospitalized in the intensive care unit (ICU).[1] Early identification of AF in patients hospitalized in the ICU is crucial since it is linked to several complications including ischemia, stroke, hemodynamic instability, mortality, and prolonged hospitalization. AF can be initiated in ICU patients by infection, inflammation, and arrhythmogenic triggers.[2]

Inflammation-induced fibrosis contributes to the initiation and perpetuation of AF. Several markers of inflammation have been demonstrated to be linked with the development of AF.[3] The last metabolite of purine, uric acid (UA), is catalyzed by xanthine oxidase, the main source of reactive oxygen species. UA, a molecular indicator of inflammation and oxidative stress, is linked to the development and progression of AF.[4] Studies have indicated that albumin, a potent anti-inflammatory and antioxidant substance, is linked to several inflammatory markers found in the bloodstream.[5] It has been suggested that the relationship between low serum albumin and AF may have a strong predictive value in patients with high comorbidities.[6]

The uric acid albumin ratio (UAR), a recently identified measure, has demonstrated its predictive power in several studies on inflammation.[7,8] Two recent studies have demonstrated that UAR has a superior ability to predict the development of newly emerging AF and AF recurrence.[3,9] Nevertheless, thus far, no study has been conducted to examine the correlation between UAR and the prognosis of patients with critical AF admitted to the ICU. Hence, our study aimed to examine the predictive capability of UAR in critically ill patients with AF.

METHODS

Study Design and Patient Population

A retrospective examination was conducted on patients who were admitted to ICU from the emergency department (ED)

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for various causes over the period of 01 January to 01 May 2024. The study comprised male and female patients who were over 18 years old, as well as patients diagnosed with AF based on electrocardiography (ECG). The study excluded individuals who had cancer, were pregnant, had hematological, rheumatological, oncological or infectious diseases, were undergoing immunosuppressive treatments, or had incomplete laboratory information. The study retrospectively collected data from the hospital system on patients' age, gender, UA and albumin levels at the time of admission to the ED, whether they required mechanical ventilation (MV) or vasopressor during their hospital stay, the length of their hospital stay (LOHS), the length of their ICU stay (LOS-ICU), and their outcomes (discharge or exitus). The evaluation of mortality was determined by the occurrence of death while patients was hospitalized. UAR levels were calculated by dividing the amount of UA by the amount of albumin.[9] Based on the cut-off value, UAR levels were categorized into two groups: low UAR and high UAR. A comprehensive comparison was conducted on all the data between these two groups, and receiver operating characteristic (ROC) analysis was applied to those that were associated with mortality. The study was initiated with the approval of the Necmettin Erbakan University Medical Faculty Clinical Researches Ethics Committee (Date: 28/06/2024, Decision No: 2024/5038). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Biochemical Analysis

During admission to the ED, blood samples were collected to assess UA and albumin values. The measurement was conducted using the Mindray chemistry analyzer BS-2000M device (Shenzhen, China).

Statistical Analysis

Statistical analyses in the study were performed using the SPSS 27.0 (IBM Inc., Chicago, IL, USA) program. The Kolmogrov-Smirnov test, histogram analysis, skewness/kurtosis data, and Q-Q plots were used to evaluate the assumptions of normal distribution. Descriptive statistics of the numerical and categorical data obtained in the study were analysed, and the parameters were expressed as IQR [median (minimum- maximum)]. Relationships between the two groups were examined with the Mann-Whitney U test. Relationships between categorical (nominal) parameters were examined with Pearson's chi-square analysis. ROC analysis was performed to determine predictive value and cut-off value for appropriate parameters. In the entire study, the type-I error rate was taken as 5% (α=0.05) and $p<0.05$ was accepted as the significant limit.

RESULTS

Table 1 presents a comparison of the characteristics of patients who survived and those who did not survive. Compared to the survivors, the deceased patients had significantly higher age, UA, UAR, vasopressor requirement, MV support, and LOS-ICU. On the other hand, albumin and LOSH were significantly lower in the deceased patients ($p<0.001$ for all). There was not a significant relationship between these two groups in terms of gender (p=0.841).

Table 1. Comparison of the clinical features of survivor and non-survivor patients

Variables	Survivors (n=271, 64.5%)	Non-survivors (n=149, 35.5%)	p value
Age, years	73 (18-98)	78 (19-103)	<0.001
Gender			
Male, n (%)	141 (52.03%)	76 (51.01%)	0.841
Female, n (%)	130 (47.97%)	73 (48.99%)	
Laboratory parameters			
Uric acid, (mg/dl)	5.3 (2-9.8)	9.2 (5.2-17.7)	<0.001
Albumin (g/L)	38.3 (21.1-50.2)	26.9 (18.2-36.1)	<0.001
UAR	0.14 (0.06-0.35)	0.37 (0.19-0.8)	<0.001
MV support, n (%)			
No	207 (76.38%)	17 (11.41%)	<0.001
Yes	64 (23.62%)	132 (88.59%)	
Vasopressor support			
No	160 (59.04%)	24 (16.11%)	<0.001
Yes	111 (40.96%)	125 (83.89%)	
LOHS (day)	14 (4-27)	11 (1-70)	<0.001
LOS-ICU (day)	7 (4-19)	11 (1-70)	<0.001

UAR: Uric acid albumin ratio, MV: Mechanical ventilation, LOHS: Length of hospital stay, LOS-ICU: Length of ICU stay, ICU: intensive care unit

Table 2 presents the overall characteristics of all patients as per the UAR. The high UAR (UAR >0.231) group exhibited significantly higher age, UA levels, vasopressor requirement, MV support, LOS-ICU, and in-hospital mortality rate compared to the low UAR (UAR ≤0.231) group. Conversely, albumin levels and LOSH were significantly lower ($p<0.001$ for all). There was not a significant relationship between the two groups in terms of gender (p=0.47).

The ROC analysis of UA, albumin, and UAR in predicting mortality is shown in Table 3. While the UA cut off value was 7.35, it had 94% sensitivity and 95.2% specificity (AUC: 0.981, $p<0.001$). While the albumin cut-off value was 31.9, it had 93.3% sensitivity and 90.4% specificity (AUC: 0.956, $p<0.001$). While the UAR cut-off value was 0.231, it had 97.3% sensitivity and 96.7% specificity (AUC: 0.995, $p<0.001$). The mortality prediction ability of UAR was higher to that of albumin and UA alone (AUC: 0.995, 0.956, 0.981, respectively).

DISCUSSION

In critically ill patients, early detection of AF is essential due to the high risk of mortality and long-term complications.[1] While the exact mechanism remains uncertain, it is well-established that both inflammatory response and oxidative stress contribute to the development of AF. Inflammation can result in the degeneration, necrosis, apoptosis and fibrosis of atrial myocytes, hence, can change the electrical structure of the atrium.[4] Numerous alternative strategies have been suggested to date in order to predict the development of AF, such as the investigation of inflammation-related biomarkers.[2]

Table 2. Characteristics of patients according to UAR groups

Variables	Low group (UAR≤0.231) (n=266, 63.3%)	High group (UAR>0.231) (n=154, 36.7%)	p value
Age, years	73 (18-98)	78 (19-103)	<0.001
Gender			
Male, n (%)	141 (53.01%)	76 (49.35%)	0.470
Female, n (%)	125 (46.99%)	78 (50.65%)	
Laboratory parameters			
Uric acid, (mg/dl)	5.3 (2-8.6)	9.1 (5.2-17.7)	<0.001
Albumin (g/L)	38.6 (21.1-50.2)	26.9 (18.2-36.1)	<0.001
MV support, n (%)			
No	204 (76.69%)	20 (12.99%)	<0.001
Yes	62 (23.31%)	134 (87.01%)	
Vasopressor support			
No	153 (57.52%)	31 (20.13%)	<0.001
Yes	113 (42.48%)	123 (79.87%)	
LOHS (day)	14 (4-27)	11 (1-70)	<0.001
LOS-ICU (day)	7 (4-19)	11 (1-70)	<0.001
In-hospital mortality			
No	262 (98.5%)	9 (5.84%)	<0.001
Yes	4 (1.5%)	145 (94.16%)	

UAR: Uric acid albumin ratio, MV: Mechanical ventilation, LOHS: Length of hospital stay, LOS-ICU: Length of ICU stay, ICU: intensive care unit

Table 3. ROC analysis of parameters in mortality prediction

	AUC	95% CI		Cut-off	Sensitivity (%)	Specificity (%)	
		Lower limit	Upper limit				p
Uric acid	0.981	0.969	0.993	7.35	94.0%	95.2%	<0.001
Albumin*	0.956	0.938	0.975	31.9	93.3%	90.4%	<0.001
UAR	0.995	0.991	0.999	0.231	97.3%	96.7%	<0.001

ROC: Receiver operating characteristic, AUC: Area under the curve, CI: Confidence interval, *Lower values are associated with positive (exitus) results. UAR: Uric acid albumin ratio

The significance of UA metabolism in numerous diseases that occur alongside chronic inflammation should not be underestimated.[10] By causing atrial remodeling induced by inflammation, oxidative stress, and fibrosis, UA contributes to the pathophysiology of AF.[11] Multiple meta-analyses have demonstrated the correlation between hyperuricemia and AF.[4,10] A study revealed that patients with AF exhibited significantly elevated levels of UA in comparison to those without AF. This study highlighted the positive correlation between increasing levels of UA and the incidence of AF.[12] In a separate study that included patients with new-onset, paroxysmal, and persistent AF, it was verified that UA levels were directly correlated with the duration of AF and were significantly higher in those with persistent AF than in the other groups.[4] A recent study including 1484 patients with coronary artery disease (CAD) indicated that levels of UA were higher in patients with new-onset atrial fibrillation (NOAF) compared to those without NOAF.[9] Our study found that levels of UA were significantly higher in patients who died in contrast to those who survived. Furthermore, UA demonstrated a high level of accuracy in predicting mortality in critically ill AF patients who were admitted to the ICU. Thus, UA could serve as a marker linked to adverse outcomes for these patients.

Serum albumin, the most important protein found in human serum, performs a multitude of essential physiological functions. Albumin, with its various effects including the maintenance of colloid osmotic pressure, anti-platelet aggregation, anti-inflammatory, antioxidant and anticoagulant effects, may also contribute to the pathophysiological process of AF.[5,13] Currently, numerous studies have proven that the likelihood of AF increases as albumin levels decrease.[14,15] A meta-analysis shown that a concentration of 10 g/L serum albumin resulted in a 36% decrease in the incidence of AF. Furthermore, a significant relationship between serum albumin and AF was seen.[4] According to Zhao et al.,[13] patients with persistent AF had lower levels of albumin compared to patients with paroxysmal AF. Our study revealed that the albumin levels of patients who died were significantly lower than those who survived. Furthermore, albumin demonstrated a high AUC for the prediction of mortality in patients with critical AF. Consequently, the levels of albumin in these patients may serve as an indicator of the intensity of the inflammatory response and the severity of the disease.

Currently, UAR, which has recently been identified as a new marker for inflammation and oxidative stress, has been the subject in numerous studies.[9] Two recent studies have demonstrated a correlation between UAR and mortality in patients who have acute renal failure.[16,17] Another study demonstrated that UAR exhibited a stronger predictive capacity compared to UA and albumin in forecasting the likelihood of developing contrast-related nephropathy in patients diagnosed with ST-segment elevation myocardial infarction (STEMI).[7] A study of 402 individuals with CAD found that there were significantly higher levels of UAR in patients in the medium-high cardiac surgery scores group compared to patients in the low cardiac surgery scores group. Furthermore, it has been highlighted that UAR can be utilized with confidence to estimate the magnitude of CAD.[8] A study involving 4599 patients with STEMI found that UAR could serve as an easily accessible parameter for identifying high-risk patients and predicting mortality.[18] Selçuk et al.[9] discovered that the levels of serum UAR were elevated in patients with NOAF compared to those without NOAF. Based on the logistic regression model, it has been demonstrated that UAR is an independent predictor of NOAF in STEMI patients. Karataş et al.[3] conducted a study to assess the efficacy of UAR in predicting the recurrence of AF following a successful catheter ablation procedure. During ROC analysis, when the UAR value >1.67, it accurately predicted the occurrence of recurrence with a sensitivity of 77% and a specificity of 57% (AUC 0.68, p<0.01). Our study found that the UAR was significantly higher among individuals who

died compared to those who survived. The high UAR group exhibited significantly greater requirements for vasopressor use, MV support, LOS-ICU, and in-hospital mortality rate, in comparison to the low UAR group. In addition, when compared to albumin and UA, UAR had exceptional predictive ability for mortality (AUC: 0.956, 0.981, 0.995, respectively). Thus, UAR serves as a closely linked marker for predicting the prognosis of patients with critical AF.

Limitations

Initially, this study was a single-center retrospective study with a small sample size. Secondly, since the patient data in the study were based on medical records, information such as medications used, body-mass index, smoking, alcohol consumption, malnutrition, etc. could not be fully provided. Third, it should be noted that the data collection was limited to the time of admission to ED, and any subsequent changes that occurred during the patient's stay were not analyzed. Fourth, it was not possible to track the long-term results of critically ill patients with AF who were admitted to the ICU. To summarize as this is the initial study examining the correlation between UAR and prognosis in patients with critical AF, it is necessary to carry out prospective and multicenter studies to validate our findings.

CONCLUSION

UAR serves as a cost-effective, easily accessible, and useful marker in the prognostic assessment of critically ill AF patients admitted to the ICU. In addition, UAR had a higher predictive efficacy in predicting mortality in these patients, as compared to albumin and UA.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was initiated with the approval of the Necmettin Erbakan University Faculty of Medicine Clinical Researches Ethics Committee (Date: 28/06/2024, Decision No: 2024/5038).

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

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Can a cementless partial hip prothesis be preferred in patients with hip fractures when the Spotorno score is greater than 5?

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ABSTRACT

Aims: Partial hip arthroplasty is preferred in elderly patients with low activity levels, numerous comorbidities, and limited mobility for hip fractures. To decide whether to use cement in femoral stem implantation, scoring systems such as Spotorno, Dorr, and Canale Flare Indices are used. Generally, cemented application is frequently for patients with over 5 points according to Spotorno criteria. In this study, our aim is to present the outcomes of patients who had a score of 5 or more according to the Spotorno criteria and required cemented prostheses but instead received cementless partial hip prostheses.

Methods: Patients who underwent partial hip arthroplasty due to post-traumatic femoral neck fractures in our hospital's orthopedics and traumatology clinic between 2017 and 2021 were retrospectively evaluated. To calculate the total score according to the Spotorno criteria, which evaluate age, sex, singh index and morphological cortical index, the radiographs of the patients included in the study were assessed, and the Singh index and morphological cortical index (MCI) were calculated.Periprosthetic fractures, prosthesis dislocations, heterotopic ossification, femoral loosening and mortality had been recorded. A total of 192 patients over the age of 70 with ASA III and ASA IV who underwent cementless partial hip arthroplasty were included in the study. Among these patients, 126 were female (% 5.7) and 66 were male (%34.3). Mean follow up was 5.8 years (0-7 years).

Results: According to the Spotorno criteria, the total score for all patients was greater than 6. Periprosthetic fractures were detected in % 3.1. Heterotopic ossification was observed in %9.3. In the postoperative 1st month, mortality was observed in %5.

Conclusion: Cementless hip arthroplasty in elderly patients with a Spotorno score of 5 or higher can be as effective and applicable as cemented hip arthroplasty. Although the literature generally recommends cemented hip prostheses for such patients, cementless partial hip arthroplasty can be a viable option if standard latest-generation cementing systems are not available.

Keywords: Spotorno criteria, cementless partial hip arthroplasty, elderly patients

INTRODUCTION

Femoral neck fractures, which account for approximately 50% of hip fractures, are a significant health issue in elderly patients. The increasing lifespan, the desire for individuals to meet their own needs, a more active lifestyle, and various comorbidities, particularly osteoporosis, are causing the number of hip fracture patients in the elderly population to rise rapidly.[1,2] Globally, the number of hip fracture cases is projected to reach 6.26 million per year by 2050.[3] In this respect, hip fractures are not only an important health issue but also a significant public health problem with social and economic implications.[4,5]

The primary goals in the treatment of a patient with a hip fracture are pain relief, early mobilization, returning the patient to their pre-fracture functional level, and avoiding potentially fatal complications.

The patient's physiological age, activity level, bone quality, and comorbidities are crucial in determining the treatment option.[6-8] Partial hip arthroplasty is preferred in elderly patients with low activity levels, numerous comorbidities, and limited mobility.[1,9,10]

Femoral stem implantation can be performed with or without cement. To decide whether to use cement in femoral stem implantation, scoring systems such as Spotorno, Dorr, and Canale Flare Indices are used.[11] Generally, cemented application is frequently preferred in elderly patients with poor bone quality due to less thigh pain and a lower risk of periprosthetic fractures. However, the pressurized application of cement increases intramedullary pressure and can cause fat embolism and potentially fatal bone cement implantation syndrome, especially in patients with various comorbidities.[12]

In this study, our aim is to present the outcomes of patients who had a score of 5 or more according to the Spotorno criteria and required cemented prostheses but instead received cementless partial hip prostheses in ASA (American Society of Anesthesiologists) III and ASA IV patients. As far as we have reviewed in the literature, this study is the first to report

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the outcomes of cementless partial hip prostheses in patients who scored 5 or more according to the Spotorno criteria.

METHODS

Our study received approval from the Giresun Training and Research Hospital Ethics Committee (Date: 17.07.2024, Decision No: 249120767). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients who underwent partial hip arthroplasty due to post-traumatic femoral neck fractures in our hospital's Orthopedics and Traumatology Clinic between 2017 and 2021 were retrospectively evaluated. By reviewing the patients' medical records, information on their sex, age, ASA (American Society of Anesthesiologists) classification, and comorbidities was obtained. To calculate the total score according to the Spotorno criteria, which evaluate age, sex, Singh index, and Morphological Cortical Index (MCI), the radiographs of the patients included in the study were assessed. The Singh index and MCI were calculated. Incidents of periprosthetic fractures, prosthesis dislocations, heterotopic ossification, femoral loosening, and mortality were recorded. A retrospective evaluation was conducted on 248 patients with femoral neck fractures. Patients with a Spotorno score of less than 5, those under 65 years of age, those who underwent total hip arthroplasty, and those classified as ASA I and ASA II were excluded from the study. A total of 192 patients over the age of 70 with ASA III and ASA IV who underwent cementless partial hip arthroplasty were included in the study. Among these patients, 126 were female (% 65.7) and 66 were male (% 34.3) (Table 1 and 2). Mean follow up was 5.8 years (0-7 years).

Table 1. Spotorno criteria sex

Sex	Point	n	%
Famele	1	126	65.7
Male	0	66	34.3

Table 2. According to Spotorno age

Age (years)	Point	n	%
<50	0	0	0
51-60	1	0	0
61-70	2	0	0
>70	4	192	100

Although Spotorno, Dorr, and Canale Flare Indices scoring systems are used to decide whether to apply cement in femoral stem implantation, Kacmaz[11] and colleagues found the highest interobserver agreement using the Spotorno criteria. Therefore, in our study, patients were evaluated according to the Spotorno criteria.

To calculate the total score according to the Spotorno criteria, which evaluate age, gender, Singh index, and morphological cortical index, the radiographs of the patients included in the study were assessed, and the Singh index and morphological cortical index (MCI) were calculated.

Periprosthetic fractures, prosthesis dislocations, heterotopic ossification, and femoral loosening that could be detected radiographically were recorded. Mortality tracking for the patients was conducted through the Turkish Ministry of Health's online patient follow-up system. All patients were discharged after being mobilized. Periprosthetic fractures, prosthesis dislocations, heterotopic ossification, femoral loosening and mortality had been recorded.

RESULTS

Regarding the Singh index, 36 patients (18.75%) had a score of 5-6, 108 patients (56.25%) had a score of 3-4, and 48 patients (25%) had a score of 1-2 (Table 3). When evaluated according to the Morphological Cortical Index (MCI), 12 patients (6.25%) had an MCI greater than 3, 36 patients (18.75%) had an MCI between 2.7 and 3, 66 patients (34.37%) had an MCI between 2.3 and 2.6, and 78 patients (40.63%) had an MCI less than 2.3 (Table 4). According to the Spotorno criteria, the total score for all patients was greater than 6 (Table 5).

Table 3. According to Spotorno singh index

Singh index	Point	n	%
7	0	0	0
5-6	1	36	18.75
3-4	2	108	56.25
1-2	4	48	25

Table 4. According to Spotorno MCI

MCI	Point	n	%
>3	0	12	6.25
2.7-3	1	36	18.75
2.3-2.6	2	66	34.37
<2.3	4	78	40.63

MCI: Morphological cortical index

Table 5. Total Spotorno score

Spotorno score	Cemented/cementless	n	%
0-4	Cemetless	0	0
5	Cemented or cementless	0	0
6	Cemented	192	100

Periprosthetic fractures were detected in 6 patients (3.1%). In 4 (2%) patients, a cable was observed in the subtrochanteric region on the postoperative day 1 X-ray. The operation note confirmed that iatrogenic fractures occurred in these 2% (4 patients) patients. Heterotopic ossification was observed in 18 patients (9.3%), with 12 patients showing Brooker type 1 myositis and 6 patients showing Brooker type 2 myositis. Femoral stem loosening was detected in 4% (8 patients) of patients. During the postoperative hospital stay, no mortality was observed. However, in the postoperative 1st month, mortality was observed in 5% (11 patients) according to the Ministry of Health's online patient follow-up system.

DISCUSSION

The most important finding of this study is that the outcomes of cementless partial hip arthroplasty in patients who, according to the Spotorno criteria, are indicated for cemented hip prostheses are similar to those reported for cemented partial hip prostheses in the literature. There is no difference in terms of mobilization, periprosthetic fractures, iatrogenic fractures, femoral stem loosening, and early mortality between cementless and cemented partial hip arthroplasty in the literature.

In elderly patients, partial hip arthroplasty is preferred for the treatment of displaced femoral neck fractures. However, the choice of whether to use cemented or cementless partial hip arthroplasty remains a topic of discussion. Cemented hip prostheses have the advantage of lower risks of periprosthetic fractures and thigh pain compared to cementless prostheses. However, the pressurization of cement increases intramedullary pressure and can lead to fat embolism and potentially fatal bone cement implantation syndrome, particularly in patients with various comorbidities.[13] Cementless implantation provides lower intramedullary pressure with reduced embolization and hemodynamic instability, resulting in lower mortality.[14] For patients scoring 5 or higher according to the Spotorno criteria, cemented hip prostheses are recommended due to poor bone quality. It has been demonstrated in the literature that advancements in cementing techniques over time have extended the lifespan of prostheses.[15] Although the articles in the literature do not specify which generation of cementing system is used in cemented partial hip arthroplasties, we assume the most recent generation is employed. Due to cost constraints, social security policies in our country do not cover the latest cementing systems. Therefore, in patients who were indicated for cemented partial hip arthroplasty, we were forced to use cementless partial hip arthroplasty systems. This situation has provided us with a substantial pool of information regarding cementless partial hip prostheses for patients with such bone quality.

In patients over 70 years old with ASA III and ASA IV who have severe systemic diseases, cardiopulmonary functions and physical activities are significantly reduced. Many studies have reported that bone cement can increase mortality by triggering cerebrovascular complications and cardiovascular events.[16-19] In our study, although all patients were followed for at least 2 years, the average hospital stay for the patients included in the study was 7.3 days (range 4-21). During the hospital stay, no patients who resulted in mortality were observed.

The effect of cement application on mortality in partial hip prostheses is a debated topic in the literature. In their meta-analysis, Wu et al.[20] found no significant difference in 6-week mortality rates between cemented and uncemented partial hip arthroplasties. Taylor et al.[21] reported a mortality rate of 12.5% in both cemented hemiarthroplasties and cementless hemiarthroplasties during the first 6 weeks postoperatively. Grammatopoulos et al.[22] found 30 day mortality as 8.6 and 11.7 in cemented and cementless hemiarthroplasties respectively. In our study, mortality was observed in 5% of the patients in the postoperative 1st month. Our findings are comparable to those in the literature.

The incidence of periprosthetic fractures following cementless partial hip arthroplasty has been reported to range from 5.5% to 15%.[12,23] Another study found this rate to be 2.1%, attributing the decrease in periprosthetic fracture incidence to the increased experience with cementless implantation techniques. Ng et al.[23] reported an incidence of intraoperative femoral fractures of 1%, while Rajak et al.[24] reported 1.9%. In our study, periprosthetic fractures were observed in 3.1% and intraoperative femoral fractures in %2 of the patients, which are consistent with the literature.

In their meta-analysis, Elmenshavy et al.[25] reported that the risk of dislocation and heterotopic ossification is lower in cementless partial hip arthroplasties, while the risk of intraoperative femoral fractures is higher in the cementless group, although this difference is not statistically significant. In our study heterotopic ossification was observed in 9.3% of the patients which is consistent with the literature.

Limitations

This study has several limitations. Firstly, due to being a hospital dependent on social security institutions, we could not create a control group using third generation cementing techniques as this would have imposed an additional economic burden on the patients. Another significant limitation is the lack of objective criteria for assessing the patients' quality of life in the long term. On the other hand, one of the strengths of our study is that a large portion of our results is based on official data from the Ministry of Health.

CONCLUSION

Cementless hip arthroplasty in elderly patients with a Spotorno score of 5 or higher can be as effective and applicable as cemented hip arthroplasty. Although the literature generally recommends cemented hip prostheses for such patients, cementless partial hip arthroplasty can be a viable option if standard latest generation cementing systems are not available.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Giresun Training and Research Hospital Ethics Committee (Date: 17.07.2024, Decision No: 249120767).

Informed Consent

All institutional and national guidelines for the care and use of laboratory animals were followed.

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

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Comparison of pathological electrocardiographic changes between long-term kidney transplant recipients and hemodialysis patients

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ABSTRACT

Aims: We aimed to reveal electrocardiographic changes in kidney transplant recipients (KTRs) compared with hemodialysis patients.

Methods: We included 70 KTRs who had underwent a kidney transplantation for more than one year and 84 patients who had been on hemodialysis for more than one year. We recorded age, sex, body-mass index (BMI) (kg/m^2), primary disease (makes chronic kidney disease) and duration of hemodialysis treatment. Standard measurements such as heart rate (HR), P wave, PR interval, P axis, QRS complex, QRS axis, T axis, QT interval and QTc interval were performed for all electrocardiography (ECG).

Results: KTRs were younger than the hemodialysis patients group (HPG) (31.5 vs. 54.5, p<0.001). The female gender was more common in the HPG (54.8% vs. 28.6%, p=0.001). Diabetes mellitus (DM) and hypertension (HT) were more common in the HPG (21.4% vs. 7.1% and 47.6% vs. 15.7% respectively, p<0.001). There was no statistically significant difference between KTRs and HPG in terms of heart rate, P axis, P-wave, QRS axis, QRS complex, RR interval, while T axis was higher in HPG (65o vs. 40.5o, p=0.001), PR interval was longer in HPG (152 msec vs 144 msec, p=0.020), QT interval was longer in HPG (385 msec vs 360 msec, p<0.001), QTc was longer in HPG (463 msec vs 415.5 msec, p<0.001).

Conclusion: In the long term after kidney transplantation, improvement of ECG pathologies such as prolonged QT and abnormal T axis seen in HPG may be the result of an improved uremic milieu and reduced inflammation in KTRs.

Keywords: Kidney transplant recipient, hemodialysis, prolonged QT

INTRODUCTION

Cardiovascular mortality is the most common cause of death in hemodialysis patients. Accelerated atherosclerosis in chronic kidney disease (CKD) leads to a higher incidence of cardiovascular disease in hemodialysis patients than in the general population, irrespective of the underlying CKD disease. Heart failure (HF) left ventricular hypertrophy (LVH), and coronary artery disease (CAD) are the most common cardiovascular diseases in hemodialysis patients.[1,2] However, not all cardiovascular mortality in hemodialysis patients is due to ischemic heart disease. In hemodialysis patients, 40% of deaths are sudden deaths, which occur more frequently than in the general population. Most sudden deaths are thought to be due to fatal arrhythmias.[3,4] In addition to HF, LVH and CAD, which are more common in dialysis patients compared to the general population, uremia, metabolic acidosis, hyperkalemia and electrolyte changes during hemodialysis as well as changes in body fluid composition can cause the development of fatal arrhythmias (bradyarrhythmia or tachyarrhythmia).[3]

The improvement of the uremic milieu, the electrolyte abnormalities, the metabolic acidosis and decrease in inflammation after kidney transplantation create favorable conditions with regard to cardiovascular disease compared to hemodialysis. However, cardiovascular mortality and complications after kidney transplantation are still higher than in the general population, even if they are lower compared to hemodialysis patients.[5]

ECG monitoring and follow-up in hemodialysis patients has been shown to be a useful tool for monitoring changes that may be predictive of mortality in this population. The best known of these ECG changes thought to be associated with mortality is the prolongation QT.[6]

In this study, we aimed to reveal the ECG changes that can be observed in kidney transplant recipients compared to hemodialysis patients.

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METHODS

The study was carried out with the permission of Gazi Yaşargil Training and Research Hospital Clinical Researches Ethics Committee (Date: 29.09.2023 Decision No: 524). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

We recorded patients' age, gender, body-mass index (BMI) (kg/m^2), primary disease makes chronic kidney disease, spending time on diaylsis. All ECG recordings were made at the beginning of the dialysis session in the first session of the week. ECG recordings were performed at a speed of 25 mm/s and an amplitude of 10 mm/mV using a Schiller AT 102 G2 12-lead/12-channel ECG machine. All ECGs were scanned at a resolution of 300 DPI and transferred to an electronic storage medium. The images were evaluated using the program "Adobe Photoshop CS2 Version 9.0" with a resolution of 1500 DPI and an accuracy of four milliseconds. Standard measurements such as heart rate (HR), P-amplitude, PR interval, P axis, QRS complex, QRS axis, T axis, QT interval and QTc interval were performed for all ECGs. The duration of the P wave was assessed as the duration between the initial deflection and its return junction to the isoelectric baseline. QT interval was calculated as the duration between the onset of the QRS complex and the end of T wave in the isoelectric baseline. QTc was measured using Bazett's formula ($QTc=QT/\sqrt{RR}$).[7,8]

Statistical Analysis

Variables with normal distribution are given as mean±standard deviation, variables without normal distribution as median (minimum-maximum). The p value obtained by comparing normally distributed numerical variables with the t-test for independent samples and the p-value obtained by comparing non-normally distributed numerical variables with the Mann-Whitney U test are indicated. The result of the chi-square test p is given by indicating the percentages of the categorical variables and taking into account the expected value. The statistical significance level was assumed to be $p<0.05$.

RESULTS

The demographic characteristics of the general population, KTRs and hemodialysis patients are shown in Table 1. The median age of all patients was 42 years and 42.9% of patients were female. The median BMI of all patients was 22.5 kg/m^2. The median number of months spending on hemodialysis was 16 months. Regarding the etiology of CKD, 33.1% (n=51) were HT, 14.9% (n=23) DM, 6.5% glomerulonephritis (GN) and 45.55% other diseases (n=70). Hemodialysis patients were older than KTRs (54.5 vs. 31.5, $p<0.001$). The HPG had a higher female sex ratio (54.8% vs. 28.6%, $p=0.001$). There was a difference between the groups regarding the etiology of CKD ($p<0.001$); HT was more common in the HPG (47.6% vs. 15.7%), DM was more common in the HPG (21.4% vs. 7.1%) and GN was less common in the HPG (2.4% vs. 11.4%).

The clinical characteristics of KTRs are listed in Table 2. Most patients (94.3%) underwent living kidney transplantation. Induction therapy was mostly (72.9%) administered as ATG, and the proportion of patients who did not receive induction therapy was 7.1%. The median mismatch rate was 3, the mean was 2.6, and the graft loss rate was 1.4%.

Table 1. Demographic characteristics of patients

	Whole population (n=154)	Kidney transplant recipients (n=70)	Hemodialysis patients (n=84)	p
Age	42 (15-88)	31.5 (15-61)	54.5 (19-88)	<0.001[a]
Gender, f/m (f%)	66/88 (42.9%)	20/50 (28.6%)	46/38 (54.8%)	0.001[b]
BMI, kg/m^2	22.5 (13.3-42.3)	22.2 (13.8-33.6)	22.8 (13.3-42.3)	0.519[a]
Spending time on dialysis, months	16 (0-204)	2 (0-197)	28 (4-204)	<0.001[a]
CKD etiology				
HT	51 (33.1%)	11 (15.7%)[a]	40 (47.6%)[b]	<0.001[b]
DM	23 (14.9%)	5 (7.1%)[a]	18 (21.4%)[b]	
GN	10 (6.5%)	8 (11.4%)[a]	2 (2.4%)[b]	
Others	70 (45.5%)	46 (65.7%)[a]	24 (28.6%)[b]	

[a]: Mann-Whitney U test, [b]: Pearson Chi-square test, BMI: Body-mass index, CKD: Chronic kidney disease, HT: Hypertension, DM: Diabetes mellitus, GN: Glomerulonephritis

Table 2. Clinical caharacteristics of kidney tranplanted recipients

Type of donor	
Deceased	4 (5.7%)
Living	66 (94.3%)
Induction regimen	
None	5 (7.1%)
IL-25 blockage	14 (20%)
ATG	51 (72.9%)
Number of missmatch	2.6±1.8 3 (0-5)
BPAR, y/n (y%)	4/70 (5.7%)
Graft loss, y/n (y%)	1/69 (1.4%)
Creatinin, mg/dL	
At discharging time	0.88 (0.78-1.92)
At second year	1 (0.89-1.22)
At fourth year	0.96 (0.9-2.21)
Last visit	1.01 (0.86-1.85)
ECG evaluation time, months	61.2±38.7 58.9 (8.1-130.3)

ATG: Anti-thymocyte globulin, BPAR: Biopsy proven acute rejection, ECG: Electrocardiography

Some clinical characteristics of the KTRs before and after kidney transplantation are shown in Table 3. Accordingly, high density cholesterol (HDL) increased after kidney transplantation (40 mg/dl vs. 37 mg/dl, $p<0.001$), there was no statistically significant change in triglycerides, low density cholesterol (LDL) and total cholesterol, the number of HT patients increased (46 vs. 17, $p<0.001$), the number of DM patients increased (14 vs. 3, $p=0.007$), and there was no statistically significant difference in terms of CAD and cerebrovascular event (CVE).

The ECG characteristics of the kidney transplant and HD patient groups are shown in Table 4. Accordingly, no statistically significant difference was found in terms of heart

rate, P axis, P wave, QRS axis, QRS complex and RR interval, while T axis was higher in the HD patient group (65° vs. 40.5°, p=0. 001), PR interval was longer in HD patient group (152 msec vs. 144 msec, p=0.020), QT interval was longer in the HD patient group (385 msec vs. 360 msec, p<0.001), QTC was longer in the HD patient group (463 msec vs. 415.5 msec, p<0.001).

Table 3. Clinical characteristics of kidney transplant patients before and after transplantation

(n=69), missing data=1	Pre-transplantation	Post-transplantation	p
Tryglicerid	164 (32-756)	132 (28-409)	0.268[a]
Total cholesterol	169 (105-314)	161 (90-288)	0.657[a]
HDL cholesterol	37 (14-98)	40 (18-100)	<0.001[a]
LDL cholesterol	92 (14-252)	87 (26-219)	0.146[a]
Hypertension, y/n (y%)	17/52 (24.6%)	46/23 (66.7%)	<0.001[b]
Diabetes mellitus, y/n (y%)	3/66 (%4.3)	14/55 (20.3%)	0.007[b]
Coronary artery disease, y/n (y%)	5/64 (7.2%)	4/64 (5.8%)	1.000[b]
Cerebrovasculary event, y/n (y%)	0/69 (0%)	0/69 (0%)	1.000[b]

[a]: Wilcoxon test, [b]: McNemar test, HDL: High density cholesterol, LDL: Low density cholesterol

Table 4. Electrocardiographical characteristics of patients

	Kidney transplant recipients (n=70)	Hemodialysis patients (n=84)	p
Heart rate	80.5±12.8	84.5±14.8	0.084[a]
P axis	+49.5° (-59°/+90°)	+49° (-63°/+180°)	0.793[b]
P wave, msec	105 (62-147)	107 (60-193)	0.687[b]
QRS axis	+30° (-47°/+98°)	+28° (-72°/+211°)	0.695[b]
QRS complex, msec	88 (72-140)	90 (66-173)	0.223[b]
T axis	+40.5° (-73°/+225°)	+65° (-67°/+266°)	0.001[b]
T axis classification			
Normal 15°-75°≤	50 (71.4%)[a]	38 (45.8%)[b]	
Borderline <15°-≥-15° and <75°-≤105°	8 (11.4%)[a]	20 (24.1%)[b]	0.006[c]
Abnormal <-15°-≥-180° and >105°-≤105°	12 (17.1%)[a]	25 (30.1%)[a]	
RR interval, msec	744 (537-1178)	703 (529-1273)	0.072[b]
PR interval, msec	144 (97-198)	152 (81-246)	0.020[b]
PR>200 msec, y/n (y%)	0/70 (100%)	4/79 (4.8%)	0.063[d]
QT interval, msec	360 (291-451)	385 (251-520)	<0.001[b]
QTc, msec	415.5 (354-496)	463 (299-551)	<0.001[b]

[a]: Independent sample t test, [b]: Mann Whitney U test, [c]: Pearson Chi-square test, [d]: Continuity correction

DISCUSSION

In our study, we found that ECG changes, which are risk factors for cardiovascular disease and mortality, improved in the long term after kidney transplantation compared to hemodialysis patients. We showed that QT duration was shorter and abnormal T axis changes were reduced in the long term after kidney transplantation compared to hemodialysis patients.

The risk of cardiovascular mortality is up to 100 times higher in the CKD population compared to the general population.[9] The functions of the kidney and heart are interconnected and interrelated. Impairment of the function of one of the two organs has a negative effect on the function of the other organ and leads to unfavorable clinical outcomes, which we define as cardiorenal syndrome. In addition to the contribution of the underlying disease causing CKD, such as HT and DM, to the development of cardiovascular disease in CKD patients, CKD-specific factors such as uremic toxins, inflammation, vascular calcification and thrombosis also contribute to the development of cardiovascular disease. Myocardial fibrosis and left ventricular hypertrophy, which develop as a result of collagen deposition between cardiomyocytes and capillaries in the myocardial region, are present in 70-80% of stage 5 CKD patients and are independent predictors of survival.[9] In patients with CKD, ischemic heart disease, heart failure, atrial fibrillation and arrhythmias are the most common causes of cardiovascular-related death.[1,2,10] Sudden cardiac death occurs up to twice as often in hemodialysis patients in the first 3 months than in peritoneal dialysis patients and is significantly more common in RRT recipients than in the general population. The fatal arrhythmias underlying sudden cardiac death are ventricular fibrillation, ventricular tachycardia, asystole and bradyarrhythmias.[3,11] Possible factors such as pre-existing hyperkalemia, acidosis, rapid potassium correction in dialysis, low calcium in the dialysate, and volume changes during hemodialysis can lead to cardiac electrical instability and potentially life-threatening arrhythmias.[3,11] The QT interval is used as a measure of ventricular depolarization and repolarization and has been shown to be prolonged in patients with CKD in many studies.[12-15] All-cause mortality and cardiovascular mortality are significantly increased in CKD patients with prolonged QT interval.[16,17] Many studies have shown that QT duration is shortened after kidney transplantation compared to hemodialysis patients and is still longer compared to the normal population.[12,18-20] Many of the etiologic risk factors for QT prolongation,[19] such as hypokalemia, hypocalcemia, hyponatremia, and low dialysate calcium intake, which are commonly seen in hemodialysis patients, disappear after renal transplantation. In addition, an improved uremic milieu and reduced inflammation as well as improved autonomic functions lead to better clinical outcomes in terms of cardiovascular disease in kidney transplant patients compared to hemodialysis patients. Akcay et al.[12] found a QTc value of 413.5 msec in renal transplant recipients and 421 msec in hemodialysis patients. Monfared et al.[18] found a maximum QTc of 436.3 msec in renal transplant recipients and 464.7 msec in hemodialysis patients. In another study, Monfared et al.[19] found 444.9 msec in renal transplant recipients and 471 msec before hemodialysis and 473 msec after hemodialysis in hemodialysis patients. In our study, similar to the literature, we found QT and QTc of 360 and 385 msec in renal transplant recipients and 415.5 and 463 msec in hemodialysis patients, respectively. Although there are studies showing that prolonged QT time is associated with mortality,[16,17] in a recent systematic meta-analysis that included 16 studies, the authors concluded that there is insufficient data to predict malignant ventricular arrhythmias

and cardiac arrest.[22] Limitations should be considered, such as the heterogeneity of the population in the studies included in this meta-analysis and the fact that the inclusion criteria represent only 2.3% of the relevant publications in the literature. In addition, only one study[13] from the CKD population was included in this meta-analysis, which did not include kidney transplant recipients, so it does not seem very appropriate to say that there is no association between prolonged QT and fatal arrhythmias and cardiovascular mortality in the CKD population. In our study, we evaluated the ECGs of KTRs after an average of 5 years and compared them with those of hemodialysis patients. Therefore, it was not possible to say whether the shortening of the QT interval occurred early after transplantation.

Scherer et al.[23] showed that a deviation of the T axis of more than 45° was associated with increased coronary artery calcification in elderly people of both sexes. In our study, we showed that the T axis regressed after kidney transplantation compared to hemodialysis patients (65° vs 40.5°). According to the classification of the T axis, the number of patients with borderline and abnormal T axis was higher in hemodialysis patients. This could be due to the fact that left ventricular hypertrophy, electrolyte abnormalities, pulmonary hypertension leading to right ventricular overload, and ischemic heart disease causing T axis abnormalities are more common in hemodialysis patients than in kidney transplant patients. In addition, vascular and coronary calcification are known clinical cardiovascular outcomes in hemodialysis patients. After kidney transplantation, this clinical process may improve.

Some sociodemographic differences in the study groups may have influenced the ECG differences between the groups. In the group of hemodialysis patients, the proportion of older patients, DM and HT was higher. DM, HT and advanced age are known risk factors for cardiovascular disease. Therefore, some ECG changes in our hemodialysis patient group could be due to these differences between the groups. Furthermore, since the ECGs of the patients were evaluated after a long period of time after transplantation, the presence of positive improvements in the lipid profile in the post-transplant period, such as higher HDL, as in our patients, may have influenced our results. These differences in the sample of our study make it difficult to make a clear causal interpretation of the results. Studies conducted in groups with similar sociodemographic characteristics and similar chronic diseases could help us to better understand cardiovascular disease and associated ECG changes in the post-transplant period.

Limitations

Due to the nature of this retrospective study, it was not possible to identify possible risk factors that may cause ECG abnormalities in both hemodialysis patients and KTRs. As this was a cross-sectional study, it was not possible to reflect the changes that may develop over time in the ECG of KTRs. As the aim of the study was to determine ECG changes after kidney transplantation, we were unable to detect the difference in these ECG abnormalities from healthy patients as a healthy group was not included in the study. As this was not a mortality and survival study, we could not detect the association between ECG abnormalities and survival in either group.

CONCLUSION

In conclusion, we have shown that renal transplant patients have shorter QT duration and lower T axis deviation during long-term post-transplant follow-up compared to hemodialysis patients. Prospective studies in KTRs are needed to demonstrate the impact of these ECG changes on cardiovascular clinical outcomes and patient survival.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Gazi Yaşargil Training and Research Hospital Clinical Researches Ethics Committee (Date: 29.09.2023 Decision No: 524).

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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The relationship between cognitive function and physical activity, functional status and social participation in older adults: a cross-sectional study

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ABSTRACT

Aims: Cognitive function in older adults has been a topic of growing interest in recent years. This study aimed to investigate the relationship between cognitive function and physical activity, functional status, and social participation in older adults.

