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Book

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Chapter in a book

Meltzer PS, Kallioniemi A, Trent JM. Chromosome alterations in human solid tumors. I n: Vogelstein B, Kinzler KW, editors. The genetic basis of human cancer. New York: McGraw-Hill; 2002. p. 93113.

Journal article on the Internet

Abood S. Quality improvement initiative in nursing homes: The ANA acts in an advisory role. Am J Nurs [serial on the Internet] 2002 [cited 12 Aug 2002]; 102. Available from: www.nursingworld.org/AJN/2002/june/wawatch.htm

Website

Cancer-pain.org [homepage on the Internet]. New York: Association of Cancer Online Resources [updated 16 May 2002; cited 9 Jul 2002]. Available from: www.cancer-pain.org

An organization as an author

The Intensive Care Society of Australia and New Zealand. Mechanical ventilation strategy in ARDS: Guidelines. Int Care J Aust 1996;164:282-4.

Acknowledgements

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

Tables

Tables should be complementary, but not duplicate information contained in the text. Tables should be numbered consecutively in Arabic numbers, with a descriptive, self-explanatory title above the table. All abbreviations should be explained in a footnote. Footnotes should be designated by symbols in the following order: *,†, ‡, §, ¶.

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Original Article / Orijinal Araştırma

Fecal Calprotectin at the Time of Diagnosis May Indicate the Presence of Complications In Inflammatory Bowel Disease

İnflamatuvar Bağırsak Hastalığında Tanı Anındaki Fekal Kalprotektin Komplikasyon Varlığını Gösterebilir

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Abstract

Aim: Our objective was to explore the correlation between the occurrence of complications at the time of diagnosis or during follow-up and fecal calprotectin levels in patients diagnosed with inflammatory bowel disease.

Material and Method: The fecal calprotectin level was examined utilizing the chromatographic lateral flow immunoassay method.

Results: A total of 76 patients were enrolled in the study, comprising 26 (34%) individuals with Crohn's disease and 50 (66%) with ulcerative colitis. Complications were observed in 17 (22%) patients at the time of diagnosis and in 20 (26%) patients during follow-up. Upon diagnosis, fecal calprotectin levels were categorized as low (<50 mg/kg) in 26 (34%) patients, borderline (50-100 mg/kg) in 16 (21%) patients, and high (>100 mg/kg) in 34 (45%) patients. Patients with high fecal calprotectin levels exhibited lower hemoglobin and albumin levels (p=0.013, p=0.012, respectively), and higher platelet count, erythrocyte sedimentation rate, and C-reactive protein levels (p<0.001, p=0.004, p<0.001, respectively) compared to those with low fecal calprotectin levels. Complications were more prevalent in patients with high fecal calprotectin levels than in those with low and borderline levels both at the time of diagnosis and during follow-up (p=0.001). The risk of developing complications was found to be 26 times higher at the time of diagnosis in patients with fecal calprotectin levels >100 µg/g compared to those with levels below this threshold. Similarly, the risk was 8 times higher during follow-up (p=0.006, p=0.015, respectively).

Conclusion: The utilization of fecal calprotectin levels in conjunction with tests indicating acute inflammation in inflammatory bowel disease may serve as a predictive factor for the onset of complications.

Keywords: Fecal calprotectin, inflammatory bowel disease, complications, acute phase reactants

Öz

Amaç: İnflamatuvar bağırsak hastalığı olan hastalarda tanı anında ya da takip esnasındaki komplikasyon varlığı ile fekal kalprotektin arasındaki ilişkiyi değerlendirmeyi amaçladık.

Gereç ve Yöntem: Fekal kalprotektin düzeyi, kromatografik lateral akım immünoassay metodu ile çalışıldı

Bulgular: Çalışmaya 26'sı (%34) Crohn's hastalığı ve 50'si (%66) ülseratif kolit olan toplam 76 hasta alındı. Tanı anı ve takip sırasında hastaların sırasıyla 17 (%22) ve 20'sinde (%26) komplikasyon gözlendi. Tanı anında fekal kalprotektin düzeyi 26 (%34) hastada düşük (<50 mg/kg), 16 (%21) hastada sınırda (50-100 mg/kg) ve 34 (%45) hastada yüksek (>100 mg/kg) idi. Fekal kalprotektin düzeyi yüksek olan hastalarda düşük olan hastalara göre hemoglobin ve albümin düzeyleri daha düşük (sırasıyla, p=0.013, p=0.012), trombosit, eritrosit sedimentasyon hızı ve C-reaktif protein düzeyleri daha yüksekti (sırasıyla, p<0.001, p=0.004, p<0.001). Hastaların tanı anı ve takipleri sırasında komplikasyon varlığı fekal kalprotektin düzeyi yüksek olanlarda, düşük ve sınırda olanlara göre daha yüksek oranda olduğu gözlendi (p=0.001). Fekal kalprotektin düzeyi >100 mg/kg olan hastalarda bu değerin altında olan hastalara göre tanı anında komplikasyon gelişme riskinin 26 kat, takip esnasında ise 8 kat daha yüksek olduğu tespit edildi (sırasıyla, p=0.006, p=0.015).

Sonuç: İnflamatuvar bağırsak hastalığında akut inflamasyonu gösteren tetkiklerle birlikte fekal kalprotektin düzeyinin kullanılması komplikasyon gelişimini öngörebilir.

Anahtar Kelimeler: Fekal kalprotektin, inflamatuvar bağırsak hastalığı, komplikasyonlar, akut faz reaktanları

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INTRODUCTION

Inflammatory bowel disease (IBD) is characterized by chronic inflammation of the gastrointestinal system (GIS), presenting in two distinct types: Crohn's disease (CD) and ulcerative colitis (UC), each exhibiting diverse clinical symptoms and outcomes. CD manifests as transmural inflammation affecting any segment of the GIS, while UC is confined to the mucosal layer of the colon.[1] Complications such as toxic megacolon, perforation, abscess, stricture, obstruction, bleeding, and fistula may arise in these patients, significantly compromising quality of life, necessitating hospitalization, surgical interventions, and potentially posing life-threatening risks.[2] Although more assertive treatment approaches mitigate intestinal damage and reduce the likelihood of complications, hospitalization, and the need for surgery, the associated side effects and increased treatment costs may yield unfavorable outcomes.

Calprotectin is a 36-kDa protein, a member of the S100 calcium-binding family. Primarily originating from neutrophils, it is also found to a lesser extent in monocytes and macrophages. Fecal calprotectin (FC) exhibits a concentration approximately six times higher in stool compared to healthy individuals' blood. This parameter serves as a valuable tool in distinguishing between non-inflammatory gastrointestinal diseases and IBD, offering insights into IBD response status and the presence of relapse.[3] For a recently diagnosed patient, the ability to predict the future course of the disease holds significance in shaping patient expectations and guiding treatment decisions. Consequently, there arises a necessity for the utilization of tests that are facile, non-invasive, expeditious, reliable, and cost-effective to assess the risk of complications. In our study, we specifically explored the correlation between the presence of complications at the time of diagnosis or during follow-up and FC levels in patients with IBD.

MATERIAL AND METHOD

This study represents a single-center, retrospective, observational investigation assessing patients diagnosed with IBD within the timeframe spanning January 2017 to December 2020 at Gastroenterology Clinic of Karadeniz Technical University Faculty of Medicine. Patient data were acquired through the electronic data recording system of the hospital, utilizing specific codes corresponding to IBD, CD, and UC. The study was carried out with the permission of Karadeniz Technical University Faculty of Medicine Ethics Committee (Date: 03.02.2022, Decision No: 24237859-70).

Inclusion and Exclusion Criteria

This study enrolled patients who had received a diagnosis of IBD. Clinical, endoscopic, radiological, and histological findings were systematically evaluated to facilitate the diagnosis and differentiation of distinct IBD types. The inclusion criteria comprised patients aged 18 years and above. Conversely, patients with diagnoses of infectious gastroenteritis, Celiac disease, diverticulitis, microscopic colitis, autoimmune enteropathy, food allergy, cystic fibrosis, liver cirrhosis, infection, cancer, and those employing specific medications (proton pump inhibitor, non-steroidal anti-inflammatory drug) were excluded from the study. The patient inclusion and exclusion criteria are visually represented in **Figure 1**.