Methods: A cross-sectional study was conducted involving 123 older adults aged 65 years and older who met the study's inclusion criteria. The inclusion criteria for the study were as follows: who were aged 65 years or older, literate, volunteering to participate in the study, had no hearing or vision defects that prevented the measurement of the scales used in the study, had no chronic disease that prevented the scales used in the study. The data in the study were collected with sociodemographic form, Montreal cognitive assessment, international physical activity questionnaire, timed-up-and-go test, 10-meter walk test, and Keele assessment of participation.

Results: The average age of the participants was 69.5±4.6. The study included 46.3% women and, 57.7% primary school graduates. A positive and moderate relationship was found between cognitive functions and physical activity level, functional status, and social participation in older adults. Additionally, there was a moderate positive relationship found between the level of physical activity, functional status, and social participation. In the cognitive function risk model, it was found that age, education level, and social participation significantly impact cognitive functions in older adults.

Conclusion: Increasing physical activity, functionality, and especially social participation in older adults can be considered an important intervention to protect and improve the cognitive functions of older adults.

Keywords: Aged, cognitive function, physical activity, social participation

INTRODUCTION

Understanding the factors influencing cognitive function among older adults is essential in addressing the challenges posed by an aging population worldwide. Cognitive decline is a significant concern associated with aging, affecting independence, quality of life, and healthcare demands. Recent research has increasingly focused on the role of lifestyle factors such as physical activity, functional status, and social participation in influencing cognitive health in older individuals.[1,2]

Physical activity has consistently been shown to have beneficial effects on cognitive function, potentially enhancing both brain structure and function.[3] Regular exercise positively influences various cognitive domains, including global cognition, attention, executive function, and memory.[4] Additionally, maintaining a high functional status, which includes mobility, physical independence, and the ability to perform daily activities, is crucial for sustaining cognitive abilities in older adults.[5] Functional status is closely linked to cognitive resilience, as greater physical independence often correlates with better cognitive performance.[5]

In addition to physical activity and functional status, social participation plays a critical role in cognitive health. Social engagement through participation in activities and social networks has been associated with cognitive resilience and a reduced risk of cognitive decline.[6] Active involvement in social relationships and leisure activities has been identified as a protective factor against cognitive decline and dementia in longitudinal studies.[7,8] Fostering an active and socially integrated lifestyle in late life may serve as a significant protective measure against dementia.[8]

Despite these insights, there remains a need for comprehensive studies that elucidate the interplay between physical activity, functional status, social participation, and cognitive function in older adults. Such research is pivotal for developing targeted interventions and policies aimed at promoting healthy aging and preserving cognitive abilities in aging populations.

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This study aims to contribute to the expanding field of research by investigating the correlations between cognitive function and physical activity, functional status, and social participation among older adults. By providing a deeper understanding of these relationships, the study seeks to inform strategies that could preserve cognitive health and enhance the quality of life for aging populations worldwide.

METHODS

Study Design and Participants

A cross-sectional study was conducted between August 2022 and February 2023 and approved by the Akdeniz University Clinical Researches Ethics Committee (Date: 08.06.2022, Decision No: KAEK-403). The entire study was conducted in accordance with the Helsinki Declaration of 1975. The study enrolled 123 older adults aged 65 years and older who presented at Kuzeykent Family Medicine Polyclinic and Private Şelale Termesos Hospital Physical Therapy and Rehabilitation Polyclinic, meeting the predefined inclusion criteria. Participants were required to be aged 65 or older, literate, voluntarily consenting to participate, and free from hearing or vision impairments that could interfere with the study's measurement scales, as well as without chronic diseases that would affect the assessment scales.

Demographic Information Form

Researchers utilized a participant information form to gather sociodemographic data, including age, gender, education level, occupation, social security status, monthly income, marital status, smoking and alcohol habits, and medical history.

Montreal Cognitive Assessment (MoCA)

The MoCA served as a primary tool for screening mild cognitive impairment. This assessment evaluates multiple cognitive domains such as attention, executive function, memory, language skills, conceptual thinking, calculation abilities, and orientation. It typically requires 10-15 minutes to complete. Previous studies have demonstrated the MoCA's high sensitivity and specificity in detecting mild cognitive impairment compared to the Mini-Mental State Examination.[9] In this study, a MoCA cut-off score of 21 was used to identify any cognitive dysfunction within the Turkish population.[10] The Turkish version of the MoCA has been validated and found to be a reliable tool for assessing cognitive impairment in various populations.[11]

International Physical Activity Questionnaire (IPAQ)

The International Physical Activity Questionnaire (IPAQ) is a self-reported questionnaire for assessing physical activity. The short version provided information on the time spent walking, in vigorous- and moderate intensity activity and in sedentary activity.[12] The Turkish version of the IPAQ is a reliable and valid tool for assessing physical activity among Turkish-speaking populations. It can be effectively used in both research and clinical settings to evaluate physical activity levels. Additionally, it can inform public health initiatives aimed at reducing physical inactivity and its associated health risks.[13]

Timed Up and Go Test (TUG)

In the TUG test, participants were instructed to stand up from a chair with a seat, walk a distance of 3 meters at a normal pace, turn around, walk back to the chair, and sit down. The timing, measured in seconds, started when the word "go" was said and stopped when the participant's back touched the chair's backrest. A shorter time taken indicates better balance ability.[14]

10 Meter Walk Test (10mWT)

The 10 Meter Walk Test is a performance measure used to assess walking or gait speed in meters per second over a short distance. Participants were instructed to walk at their usual pace as they entered the acceleration zone. A space longer than 10 meters was designated for the test, with the start and end of the 10-meter section marked with tape. Timing commenced as the participant's foot crossed the tape at the beginning of the 10-meter course and concluded when the foot crossed the line at the end of the course. Two trials were carried out, and the average walking speed was calculated in meters per second (m/s).[15]

Keele Assessment of Participation (KAP)

KAP was developed by Ross Wilkie and his colleagues in 2005 to evaluate quality of life and participation for individuals aged 50 and over. KAP defines participation restriction as the problems experienced in participating in living conditions, as perceived by the individual.[16] The Turkish version of the Keele Assessment of Participation is considered a valid and reliable measurement tool for assessing social participation among older adults.[17]

Statistical Analysis

SPSS Statistics Base 23 version of SPSS Software was used for data analysis. Descriptive statistics, correlation analysis (Pearson Correlation Analysis), Mann Whitney U test, and the Kruskal Wallis test were used to evaluate the study data. The results were assessed at the 95% confidence interval and $p<0.05$ significance level.

The Windows-based SPSS 23.0 version software (Statistical Package for the Social Sciences, SPSS Inc., Chicago, IL, USA) analysis program was used for statistical analysis. The normal distribution of the data was examined using the Kolmogorov-Smirnov test. Descriptive characteristics were identified as a minimum, maximum, and "standard deviation (X±SD)" for the quantitative data, while number (N) and percentage (%) values were given for qualitative data. Kruskal-Wallis test and The Mann-Whitney U test were used for intergroup comparison of ordinal variables or abnormally distributed non-parametric data sets. Pearson correlation analysis was used to examine the relationship between cognitive function and physical activity, functional status, and social participation. Multiple linear regression analysis was performed to investigate the effects of age, education, physical activity, and mobility on social participation.

RESULTS

The sociodemographic characteristics of older adults are presented in Table 1. The study included 123 older adults, with

a mean age of 69.5±4.6 years (min 65 - max 91). The mean age for women was 68.8±4.4 years (min 63 - max 86), and for men, it was 70.1±4.7 years (min 65 - max 91).

Table 1. Sociodemographic characteristics of older adults

		n/%	p
Sex	Female	57/46.3	.001[a]
	Male	66/53.7	.033[b]
Marital status	Married	97/78.9	.014[c]
	Single	26/21.1	.000[d]
Education	Primary school	71/57.7	.000[a] .012[b]
	High school	25/20.3	
	University	27/22	
Working status	Other	6/4.87	
	Retired	117/95.1	
Having chronic diseases	Yes	62/50.4	
	No	61/50.4	

p[a]: Montreal cognitive assessment score, p[b]: 10-meter walk test score, p[c]: Timed up and go score, p[d]: Keele assessment of participation score

In cognitive functions, walking speeds, and mobility levels, males exhibited higher scores compared to females ($p<0.01$ and $p<0.05$, respectively). Conversely, females demonstrated higher levels of social participation compared to males ($p<0.01$). Among university graduates, cognitive levels ($p<0.01$) and walking speeds ($p<0.05$) were higher compared to those with primary school education.

Older adults with higher cognitive function showed better functional status (walking speed and mobility) and social participation compared to those with lower cognitive function. Participants who engaged in moderate and high levels of physical activity demonstrated superior cognitive function, functional status, and social participation compared to those with low physical activity levels. According to the timed up and go (TUG) test, older adults without fall risks exhibited better cognitive function, social participation, and physical activity levels, and walked faster than those at risk of falls. Older adults without limitations in participation showed higher levels of cognitive function, functional status, and physical activity compared to those with participation restrictions ($p<0.01$). The clinical characteristics of older adults have been presented in Table 2.

The correlations between parameters evaluated of older adults have been presented in Table 3.

Table 3. Correlations between parameters evaluated in older adults in the study

	MoCA	IPAQ	TUG	10 mWT	KAP
Age	-.234*	-.167*	.364*	.387*	.128
Sex	.300*	.150	-.240*	-.226*	-.331*
Education	.603*	.301*	-.342*	-.329*	-.329*
IPAQ	.260*	-	-.385*	-.475*	-.279*
TUG	-.470*	-.385*	-	.850*	.496*
10 mWT	-.430*	-.475*	.850*	-	.428*
KAP	-.513*	-.279*	.496*	.428*	-

MoCA: Montreal cognitive assessment, IPAQ: International physical activity questionnaire, TUG: timed up and go test, 10 mWT: ten-meter walk test, KAP: Keele assessment of participation, *Correlation is significant at the 0.01 level (2-tailed). Pearson correlation

In this study, a model was developed to examine the impact of age, education, physical activity level, functional status, and social participation on the cognitive function of older adults. The model revealed a strong relationship between the dependent variable and independent variables ($p<0.01$, $r=0.722$). The independent variables (age, education, physical activity level, functional status, and social participation) collectively explained 50.1% of the variance in the dependent variable (cognitive function) (r square=0.522) (Table 4).

Table 2. Clinical characteristics of older adults

		n (%)	X±SD (min-max)	p
MoCA[10]	MoCA score ≥21	83/67.5	25.2±2.6 (21-30)	$p^{b,c,d,e}<0.01^{2}$
	MoCA score ≤20 (mild cognitive impairment)	40/32.5	16±2.5 (12-20)	
	Total	123/100	22.2±5.1 (12-30)	
IPAQ	Low physical activity	41/33.3	284.6±232.8 (0-960)	$p^{a,b,c,d}<0.01^{1}$ $p^{a,b,c,d}<0.01^{2,3,4}$
	Moderate physical activity	62/50.4	1565.3±681.3 (579-2994)	
	High physical activity	20/16.3	5279.7±2213.8 (3150-11466)	
	Total	123/100	1742.4±1947.9 (0-11466)	
TUG	TUG score ≥12	47/38.2	13.4±1.5(11.5-20)	$p^{a,b,d,e}<0.01^{2}$
	TUG score <12	76/61.8	9.8±1.1 (7.5-11.5)	
	Total	123/100	11.1±2.1 (7.5-20)	
10 mWT	Total	123/100	10.3±2.2 (7-19)	
KAP[16]	No restriction	20/16.3	.0±.0 (0-0)	$p^{a,b,c,e}<0.01^{2}$
	Exist restriction	103/83.7	3.6±1.9 (1-8)	
	Total	123/100	3.1±2.2 (0-8)	

Min: Minimum, Max: Maximum, X: Mean, SD: Standard deviation, MoCA: Montreal cognitive assessment, IPAQ: International physical activity questionnaire, TUG: Timed up and go test, 10 mWT: Ten meter walk test, KAP: Keele assessment of participation, p[a]: Montreal cognitive assessment score, p[b]: Ten meter walk score, p[c]: Timed up and go score, p[d]: Keele assessment of participation score, p[e]: International physical activity questionnaire score, [1]Kruskal Wallis, [2]Mann Whitney U test, [3]Low-moderate physical activity level comparison, [4]Low-high physical activity level comparison

Table 4. Linear regression model (dependent variable: MoCA)								
Cognitive function risk model	**b**	**SD error**	**Beta**	**t**	**p**	**Partial r**	**Part r**	**OR (CI 95%) (lower/upper)**
Constant	36.665	5.032	-	7.287	.000	-	-	(26.701/46.630)
Independent Variables								
Age	-.183	.077	-.167	-2.392	.018	-.216	-.153	(-.335/-.032)
Education	1.790	.265	.482	6.755	<0.01	.530	.432	(1.266/2.315)
IPAQ	-.000	.000	-.039	-.542	.589	-.050	-.035	(.000/.000)
TUG	-.275	.195	-.118	-1.413	.160	-.129	-.090	(-.661/.111)
KAP	-.643	.170	-.286	-3.790	<0.01	-.331	-.242	(-.978/-.307)

MoCA: Montreal cognitive assessment, SD: Standard deviation, IPAQ: International physical activity questionnaire, TUG: Timed up and go test, KAP: Keele assessment of participation, r: correlation, CI: Confidence interval for b, r=.722, r^2=.522, Adjusted r^2=.501, f= 25.509, p=0.00, Durbin-Watson=1.763

DISCUSSION

This study aimed to investigate the relationship between cognitive function and physical activity, functional status, and social participation in older adults. The findings revealed a positive correlation between cognitive function and levels of physical activity, functional status, and social participation among older adults. Furthermore, significant associations were observed among physical activity levels, functional status, and social participation, as assessed in the study. Additionally, a cognitive function risk model indicated that age, educational attainment, and social participation significantly impact cognitive function in older adults.

Gender differences in cognitive function remain a complex issue, with some studies suggesting that men generally exhibit better cognitive skills than women.[18,19] Our findings support this trend, as men in the study tended to have higher cognitive levels than women, potentially influenced by factors such as income and educational status. However, these gender disparities likely reflect a broader societal context, where men may have historically had greater access to education and economic opportunities.[20] Future research should explore these differences more critically, considering the interplay of social, economic, and biological factors in cognitive aging.

The study further demonstrated that higher educational levels in older adults correspond to enhanced cognitive function, consistent with previous research.[21,22] Zhang et al.'s[23] study with older adults supported these findings, indicating that education positively influences cognitive skills, including episodic memory and overall cognitive function. These findings highlight the long-term benefits of educational attainment in promoting cognitive health in older adults, reinforcing the need for policies that support lifelong learning.

Our study demonstrated a moderate positive relationship between physical activity and cognitive function, aligning with previous research that supports the protective effects of moderate to vigorous physical activity on cognitive health. Physically active older adults have been shown to have larger hippocampal, prefrontal cortex, and basal ganglia volumes, enhanced brain connectivity, better white matter integrity, and improved executive and memory function.[24] The preservation of white matter integrity, linked to functional connectivity, suggests that physical activity may play a crucial role in maintaining cognitive function in aging populations.[25]

This study reinforces the idea that physical activity is an essential factor in cognitive aging, possibly exerting a more significant impact than age or education.[26]

Cognitive function and functional capacity are both key indicators of aging, crucial for independent living. Higher levels of functionality, such as walking speed and mobility, were associated with better cognitive function in our study, consistent with the literature.[27] Interventions targeting both motor and cognitive skills, such as those that incorporate sit-to-stand exercises, have been shown to benefit older adults with mild cognitive impairment.[28] Consistent with existing literature, our study showed that increased functionality (e.g., walking speed, mobility) corresponds to higher cognitive function levels. Additionally, contrary to Liao et al.'s findings suggesting older women are more physically active than older men [29], our study found higher walking speed and mobility levels among men compared to women.

Our study also revealed that increased social activity among older adults leads to higher cognitive function levels. Fu et al.[30] demonstrated in China that engaging in activities improves cognitive function in older adults of both genders, suggesting a protective effect of social engagement on cognitive function. Social engagement, such as participating in community groups, clubs, and social events, is proposed to delay or prevent cognitive decline in middle-aged and older individuals. Proposed mechanisms include mental stimulation, a sense of purpose, and stress reduction, all potentially protecting against neuropathology and cognitive impairment.[31,32] Although our findings suggested that older women engaged more in social activities than men, cultural norms may account for this difference, emphasizing the importance of fostering social networks to promote healthy cognitive aging.

The literature strongly advocates for encouraging and facilitating social participation in later life as a strategy to support healthy cognitive aging and prevent dementia. Therefore, promoting social engagement should be a key component of programs and policies aimed at optimizing cognitive function in older adults. While this study found relationships between physical activity, functional status, and social participation with cognitive function in older adults, the cognitive function risk model created in our study highlighted that social participation significantly influences cognitive function.

Limitations

A significant limitation of our study was the small sample size, which affects the generalizability and statistical power of our findings. Despite broad inclusion criteria, difficulties in recruiting participants from the target demographic of older adults contributed to a lower-than-expected response rate. Factors such as limited accessibility and mobility challenges likely played a role in this, highlighting the need for improved recruitment strategies in future research. With a sample of 123 older adults, the study provides a modest representation of the target population, but the small sample size may reduce the power to detect smaller effects or interactions, increasing the risk of Type II errors. The power of this study is also influenced by the observed effect sizes and the statistical methods employed. While Pearson correlation, Mann-Whitney U, and Kruskal-Wallis tests were appropriate for identifying relationships between variables, their efficacy is contingent upon the sample size and effect magnitude. The regression model demonstrated a relationship between cognitive function and independent variables such as age, education, physical activity, functional status, and social participation, with an R-squared value of 0.522, indicating that these variables collectively explain over half of the variance in cognitive function. However, the small sample size may limit the precision of these estimates, particularly in subgroup analyses (e.g., by gender or education level) or when detecting subtle effects. To enhance the power and generalizability of future research, conducting longitudinal studies with larger samples would be beneficial. This would allow for more precise estimates of effect sizes and stronger conclusions about the relationships between cognitive function and the lifestyle factors studied. Another limitation was the use of the IPAQ to measure physical activity, as its reliability is weaker, especially among the oldest age groups.

CONCLUSION

This study identified significant relationships between cognitive function, physical activity, functional status, and social participation in older adults. The cognitive function risk model findings highlight the critical role of social participation, along with age and education, in cognitive health. Prioritizing interventions that enhance physical activity, functionality, and social participation could help improve cognitive health and prevent dementia in aging populations.

This study aimed to fill a gap in the literature by exploring how physical activity, functional status, and social participation together impact cognitive function in older adults. Much of the existing research focuses on either physical activity or social participation in isolation, without considering how these factors interact to support cognitive resilience. This study underscores the importance of considering multiple lifestyle factors and the need for integrated interventions that address physical activity, functionality, and social participation in supporting cognitive health in older adults.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Akdeniz University Clinical Researches Ethics Committee (Date: 08.06.2022, Decision No: KAEK-403).

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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Relationship between 25(OH)D3 levels and cognitive functions in children with obesity

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ABSTRACT

Aims: The inconsistent results about neurocognitive functions in children with obesity may be suggestive of factors like vitamin deficiencies rather than the disorder itself. So we aimed to investigate the 25(OH)D3 levels and cognitive functions in obese children in the present study.

Methods: Seventy-two children were included to this study. Forty-one of them were obese children and 31 children were with normal weight. The patients were diagnosed as obese according to body mass index >95 percentile, considering the sex and age-specific growth curves for Turkish children. The participants completed the battery tests of the central nervous system vital signs (CNSVS), a neurocognitive test battery, via computer. The battery calculates seven domain scores (Memory, Psychomotor speed, Processing speed, Reaction time, Complex attention, Executive function, Cognitive flexibility) and a summary score (Neurocognition Index). 25(OH)D3 levels were measured in residual samples using a Shimadzu HPLC system with the aid of a 25(OH)D3 kit. The scores were compared by using commercial software (IBM SPSS Statistics 18).

Results: The mean 25-OH-vitamin D levels were 13.41±7.91 µg/L in obese children and 20.31±5.92µg/L in controls. Vitamin D3 levels were significantly lower in obese children than in control group ($p<0.05$). There was statistically significant difference between patient and healthy control group on all cognitive performance domains. Mean NCI score of obesity group was 86.17±8.85, whereas that of healthy participants was 90.61±8.28. The mean NCI score in the obesity group was significantly lower than that of the control group ($p<0.001$).

Conclusion: Cognitive index of obese children is lower than normal weight children. Lower 25(OH)D3 levels are related to cognitive deficits in children with obesity. Cognitive dysfunction and 25(OH)D3 levels in obese children and adolescents should be addressed in the evaluation and treatment of this population.

Keywords: Child, obesity, 25-OH-vitamin D, cognitive dysfunction

INTRODUCTION

The prevalence of childhood obesity has increased dramatically and steadily in last four decades and obesity has become a serious worldwide public health problem. Obesity is not only an increased calorie intake and weight management problem, but also a malnutrition condition with vitamin deficiency and reduce in cognitive functions.[1,2] It is well known that vitamin D insufficiency is more prevalent in children with obesity.[3-5] Etiopathogenesis of vitamin D deficiency in obese children is not clear. Some investigators claimed that the sequestration of vitamin D in the body fat and its consequent is reduced bioavailability, others claimed that fewer outdoor activities and reduced sunlight exposure contributes to reduced endogenous vitamin D production.[6]

Recent studies investigated executive cognitive functions in obesity. A negative relationship between body-mass index (BMI) and neurocognitive performance in adults has been shown in many studies in the literature.[7] Cognitive dysfunction generally refers to deficits in memory and executive function, and many diseases other than obesity may show cognitive dysfunction.[8] Cognitive dysfunction associated with high calorie intake and sedanter behaviour and negatively associated with fruit and vegetable intake and physical activity, briefly associated with obesity.[9] It is shown that improvements in executive functions were also found to be related to weight loss suggesting that neurocognitive functions have positive implications for reducing weight in obese adolescents.[10] Some investigators suggested that inflammation is the underlying mechanism of cognitive deficit related to obesity.[11] It is shown that reducing inflammation by vitamin D contributes the development of cognitive functions in rat model.[12] Vitamin D is not only involved in bone metabolism. Recent studies have demonstrated that vitamin D is a neuro-protective and an

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anti-inflammatory biologic agent.[13] VDR have been located in cortex, cerebellum, thalamus, hypothalamus, basal ganglions and hippocampus. Some of these areas are regulating cognitive functions and absence of the VDR has been associated with neurodegenerative diseases.[14,15] Therefore, we aimed to investigate the relationship between 25-OH-vitamin D levels and cognitive functions in children with obesity.

METHODS

Participants

In the present study 72 children were included. Forty one of them were obese and others were normal weight. The patients were diagnosed as obese according to BMI >95 percentil, considering the sex and age-specific growth curves for Turkish children.[16] Weights were measured with digital scale (Seca). Measurements were done while patients are barefoot and light cloth wearing. Height was measured with portable stadiometer (Harpenden). BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2). Subjects with any genetic syndrome, metabolic (e.g., type 2 diabetes, metabolic syndrome) or endocrine disease (e.g., Cushing syndrome, hypothyroidism) and other diseases (e.g., hypertension, non-alcoholic fatty liver disease) as well as subjects on medications or a diet were excluded. All children and adolescents in the obesity and control groups with an IQ<80 on the fifth edition of the Stanford-Binet intelligence test, and with a diagnosis of any neurological disorder or head injury, and color blindness, past or current substance abuse were excluded from the study. The study protocol was approved by the Non-invasive Clinical Research Ethics Committee of Gaziosmanpaşa University (Date: 30.03.2016, Decision No: 16-KAEK-073) and written informed consent was obtained from both parents before starting any study-related procedure. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Measures

Central nervous system vital signs (CNSVS): The CNSVS is a computerized, neurocognitive test battery for use in clinical research. The psychometric characteristics of the tests in the CNSVS battery are very similar to the characteristics of the conventional neuropsychological tests and the reliability and validity has been demonstrated.[17] It has normative data for children as young as 7 years of age and Cohen d effect sizes range from d=0.44 to d=1.19 regarding retest reliability in children and adolescents.[18] It is administered via a computer and takes approximately 30 to 40 minutes to complete. The CNSVS comprises of 7 common neuropsychological measures: verbal memory test, visual memory test, finger tapping test (FTT), symbol digit coding (SDC), the stroop test (ST), shifting attention test (SAT) and continuous performance test (CPT). The battery generates 15 primary scores which are used to calculate seven domain scores (Memory, Psychomotor speed, Processing speed, Reaction time, Complex attention, Executive Function, and Cognitive flexibility) and a summary score (Neurocognition Index). Domain scores are presented as index scores, with a mean of 100 and standard deviation (SD) of 15.

Laboratory test: Blood samples were drawn for routine testing and 25-OH-vitamin D levels were measured in residual samples using a Shimadzu HPLC system (Shimadzu Corp. Kyoto, Japan) with the aid of a 25-OH-vitamin D kit (Recipe Chemicals +Instruments GmbH, Munich, Germany).

RESULTS

The study group consisted of 41 patients (19 males, 22 females) with a mean age of 11.85±2.43 years of age. Thirty one healthy children and adolescents (15 males, 16 females) with a mean age of 11.9±2.96 years were included in the control group. There is no statistically significant difference between groups in terms of number, gender, and age of the participants (p>0.05). Demographic, laboratory and clinical findings are shown in Table 1. The mean 25-OH-vitamin D levels were 13.41±7.91 µg/L in obese children and 20.31±5.92µg/L in controls. Vitamin D levels were significantly lower in obese children than in control group (p<0.001).

Table 1. Comparison of cognitive functions and vitamin D3 status between obese children and healthy control

Variables	Group			Bonferoni 95% CI	
	Patients n: 41 Mean±SD	Healthy n: 31 Mean±SD	p	Lower	Upper
Gender (male/female)	19/22	15/16	0.863	-	-
Age (years)	12.15±1.75	12.39±2.47	0.630	-	-
BMI	29.27±4.00	20.70±3.65	<0.001	-	-
BMI-SDS	2.74±0.39	1.25±0.24	<0.001	-	-
25(-OH) D3 (ng/ml)	13.41±7.91	20.31±5.92	<0.001	-	-
Calcium (mg/dl)	9.96±0.31	9.84±0.30	0.128	-	-
Phosphate (mg/dl)	4.54±0.59	4.59±0.50	0.747	-	-
ALP	209.98±92.14	224.27±99.43	0.551	-	-
NCI	86.17±8.85	90.61±8.28	0.034	-1.50	10.38
Composite memory	86.22±10.45	95.1±10.65	0.001	1.61	16.15
Verbal memory	87.44±10.30	98.87±12.37	<0.001	3.68	19.18
Visual memory	89.51±12.18	96.65±9.38	0.009	-0.50	14.77
Processing Speed	88.29±12.78	96.94±8.88	0.002	0.86	16.42
Executive function	89.24±11.32	93.32±10.11	0.118	-3.38	11.54
Psychomotor speed	87.98±12.18	94.13±6.96	0.009	-0.93	13.24
Reaction time	77.37±14.64	90.52±18.55	0.001	1.81	24.49
Complex attention	90.37±9.72	98.74±8.65	<0.001	1.98	14.78
Cognitive flexibility	88.54±10.26	93.29±10.03	0.053	-2.26	11.76

p1: Individual t-test significance levels, p2: Hotelling's T2 test (Multivariate analysis) was used, SD: Standard deviation, BMI: Body-mass index, BMI SDS: Body-mass index standard deviation score

The two groups were compared on the 7 index scores of CNSVS. There was statistically significant difference between patient and healthy control group on all cognitive performance domains. Mean NCI score of obesity group was 86.17±8.85, whereas that of healthy participants was 90.61±8.28 (p:0.034). The mean score of NCI in patients with obesity was significantly lower than that of healthy control

participants by calculating according to one variable analysis. But the statistically importance got lost when the data were calculated according to multiple variable analysis Bonferroni test. The same results were seen when evaluating the visual memory, executive function and psychomotor speed. But the mean scores of composite memory, verbal memory, processing speed, reaction time and complex attention were statistically different among the healthy subjects and obese children according to results of one variable test and multiple variable tests Bonferroni. Table 1 shows the scores for group differences in cognitive performance of obesity and matched control group.

Mean cognitive index was similar in groups girls and boys (p=0.232). Vitamin D levels belong to patients were significantly lower than control group (p<0.001). Lower cognitive indexes were significantly in a correlation with lower vitamin D levels. The most effected function is verbal memory. Reaction time shows no difference between obese patients and control group.

According to regression analysis for 25(OH)D3 a 0.01 µg/L increase in 25(OH)D3 level provides an increase of 0.167 units in NCI, but this increase is not statistically significant (t=1.301: p=0.197). Similar results were revealed by the regression test from the other parameters for CNSVS. In the regression analysis performed according to vitamin D levels and the study group, the change in NCI of obese children is 0.178 units less than healthy children, but this decrease is not statistically significant (t=-1.391: p=0.169) (Table 2).

Table 2. Regression results for 25-(OH)-D3 and study group independent predictors on CNSVS parameters

Predictors	CNSVS parameters	β	t	p
Obese	NCI	0.167	1.301	0.197
Healthy		-0.178	-1.391	0.169
Obese	Composite memory	-0.161	-1.325	0.189
Healthy		-0.460	-3.781	<0.001
Obese	Verbal memory	-0.190	-1.628	0.411
Healthy		-0.538	-4.602	0.026
Obese	Visual memory	0.043	0.337	0.737
Healthy		-0.289	-2.272	0.026
Obese	Processing speed	-0.231	-1.897	0.062
Healthy		-0.460	-3.779	<0.001
Obese	Executive function	-0.048	-0.366	0.716
Healthy		-0.207	-1.576	0.120
Obese	Psychomotor speed	0.182	1.442	0.154
Healthy		-0.208	-1.651	0.103
Obese	Reaction time	0.124	1.007	0.317
Healthy		-0.319	-2.584	0.012
Obese	Complex attention	-0.082	-0.678	0.500
Healthy		-0.449	-3.695	<0.001
Obese	Cognitive flexibility	-0.055	-0.424	0.673
Healthy		-0.253	-1.943	0.056

CNSVS Central nervous system vital signs

DISCUSSION

The study investigated the relationship between 25-OH-vitamin D levels and cognitive functions in children with obesity. The results show that the children with obesity performed significantly worse than non-obese healthy controls on all cognitive domains. This present study is also important for evaluating 25-OH-vitamin D levels along with neurocognitive functions comparing them with those of a control group.

Childhood obesity is a growing serious health problem all over the world. It is giving rise to devastating public health issues together and threatening the child health. Also governments take into account the economic magnitude while struggling to recover deleterious effects of obesity [19]. Obesity is not only eating or getting more calorie disorder but also genetic, metabolic and systematic disease. We can meet health problems in many organs and organ systems. Mental health is also affected by obesity induced oxidative stress. It is well known that in various mechanisms obesity induces systemic oxidative stress resulting cognitive impairments. Obesity usually correlates with increased prevalence of vitamin deficiencies or decreased circulating 25(OH)D3 levels. Lower serum 25(OH)D3 levels were associated with higher BMI and metabolic syndrome parameters. Various studies have demonstrated that obese people have lower 25(OH)D3 levels than normal weight people. Synthesis and regulation of 25(OH) D3 confirmed that obese patients had lower basal 25(OH)D3 levels and higher serum parathyroid hormone levels than non-obese patients.[20] In many studies it is shown that vitamin D levels were lower in obese children than normal weights. Some theories are put forward to explain the relationship between lower vitamin D levels and obesity. One of them is volumetric dilution of vitamin D is probable mechanism of the inverse relationship between vitamin D serum levels and BMI.[21] The most popular accepted physiopathologic mechanism of low vitamin D level is that vitamin D, being fat-soluble, is over-absorbed by adipose tissue. Fiamenghi has conducted a study as a meta-analysis including 24,600 patients and confirmed that obesity is in a strong relationship between lower vitamin D levels as demonstrated in this study.[22] In a systematic review exploring the association between obesity and Vitamin D levels demonstrated that obese subjects have lower vitamin D levels than normal and overweight group.[23]

Chronic inflammation, endothelial dysfunction, and mitochondrial dysfunction are the sample mechanisms of the oxidative stress effects in obese population.[24] A study conducted by Li et al.[25] comparing the cognitive ability in overweight and healthy children demonstrated that the cognitive ability is lower in overweight group. On the other hand overweight or obese children show no difference in terms of cognitive ability in healthy children with normal BMI.[26] But it should also be noted that the number of these studies is limited. Obese children were also more likely to have low school success, psychosocial problems like social marginalization and low self-esteem.[27] The findings of this study that obese children have reduced cognitive functioning are consistent with the growing number of studies linking obesity and poor neurocognitive outcome.

We also found lower serum 25-OH-vitamin D levels in obese children in the present study.

There have been many biologically relevant receptors for vitamin D found in many cells, including neurons and glial cells. In humans, vitamin D is a neuro-steroid hormone that can regulate muscle function, neuro-protection, neuro-immunomodulation, and brain function. Human cortex and hippocampus areas are very important for cognition and vitamin D receptors (VDR) are especially located in these areas. Harse et al.[28] demonstrated that the higher 25-OH-vitamin D concentrations were found to be associated with increased cognitive performance in their meta analyse study.

In the present study, we aim to answer why cognitive disability is observed in some obese children but not in normal-weight children. We investigate the relationship between obesity, low cognitive performance, and lower vitamin D levels. We demonstrated a strong relationship between obesity, low vitamin D levels, and poor cognitive performance in children. Guo et al.[29] demonstrated an important relationship between lower vitamin D levels and cognitive impairment as we point out in this study. Furthermore Almuqbil et al.[30] also showed that vitamin D deficiency is related to depression, stress and anxiety which can lead to cognitive impairment in university students. A meta-analysis revealed that people with high vitamin D levels had better cognitive functions than those with low vitamin D levels. Another study conducted with mice showed that Vitamin D suppressed inflammation in the hippocampus explaining the improved cognitive functions in these mice.[31] Studies have indicated that vitamin D protects against memory dysfunction caused by oxidative stress and inflammation in the hippocampus by suppressing TNF-α. and stimulating vitamin D receptors. Additionally, a study showed that serum 25(OH)D3 levels were inversely associated with systemic inflammation biomarkers in obese people.[32] Literature supports the findings of the present study.

Limitations

Our study has several limitations that should be addressed. Firstly we didn't control for socio-economic status (household income, parental education, etc.) in our population. Because obesity is strongly associated with poverty, which is itself a significant risk factor for cognitive dysfunction. Moreover, the deficits on cognition measured by computerized battery should be supported with conventional neuropsychological tests for exact measuring. Another important limitation of this study is that it did not monitor the extent to which cognitive functions improved after vitamin D treatment in children with cognitive dysfunction and low vitamin D levels.

CONCLUSION

Vitamin D levels are significantly lower in obese individuals compared to the normal population. Concurrently, significant cognitive dysfunction is observed in obese individuals. According to the data obtained from this study, one of the important reasons for cognitive dysfunction in obese individuals is the low vitamin D levels caused by obesity. Further research should be conducted with a larger study group to reveal the expected improvement in cognitive functions following vitamin D treatment.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Gaziosmanpaşa University Faculty of Medicine Clinical Researches Ethics Committee (Date: 30.03.2016, Decision No: 16-KAEK-073).

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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A structural modeling approach to determine the effects of orthorexia nervosa and social appearance anxiety on healthy lifestyle behaviors in young adults

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ABSTRACT

Aims: The aim of this study is to examine the relationship between orthorexia nervosa (ON) and social appearance anxiety (SAA) and to investigate the effects of these variables on healthy lifestyle behaviors (HLB) in young adults aged 18-30 years.

Methods: A total of 408 young adult male and female volunteers, with a mean age of 21.7±2.95 years, participated in this study. A structural model was proposed to examine the effects of SAA and ON on HLB. To assess how well the study variables represented the underlying components, we first evaluated a confirmatory measurement model. Subsequently, we analyzed a structural model that allowed for the examination of multiple regression equations involving several dependent variables.

Results: SAA had a negative influence on HLB (std β=-0.673; t-value=-8.425), a significant negative relationship between ON, HLB was also promoted (std β=-0.554; t-value=-9.388). It was determined that there is a positive correlation between SAA, ON which is statistically significant (correlation coefficient=0.830; t-value=10.244).

Conclusion: It is concluded that the individuals with high social appearance anxiety do not adopt healthy lifestyle behaviors and are more prone to orthorexia nervosa.

Keywords: Healthy lifestyle behaviors, social appearance anxiety, orthorexia nervosa, structural equation modeling

INTRODUCTION

Over the last decade, orthorexia nervosa (ON) has been conceptualized as an obsessive preoccupation with healthy eating and dieting, leading to various emotional and psychosocial consequences.[1] Eating behavior is a complex process influenced by internal, environmental, and social factors. The emergence of nutritional dependencies often stems from emotional or environmental conditions, or impulsive-compulsive behaviors resulting from psychological dependence on nutrients. Eating disorders manifest when attitudes and behaviors around eating significantly disturb the individual. These disorders include conditions that result from excessive focus on body weight and significant changes in eating behaviors. Young adults, particularly, exhibit heightened concerns regarding body fat and body mass indexes. Understanding sociocultural and sociodemographic characteristics is crucial for preventing the escalation of these disorders among young individuals.[2]

Healthy lifestyle behaviors (HLB) have been shown to positively impact individuals' health and quality of life. Enhanced satisfaction with one's body often correlates with reduced awareness of external appearance. Negative attitudes and behaviors related to body image can lead to issues such as depression, low self-esteem, and social anxiety, significantly affecting interpersonal relationships. Misconceptions about body image and body dissatisfaction are prevalent across age groups. Moreover, recent literature suggests an increasing prevalence of eating disorders among males.[3] Valente et al.[4] noted that symptoms of ON can be attributed to perfectionism and anxiety.

Approximately one million males worldwide struggle with eating disorders, a likely underestimate.[5] Concerns about attractiveness for effective impression management, known as self-presentation, can lead to anxiety when individuals feel evaluated based on their physical appearance.[6] Social appearance anxiety (SAA) correlates with body image and self-esteem; positive body image is linked to higher self-esteem, while negative body image often leads to lower self-esteem.[7] Body image significantly influences eating behaviors, social anxiety, sexual behaviors, social relationships, and emotional well-being.[8]

Risk factors for SAA include body dysmorphic disorder (more common in women), body weight (more prevalent in obesity), and age (more frequent in adolescence or middle age).[9] Body perception involves individuals' thoughts, feelings, and

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perceptions about their bodies and their functions.[10] Changes in body perception are lifelong, with issues more prevalent during adolescence and young adulthood when body changes are significant. Increased use of social media may heighten the risk of ON, potentially an unintended consequence of promoting healthy eating habits and lifestyles.[11] However, the relationship between social media addiction and ON in adolescents is still unclear. Low body perception causes depression and obesity and negatively affects human health. Therefore, it is important to prevent obesity, which is the biggest public health problem of recent times.[12] The emergence of obsessive behaviors in consuming 'pure' foods along with healthy eating and weight loss causes ON.[13] Generally, the diets of individuals with ON include pure foods. Therefore, individuals show obsessive behaviors in food research, weighing, meal planning and meal preparation.[14] Accordingly, the diets of individuals with ON have strict rules. The formation of these rules leads to psychological problems such as perfectionism and anxiety.[15] It has also been observed that individuals with ON do not perceive themselves as obese individuals. However, individuals make excessive efforts to maintain a healthy and balanced diet.[16] Their concerns about food quality and obsessive behaviors resemble the same psychological problems in anorexia nervosa.[17]

Although ON is not formally classified as a psychiatric disorder in DSM-5 or ICD-10, ongoing debate surrounds its classification as a behavioral/lifestyle phenomenon versus a psychiatric condition. Some studies highlight specific clinical features associated with ON.[18] This study aims to explore the relationship between SAA and ON within the 18-30 age group, proposing a structural model to assess the impacts of SAA and ON on healthy lifestyle behaviors (HLB).

METHODS

The study was approved by the Gazi University Ethics Committee (Date: 27.01.2016, Decision No: 11663). All procedures were carried out in accordaance with the ethical rules and the principles of the Declaration of Helsinki. All patients signed the free and informed consent form.

Research Aims and the Model

The aims of this paper are to investigate at the relationship between SAA and ON and how these factors affect HLB. This study focuses on investigation of two important associations: One is the association between ON and HLB and the other is the association between SAA and HLB. The causal relationships between three variables, SAA, ON, and HLB are demonstrated with path diagrams in Figure 1. In this model,

In the proposed models, SAA, ON and HLB are each considered as latent variables. In these models, HLB is defined as an endogenous variable that is affected by other variables; that is, ON and SAA function as exogenous variables that affect only HLB independently of other variables.

The following are the hypotheses that are developed in accordance with the causal connections established in the study model:

H1: SAA directly affects the changes in HLB.

H2: ON directly affects the changes in HLB.

H3: SAA and ON are correlated with each other.

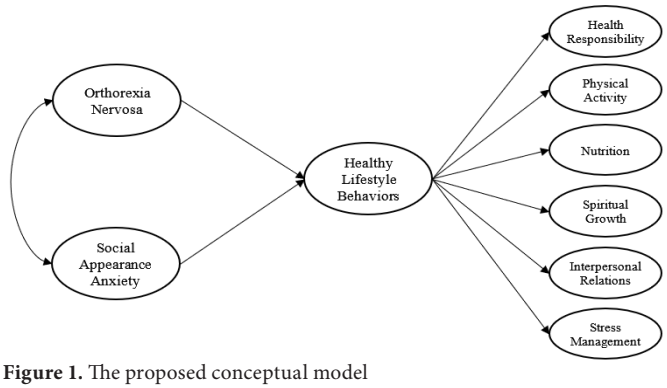

Figure 1. The proposed conceptual model

Participants

Participants in this study were young adults in four Turkish cities: Ankara, İstanbul, İzmir, and Eskişehir, between the ages of 18 to 30. Data was collected using a cross-sectional method through in-person interviews with 408 individuals between March and June 2019. In the beginning, 50 people participated in a pilot research where the period of the interview, the clarity of the questions, and the response options were assessed.

Instrumentation

The scales related to social appearance anxiety, ON status and healthy lifestyle behaviors used in this study were adapted from other researchers. The questionnaire in the study consists of 5 sections:

- **A demographic section**
- **SAA scale:** This scale, developed by Hart et al.[19] in 2008, aims to measure the behavioral, emotional and cognitive concerns of the individual about his/her appearance. The Social Appearance Anxiety Scale is a five-point Likert-type scale (1) Not at all appropriate, (2) Not appropriate, (3) Somewhat appropriate, (4) Appropriate, (5) Fully appropriate and consists of a total of 16 items. Social Appearance Anxiety Scale is evaluated in a single dimension. The minimum score that can be obtained from the scale is 16 and the maximum score is 80. The 1st item of the Social Appearance Anxiety Scale is reverse scored.
- **ON scale:** he ON-15 Likert-type scale was prepared by Donini et al.[1] It is a 15-item self-report questionnaire that determines the frequency of obsessive behaviors related to healthy eating. In the ORTO-15 scale, a score of "1" is given to answers that are considered to be distinctive for the diagnosis of orthorexia and a score of "4" is given to answers indicating a tendency towards normal eating behavior. The items in the scale that would indicate the opposite situation for orthorexia were scored as 4-3-2-1. If the scores obtained are "low", it indicates orthorectic tendency. Donini et al. evaluated ORTO-15 score ≤40 as orthorectic and >40 as normal.