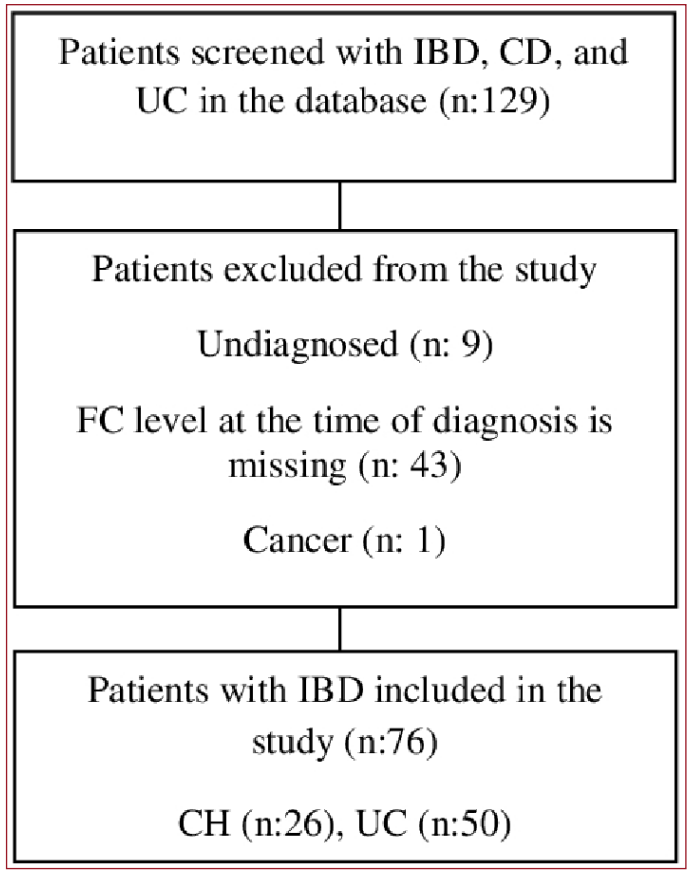

Figure 1: Flow chart of patients

Study Design

Patients diagnosed with IBD were stratified into three groups based on FC levels: FC level <50 µg/g (low), FC level 50-100 µg/g (borderline), and FC level >100 µg/g (high). Comparative analyses were conducted among these groups concerning the presence of complications at the time of diagnosis and during treatment. Complications, as defined, included toxic megacolon, bleeding, obstruction, perforation, stricture, abscess, and fistula.[2,4] Additionally, the groups were scrutinized with respect to age, gender, hemoglobin (Hb) level, leukocyte and platelet count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and albumin levels. Further considerations encompassed the location of involvement, extraintestinal manifestations, treatment modalities, anemia, infection at diagnosis, and the occurrence of surgical interventions. Following this comprehensive analysis, the same assessments were subsequently applied within the subgroups of CD and UC.

Fecal Calprotectin

For spot stool samples obtained from the patients, the FC antigen level was determined within 2 hours of their admission to the medical microbiology laboratory. The analysis involved the use of the Calprotectin Rapid Test Cassette kit (Feces) from ACRO Biotech Inc, Rancho Cucamonga, USA. Stool samples were subjected to examination through the chromatographic lateral flow immunoassay method, following the manufacturer's guidelines. The resulting bands were quantitatively measured utilizing the ACROLF Reader, also from ACRO Biotech Inc, Rancho Cucamonga, USA. Values below 50 µg/g were considered within the normal range.

Statistical Analysis

The statistical analysis was conducted using SPSS version 23. Descriptive statistics were reported as mean and standard deviation (SD) or median, minimum, and maximum based on the distribution of results. The Kolmogorov-Smirnov test was employed to assess the distribution of variables. For the comparison of data across three independent groups, the Chi-square test was applied for categorical variables, the ANOVA test for numerical variables with a normal distribution, and the Kruskal-Wallis test for numerical variables without a normal distribution. Logistic regression analysis was performed to investigate the association between the presence of complications at the time of diagnosis and during follow-up, and several factors including age, gender, extraintestinal manifestation, Hb and CRP, platelet count, and FC group at the time of diagnosis. In the logistic regression analysis, the FC group was dichotomized as <100 µg/g and ≥100 µg/g. The statistical significance level was set at $p<0.05$.

RESULTS

Patients

The study comprised a total of 76 patients, with 26 (34%) diagnosed with CD and 50 (66%) with UC. Among the participants, 43 (57%) were male, and 33 (43%) were female, with a mean age of 36±14 years. Extraintestinal manifestations were present in 13 (17%) patients. A majority of the patients, 73 (95%), received 5-aminosalicylic acid (5-ASA), while 23 (30%) received corticosteroids, 26 (34%) received thiopurines, and 8 (10%) received biologic agents. Anemia was present in 30 (40%) patients at the time of diagnosis. At the initial diagnosis, amebiasis was detected in 8 (11%) patients, Clostridium difficile infection (CDI) in 2 (3%) patients, and cytomegalovirus (CMV) infection in 4 (5%) patients. Thromboembolism was present in 2 (3%) patients.

Complications were observed in 17 (22%) patients at the time of diagnosis, with no complications observed in 59 (78%) patients. During follow-up, complications were noted in 20 (26%) patients, while 56 (74%) patients remained complication-free. Specifically, complications were observed in 15 (58%) patients with CD at the time of diagnosis and 17 (65%) during follow-up, while complications were observed in 2 (4%) patients with UC at the time of diagnosis and 3 (6%) during follow-up. Surgical intervention was performed in 7 (9%) patients. The detailed characteristics of the patients are presented in **Table 1**.

Table 1. Patient Characteristics

Characteristics	Total (n=76)	CD (n=26)	UC (n=50)
Age years, mean (±SD)	36 (±14)	32 (±13)	38 (±14)
Gender, n (%)			
Female	33 (43)	10 (39)	23 (46)
Male	43 (57)	16 (61)	27 (54)
Hb g/dl, mean (±SD)	12.8 (±2.1)	12.5 (±1.9)	13 (±2.2)
Leukocyte $\times10^9$/l, median (range)	7.9 (3.3-22)	7.8 (4.4-20)	8.3 (3.3-22)
Platelet $\times10^9$/l, median (range)	304 (172-638)	355 (199-638)	267 (172-541)
ESR mm/h, median (range)	14 (2-66)	23 (2-56)	10 (2-66)
CRP mg/l, median (range)	0.6 (0.1-116)	2.2 (0.1-116)	0.2 (0.1-29)
Albumin mg/dl, median (range)	4.1 (2.2-4.9)	3.9 (2.2-4.8)	4.2 (2.3-4.9)
Extraintestinal manifestation, n (%)	13 (17)	8 (31)	5 (10)
Treatment, n (%)			
5-ASA	73 (95)	24 (91)	50 (100)
Corticosteroids	23 (30)	15 (57)	8 (16)
Thiopurines	26 (34)	17 (65)	9 (18)
Biologic agents	8 (10)	6 (23)	2 (4)
Infection at the time of diagnosis, n (%)			
Amebiasis	8 (11)	2 (8)	6 (12)
CDI	2 (3)	2 (8)	0 (0)
CMV infection	4 (5)	0 (0)	4 (8)
Anemia at the time of diagnosis, n (%)	30 (40)	13 (50)	17 (34)
Thromboembolism, n (%)	2 (3)	0 (0)	2 (4)
Complications at the time of diagnosis, n (%)	17 (22)	15 (58)	2 (4)
Stricture	3 (4)	3 (12)	0 (0)
Obstruction	1 (1)	1 (4)	0 (0)
Bleeding	1 (1)	0 (0)	1 (2)
Fistula	3 (4)	3 (12)	0 (0)
Stricture+perforation	1 (1)	1 (4)	0 (0)
Abscess+fistula	4 (5)	4 (15)	0 (0)
Stricture+fistula	1 (1)	1 (4)	0 (0)
Obstruction+fistula	1 (1)	1 (4)	0 (0)
Bleeding+toxic megacolon	1 (1)	0 (0)	1 (2)
Stricture+abscess+fistula	1 (1)	1 (4)	0 (0)
Complications during the follow-up, n (%)	20 (26)	17 (65)	3 (6)
Stricture	3 (4)	3 (12)	0 (0)
Obstruction	1 (1)	1 (4)	0 (0)
Bleeding	1 (1)	0 (0)	1 (2)
Fistula	4 (5)	3 (12)	1 (2)
Stricture+perforation	1 (1)	1 (4)	0 (0)
Abscess+fistula	5 (7)	5 (19)	0 (0)
Stricture+fistula	1 (1)	1 (4)	0 (0)
Obstruction+fistula	1 (1)	1 (4)	0 (0)
Bleeding+toxic megacolon	1 (1)	0 (0)	1 (2)
Perforation+abscess+fistula	2 (3)	2 (8)	0 (0)
Surgical intervention, n (%)	7 (9)	7 (27)	0 (0)
Abscess	3 (4)	3 (12)	0 (0)
Stricture	1 (1)	1 (4)	0 (0)
Fistula	2 (3)	2 (10)	0 (0)
Stricture+ perforation	1 (1)	1 (4)	0 (0)

CD: Crohn's disease; UC: Ulcerative colitis; SD: Standard deviation; Hb: Hemoglobin; ESR: Erytrocyte sedimentation rate; CRP: C-reactive protein; GIS: Gastrointestinal system; 5-ASA: 5-aminosalicylic acid; CDI: Clostridium difficile infection; CMV: Sitomegalovirüs.