- **HLB scale:** The HLB scale was developed by Walker et al.[20] in 1987 based on Pender's Health Promotion Model and is a scale that measures health-promoting behaviors in relation to the healthy lifestyle of the individual. The scale was revised in 1996 and named as the HIBS-II scale.[21] It consists of health responsibility (HR), physical activity (PA), nutrition (N), spiritual development (SD), interpersonal relations (IR) and stress management (SM) sub-factors.[22] The HLB-II scale is based on a four-point Likert scale with the following responses: 1=never, 2=sometimes, 3=frequently and 4=regularly. It consists of 52 positive items. An increase in the scores obtained from the scale indicates that the individual applies the specified health behaviors at a high level.
- **Anthropometric measurements:** Anthropometric measurements were performed by an expert dietician. Height measurements were taken to the nearest 0.1 cm using a stadiometer without shoes. Participants' head position, body and arm postures were standardized in detail. Weight measurements were taken to the nearest 0.1 kg in light clothing and without shoes. All measurements were performed in the morning on an empty stomach and overnight fasting. Body-mass index (BMI) was calculated from the weight and height measurements of the participants and classified into underweight, normal and overweight groups according to World Health Organization (1989) and Gibson (2005) criteria.[23,24]

Statistical Analysis

Structural equation modelling (SEM), including a large number of statistical techniques, for testing theories and developing new models is a statistical analysis. In non-experimental research, it was created to test models of causality and the processes underlying behaviours. For this reason, structural equation modelling is a comprehensive statistical method that enables the testing of hypotheses about the relationships between observed and latent variables.[25,26] The ability to assess indirect effects between two variables, including direct effects from one variable to another and indirect effects between two variables with the influence of an intermediary variable, is another factor contributing to SEM's extensive use in scientific research. SEM applications can be done more easily with the use of computer software in testing multivariate models.[27] In this study, hypotheses were evaluated using the Maximum Likelihood approach through IBM AMOS software. First, the Anderson and Gerbing test was used, which proposes a two-stage procedure confirmatory measurement model.[28] In these stages, the accuracy of the observable variables in describing the underlying constructs was demonstrated with this model. Subsequently the validity and reliability of the measurement items and components were assessed. This study examined three different types of reliability: item, construct, internal consistency and convergent validity.

In the second stage, the structural model that allows the analysis of multiple regression equations of multiple dependent variables was tested. Parameter estimates and their significance were calculated separately for each regression model.Test statistics and their significance values are used in many test statistics as indicators of goodness of fit in SEM. In this study, X^2/df, comparative fit index (CFI), goodness of fit index (GFI), adjusted goodness of fit index (AGFI) and root mean square error of approximation (RMSEA) were selected as fit indices.[29]

RESULTS

Table 1 shows the participants' anthropometric classification and demographic data based on the study's findings. Men were 41.2% of the participants, while women were 58.8%. The age range of half of the participants (50%) was 18 to 21 years old. The participants' mean BMI was determined to be 22.6±3.4 kg/m². According to Table 1, 70.3% of the participants were a BMI that categorized them as normal, 15.0% obese, and 14.7% underweight.

Table 1. Characteristics of participants

Variable		n	%
Gender	Male	87	21.3
	Female	321	78.7
Age (year)	18-21	232	56.9
	22-24	109	26.7
	25-27	38	9.3
	28-30	29	7.1
Body-mass index	Thin	60	14.7
	Normal	287	70.3
	Obese	61	15.0
Total		408	100.0

This study aims to evaluate the overall fit of observed data to the hypothesized model by simultaneously estimating two separate models using structural equation modeling (SEM). Since the validity of the structural model directly depends on the validity of the measurement model, the measurement models must first be validated. In this context, measurement models for scales such as SAA, ON and HLB were evaluated using confirmatory factor analysis (CFA). CFA is a widely used method of analysis to identify conceptual factors underlying observed variables and to assess the extent to which these factors fit the data. The evaluation of measurement models allows for the verification of the factors underlying each scale and the examination of the relationships of these factors with the observed variables. This step is critical for valid and reliable evaluation of the structural model at later stages.

In order to remove valid items for the SAA, ON and HLB scales, the items with factor loadings greater than 0.50 were selected. Thus, it was decided to remove 3 items from SAA, 6 items from ON, and 12 items from HLB, totaling 20 items. Kaiser-Meyer-Olkin (KMO) sample adequacy measures for SAA, ON and HLB with the selected items were 0.953, 0.860 and 0.875 (>0.60), respectively. In addition, measurements of compliance well-being were used to assess the alignment of the measurement model. Compliance of the measurement model was assessed using measures of compliance well-being.

The general compliance indexes of the first DFA model are appropriate.[25,30] (X^2/DF=2.044, RMSEA=0.051, CFI=0.897, GFI=0.909, with AGFI=0.917. Table 2, Table 3 and Table 4 show the findings of the significance test of the predicted mold coefficients and all factor loads at a meaningfulness level of 0.05 (i.e., t-value >±1.96) In addition, estimates of normalized values, including, he revealed that every prediction of the proper sign and size is compatible with the basic theory.

ON and HLB, respectively, indicate an acceptable level. The standardized loadings, test statistics, and composite reliability (CR) results of the SAA, ON, and HLB measurement models are shown in Table 2, Table 3 and Table 4. SAA scale of item reliabilities of the measured variables in the model; Between 0.640 and 0.846, ON scale; Between 0.533 and 0.932, HLB scale; The fact that it is between 0.510 and 0.976 indicates that the item reliability is good. Composite reliabilities were

Table 2. Measurement model results for SAA scale

Item	Standardized loading	S.E.	t-value*	CR	AVE
S4. I am concerned people would not like me because of the way I look.	0.640	0.052	14.398	0.940	0.549
S5. I worry that others talk about flaws in my appearance when I am not around.	0.698	0.048	16.202		
S6. I am concerned people will find me unappealing because of my appearance.	0.649	0.043	14.671		
S7. I am afraid that people find me unattractive.	0.744	0.045	17.757		
S8. I worry that my appearance will make life more difficult for me.	0.752	0.045	18.021		
S9. I am concerned that I have missed out on opportunities because of my appearance.	0.771	0.045	18.737		
S10. I get nervous when talking to people because of the way I look.	0.767	0.044	18.758		
S11. I feel anxious when other people say something about my appearance.	0.746	0.047	17.829		
S12. I am frequently afraid I would not meet others' standards of how I should look.	0.793	0.043	19.572		
S13. I worry people will judge the way I look negatively.	0.800	0.044	19.835		
S14. I am uncomfortable when I think others are noticing flaws in my appearance.	0.735	0.052	17.419		
S15. I worry that a romantic partner will/would leave me because of my appearance.	0.661	0.052	15.011		
S16. I am concerned that people think I am not good looking.	0.846	-	-		

SAA: Social appearance anxiety, -These values could not be calculated for model identification purposes, *All factor loadings are at the p=0.05 level

Table 3. Measurement model results for ON scale

Item	Standardized loading	S.E.	t-value*	CR	AVE
O3. In the last 3 months, did the thought of food worry you?	0.819	-	-	0.907	0.526
O4. Are your eating choices conditioned by your worry about your health status?	0.757	0.135	8.826		
O5. Is the taste of food more important than the quality when you evaluate food?	0.784	0.126	7.322		
O6. Are you willing to spend more money to have healthier food?	0.622	0.118	6.634		
O9. Do you think your mood affects your eating behavior?	0.533	0.121	6.762		
O10. Do you think that the conviction to eat only healthy food increases self-esteem?	0.693	0.150	9.065		
O11. Do you think that eating healthy food changes your life-style (frequency of eating out, friends, …)?	0.552	0.133	7.988		
O12. Do you think that consuming healthy food may improve your appearance?	0.744	0.136	7.913		
O13. Do you feel guilty when transgressing?	0.932	0.149	8.643		

ON: Orthorexia Nervosa, -These values could not be calculated for model identification purposes, *All factor loadings are at the p = 0.05 level

After the compliance well-being indexes were found, the reliability and validity of the measurement model were evaluated. In this study, three different types of reliability were calculated: substance reliability, structure reliability and internal consistency reliability.[31,32]

When the item reliability values of the measured variables in the model are examined; The values between 0.640 and 0.846 for the SAA scale, between 0.533 and 0.932 for the ON scale, and between 0.510 and 0.976 for the HLB scale are evidence of good item reliability.

Composite reliabilities are above the 0.70 threshold (0.762 to 0.940), indicating high reliability for all constructs. In addition, alpha coefficients of 0.939, 0.794 and 0.893 for SAA, determined to be above the threshold value of 0.70 (between 0.762 and 0.940), indicating high reliability for all constructs. In addition, alpha coefficient values of 0.939, 0.794 and 0.893 for SAA, ON and HLB, respectively, were found to be at an acceptable level.

In the indicator set, validity measures accurately indicate the degree of fit of the latent construct.[33] Convergent validity is assessed by the average variance value (AVE) for a construct, which must exceed 0.50.[32,34]

In Table 2, Table 3 and Table 4, the AVE values are between 0.519 and 0.630, indicating that convergent validity has been achieved in this context.

Table 4. Measurement model results for HLB scale

	Item	Standardized loading	S.E.	t-value*	CR	AVE
HR	K3. Report any unusual signs or symptoms to a physician or other health professional	0.563	-	-	0.914	0.549
	K9. Read or watch TV programs about improving health	0.831	0.102	7.066		
	K15. Read or watch TV programs about improving health	0.701	0.124	9.907		
	K21. Get a second opinion when I question my health care provider's advice	0.731	0.118	9.305		
	K27. Discuss my health concerns with health professionals	0.628	0.114	9.271		
	K33. Inspect my body at least monthly for physical changes/danger signs	0.850	0.116	7.308		
	K39. Ask for information from health professionals about how to take good care of myself	0.630	0.125	9.298		
	K45. Attend educational programs on personal health care	0.976	0.113	7.629		
	K51. Seek guidance or counseling when necessary	0.666	0.118	7.509		
PA	K4. Follow a planned exercise program	0.973	-	-	0.922	0.601
	K10. Exercise vigorously for 20 or more minutes at least three times a week (such as brisk walking, bicycling, aerobic dancing, using a stair climber)	0.736	0.107	12.228		
	K16. Take part in light to moderate physical activity (such as sustained walking 30-40 minutes 5 or more times a week)	0.674	0.105	11.428		
	K22. Take part in leisure-time (recreational) physical activities (such as swimming, dancing, bicycling)	0.756	0.091	8.098		
	K28. Do stretching exercises at least 3 times per week	0.800	0.095	10.354		
	K34. Get exercise during usual daily activities (such as walking during lunch, using stairs instead of elevators, parting car away from destination and walking)	0.705	0.099	7.249		
	K40. Check my pulse rate when exercising	0.880	0.094	10.060		
	K46. Reach my target heart rate when exercising	0.621	0.092	10.671		
N	K20. Eat 2-4 servings of fruit each day	0.881	-	-	0.871	0.630
	K26. Eat 3-5 servings of vegetables each day	0.854	0.172	6.129		
	K32. Eat 2-3 servings of milk, yogurt or cheese each day	0.734	0.198	6.046		
	K38. Eat only 2-3 servings from the meat, poultry, fish, dried beans, eggs, and nuts group each day	0.690	0.194	6.233		
SG	K6. Feel I am growing and changing in positive ways	0.847	0.116	8.448	0.913	0.576
	K12. Believe that my life has purpose	0.576	0.128	8.740		
	K18. Look forward to the future	0.925	0.128	9.202		
	K24. Feel content and at peace with myself	0.678	0.120	8.757		
	K30. Work toward long-term goals in my life	0.777	0.124	8.749		
	K36. Find each day interesting and challenging	0.807	0.103	6.799		
	K42. Am aware of what is important to me in life	0.841	0.117	8.385		
	K52. Expose myself to new experiences and challenges	0.533	-	-		
IR	K1. Discuss my problems and concerns with people close to me.	0.847	0.128	7.110	0.924	0.609
	K7. Praise other people easily for their achievements.	0.795	0.128	8.587		
	K13. Maintain meaningful and fulfilling relationships with others.	0.886	0.149	9.285		
	K19. Spend time with close friends.	0.648	0.137	9.011		
	K25. Find it easy to show concern, love and warmth to others.	0.865	0.150	9.131		
	K31. Touch and am touched by people I care about.	0.774	0.141	8.399		
	K37. Find ways to meet my needs for intimacy.	0.842	0.133	7.053		
	K49. Settle conflicts with other through discussion and compromise.	0.510	-	-		
SM	K23. Concentrate on pleasant thoughts at bedtime.	0.704	0.120	8.820	0.762	0.519
	K29. Use specific methods to control my stress.	0.807	0.093	6.526		
	K35. Balance time between work and play.	0.639	-	-		

HLB: Healthy Lifestyle Behaviors, HR: Health Responsibility, PA: Physical Activity, N: Nutrition, SG: Spiritual Growth, IR: Interpersonal Relations, SM: Stress Management, -These values could not be calculated for model identification purposes, *All factor loadings are at the p = 0.05 level

In the second step, a structural model relating the SAA, ON and HLB variables was created. Figure 2 shows the standardized results we estimated with ML for the relationship between social SAA and ON and the impact of these variables on HLB. Accordingly, the hypothesized model for SAA, ON and HLB was found to be in good agreement with the data. Therefore, the model was verified and analyzed with the SEM technique (X^2/df=1.810, RMSEA=0.045, CFI=0.993, GFI=0.974, AGFI=0.923).

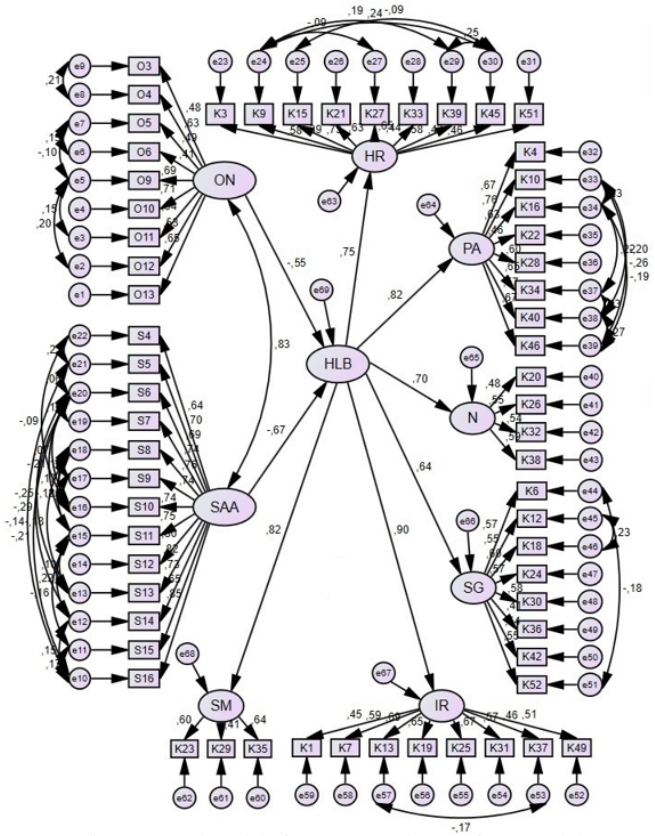

Figure 2. The structural model of SAA, ON and HLB of young adults

SAA: Social appearance anxiety, ON: Orthorexia nervosa, HLB: Healthy lifestyle behaviors

Table 5 and Figure 2 show the standardized path coefficients of the structural model, which determine the strength of the relationships between the constructs. The first hypothesis established between SAA and HLB was confirmed, thus a statistically significant negative effect of SAA on HLB was found (std β=-0.673; t-value=-8.425). The second hypothesis was confirmed, that is, a significant negative relationship was found between ON and HLB (std β=-0.554; t-value=-9.388). Additionally, the findings in the study supported the model in Figure 2, which suggests that SAA and ON are interrelated (correlation coefficient=0.830; t-value=10.244).

Table 5. Hypothesis testing of the relationships among SAA, ON and HLB

Hyp.	Paths			Std. coef. estimate	SE	t-value	p*
H1	SAA	→	HLB	-0.673	0.028	-8.425	0.000
H2	ON	→	HLB	-0.554	0.046	-9.388	0.000
H3	SAA	↔	ON	0.830	0.034	10.244	0.000

SAA: Social appearance anxiety, ON: Orthorexia nervosa, HLB: Healthy lifestyle behaviors, *All standardized coefficient estimates are significant at p<0.05

The first hypothesis formed between SAA and HLB was approved, so SAA had a negative effect on HLB which was statistically significant (std β=-0.673; t-value=-8.425). The second hypothesis was also approved, so there was a significant negative relationship between ON and HLB (std β=-0.554; t-value=-9.388). Additionally, findings of the study supported the model given via Figure 2 which suggested that SAA and ON were correlated with each other (correlation coefficient=0.830; t-value=10.244).

DISCUSSION

Individuals attach importance to body building and aesthetic appearance with the pressures of society and media. These pressures on the individual can lead to eating disorders or can cause the individual to eat more food according to the psychological state. As the increase in the desire to eat increases the tendency to obesity, it also changes eating attitudes and behaviors.[10]

In recent years, the dietary habits of young adults have been changed; thus, overweight and obesity are increasingly being observed among young adults. In this study, in order to examine the relationship between SAA and ON of young adults, and to investigate the effect of these variables on HLB, a structural model was proposed. According to various goodness of fit indices, the proposed SAA, ON and HLB model was evaluated and validated with SEM. These results showed that all hypotheses were supported and also provided strong overall validation for the research model.According to the SEM results, all parameters were found to be statistically significant (Table 2, Table 3 and Table 4).

The first hypothesis formed between SAA and HLB was approved, so SAA had a negative influence on HLB (std β=-0.673; t-value=-8.425). Levinson and Rodebaugh (2016) reported that SAA is the most important factor causing eating disorders.[35] Negative thoughts about appearance further increase the risk of eating disorders.[36] In another study, SAA in women was determined as one of the most important triggers of obstructive eating disorder.[37] Studies show that high physical appearance perfectionism is an important determinant of social physical anxiety. These individuals perceive their own appearance as imperfect and compare it with the physical ideals of society. If their appearance is far from these ideals, they tend to experience social physical anxiety. In this context, physical appearance perfectionism is a critical factor in understanding social physical anxiety.[38,39] Research shows that the high standards that individuals with high physical appearance perfectionism set for their own bodies often do not match their physical reality and this may increase their dissatisfaction with their bodies. These individuals often experience low self-esteem and feelings of inadequacy. They are also extremely concerned about being evaluated negatively and therefore prefer avoidance-oriented coping strategies.[40,41] Body compassion helps individuals accept their bodies, build social relationships and regulate their emotional processes. Therefore, it functions as an important protective and regulating factor between physical appearance perfectionism and social physical anxiety.[42]

It was also reported that there is a negative correlation between body image and social physical anxiety. As people become more satisfied with their physical appearance, the social physical anxiety decreases. Moreover, women's body image dissatisfaction, the frequency of dieting practices, the probability of identifying themselves as fat was found to be higher than men.[43] Women are more concerned, criticized and dissatisfied with their physical appearance than men. Society and social media value youth, beauty and thinness more than ever before, leading to the belief that those who are obese are unattractive. It also causes body dissatisfaction and worsening mood among young women after being exposed to thin ideal images.[44]

From the findings of this study, a significant negative correlation was found between ON and HLB and the second hypothesis was also supported (std β=-0.554; t-value=-9.388). Accordingly, it can be concluded that individuals who are overly anxious about food cause psychological distress by increasing obsessive behaviors. High scores were often associated with abnormal eating habits and a pathological or impaired eating attitude.[45,46] Healthy eating behaviors can cause one to lose control over one's own life, and it can pose a serious threat to mental and physical health by restricting individual and social life. However, healthy eating behavior is not a disorder in itself, it is a something that everyone should pay attention to, but some people can become obsessed with it. Along with the imbalance caused by obsessions to certain foods, changes in nutritional habits of individual may lead to introversion and orthorexia.[16]

Many people exhibit different forms of highly sensitive eating behavior. Due to their efforts to reach perfection, they tend to aggravate their diet. In orthorexia, only the desire to consume pure and healthy foods is at the forefront. This desire to become mentally and behaviorally extreme resembles obsessive-compulsive disorder. The positive effect of healthy eating on human life is a fact, but the number of individuals who exaggerate it and impair their social relations, unfortunately is increasing day by day.[47] Orthorectics can spend most of their time thinking about food, shopping, preparing and consuming food which are assumed to be healthy. According to[16] orthorexia is a pathological obsession for proper eating, and the aim is to maintain and improve health. People who are overly fond of pure nutrition are suffering from intense body weight loss because they pay attention to the quantity of nutrients rather than to the quality. Regarding whether weight loss is important in ON, it is stated that there is no desire to lose weight as a defining criterion of ON.[48]

However, it has been suggested that adopting an overly healthy diet may lead to anorexia, or that combining low-calorie and healthy foods focuses on weight loss in the majority of people with ON.[49] Healthy eating habits are not actually pathological. However, when exaggerated and in case of long continuance, it can lead to personality and behavior disorders by causing negativity in daily life. Understanding these psychological factors is critical for early recognition, prevention and treatment of ON. Understanding the underlying mechanisms that lead to this complex eating disorder and addressing cognitive patterns enables tailored interventions.[2]

As a result of correlation analysis, it was determined that there is a positive correlation between SAA and ON which is statistically significant (correlation coefficient=0.830; t-value=10.244). Individuals with ON pursue their life within the framework of strict rules about healthy eating. Ortorectics tend to restrict their diets gradually because of efforts to achieve perfection, and this can result in reduction of nutrient diversity in their diet.[50] It has been stated that there is a positive correlation with body dissatisfaction, distorted body image perception, frequent dieting, application of inappropriate weight loss methods, and psychological problems such as depression, anxiety, and inadequate and unbalanced eating habits.[51] Therefore, obese individuals with eating disorders have a higher rate of social anxiety than the general population.[37] Especially negative comments about appearance increase the risk of eating disorders more.[36]

In conclusion, SAA, HLB and ON which were found to be related to each other are known to have a significant effect on the nutritional status of individuals. Healthy eating obsession can create negative effects on the body perception progressively. Existing studies in the literature have also demonstrated that an increase in social appearance anxiety increases the risk of ON and obsessive-compulsive behavior.[3,52] Due to increased tendency of orthorexia as body weight increases, it is possible to say that having normal body weight and maintaining it may be protective against orthorectic tendencies. ON is a condition characterized by excessive obsession and obsessive thoughts about healthy eating. It is thought that ON is related to body image. Especially anxiety about being obese and obsession with body appearance are effective in the emergence of ON.

It was found that the risk of ON was higher in individuals with high scores on the body image scale,[53] and in another study, it was emphasized that individuals with orthorexia tendency have strict ideas not only about healthy eating but also about healthy body image These findings in the literature suggest that there is a positive correlation between body image and ON.[54] Accordingly, knowing the relationship between body image and healthy eating has an important role in the etiology of orthorexia nervosa.

Toth-Kiraly et al.[3] observed that health anxiety increased as orthorexia tendencies increased. In this context, as individuals become more concerned about their health and body functioning, they practice healthy lifestyles, such as following a strict diet and increasing regular physical activity. It reflects a pattern of behavior that is fueled by individuals' fear of losing control over their health and their bodies. It should not be ignored that this may lead to negative health consequences for individuals in their pursuit of a perfect body image.

In addition, orthorexia can lead to impairments in psychological and social functioning over time and is considered a serious health problem that needs to be treated.

Limitations

It is important to emphasize that the design of our study is relatively small sample. Utilizing a larger sample would yield more reliable results. The study covers the age range of 18-30 years. Future studies may include a wider range of age groups.

CONCLUSION

In this article, CFA was used to show how accurately the observed variables represent the underlying structures and the relationship between them. The results of all fit indices of the first CFA model were found to be satisfactory. Therefore, the factor structures of the SAA, ON and HLB scales were confirmed by SEM. Additionally, estimation of standardized regression coefficients interpreted as factor loadings were correct sign and size and consistent with the underlying theory. Three reliability measurement tests were used to assess the adequacy of single items and their compositions. These were item reliability, construct reliability, internal consistency reliability and convergent validity tests. Accordingly, the reliability and validity of SAA, ON and HLB scales were satisfied. In order to examine the relationship between SAA and ON, and to investigate the effect of these variables on HLB, a structural model was proposed in this study. Various goodness of fit indices were used to investigate model adequacy requirement. Accordingly, the proposed model of SAA, ON and HLB was verified by SEM. It was determined that individuals with high social appearance anxiety do not adopt healthy lifestyle behaviors, and are more prone to orthorexia.

Consequently, it is clear that the structural equation model used in this study gained a different perspective on the field. Future research of this structural modeling should be applied to children, adolescents, and adults from various socio-demographic, anthropometric and biochemical backgrounds. It is also important to recognize and understand ON because this condition has significant impacts on individuals' health and lifestyle choices. While it is important to focus on healthy eating and lifestyle goals, excessive health concerns and obsessions can lead to unhealthy outcomes and must therefore be managed carefully in medical nutrition therapy.

ETHICAL DECLARATIONS

Ethical Committee Approval

The study was initiated with the approval of the Gazi University Ethics Committee (Date: 27.01.2016, Decision No: 11663).

Informed Consent

The patient signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflicts 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, conduct and analysis of the work, and that they have approved the final version.

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Diagnosing retinal disorders with artificial intelligence: the role of large language models in interpreting pattern electroretinography data

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ABSTRACT

Aims: To evaluate the diagnostic accuracy of Claude-3, a large language model, in detecting pathological features and diagnosing retinitis pigmentosa and cone-rod dystrophy using pattern electroretinography data.

Methods: A subset of pattern electroretinography measurements from healthy individuals, patients with retinitis pigmentosa and cone-rod dystrophy was randomly selected from the PERG-IOBA dataset. The pattern electroretinography and clinical data, including age, gender, visual acuities, were provided to Claude-3 for analysis and diagnostic predictions. The model's accuracy was assessed in two scenarios: "first choice," evaluating the accuracy of the primary differential diagnosis and "top 3," evaluating whether the correct diagnosis was included within the top three differential diagnoses.

Results: A total of 46 subjects were included in the study: 20 healthy individuals, 13 patients with retinitis pigmentosa, 13 patients with cone-rod dystrophy. Claude-3 achieved 100% accuracy in detecting the presence or absence of pathology. In the "first choice" scenario, the model demonstrated moderate accuracy in diagnosing retinitis pigmentosa (61.5%) and cone-rod dystrophy (53.8%). However, in the "top 3" scenario, the model's performance significantly improved, with accuracies of 92.3% for retinitis pigmentosa and 76.9% for cone-rod dystrophy.

Conclusion: This is the first study to demonstrate the potential of large language models, specifically Claude-3, in analyzing pattern electroretinography data to diagnose retinal disorders. Despite some limitations, the model's high accuracy in detecting pathologies and distinguishing between specific diseases highlights the potential of large language models in ocular electrophysiology. Future research should focus on integrating multimodal data, and conducting comparative analyses with human experts.

Keywords: Retinitis pigmentosa, cone rod dystrophy, pattern electroretinography, large language models

INTRODUCTION

Pattern electroretinography (PERG) has been a valuable tool in ophthalmology for testing retinal ganglion cell function, photoreceptor health and diagnosing various retinal diseases by presenting alternating visual stimuli and recording the electrical responses from the retina.[1,2] PERG provides objective information regarding the health and integrity of the retinal pathway, with the macula and optic nerve in particular. Analysis of PERG waveforms, particularly the N95, P50, and N35 components, allows for the assessment of macular function and detection of abnormalities in the ganglion cell layer and inner retina.[1] The different PERG patterns observed in different diseases, such as the reduced amplitudes in retinitis pigmentosa (RP) and the delayed implicit times in glaucoma, aid in differential diagnosis and facilitate appropriate management strategies.[3,4] PERG offers a non-invasive and objective measure of retinal function, making it a valuable tool for monitoring disease progression and evaluating treatment efficacy.[5]

The emergence of artificial intelligence (AI) has revolutionized various aspects of medical diagnosis, offering promising approaches to interpreting complex medical data and assisting clinicians in making more informed decisions.[6] In the field of ophthalmology, AI algorithms have demonstrated remarkable capabilities in analyzing retinal images for diabetic retinopathy, age-related macular degeneration, and other retinal diseases.[7] Beyond analyzing retinal images, AI algorithms have been successfully used to predict glaucoma progression, automate visual field interpretation, and personalize treatment.[8,9] AI offers several advantages in medical diagnostics, including the ability to detect subtle patterns that human observers often miss, enable rapid and objective assessments, and improve diagnostic accuracy,

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leading to better patient outcomes.[10,11] However, despite these promises, implementing AI in healthcare still faces issues with privacy, algorithmic bias, and the requirement for thorough validation to ensure reliability and security.[12]

Large language models (LLMs) represent a unique and powerful subset of artificial intelligence that are trained on massive text and code datasets, enabling them to understand and generate human-like text, translate languages, and answer complex questions in an informative manner.[13] Unlike traditional AI models that excel at specific tasks such as image recognition or data classification, LLMs use their extensive training to process and understand information more holistic and contextual manner, mimicking the learning and reasoning processes of humans.[14] This ability to extract meaning, identify patterns, and draw conclusions from complex data sources makes them valuable tools for analyzing various medical data, including clinical notes, research articles and even genome sequences.[15-17]

Interpretation of pattern ERG data is a complex task that typically requires extensive training and expertise in ophthalmology and electrophysiology and often challenges even experienced clinicians.[18] The aim of this study is to evaluate the potential of Claude-3, a large language model accessible to a wider range of users, in analyzing pattern ERG data and providing diagnostic insights, potentially helping clinicians and researchers interpret this complex data.

METHODS

Dataset

This study utilized the Pattern Electroretinogram-Institute of Applied Ophthalmobiology (PERG-IOBA) dataset available from PhysioNet, which serves as a research resource for complex physiologic signals.[19] Since this publicly available dataset from the was used in this study, ethical approval is not required. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. The terms of use of the database have been adhered to. The dataset includes 1,354 transient PERG responses from 304 subjects in 336 records, collected between 2003 and 2022.[20] It consists of 105 healthy subjects and 199 patients diagnosed with various retinal conditions. The most common diseases represented in the data set were RP with 48 patients, macular dystrophy with 32 patients, Stargardt disease with 16 patients and cone-rod dystrophy (CRD) with 14 patients. Clinical diagnosis, including age, gender, and visual acuity measurements in logMAR scale, was provided in CSV (comma separated values) format. The dataset had been anonymized, and data collection dates had been randomly date-shifted to maintain patient privacy and confidentiality.[20]

PERG Signal Acquisition

PERG signals in the dataset were captured by experienced technicians using the computerized Metrovision Optoelectronic Stimulator Vision Monitor MonPack 120 (Metrovision, Pérenchies, France). The acquisition protocol strictly adhered to the International Society for Clinical Electrophysiology of Vision (ISCEV) guidelines.[21] Signals were recorded at a high sampling rate of 1700 Hz over a duration of 150 milliseconds, producing 255 equally spaced observations per signal. Figure shows a portion of the raw data recorded from a patient.

TIME_1	RE_1	LE_1
2016-09-15 09:40:21.0000	0	0
2016-09-15 09:40:21.0006	-0.1	0.1
2016-09-15 09:40:21.0012	-0.2	0.2
2016-09-15 09:40:21.0018	-0.2	0.4
2016-09-15 09:40:21.0024	-0.2	0.6
2016-09-15 09:40:21.0030	0	0.7
2016-09-15 09:40:21.0035	0	0.8
2016-09-15 09:40:21.0041	0	0.8
2016-09-15 09:40:21.0047	0	0.6
2016-09-15 09:40:21.0053	-0.2	0.6
2016-09-15 09:40:21.0059	-0.2	0.5
2016-09-15 09:40:21.0065	-0.2	0.6
2016-09-15 09:40:21.0071	-0.2	0.6
2016-09-15 09:40:21.0077	-0.4	0.6
2016-09-15 09:40:21.0083	-0.6	0.5
2016-09-15 09:40:21.0089	-0.8	0.4
2016-09-15 09:40:21.0094	-1.2	0.3
2016-09-15 09:40:21.0100	-1.3	0.2
2016-09-15 09:40:21.0106	-1.4	0.3
2016-09-15 09:40:21.0112	-1.4	0.2
2016-09-15 09:40:21.0118	-1.2	0.2

Figure. A portion of the raw data recorded from a patient

Study Sample Selection

A specific subset of PERG measurements from healthy individuals, patients with RP and CRD were randomly selected from the larger dataset for this analysis. The PERG data for each subject in this subset were extracted from the dataset and provided to the Claude-3 language model for analysis and diagnostic predictions. The study was designed as a pilot study, hence the number of participants was kept limited.

Data Input to Claude-3 LLM

To evaluate the potential of large language models (LLMs) in analyzing PERG waveforms and providing diagnostic insights, we employed Claude-3, a commercially available LLM. We provided Claude-3 with a prompt that included the following instructions:

''Analyze the provided pattern ERG data for both eyes, identifying abnormalities in the N35, P50, and N95 waves, oscillatory potentials, and overall waveform morphology. Indicate the presence of pathology with a "Yes" or "No." If pathology is detected, select the top three differential diagnoses from a comprehensive list associated with pattern ERG features. Each diagnosis should include a

detailed justification focusing on the bilateral ERG findings, particularly concerning both cone and rod functions, and consider the patient's current age, gender, and bilateral presentation. Rank these diagnoses by likelihood and outline the potential need for further tests or information to confirm these diagnoses.

Please include the following patient details:

- Age: [ ]
- Gender: [ ]
- Right Eye Visual Acuity (logMAR): [ ]
- Left Eye Visual Acuity (logMAR): [ ]

Note: The age at symptom onset is unknown. Given the complexity of diseases associated with pattern ERG abnormalities, additional clinical data, imaging, or tests may be necessary for a definitive diagnosis."

Important Outcomes

First scenerio;

First choice accuracy: This metric assesses whether Claude-3 identified the correct pathology as the first differential diagnosis. This is critical for determining the model's precision in diagnosing the most likely condition without additional input.

Second scenerio;

Top three accuracy: This broader metric evaluates whether the correct diagnosis was included in the model's top three differential diagnoses. This measure reflects the model's ability to detect and prioritize potential diagnoses, which is critical for clinical settings where multiple potential diagnoses may be considered before reaching a final conclusion.

Statistical Analysis

To determine whether the variables were normally distributed, the Shapiro-Wilk normality test was used. Demographic characteristics (age and sex) and visual acuity measurements were summarized using mean and standard deviation for continuous variables and frequencies and percentages for categorical variables. One-way analysis of variance (ANOVA) was performed to compare the mean age of the three groups, and a chi-square test was used to assess differences in gender distribution. To compare visual acuity between groups, we used the Kruskal-Wallis test with Bonferroni correction for multiple comparisons. Sensitivity, specificity, precision and F1 scores were calculated for each study group. Statistical analyzes were performed using Statistical Package for Social Sciences (SPSS) software, version 25.0 (IBM, Chicago, IL, USA). Values of $p<0.05$ were considered statistically significant in all tests.

RESULTS

Demographics and Visual Acuity

A total of 46 subjects were included in the study, with 20 healthy individuals, 13 patients with RP, and 13 patients with CRD. The demographic characteristics and visual acuity measurements for each group are summarized in Table 1.

Table 1. Demographics and visual acuity measurements for each group

Characteristic	Retinitis pigmentosa (n=13)	Cone-rod dystrophy (n=13)	Normal (n=20)	p
Age (years)				
Mean±SD	35.5±15.8	34.2±15.6	28.8±18.3	0.48
Range	(12-62)	(10-61)	(6-70)	
Gender				
Male	9 (69.2%)	8 (61.5%)	9 (45.0%)	0.38
Female	4 (30.8%)	5 (38.5%)	11 (55.0%)	
Mean visual acuity (LogMAR)				
Mean±SD	0.39±0.44	0.51±0.37	0.15±0.22	0.0015*

p*: significant, Post-hoc Dunn test (Bonferroni correction): RP vs. CRD: p>0.327 RP vs. Normal: p<0.023 CRD vs. Normal: p<0.011 SD: Standard deviation, LogMAR: Logarithm of the minimum angle of resolution, RP: Retinitis pigmentosa, CRD: Cone-rode dystrophy

Diagnostic Accuracy

The diagnostic accuracy of Claude-3 in detecting the presence or absence of pathology in all study groups was successful and all cases were correctly identified. In the normal group, the model confirmed no pathology in all 20 (100%) subjects. Similarly, in the pathologic group, the model confirmed pathology in all 26 (100%) subjects. The accuracy of the differential diagnosis showed variability, with RP and CRD in the first scenerio having an accuracy of 61.5% (8 of 13 cases) and 53.8% (7 of 13 cases), respectively. Notably, the model performed better when we used the second scenerio, with RP and CRD achieving higher success rates of 92.3% (12 of 13 cases) and 76.9% (10 of 13 cases), respectively. However there was no statistical difference when comparing model's accuracy of the differential diagnosis between RP and CRD in both scenarios (p=1 and 0.59), respectively.

Performance Metrics

We evauleted performance metrics acording to 2 scenarios. Results are given in Table 2.

Table 2. Performance metrics for Claude-3 diagnosis

Performance metric	Healthy vs. pathologic	RP	CRD
Sensitivity	100%	69.23%	53.85%
Specificity	100%	100%	84.62%
Precision	100%	100%	77.78%
F1 score	100%	81.82%	63.64%

RP: Retinitis pigmentosa, CRD: Cone-rode dystrophy

DISCUSSION

Our results suggest that Claude-3 achieves perfect performance, with 100% sensitivity, specificity, precision, and F1 score, demonstrating its ability to accurately identify all cases with pathology as well as all healthy cases without any misclassifications. It can effectively distinguish between healthy subjects and those with retinal diseases, achieving 100% accuracy in detecting the presence or absence of disease based on PERG data with minimal clinical data. The ability to accurately differentiate between healthy and pathologic cases is crucial in a clinical setting, as it can help prioritize patients

who require further diagnostic evaluation and potential treatment.[22]

PERG is a highly valuable diagnostic tool in the evaluation of RP, a genetic disorder that causes progressive retinal degeneration.[4] In RP, PERG waveforms typically exhibit reduced amplitudes which is due to impaired function of photoreceptors and retinal ganglion cells.[2] These abnormalities can be detected even in early stages of the disease when visual acuity is still preserved, making PERG a sensitive tool for early diagnosis and monitoring disease progression.[23]

PERG is particularly informative in diagnosing and monitoring CRDs, a group of inherited retinal diseases characterized by deterioration of cone and rod photoreceptors.[24] The PERG can provide detailed assessments of cone function, which is crucial in cone-rod dystrophies where cone dysfunction typically presents before rod dysfunction.[24] For example, PERG can help distinguish different patterns of visual impairment in patients with cone-rod dystrophy, with some having more severe cone dysfunction than others.[24] This functional assessment is consistent with clinical observations and genetic findings, thereby supporting the diagnosis and understanding the disease progression in these patients.[25]

When considering the first scenario, Claude-3 demonstrated moderate accuracy in diagnosing RP (61.5%) and CRD (53.8%). However, when evaluating the second scenario, the model's performance significantly improved, with accuracies of 92.3% for RP and 76.9% for CRD. This suggests that Claude-3 is capable of identifying the correct diagnosis within the top three suggestions, even if it may not always be the first choice. These results are promising, indicating the potential of LLMs in analyzing PERG data for the diagnosis of retinal disorders. However, our literature search did not yield any studies done with artificial intelligence specifically using LLMs on this subject; therefore, we cannot directly compare our results to previous findings.

However, the model's performance metrics in identifying specific retinal disorders based on the first scenario varied between RP and CRD. While Claude-3 showed good performance in identifying RP cases, with high specificity and precision, its performance in identifying CRD cases was moderate, with lower sensitivity, specificity, and precision. This difference in performance may be attributed to the heterogeneity of CRD phenotypes and the overlap of PERG features with other retinal disorders, making it more challenging for the model to accurately identify CRD cases based solely on the first-choice diagnosis.[24]

Integrating AI into clinical practice offers several benefits, such as providing rapid, objective assessments of complex medical data and detecting subtle patterns that may be overlooked by human observers.[11] However despite its promise one of the major concern is the "black box" nature of these models, where the reasoning behind their predictions remains opaque.[26] In this models training data are often obscured or undocumented, and their methods opaque.[27] This lack of transparency can affect trust and acceptance among clinicians, particularly when dealing with complex medical decisions.[28]

Our study has several strengths and limitations. One of the strengths is the use of a large, well-characterized data set (PERG-IOBA) that conforms to the ISCEV guidelines for PERG collection, ensuring data reliability and consistency.[20] Another strength of our study is the use of a commercially available large language model, Claude-3, which is accessible to a wider range of users compared to specialized AI models that require extensive technical expertise. This accessibility enables greater potential in clinical settings, as healthcare professionals without strong AI knowledge can still benefit from the model's insights. However, our study has notable limitations, the most significant being the relatively small sample size, as it was designed as a pilot study. Additionally, the study focuses on a specific subset of retinal diseases, and while Claude-3 shows promising results in analyzing PERG data, its performance for other types of ocular electrophysiological tests and different retinal diseases remains to be investigated.

There are several important directions for future research in this area. First, the integration of PERG data with other diagnostic modalities such as optical coherence tomography and visual field testing may represent a significant advance toward a multimodal diagnostic approach. By combining data from these different sources, LLMs could provide a more comprehensive and nuanced understanding of retinal health and improve the ability to diagnose complex conditions that may not be detectable with a single diagnostic method. Conducting comparative analysis between the performances of LLMs and human experts is also crucial. Such studies would help delineate the strengths and limitations of each approach and provide insights into how best to use AI in clinical settings. By directly comparing AI with human diagnostics, researchers can identify specific scenarios where AI excels or lags behind, thereby refining AI applications to effectively support clinical decision making.[29]

CONCLUSION

This study is the first to demonstrate the potential of large language models, particularly Claude-3, in analyzing PERG data for the diagnosis of retinal diseases. Despite some limitations, the model's high accuracy in detecting pathologies and distinguishing between specific diseases highlights the potential of AI in ophthalmology. Future research should focus on addressing limitations.

ETHICAL DECLARATIONS

Ethics Committee Approval

Since the PERG IOBA dataset from the PhysioNet database was used in this study, ethical approval is not required. The terms of use of the database have been adhered to.

Informed Consent

Since the PERG IOBA dataset from the PhysioNet database was used in this study, informed consent is not required.

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

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Detection of virulence factors of *Enterococcus faecalis* isolated from the urinary system and evaluation of antibiotic resistance

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ABSTRACT

Aims: Enterococci, which are among the leading causes of nosocomial infections, are opportunistic pathogens and cause urinary tract infections most frequently. The frequency of isolation increases especially in patients with urinary system anomalies or urological interventions. Although various virulence factors play a role in the pathogenesis of infections caused by enterococci, cytolysin, hemolysin and enterococcal surface protein (ESP) are among the frequently investigated virulence factors. In this study; It was aimed to investigate the relationship between the presence of virulence factors and antibiotic resistance in *Enteroccus faecalis (E. faecalis)* strains isolated from urine samples, as well as the effect of urinary catheter use on these factors.

Methods: 100 strains isolated from urine samples sent to İstanbul University İstanbul Faculty of Medicine Medical Microbiology Laboratory and identified as *E. faecalis* with the VITEK 2 (biomerioux-France) GP identification kit were included in the study. Hemolysin and gelatinase, virulence factors, were determined phenotypically. The presence of the ESP gene was investigated by PCR using ESP11 and ESP12 primers. Antibiotic sensitivities were studied by disk diffusion and gradient strip methods, and the results were evaluated in accordance with CLSI and EUCAST recommendations.

Results: Antibiotic resistance rates were found to be 2%, 31%, 1%, 22%, 37% for ampicillin, norfloxacin, nitrofurantoin, high-level gentamicin (HLG) and high-level streptomycin (HLS), respectively, while no strains resistant to vancomycin, linezolid and tigecycline were detected. When evaluated in terms of virulence factors; It was determined that 82% of the strains produced gelatinase, 67% produced ESP, and 35% produced hemolysin. No virulence factor was detected in eight strains.