Comparison According to Fecal Calprotectin Group of Patients with Inflammatory Bowel Disease

At the time of diagnosis, FC) levels were categorized as follows: low (<50 µg/g) in 26 (34%) patients, borderline (50-100 µg/g) in 16 (21%) patients, and high (>100 µg/g) in 34 (45%) patients. Patients with borderline FC levels exhibited a higher age compared to those with low and high FC levels (p=0.009, p=0.020, respectively). No significant difference was observed between FC levels and gender. Patients with high FC levels had lower Hb and albumin levels (p=0.016, p=0.012, respectively). Additionally, platelet count, ESR, and CRP levels were higher in patients with high FC levels compared to those with low FC levels (p<0.001, p=0.004, p<0.001, respectively).

Extraintestinal involvement was more common in patients with high FC levels compared to those with low and borderline FC levels (p=0.002). The utilization of corticosteroids, thiopurines, and biological agents was higher in patients with high FC levels than in those with low and borderline levels, although this trend was observed to be statistically borderline (p=0.053). Amebiasis was observed in 3 (19%) patients, CDI in 1 (6%) patient, and CMV infection in 2 (13%) patients with borderline FC levels. In contrast, amebiasis was detected in 5 (15%) patients, CDI in 1 (3%) patient, and CMV infection in 2 (6%) patients with high FC levels. No infection was observed in patients with low FC levels.

Complications at the time of diagnosis and during follow-up were more frequent in patients with high FC levels compared to those with low and borderline levels (p<0.001, p<0.001, respectively). The rate of surgical intervention was higher in patients with high FC levels compared to those with low and borderline FC levels (p=0.038) (**Table 2**).

In the logistic regression analysis, it was observed that the risk of complications at the time of diagnosis and during follow-up was 26 and 8 times higher, respectively, in patients with fecal calprotectin (FC) levels >100 µg/g compared to those with FC levels below this threshold (p=0.006, p=0.015, respectively). The logistic regression model is presented in **Table 3**.

Table 2. Comparison According to Fecal Calprotectin Group of Patients with Inflammatory Bowel Disease

Characteristics	FC level (<50 µg/g) (n=26)	FC level (50-100 µg/g) (n=16)	FC level (>100 µg/g) (n=34)	p
Age years, mean (±SD)	32±13	45±15	34±13	0.007*
Gender, n (%)				
Female	8 (31)	10 (63)	15 (44)	0.131
Male	18 (69)	6 (37)	19 (56)	
Hb g/dl, mean (±SD)	13.7±1.7	12.9±2.4	12.1±2	0.016*
Leukocyte $\times 10^9$/l, median (range)	8 (5.1-12)	7.5 (4.5-11.3)	7.3 (3.3-22)	0.808
Platelet $\times 10^9$/l, median (range)	254 (172-374)	279 (185-509)	360 (196-638)	<0.001*
ESR mm/h, median (range)	6 (2-36)	12 (3-66)	23 (2-63)	0.004*
CRP mg/l, median (range)	0.2 (0.1-9.8)	0.4 (0.1-29)	2.3 (0.1-116)	<0.001*
Albumin mg/dl, median (range)	4.3 (2.8-4.9)	4.1 (2.3-4.7)	3.9 (2.2-4.8)	0.012*
Extraintestinal manifestation, n (%)				
Yes	2 (8)	0 (0)	11 (32)	0.004*
No	24 (92)	16 (100)	23 (68)	
Treatment, n (%)				
5-ASA	26 (100)	16 (100)	31 (90)	0.053
Corticosteroids	3 (11)	5 (32)	15 (44)	
Thiopurines	4 (15)	5 (32)	17 (49)	
Biologic agents	0 (0)	1 (6)	7 (20)	
Infection at the time of diagnosis, n (%)				
Amebiasis	0 (0)	3 (19)	5 (15)	0.087
CDI	0 (0)	1 (6)	1 (3)	0.069
CMV infection	0 (0)	2 (13)	2 (6)	0.260
Anemia at the time of diagnosis, n (%)				
Yes	6 (23)	5 (31)	19 (56)	0.027*
No	20 (77)	11 (69)	15 (44)	
Complications at the time of diagnosis, n (%)				
Yes	1 (4)	0 (0)	16 (47)	<0.001*
No	25 (96)	16 (100)	18 (53)	
Complications during the follow-up, n (%)				
Yes	3 (12)	0 (0)	17 (50)	<0.001*
No	23 (88)	16 (100)	17 (50)	
Surgical intervention, n (%)				
Yes	1 (4)	0 (0)	6 (18)	0.074
No	25 (96)	16 (100)	28 (82)	

FC: Fecal calprotectin; SD: Standard deviation; Hb: Hemoglobin; ESR: Erytrocyte sedimentation rate; CRP: C-reactive protein; GIS: Gastrointestinal system; 5-ASA: 5-aminosalicylic acid; CDI: Clostridium difficile infection; CMV: Sitomegalovirüs. * Statistically significant.

Table 3. Logistic Regression Model Associated with the Presence of Complications

Complications at the time of diagnosis	p	Exp (B)	Exp (B) for 95% confidence interval	
			Düşük	Yüksek
Age	0.147	0.949	0.884	1.019
Gender	0.394	0.432	0.063	2.972
Extraintestinal manifestation	0.359	0.438	0.075	2.557
Hb level at the time of diagnosis	0.403	0.824	0.523	1.298
Platelet count at the time of diagnosis	0.174	1.000	1.000	1.000
CRP level at the time of diagnosis	0.896	0.996	0.934	1.062
Calprotectin group	0.006*	25.967	2.502	269.482
Complications during the follow-up				
Age	0.094	0.950	0.894	1.009
Gender	0.316	0.424	0.079	2.270
Extraintestinal manifestation	0.698	0.720	0.137	3.785
Hb level at the time of diagnosis	0.360	0.834	0.566	1.230
Platelet count at the time of diagnosis	0.175	1.000	1.000	1.000
CRP level at the time of diagnosis	0.960	1.002	0.927	1.083
Calprotectin group	0.015*	7.885	1.497	41.544

Hb: Hemoglobin; CRP: C-reactive protein. The time of diagnosis: Nagelkerke R2=0.581; Omnibus chi-square=36.338, df=7, p=<0.001; Hosmer and Lemeshow=0.586. During the follow-up: Nagelkerke R2=0.499; Omnibus chi-square=31.741, df=3, p=<0.001; Hosmer and Lemeshow=0.677. * Statistically significant.

Comparison According to Fecal Calprotectin Group of Patients with Crohn's Disease and Ulcerative Colitis

Due to the limited number of patients with CD and UC, statistical comparisons could not be conducted for some values, and the patient data were presented in ratios.

In CD patients, lower Hb and albumin levels were observed in individuals with high FC levels, while platelet count and CRP levels were higher (p=0.035, p=0.028, p=0.011, p=0.004, respectively). The rate of extraintestinal manifestations was 0% (0/6) in patients with low FC levels, 0% (0/2) in patients with borderline FC levels, and 44% (8/18) in patients with high FC levels (p=0.025). The use of corticosteroids, thiopurines, and biologic agents was reported as 33% (2/6), 33% (2/6), 0% (0/6) in patients with low FC levels, 100% (2/2), 100% (2/2), 0% (0/2) in patients with borderline FC levels, and 62% (11/18), 73% (13/18), 34% (6/18) in patients with high FC levels, respectively. Amebiasis and CDI were not observed in patients with low FC levels, while they were present in 50% (1/2) of patients with borderline FC levels and 6% (1/18) of patients with high FC levels.

The rate of complications at the time of diagnosis was 17% (1/6) in patients with low FC levels and 0% (0/2) in patients with borderline FC levels, whereas it was 78% (14/18) in patients with high FC levels (p=0.004). Similarly, the rate of complications during follow-up was 33% (2/6) in patients with low FC levels and 0% (0/2) in patients with borderline FC levels, while it was 83% (15/18) in patients with high FC levels (p=0.008). The rate of surgical intervention was 17% (1/6) in patients with low FC levels, 0% (0/2) in patients with borderline FC levels, and 33% (6/18) in patients with high FC levels (**Table 4**).

UC patients, higher platelet count, ESR, and CRP levels were observed in individuals with high FC levels compared to those with low FC levels (p=0.029, p=0.034, p=0.039, respectively). The rate of extraintestinal involvement was 10% (2/20) in patients with low FC levels, 0% (0/14) in patients with borderline FC levels, and 19% (3/16) in patients with high FC levels. The utilization rates of corticosteroids, thiopurines, and biologic agents were reported as 5% (1/20), 10% (2/20), 0% (0/20) in patients with low FC levels, 21% (3/14), 21% (3/14), 7% (1/14) in patients with borderline FC levels, and 32% (5/16), 25% (4/16), and 6% (1/16) in patients with high FC levels, respectively. Amebiasis and CMV infections were not observed in patients with low FC levels, while they were detected in 14% (2/14) of patients with borderline FC levels. Amebiasis was observed in 2% (4/16) and CMV infection in 13% (2/16) of patients with high FC levels.