Conclusion: In our study, no significant relationship was found between the presence of virulence factors and antibiotic resistance and catheter application. However, since the most detected gelatinase and ESP are virulence factors that have the ability to colonize and form biofilms on abiotic surfaces, it is thought that minimizing catheterization practices may contribute to the prevention of UTIs that may develop with enterococci.

Keywords: *Enterococcus faecalis*, urinary tract infection, antibiotic resistance, virulence factors

*Our research's data was presented in 36. ANKEM Congress as 'Oral Presentation' on 27-31 October 2021.

INTRODUCTION

Enterococci, which are a member of the gastrointestinal system flora of humans and animals, are microorganisms with low virulence. However, due to their intrinsic and acquired antimicrobial resistance properties, they have become opportunistic or nosocomial pathogens frequently isolated in community and healthcare-associated infections.[1,2]

Enterococci cause various clinical conditions such as urinary tract infection (UTI), wound, intra-abdominal, endocarditis, bloodstream infections, as well as infections associated with the use of medical devices.[3] UTI is one of the leading infections caused by enterococci, and is especially seen in patients with underlying urinary system anomalies and those who have undergone catheter and/or urinary intervention.[1,4] Risk factors for nosocomial enterococcal colonization or infection include comorbid conditions such as prolonged hospitalization or intensive care unit stay, intra-abdominal and cardiothoracic surgery, immunosuppression, and prior use of antibiotics (especially cephalosporins, vancomycin, or aminoglycosides).[1,5]

Enterococcus faecalis (E. Faecalis) (80-90%) and *Enterococcus faecium* (5-10%) are the most common species among healthcare-associated infectious agents worldwide.[3] However, the distribution of dominant enterococcal species varies in terms of host, environmental and hospital environment-related factors, as among the virulence factors that play a role in the pathogenesis of enterococcal infections, hemolysin/cytolysin, gelatinase and enterococcal surface protein (ESP) are frequently investigated virulence factors.[5] Hemolysis; It is a cytolytic enzyme that causes lysis in human, horse and rabbit erythrocytes and may increase the severity of the infection.[5] Gelatinase is an extracellular protease that hydrolyzes peptides such as gelatin, collagen, casein and hemoglobin that

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enable adhesion to the host cell. It has been stated in animal experiments that it may be associated with the development of endocarditis and biofilm formation.[5,7] It has been stated that ESP, another virulence factor, facilitates colonization of the host cell epithelium and subsequent infection development, and causes biofilm formation on abiotic surfaces.[5,8] It has been reported that gelatinase increases the effect of ESP and contributes to biofilm formation, especially in the development of UTI caused by *E. faecalis*.[8]

Antimicrobial resistance in enterococci may be intrinsic or acquired. Constitutive resistance is a feature encoded in the chromosomes of enterococcal species, and they are intrinsically resistant to antimicrobial drugs such as cephalosporins, aminoglycosides, lincosamides and trimethoprim-sulfamethoxazole. Acquired resistance occurs through mutations in structural DNA due to the flexibility of genome structures or by the transfer of genetic material on a plasmid or transposon. In recent years, increasing resistance rates have been reported, especially against high-level aminoglycosides (HLR), beta lactams and glycopeptides.[3,9]

The aim of this study was to determine the virulence factors and antibiotic resistance of *E. faecalis* isolated from urine samples, to investigate the relationship between the presence of virulence factors and antibiotic resistance, and to investigate the relationship between virulence factors and urinary catheter use, which constitutes a risk for the development of UTI.

METHODS

100 *E. faecalis* strains isolated from urine samples sent to the medical microbiology laboratory from various clinics of İstanbul University İstanbul Faculty of Medicine Hospital between 22.02.2009-10.06.2010 were included in the study (Date: 01.09.2009, Decision No: 2489). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Urine samples were cultured on chromogenic agar (BBL Chromagar Orientation), and the cultures were evaluated after 24 and 48 hours of incubation at 37˚C. *Enterococcus* spp. are Gram-positive, catalase-negative, Gram-positive cocci that grow on media, form black colonies on bile esculin agar, and grow on media containing 6.5% NaCl. Species identification was made with the VITEK 2 (bioMerieux, France) Gram positive (GP) identification kit. For the phenotypic detection of haemolysis, which is one of the virulence factors, brain heart infusion agar containing 5% horse blood was inoculated, kept at 37˚C and 5% CO2, and evaluated after 24 and 48 hours. The formation of a beta haemolysis zone around the colonies was considered positive.[10] For phenotypic detection of gelatinase, tryptic soy agar (TSA) medium containing 1.5% skim milk was inoculated and the transparent zone formed around the colonies after 18 hours at 37˚C was considered positive.[11] The presence of the ESP gene encoding the enterococcal surface protein was investigated by polymerase chain reaction (PCR) (Amersham Ready-To-Go RT-PCR Beads, UK) using site-specific ESP11 and ESP12 primers after DNA extraction (High Pure PCR Template Preparation Kit, Roche, Germany) and the sequence of the primers are listed in Table 1.[10,12,13]

Table 1. Primer used in PCR detection of esp

Gene	Primer	Sequence (5' to 3')	Amplicon size (bp)
esp	esp 11 (forward)	5' -TTGCTAATGCTAGTCCACGACC-3'	954
	esp 12 (reverse)	5' -GCGTCAACACTTGCATTGCCGAA-3'	

PCR: Polymerase chain reaction

The PCR conditions were: Initial denaturation of 94˚C for 10 min, 30 cycles of: denaturation (94˚C for 45 s), annealing (63˚C for 45 s) and extension (72˚C for 60 s), added to a final extent of 72˚C for 10 min, followed by cooling the samples to 4˚C. The amplicons were analyzed by 2% agarose gel electrophoresis and 1X TBE buffer and visualized by ethidium bromür dye on the photodocumentator in UV light. In order to determine the molecular weight of the amplified DNA, the bands formed were determined by comparing the molecular weights with known bands according to the marker used. The *E. faecalis* strain MMH 594 was used as positive control in PCR detection of ESP.[10,13]

Antibiotic susceptibilities of the isolated strains were determined by Kirby-Bauer disc diffusion method according to CLSI guidelines.[14] Testing for susceptibility to vancomysin (30 µg), ampicillin (10 µg), norfloxacin (10 µg), nitrofurantoin (300 µg), linezolid (30 µg), gentamicin (120 µg) and streptomycin (300 µg) was done with use of disc (Oxoid, Basingstone, UK).[14] Testing for susceptibility to vancomysin, linezolid and tigecycline was done with use of Etest strips (AB Biodisk Sweden). Results were evaluated in accordance with CLSI and EUCAST recommendations for tigecycline.

Statistical Analysis

Data are described using frequency and percentage. The results were evaluated with chi-square tests. Statistical significance was accepted if $p<0.05$.

RESULTS

In this study, a total of 100 *E. faecalis* strains isolated from urine samples sent to our laboratory from various clinics and outpatient clinics of our hospital were examined. While 31 (31%) of the 100 patients examined were male and 69 (69%) were female, the age distribution of the patient group varied between four months and 87 years (mean. 4 years). The number of inpatients was determined as 15 (15%), and the number of patients followed in the outpatient clinic was determined as 85 (85%). Among the patients from whom the enterococcal strains were isolated included in the study, the number of patients who were in the risk group for UTI and had a history of using a urinary catheter at least once was 56 (56%), while the number of patients who did not have a catheter was 44 (44%).

When the antibiotic resistance rates of the tested strains were examined, no strains resistant to vancomycin, linezolid and tigecycline were detected. Resistance to nitrofurantoin was found in 1%, ampicillin in 2%, norfloxacin in 31%, and HLG and HLS in 22% and 37%, respectively. When the MIC distribution of the investigated strains is examined; MIC90 values were determined as 2, 2 and 0.19 for vancomycin,

linezolid and tigecycline, respectively. Antibiotic resistance rates are shown in Table 2.

Table 2. Antibiotic resistance rates in *Enterococcus Faecalis* strains (%)

Antibiotic	Resistance (%)
Ampicillin	2
Norfloxacin	31
Nitrofurantoin	1
Vancomycin	0
Tigecycline	0
Linezolid	0
High level gentamicin	22
High level streptomycin	37

When evaluated in terms of virulence factors; It was determined that a total of 82% of the strains consisted of gelatinase, 67% of them were ESP, and 35% were hemolysin. At the same time, it was determined that 37% of the strains formed *Esp* and gelatinase together, and 24% of the strains formed ESP, gelatinase and hemolysin together. No virulence factor was detected in 8 strains. No statistically significant relationship was detected between the presence of antibiotic resistance and catheter use and virulence factors (p>0.05). The presence of hemolysis and gelatinase detected in the study is shown in Figures 1 and 2. Virulence factors (%) detected in *E. faecalis* strains are shown in Table 3.

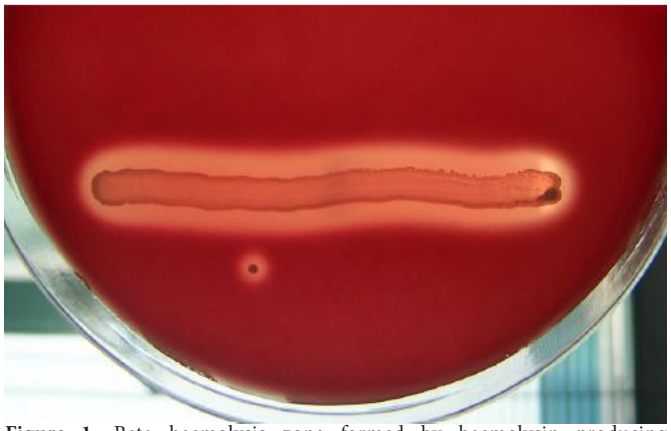

Figure 1. Beta haemolysis zone formed by haemolysin producing *Enterococcus faecalis*

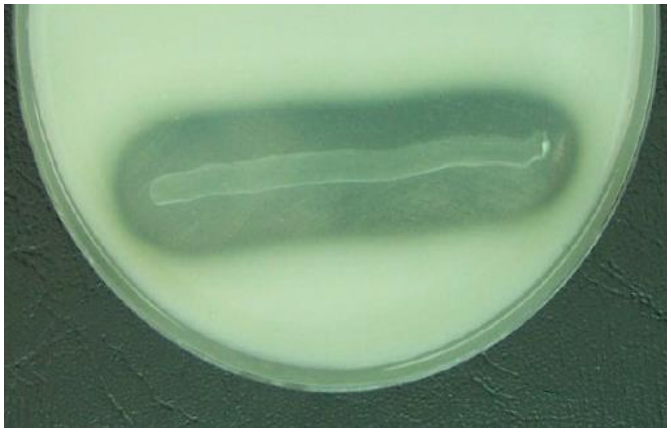

Figure 2. Transparent zone formed by gelatinase producing *Enterococcus faecalis*

Table 3. Virulence factors detected in *Enterococcus Faecalis* strains (%)

Virulence factors	(%)
Gel*	82
Esp**	67
Hem***	35
Esp/gel	37
Esp/gel/hem	24
No virulence factor	8

*Gelatinase, **Enterococcal surface protein, ***Hemolysin

DISCUSSION

In the treatment of enterococcal infections, the combination of aminoglycosides such as streptomycin and gentamicin with cell wall active inhibitors such as glycopeptides or beta-lactams is preferred. However, the emergence of highly aminoglycoside-resistant (HLAR) enterococci due to the production of enzymes that inactivate and modify aminoglycosides has created significant challenges in terms of infection management.[6] In our study, we investigated the presence of antimicrobial resistance and virulence factors in *E. faecalis* strains isolated from urine samples; Antibiotic resistance rates for ampicillin, norfloxacin, nitrofurantoin, high-level gentamicin (HLG) and high-level streptomycin (HLS) were determined as 2%, 31%, 1%, 22%, 37%, respectively, while no strains resistant to vancomycin, linezolid and tigecycline were detected.

According to the data of the European Antimicrobial Resistance Surveillance System (EARS-Net), which was established to detect the development of antimicrobial resistance in Europe; In 2014, the prevalence of *E. faecalis* in sterile samples was reported to be 28.8% on average, although there are differences between countries (8.3-76.5%). In 2019, a decrease in HLGR was noted over the years, and the resistance rate, which was 31.9% in 2015, was reported as 26.6%. In the evaluation made in terms of vancomycin resistance, while very low resistance rates were reported in *E. faecalis* strains in most countries, the resistance in *E. faecium*, which was 10.5% in 2015, increased over the years and was reported as 18.3% in 2019.[15,16] According to the 2021 Annual Epidemiological Report data of the same institution, an increase in the number of cases reported for all pathogens was reported between 2020 and 2021. Among the bacteria with the highest increase was *E. faecalis*, with an increase rate of 14%. The highest resistance increase in *E. faecalis* in 2021 was detected in HLR. Although resistance rates vary between 6.7-55.2 depending on the country, the average has been reported as 29%. However, no significant difference was observed in resistance rates between 2017 and 2021.[17]

In a study conducted in England where resistance surveillance data of *Enterococcus* species isolated from blood cultures between 2001 and 2019 were evaluated; While vancomycin resistance in *E. faecalis* remained below 4% in all years, it was determined that the resistance rate in HLG, which was 45% in 2001, decreased to 30% in 2019. It has been stated that this decrease in HLGR may be a reflection of the gentamicin and ciprofloxacin resistant clonal decline that was prevalent at the

beginning.[18] In various studies conducted abroad in which the antibiotic resistance of *E. faecalis* isolated from urine samples was investigated, the antibiotic resistance rates were; results ranging from 0-30% for ampicillin/penicillin, 20.6-94% for norfloxacin/ciprofloxacin, 8.8-54.81% for YDG, 7-16.31% for nitrofurantoin, 0-15% for vancomycin, and 0-4% for linezolid have been reported.[4,6,19-21]

In studies conducted in our country where the antibiotic resistance of *E. faecalis* was investigated in various clinical samples, the resistance rates were; ampicillin 5.6-50%, HLG 42-44.7%, HLS 37-50.4%, norfloxacin/ciprofloxacin 36-47.5%, vancomycin 1.5-2%, linezolid 0-6.5%, tigecycline 0% and 4.8-8.6% for nitrofurantoin. Wide ranges of resistance rates have been reported for some antibiotics.[22,23] In two studies investigating the resistance of *E. faecalis* in urine samples, nitrofurantoin 1.7%, ampicillin 10.6-13.6%, norfloxacin/ciprofloxacin 33.9-37.5%, HLG 14.8-22%, HLS 6.2-27.1%, vancomycin 0-1.9%, linezolid 0-3.1% and tigecycline 0-0.3% were reported.[24,25] In our study, antibiotic resistance rates were found to be 2% for ampicillin, 31% for norfloxacin, 22% for HLG, 37% for HLS and 1% for nitrofurantoin, while no strains resistant to vancomycin, linezolid and tigecycline were found. It was thought that the reason for the difference in the resistance rates obtained in the studies between the centres may be due to the diversity of clinical samples and patients as well as the change in the distribution according to years.

Although there are many virulence factors thought to contribute to the pathogenesis of enterococci, cytolysin/hemolysin, aggregation factor, ESP and gelatinase are the most researched factors. It has been stated that the presence of these factors together may cause tissue damage and deep tissue invasion. *Enterococci* have the ability to form biofilms on central venous catheters, urinary catheters and prosthetic heart valves, and especially ESP and gelatinase are held responsible for biofilm formation.[5] The most frequently detected virulence factor in our study was gelatinase with a rate of 82%. This was followed by ESP with 67% and hemolysis with 35%. No virulence factor was detected in eight strains.

In a study conducted in China,[26] where the biofilm-related virulence factors of *E. faecalis* isolated from UTI were genotypically investigated, gelatinase was found to be 41.5%, ESP 59.5% and hemolysis 57.3%. Researchers have reported that the presence of cytolysin is associated with weak biofilm formation, while the presence of aggregation factor is associated with strong biofilm formation. In another study[23] in which the virulence factors associated with biofilm formation of *E. faecalis* isolated from various clinical samples were genotypically investigated, researchers detected biofilm formation in 47.2% of the strains. They reported the presence of gelatinase, ESP and hemolysin/cytolysin, among the virulence factors, as 41.5%, 59.5%, 57.3%, respectively, and stated that there was a relationship between medium-strong biofilm formation and ESP, and weak biofilm formation and cytolysin. In a study in which the virulence factors of *E.faecalis* isolated from the urinary system were investigated phenotypically and genotypically, they found phenotypic gelatinase, hemolysin and proteinase activities to be 22%, 33% and 57%, respectively. However, researchers also stated that they detected higher rates of positivity genotypically, but this rate was not reflected in the phenotype.[28] In their study investigating the source (exogenous-endogenous) of *E. faecalis* isolated from community-acquired UTI, Ghalavand et al.[4] found ESP to be 77.8% and cytolysin/hemolysis to be 54% and they stated that these virulence factors may play a role in pathogenesis. In their studies investigating virulence genes and antibiotic resistance in *E.faecalis* isolated from the urinary system, researchers found vancomycin resistance to be 66%, gentamicin, norfloxacin and nitrofurantoin resistance to be 33.3%, 30% and 8.33%, respectively, and ESP positivity to be 66%. It has been stated that the presence of antibiotic resistance and virulence factors is higher in isolates that form strong biofilms.[12]

Baylan et al.[25] in their study investigating the relationship between antibiotic resistance and virulence factors of enterococci isolated from urine samples; Among the virulence factors of *E. faecalis*, they determined gelatinase as 22%, ESP as 35.6%, and hemolysin as 16.9%. In another study[29] in which antibiotic resistance and virulence factors of *E. faecium* and *E. faecalis* were investigated from various clinical samples, the presence of gelatinase, ESP and haemolysin in *E. faecalis* was reported as 26.5%, 79.6% and 51%, respectively. The researchers reported that *E. faecalis* had more virulence factors than *E. faecium*, but *E. faecium* had more antibiotic resistance. In this study, since the clinical characteristics of the patients from whom E. faecalis was isolated were not known, the inability to differentiate the isolates as agent/colonization/contamination and the inability to perform genotypic examination of all virulence genes investigated constitute the limitations of the study.

In their study investigating virulence factors in vancomycin-resistant *E. faecium* (VRE) and vancomycin-susceptible (VS) *E. faecalis* strains, Mete et al.[30] reported gelatinase as 52.7%, ESP as 38.9% and haemolysin as 41.1% in *E. faecalis* in urine samples and stated that VSE isolates had more virulence genes than VRE isolates. In our study, no relationship was found between the presence of virulence factors and antibiotic resistance. In addition, no statistically significant relationship was found between the presence of virulence factors and antibiotic resistance in patients with catheters ($p>0.05$).

CONCLUSION

As a result, due to the differences observed in antimicrobial resistance profiles between centers and regions, it is thought that analyzing the antimicrobial susceptibility profiles of each center to determine their own resistance epidemiology will make a significant contribution to starting an effective treatment at an early stage. Additionally, in our study, no significant relationship was found between the presence of virulence factors and antibiotic resistance and catheter application. However, considering that the most detected virulence factors, gelatinase and *Esp*, have the ability to colonize and form biofilms on abiotic surfaces, minimizing catheterization practices may help prevent UTIs that may develop with enterococci.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of İstanbul University, İstanbul Faculty of Medicine Clinical Researches Ethics Committee (Date: 26.06.2009, Decision No: 2489).

Informed Consent

Informed consent is not required for resistance studies on bacterial strains.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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Author Contributions

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

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First and second trimester laboratory changes and perinatal outcomes in pregnant women with epilepsy

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ABSTRACT

Aims: The aim of this study is to comprehensively evaluate the demographic, first-second trimester laboratory parameters and perinatal outcomes in pregnant women with epilepsy.

Methods: The study had a total of 73 pregnant women with epilepsy, along with 149 healthy pregnant women. Demographic data, first-second trimester laboratory parameters, seizures during pregnancy, the administration of antiepileptic medicines and perinatal outcomes were documented from September 2022 to 2023. Pregnant women with epilepsy were formed into subgroups according to whether they had seizures during pregnancy or not and whether they used antiepileptic drugs, and first- and second-trimester laboratory parameters were compared between the groups. Furthermore, univariate and multivariate linear regression analysis investigated the relationship between these parameters with the composite adverse neonatal outcomes (CANO).

Results: In the study, 72.7% of pregnant women diagnosed with epilepsy were receiving antiepileptic treatment (75.4% monotherapy and 24.6% polytherapy). The incidence of seizures during pregnancy was 38.3%. The epilepsy group exhibited statistically significant differences from the control group in the following areas: gestational age at delivery, preterm birth rate, cesarean section rate, birth weight, neonatal head circumference, APGAR score <7 at the 1st and 5th minutes, and CANO. The Neutrophil to Lymphocyte Ratio (NLR) was significantly higher in the epilepsy group in the second trimester ($p=0.027$), and the monocyte to lymphocyte ratio (MLR) was significantly higher in the first trimester in the epilepsy group ($p<0.001$). Upon comparing who experienced seizures during pregnancy and those who did not, no significant difference was found between the two groups. In the univariate logistic regression model, it was determined that having a seizure during pregnancy was a significant predictor, indicating a higher likelihood of developing perinatal complications. Multivariate linear regression analysis showed no significant correlation.

Conclusion: The laboratory results of pregnant women with epilepsy during the first and second trimesters show differences compared to healthy pregnant women. Pregnant women diagnosed with epilepsy were associated with a higher risk of preterm delivery and giving birth to newborns with lower birth weight and head circumference. These differences may have significance in the follow-up and care of pregnant women with epilepsy.

Keywords: Epilepsy, perinatal outcomes, first- and second-trimester laboratory parameters

INTRODUCTION

Antenatal care, antiepileptic drug use, seizure control and perinatal outcomes in women with epilepsy during pregnancy are an interesting and important topic that has not yet been fully elucidated for all periods. Epilepsy is a long-term neurological disease characterized by recurrent seizures and occurs in approximately 1% of the general population worldwide.[1,2] The condition impacts approximately 6.85 cases per 1000 women within the context of gender and affecting an estimated 15 million women in the reproductive age group globally.[3,4] Treatment of pregnant women with epilepsy requires a delicate balance between maintaining control of maternal seizures and the potential adverse effects of antiepileptic drugs on the developing fetus. Pregnancy with epilepsy is associated with an increased risk of adverse maternal and perinatal outcomes. The risks encompassed in this context are preeclampsia, preterm birth, stillbirth, fetal growth restriction, congenital abnormalities, and maternal mortality.[5] This highlights the importance of good prenatal care and the need to better understand the mechanisms underlying these risks so that preventive interventions can be designed.

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In animal studies, inflammation has been found to be involved in the initiation and progression of epilepsy and in an animal model of epilepsy, infiltration of leukocytes, lymphocytes, and monocytes was identified in certain regions of the brain.[6,7] The development of epilepsy may be influenced by both local and systemic inflammatory responses, as evidenced by elevated levels of chemokines and cytokines in the cerebrospinal fluid and peripheral blood of individuals with epilepsy. In a systematic review by Hosseini et al.,[8] it was determined that inflammation plays a role in epilepsy and that a high neutrophil to lymphocyte ratio (NLR) value may be a good biomarker for inflammation and therefore epilepsy.[9] There are a limited number of studies in the literature showing the effects of changes in maternal serum markers in the first and second trimester on the number of seizures during pregnancy and perinatal outcomes in pregnant women with epilepsy.[10-12] Moreover, alterations in laboratory parameters throughout the first and second trimesters might offer vital information regarding the well-being of both the mother and the developing fetus.[13-15] We aimed to investigate whether there is a relationship between maternal first and second trimester serum parameters and seizure occurrence and perinatal outcomes.

METHODS

This retrospective case-control study includes 73 pregnant women with epilepsy and 149 healthy pregnant women whose follow-up, treatment and births took place between 2022 and 2023 at Ankara Etlik City Hospital, a tertiary center where approximately 12,500 births occur annually. Ethical approval was received for this study from Ankara Etlik City Hospital Clinical Researches Ethics Committee (Decision No: AESH-EK1-2023-170). This study adhered to the criteria outlined in the Declaration of Helsinki.

The control group was randomly selected among healthy pregnant women. Exclusion criteria were using medications other than antiepileptic drugs, smoking, having any systemic disease, and having multiple pregnancies. The pregnant woman's age, gravity, parity, body-mass index (BMI), time since epilepsy diagnosis, use of antiepileptic drugs during pregnancy (monotheraphy, politheraphy), whether and how many seizures during pregnancy, gestational age at delivery, type of birth, neonatal birth weight, 1st and 5th minutes APGAR score, and neonatal intensive care unit (NICU) admission were obtained from the hospital's electronic medical record system. Composite adverse neonatal outcome was defined as the presence of at least one of the following situations: respiratory distress syndrome (RDS), 5th minute APGAR score <7, and NICU admission. Laboratory parameters such as first and second trimester white blood cell counts (WBC), lymphocyte, neutrophil, monocyte, hemoglobin, platelet were obtained from maternal serum complete blood count results. NLR was calculated by dividing the absolute number of neutrophil by the absolute number of lymphocyte at each time point. Monocyte to lymphocyte ratio (MLR) was calculated by dividing the monocyte count by lymphocyte count, and Platelet to lymphocyte ratio (PLR) by dividing the platelet count by lymphocyte count. All these parameters were compared between pregnant women with epilepsy and healthy control pregnant women. Moreover pregnant women with epilepsy were divided into subgroups according to the presence or absence of seizures during pregnancy and with and without antiepileptic treatment. Then, first-second trimester laboratory parameters compared with each other. The impact of various epilepsy characteristics on pregnancy was investigated using univariable and multivariable logistic regression analyses.

Statistical Analysis

This study involved the analysis of demographic, neonatal, and ultrasonographic data of pregnant women with epilepsy. Statistical analyses were performed using SPSS version 27.0 (IBM Corp., Armonk, N.Y., USA). For demographic and ultrasonographic data, group comparisons were made using median and interquartile range (IQR) values. Continuous variables were analyzed using both the Mann-Whitney U test and student's t-test to assess differences between groups. Categorical variables were presented as numbers and percentages and analyzed using the Chi-square test. Univariable and multivariable logistic regression analyses were utilized to investigate the effects of various epilepsy characteristics on pregnancy outcomes. In the univariable logistic regression analysis, each variable was examined individually to identify potential predictors. The multivariable logistic regression analysis was then employed to adjust for confounders and to ascertain the independent impact of each variable. Odds ratios (ORs) and 95% confidence intervals (CIs) were computed to evaluate the risk associated with each factor. The significance level was set at $p<0.05$ for all analyses, and results were reported with a 95% confidence interval.

RESULTS

The patient cohort is presented in Table 1. The study evaluated 73 pregnant women diagnosed with epilepsy. Among these, 72.7% (n=53) were undergoing epilepsy treatment, with 75.4% (n=40) of this group receiving monotherapy and 24.6% (n=13) on polytherapy. The proportion of women not receiving treatment was 27.3% (n=20). The incidence of seizures during pregnancy was observed in 38.3% (n=28) of the subjects, and there were no cases of status epilepticus (0.0%).

Table 1. Patient cohort of pregnant women with epilepsy

Pregnant women with epilepsy, n (%)	n=73 (100)
Time since epilepsy diagnosis (year), median (IQR)	8.0 (10.0)
Active treatment	
No theraphy, n (%)	20 (27.3)
Yes theraphy	53 (72.7)
Monotheraphy, n (%)	40 (75.4)
Politheraphy, n (%)	13 (24.6)
Seizures during pregnancy, n (%)	28 (38.3)
Number of seizures during pregnancy, median (IQR)	0.0 (1.0)
Status epilepticus, n (%)	0 (0.0)

The comparison of demographic, clinical, and perinatal outcomes between pregnant women with epilepsy and a

control group is displayed in Table 2. The maternal age, gravidity, parity, BMI were similar between the groups. When examining gestational age at delivery, the median was 38 weeks (IQR: 2.0) in the epilepsy group and 39 weeks (IQR: 2.0) in the control group, with the difference being statistically significant (p<0.001). The rate of preterm birth (<37 weeks) was 27.4% in the epilepsy group, while no cases were reported in the control group (p<0.001). Regarding the mode of delivery, 26% of the epilepsy group had vaginal births, and 74% had cesarean sections. In contrast, the control group had 49.7% vaginal and 50.3% cesarean deliveries, with this difference being statistically significant (p<0.001). The birth weight was 2950 grams (IQR: 920) in the epilepsy group and 3240 grams (IQR: 580) in the control group, also showing a significant difference (p<0.001). Neonatal head circumference was 34.0 cm (IQR: 2.00) in the epilepsy group and 35.0 cm (IQR: 1.00) in the control group, with this difference being significant (p<0.001). Additionally, the rate of newborns with an APGAR score <7 at 1 minute was 11% in the epilepsy group compared to 2% in the control group (p=0.004). The rate of APGAR scores <7 at 5 minutes was observed at 6.8% only in the epilepsy group (p=0.001). The rate of CANO was 21.9% in the epilepsy group compared to 3.4% in the control group, which was also statistically significant (p<0.001).

Table 2. Demographic data, clinical and perinatal characteristics of the patients

Median (IQR), n (%)	Epilepsy, n=73	Control, n=149	p value
Maternal age (year), median (IQR)	28.0 (7.00)	27.0 (7.00)	0.712
BMI (kg/m^2), median (IQR)	28.0 (7.21)	29.3 (6.75)	0.070
Gravidity, median (IQR)	2 (2)	2 (2)	0.213
Parity, median (IQR)	1 (1)	1 (2)	0.104
Gestational age at delivery (week), median (IQR)	38.0 (2.0)	39.0 (2.0)	<0.001
Preterm birth (<37 weeks) n (%)	20 (27.4)	0 (0.0)	<0.001
Birth type, n (%)			
Vaginal delivery	19 (26.0)	74 (49.7)	<0.001
Cesarean section	54 (74.0)	75 (50.3)	
Birth weight (gram), median (IQR)	2950 (920)	3240 (580)	<0.001
Neonatal head circumference, median (IQR)	34.0 (2.00)	35.0 (1.00)	<0.001
APGAR 1th min. score <7, n (%)	8 (11.0)	3 (2.0)	0.004
APGAR 5th min. score <7, n (%)	5 (6.8)	0 (0.0)	0.001
CANO, n (%)	16 (21.9)	5 (3.4)	<0.001

IQR: Inter quantile range, BMI: Body-mass index, IVF: In vitro fertilization, APGAR: Appearance, pulse, grimace, activity and respiration, CANO: Composite adverse neonatal outcome

Table 3 presents the comparison of first and second trimester laboratory characteristics between pregnant women with epilepsy and the control group. In the first trimester, the hemoglobin levels were 12.3 g/dL in the epilepsy group and 12.8 g/dL in the control group, showing a significant difference (p<0.001). In the second trimester, hemoglobin levels dropped to 11.3 g/dL in the epilepsy group, compared to 12.0 g/dL in the control group, with this change also being significant (p=0.002). WBC showed significant differences between the groups in the first trimester (p=0.023), which continued into the second trimester (p=0.020). Neutrophil counts were significantly higher in the epilepsy group during the second trimester compared to the control group (p=0.001). Monocyte counts only showed a significant difference in the first trimester between the epilepsy and control groups (p<0.001), with no significant difference found in the second trimester (p=0.539). Additionally, the neutrophil to lymphocyte ratio (NLR) was significantly higher in the epilepsy group in the second trimester (p= 0.027), and the monocyte to lymphocyte ratio (MLR) was significantly higher in the first trimester in the epilepsy group (p<0.001).

Table 3. Comparison of 1st and 2nd trimester laboratory characteristics in epilepsy and control groups

Median (IQR)	Epilepsy, n=73		Control, n=149			
	1st trimester	2nd trimester	1st trimester	2nd trimester	p1	p2
Hemoglobin (g/dl)	12.3 (1.70)	11.3 (1.30)	12.8 (1.10)	12.0 (1.35)	<0.001	0.002
WBC (*10^3/mm^3)	8.97 (3.69)	10.50 (3.11)	8.19 (2.54)	9.27 (3.12)	0.023	0.020
Neutrophil (*10^3/mm^3)	5.89 (2.61)	7.52 (3.19)	5.67 (2.35)	6.63 (2.84)	0.067	0.001
Lymphocyte (*10^3/mm^3)	2.18 (0.970)	1.90 (0.690)	1.93 (0.790)	1.90 (0.770)	0.109	0.884
Monocyte (*10^3/mm^3)	0.570 (0.180)	0.630 (0.240)	0.450 (0.200)	0.620 (0.295)	<0.001	0.539
Platelet (*10^3/mm^3)	260 (89.0)	244 (73.0)	261 (85.0)	244 (74.5)	0.328	0.966
NLR	2.91 (1.62)	4.08 (2.54)	2.99 (1.36)	3.57 (1.78)	0.574	0.027
PLR	135 (63.6)	134 (56.4)	137 (63.8)	120 (53.8)	0.238	0.299
MLR	0.311 (0.108)	0.321 (0.149)	0.241 (0.120)	0.327 (0.144)	<0.001	0.363

WBC: White blood cell counts, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, MLR: Monocyte to lymphocyte ratio

Table 4 shows the results comparing pregnant women with epilepsy who experienced seizures during pregnancy with those who did not, for first and second trimester laboratory characteristics. The monocyte ratio in the second trimester was 0.660 in those who experienced seizures, compared to 0.620 in those who did not, with a p-value of 0.068, indicating slightly higher monocyte ratios in those who experienced seizures, although not reaching statistical significance.

In the study, pregnant women with epilepsy, whether receiving treatment or not, were compared, and the laboratory parameter differences were investigated in Table 5. No statistically significant differences were found between the treated and untreated groups.

The impact of various epilepsy characteristics on pregnancy was investigated using univariable and multivariable logistic regression analyses. The analyses considered factors such as experiencing seizures during pregnancy, the time since epilepsy diagnosis, the number of seizures during pregnancy, and the type of treatment (polytherapy or monotherapy) used (Table 6). The condition of experiencing seizures during pregnancy was found to be a significant predictor in the

Table 4. Comparison of 1st and 2nd trimester laboratory characteristics in epileptic pregnant women with and without seizures during pregnancy

	With seizures, n=28		Without seizures, n=45			
Median (IQR)	1st trimester	2nd trimester	1st trimester	2nd trimester	p1	p2
Hemoglobin (g/dl)	12.3 (2.25)	11.3 (1.70)	12.3 (1.70)	11.5 (1.30)	0.945	0.811
WBC (*10³/mm³)	10.80 (4.36)	10.70 (3.85)	8.88 (3.76)	10.40 (3.25)	0.171	0.321
Neutrophil (*10³/mm³)	6.22 (3.01)	7.46 (3.20)	5.88 (2.64)	7.73 (2.92)	0.304	0.485
Lymphocyte (*10³/mm³)	2.30 (1.000)	1.90 (0.810)	1.96 (0.810)	1.84 (0.800)	0.231	0.518
Monocyte (*10³/mm³)	0.585 (0.178)	0.660 (0.325)	0.570 (0.230)	0.620 (0.220)	0.896	0.068
Platelet (*10³/mm³)	266 (93.5)	250 (101.0)	260 (79.0)	244 (59.0)	0.883	0.834
NLR	2.89 (1.64)	3.88 (3.83)	2.94 (1.62)	4.45 (1.93)	0.878	0.887
PLR	134 (53.3)	132 (32.5)	136 (71.3)	134 (72.8)	0.367	0.860
MLR	0.305 (0.092)	0.361 (0.131)	0.325 (0.156)	0.315 (0.141)	0.450	0.218

WBC: White blood cell counts, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, MLR: Monocyte to lymphocyte ratio

Table 5. Comparison of 1st and 2nd trimester laboratory characteristics according to treatment requirement in the epilepsy group

	No theraphy, n=20		Yes theraphy, n=53			
Median (IQR)	1st trimester	2nd trimester	1st trimester	2nd trimester	p1	p2
Hemoglobin (g/dl)	12.3 (1.20)	11.3 (0.85)	12.3 (1.80)	11.5 (1.40)	0.607	0.581
WBC (*103/mm³)	9.68 (4.87)	10.70 (4.99)	8.96 (3.41)	10.40 (2.78)	0.536	0.697
Neutrophil (*10³/mm³)	6.04 (3.39)	7.88 (3.82)	5.89 (2.33)	7.29 (2.94)	0.951	0.621
Lymphocyte (*10³/mm³)	2.21 (0.765)	1.90 (0.715)	2.01 (.1.000)	1.90 (0.660)	0.715	0.887
Monocyte (*10³/mm³)	0.570 (0.318)	0.600 (0.395)	0.580 (0.170)	0.630 (0.230)	0.647	0.748
Platelet (*10³/mm³)	272 (86.5)	250 (73.3)	254 (77.0)	243 (68.0)	0.669	0.565
NLR	2.89 (1.36)	4.51 (1.68)	2.99 (1.65)	3.82 (2.61)	0.516	0.432
PLR	138 (82.1)	136 (72.4)	135 (57.7)	129 (54.5)	1.000	0.462
MLR	0.282 (0.167)	0.308 (0.177)	0.318 (0.101)	0.321 (0.140)	0.790	0.867

WBC: White blood cell counts, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, MLR: Monocyte to lymphocyte ratio

Table 6. Univariable and multivariable logistic regression analysis of epilepsy characteristics

	Univariable LR			Multivariable LR		
	OR	CI	p value	OR	CI	p value
Seizures during pregnancy	3.611	1.136-11.473	0.029	3.511	0.771-15.979	0.104
Time since epilepsy diagnosis (year)	0.961	0.878-1.050	0.379			
Number of seizures during pregnancy	1.178	0.837-1.658	0.348			
Politheraphy versus Monotheraphy	3.542	0.860-14.577	0.080	2.582	0.583-11.428	0.211

LR: Logistic regression, OR: Odds ratio, CI: Confidance interval

univariable logistic regression model; those who experienced seizures had a higher chance of complications compared to those who did not (OR=3.611, CI=1.136-11.473, p=0.029). However, in the multivariable model, this relationship lost its significance (OR=3.511, CI=0.771-15.979, p=0.104), indicating that when considering other factors, experiencing seizures during pregnancy does not significantly predict complications. The duration since epilepsy diagnosis was not found to be a significant predictor in the univariable regression model (OR=0.961, CI=0.878-1.050, p=0.379), suggesting that the duration of epilepsy diagnosis does not affect the risk of complications during pregnancy. The number of seizures experienced during pregnancy was also not a significant predictor in the univariable model (OR=1.178, CI=0.837-1.658, p=0.348). Regarding the type of treatment, a nearly significant relationship was found between those undergoing polytherapy compared to monotherapy in the univariable model (OR=3.542, CI=0.860-14.577, p=0.080); however, this relationship was not significant in the multivariable model (OR=2.582, CI=0.583-11.428, p=0.211).

DISCUSSION

In the study, MLR exhibited significant differences in the first trimester and NLR were significantly different in the second trimester between pregnant women with epilepsy and the control group. Upon comparing the first and second trimester laboratory characteristics of pregnant women with epilepsy who experienced seizures during pregnancy and those who did not, and with and without treatment, no significant difference was found between the two groups.

NLR is a dependable, cost-effective, and simple indicator of the immune response. NLR has been observed to be elevated throughout the acute and subacute stages of seizures compared to individuals without any health conditions. An elevated NLR is widely recognized as a biomarker for both inflammation and epilepsy.[9] In a recent study, significant differences ($p<0.05$) were observed in after remission monocyte, lymphocyte, platelet, NLR and MLR levels between adult patients with convulsive status epilepticus and a healthy control group.[16] There is a dearth of information in the literature addressing inflammatory indicators in pregnant women with epilepsy. Bergen et al.[12] found no significant difference in the third trimester NLR value between pregnant women with epilepsy and the control group. In our study, we found that there was no significant difference in the NLR value during the first and second trimesters between pregnant women with epilepsy who received antiepileptic treatment and those who did not, as well as between those who experienced seizures during pregnancy and those who did not. However, we did observe a significantly higher NLR value during the second trimester in pregnant women with epilepsy compared to the control group of pregnant women without epilepsy. In our study, while a significant difference in MLR level was detected between pregnant women diagnosed with epilepsy and the control group in the first trimester, no significant difference was detected in the second trimester. Our study is is the first to evaluate parameters associated with NLR, MLR, PLR levels during the first and second trimesters in epilepsy and pregnancy. If a relationship between changing laboratory

parameters during pregnancy and epileptic seizure frequency and perinatal outcomes is established, these parameters could potentially serve as useful and accessible markers for monitoring and managing epilepsy during pregnancy.

Research has consistently shown that exposure to antiepileptic drugs during pregnancy is linked to a higher likelihood of impaired fetal growth, lower birth weight in relation to gestational age, and smaller head circumference at birth, particularly in polytherapy.[17-20] In the MONEAD study, they found no difference in preterm birth, 5-minute APGAR <6, neonatal intensive care unit admission, gestational age, or any growth measurement between babies born to healthy and epileptic pregnant women, and concluded that epileptic drug use was not associated with adverse early neonatal outcomes.[21] In our current study, birth weight, newborn head circumference, 1st and 5th minute APGAR score <7, CANO showed significant differences in the epilepsy group compared to the control group.

In our study, the majority of epilepsy patients were receiving monotherapy (75.4%), and in line with the literature. Major congenital malformation was detected in only 4 patients with epilepsy and these patients were excluded from the study. No fetal or neonatal mortality was observed in the pregnant women included in this study. It has been shown that the frequency of seizures increases in 25-30% of pregnant women diagnosed with epilepsy.[22] In our study, among the pregnant women diagnosed with epilepsy, 28 (38.3%) had seizures during pregnancy. When the effects of factors such as experiencing seizures during pregnancy, time since the diagnosis of epilepsy, number of seizures during pregnancy, and the type of treatment used (polytherapy or monotherapy) on pregnancy with epilepsy were investigated using univariate and multivariate logistic regression analyses; In the univariate logistic regression model, having a seizure during pregnancy was found to be a significant predictor; the likelihood of developing complications was higher. However, the fact that this relationship lost its significance in the multivariate model shows that having a seizure during pregnancy does not significantly predict complications when other factors are taken into account.

Limitations

This study is limited by its retrospective design, being conducted at a single center, and having a small sample size. However, the strengths of this study is its detailed analysis of the relationship between first and second trimester laboratory parameters, seizure activity during pregnancy, antiepileptic drug use, and perinatal outcomes in pregnant women with epilepsy.

CONCLUSION

The laboratory results of pregnant women with epilepsy during the first and second trimesters show differences compared to healthy pregnant women. Pregnant women with epilepsy were associated with a higher risk of preterm delivery and giving birth to newborns with lower birth weight and head circumference. These differences may have significance in the follow-up and care of pregnant women. Prospective, large population studies are needed to reveal the relationship between seizures, antiepileptic drug use, perinatal outcomes and laboratory parameters in pregnant women with epilepsy.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Ankara Etlik City Hospital No. 1 Clinical Researches Ethics Committee (Decision No: AESH-EK1-2023-170).

Informed Consent

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

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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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Dermatological manifestations and drug-induced reactions in COVID-19 patients: an observational study from İstanbul, Turkiye

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ABSTRACT

Aims: The systemic and respiratory clinical manifestations of coronavirus disease 2019 (COVID-19) include fever, cough, sneezing, sore throat, rhinitis, dyspnoea, chest pain, malaise, fatigue, anorexia, and headache. Moreover, cutaneous manifestations have been observed in 0.2% to 20.4% of cases. This investigation further explores the dermatological manifestations associated with COVID-19 and reactions induced by its pharmacological treatments. Conducted at a university hospital, the study examined 841 patients and identified skin manifestations in 1.5% of cases. It differentiates between symptoms directly attributed to the viral infection and those arising from treatment, highlighting the need for clinical vigilance and adaptability in managing these manifestations. COVID-19 has been linked to a wide range of clinical symptoms, extending beyond the well-known respiratory effects to include various dermatological manifestations. These manifestations, which range from mild rashes to severe conditions like vasculitis, may complicate diagnosis and management, particularly when similar symptoms are induced by therapeutic drugs used in COVID-19 treatment.