No complications were observed in patients with low and borderline FC levels at the time of diagnosis. However, complications were detected in 13% (2/16) of patients with high FC levels. During the follow-up period, the rate of complications was 5% (1/20) in patients with low FC levels, 0% (0/14) in patients with borderline FC levels, and 13% (2/16) in patients with high FC levels (**Table 4**).

DISCUSSION

FC is employed for the assessment of intestinal inflammation in patients with IBD.[5] A crucial application of FC is its utility in distinguishing between IBD and irritable bowel syndrome (IBS) without necessitating invasive procedures or endoscopy.[6] In the context of differential diagnosis, it has been observed that in patients with an FC level <50 µg/g, FC exhibits a sensitivity of 100% and a specificity ranging from 51% to 100%.[7] Furthermore, FC serves as an indicator of treatment response and relapse status in individuals with IBD.[6] Additionally, studies have demonstrated a correlation between FC levels and both endoscopic and histological findings.[8]

In IBD, serious and life-threatening complications can arise. To assess the progression of these patients, various factors are considered, including patient characteristics (such as symptoms, quality of life, daily activity, and previous treatments), inflammation status (disease prevalence, findings from endoscopy and imaging methods, and biological markers), and the presence of complications (intestinal injury, history of surgery). Different scoring systems are utilized to gauge disease activity, incorporating these diverse criteria.[9]

For CD, the CD activity index (CDAI) includes extraintestinal complications and hematocrit among its criteria.[10] In the case of UC, the Truelove-Witts severity index criteria involve Hb and ESR.[11] Moreover, various scoring systems assessing disease activity in IBD incorporate criteria such as CRP and albumin levels, anemia, and the use of corticosteroids and biological agents. The UC activity index in the American College of Gastroenterology (ACG) guide specifically includes Hb, ESR, CRP, and FC levels.[12] These criteria collectively contribute to a comprehensive evaluation of disease activity in individuals with IBD.

Table 4. Comparison According to Fecal Calprotectin Group of Patients with Crohn's Disease and Ulcerative Colitis