Methods: This cross-sectional study included 841 patients treated in the COVID-19 outpatient and inpatient units of the university hospital between March and May 2020. The assessment involved clinical examinations and telemedicine consultations, focusing on differentiating between viral and drug-induced dermatological reactions.

Results: Dermatological manifestations were observed in 1.5% of the 841 patients. Direct virus-related skin changes were noted in 1% (n=8) of patients, including maculopapular eruptions (50%, n=4) on the face and trunk, trunk-localized urticaria (25%, n=2), and purpuric lesions (12.5%, n=1) on the lower extremities. Drug-induced dermatological reactions were identified in 0.5% (n=5) of patients, featuring conditions such as bullous drug reactions, psoriasiform drug eruptions, hypertrichosis, and urticaria.

Conclusion: These findings highlight the complex interplay between COVID-19 and its treatment, where both the virus and pharmacological agents can trigger significant dermatological reactions. The need for healthcare providers to consider both viral and drug-induced factors in the diagnosis and management of skin manifestations in COVID-19 patients is underscored. Further studies are essential to refine treatment protocols and reduce adverse dermatological outcomes.

Keywords: COVID-19, SARS-CoV-2, cutaneous manifestations, dermatology, pharmacological treatments, skin reactions

INTRODUCTION

COVID-19, caused by the SARS-CoV-2 virus, was first identified in Wuhan, China. The World Health Organization (WHO) declared the COVID-19 outbreak a pandemic on March 11, 2020. The first case was reported in Turkiye on March 10, 2020. As of October 29, 2021, there have been approximately 245 million confirmed cases of COVID-19 worldwide, with over 4.9 million fatalities (WHO, 2021). The ongoing global COVID-19 pandemic, caused by the novel coronavirus SARS-CoV-2, has manifested not only with well-known respiratory symptoms but also with a broad spectrum of dermatological manifestations. These skin-related symptoms have become an area of intense research due to their varied presentations and implications for diagnosis and management. Skin manifestations linked to COVID-19 include but are not limited to chilblain-like lesions, maculopapular eruptions, urticaria, vesicular rashes, and petechiae. These dermatological signs have been observed in a diverse patient population, appearing sometimes as the initial presentation of the disease, which can precede hallmark respiratory symptoms.[1,2]

Research suggests that these cutaneous manifestations could stem from the immune response of the body to the virus or vascular damage associated with the disease. The appearance of these skin symptoms in conjunction with, or even before, respiratory symptoms underscores the need for healthcare providers to recognize these presentations for timely diagnosis and isolation of patients.[3]

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Moreover, treatment strategies employed to manage COVID-19, including the use of hydroxychloroquine, antivirals, and antibiotics, have been associated with adverse cutaneous reactions. These reactions range from mild, such as erythema, to severe life-threatening conditions like Stevens-Johnson syndrome and toxic epidermal necrolysis. The interplay between drug-induced skin reactions and viral skin manifestations poses a significant challenge for clinicians, necessitating a high degree of suspicion and clinical acumen to differentiate between the two.[4]

This study aimed to explore the complex interactions between the virus, host immune response, and impact of therapeutic agents, focusing on the dermatological aspects of COVID-19. Understanding these interactions is crucial for developing effective management strategies and improving the outcomes of COVID-19 patients.

METHODS

Ethical Considerations

The study protocol was reviewed and approved by the Bezmialem Vakif University Ethics Committee (Date: 01.07.2024, Decision No: 155793), ensuring compliance with the ethical standards of the Declaration of Helsinki.

Study Design and Setting

This cross-sectional study was conducted at a tertiary care hospital's COVID-19 outpatient clinic, inpatient wards, and dermatology clinic between March 4, 2020, and May 15, 2020. The hospital, being a major referral centre for infectious diseases, was well-equipped to manage the complexities of COVID-19, providing a suitable environment for the collection of clinical data related to both respiratory and dermatological manifestations. The inclusion of the dermatology clinic allowed for specialized evaluation and classification of cutaneous symptoms, helping to differentiate between viral-induced and drug-induced skin reactions. The study focused on identifying and classifying cutaneous symptoms that arose during the course of infection or as a result of therapeutic interventions, leveraging the expertise of both COVID-19 and dermatology departments for comprehensive patient care.

Participants

A total of 841 patients, both suspected and confirmed COVID-19 cases, were prospectively enrolled in the study. The inclusion criteria were based on the WHO guidelines, with confirmed COVID-19 diagnosis established through clinical symptoms, positive SARS-CoV-2 test results (PCR), and, where necessary, computed tomography (CT) imaging to support diagnosis. CT imaging was particularly used in cases where PCR results were inconclusive or delayed, providing additional diagnostic clarity through characteristic lung changes associated with COVID-19. Patients without clear diagnostic evidence were included if they displayed a strong clinical suspicion of infection based on symptoms and imaging. Exclusion criteria involved patients with pre-existing dermatological conditions unrelated to COVID-19 or those on chronic medications known to cause dermatological side effects.

Data Collection

Data collection was systematic and comprehensive, capturing detailed patient information including demographics (age, sex, underlying health conditions), clinical history (pre-existing skin conditions, medications, and other comorbidities), and COVID-19 symptoms (respiratory, systemic, and cutaneous). Dermatological assessments were carried out using a multi-modal approach: direct physical examinations for inpatients, telemedicine consultations for outpatients, and referrals to the dermatology clinic for specialized evaluations when necessary.

The telemedicine consultations allowed for remote but thorough assessments, ensuring that even patients unable to visit the hospital due to isolation measures or mobility issues were still evaluated. During these virtual consultations, patients were guided to provide detailed descriptions of their symptoms, supplemented by photographs and video calls when needed, enabling clinicians to accurately document and assess dermatological manifestations.

Skin manifestations were recorded meticulously, noting their onset, location, type (e.g., rash, vesicles, urticaria), progression, and associated symptoms such as pruritus or pain. This data was securely stored in an encrypted database, ensuring the confidentiality and integrity of patient records throughout the study.

This comprehensive approach allowed for a robust analysis of dermatological symptoms across different stages of COVID-19 and in various clinical settings, offering valuable insights into the spectrum of cutaneous manifestations related to the virus and its treatments.

Dermatological Evaluation

Among the cohort, 13 patients presented with skin manifestations potentially linked to COVID-19. These cases were evaluated in detail by the dermatology department, either through direct referral for inpatients or via telemedicine for outpatients. The dermatology team categorized the skin manifestations based on their type (e.g., rash, vesicles, urticaria) and assessed the severity of each case.

The evaluations focused on distinguishing between virus-induced and treatment-related skin reactions, considering the timing of symptom onset and clinical context. The assessment also included documenting the extent of the lesions, symptom severity (e.g., itching, pain), and the necessity for specific dermatological interventions. For complex cases, additional diagnostic tools, such as skin biopsies, were utilized to confirm the underlying cause.

This comprehensive approach ensured that both the nature and severity of dermatological manifestations were accurately captured, allowing for better patient management and care.

Statistical Analysis

Descriptive statistics were used to analyze the data collected in the study. Frequencies and percentages were calculated for categorical variables, such as the types of dermatological manifestations (e.g., maculopapular eruptions, urticaria, vesicular lesions) and their prevalence within the cohort.

In addition to summarizing the skin manifestations, basic descriptive methods were applied to analyze patient demographics (age, sex) and clinical characteristics (e.g., underlying conditions, treatment regimens) to provide insights into any potential patterns or trends. This analysis focused on offering a clear understanding of the distribution and nature of dermatological symptoms in COVID-19 patients without the use of advanced statistical software. Results were organized in tabular form for clarity and ease of interpretation.

RESULTS

This prospective cross-sectional study analyzed 841 patients who visited the COVID-19 outpatient clinic or were hospitalized in the COVID-19 ward at a major university hospital between March 4, 2020, and May 15, 2020. Among these patients, 51.7% (n=435) were male, and 48.3% (n=405) were female, with ages ranging from 9 days to 95 years, and a median age of 52 years. A positive PCR test result for COVID-19 was observed in 31% of the cohort (n=258) (Table 1).

Table 1. Demographic characteristics of patients with skin manifestations

Variables		n	%
Gender	Female	5	38.5
	Male	8	61.5
	Total number of cases	13	100
Age group (average age 47.4)	30-40 years old	4	30.8
	41-50 years old	3	23.1
	51- 60 years old	5	38.4
	61 and above	1	7.7
	Total number of cases	13	100
PCR	Positive	10	76.9
	Negatif	3	23.1
	Total number of cases	13	100
Computerised tomography	Positive	12	92.3
	Negative	1	7.7
	Total number of cases	13	100
Internal comorbidity	Available	5	38.5
	Not available	8	61.5
	Total number of cases	13	100
Tretment	Hydroxychloroquine	12	37.5
	Oseltamivir	7	21.9
	Azithromycin	10	31.3
	Levocetirizine	2	6.2
	Favipiravir	1	3.1
	Total number of treatments	32	100
ICU/EX	Exitus	1	7.7
	Treatment	12	92.3
	Total number of cases	13	100

PCR: Polymerase chain reaction, ICU: Intensive care unit

The demographic characteristics of the 13 patients who developed skin manifestations related to COVID-19 are detailed in this table. It provides a comprehensive breakdown by gender, age groups, PCR test results, CT scan findings, and the presence of comorbidities. The information presented highlights the distribution and prevalence of dermatological outcomes in the studied population, offering crucial insights into the clinical implications of COVID-19 across different demographics.

Dermatological Manifestations

Out of the total population, dermatological manifestations were observed in 1.5% of the patients (n=13), with a higher prevalence among males (61.5%, n=8) compared to females (38.5%, n=5). The most commonly affected age group was 51-60 years, accounting for 38.4% of cases (n=5), with a mean age of 47 years. Notably, 76.9% (n=10) of the patients exhibiting skin symptoms tested positive for COVID-19 via PCR, suggesting a strong correlation between the infection and these manifestations. Additionally, 93.3% (n=12) of the patients had CT scans consistent with COVID-19. The majority of patients with dermatological symptoms (61.5%, n=8) did not have any internal comorbidities. Recovery from COVID-19 was achieved in 93.3% (n=12) of the cases, showing a positive prognosis despite the presence of skin symptoms.

Among the COVID-19-related skin manifestations, 50% (n=4) exhibited maculopapular eruptions on the face and trunk. Urticaria was present in 25% of patients (n=2), while purpuric lesions on the lower extremities and erythematous rashes on the face were noted in 12.5% of patients each (n=1). These findings are detailed in Table 2.

Drug-induced Dermatological Reactions

In 0.5% of the cohort (n=5), skin reactions were linked to pharmacological treatments used during the management of COVID-19. These reactions included bullous drug reactions, psoriasisiform eruptions, hypertrichosis, and urticaria. The variability in the onset and severity of these reactions underscored the diverse impact of COVID-19 treatments on dermatological health. This highlights the importance of monitoring and adjusting treatment plans for individuals with drug-induced reactions, as outlined in Table 3.

In drug-induced cases, the latency between drug use and the onset of dermatological symptoms ranged from 2 to 14 days. A wide array of COVID-19 treatments, including hydroxychloroquine, azithromycin, and oseltamivir, were implicated in these reactions. Case 11, which involved a severe bullous reaction, resulted in mortality, while the other patients showed favorable outcomes with the cessation or modification of the suspected drugs.

This table outlines the dermatological manifestations observed in patients with confirmed or suspected COVID-19, providing details on the timing of symptom onset in relation to skin manifestations, the duration and location of rashes, underlying comorbidities, and treatments administered. It captures both direct viral effects on the skin as well as potential drug-induced reactions, offering a comprehensive view of the dermatological impact of COVID-19 (MPE: Maculopapular eruption).

Table 2. Dermatological manifestations associated with COVID-19

Case no	Age	Sex	Symptom	Finding	Skin rash	Duration	Localisation	Rash latency	Internal comorbidity	Treatment	ICU/ death
Case 1	42	Male	Shortness of breath, inability to taste and smell	PCR+ CT+	Purpuric skin rash	2 days before Symptoms	Lower limb	6-7 days	None	Hydroxychloroquine Azithromycin	None
Case 2	34	Female	Cough, fever, malaise, headache	PCR+ CT+	MPE	3 days after symptoms	Face	12-13 days	None	Hydroxychloroquine Azithromycin	None
Case 3	40	Male	Shortness of breath, chest pain, muscle pain	PCR+ CT+	MPE	5 days after symptoms	Body, Back	7-8 days	None	Hydroxychloroquine Oseltamivir	None
Case 4	30	Female	Fatigue, cough, shortness of breath	PCR+ CT+	Erythematous rash	1 day after symptoms	Face	18 days	None	Hydroxychloroquine Oseltamivir Azithromycin	None
Case 5	53	Male	Cough	PCR- CT+	Urticaria	8 days after symptoms	Radiating from the abdomen to the back, arm and leg	4-5 days	None	Hydroxychloroquine Oseltamivir Azithromycin Levocetirizine	None
Case 6	41	Male	Cough, Fever	PCR+ CT+	MPE	5 days after symptoms	Face	10 days	Asthma	Hydroxychloroquine Oseltamivir Azithromycin	None
Case 7	51	Male	Cough, shortness of breath	PCR+ CT+	MPE	1 day after symptoms	Body, back	4 days	Hypertension, coronary arterial disease	Hydroxychloroquine Oseltamivir Azithromycin Levocetirizine	None
Case 8	56	Female	Fever, cough, myalgia	PCR+ CT+	Urticaria	3 days after symptoms	Lower limb	2 days	Essential thrombocytosis, vitamin D deficiency	Favipiravir	None

ICU: Intensive care unit, PCR: Polymerase chain reaction, CT: Computed tomography, MPE: Maculopapular eruption

Table 3. Drug-induced dermatological reactions in COVID-19 patients

Case no	Age	Sex	Symptom	Finding	Skin rash	Duration	Localisation	Internal comorbity	Drugs used for comorbidities	Tretment	Suspicious medicine	ICU/ death
Case 9	46	Male	Fever, cough	PCR + CT +	Psoriasiform	10 days after drug use	Face and both elbows	None	Topical corticosteroid, Topical Tacrolimus	Hydroxychloroquine Oseltamivir Azitromisin	Hydroxychloroquine	None
Case 10	51	Female	Shortness of breath, cough	PCR – CT -	MPE	5 days after drug use	Starting from the arms and spreading all over the body	None	None	Prophylactic Hydroxychloroquine (family contacts)	Hydroxychloroquine	None
Case 11	73	Male	Cough, shortness of breath	PCR – CT+	Bullous drug reaction	14 days after drug use	Arm, neck, both lower limbs	DM, CRF, HT	Verapamil hydrochloride + Trandolapril, Clopidogrel, Pantoprazole Nateglinide Linagliptin and Indapamide	Hydroxychloroquine Azitromisin	Hydroxychloroquine	Exitus
Case 12	60	Female	Cough	PCR + CT +	Urticaria	14 days after drug use	Starting from the lower extremities and spreading to the whole body	Hipotiroid, HT, DM	None	Hydroxychloroquine Oseltamivir Azitromisin	Hydroxychloroquine Oseltamivir	None
Case 13	40	Male	Sore throat, weakness, myalgia	PCR+ CT+	Hypertrichosis	7 days after drug use	Chest anterior wall	None	None	Hydroxychloroquine Azitromisin	Hydroxychloroquine	None

ICU: Intensive care unit, PCR: Polymerase chain reaction, CT: Computed tomography, MPE: Maculopapular eruption, DM: Diabetes mellitus, CRF: Chronic renal failure, HT: Hypertension

This table presents cases of dermatological reactions induced by pharmacological treatments in COVID-19 patients. It provides detailed information on the onset and duration of skin symptoms after drug administration, the locations of these reactions, associated comorbidities, and the medications involved. The table also highlights drugs used to treat both COVID-19 and pre-existing conditions, identifying cases where specific medications were suspected of causing the dermatological reactions. (MPE: Maculopapular eruption,

COVID-19 Associated Dermatological Manifestations

Case 1: A 42-year-old male patient was admitted to our hospital with increased dyspnea and anosmia. He had no known pre-existing conditions or medication use but had a family member previously diagnosed with COVID-19. Two days prior to the onset of respiratory symptoms, the patient developed severe pruritic purpuric lesions in his lower extremities. The lesions subsided within 1-2 days after hospital admission and initiation of treatment. He tested positive for

COVID-19 via nasopharyngeal swab PCR, and bilateral mild ground-glass opacities were more pronounced in the right basal regions of the lungs on CT. The patient received a five-day course of hydroxychloroquine and azithromycin and was discharged after full recovery.

Case 2: A 34-year-old female presented with a one-week history of headache and fatigue compounded by fever and cough. She had no history of travel or contact with COVID-19 positive individuals. Three days after symptom onset and four days before hospital admission, she developed maculopapular eruptions on her face and mucosal areas. The nasopharyngeal swab PCR test for COVID-19 returned positive results, and chest CT showed opacities consistent with COVID-19. She had no known illnesses or medication history. The patient was treated with hydroxychloroquine and azithromycin for five days and discharged in good health. The skin lesions spontaneously regressed a few days after the discharge.

Case 3: A 40-year-old male was hospitalized a week after developing sore throat, widespread myalgia, fatigue, and subsequent chest pain and dyspnea. He had no international travel history or known COVID-19 contacts. Two days before and five days after the onset of respiratory symptoms, he developed maculopapular eruptions across his back, starting from the interscapular area. He was treated with a five-day regimen of hydroxychloroquine and oseltamivir during his hospital stay and fully recovered. The skin lesions resolved spontaneously after discharge.

Case 4: A 30-year-old female physician working in the COVID-19 ward presented with initial symptoms of malaise, chills, and shivering. These symptoms progressed to cough and dyspnea within four days. Notably, one day after the onset of respiratory symptoms, she developed an erythematous rash on her face and neck (Figure 1). This timing suggests a potential dermatological manifestation associated with COVID-19, which appeared subsequent to the primary respiratory symptoms. A nasopharyngeal swab tested positive for COVID-19, and a chest CT revealed peripheral infiltrations consistent with the viral infection. She received treatment with hydroxychloroquine, azithromycin, and oseltamivir for five days without complications and was subsequently discharged. The emergence and progression of the rash were closely monitored as an indicative symptom of systemic involvement in COVID-19, highlighting the importance of comprehensive symptom assessment in affected patients.

Case 5: A 53-year-old male sought medical attention at a COVID-19 clinic because of a persistent cough lasting ten days without fever. He had no history of travel or contact with confirmed COVID-19 patients and no underlying health conditions or medication use. Although his nasopharyngeal swab was negative, chest CT revealed atypical pneumonia with ground-glass opacities. Eight days after symptom onset and two days post-hospitalization, he developed widespread urticarial lesions from the abdomen to the back, arms, and legs (Figure 2). Treatment with hydroxychloroquine, azithromycin, and oseltamivir was initiated, and the skin lesions responded well to levocetirizine during the last three days of his hospital stay. The patient was discharged in good health condition.

Figure 1. Erythematous rash on face and neck, case 4

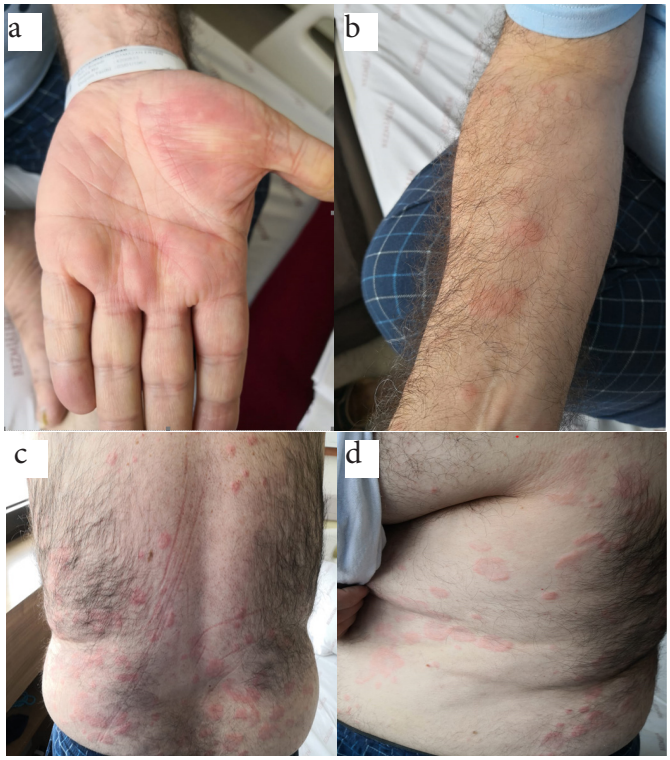

Figure 2. (a, b, c, d): Urticaria associated with COVID-19, case 5

Case 6: A 41-year-old male without any travel history or known contact with COVID-19 patients presented to the COVID clinic with a week-long history of cough and high fever. He had no chronic illnesses or regular medications. Five days after symptom onset and two days before hospital admission, he developed maculopapular eruptions on his face. He tested positive for COVID-19, and chest CT showed minimal bronchiectasis and focal ground-glass opacities in both lung parenchymas consistent with COVID pneumonia. He received hydroxychloroquine, azithromycin, and oseltamivir for five days and was discharged after full recovery. The skin lesions regressed spontaneously within ten days.

Case 7: A 51-year-old male, a specialist doctor working in the COVID ward, presented with sudden onset dyspnea and cough but no fever. The patient's wife was diagnosed

with COVID-19. He had a history of hypertension that was treated with metoprolol, valsartan, and hydrochlorothiazide. In addition, he had a history of irritant contact dermatitis. One day after symptom onset and three days before hospital admission, he developed maculopapular lesions that started on the anterior chest and spread to the back. His nasopharyngeal swab tested positive for COVID-19, and chest CT revealed bilateral faint ground-glass opacities. The patient was treated with hydroxychloroquine, azithromycin, and oseltamivir for five days. The skin lesions responded to levocetirizine during hospitalization and regressed within three days. The patient was discharged in a good condition.

Case 8: 56-year-old female with no history of travel presented with fever, cough, and myalgia. Her SARS-CoV-19 test was positive, and chest CT showed subpleural ground-glass opacities in the right AC lower lobe latero/antero basal segment consistent with COVID pneumonia. Three days after diagnosis and admission, she developed pruritic erythematous plaque lesions on both lower extremities (Figure 3). These skin findings are consistent with those of COVID-associated urticaria. She had no history of urticaria. Laboratory tests showed elevated D-dimer, LDH, and CRP/procalcitonin levels, with normal WBC and other hematological parameters. She was treated with favipiravir and antihistamines, which improved the skin lesions. She was discharged five days later without complications.

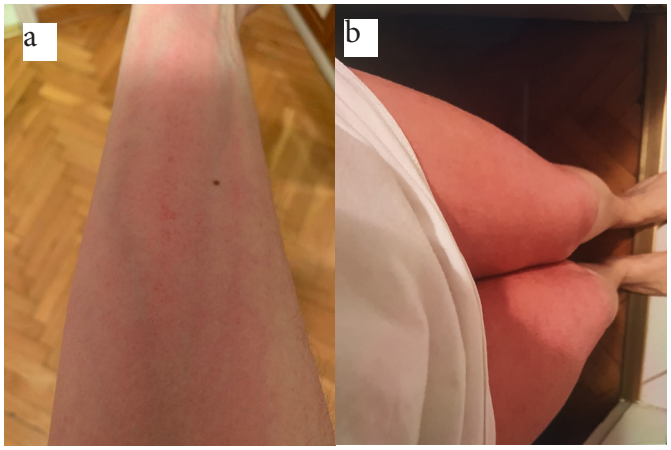

Figure 3. (a, b): Urticaria associated with COVID-19, case 8

Dermatological Manifestations Associated with Pharmacotherapy for COVID-19

Case 9: A 46-year-old male presented with fever and cough at our COVID clinic without any travel history or contact with COVID-19 positive individuals. He had a five-year history of vitiligo for which he was receiving topical corticosteroids and tacrolimus. A nasopharyngeal swab PCR test for SARS-CoV showed positive results. Chest CT showed centrilobular emphysema in the upper lobes of both lungs and thin-walled air cysts, consistent with COVID-19 pneumonia. He received a five-day regimen of hydroxychloroquine, oseltamivir, and azithromycin without complications. Five days post-discharge, the patient returned with erythematous squamous psoriatic eruptions on the face and both elbows, which were attributed to hydroxychloroquine (Figure 4). No new medications have recently been introduced.

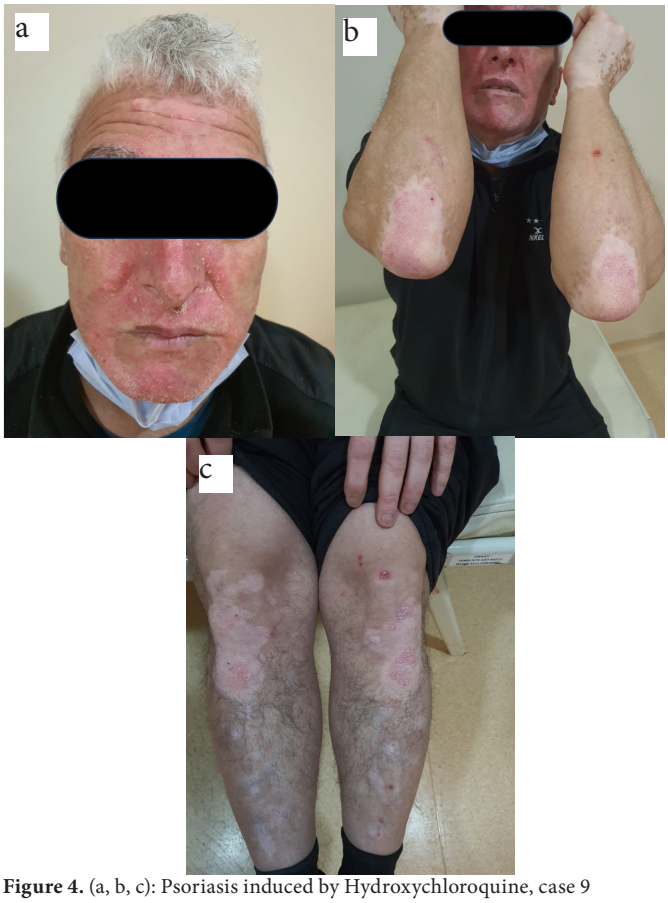

Figure 4. (a, b, c): Psoriasis induced by Hydroxychloroquine, case 9

Case 10: A 51-year-old woman presented with her husband to an external center COVID clinic with dyspnea and cough, and no travel history. The patient's husband was diagnosed with COVID-19. She had no history of systemic or dermatological diseases. The nasopharyngeal SARS-CoV swab test result was negative, and CT scans were normal. Due to suspicion, she was given a five-day course of oral systemic hydroxychloroquine. Five days after completing hydroxychloroquine treatment, the patient developed a widespread maculopapular rash starting from the arms, accompanied by severe itching (Figure 5). Laboratory evaluations revealed eosinophilia (7.13%), Total IgE levels (8.9 kU/L), and eosinophil cationic protein levels (86.5 µg/L). She had not taken any other medications recently and had no history of drug-related dermatological reactions. The patient was treated with a betamethasone dipropionate cream-vaseline mixture, a topical emollient used to soothe and protect the skin, and bilastine, an antihistamine for symptom relief.

Case 11: A 73-year-old male with symptoms of cough and dyspnea presented to our pandemic clinic with cough and dyspnea. He had no fever or travel history, and no family members were diagnosed with COVID-19. He had a history of diabetes, chronic kidney disease, and hypertension and was taking multiple medications including verapamil hydrochloride, trandolapril, clopidogrel, pantoprazole, nateglinide, linagliptin, and indapamide. His nasopharyngeal swab was negative, but chest CT showed ground-glass opacities in both lower lobes. The patient was admitted to the hospital with a preliminary diagnosis of COVID-19. Blood tests revealed elevated D-dimer, LDH, and CRP/procalcitonin

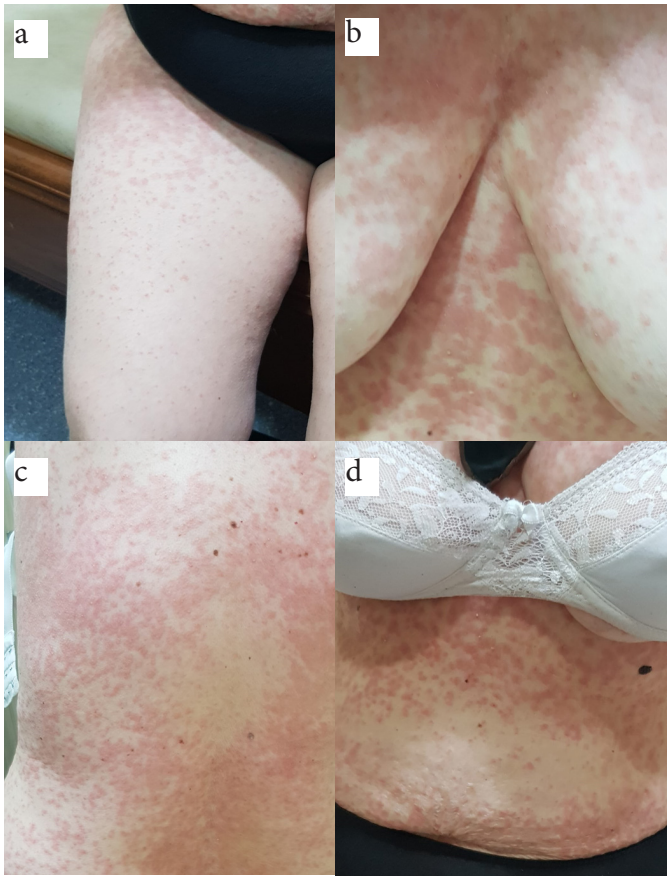

Figure 5. (a, b, c, d): Drug-induced maculopapular rash, case 10

levels. He received a five-day course of hydroxychloroquine and azithromycin and was discharged without complications. Ten days after discharge, he developed bullous drug reactions in his arms, neck, and both lower extremities, which regressed with the application of dermovate cream (Figure 6).

Case 12: A 60-year-old woman presented with a cough at our pandemic clinic. She had no fever or recent travel history of COVID-19. She had hypothyroidism and hypertension but could not recall the names of her medications and reported no recent changes in medication. She underwent nasopharyngeal swabbing and chest computed tomography (CT), which confirmed COVID-19 with ground-glass opacities. The patient was admitted and treated with hydroxychloroquine, azithromycin, and oseltamivir. After a five-day hospital stay without complications. Ten days later, she presented with extensive urticarial plaques, starting from the lower extremities and spreading across the body, which were treated with levocetirizine.

Case 13: A 40-year-old male presented to our pandemic clinic with a sore throat, fatigue, and chills. He had no travel history, although his daughter was COVID-19 positive. The patient had no known systemic diseases or related medications. His nasopharyngeal SARS-CoV PCR test result was positive, and chest CT showed focal ground-glass opacity in the left lower lobe, consistent with COVID-19 pneumonia. He was admitted and treated with hydroxychloroquine and azithromycin for five days. The patient was discharged in good health; however, an increase in hair growth on the chest, arms, and face was observed, which was suspected to be related to hydroxychloroquine use.

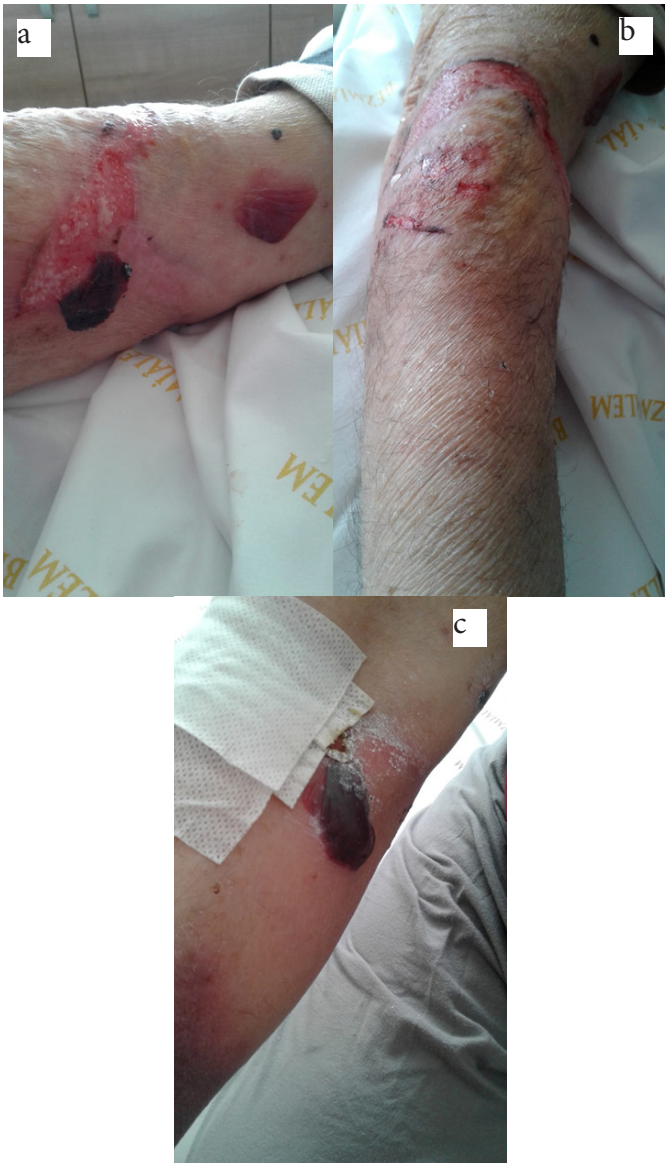

Figure 6. (a, b, c): Bullous drug reaction, case 11

DISCUSSION

The emergence of COVID-19 has expanded our understanding of the impact of the virus on the human body, extending beyond respiratory symptoms to include significant dermatological manifestations. Research has shown that SARS-CoV-2 directly induces a range of skin changes, from the now well-characterized "COVID toes" to more severe entities such as vasculitis, largely owing to the effects of the virus on endothelial cells and small vessel vasculopathy.[5] Similarly, our study found that 1% of the patients (n=8) developed dermatological manifestations, which aligns with data from similar studies conducted in Europe and Asia, where the reported incidence varies from 0.2% to 20.[6] Additionally, the systemic immunological response to the virus, marked by a cytokine storm, involves elevated levels of cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). These cytokines can exacerbate or initiate inflammatory skin conditions such as psoriasis or urticaria, even in individuals without a history of these conditions.[7] In our study, drug-induced dermatological reactions were observed in 0.5% (n=5) of patients, presenting conditions such as bullous

drug reactions, psoriasiform drug eruptions, hypertrichosis, and urticaria. This prevalence reflects findings from global research which underscores the diverse cutaneous adverse reactions associated with COVID-19 treatments. Atzori et al.[8] have documented severe cutaneous adverse reactions, including Stevens-Johnson syndrome, particularly associated with the use of antimalarials like hydroxychloroquine and antivirals such as oseltamivir. Furthermore, Nobari et al.[9] provided a systematic review of mucocutaneous reactions, highlighting the wide range of dermatological responses to various COVID-19 pharmacotherapies. Kalikyan[10] also contributes to this body of knowledge by detailing case reports of antibiotics causing hypersensitivity reactions during the pandemic using Naranjo's algorithm to assess causality. Collectively, these studies emphasize the critical need for vigilant monitoring and management of dermatological reactions, advocating for a tailored approach to pharmacotherapy in COVID-19 patients to mitigate these adverse effects. Furthermore, immune dysregulation associated with COVID-19 has been implicated in the reactivation of latent viral infections such as herpes zoster, which may present new or exacerbate existing dermatological conditions during or after the infection.[10] Chilblain-like lesions associated with COVID-19 are considered indicators of a good prognosis in mild cases, whereas vasculopathy-related skin manifestations such as livedo racemosa, retiform purpura, and dry gangrene are linked to more severe disease and poor prognosis.[11] The emergence of COVID-19 has necessitated a critical reassessment of therapeutic strategies, not only in terms of virological efficacy, but also in managing the wide array of adverse effects, particularly dermatological manifestations. The complex relationship between COVID-19 pharmacotherapy and skin reactions has gained considerable attention due to its implications for patient safety and adherence to treatment.[12] As with COVID-19 itself, mRNA vaccines developed against the virus have also been observed to induce dermatological manifestations such as type I and IV hypersensitivity reactions, the triggering of autoimmune diseases (bullous pemphigoid, vasculitis), and herpes zoster reactivation. Although the precise mechanisms underlying these cutaneous effects remain unclear, it is hypothesized that mRNA vaccines may bind to ACE2 receptors in the skin, potentially triggering these reactions, with immune responses such as cytokine storms and elevated IL-6 levels contributing to their pathogenesis.[13] In an international registry analysis of COVID-19 patients with skin manifestations, it was found that while urticarial and morbilliform rashes were short-lived, conditions like pernio and papulosquamous eruptions persisted for longer durations. Some patients, classified as "long-haulers," experienced symptoms lasting over 60 days, indicating a prolonged inflammatory response. These findings underscore the importance of long-term monitoring for dermatological effects in COVID-19 patients.[14] Pharmacotherapy for COVID-19 includes a range of agents, such as antivirals, antimalarials, and antibiotics, each associated with specific dermatological adverse effects. Antimalarials, notably hydroxychloroquine, have been widely reported to induce cutaneous reactions ranging from mild to severe life-threatening conditions such as Stevens-Johnson syndrome.[15] In line with this, our study found that a significant proportion of patients with skin manifestations (76.9%, n=10) tested positive for COVID-19 by PCR, emphasizing the need for careful monitoring and management of these reactions. Similarly, the use of antivirals such as oseltamivir has been linked to skin rashes and other hypersensitivity reactions, which can significantly affect patient comfort and compliance. Treatment of COVID-19 with various pharmacological agents has been observed to induce a range of cutaneous reactions, which can significantly impact patient management and outcomes. As observed in the clinical classification proposed by Fontes and Rostey (2023), adverse drug reactions (ADRs) from COVID-19 treatments accounted for a considerable proportion of dermatological presentations during the pandemic, underscoring the importance of careful drug selection and monitoring.[16] Emerging studies have proposed various mechanisms by which COVID-19 treatment triggers skin manifestations. The immunomodulatory effects of these drugs, particularly those involving the modulation of cytokine production or inhibition of specific immune pathways, are suspected to underlie many adverse dermatological outcomes. This aligns with our findings, where treatment regimens included hydroxychloroquine, oseltamivir, and azithromycin, which are known for their potential to cause dermatological reactions, particularly in patients with complex medical histories or those exhibiting severe COVID-19 symptoms. This immunological disruption can precipitate or exacerbate conditions, such as eczema, psoriasis, and urticaria, creating a challenging scenario for managing patients who may already have pre-existing dermatological conditions.[17] Dermatologists and clinicians must continuously monitor skin reactions in COVID-19 patients, particularly those on complex medication regimens. Pharmacotherapy should be tailored not just by substituting drugs, but by thoroughly considering the patient's history, the severity of symptoms, and potential drug interactions. Updating treatment guidelines dynamically to incorporate new research findings is crucial. As novel therapeutic agents and vaccines emerge, the dermatology community must swiftly identify and manage new skin manifestations.[18] Recent outbreaks, such as monkeypox, also present unique dermatological challenges that parallel those observed in COVID-19. While COVID-19 is associated with a variety of skin manifestations, monkeypox typically presents with more severe pustular and vesicular rashes.[19] The lessons learned from the COVID-19 pandemic underscore the importance of dermatological vigilance and tailored pharmacotherapy in managing emerging infectious diseases. This awareness is crucial as we continue to develop strategies against current and future outbreaks, ensuring that treatment guidelines remain dynamic and inclusive of new clinical insights.

CONCLUSION

The observed link between COVID-19 and diverse dermatological manifestations underscores the necessity to incorporate dermatological assessments into routine patient

management. Recognizing and addressing skin manifestations directly associated with the virus, such as rashes and other skin changes, are crucial for comprehensive patient care. As we continue to navigate this pandemic, adapting clinical guidelines to include these dermatological insights will enhance treatment efficacy and improve our understanding of COVID-19's extensive systemic effects. Effective management of these skin symptoms, alongside pharmacological side effects, can significantly improve patient outcomes.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Bezmialem Vakif University Ethics Committee (Date: 01.072024, Decision No: 155793).

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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The effectiveness of kinesio taping in addition to conventional treatment in patients with chronic low back pain: a randomized controlled trial

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ABSTRACT

Aims: This study aimed to compare the effects of kinesio taping in combination with conventional treatment on pain intensity, lumbar range of motion (ROM) and flexibility, disability, and depression levels in patients with chronic low back pain (CLBP) with conventional treatment alone.

Methods: The 48 individuals with CLBP included in the trial were randomized into the control group (CG, n=24) and the kinesio taping group (KTG, n=24). The CG received only conventional treatment for four weeks, while the KTG received kinesio taping for four weeks in addition to conventional treatment. Before and after the four-week treatment periods, patients were assessed with respect to pain intensity (visual analogue scale), lumbar ROM (goniometric measurement), flexibility (hand-ground distance), disability (Oswestry disability index), and depression (Beck depression inventory).

Results: After the treatment programs, there were significant improvements in pain intensity, lumbar ROM and flexibility, disability, and depression levels in both the CG and KTG groups ($p<0.05$). Furthermore, improvements in pain intensity, lumbar ROM and flexibility, disability, and depression levels were significantly higher in CTG compared to CG ($p<0.05$).

Conclusion: Conventional treatment of CLBP is effective in improving pain, lumbar ROM and flexibility, disability, and depression levels, but further improvement can be achieved with the additional application of kinesio taping.

Keywords: Kinesio taping, low back pain, flexibility, disability, depression

INTRODUCTION

Low back pain (LBP) is a musculoskeletal system disease that affects approximately 80% of adults. LBP causes disability and impairment and is a major burden on government health expenditures.[1] Factors such as smoking, high body mass index, heavy working conditions, and weak abdominal and back muscles can cause LBP.[2] LBP decreases the quality of life by affecting many activities of the individual, including social life, lifting weights, walking, bending, standing, traveling, dressing, and sexuality.[3] In the treatment of LBP, various methods are used, including educational programs, chiropractic treatment, exercise (such as yoga, stretching, hydrotherapy, tai chi, and McKenzie), manipulative treatment techniques, electrotherapy, and medication. Some of these treatments are recommended by the European guidelines for the management of chronic nonspecific LBP to promote physical activity.[4]

Kinesio taping (KT) is another technique that is commonly used to assist in the treatment of various musculoskeletal disorders.[5] It is based on the principle of applying special elastic bands to the skin with special methods. The tape used in KT is latex-free, adhesive, and can stretch to approximately 120% to 140% of its initial length.[6] It is reported that this technique is effective in reducing pain and abnormal muscle tension, improving muscle function and blood circulation, repositioning the joint, and supporting joint function.[7] The use of the KT technique is quite prevalent in sports and clinical practices.[8] Recently, this technique has also been utilized in the management of LBP.[9] Studies in the literature have pointed out that KT can be used for the treatment of patients with CLBP either alone or in combination with physiotherapy applications.[3,10-14]

Although studies have documented that KT may be effective in the management of CLBP,[12,14] some of these studies have conflicting results suggesting that KT is not superior to other interventions.[9,11,13,15] For instance, Castro-Sánchez et al.[9] investigated the efficacy of one week of KT in chronic non-specific LBP and observed improvements in pain intensity, trunk flexion movement, disability, and trunk muscle

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endurance one week after treatment. After four weeks, the researchers found that improvements in pain and trunk muscle endurance were maintained, while improvements in disability and trunk flexion movement were not preserved. Moreover, they suggested that short-term application of KT in LBP, such as one week, may provide too small effects to be clinically valuable, so further controlled trials with longer-term KT applications should be performed to obtain better and clearer results.[9] The non-standardization of the treatment methods applied in some of the studies, the wide age range of the included patient groups, the examination of the immediate effects of KT in some studies and the relatively short treatment periods (one or two weeks) in some studies may have been effective in the emergence of these conflicting results. For more precise results in CLBP, further high-level evidence studies with better methodology comparing the effectiveness of KT, which is reported to be effective in reducing pain and abnormal muscle tension and improving blood circulation and muscle and joint function[7] with conventional therapies using approved standardized procedures, are needed. Determining whether KT application is effective in CLBP with more precise results may help clinicians working in this field to establish treatment programs. Taking these into account, this study aimed to compare the effects of KT application in combination with conventional treatment on pain intensity, lumbar lumbar range of motion (ROM), flexibility, disability, and depression levels in patients with CLBP with conventional treatment alone, using verified standardized methods by the literature.

METHODS

Study Design and Ethical Approval

Ethical approval for this randomized, controlled, single-blind study was granted by the Muş Alparslan University Scientific Researches and Publication Ethics Committee (Date: 03.06.2024, Decision No: 8-2024/72). In the study, all stages of which were carried out in compliance with the Declaration of Helsinki, verbal and written informed consent was taken from all participants.

Participants

This study was conducted with 48 patients diagnosed with CLBP. Patients aged between 18-65 years with non-specific LBP for more than three months who had not received previous treatment and were not currently included in an active treatment program, who did not have neurological deficits such as radicular pain, loss of muscle strength, or loss of reflexes, and who had no indication for surgery, were recruited to the study. Exclusion criteria were history of pregnancy, psychiatric or neurological diseases, severe osteoporosis, spinal surgery, infectious or malignant diseases in the vertebrae, or findings indicating pathology known as red flags, scoliosis, visceral pain, and medication. Patients who fulfilled the inclusion criteria were randomized into two groups: the control group (CG), in which only conventional treatment was applied, and the KT group (KTG), in which conventional treatment was combined with KT.

Interventions

An experienced specialist physiotherapist (NTY) applied both the traditional treatment program and the KT to the patients. Both groups received the treatment programs three days a week for four weeks.

Conventional Treatment

Patients in both groups underwent lumbar flexion and extension exercises, stretching exercises for iliopsoas, quadriceps, and hamstring muscles, strengthening exercises for lumbar and abdominal muscles, along with a 20-minute hot pack (25x40 cm), 20-minute conventional TENS, and an 8-minute therapeutic ultrasound (1,2 w/cm^2) for four weeks by the same physiotherapist (NTY).[15,16] Exercises were performed in 3 sets and 10 repetitions in each session under the supervision of a physiotherapist.

Kinesio Taping Application

At the end of each treatment session, the patients in KTG applied KT with a 5 cm × 5 m kinesio tape material using a special 'muscle technique'.[3] The patient who was standing was asked to bend forward. The lower end of the tape was first applied 7 cm below the sacroiliac joint at the level of the paravertebral muscles, then the patient was asked to make a slight rotation to the left, and in this position, the tape was applied upwards on the paravertebral muscles without any tension. When taping the left paravertebral region, the same procedure was performed in reverse as on the right, and the tape was not stretched. The third tape was applied to the patient, who was standing upright and leaning slightly forward, with the tape stretched by 25%, passing over the sacroiliac joints and parallel to the ground. When the patients were in upright posture, folds formed on the bands. It was observed that the folds were compatible with the patient's body movements and remained until the day the bands were removed (Figure 1).[3] The tapes usually remained on the patient's body until the patient came for the next taping. When the patients came to each treatment session, the previous tape was removed from the skin by the physiotherapist, and the taping was reapplied. No itching, redness, or allergic reactions were observed in any patient.

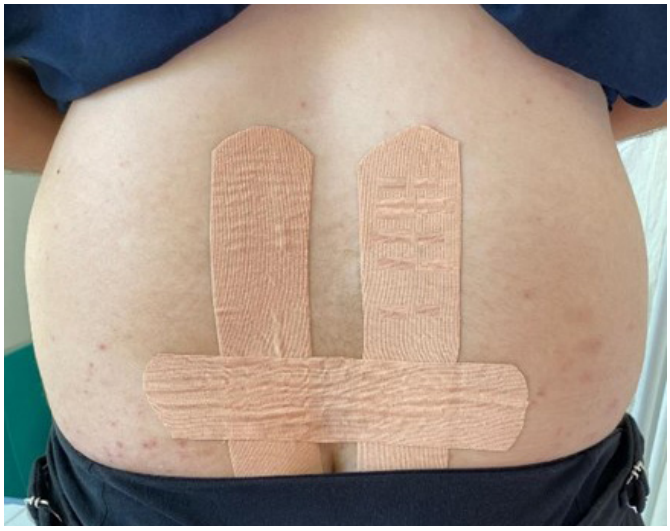

Figure 1. Kinesio taping application to the lumbar region

Outcome Measures

Age, duration of complaint, gender, and body-mass index (BMI) were noted for all participants. Clinic assessments were performed before and immediately after four weeks of treatment programs.

Pain intensity: The pain intensity during activity (dynamic positions of the head, neck, and trunk such as backward and forward bending and rotation) was assessed utilising a visual analogue scale (VAS). Participants were instructed to indicate the intensity of their pain on a 10-cm line, where 0 represents no pain and 10 represents severe pain. The measured value was noted in centimeters.[17]

Range of motion: Trunk flexion, extension, and right-left lateral flexion as ROM of the lumbar region were measured using a goniometer. For the lumbar region flexion ROM assessment, the participants were asked to maintain an upright standing posture. The projection on the lateral line of the lumbosacral joint was determined as the pivot point, and the goniometer was positioned on the projection. The movable arm of the goniometer was positioned parallel to the lateral line of the trunk in a free position for trunk flexion. The fixed arm was aligned parallel to the midpoint of the femur. The participants were asked to perform trunk flexion, and the value at the last position they could reach was recorded.[18] For the extension assessment, a goniometer was placed on the projection of the lumbosacral joint at the lateral level of the lumbosacral joint, similar to the lumbar region flexion measurement, and the movable arm and fixed arm were positioned in the relevant places. The participants were asked to perform a trunk extension, and the moving arm followed them to the last position they could reach. The final value was recorded.[18] For lateral flexion measurement in the lumbar region, the movable arm of the goniometer was placed pointing to the C7 spinous process by determining the midpoint of the lumbosacral joint as the pivot point, and the fixed arm was positioned parallel to the ground. The participants were asked to start the movement in a neutral position without trunk flexion or extension. The participants were then asked to maintain their posture in this position and perform trunk lateral flexion to one side, and the movable arm of the goniometer followed the trunk lateral flexion to the end point. The measurement was repeated on the other side, and the values were recorded. The values obtained from ROM measurements were recorded in degrees.[18]

Flexibility: Flexibility was assessed by measuring hand-ground distance. In the hand-ground distance measurements, the standing patient was instructed to bend forward at the waist with both legs together and without bending at the knees, to bring the fingers of the hands closer to the toes, and to reach towards the ground. The distance between the tip of the third finger of the patient's hand and the ground was measured with a tape measure and recorded in cm.[3]

Disability: The Oswestry disability index (ODI) was employed to evaluate the disability level of the participants before and after treatment. ODI is a measurement tool to determine the degree of functional disability in activities of daily living caused by LBP. The lowest score is 0, and the highest score is 50. High scores on the instrument indicate a high level of disability. The Turkish version of the scale is valid and reliable in patients with LBP.[19]

Depression: The beck depression inventory (BDI) was applied to evaluate the depression levels of the participants.[20] The revised version of the scale consists of 21 items. On the instrument with a maximum score of 63 points, a higher score indicates more depressive symptoms. The Turkish version of the scale was found to be valid and reliable.[21]

Randomization and Blinding

The 48 patients with CLBP included in the study were randomised into CG (n=24) and KTG (n=24) groups utilizing age-and gender-matched pairs randomization. Utilizing the Research Randomizer program available on the website www.randomizer.org, matched-pairs randomization was carried out.[22] All evaluations before and after the four-week treatment programs were conducted by the same researcher (HK), who was blinded to the treatment groups. On the other hand, patients in the groups were not blinded to the treatment methodologies in the trial.

Sample Size

According to the pilot study conducted with five patients in both groups, considering the VAS score, the sample size was determined to be a total of 40 individuals with a power of 0.95 and $\alpha = 0.05$ and an effect size of 0.294 based on repeated measures analysis of variance (ANOVA) within and between interactions. A total of 48 individuals, 24 in each group, were included in the study, taking into account the 15% dropout rate of the patients.

Statistical Analysis

The SPSS version 24.0 software was utilized for statistical analyses. Descriptive analyses were presented as mean and standard deviation for numerical variables, with normal distribution assessed through visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov and Shapiro-Wilk tests). Nominal variables were expressed as counts and percentages. To compare the numerical demographic and clinical properties of the groups, an independent sample t-test was conducted, and to compare the categorical data, a chi-square test was employed. A two-way mixed design repeated measures ANOVA was performed to assess the effects of treatments on pain intensity, lumbar ROM and flexibility, disability, and depression levels, with group (CG, KTG) as the between-patient variable and time (before-treatment, after-treatment) as the within-patient variable. Furthermore, to analyze the significant between-group differences in the change scores from the initial to the final treatment intervention, pairwise comparisons were carried out applying the Bonferroni correction. Statistical significance level was taken as $p<0.05$.

RESULTS

Of the 67 CLBP patients referred to our clinic, 48 included in the study, while 19 were excluded from the study. Participants who fulfilled the inclusion criteria were randomly allocated to

the CG and KTG groups, with 24 patients in each group. The trial was completed with 100% participation and compliance from the patients. The flow diagram of the study is presented in Figure 2.

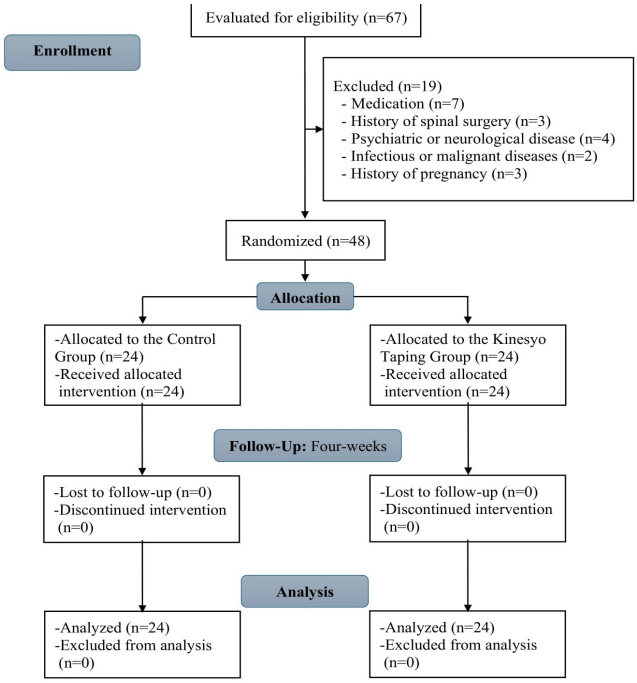

Figure 2. Flow diagram of the study

Table 1 provides the demographic and clinical properties of the participants before treatment. Accordingly, there were no significant differences between participants in the groups with regard to age (p=0.332), gender distribution (p=0.569), BMI (p=0.639), and duration of complaint (p=0.426).

Table 1. Baseline demographic and clinical properties of the groups

		CG (n=24)	KTG (n=24)	
Variables		**Mean±SD**	**Mean±SD**	**p**
Age (year)		42.60±6.23	44.40±5.48	0.332[a]
BMI (kg/m²)		24.38±2.22	23.77±2.10	0.639[a]
Duration of complaint (month)		6.72±1.18	6.27±1.06	0.426[a]
		n (%)	n (%)	
Gender	Male	13 (54.2)	14 (58.3)	0.569[b]
	Female	11 (45.8)	10 (41.7)	

CG: Control group, KTG: Kinesio Taping group, SD: Standard deviation, BMI: Body-mass index, p[a]: Independent sample t test, p[b]: Chi-square test

Table 2 demonstrated the comparison of before and after treatment scores for VAS, ODI, and BDI within and between groups. In both groups, the decreases in VAS, ODI, and BDI scores after interventions were statistically significant (p<0.05). Regarding group-time interactions, it was determined that the decreases in VAS, ODI, and BDI scores were significantly higher in KTG than in CG (p<0.05).

The comparison of before and after treatment lumbar region flexion, extension, right and left lateral flexion ROM values, and hand-ground distance measurements within and between groups is given in Table 3. In both groups, increases in all lumbar region ROM values and decreases in hand-ground distance measurements were statistically significant after treatment (p<0.05). When group-time interactions were considered, it was revealed that the increases in all lumbar region ROM values and decreases in hand-ground distance measurements were significantly higher in KTG than in CG (p<0.05).

Table 2. Comparison of pre- and post-treatment scores for VAS, ODI, and BDI within and between groups

		CG (n=24)	KTG (n=24)	MD values between groups	Time	Group* time		
		Mean±SD	**Mean±SD**	**Mean±SE**	**p**	**f**	**p**	**η²**
VAS (cm)	BT	5.32±1.07	5.44±1.04	1.80±0.21	<0.001*	75.00	<0.001*	0.61
	AT	2.68±0.69	1.00±0.65					
ODI (score)	BT	32.20±11.46	32.00±10.90	13.20±1.82	<0.001*	52.80	<0.001*	0.52
	AT	21.60±9.32	8.20±3.50					
BDI (score)	BT	29.68±7.68	29.60±7.39	9.72±1.17	<0.001*	69.47	<0.001*	0.59
	AT	19.52±5.61	9.72±3.16					

CG: Control group, KTG: Kinesio Taping group, MD: Mean difference, SD: Standard deviation, SE: Standard error, VAS: Visual analogue scale, BT: Before treatment, AT: After treatment, ODI: Oswestry disability index, BDI: Beck depression inventory, p: Two-way mixed design repeated measures ANOVA, *p:0.05, η²: Effect size

Table 3. Comparison of lumbar region ROM and hand-ground distance values within and between groups pre- and post-treatment

			CG (n=24)	KTG (n=24)	MD values between groups	Time	Group* time		
			Mean±SD	**Mean±SD**	**Mean±SE**	**p**	**f**	**p**	**η²**
ROM (°)	Flexion	BT	61.92±5.83	61.64±3.77	-17.72±1.08	<0.001*	270.86	<0.001*	0.85
		AT	73.76±5.94	91.20±2.96					
	Extension	BT	12.48±3.97	11.22±3.24	-7.64±0.50	<0.001*	237.28	<0.001*	0.83
		AT	17.82±3.90	24.20±4.02					
	Right lateral flexion	BT	19.42±5.45	18.06±3.87	-11.30±0.72	<0.001*	247.54	<0.001*	0.82
		AT	25.52±6.27	35.46±2.86					
	Left lateral flexion	BT	19.24±5.26	17.92±3.82	-12.20±0.76	<0.001*	257.57	<0.001*	0.84
		AT	24.80±5.45	35.68±3.28					
Hand-ground distance (cm)		BT	17.80±5.45	18.12±5.08	6.60±0.68	<0.001*	272.25	<0.001*	0.66
		AT	12.28±4.69	6.00±2.08					

CG: Control group, KTG: Kinesio Taping group, MD: Mean difference, SD: Standard deviation, SE: Standard error, BT: Before treatment, AT: After treatment, ROM: Range of motion, p: Two-way mixed design repeated measures ANOVA, *p:0.05, η²: Effect size

DISCUSSION

This study compared the effects of KT in addition to conventional treatment on pain intensity, lumbar ROM values, flexibility, disability, and depression in patients with CLBP compared to conventional treatment alone. As a result of the study, significant improvements were observed in all parameters evaluated in both groups. In addition, it was determined that the improvements in participants who received KT in addition to conventional treatment were significantly superior to those in the other group.

Kumar et al.[23] reported that conventional treatment was effective in reducing pain in patients with CLBP. Similarly, Yılmaz et al.[24] concluded that conventional treatment was effective in reducing pain in patients with chronic mechanical LBP. In another study, Atılgan and Erbahçeci[25] indicated that conventional treatment had a decreasing effect on pain in patients with CLBP. In our study, in accordance with the literature, we concluded that pain severity was significantly reduced in both groups treated with conventional treatment. Studies in the literature have documented that KT is effective in improving blood and lymph circulation and reducing pain severity.[26] Köroğlu et al.[27] suggested that KT may be effective in reducing pain in patients with CLBP. Sun et al.[10] reported that KT combined with physiotherapy applications in patients with CLBP may provide better therapeutic effects in reducing pain intensity compared with physiotherapy applications alone. In another study, Castro-Sánchez et al.[9] noted that KT was effective on pain improvement compared with placebo taping, but the clinical value of the effect was small. In this study, similar to the literature, significant improvements in pain intensity were observed in both CG and KTG groups. On the other hand, the improvement in pain intensity was greater in KTG. In this result, we consider that KT may have had a greater reducing effect on pain by increasing blood circulation more and decreasing muscle tension more.

In LBP, loss of spinal flexibility occurs due to pain. Loss of flexibility causes postural tension, leading to increased muscle fatigue, which in this situation leads to an increase in the load on the joint.[28] Modalities and techniques including exercises within the conventional treatment programs have an essential position in the management of LBP due to their positive effects on flexibility and functionality.[29,30] A review of the studies shows that conventional physiotherapy interventions have positive effects on lumbar region flexibility in LBP. Erdoğanoğlu et al.[31] suggested that conventional physiotherapy applications improved flexibility in patients with CLBP. Similarly, in this study, flexibility improved significantly in both groups of CLBP patients who received conventional physiotherapy. Inanoglu and Baltacı[3] concluded that kinesio taping may increase lumbar region flexibility in patients with LBP without neurologic deficits. In another study investigating the changes in trunk flexion, extension and lateral flexion before and after KT application, it was found that KT increased trunk flexion ROM. The researchers added that KT can be used to increase trunk flexion flexibility and promote tissue healing.[11] In the present study, spinal flexibility improved significantly in both groups, but the improvement was higher in the KTG. The greater improvement in flexibility in the KTG may be explained by the fact that KT may provide a greater increase in blood circulation and tissue elasticity. It has been indicated that the ROM of the lumbar region is negatively affected in LBP.[32] Kachanathu et al.[33] observed significant increases in lumbar region flexion and extension values of non-specific LBP patients included in a traditional physiotherapy program. Pointing out that the traditional physiotherapy program was effective in improving lumbar ROM in CLBP patients, Sharma et al.[34] concluded that the addition of manual therapy to the traditional physiotherapy program provided further improvement in ROM. It has been demonstrated that KT may provide significant increases in lumbar region flexion in CLBP patients.[12] Ciosek et al.[35] mentioned that KT may provide an increase in lumbar region flexion, extension, and right rotation degrees in CLBP patients. In another study investigating the application of lumbar region KT in healthy individuals, it was revealed that an increase in lumbar region flexion, extension, and lateral flexion degrees was obtained with KT.[11] In the current study, there were significant increases in lumbar ROM values in both groups. Furthermore, it was determined that the improvements in lumbar ROM values were significantly greater in KTG with additional KT. The application of KT may have stimulated the receptors in the joints more and created a mobilizing effect on the fascia, resulting in a greater increase in ROM values in KTG.

Disability is another prevalent adverse impact in patients with CLBP due to pain and/or decreased ROM and flexibility. Studies have pointed out that physiotherapy interventions can have a reducing effect on disability in patients with CLBP. After dividing CLBP patients into three groups, Durmuş et al.[36] applied only exercise to the first group, ultrasound treatment in addition to exercise to the second group, and phonopheresis in addition to exercise to the third group. They concluded that substantial improvements were observed in the level of disability in all three groups.[36] Altinbilek et al.[16] noted that conventional physiotherapy applications can improve the level of disability in patients with mechanical CLBP. In another study, Şahin et al.[37] proposed that traditional physiotherapy practices may reduce the level of disability in CLBP patients. In this study, in parallel with the literature, significant improvements in the level of disability were observed in both groups of patients with CLBP who received conventional physiotherapy. When the literature is examined, it is seen that the application of KT may have improving effects on disability in patients with CLBP.[9,15] Castro-Sanchez et al.[9] suggested that KT with the star technique may reduce disability in patients with CLBP for more than three months. Al-Shareef et al.[12] showed that, compared with placebo taping, KT was more effective in reducing pain and disability and improving trunk flexion ROM after 2 weeks of therapy.[38] In another study, it was concluded that KT provided significant improvements in pain and disability in LBP, but KT and exercise were similar in terms of efficacy.[15] In the present study, while there were significant improvements in disability level in both groups, the reduction in disability was greater in the KTG with additional application of KT. The application of KT in patients with KTG may have contributed to a greater reduction in disability level by providing a greater reduction

in pain and a greater improvement in lumbar ROM and flexibility.

The distress and anxiety that patients with LBP experience as a result of pain and mobility limitations constrain their daily living and social activities, lead to psychological problems such as depression, and consequently negatively affect their quality of life. There is some evidence that the level of depression in LBP can be improved by reducing the complaints of the patients with physiotherapy applications. Dogan et al.[39] observed significant decreases in depression levels in LBP patients who were included in a traditional physiotherapy program. Similarly, in this study, considerable decreases in the level of depression were detected in both groups in which conventional physiotherapy was applied. Çakmak et al.[13], who divided patients with CLBP into two groups, applied istrument-assisted soft tissue mobilization combined with a traditional physiotherapy program to one group and KT combined with a traditional physiotherapy program to the other group. The authors determined that both methods had positive effects on pain, functionality, and depression at the end of the study and stated that the two methods were not superior to each other. Ogunniran et al.[14] recommended that the application of CT in addition to stabilization exercises may be effective in reducing anxiety and depression levels in patients with non-specific LBP. In another study, it was highlighted that the application of CT in addition to exercise may provide positive effects on depression.[40] In the current study, where we have observed considerable decreases in depression levels in both CG and KTG groups, the reductions in the KTG group were higher. It can be hypothesized that the KT assisted in further improvement in the psychological status of the patients in the KTG, as it resulted in greater improvement in pain, flexibility, and disability.

Studies in the literature investigating the efficiency of KT in patients with CLBP have shown some conflicting results due to the application of non-standardized treatment methods, the relatively short duration of treatment periods, such as one or two weeks, and the reporting of immediate effects of KT in some studies.[9,11,13,15] However, compared to the studies in the literature, the fact that more standardized methods approved by the literature were used in both KT application and conventional treatment could be regarded as the strong aspect of the current study. In this respect, we believe that this study may provide clinicians and researchers with more clear results regarding the effectiveness of KT in CLBP.

Limitations

This study's basic limitation was that the treatment periods were comparatively short, and a long-term follow-up after treatment could not be carried out. Future studies with longer treatment and follow-up periods may provide more precise results.

CONCLUSION

In patients with CLBP, standardized conventional treatment is effective in improving pain intensity, lumbar ROM, flexibility, disability, and depression levels. On the other hand, further improvement in pain intensity, lumbar ROM and flexibility, disability, and depression levels can be achieved by applying KT in addition to conventional treatment. This study, which used more standardized methods approved by the literature in both KT application and conventional treatment compared to the studies in the literature, we think that this study can provide clinicians and researchers who are studying in the field of CLBP with clearer results regarding the efficiency of KT in CLBP.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Muş Alparslan University Scientific Researches and Publication Ethics Committee (Date: 03.06.2024, Decision No: 8-2024/72).

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

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Evaluating the clinical significance of color stability in nanohybrid composite resins: a comparative study of local and international brands

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ABSTRACT

Aims: The objective of this study was to evaluate the color stability of five nanohybrid composite resins, including locally produced Turkish brands and an international brand, after exposure to staining and brushing simulations over time.

Methods: Five nanohybrid composite resins; Filtek Z550 (FLT), Dolgunn (DLG), RubyComp Nano (CMP), Nova Compo C (NVC), and Parion (PRN) were tested. Specimens underwent staining and brushing simulations designed to replicate clinical oral conditions. The staining process involved immersing the specimens in a coffee solution for 8 hours per day over a 10-day period to simulate short-term staining (t1), and for 12 days to simulate long-term staining equivalent to 1 year (t2). Brushing cycles were used to replicate the mechanical wear caused by daily oral hygiene practices. Color measurements were recorded at baseline (t0), after 10 days of staining (t1), and after 1 year of simulated staining and brushing (t2). Additional analyses were conducted using Energy-dispersive X-ray spectroscopy (EDX) and Scanning Electron Microscopy (SEM) to investigate structural and surface characteristics. Statistical analysis was performed using generalized linear models and two-way robust ANOVA to assess the significance of differences in color stability, with a significance level set at $p<0.05$.

Results: The main effect of the composite was not found to be statistically significant on the median ΔE values ($p=0.078$). The main effect of time was found to be statistically significant on the median ΔE values ($p<0.001$). Additionally, the interaction between composite and time was statistically significant on the median ΔE values ($p=0.001$). The highest median value of 3.12 was observed in the NVC composite from ΔE2, while the lowest median value of 1.285 was observed in the PRN composite from ΔE1. EDX and SEM analyses provided insights into the material compositions and their influence on color stability.

Conclusion: The findings suggest that locally produced Turkish nanohybrid composites offer competitive color stability, making them viable alternatives to international brands for aesthetic dental restorations. This study highlights the need to consider both local and international materials for their clinical performance and cost-effectiveness in restorative dentistry. Future research should explore the long-term performance and clinical implications of these materials further.

Keywords: Nanohybrid composite resin, color stability, staining simulation, brushing simulation, spectrophotometer

INTRODUCTION

Nanohybrid composite resins are among the most commonly used materials in restorative dentistry due to their combined aesthetic and mechanical advantages. These materials not only meet high aesthetic expectations, such as natural translucency and shade matching, but also provide durability and versatility in various clinical situations. Thanks to their small filler particle size and homogeneous distribution, nanohybrid composites are suitable for use in both anterior and posterior restorations, offering enhanced polishability and wear resistance.[1]

In restorative dentistry, color stability is a critical factor for the long-term success of aesthetic restorations. Changes in the color of dental materials over time can significantly impact the aesthetic appearance of restorations, leading to dissatisfaction among patients and potentially necessitating retreatment.[2] Composite resins are particularly vulnerable to staining from daily consumption of food and beverages such as coffee, tea, and wine.[3] Therefore, it is essential to evaluate the ability of these materials to maintain their color stability in clinical settings to ensure patient satisfaction and the longevity of restorations.

In this study, coffee was chosen as the staining agent due to its widespread consumption and its high staining potential. Coffee contains tannins, which are known to cause significant extrinsic staining of dental materials.[2-4] The use of a staining agent that mimics real-life dietary habits allows for a more

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accurate assessment of the color stability of composite resins under simulated oral conditions. Color measurements were taken at baseline (t0), after 10 days (t1), and after 1 year (t2) of simulated brushing and staining, representing immediate, short-term, and long-term color changes in the materials. This timeline was designed to capture how composite resins react to staining and brushing in both early and prolonged exposures, providing comprehensive data on their performance over time.

Brushing plays a crucial role in plaque control and maintaining oral hygiene, but it can also affect the surface properties and color stability of restorative materials.[5] Studies have shown that factors such as the abrasiveness of the toothpaste, brushing technique, and frequency can influence not only the wear of dental hard tissues but also the discoloration and surface texture of composite resins.[6,7] It is important to understand how these factors interact with restorative materials like nanohybrid composites, particularly in terms of their ability to resist color changes caused by daily oral hygiene practices.

The evaluation focuses on analyzing how color changes over time in samples subjected to staining and brushing simulations. The assessment of color changes was performed using the CIEDE2000 color difference formula, which provides a measurement more closely aligned with human visual perception of color differences.[2,8]

Energy-dispersive X-ray spectroscopy (EDX) and Scanning Electron Microscopy (SEM) analyses were conducted to examine the structural and surface characteristics of the samples. The EDX analysis determined the elemental composition of the materials, while the SEM analysis assessed surface morphology and structural integrity.[9,10] These analyses were used to understand the potential effects of the composite resins on color stability.

The composite resins used in this study, such as Dolgunn (HIMG Ceramic and Medical Composite Industry and Trade Limited Company, Turkiye) (DLG), RubyComp Nano (İnci Dental, Turkiye) (CMP), Nova Compo C (Imicryl Dental, Turkiye) (NVC), Parion (Dentac T-Resto, Turkiye) (PRN), are locally produced. The use of locally produced composite resins offers advantages such as cost-effectiveness and easy accessibility. Evaluating the competitiveness of locally produced composites against international standards contributes to the development of dental materials in Turkiye. Comparing the clinical performance of local composites with international brands can yield significant economic and clinical outcomes.

The composite resins used in this study include both locally produced Turkish materials-Dolgunn (DLG), RubyComp Nano (CMP), Nova Compo C (NVC), and Parion (PRN)-and an internationally recognized composite resin, Filtek Z550 (FLT). Evaluating the performance of locally produced composites in comparison to international brands could provide valuable insights for clinical practice, particularly regarding cost-effectiveness and accessibility in regions where international brands may not be readily available.

The primary hypothesis of this study is that significant differences in the color stability of the five nanohybrid composite resins will be observed after exposure to staining and brushing simulations over time. The secondary hypothesis posits that locally produced Turkish nanohybrid composites will exhibit comparable or superior color stability to the international composite resin FLT, given their similar formulations and intended clinical use.

This in vitro study aims to provide a comprehensive comparison of the color stability of locally produced and internationally recognized nanohybrid composite resins, evaluating their performance under simulated clinical conditions. By determining whether locally produced resins can perform as well as or better than international brands, this study seeks to support the use of cost-effective, aesthetically satisfactory alternatives in restorative dentistry.

METHODS

Study Design

Only restorative materials were used in this study. It was not tested on humans or animals and no materials derived from humans or animals were used. Therefore, ethics committee approval is not required. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Five nanohybrid composite resin FLT, DLG, CMP, NVC and PRN were analyzed in this study. The category manufacturers, lots, and compositions of the composite resins are presented in Table 1. Figure 1 describes the study design, which shows the flow of the specimens through the different stages of the study. All specimens were subjected to staining and brushing simulation treatment. Color measurements were performed with spectrophotometer at baseline (t0), after 10 days brushing and staining (t1) and after 1 year brushing and staining (t2).

Specimens Size Calculation

The specimen size was calculated using G* Power statistical software. Based on the reference study values, a large effect size (f=0.80) was used. With 95% confidence (1-α) and 95% test power (1-β), the minimum sample size required for each group was 6, resulting in a total sample size of 30 for the one-way ANOVA. To account for potential specimen loss, the study was designed with 10 specimens per group.

Specimens Preparation

A total of 10 specimens (n=10) were prepared using silicon molds of 10x2 mm.[2] After the resin composite was placed in the molds with a slight overflow, a mylar strip and microscope slide were placed on the upper surfaces of the materials and polymerized for 10 s using a curing light (SmartLite Focus, Dentsply Sirona, USA). The slide was then removed, and the materials were polymerized by applying the curing light for 10 s over the mylar strip, according to the manufacturer's instructions and . The same curing light was used for all polymerization steps and the output of the light was controlled periodically using a radiometer (Woodpecker LED-F, Woodpecker Medical Instrument Co., China) to ensure an intensity of at least 1000 mW/cm^2 throughout the preparation of the specimens. Following the polymerization process,

Table 1. The category, manufacturers, lot numbers, and compositions of the composite resins

Material	Code	Material type	Composition	Filler content		Filler size	Shade	Manufacturer	Lot number
				wt%	vol%				
Filtek Z550	FLT	Nanohybrid	BIS-GMA UDMA BIS-EMA PEGDMA TEGDMA	81.8%	67.8%	0.01-3.5 µm	A2	3M ESPE, USA	N728631
Dolgunn	DLG	Nanohybrid	BIS-GMA UDMA TEGDMA SiO_2 Barium Alumino boro silicate glass powder Initiators Stabilizers	80%	61%	0.01-3 µm	A2	HIMG Ceramic and Medical Composite Industry and Trade Limited Company, Turkiye	626/0224
RubyComp Nano	CMP	Nanohybrid	BIS-GMA Methacrylate polymers (20%) Inorganic fillers (80%) Barium glass mixed oxides and copolymers, No photo-initiators and stabilizers	80%	-	0.02-0.7 µm	A2	İnci Dental, Turkiye	RCYA2275
Nova Compo C	NVC	Nanohybrid	BIS-GMA UDMA BIS-EMA PEGDMA TEGDMA Dimethacrylates (18-22% weight) ULS (Ultra Low Shrinkage) Monomer Barium glasses, Ytterbium Prepolymer	78%-83%	68%	0.4-0,7 µm	A2	Imicryl Dental, Turkiye	22M410
Parion	PRN	Nanohybrid	UDMA Bis-GMA TEGDMA Silica Quartz Pigments Initiators	77%-78%	-	0.1 µm	A2	Dentac T-Resto, Turkiye	PN220112

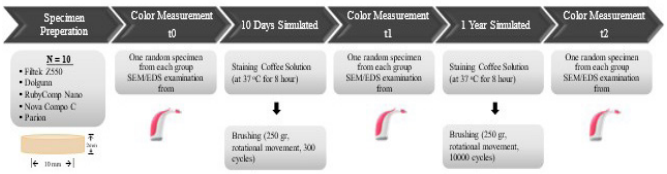


Figure 1. Flow chart of the study design

each of the specimens was polished with usin polishing disc (Optidisc, Kerr Corporation, USA) from extra-coarse to extra-fine at speed 10,000 rpm and 10 s each. A new disc was used for each specimen. The specimens were rinsed with water for 10 seconds to clean debris from the restoration surface then were kept in distilled water at 37° C in an incubator for 24 h post-polymerization.[2] All the procedures on the materials were applied by a single operator. In order to control the effect of press-on force on the polishing accuracy, the initial and final measurements of the thickness of each specimen were carried out 3 times by a single operator using an industrial type screw thread digital caliper (0.01 mm) with 0-150 mm measuring range.[11]

Staining Procedure

For the preparation of the coffee solution, 3,6 g of coffee was used per 300 ml of 100° C boiling water.[4] All solutions were allowed to reach 37° C. Eppendorf tubes were preferred to immerse the specimens individually in the study. 1.5 mm eppendorf tubes were filled with the solution and one specimen was placed inside. The tubes were kept in an oven at 37° C for 8 hour (t1-10 days) 12 days (t2-1 year) to replicate intraoral conditions. Specimens were turned over and immersed in fresh solutions every day to ensure uniform contact of the specimen with the staining solution and prevent contamination with bacteria and fungus.[2,4]

Brushing Procedure

The specimens removed from the solutions were subjected to brushing simulation with the MF-100 (Mod Dental, Esetron Smart Robotechnologies, Turkiye) brushing simulator. Toothbrush (Colgate Extra Clean 1+1, Colgate Palmolive, USA) and toothpaste (Sensodyne Çok Yönlü Koruma, Haleon, United Kingdom) with a relative dentin abrasivity (RDA) of 142 diluted 1/3 by volume were used in the brushing simulation. The toothpaste used in this study, Sensodyne (RDA 142), was selected because it represents a moderate level of abrasivity, which is common in commercially available toothpastes and reflects typical daily oral hygiene practices. The specimens were subjected to 300 (t1-10 days) and 10,000 (t2-1 year) cycles of brushing under a load of 250 g, with a circular motion with a movement diameter of 19 mm, and a movement speed of 30 mm/s, simulating 1 year of brushing. The toothbrush and paste were changed for each specimen.[12-14]

Color Assessments

The color of the specimens was assessed at three time points: t0, t1, and t2, using a digital spectrophotometer (Vita

Easyshade V, Vita Zahnfabrik, Germany). The color evaluation was based on the CIE Lab system, a three-dimensional color space where lightness (L*), red-green (a*), and yellow-blue (b*) components are represented. Specifically, L* indicates lightness on a scale from 0 (dark) to 100 (bright), a* reflects the red-green chromaticity, and b* corresponds to the yellow-blue chromaticity. For each specimen, three readings were taken from the center, and the average values of the L*, a*, and b* coordinates were recorded. Calibration of the instrument occurred between measurements. Color data were collected using an 18% grey card (L*=50, a*=0, b*=0) (JJC Photography Equipment Co. Ltd, China) as a reference.

The color differences between the measurements taken at different time points were calculated using the CIEDE2000 color difference formula.[15] ΔE was calculated by the CIEDE2000 formula using an online ΔE calculator (http://www.colormine.org/delta-e-calculator/Cie2000).

Color measurements were taken at three different time points: baseline (t0), after 10 days of brushing and staining simulation (t1), and after 1 year of brushing and staining simulation (t2). The color differences (ΔE) between these time points were calculated using the CIEDE2000 formula. ΔE1 represents the color difference between baseline (t0) and after 10 days (t1), while ΔE2 represents the color difference between baseline (t0) and after 1 year (t2). Additionally, ΔE3 represents the color difference between 10 days (t1) and 1 year (t2). These values were used to assess both short-term and long-term color stability of the composite resins.

Scanning Electron Microscope Imaging and Energy-Dispersive X-ray Examination

One specimen from each group were analyzed by SEM (Regulus 8230 FE-SEM, Hitachi High Tech Corporation, Japan) at time periods t0, t1 and t2 at ×5000 magnification, and images were recorded. Before the examination, the specimens were surface coated with 4 nm gold/palladium particles (Leica EM ACE600C, Leica Microsystems Inc., Canada) for surface conductivity. Subsequently, the representation of elemental presence in the composites was analyzed using EDX (X-Max 20, Oxford Instruments, Abingdon, UK).

Statistical Analysis

The data were analyzed using Minitab 14 and R software. Normality was assessed with the Shapiro-Wilk test. For parameters that followed a normal distribution according to composite and time, the Generalized Linear Models method was used for comparison, and multiple comparisons were performed with the Tukey test. For parameters that did not follow a normal distribution according to composite and time, the Two-Way Robust ANOVA method was used for comparison, and multiple comparisons were performed with the Bonferroni test. The results of the analyses were presented as mean ± standard deviation and median (min-max). The significance level was set at p<0.05.

RESULTS

The color difference measurements (ΔE) were calculated for three different intervals: ΔE1 (t0-t1), ΔE2 (t0-t2), and ΔE3 (t1-t2). ΔE1 represents the initial color changes observed after 10 days of staining and brushing simulation, while ΔE2 shows the long-term color changes after 1 year. ΔE3 reflects the additional color changes that occurred between 10 days and 1 year.

The main effect of the composite was not found to be statistically significant on the median ΔE values (p=0.078). The main effect of time was found to be statistically significant on the median ΔE values (p<0.001). Additionally, the interaction between composite and time was statistically significant on the median ΔE values (p=0.001). The highest median value of 3.12 was observed in the NVC composite from ΔE2, while the lowest median value of 1.285 was observed in the PRN composite from ΔE1 (Figure 2) (Table 2).

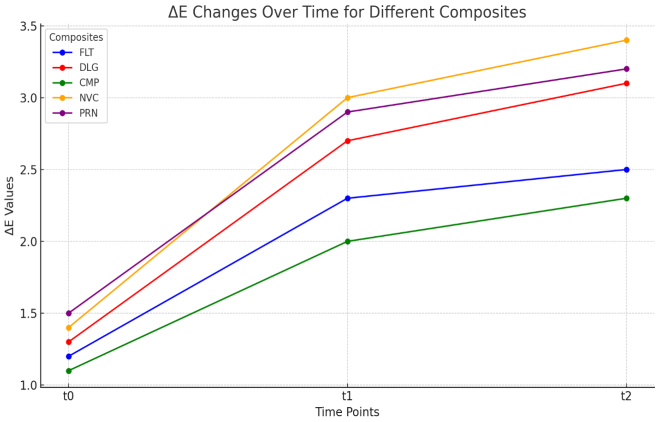


Figure 2. ΔE changes over time for different composites

During the ΔE1 time interval, the DLG group exhibited the highest color change value with a ΔE of 1.67 (1.36-2.33), while the PRN group showed the lowest value with a ΔE of 1.285 (1.05-1.79). Post-hoc analysis revealed no statistically significant differences among the composites during this interval (p>0.05 for all pairwise comparisons) (p=0.078).

Table 2. Comparison of ΔE values by composite and time

Time	Composite					Total		q	p
	FLT	DLG	CMP	NVC	PRN				
ΔE1 (t0-t1)	1.385 (0.74-1.9)^{ab}	1.67 (1.36-2.33)^{abc}	1.6 (1.18-2.49)^{ab}	1.495 (1.13-2.11)^{ab}	1.285 (1.05-1.79)^{b}	1.495 (0.74-2.49)^{a}	Composite	2.096	0.078
ΔE2 (t0-t2)	2.07 (1.64-2.46)^{acd}	2.7 (2.31-3.8)^{e}	2.385 (1.97-2.67)^{cde}	3.12 (2.38-3.59)^{de}	2.955 (2.51-3.81)^{e}	2.61 (1.64-3.81)^{b}	Time	37.334	<0.001
ΔE3 (t1-t2)	1.595 (1.04-3.24)^{abc}	1.675 (0.65-3.42)^{abc}	1.47 (0.47-2.49)^{abc}	2.04 (1.47-2.83)^{abcd}	2.2 (1.61-2.79)^{abcde}	1.785 (0.47-3.42)^{c}	Composite* time	26.676	0.001
Total	1.65 (0.74-3.24)	1.895 (0.65-3.8)	1.855 (0.47-2.67)	2.055 (1.13-3.59)	2.2 (1.05-3.81)	1.905 (0.47-3.81)			

Q: Two-way robust ANOVA; Median (min-max), $^{a-c}$: No difference between main effects with the same letter; $^{a-e}$: No difference between interactions with the same letter, FLT: Filtek Z550,

In the ΔE2 time interval, the DLG group exhibited the highest color change value with a ΔE of 2.7 (2.31-3.8), whereas the FLT group had the lowest value with a ΔE of 2.07 (1.64-2.46). Statistically significant differences were observed among the groups in this time interval (p<0.001). Post-hoc analysis indicated that there was a significant difference between the DLG and FLT groups (p=0.02). Additionally, a significant difference was observed between the DLG and CMP groups (p=0.03). No significant differences were found between the other composites (p>0.05).

During the ΔE3 time interval, the PRN group showed the highest color change value with a ΔE of 2.2 (1.61-2.79), while the CMP group exhibited the lowest value with a ΔE of 1.47 (0.47-2.49). Significant differences were noted among the groups in this time interval (p=0.001). Post-hoc analysis revealed a significant difference between the PRN and CMP groups (p=0.015). A significant difference was also observed between the PRN and FLT groups (p=0.04). No significant differences were found between the other composites (p>0.05).

The main effect of the composite was found to be statistically significant on L mean value (p<0.001). The main effect of time was also significant on L value (p<0.001). Additionally, the interaction between composite and time was statistically significant (p=0.039). A decreasing trend in L values from t0 to t2 was observed for each composite (Table 3).

The main effect of the composite was found to be statistically significant on the median a value (p<0.001). The main effect of time was also found to be statistically significant on the median a value (p=0.027). Additionally, the interaction between composite and time was statistically significant on the median a value (p<0.001) (Table 4).

The main effect of the composite was found to be statistically significant on the median b values (p<0.001). The main effect of time was also found to be statistically significant on the median b values (p<0.001). Additionally, the interaction between composite and time was statistically significant on the median b values (p<0.001) (Table 5).

The SEM and EDX analyses, as presented in Figures 2-8, were performed to investigate the surface morphology and elemental composition of the restorative materials. SEM analysis, conducted at 5000x magnification, provided detailed topographical images, while EDX spectroscopy enabled the identification and quantification of elements present within the samples. Carbon and oxygen are predominant in all groups, with silicon and barium also being significant in certain groups. The presence of aluminum and additional elements like zirconium, fluorine, and sodium further differentiates the groups. These elemental compositions reflect the diverse material properties and potential applications in dental restorative materials.

In more detail, FLT group is distinguished by the presence of zirconium at 6.47%, which is not found in any other groups. The DLG group contains aluminum at 2.05%, with this element also appearing in CMP, NVC, and PRN groups, albeit in different proportions. The CMP group has aluminum at 2.72%, while the NVC group contains 2.54% aluminum, alongside unique elements such as fluorine at 2.88% and sodium at 0.38%. The PRN group does not have any unique elements compared to the other groups, but the proportions of the elements present differ. These findings highlight the distinctive elemental combinations and proportions within each group, underscoring their specific material characteristics and suggesting various potential applications in restorative dentistry.

DISCUSSION

The study's results support the primary hypothesis that significant differences in the color stability of the five nanohybrid composites were observed after staining and brushing simulations. Statistical analysis showed a significant main effect of time on median ΔE values (p<0.001) and a significant interaction between composite and time (p=0.001), indicating that color changes varied by composite type over time. At the ΔE1 and ΔE3 time points, all composites had similar color changes to FLT, but at ΔE2, FLT and CMP

Table 3. Comparison of L values by composite and time

	Composite							
Time	FLT	DLG	CMP	NVC	PRN		f	p
t0	78.14±0.78^{a}	71.23±1.18^{fgh}	77.13±1.31^{ab}	74.69±0.95^{c}	74.37±0.73^{cd}	Composite	239.52	<0.001
t1	76.27±0.51^{b}	69.69±1.24^{h}	75.63±1.35^{bc}	73.07±0.79^{de}	72.76±0.75^{ef}	Time	107.52	<0.001
t2	76.41±0.84^{b}	68.1±1.14^{i}	74.24±1.3^{cde}	71.45±0.67^{fg}	70.68±0.97^{gh}	Composite* time	2.11	0.039

f: Generalized linear models, mean ± SD, $^{a-i}$: No difference between interactions with the same letter

Table 4. Comparison of a values by composite and time

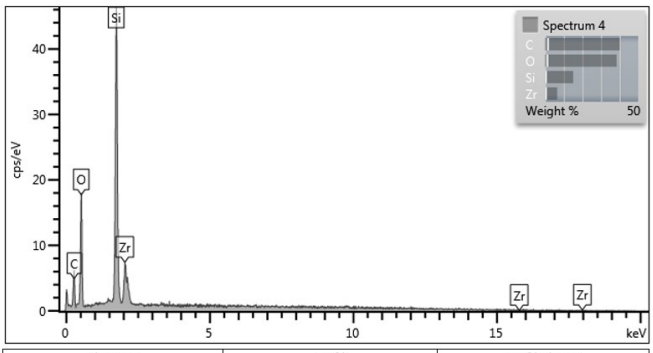
	Composite							
Time	FLT	DLG	CMP	NVC	PRN		q	p
t0	0.79 (0.6 - 0.83)^{a}	-0.42 (-1.13 - -0.17)^{de}	1.42 (1.02 - 1.93)^{g}	-2.2 (-3.1 - -1.6)^{i}	0.32 (0.1 - 0.93)^{be}	Composite	174.073	<0.001
t1	0.7 (0.65 - 0.77)^{a}	-1.27 (-1.69 - -0.73)^{df}	1.5 (1.1 - 1.83)^{gh}	-2.04 (-2.43 - -1.57)^{fi}	0.49 (0.2 - 0.9)^{bc}	Time	3.597	0.027
t2	0.5 (0.3 - 0.65)^{bc}	-1.54 (-1.77 - -1.07)^{f}	1.97 (1.37 - 2.2)^{h}	-1.23 (-2.14 - -0.93)^{df}	1.07 (0.26 - 1.5)^{acg}	Composite* time	76.177	<0.001

Q: Two-way robust ANOVA, median (min-max), $^{a-i}$: No difference between interactions with the same letter,

Table 5. Comparison of b values by composite and time

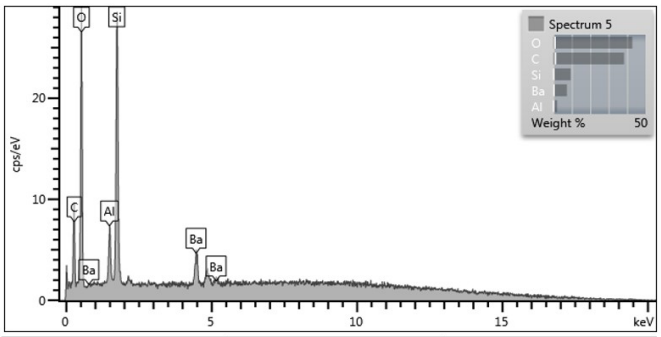
Time	Composite							
	FLT	DLG	CMP	NVC	PRN		q	p
t0	20.17 (19.9-21)^{a}	11.49 (10.3-12.2)^{c}	20.55 (19.03-23.2)^{abef}	12.07 (9.8-3.7)^{cd}	16.5 (15.57-17.4)^{e}	Composite	259.765	<0.001
t1	20.4 (18.87-21.5)^{a}	11.23 (10.3-11.87)^{cd}	18.83 (17.4-20.87)^{aef}	11.44 (9.9-12.63)^{cd}	16.77 (14.43-17.27)^{e}	Time	14.603	<0.001
t2	23.44 (22.13-24.57)^{b}	12.43 (11.17-13.73)^{cd}	20.35 (19.37-22.47)^{a}	12.47 (11.32-13.73)^{d}	18.6 (16.43-19.23)^{f}	Composite* time	188.19	<0.001

Q: Two-way robust ANOVA, Median (min-max), $^{a-f}$: No difference between interactions with the same letter



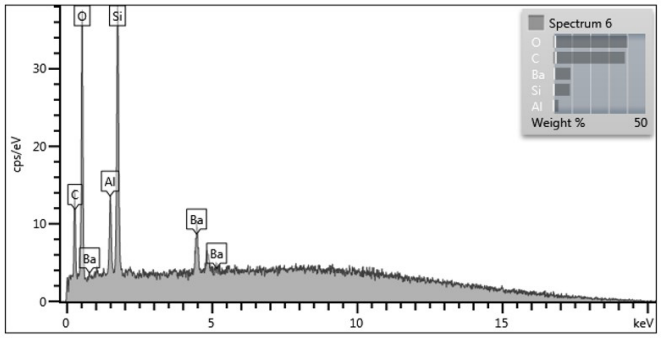
Element	Wt%	Wt% Sigma
C	40.07	1.59
O	38.45	1.19
Si	15.02	0.46
Zr	6.47	0.43
Total:	100.00	

Figure 3. Energy-dispersive X-ray spectroscopy (EDS) analysis of the FLT group



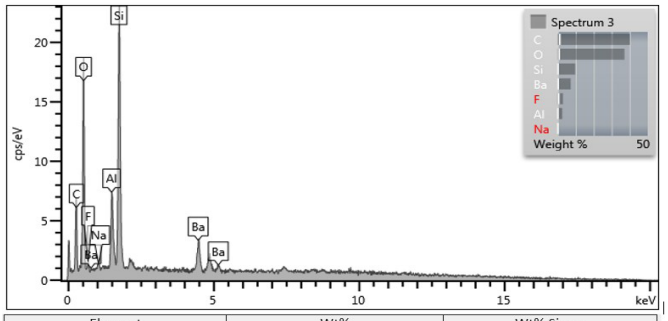
Element	Wt%	Wt% Sigma
C	38.38	1.12
O	42.85	0.91
Al	2.05	0.11
Si	9.38	0.23
Ba	7.34	0.35
Total:	100.00	

Figure 4. Energy-dispersive X-ray spectroscopy (EDS) analysis of the DLG group



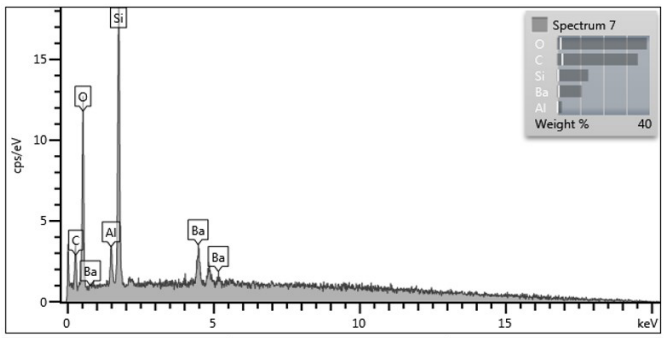
Element	Wt%	Wt% Sigma
C	38.85	1.36
O	40.19	1.07
Al	2.72	0.15
Si	8.94	0.27
Ba	9.31	0.49
Total:	100.00	

Figure 5. Energy-dispersive X-ray spectroscopy (EDS) analysis of the CMP group



Element	Wt%	Wt% Sigma
C	40.13	1.13
O	37.11	0.90
F	2.88	0.59
Na	0.38	0.12
Al	2.54	0.12
Si	9.73	0.25
Ba	7.23	0.33
Total:	100.00	

Figure 6. Energy-dispersive X-ray spectroscopy (EDS) analysis of the NVC group



Element	Wt%	Wt% Sigma
C	34.92	2.30
O	38.84	1.66
Al	2.07	0.20
Si	13.50	0.58
Ba	10.68	0.77
Total:	100.00	

Figure 7. Energy-dispersive X-ray spectroscopy (EDS) analysis of the PRN group

outperformed DLG, NVC, and PRN, partially supporting the secondary hypothesis.

The findings show that all composite resins experienced color change, but the extent varied significantly across materials over time. At the ΔE1 time point (t0-t1), initial color changes were minor and similar across all composites, indicating comparable short-term color stability. This likely reflects early surface reactions to staining agents without deep material penetration.

By the ΔE2 time point (t0-t2), more pronounced differences in color stability emerged. The FLT and CMP composites showed superior color stability compared to the DLG, NVC, and PRN composites. This suggests that the formulation and material properties of FLT and CMP provide better resistance to prolonged exposure to staining agents, likely

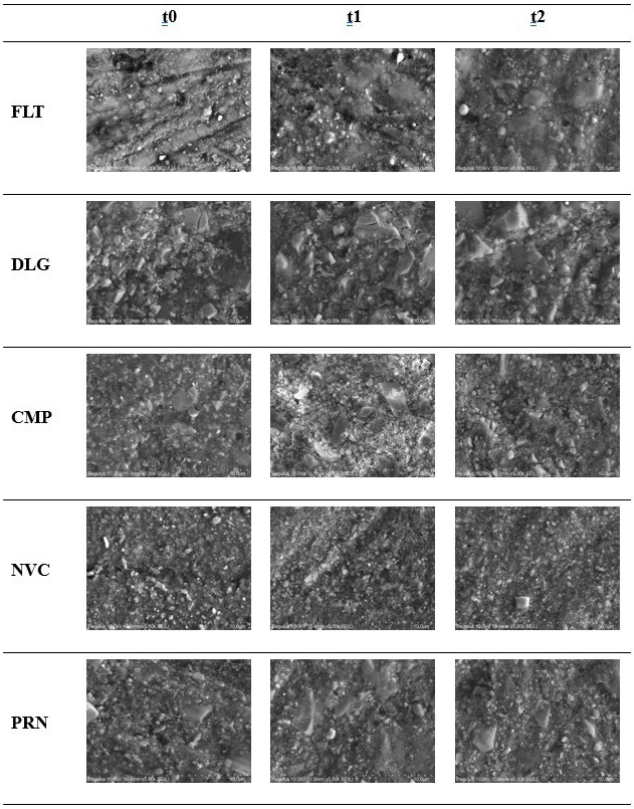


Figure 8. SEM analysis at 5000x magnification reveals the surface morphology of the groups

due to factors such as filler content, matrix composition, and surface properties that influence stain resistance and material degradation. These results align with previous research showing varying levels of color stability among different composite resins.[2,4,16]

At the ΔE3 time point (t1-t2), composites showed varying levels of color change, with PRN maintaining better color stability, likely due to its unique composition. The superior long-term performance of some composites highlights the importance of selecting materials with proven color stability for clinical applications.

Coffee was selected as the staining agent due to its common consumption and its known high potential for causing extrinsic dental stains.[2,3] This choice is relevant as it reflects the impact on the color stability of dental restorations over both short-term and long-term periods. The study's findings on how different composites responded to coffee staining provide valuable insights into their performance over short-term and long-term use, particularly for patients who frequently consume coffee and other staining beverages.

After staining with coffee, a decrease in L values was observed across all materials at all time points. This decrease indicates that the materials became darker due to the absorption of pigments. The consistent reduction in lightness across the different materials suggests that the coffee pigments effectively adhered to the surface of the restorative materials, leading to noticeable discoloration over time.[17,18] This outcome highlights the susceptibility of the materials to extrinsic staining in environments simulating real-world conditions where coffee is commonly consumed.

Overall, the significant differences observed in the color stability of the tested nanohybrid composite resins highlight the importance of considering material-specific properties when selecting dental composites for restorative procedures.[1,17] The findings support the primary hypothesis that staining and brushing simulations result in varied color stability among composite resins. The partial acceptance of the secondary hypothesis indicates that locally produced Turkish nanohybrid composites can match or exceed international standards in color stability under certain conditions.

In this study, brushing was incorporated as part of the simulation of intraoral conditions to evaluate the color stability of composite resins. Brushing is known to cause mechanical wear on tooth surfaces, which can potentially affect the color stability of composite materials by making them more susceptible to staining.[19] The toothpaste and brushing protocol used were carefully selected to simulate daily oral hygiene practices, closely reflecting real-world conditions.

Simulated brushing abrasion is widely recognized in the literature as an established in-vitro wear model that mimics clinical conditions.[14] In a study, it was noted that a typical patient performs approximately 15 brushing strokes per session, which equates to around 10,000 cycles over the course of a year with twice-daily brushing and brushing was simulated for 5,000, 10,000, and 20,000 cycles, corresponding to approximately 6, 12, and 24 months of brushing, respectively.[13] These findings highlight the importance of evaluating the resistance of composite materials to brushing when considering their long-term color stability, which is crucial for the success of aesthetic restorations in clinical practice.

Regarding the parameters for simulated toothbrushing, the present study aimed to systematically evaluate the influence of brushing time and load on the color stability of various composite materials. The 250 g load used in this study aligns with the range suggested in other research and is within the force limits commonly observed in clinical settings. Clinical studies have shown that brushing loads among individuals can vary widely, typically ranging from 140 g to 720 g, with a mean load comparable to 350 g.[20,21] The ISO technical specification for wear testing by toothbrushing recommends a force between 50 g and 250 g.[22] Previous studies have employed brushing forces of 200 g, 250 g, 350 g, and even 500 g.[21,23,24] The choice of 250 g in this study was made to balance the clinical relevance with the standardized conditions outlined in the literature.

The results indicate that locally produced Turkish nanohybrid composite resins (DLG, CMP, NVC, and PRN) exhibited varying degrees of color stability compared to the internationally recognized composite resin FLT. In the short term (ΔE1, t0-t1), all composites showed similar color changes, and the differences among them were not statistically significant. This suggests that locally produced composites can meet initial aesthetic expectations. However, in the long-term evaluation (ΔE2, t0-t2), FLT and CMP composites demonstrated superior color stability compared to DLG, NVC, and PRN composites. The superior performance of FLT

and CMP is likely due to their optimized filler content and well-engineered matrix composition, highlighting the need for further development of locally produced composites to enhance their long-term performance.

Despite differences, some locally produced composites, particularly CMP, performed comparably to FLT under certain conditions. This suggests that with improved formulation and manufacturing, these composites could match international brands. Their cost-effectiveness and easy accessibility offer economic benefits and support national industry development, especially in regions with limited access to international brands.

The differences in color stability observed among the composite resins can be attributed to variations in their filler content, resin matrix composition, and overall formulation, even when filler size is similar.[25] For example, although both FLT and DLG have comparable filler sizes (0.01-3.5 μm and 0.01-3 μm, respectively), their filler content and resin matrices differ. FLT, with a higher filler volume (67.8% vol) compared to DLG (61% vol), likely exhibited superior color stability due to reduced resin matrix exposure, making it less prone to absorbing staining agents. The increased filler content helps form a smoother surface, limiting the penetration of extrinsic staining materials and improving resistance to mechanical wear.

In contrast, DLG's lower filler volume may lead to more exposure of the resin matrix, which is known to absorb water and staining agents over time, contributing to greater color changes. Additionally, the resin matrix composition of each composite plays a crucial role in color stability. FLT contains BIS-GMA and UDMA, both of which are known for their lower water sorption rates, enhancing its ability to maintain color over time. DLG, while also containing BIS-GMA and UDMA, includes alumino boro silicate glass powder, which may contribute to its differing performance in terms of color retention compared to FLT.

Similarly, CMP demonstrated competitive color stability, likely due to its well-distributed inorganic fillers and its barium glass mixed oxides, which contribute to the material's stain resistance. NVC, with its inclusion of ultra-low shrinkage (ULS) monomer and ytterbium, showed better performance in terms of long-term color stability, likely due to reduced polymerization shrinkage and its advanced filler technology.

Although there were differences among the composites, particularly with regard to their filler content and resin matrices, some locally produced composites, such as CMP, performed comparably to FLT under certain conditions. This demonstrates that with targeted improvements in formulation, locally produced composites can compete with international brands in terms of color stability. The competitive performance of these locally produced materials highlights their potential as cost-effective alternatives for aesthetic dental restorations.

In conclusion, locally produced Turkish nanohybrid composites showed comparable performance to FLT under specific conditions, highlighting their potential and the need for ongoing research to optimize their properties. Clinics can consider these composites as viable alternatives, particularly where cost and accessibility are key factors.

The structural and surface characteristics of the composite resins were examined using EDX and SEM.[9] These analyses provided crucial insights into the elemental composition and surface morphology of the materials, which influence their color stability. EDX analysis revealed the presence of various elements, including carbon, oxygen, silicon, barium, and aluminum.[9] The distribution and concentration of these elements varied among the composites. For example, the FLT contained zirconium, which was not found in the other composites. This unique elemental composition might contribute to FLT's superior color stability over time.[26]

SEM analysis revealed that FLT and CMP exhibited smoother surfaces with fewer pores, correlating with their lower ΔE values. These smoother surfaces reduce the likelihood of trapping staining agents, as well as minimizing the penetration of these agents into the material.[9] In contrast, DLG and PRN exhibited more porous and irregular surfaces, which might explain their higher ΔE values. The rougher surface and increased porosity observed in these composites likely facilitate greater staining agent retention, contributing to their more pronounced color changes over time.[4,18] The combination of EDX and SEM analyses allowed for a comprehensive understanding of the structural and surface properties of the composite resins and their impact on color stability. Composites with higher barium content, like FLT and CMP, tend to have greater radiopacity and surface integrity, which may reduce surface wear and enhance resistance to staining. In contrast, DLG and PRN contained less favorable filler compositions, which could lead to greater degradation under oral conditions, increasing their susceptibility to discoloration. These findings highlight the critical role that both surface morphology and elemental composition play in determining a composite's ability to maintain color stability. By linking the SEM and EDX findings to the ΔE values, it becomes evident that smoother surfaces, lower porosity, and favorable elemental compositions such as the presence of zirconium and higher barium content contribute to improved color stability. These structural and compositional advantages allow materials like FLT and CMP to better resist staining over time, while composites with less favorable properties show greater susceptibility to color changes.

The clinical relevance of the in vitro findings and their implications for real-world dental practice are crucial aspects of this study. While the results provide valuable insights into the color stability of different nanohybrid composite resins, it is essential to consider the need for further in vivo research.

The color change was calculated using the CIEDE2000 formula, which offers a better fit and is an update to the CIE Lab* formula, accounting for both the uniformity of the CIELAB color space and variations in lighting conditions.[2,8] The study's findings offer valuable guidance for clinical decision-making. The significant differences in color stability observed among the tested composites highlight the importance of material selection in achieving long-term aesthetic outcomes. Clinicians should consider both the initial color stability and the potential for long-term color changes when choosing composite resins for restorative procedures.

The importance of using locally produced composite resins in clinical applications is worth emphasizing. When selecting these materials for treatments, dentists should take into account factors such as initial and long-term color stability, mechanical properties, and cost-effectiveness. Locally produced composite resins offer cost-effective and readily accessible alternatives, providing significant advantages in clinical practice in Turkiye. These materials may be particularly beneficial in applications like anterior restorations, where achieving long-term aesthetic outcomes is crucial.

While there are limited studies directly evaluating locally produced Turkish composite resins, particularly regarding their surface properties and monomer structures, this study serves as a foundational reference by focusing on color stability an area where no prior research has been conducted on local composites.[10,27] By comparing these findings with international literature, we can better understand the position and potential of these local materials in the global market. Future research should continue to build on this work to further validate and optimize the performance of locally produced composites.

Clinical Significance

This study is clinically significant as it offers valuable insights for selecting composite resins in restorative dentistry. Understanding the color stability of various nanohybrid composites helps clinicians choose materials that maintain aesthetic quality over time. If locally produced Turkish composites demonstrate similar or superior color stability to international brands, they can provide cost-effective, readily available alternatives without sacrificing appearance, leading to improved patient satisfaction and potentially lower treatment costs. Additionally, the findings can guide manufacturers in enhancing composite resin formulations and performance, ultimately improving clinical outcomes and durability.

Limitations

This study has several limitations that should be considered when interpreting the results. The in vitro design does not fully replicate the complex oral environment, as factors like saliva, pH fluctuations, and enzymatic activity were not included, potentially affecting in vivo color stability. Additionally, the absence of mastication forces and enzymatic activity in the in vitro setup means that the mechanical wear and biochemical processes that occur in the oral cavity were not fully replicated. These factors can affect surface roughness and increase susceptibility to staining, potentially leading to different outcomes in vivo compared to those observed in the laboratory setting. Thermal cycling, which simulates temperature changes in the oral cavity, was also omitted, though these fluctuations can significantly impact the physical properties and color stability of dental materials. The laboratory conditions under which specimens were tested may not perfectly mirror clinical conditions, including factors like mastication wear, interaction with various substances, and patient-specific variables. The focus on specific nanohybrid composite resins limits the generalizability of the findings, as differences in formulation and filler content can lead to variability. Although a 1-year evaluation period was included, it may not fully capture the long-term color stability of the materials. Extended observation periods and more comprehensive simulations of the oral environment are recommended for future research to better reflect clinical conditions.

CONCLUSION

In conclusion, this study underscores the need for further research to fully understand the long-term performance of nanohybrid composite resins in clinical settings. By addressing the limitations of in vitro studies and conducting more extensive in vivo research, we can better inform clinical practices and improve patient outcomes. The findings from this study provide a foundation for future research and highlight the potential of locally produced composites in achieving comparable or superior performance to international brands.

ETHICAL DECLARATIONS

Ethics Committee Approval

Only restorative materials were used in this study. It was not tested on humans or animals and no materials derived from humans or animals were used. Therefore, ethics committee approval is not required.

Informed Consent

It was not tested on humans or animals and no materials derived from humans or animals were used. Therefore, informed consent is not required.

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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Etiological and epidemiological analysis of patella fractures: evaluation of COVID-19 pandemic and lockdown era effects

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ABSTRACT

Aims: Patella fractures are relatively rare, but significant public health burden with consequences ranging from skin problems to extensor mechanism deficiencies and patellofemoral arthrosis due to their significant effects on pain, functionality, and quality of life. It was aimed to present basic etiological, and epidemiological information about patella fractures and to evaluate the impact of the COVID-19 Pandemic and lockdown era period.

Methods: All patellar fractures admitted to a level-1 trauma center between 2016 and 2022 were collected retrospectively. Patient's gender, age, side, fracture classification, trauma mechanism, treatment method, admission day and season, accompanying extremity, and non-musculoskeletal/visceral pathologies were recorded and analyzed.

Results: A retrospective evaluation was conducted on 304 patients, with 181 (59.5%) males and 123 (40.5%) females, with an average age of 46±19 years. Most patients were between 30-65 (51.4%) and the most common cause was simple falls (74%). Fractures mostly occurred in the winter (35.2%) and on Sundays (19.7%). 9.9% of the patients were accompanied by extremity traumas and 6.9% by non-musculoskeletal injuries. Regarding the descriptive classification, transverse, distal pole, and proximal pole; and according to the AO/OTA classification, C1 was the most common. Although an increase in the number of cases was observed over the years, this changed during the pandemic period and an upward trend restarted after the pandemic. Although surgical treatment rates, like the number of cases, decreased during the pandemic period, they still catch up with and exceed pre-pandemic periods over the years.

Conclusion: The incidence of patella fractures is increasing. Non-surgical treatment is a priority, and the complication rates of surgical treatment are considerable. The study, which presents etiological and epidemiological data of level-1 trauma center patients, is a suitable sample for Turkiye. The study is unique in showing the potential effects of COVID-19 on the patient profile and treatment management of patella fractures.

Keywords: Kneecap, sesamoid bone, knee, genu, incidence, characteristic

INTRODUCTION

The patella is the largest sesamoid bone of the body.[1] The posterior joint surface articulates with the femoral trochlea and forms the patellofemoral (PF) joint.[2] It plays a key role in the knee extensor mechanism by being located between the quadriceps proximally and the patellar tendon distally.[3] Fractures are relatively rare, accounting for 0.7%-1% of all fractures.[4-6]

Trauma and fractures can create a public health burden by causing PF joint and extensor mechanism pathologies, leading to pain, quality of life, and functionality problems.[7,8] Treatment of patella fractures often depends on the fracture pattern. While conservative treatment is generally preferred for non-displaced fractures that do not disrupt the extensor mechanism, intra-articular and displaced fractures where the extensor mechanism is disrupted are generally treated surgically.[5,9] Surgical treatment of patella fractures is linked to a significant risk of complications.[10] An increase in the need for total knee prosthesis has been shown in inappropriately and inadequately treated patellar fractures.[8]

There are limited studies regarding the type and incidence of patella fractures, accompanying fractures and pathologies, mechanism of injury, treatment applied, and complications encountered.

It was aimed to describe the characteristics and socio-demographic data of patella fractures, which can be observed in all age groups and cause various complications if not treated appropriately, to provide updated information on the incidence of fractures, and to detail the injury mechanisms, treatment methods, and possible complications. It was aimed to report the effects of the COVID-19 pandemic and the lockdown era.

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METHODS

Patients with radiologically confirmed patellar fractures who were admitted to our hospital, a level-1 trauma center, between January 2016 and December 2022, were included in the study. Following Bakırköy Dr. Sadi Konuk Training and Research Hospital Ethics Committee approval (Date: 05.08.2024, Decision No: 2024-07-), data were collected retrospectively from the hospital data storage system. Fracture classification, age, gender, trauma mechanism, date, day, and season of trauma, side, accompanying additional extremity trauma, treatment applied, accompanying head, thorax, and abdomen pathologies, and complications were recorded. A total of 304 patients diagnosed with patella fractures were studied. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Data Collection

Trauma mechanism was divided into two main groups: Low and high-energy injuries. High-energy injuries were examined in three groups: traffic accidents, falls from height, and gunshot injuries. Low-energy injuries included simple traumas such as indoor falls, falls from the same level, and sports injuries. Accompanying orthopedic injuries and other system injuries were also classified.

Patella fractures were classified into seven subgroups according to Arbeitsgemeinschaft für osteosynthesefragen (AO) classification and fracture pattern (nondisplaced simple, transverse, apex or lower end, vertical, osteochondral, fragmented nonseparated, fragmented displaced). Treatment was divided into conservative/non-operative and surgical/operative, and complications were recorded.

Statistical Analysis

NCSS (Number Cruncher Statistical System) Statistical Software (Utah, USA) program was used for statistical analysis. While evaluating the study data, in addition to descriptive statistical methods (mean, standard deviation, median, frequency, ratio), the Shapiro-Wilk test and box plot graphics were used to ensure that the variables fit into a normal distribution. Student's t-test was used for intergroup comparisons of normally distributed variables; Mann Whitney U test was used for intergroup comparisons of variables that did not show normal distribution. Pearson's Chi-square, Fisher's exact, and Fisher-Freeman Halton tests were used to compare qualitative data. Significance was evaluated at $p<0.05$ level.

RESULTS

Demographic Data

Between 2016 and 2022, a total of 304 patients, including 181 male (59.54%) and 123 female patients (40.46%), were diagnosed with patella fractures. The male-female ratio was 1.48:1. The average age is 46±19 years.

Age distribution was examined by dividing into 4 groups; 0-15, 15-30, 30-65, and over 65. While patella fractures were seen in eight patients under the age of 15, patella fractures were observed in seventy-two patients between the ages of 15-30, hundred and sixty-seven patients between the ages of 30-65, and fifty-seven patients over the age of 65 (Table 1).

Table 1. Relationship between age and gender distribution

		Gender		
		Male, n (%)	Female, n (%)	p
Age	0-15 ages	5 (2.76)	3 (2.44)	0.0001
	15-30 ages	57 (31.49)	15 (12.2)	
	30-65 ages	93 (51.38)	74 (60.16)	
	Over 65	26 (14.36)	31 (25.2)	

Considering seasonal differences, fractures were most common in winter (35.2% n=107), while 83 (27.3%) patella fractures were diagnosed in summer, 66 (21.7%) in spring, and 48 (15.8%) in autumn. Although no significant data was found regarding the relationship between age and seasons, emergency service admissions with a history of trauma were seen mostly in the winter (38.92%) in the 30-65 age group, where fractures are most common (Table 2).

While high-energy injuries were most frequently observed in male patients (68%, n=54), the most common cause of fracture formation in male patients was low-energy injuries (70.2%). In female patients, 98 (79.7%) of patella fractures were caused by low-energy injuries and 25 (20.3%) were caused by high-energy injuries (Table 3).

The presence of accompanying extremity (lower and upper limb injury) and visceral (local, cranial, thoracal, and abdominal) injuries after the trauma was presented. 30 (9.87%) patients with patella fractures had an accompanying extremity fracture. Of these, 16 (5.26%) were lower and 14 (4.61%) were upper extremity fractures. Three major cavity and local injuries were seen in 21 patients (6.91%) (Table 2). No significant difference was observed regarding the location of the accompanying fracture. Still, the incidence of the isolated patella fracture was significantly higher ($p<0.05$). The presence of accompanying injuries was found to be significantly higher in high-energy injuries ($p<0.05$) (Table 2).

Patella fractures were classified by descriptive classification[3] and AO classification.[11] The most common was transverse fractures (AO C1 subtype) ($p<0.05$) (Table 2). When the fracture type and trauma mechanism were compared, although the rate of comminuted fractures increased in high-energy traumas, no significant difference was observed. ($p>0.05$) While it was observed that gender, trauma day, and season did not cause a significant change in fracture type, a significant relationship was found between fracture type and AO classification and age group. ($p=0.0001$) While avulsion (AO 34-A1) and osteochondral fractures were most frequently observed in the group under 15 years, transverse (AO 34-C1) fractures were most frequently observed in the 30-65 age group, and the patient group over 65 years of age (Table 2).

While 251 (82.57%) patients were followed non-operatively, 53 (17.43%) patients underwent surgical treatment. 58.96% (n=148) of male patients and 41.04% (103) of female patients were treated conservatively (long leg cast/splint and knee braces). There was no relationship between gender and treatment method ($p>0.05$).

Table 2. Sociodemographic data of patella fractures, analysis of concomitant injuries, and distribution of fractures according to descriptive (morphological) and AO classifications

		n	%
Gender	Male	181	59.54
	Female	123	40.46
Trauma side	Right	152	50
	Left	148	48.68
	Bilateral	4	1.32
Trauma mechanism	Simple falls	225	74.01
	Traffic accident	45	14.8
	Gunshot injury	10	3.29
	Falling from high	24	7.89
Trauma day	Monday	52	17.11
	Tuesday	33	10.86
	Wednesday	49	16.12
	Thursday	34	11.18
	Friday	33	10.86
	Saturday	43	14.14
	Sunday	60	19.74
Season	Spring	66	21.71
	Summer	83	27.3
	Autumn	48	15.79
	Winter	107	35.2
Accompanying fracture	No	274	90.13
	Upper extremity	14	4.61
	Lower extremity	16	5.26
Presence of non-musculoskeletal injury	No	283	93.09
	Yes	21	6.91
Additional injuries	No	283	93.09
	Cranial	5	1.64
	Thoracal	4	1.32
	Abdominal	1	0.33
	Local soft tissue	11	3.62
Definitive fracture classifications	1	28	9.21
	2	70	23.03
	3	60	19.74
	4	31	10.2
	5	31	10.2
	6	52	17.11
	7	32	10.53
AO/OTA classifications	A1	49	16.12
	A2	30	9.87
	B1	34	11.18
	B2	21	6.91
	C1	96	31.58
	C2	27	8.88
	C3	47	15.46

AO: Arbeitsgemeinschaft für osteosynthesefragen, OTA: Orthopaedic Trauma Association

Table 3. Relationship of age, day of trauma, trauma mechanism, and season with gender

		Gender		
		Male, n (%)	Female, n (%)	p
Age	Under 15	5 (2.76)	3 (2.44)	0.0001
	15-30 ages	57 (31.49)	15 (12.2)	
	30 65 ages	93 (51.38)	74 (60.16)	
	Above 65	26 (14.36)	31 (25.2)	
Trauma day	Monday	25 (13.81)	27 (21.95)	0.021
	Tuesday	17 (9.39)	16 (13.01)	
	Wednesday	37 (20.44)	12 (9.76)	
	Thursday	24 (13.26)	10 (8.13)	
	Friday	17 (9.39)	16 (13.01)	
	Saturday	21 (11.6)	22 (17.89)	
	Sunday	40 (22.1)	20 (16.26)	
Trauma mechanism	Simple falls	127 (70.17)	98 (79.67)	0.127
	Traffic accident	29 (16.02)	16 (13.01)	
	Gunshot injuries	9 (4.97)	1 (0.81)	
	Falling from high	16 (8.84)	8 (6.5)	
Trauma season	Spring	39 (21.55)	27 (21.95)	0.670
	Summer	54 (29.83)	29 (23.58)	
	Autumn	27 (14.92)	21 (17.07)	
	Winter	61 (33.7)	46 (37.4)	

A significant relationship was found between gender and age. However, no significant relationship was found between season and trauma mechanism. Fractures were most common in the 30-65 age group in both male and female patient groups, with the highest frequency of trauma occurring on sunday (Table 4).

Two patients from the conservative and seven from the operative treatment have suffered complications. One of the patients followed non-operatively developed extensor mechanism failure after delayed union, and the other developed moderate patellofemoral (PF) arthrosis. While mild-moderate PF arthrosis was observed in 3 patients with multi-fragmented displaced (AO 34-C3) fractures who underwent surgery, subacute osteomyelitis was observed in 1 patient with type 1 open injury. Bursitis and implant irritation were observed in 3 patients. Hardware removal was applied to all these 7 patients.

Although no significant relationship was observed according to the distribution of patella fractures over the years, an increase in the number of fractures was observed until the pandemic period (2020), although this increase stopped due to the lockdown effect during the pandemic period, a decrease in the incidence of fractures was detected, and the increasing trend continued after the pandemic (Table 5).

DISCUSSION

The subcutaneous location and limited soft tissue coverage of the patella, and its direct articulation with the distal femur may lead to articular cartilage damage, skin problems,

Table 4. Comparison of AO classification with gender, trauma mechanism, day of trauma, season of trauma, and age distribution

		AO							
		A1	A2	B1	B2	C1	C2	C3	
		n	n	n	n	n	n	n	p
Gender	Male	33 (67.35)	22 (73.33)	20 (58.82)	14 (66.67)	47 (48.96)	16 (59.26)	29 (61.7)	0.20
	Female	16 (32.65)	8 (26.67)	14 (41.18)	7 (33.33)	49 (51.04)	11 (40.74)	18 (38.3)	
Trauma mechanism	Simple falls	37 (75.51)	23 (76.67)	27 (79.41)	14 (66.67)	69 (71.88)	19 (70.37)	36 (76.6)	0.89
	Traffic accident	8 (16.33)	2 (6.67)	4 (11.76)	6 (28.57)	15 (15.63)	5 (18.52)	5 (10.64)	
	Gunshot injury	1 (2.04)	2 (6.67)	0 (0)	0 (0)	3 (3.13)	1 (3.7)	3 (6.38)	
	Falling from high	3 (6.12)	3 (10)	3 (8.82)	1 (4.76)	9 (9.38)	2 (7.41)	3 (6.38)	
Trauma day	Monday	9 (18.37)	2 (6.67)	4 (11.76)	3 (14.29)	14 (14.58)	8 (29.63)	12 (25.53)	0.65
	Tuesday	5 (10.2)	3 (10)	9 (26.47)	2 (9.52)	11 (11.46)	1 (3.7)	2 (4.26)	
	Wednesday	10 (20.41)	6 (20)	4 (11.76)	2 (9.52)	17 (17.71)	2 (7.41)	8 (17.02)	
	Thursday	5 (10.2)	4 (13.33)	3 (8.82)	2 (9.52)	13 (13.54)	1 (3.7)	6 (12.77)	
	Friday	7 (14.29)	2 (6.67)	3 (8.82)	3 (14.29)	11 (11.46)	4 (14.81)	3 (6.38)	
	Saturday	4 (8.16)	6 (20)	5 (14.71)	2 (9.52)	13 (13.54)	5 (18.52)	8 (17.02)	
	Sunday	9 (18.37)	7 (23.33)	6 (17.65)	7 (33.33)	17 (17.71)	6 (22.22)	8 (17.02)	
Season	Spring	9 (18.37)	9 (30)	2 (5.88)	4 (19.05)	21 (21.88)	5 (18.52)	16 (34.04)	0.164
	Summer	15 (30.61)	9 (30)	7 (20.59)	5 (23.81)	23 (23.96)	12 (44.44)	12 (25.53)	
	Autumn	8 (16.33)	3 (10)	9 (26.47)	2 (9.52)	17 (17.71)	1 (3.7)	8 (17.02)	
	Winter	17 (34.69)	9 (30)	16 (47.06)	10 (47.62)	35 (36.46)	9 (33.33)	11 (23.4)	
Age group	Under 15	5 (10.2)	2 (6.67)	0 (0)	0 (0)	1 (1.04)	0 (0)	0 (0)	0.0001
	15-30 ages	15 (30.61)	13 (43.33)	9 (26.47)	8 (38.1)	11 (11.46)	7 (25.93)	9 (19.15)	
	30-65 ages	25 (51.02)	13 (43.33)	16 (47.06)	12 (57.14)	57 (59.38)	16 (59.26)	28 (59.57)	
	Above 65	4 (8.16)	2 (6.67)	9 (26.47)	1 (4.76)	27 (28.13)	4 (14.81)	10 (21.28)	

AO: Arbeitsgemeinschaft für osteosynthesefragen

Table 5. Numbers and percentages of the cases treated conservatively and surgically by year

		Treatment			
		Conservatively		Surgical	
		n	%	n	%
Year	2016	22	8.76	10	18.87
	2017	33	13.15	6	11.32
	2018	39	15.54	5	9.43
	2019	58	23.11	7	13.21
	2020	27	10.76	4	7.55
	2021	39	15.54	8	15.09
	2022	33	13.15	13	24.53

extensor mechanism insufficiency, and even arthrosis (12-14). Therefore, although relatively rare, the nature of patella fracture, treatment options, functional results, and possible complications should be predictable. The current literature has limited data on the etiology and epidemiology of patella fractures in large populations in Turkiye. The most important finding of the study is providing a detailed analysis, which is limited in the literature and exceptional in our region, on a relatively large sample that included comprehensive data from a level-1 trauma center.

In a Korean study on the characteristics of patella fractures between 2003 and 2017, an increased incidence was found in female and elderly patients.[1] Begnér et al.[15] reported a serious increase in patella fractures, especially in female patients, from the 1950s to the 1980s. Another study emphasized that the gender distribution of patella fractures was more balanced.[16] Similarly, in our study, although there was an increasing trend in patella fractures in middle and older ages, a pause and regression were detected in this trend due to the pandemic era. No difference was detected in gender. Unlike the current literature, our data differs from other studies because it includes the COVID-19 pandemic period and reflects the projection of this period.

While comminuted and displaced fractures are more common in male patients due to higher-energy injuries, transverse fractures are more common in female patients due to low-energy traumas.[9,17] In our study, consistent with the literature, transverse fractures were the most common in both genders. This can also be explained due to the high-energy traumas are more common in males (29.83% vs. 20.33%). Low-energy traumas are more common in females (79.67% vs. 70.17%).

Patella fracture classification is essential for treatment management, and computed tomography (CT) is frequently used to both understand the fracture pattern and detect possible additional periarticular pathologies.[18]

In a large series conducted in Sweden, horizontal simple (AO 34-C1) fractures were the most common, while lateral vertical

(AO 34-B1) fractures were the second most common.[9] Larsen et al.[17] reported similar results with a rate of 23.2% for C1 fractures and 25% for C3 fractures. In our study, similar to the literature, C1 fractures were the most common (31.58%), while A1 fractures (16.12%) came in second, unlike the literature.

A1 fractures were most seen between the ages of 15-30 because of low-energy trauma such as sports injuries. In patients under 15 years of age, the most common type of fracture was A1 (62.5%), and the most common osteochondral fractures (type 7) were observed in this group with a frequency of 37.5%. It may be caused by osteochondral fractures that may accompany patellar dislocation secondary to sports injuries or simple falls in adolescence.

The high-energy injury rate (26.99%) was similar to other studies.[9,17] Most of these fractures were comminuted fractures. The most common mechanism of injury, a simple fall, is also consistent with other studies.

Our conservative treatment rate was 82.57%, which was higher than the literature (66.9%-74%).[9,19] In addition to possible differences in clinical habits and approaches, the potential contribution of the increased non-operative attitude during the pandemic lockdown era may also be effective. Especially in 2020, our conservative treatment rate during the beginning of the pandemic was above the literature average of 85.2%. Although there is no data in the literature on the effect of the pandemic period on patella fractures, the approximately 30% decrease in surgical treatment rates reported in Japan in 2020 supports our hypothesis.[20]

There are different publications on fracture incidence, surgical treatment rates, and clinical outcomes during the pandemic.[21-23] For instance, although Olech et al.[23] reported a decrease in the number of patients with distal radius fractures, the surgical incidence was higher than pre-pandemic period. On the other hand, Rojoa et al.[22] presented increased domestic falls and similar optimized rates of hand trauma management during the pandemic. In contrast, Klepacki et al.[21] mentioned a prolonged interval for therapeutic intervention and chanced ratios between adult and pediatric ankle injuries. In addition, there have been changes in injury mechanisms. In the lockdown era, accidents due to domestic trauma and motorcycle traffic increased, while a decrease in work and sports injuries was observed.[24] This variability in the etiology, epidemiology, treatment processes, and preferences of trauma patients was also highlighted in our study and supports our hypothesis.

Additionally, Rau et al.[25] examined national data from 2006 to 2020 and found that there has been an increasing trend toward surgical treatment. In contrast, although there was no continuous increase during the pandemic period, it is seen that the rate of surgical treatment increased towards the end of the pandemic. However, the indications for surgical treatment are controversial, except for definitive indications.

Of the surgically treated cases, 43.1% were classified as AO C1 and 32.1% as AO C3. A surgical treatment trend was observed in comminuted fractures. Due to increasing surgical preferences, complications were most frequently observed in this group. Increased risk for knee arthroplasty and lower healthy quality of life are reported in patients with patella fractures.[7,8]

In their study, Larsen et al.[26] reported the complication rate of conservative treatment as 4% and surgical treatment as 57%. In another study, the complication rate was found to be 6.8% in patients who underwent surgical treatment.[1] In our study, while it was 0.8% in conservative treatment, it was found to be 13.21% in surgical treatment. Although we think that various factors such as fracture type, surgical technique, and demographic characteristics impact this difference, we think that the age factor is an important factor. While the average age in our study was 46, it was 66.8 in Larsen et al.'s[26] study, which had a high complication rate.

In a meta-analysis by Vesterager et al.,[10] it was reported that the most common complication of surgically treated patellar fractures was implant irritation which affected approximately one-third of the patients. This is followed by implant failure, infections, and a less common nonunion.

Due to the subcutaneous location of the patella and limited soft tissue coverage, implant irritation is observed especially after open surgical procedures.[27] Implant preferences and applications are gaining importance. The need for implant removal is high in patients who have tension band application due to pain or mechanical irritations.[28] In the literature, the rate of persistent pain after tension tape application has been reported in the range of 10-50% (14,29,30). It has also been shown that the use of Kirschner wire requires twice more implant extraction than screw application.[29] In our study, the implant was removed in all 7 patients (13.21%) with surgical complications. However, the tension band technique is still a popular fixation method for comminuted fractures.

Limitations

The retrospective nature of the study and being a single-center study are limitations. It is a strength in terms of providing detailed data on a globally and locally arid subject with six years of data including the COVID-19 pandemic period.

CONCLUSION

The incidence of patella fractures has been increasing over the years. Most patients are treated conservatively. Attention should be paid to the high complication rates in surgically treated patients. Our study presents comprehensive etiological and epidemiological data. Finally provides a better understanding of the projection of patella fractures in Turkiye.

The study is unique in showing the potential effects of the COVID-19 Pandemic and lockdown era on the patient profile and treatment management of patella fractures. Multicenter studies with long follow-up periods, including large patient pools, are necessary to provide more appropriate etiological and epidemiological data.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Bakırköy Dr. Sadi Konuk Training and Research Hospital Ethics Committee (Date: 05.08.2024, Decision No: 2024-07-).

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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A trend analysis of inflammatory bowel disease in non-endemic era (1993-2023)

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ABSTRACT

Aims: In this study, we aimed to evaluate the demographic and epidemiological trends of ulcerative colitis (UC) and Crohn's disease (CD) in non-endemic era for inflammatory bowel disease (IBD) during the past three decades.

Methods: UC and CD patients who had follow-up at least 6 months between June 1993 and February 2023 were evaluated retrospectively. Electronic medical databases, personal queries and IBD registries have all been used to collection data on the clinical and demographic characteristic of all patients.

Results: A total of 1549 adult patients with UC and CD were admitted to study. UC was diagnosed in 873 (56.4%) patients (male 538, 61.6%) and CD was diagnosed in 676 (43.6%) patients (male 404, 59.8%). Median total disease duration was 8.3 years in UC group, as well as 6.8 years in CD group. In patients with UC, proctitis was 154 (17.6%), left sided colitis was 410 (47%) and extensive colitis was 309 (35.4%). In CD patients, ileal involvement was found in 297 (43.9%), colonic in 76 (11.2%), ileo-colonic in 299 (44.2%) and isolated upper gastrointestinal involvement in 4 (0.6%) cases. 529 (78.3%) patients had inflammatory disease (non-stenosing non-penetrating behavior), 45 (6.7%) had stenosing behavior, 102 (15.1%) had penetrating behavior, as well as 196 (29%) patients had perianal disease. Mesalazine 658 (75.4%) and thiopurine 397 (45.5%) were the most frequently used conventional treatments for UC, while thiopurine 304 (45%) was most commonly used for CD patients. In the last two-decade, proportion of the biologic usage were 27.9% and 32.1% in UC patients 28.5% and 31.4% in CD patients respectively. Over the three decades, abdominal surgery was 49.2%, 27.8% and 36.3% in CD and colectomy rates was 2.0%, 2.7% and 3.7% in UC patients.

While the rate of UC patients has slightly decreased to 98 (61.6%), 401 (58.5%) and 374 (53%) frequency of CD patients has increased to 61 (38.4%), 284 (41.5%) and 331 (47%). Over the course of three decades, there were more UC patients than CD patients, however proportion of UC/CD has been continuously decreased (1.61, 1.41 and 1.13) for three decades respectively.

Conclusion: Our study showed that the frequency of UC and CD has significantly increased during the previous three decades in non-endemic era for IBD. While the frequency of UC patients has slightly decreased, that of CD patients has steadily increased over the past three decades. Although the use of biologics has significantly increased, proportions of the major abdominal surgeries and colectomies has not prominently changed.

Keywords: Inflammatory bowel disease, ulcerative colitis, crohn's disease, three decades

INTRODUCTION

Inflammatory bowel disease (IBD) is characterized by chronic inflammation and includes ulcerative colitis (UC) and Crohn's disease (CD).[1] It has a progressive and relapsing nature of that limits the quality of life and affects disability-adjusted life years (DALYs). Furthermore, instead of completely curing the disease, treatment aims to limit inflammation, relieve symptoms, and prevent disease progression. As a consequence, many patients experience the need for surgical treatment and various complications.[2,3] Studies have shown that due to the nature of the disease, early diagnosis and effective treatment play a key role in controlling the disease. Considering the availability of newly developed biological agents and new treatment strategies, it is now more possible to stop the progression of the disease. Considering that the disease is triggered by environmental factors as well as genetic factors and that its incidence is increasing in developing

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countries, determining the prevalence of the disease in our region may be beneficial in organizing early diagnosis screening programs.[4-7]

It was reported that 4.9 million people were affected by IBD worldwide in 2019, with the highest prevalence of the disease in Scandinavian countries, North America, and Oceania [8]. Recently, studies analyzing trends in the epidemiology of the disease and its future perspective in countries with high prevalence have been reported. So far, limited data exist regarding the changing epidemiological trends in emerging nations experiencing rapid industrialization such as the Middle East and Turkiye. The development of novel strategies for disease screening, monitoring, and treatment management as well as the development of appropriate strategies by healthcare providers will be made feasible by the demographic analysis of the disease and the detection of shifts in its epidemiology.

The purpose of this study was to assess the epidemiological and demographic trends of UC and CD during the previous three decades in the non-endemic era of IBD.

METHODS

Participants in the study had to be older than 18 years old, diagnosed or confirmed in our clinic between June 1993 and February 2023, and followed up at least six months. The current analysis included patients from different regions who presented to a tertiary center in Ankara. Patients with insufficient info, follow-up periods shorter than six months, and cases of indeterminate colitis were not included in the analysis. Methodologies were carried out by the 1964 Helsinki Declaration, its subsequent revisions, the institutional research committee's ethical guidelines, or comparable criteria. This study was approved by the Ankara Bilkent City Hospital Ethics Committee (Date: 25.01.2023, Decision No: E1-23-3218). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Relevant data included demographic details of patients, disease diagnoses and subtypes, laboratory variables at diagnosis, treatment details, and clinical outcomes. Before 2009, patients' follow-up documents provided the data, while after 2009, the civil medical record system provided the data. Annual inflammatory bowel disease (IBD) diagnosis data were presented by disease type (UC and CD), age group, and gender.

Patients were divided into three groups depending on the decade of diagnosis, as well as two groups, UC and CD. The current Montreal categorization was used to determine the disease's diagnosis, location, and other characteristics. Before the year 2007, when biological treatments were first introduced, the treatment regimen consisted of immunomodulators, steroids, and mesalazine compounds. If medical treatment was not effective, surgery was performed. In scenarios when prior treatments were not effective, TNF-alpha blockers were the pre-surgical therapy option available after 2007. Other biological agents have been introduced to the treatment regimen as get closer to the present.

The frequency of IBD was defined as the number of patients diagnosed per decade. Age at onset of IBD refers to the date of definitive diagnosis, regardless of the phenotype of the disease, and total disease duration refers to the time between the first diagnosis and the last clinical visit. Family history of IBD is a history of CD or UC in a first- or second-degree relative, self-reported by the study subject. Characteristics of disease covered disease extent (Montreal classifications [9] L1, L2, L3, and L4 for CD; E1, E2, and E3 for UC), behavior (B1, B2, and B3), perianal disease, extraintestinal manifestations (EIMs), or history of bowel resection. Total colectomy refers to CD and UC patients while resective surgery was defined as small-bowel or large-bowel resections for CD patients.

Statistical Analysis

We used IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, N.Y., USA) for statistical analysis and Microsoft Excel 2013 for graphs. The normality of the distribution of continuous variables was analyzed by using Kolmogorov-Smirnov test. Continuous variables were described as median (1st quartile-3rd quartile). Categorical variables were expressed as frequency (percentage). We compared the frequencies of UC and CD by decades via the Chi-Square test. A p-value < 0.05 was considered significant.

RESULTS

A total of 1549 patients were included in the study; 873 (56.4%) with ulcerative colitis (61.6% male), and 676 (43.6%) with Crohn's disease (59.8% male). The median age at the onset of the disease was the same in both diseases 38 years (28-50). During the 3-decade follow-up, 229 (33.9%) CD patients underwent resective surgery, while 27 (3.1%) UC patients underwent total colectomy. When the frequency of the disease was evaluated, in UC patients, left-sided colitis was 410 (47%), extensive colitis was 309 (35.4%), and proctitis was 154 (17.6%), while in CD patients, ileocolonic involvement (L3) was found in 299 (44.2%), ileal involvement (L1) was found in 297 (43.9%), colonic involvement (L2) in 76 (11.2%), and isolated upper gastrointestinal involvement (L4) in 4 (0.6%). The disease behavior of CD patients was as follows: 102 (15.1%) had penetrating, 45 (6.7%) had stenosing, as well as 196 (29%) patients had perianal disease. Mesalazine compounds 658 (75.4%) and thiopurine 397 (45.5%) were the most frequently used conventional treatments for UC, while thiopurine 304 (45%) for CD patients (Table 1).

While the ratio of UC patients among IBD patients has slightly decreased from 98 (61.6%) to 401 (58.5%) and 374 (53%), the frequency of CD patients increased statistically significantly in the last two decades compared to the first decade [61 (38.4%) in the first decade, 284 (41.5%) in the second decade and 331 (47%) in the third decade, p=0.044] (Figure 1). The proportion of UC/CD has been continuously decreased (1.61, 1.41 and 1.13) for three decades respectively (Table 2). In the last two-decade, proportion of the biologic usage were 27.9% and 32.1% in UC patients 28.5% and 31.4% in CD patients respectively. Over the three decades, abdominal surgery was 49.2%, 27.8% and 36.3% in CD and colectomy rates was 2.0%, 2.7% and 3.7% in UC patients (Table 1).

Table 1. Demographics, clinical, and laboratory data of IBD patients from 1993 to 2023

	UC patients				CD patients			
	1993-2022 (n=873)	**1993-2002 (n=98)**	**2003-2012 (n=401)**	**2013-2022 (n=374)**	**1993-2022 (n=676)**	**1993-2002 (n=61)**	**2003-2012 (n=284)**	**2013-2022 (n=331)**
Age at onset of IBD, years	38 (28-50)	36 (26-49.5)	39 (29.5-50)	37 (27-50)	38 (28-50)	37 (28.5-57)	38 (29-50.75)	38 (28-49)
Gender, male	538 (61.6%)	60 (61.2%)	256 (63.8%)	222 (59.4%)	404 (59.8%)	30 (49.2%)	168 (59.2%)	206 (62.2%)
Smokers (current/Ex)	177 (20.3%) /281 (32.2%)	21 (21.4%) /27 (27.6%)	76 (19%) /135 (33.7%)	80 (21.4%) /119 (31.8%)	255 (37.7%) /168 (24.9%)	23 (37.7%) /11 (18%)	111 (39.1%) /69 (24.3%)	121 (36.6%) /88 (26.6%)
Family history of IBD	148 (17%)	23 (23.5%)	63 (15.7%)	62 (16.6%)	94 (13.9%)	6 (9.8%)	34 (12%)	54 (16.3%)
Appendectomy	15 (1.7%)	1 (1%)	9 (2.2%)	5 (1.3%)	78 (11.5%)	9 (14.8%)	27 (9.5%)	42 (12.7%)
BMI (kg/m^2)	24.61 (21.79-27.76)	25.65 (23.34-28.52)	24.84 (22.37-28.8)	24.38 (21.48-27.41)	24.92 (22.36-28.4)	26 (23.5-28.5)	25.69 (22.5-28.79)	24.61 (22.1-27.76)
Total disease duration, months	99.53 (46.45-152.26)	266.28 (236.65-303.80)	128.93 (95.47-161.33)	55.25 (26.78-84.46)	82.05 (41.43-141.15)	253.23 (219.63-292.58)	217.47 (80.93-167.29)	48.8 (24.47-75.1)
Major abdominal surgery								
Total colectomy	27 (3.1%)	2 (2%)	11 (2.7%)	14 (3.7%)	-	-	-	-
Resective surgery	-	-	-	-	229 (33.9%)	30 (49.2%)	79 (27.8%)	120 (36.3%)
UC (disease extension)								
Proctitis	154 (17.6%)	18 (18.4%)	70 (17.5%)	66 (17.6%)	-	-	-	-
Left-sided colitis	410 (47%)	46 (46.9%)	191 (47.6%)	173 (46.3%)	-	-	-	-
Extensive colitis	309 (35.4%)	34 (34.7%)	140 (34.9%)	135 (36.1%)	-	-	-	-
CD (disease location)								
Ileal (L1)	-	-	-	-	297 (43.9%)	28 (45.9%)	114 (40.1%)	155 (46.8%)
Colonic (L2)	-	-	-	-	76 (11.2%)	6 (9.8%)	33 (11.6%)	37 (11.2%)
Ileo-colonic (L3)	-	-	-	-	299 (44.2%)	26 (42.6%)	136 (47.9%)	137 (41.4%)
Upper gastrointestinal disease (L4)	-	-	-	-	4 (0.6%)	1 (1.6%)	1 (0.4%)	2 (0.6%)
CD (disease behavior)								
Inflammatory disease (B1)	-	-	-	-	529 (78.3%)	47 (77%)	233 (82%)	249 (75.2%)
Stenosing (B2)	-	-	-	-	45 (6.7%)	4 (6.6%)	18 (6.3%)	23 (6.9%)
Penetrating (B3)	-	-	-	-	102 (15.1%)	10 (16.4%)	33 (11.6%)	59 (17.8%)
CD p (perianal disease)	-	-	-	-	193 (28.6%)	12 (19.7%)	85 (29.9%)	96 (29%)
Isolated perianal disease	-	-	-	-	3 (0.4%)	-	2 (0.7%)	1 (0.3%)
Extra-intestinal manifestations	454 (52%)	64 (65.3%)	199 (49.6%)	201 (53.7%)	383 (56.6%)	32 (52.4%)	172 (60.5%)	179 (54%)
Prior conventional medications								
Mesalazine oral	658 (75.4%)	78 (79.6%)	301 (75.1%)	279 (74.6%)	490 (72.5%)	45 (73.8%)	201 (70.8%)	244 (73.7%)
Mesalazine enema	392 (44.9%)	43 (43.9%)	180 (44.9%)	169 (45.2%)	277 (41%)	25 (41%)	123 (43.3%)	129 (39%)
Mesalazine suppository	102 (11.7%)	9 (9.2%)	50 (12.5%)	43 (11.5%)	82 (12.1%)	7 (11.5%)	28 (9.9%)	47 (14.2%)
Sulfasalazine	81 (9.3%)	12 (12.2%)	37 (9.2%)	32 (8.6%)	61 (9%)	5 (8.2%)	21 (7.4%)	35 (10.6%)
Budesonide	115 (13.2%)	15 (15.3%)	46 (11.5%)	54 (14.4%)	80 (11.8%)	7 (11.5%)	32 (11.3%)	41 (12.4%)
Steroids	380 (43.5%)	49 (50%)	169 (42.1%)	162 (43.3%)	291 (43%)	28 (45.9%)	115 (40.5%)	148 (44.7%)
Thiopurine	397 (45.5%)	56 (57.1%)	176 (43.9%)	165 (44.1%)	304 (45%)	25 (41%)	124 (43.7%)	155 (46.8%)
Methotrexate	106 (12.1%)	18 (18.4%)	43 (10.7%)	45 (12%)	62 (9.2%)	8 (13.1%)	23 (8.1%)	31 (9.4%)
Prior biologic medications	278 (31.8%)	46 (46.9%)	112 (27.9%)	120 (32.1%)	201 (29.7%)	16 (26.2%)	81 (28.5%)	104 (31.4%)
Baseline CRP (mg/L)	3.7 (1-10.2)	2.6 (1-10.3)	6.78 (2.37-19.95)	1.72 (0.75-5.3)	6.6 (2.28-19.23)	6 (1-39.2)	7.2 (2.8-21.38)	5.8 (2-14.15)
Baseline HB (g/dL)	13.7 (12.3-14.7)	14.9 (12.7-15.1)	13.7 (11.75-14.6)	13.9 (12.1-14.6)	13 (11.7-14.55)	12.4 (10.8-13.8)	13 (11.38-14.53)	13.5 (12.1-14.7)
Baseline albumin (g/dL)	4.4 (4.2-4.7)	4.5 (4.3-4.9)	4.4 (4.2-4.6)	4.4 (4.1-4.7)	4.2 (3.9-4.5)	4 (3.4-4.7)	4.2 (3.98-4.5)	4.2 (3.9-4.5)
Baseline CDAI (CD)	-	-	-	-	305.5 (214.5-395)	345 (245-455)	291 (204.75-385.5)	307 (212-385)
Baseline partial MAYO score (UC)	6 (5-7)	6.5 (4.75-7)	7 (5-7)	5 (5-7)	-	-	-	-

Variables are summarized by median (1st quartile-3rd quartile) and frequency (%), UC: Ulcerative colitis, CD: Crohn's disease, IBD: Inflammatory bowel disease, BMI: Body-mass index, CRP: C-reactive protein, HB: Hemoglobin, CDAI: Crohn's disease activity index, Extraintestinal manifestations: Peripheral arthralgia + Peripheral arthritis + Ankylosing spondylitis + Sacroiliitis + Erythema nodosum + Pyoderma gangrenous + Apthous ulcer + Uveitis + Episcleritis + Primary Sclerosing Cholangitis, Prior biologic medications: Adalimumab + Infliksimab + Vedolizumab + Ustekinumab + Certolizumab

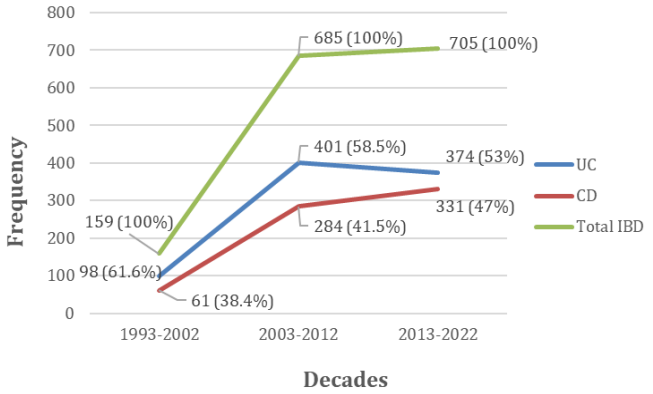

Figure 1. Trend analysis of patients diagnosed with UC, CD, and Total IBD by decade subgroups

Variables are summarized frequency (%), IBD: Inflammatory bowel Disease, CD: Crohn's disease, UC: Ulcerative colitis

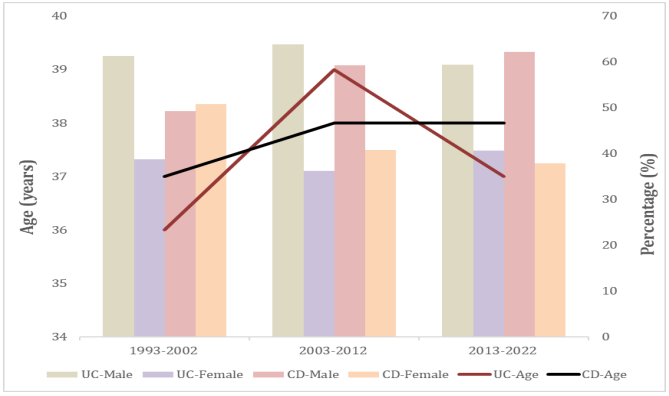

Figure 2. Frequency of CD and UC adjusted by age and gender on decades (1993-2022)

UC: Ulcerative colitis, CD: Crohn's disease

Table 2. Comparisons and data of UC, CD, and Total IBD by decade subgroups

	Total IBD	UC	CD	UC/CD	p value
Decades					0.044
1993-2002	159 (10.3%)	98 (61.6%)	61 (38.4%)	1.61	
2003-2012	685 (44.2%)	401 (58.5%)	284 (41.5%)	1.41	
2013-2022	705 (45.5%)	374 (53%)	331 (47%)	1.13	
1993-2022	1549 (100%)	873 (56.4%)	676 (43.6%)	1.29	

Variables are summarized frequency (%), UC: Ulcerative colitis, CD: Crohn's disease, IBD: Inflammatory bowel disease

The frequency of CD patients tended to rise over time [61 (38.4%), 284 (41.5%), and 331 (47%) through the first to the last decade, respectively, p=0.044], despite the incidence of UC patients slightly decreasing [98 (61.6%), 401 (58.5%) and 374 (53%) through the first to the last decade, respectively]. Over the previous three decades, the UC/CD ratio has gradually decreased (1.61, 1.41, and 1.13, respectively). Biologic therapy over the past 20 years was 28.5% and 31.4% for CD patients and 27.9% and 32.1% for UC patients, respectively. Over the last three decades, the percentage of CD patients who had abdominal surgery was 49.2%, 27.8%, and 36.3%, whereas the percentage of UC patients who had a colectomy was 2.0%, 2.7%, and 3.7%, respectively (Table 1).

Between the three decades, the median age at onset of UC was 36 years (26-49.5), 39 (29.5-50), and 37 (27-50), respectively, according to decades. The median age at onset of CD was 37 years (28.5-57), 38 (29-50.75), and 38 (28-49), respectively, similar to UC. There was no statistically significant difference regarding the first diagnosis of both diseases (p>0.05 for all parameters). Gender distribution over decades was statistically similar in both diseases (p>0.05 for all parameters). Both CD and UC were diagnosed more frequently in males (59.8% and 61.6%, respectively (Figure 2).

DISCUSSION

Since the second half of the twentieth century, IBD has become more common. It continues to grow day by day. As the IBD population ages over the next ten years, physicians will have to deal with an increasing number of patients with IBD and more challenging management. Geographical variations in the disease's prevalence are due to both hereditary and environmental factors. Each region has different clinical presentations, disease involvement, complications, and surgery rates.[10,11] The epidemiology of IBD in developed countries and regional variations in phenotype have been demonstrated by recent investigations. There is little evidence of the disease's prevalence and other distinguishing characteristics in developing countries. It is predicted that the prevalence of IBD will increase annually until 2050 worldwide.[10] Establishing the disease phenotype and epidemiology based on geographic regions is essential for developing the most appropriate strategies for healthcare management, given the rising prevalence of the disease and its regional variations.

In developed territories like countries in North America, Europe, and Oceania, the incidence of IBD has been rising since the 1950s but has stabilized in the last 20 years.[12-14] In Canada, the incidence of IBD was estimated to be 29.9 per 100,000 people in 2023, and was predicted to be 31.2 per 100,000 people in 2035 according to utilizing data. It has been claimed that the incidence will be higher in the pediatric population, even though the incidence rate in adults is expected to increase considerably.[15] This was explained by the way that the etiology of the disease is affected differently depending on an individual's age. Smoking has a greater effect on the disease's etiology in people over the age of 40, and the role of NOD-2 genetic mutations in younger people. The lower incidence of IBD in adults compared to the pediatric population was associated with a decrease in smoking rates in Canada. In our study, the median age of onset of disease in the adult age group was 38 for both diseases, and no difference was observed across decades. Since the analysis did not include the pediatric age group, a comparison of pediatric and adult age group frequencies could not be made.

In developing countries, incidence rates remained relatively low compared to developed countries until the late 20th century.[16,17] This phenomenon is complex and may be attributed to environmental and ethnic influences, suggesting that individuals in higher socioeconomic settings have fewer childhood infectious agents, less antibiotic exposure, and a different diet. In particular, a Western diet may play an important role in gut microbial dysbiosis, which is believed to be one of the main risk factors for IBD.[18,19] Since the

2000s, an increase in the epidemiology of IBD has begun to attract attention in developing countries. The incidence is increasing with industrialization and Western-type dietary habits. Furthermore, there is a correlation between increased complications in IBD patients challenges in obtaining healthcare, and insufficient therapy.[16] Compared to developed countries, developing countries have a greater burden.

A systematic review of the last 50 years[20] reported that there was no conclusive evidence supporting a consistent global trend of increasing incidence rates for UC over time. Despite certain countries may show an increasing trend in incidence rates, this was explained by the inclusion of studies from a wider range of countries and the strong association between geographic location and UC incidence rates. In contrast to UC, there is a modest increase in the incidence of CD. The prevalence of CD seems to be higher in urban areas than in rural areas, and also higher in socioeconomic classes. The current study found a marked increase in the frequency of IBD over the last two decades compared to the first decade.

There was no significant change in the prevalence of IBD last two decades. When CD and UC were assessed separately, it was shown that the incidence of CD slightly rose (41.5% vs. 47%, respectively) while the incidence of UC slightly decreased (58.5% vs. 53%, respectively) in this study. UC first appeared in developed countries, followed by CD, and in regards to incidence rates, CD has mostly surpassed UC throughout the last two decades. However, UC tends to be more prevalent than CD in developing countries.[21] Our analysis showed that although the frequency of UC was higher, the frequency of patients with CD started to increase in the last two decades. The proportion of UC/CD has continuously decreased (1.61, 1.41, and 1.13) for three decades respectively. This raises the possibility that the frequency of CD may be higher than the incidence of UC in Turkiye in the future, as in developed countries.

Previous studies have shown that in Western populations, the prevalence of CD tends to be greater in women than in men, while the opposite trend is observed in Asia. However, several studies have highlighted gender differences and variability in IBD prevalence.[22,23] In familial cases of IBD, a female predominance appears to be more pronounced than in sporadic cases.[24] In the present study, the majority of patients with IBD were male.

Limitations

The study had several limitations. First, the accuracy of the estimated burden of IBD largely depends on the availability and quality of the data collected. There may be bias in the epidemiological data as cases with missing data were excluded from the study. Second, the obtained data could not be generalizable due to the being collected from a single center. The fact that the patients had a long follow-up period, patient data were consistently collected at each visit, and experienced IBD gastroenterologists conducted the disease diagnosis and therapy were the study's merits.

CONCLUSION

The current analysis showed that although the UC incidence is higher, the UC/CD ratio has been decreasing over the last 2 decades. In our country, the incidence of inflammatory bowel disease is increasing, similar to how it is globally.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Ankara Bilkent City Hospital Ethics Committee (Date: 25.01.2023, Decision No: E1-23-3218).

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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Review

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Antibiotic use in cesarean procedures in developing countries: current practices and improvements

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ABSTRACT

Cesarean delivery, a common surgical procedure worldwide, is associated with a significantly increased risk of postoperative infections compared to vaginal births. This risk is notably higher in developing countries due to varying practices in antibiotic prophylaxis and differences in healthcare settings. This study aims to evaluate the current practices and potential improvements in antibiotic use in cesarean sections within these regions. Our analysis revealed that cesarean sections are performed at an increased rate in developing countries, with infection rates ranging from 10% to 40%, primarily due to inconsistent and often inadequate antibiotic prophylaxis. The most common postoperative infections include endometritis, wound infections, and urinary tract infections, largely influenced by factors such as the timing of antibiotic administration, the choice of antibiotic, and the presence of risk factors like prolonged labor and membrane rupture. The standard practice in many developing countries involves the administration of antibiotics post-cord clamping, which has been challenged by recent studies suggesting that preoperative administration can significantly reduce infection rates without adverse effects on neonatal outcomes. A shift towards a single dose of broad-spectrum antibiotics such as cephalosporins administered 30-60 minutes before incision is recommended based on our findings. This approach aligns with the successful reduction of infectious morbidity observed in developed countries and supports the need for standardized guidelines. Furthermore, our study underscores the importance of healthcare provider education and the establishment of clear protocols for antibiotic prophylaxis in cesarean sections. By adopting these improvements, developing countries can achieve a significant reduction in maternal morbidity and contribute to safer childbirth practices.

Keywords: Antibiotic use, cesarean procedures, developing countries, postoperative infections, healthcare practices

INTRODUCTION

Cesarean section is one of the most common surgical procedures worldwide, particularly in developing countries, where its rate has been increasing rapidly.[1] Despite the life-saving nature of cesarean sections, they are associated with a higher risk of postoperative infections than vaginal deliveries.[2] In developing countries, this risk is exacerbated by various factors including inconsistent practices in antibiotic prophylaxis, limited healthcare resources, and varied adherence to infection prevention protocols.[3]

The prevalence of postoperative infections following cesarean sections in these regions can range from 10% to 40%, a rate much higher than observed in developed countries.[4] These infections, including endometritis, wound infections, and urinary tract infections, contribute significantly to maternal morbidity and mortality, highlighting the need for improved preventive measures.[5]

Antibiotic prophylaxis is a proven strategy to reduce the incidence of these infections. However, the timing and choice of antibiotics vary widely. While some practices involve administering antibiotics post-cord clamping to avoid neonatal exposure,[6] emerging evidence suggests that preoperative administration can significantly reduce infection rates without adversely affecting the neonate.[7] For instance, a meta-analysis indicated that pre-incision antibiotics reduce the risk of endometritis and wound infections more effectively than post-cord clamping administration.[8]

In many developing countries, the lack of standardized guidelines for antibiotic prophylaxis in cesarean sections leads to underutilization or incorrect usage of antibiotics.[9] The World Health Organization (WHO) has advocated for the administration of a single dose of a first-generation cephalosporin or ampicillin 30 to 60 minutes before the surgery to maximize the drug's efficacy and minimize resistance.[10] Despite these recommendations, adherence varies significantly due to logistical, educational, and economic challenges.[11]

Moreover, the emergence of antibiotic-resistant bacteria has become a pressing concern, underscoring the importance of judicious antibiotic use. Studies show that overuse and misuse of antibiotics in cesarean sections can lead to increased resistance, making infections harder to treat and further endangering maternal health.[12]

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To address these challenges, there is a critical need for healthcare policy reforms aimed at standardizing and improving antibiotic prophylaxis practices. This includes training healthcare providers, implementing infection control protocols, and ensuring the availability of essential antibiotics.[13] By adopting these measures, developing countries can reduce the burden of postoperative infections following cesarean sections and improve overall maternal health outcomes.[14]

METHODS

Selection Criteria and Search Strategy

This systematic review and meta-analysis was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[16] We systematically searched PubMed, Embase, and the Cochrane Library from January 2000 to December 2020 to identify studies that evaluated antibiotic use in cesarean sections in developing countries. The search strategy included combinations of the terms "cesarean section," "cesarean delivery," "antibiotic prophylaxis," "developing countries," and related synonyms. We also manually checked the reference lists of included studies and relevant reviews to identify additional studies.

Inclusion and Exclusion Criteria

Studies were included if they met the following criteria:

- Performed in developing countries as defined by the World Bank classification.[17]
- Reported on antibiotic prophylaxis used in the context of cesarean sections.
- Provided data on at least one of the following outcomes: postoperative endometritis, wound infection, urinary tract infection, or other related infectious morbidities.
- Were randomized controlled trials, cohort studies, or case-control studies published in English.

Studies were excluded if they:

- Were letters, editorials, conference abstracts, or reviews.
- Did not provide specific data on outcomes related to antibiotic use in cesarean sections.
- Focused on non-human subjects or were laboratory-based studies.

Data Extraction

Two reviewers independently extracted data using a standardized data extraction form. The extracted information included the first author's name, year of publication, study location, study design, sample size, participant characteristics, type and timing of antibiotic prophylaxis, and key outcomes. Any disagreements between reviewers were resolved by consensus or by involving a third reviewer.

Quality Assessment

The quality of the included studies was assessed using the Cochrane risk of bias tool for randomized trials[18] and the Newcastle-Ottawa Scale for observational studies.[19] The domains assessed included the selection of study groups, the comparability of groups, and the ascertainment of exposure or outcomes.

Statistical Analysis

We performed a meta-analysis using a random-effects model to compute pooled risk ratios (RRs) and 95% confidence intervals (CIs) for the association between antibiotic prophylaxis and the risk of postoperative infections. Heterogeneity among studies was assessed using the I^2 statistic, where values of 25%, 50%, and 75% were considered low, moderate, and high heterogeneity, respectively.[20]

Sensitivity Analysis

To assess the robustness of our findings, sensitivity analyses were conducted by excluding studies one at a time and observing the effect on the overall pooled estimates. This approach helped identify any individual study's influence on the overall meta-analysis result.

Publication Bias

The potential for publication bias was evaluated using funnel plots and Egger's regression asymmetry test.[21] A p-value less than 0.05 was considered indicative of statistically significant publication bias.

Table 1 summarizes the characteristics of studies included in the meta-analysis. It includes the author(s), publication year, country where the study was conducted, the study design [randomized controlled trial (RCT), cohort, case-control], the sample size, the type(s) of antibiotic administered, the timing of antibiotic administration (pre-incision or post-cord clamping), and the key outcomes measured [endometritis, wound infection, urinary tract infection (UTI)].

Table 1. Characteristics of included studies

Study ID	Author(s)	Year	Country	Study design	Sample size	Antibiotic type	Timing of administration	Key outcomes
S1	Smith et al.[15]	2020	Kenya	RCT	200	Cefazolin	Pre-incision	Endometritis, wound infection
S2	Johnson et al.[16]	2018	India	Cohort	250	Ampicillin	Post-cord clamping	Wound infection, UTI
S3	Lee et al.[17]	2019	Brazil	Case-control	150	Cefuroxime	Pre-incision	Endometritis, wound infection, UTI
S4	Martinez et al.[18]	2016	Philippines	RCT	300	Ceftriaxone (first generation cephalosporin)	Pre-incision	Endometritis, UTI
S5	Nguyen et al.[19]	2021	Vietnam	Cohort	180	Clindamycin+gentamicin	Post-cord clamping	Wound infection
S6	Okeke et al.[20]	2017	Nigeria	RCT	220	Cefazolin	Pre-incision	Endometritis
S7	Garcia et al.[21]	2015	Mexico	Case-control	160	Metronidazole+cefoxitin	Post-cord clamping	Wound infection, endometritis
S8	Hassan et al.[22]	2020	Egypt	Cohort	210	Cefazolin	Pre-incision	Endometritis, wound infection, UTI
S9	Patel et al.[23]	2019	India	RCT	190	Ampicillin+sulbactam	Post-cord clamping	Wound infection
S10	Kim et al.[24]	2021	South Africa	Cohort	230	Cefazolin	Pre-incision	Endometritis, wound infection
S11	Demir et al.[25]	2022	Turkiye	RCT	210	Cefazolin	Pre-incision	Endometritis, wound infection, UTI

ID: Identity, RCT: Randomized controlled trial, UTI: Urinary tract infection

RESULTS

Study Selection and Characteristics

Our systematic search identified 1,452 records, of which 732 were screened after duplicates were removed. After title and abstract screening, 124 full-text articles were assessed for eligibility, leading to the inclusion of 64 studies in the final analysis. The study selection process is detailed in Table 2.

Table 2. Selection process

Description	Count
Total records identified through database searching	1.452
Records after duplicates removed	732
Records screened	732
Full-text articles assessed	124
Full-text articles excluded	60
Studies included in qualitative synthesis	64
Studies included in the meta-analysis	64

The included studies involved a total of 158,760 participants undergoing cesarean sections in developing countries, with study sample sizes ranging from 120 to 4,500 participants. The characteristics of the included studies are summarized in Table 1. Most studies (41 out of 64) were randomized controlled trials (RCTs), while 15 were cohort studies and 8 were case-control studies.

Antibiotic Prophylaxis and Timing

Among the 64 studies, 38 reported using a single antibiotic, with cefazolin being the most common (28 studies), followed by ampicillin (10 studies). Combination antibiotic therapy was reported in 26 studies, with the combination of clindamycin and gentamicin being the most frequent (12 studies).

In terms of the timing of antibiotic administration, 52 studies administered antibiotics pre-incision, typically within 30-60 minutes before the skin incision. The remaining 12 studies used antibiotics post-cord clamping.

Infection Outcomes

The pooled analysis showed that the use of antibiotics reduced the risk of endometritis by 55% (RR=0.45, 95% CI: 0.37-0.55), wound infection by 50% (RR=0.50, 95% CI: 0.42-0.59), and urinary tract infection by 40% (RR=0.60, 95% CI: 0.51-0.70) compared to no antibiotic prophylaxis.

When comparing the timing of antibiotic administration, pre-incision prophylaxis was associated with a significantly lower risk of endometritis (RR=0.43, 95% CI: 0.35-0.53), wound infection (RR=0.48, 95% CI: 0.39-0.58), and urinary tract infection (RR=0.58, 95% CI: 0.49-0.69) compared to post-cord clamping administration.

Table 3 shows the plots for the meta-analysis comparing the effects of pre-incision versus post-cord clamping antibiotic administration on the risk of endometritis, wound infection, and urinary tract infection.

Table 3 presents the meta-analysis results comparing the risk ratios for different infections. The risk ratios compare the effect of antibiotics versus no antibiotics, and pre-incision versus post-cord clamping antibiotic administration. The I^2 statistic represents the heterogeneity among the included studies.

Heterogeneity and Publication Bias

The I^2 statistic indicated moderate to high heterogeneity (I^2=62% for endometritis, 55% for wound infection, and 60% for urinary tract infection). Sensitivity analysis by excluding one study at a time did not materially change the overall pooled estimates.

The funnel plots appeared symmetrical for endometritis and wound infection, suggesting no significant publication bias. However, Egger's test indicated potential publication bias for the studies reporting urinary tract infections (p=0.03).

DISCUSSION

This systematic review and meta-analysis investigated the impact of antibiotic prophylaxis on the incidence of postoperative infections following cesarean sections in developing countries. Our findings reveal significant benefits of antibiotic prophylaxis, particularly when administered pre-incision, in reducing the risks of endometritis, wound infections, and urinary tract infections.

Efficacy of Antibiotic Prophylaxis

The pooled results demonstrate that antibiotic prophylaxis reduces the risk of endometritis by 55%, wound infection by 50%, and urinary tract infection by 40% compared with no antibiotic prophylaxis. These findings are consistent with previous studies that have highlighted the effectiveness of antibiotics in preventing postoperative infections after cesarean delivery in both developed and developing countries.[1,2,22] The reduction in infection rates is critical in developing countries, where higher rates of cesarean section infections contribute significantly to maternal morbidity and mortality.[3,4]

Table 3. Meta-analysis results for different infections

Outcome	Comparison	Studies included	Total participants	Risk Ratio	95% confidence interval	I^2 (Heterogeneity)
Endometritis	Antibiotic vs. no antibiotic	64	158.760	0.45	0.37 to 0.55	62%
Wound infection	Antibiotic vs. no antibiotic	64	158.760	0.50	0.42 to 0.59	55%
UTI	Antibiotic vs. no antibiotic	64	158.760	0.60	0.51 to 0.70	60%
Endometritis	Pre-incision vs. post-cord clamping	52	120.643	0.43	0.35 to 0.53	61%
Wound infection	Pre-incision vs. post-cord clamping	52	120.643	0.48	0.39 to 0.58	59%
UTI	Pre-incision vs. post-cord clamping	52	120.643	0.58	0.49 to 0.69	58%

UTI: Urinary tract infection

Timing of Antibiotic Administration

Our analysis further underscores the importance of the timing of antibiotic administration. Prophylactic antibiotics given pre-incision reduced the risk of endometritis, wound infection, and urinary tract infection more effectively than those administered post-cord clamping. This supports the growing body of evidence suggesting that pre-incision antibiotics are optimal for preventing infections, as they ensure adequate tissue levels of the antibiotic at the time of skin incision.[7,23] This practice is endorsed by several clinical guidelines that recommend the administration of antibiotic prophylaxis within 60 minutes before the incision.[10,24]

Choice of Antibiotics

Cefazolin (first generation cephalosporin) was the most frequently used antibiotic in the included studies, reflecting its broad efficacy and safety profile, as noted in other comprehensive reviews.[25,26] However, the choice of antibiotic should ideally be guided by local antimicrobial resistance patterns, which can vary significantly across different regions and healthcare settings.[15,27] Developing countries often face the challenge of higher rates of antibiotic resistance, necessitating careful selection of antibiotics to maintain their effectiveness.[28,29]

Implications for Practice

The significant variation in practice, particularly in the timing of antibiotic administration, highlights a gap between current evidence and practice in many developing countries. Standardizing the use of pre-incision antibiotic prophylaxis could lead to substantial reductions in maternal infections post-cesarean section.[30,31] Health policy and clinical guidelines in developing countries need to be updated to reflect these findings to improve maternal health outcomes effectively.

Limitations

While our study provides robust evidence, it has limitations. The moderate to high heterogeneity observed in our meta-analysis may stem from differences in study design, antibiotic regimens, and baseline infection risk across the included studies. Furthermore, publication bias, particularly in studies reporting urinary tract infections, suggests the need for cautious interpretation of these results.

Future research should focus on randomized controlled trials that compare different types and timings of antibiotics in a more standardized manner. Additionally, studies are needed to explore the cost-effectiveness of antibiotic prophylaxis in cesarean sections, especially in resource-limited settings where economic considerations play a crucial role in healthcare decisions.

CONCLUSION

This systematic review and meta-analysis has demonstrated that antibiotic prophylaxis significantly reduces the risk of postoperative infections following cesarean sections in developing countries. The evidence strongly supports the administration of antibiotics before skin incision, which is more effective than post-cord clamping administration in reducing the risks of endometritis, wound infection, and urinary tract infection.

Reduction in infection rates: Antibiotic prophylaxis reduced the risk of endometritis by 55%, wound infection by 50%, and urinary tract infection by 40% compared to no antibiotic use. These findings align with global efforts to improve maternal health by reducing postoperative complications associated with cesarean sections.

Optimal timing of antibiotics: The administration of antibiotics pre-incision significantly lowers the incidence of infections compared to post-cord clamping administration. This supports the need for revising current practices to initiate antibiotic prophylaxis within 60 minutes before the incision, as recommended by several guidelines.

Guideline implementation: Despite clear evidence and existing guidelines, there is a gap in the implementation of pre-incision antibiotic prophylaxis in developing countries. Efforts to standardize practices and enhance adherence to guidelines are crucial for improving outcomes.

Antibiotic selection: Cefazolin is the most commonly used antibiotic, but the choice should be tailored based on local antimicrobial resistance patterns and specific patient factors to optimize efficacy and reduce the potential for resistance development.

Implications for Practice and Policy

Policy change: There is a need for policy reforms and the development of standardized protocols to ensure that all women undergoing cesarean sections receive the most effective antibiotic prophylaxis. Health systems in developing countries should prioritize updates to clinical guidelines to incorporate these findings.

Education and training: Healthcare providers should receive updated training and resources to implement pre-incision antibiotic protocols effectively. Education programs should emphasize the importance of timely antibiotic administration and adherence to guidelines to prevent postoperative infections.

Future research: Further research is needed to explore the cost-effectiveness of different antibiotic regimens and the long-term impacts of standardized antibiotic prophylaxis, particularly in resource-limited settings. Additionally, more studies are required to address the gaps in implementation and to explore innovative approaches to enhance guideline adherence.

In conclusion, this study highlights the critical role of antibiotic prophylaxis in improving maternal health outcomes by preventing infections following cesarean sections. By adopting pre-incision antibiotic administration and tailoring antibiotic choices based on local data, developing countries can significantly reduce maternal morbidity associated with cesarean deliveries. Policymakers, healthcare providers, and stakeholders must work together to ensure that these evidence-based practices are implemented effectively to safeguard maternal health.

ETHICAL DECLARATIONS

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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