CD characteristics	FC level (<50 µg/g) (n=6)	FC level (50-100 µg/g) (n=2)	FC level (>100 µg/g) (n=18)	p
Age years, mean (±SD)	25±9	60±2	31±11	0.002*
Gender, n (%)				
Female	2 (33)	1 (50)	7 (39)	1.000
Male	4 (67)	1 (50)	11 (61)	
Hb g/dl, mean (±SD)	13.9±2.1	14.2±1.8	11.9±1.6	0.035*
Leukocyte $\times10^9$/l, median (range)	8.7 (7.7-10)	5.3 (5-5.6)	7.2 (4.4-20)	0.071
Platelet $\times10^9$/l, median (range)	307 (236-370)	238 (199-278)	414 (250-638)	0.011*
ESR mm/h, median (range)	10 (2-36)	25 (5-45)	23 (2-56)	0.366
CRP mg/l, median (range)	0.6 (0.1-1.5)	1.2 (0.1-2.4)	3.8 (0.1-116)	0.004*
Albumin mg/dl, median (range)	4.2 (4-4.7)	4.1 (3.9-4.4)	3.7 (2.2-4.8)	0.028*
Location of involvement, n (%)				
İleum	4 (67)	1 (50)	10 (56)	0.753
Colon	2 (33)	1 (50)	2 (11)	
İleocolon	0 (0)	0 (0)	4 (22)	
Upper GIS+ileum	0 (0)	0 (0)	1 (6)	
Upper GIS+colon	0 (0)	0 (0)	1 (6)	
Extraintestinal manifestation, n (%)				
Yes	0 (0)	0 (0)	8 (44)	0.164
No	6 (100)	2 (100)	10 (56)	
Treatment, n (%)				
5-ASA	6 (100)	2 (100)	16 (90)	0.630
Corticosteroids	2 (33)	2 (100)	11 (62)	
Thiopurines	2 (33)	2 (100)	13 (73)	
Biologic agents	0 (0)	0 (0)	6 (34)	
Infection at the time of diagnosis, n (%)				
Amebiasis	0 (0)	1 (50)	1 (6)	0.197
CDI	0 (0)	1 (50)	1 (6)	0.197
CMV infection	0 (0)	0 (0)	0 (0)	
Anemia at the time of diagnosis, n (%)				
Yes	2 (33)	0 (0)	11 (61)	0.252
No	4 (67)	2 (100)	7 (39)	
Complications at the time of diagnosis, n (%)				
Yes	1 (17)	0 (0)	14 (78)	0.004*
No	5 (83)	2 (100)	4 (22)	
Complications during the follow-up, n (%)				
Yes	2 (33)	0 (0)	15 (83)	0.008*
No	4 (67)	2 (100)	3 (17)	
Surgical intervention, n (%)				
Yes	1 (17)	0 (0)	6 (33)	0.509
No	5 (83)	2 (100)	12 (67)	
UC characteristics	**FC level (<50 µg/g) (n=20)**	**FC level (50-100 µg/g) (n=14)**	**FC level (>100 µg/g) (n=16)**	**p**
Age years, mean (±SD)	34±13	43±15	37±14	0.213
Gender, n (%)				
Female	6 (30)	9 (64)	8 (50)	1.000
Male	14 (70)	5 (36)	8 (50)	
Hb g/dl, mean (±SD)	13.6±1.7	12.7±2.5	12.3±2.4	0.204
Leukocyte $\times10^9$/l, median (range)	7.8 (5.1-12)	8.4 (4.5-11.3)	7.9 (3.3-22)	0.743
Platelet $\times10^9$/l, median (range)	241 (172-374)	290 (185-509)	312 (196-541)	0.029*
ESR mm/h, median (range)	5 (2-30)	12 (3-66)	20 (2-63)	0.034*
CRP mg/l, median (range)	0.1 (0.1-9.8)	0.3 (0.1-29)	0.6 (0.1-14)	0.039*
Albumin mg/dl, median (range)	4.3 (2.8-4.9)	4.1 (2.3-4.7)	4.1 (2.6-4.8)	0.299
Extraintestinal manifestation, n (%)				
Yes	2 (10)	0 (0)	3 (19)	0.164
No	18 (90)	14 (100)	13 (81)	
Treatment, n (%)				
5-ASA	20 (100)	14 (100)	16 (100)	0.469
Corticosteroids	1 (5)	3 (21)	5 (32)	
Thiopurines	2 (10)	3 (21)	4 (25)	
Biologic agents	0 (0)	1 (7)	1 (6)	
Infection at the time of diagnosis, n (%)				
Amebiasis	0 (0)	2 (14)	4 (25)	0.076
CDI	0 (0)	0 (0)	0 (0)	
CMV infection	0 (0)	2 (14)	2 (13)	0.220
Anemia at the time of diagnosis, n (%)				
Yes	4 (20)	5 (36)	8 (50)	0.252
No	16 (80)	9 (64)	8 (50)	
Complications at the time of diagnosis, n (%)				
Yes	0 (0)	0 (0)	2 (13)	0.172
No	20 (100)	14 (100)	14 (87)	
Complications during the follow-up, n (%)				
Yes	1 (5)	0 (0)	2 (13)	0.481
No	19 (95)	14 (100)	14 (87)	
Surgical intervention, n (%)				
Yes	0 (0)	0 (0)	0 (0)	
No	20 (100)	14 (100)	16 (100)	

CD: Crohn's disease; FC: Fecal calprotectin; SD: Standard deviation; Hb: Hemoglobin; ESR: Erytrocyte sedimentation rate; CRP: C-reactive protein; GIS: Gastrointestinal system; 5-ASA: 5-aminosalicylic acid; CDI: Clostridium difficile infection; CMV: Sitomegalovirüs, UC: Ulcerative colitis. * Statistically significant.

As FC is a protein associated with mucosal inflammation, it is hypothesized that its elevation may specifically indicate the presence of complications. In our study, we observed a higher incidence of complications at the time of diagnosis and during follow-up in patients with IBD who exhibited elevated FC levels. Furthermore, it was determined that the presence of complications at the time of diagnosis was 26 times higher, and the presence of complications during follow-up was 8 times higher in patients with FC levels exceeding 100 µg/g. Studies evaluating disease activity with FC are presented in the literature. In one study, it was determined that FC levels were higher in patients with active disease than in patients who were clinically and endoscopically in remission and had received anti-tumor necrotizing factor-α (anti-TNF-α) treatment.[13] Nevertheless, there is limited availability of studies demonstrating the relationship between the presence of complications and FC levels in patients with IBD. A study by Fabian et al. found that tissue calprotectin was not effective in revealing the development of complications in pediatric UC patients. However, FC was shown to be associated with chronic inflammation in the colonic mucosa. The study concluded that elevated FC levels in UC patients were linked to unfavorable clinical outcomes.[14] Similarly, in our study, we suggest that a high FC level in IBD patients is associated with negative outcomes.

In clinical practice, markers indicating acute inflammation, such as ESR, CRP, leukocyte and platelet counts, are commonly employed to assess disease activity in patients with IBD. Bodelier et al. demonstrated a higher rate of CRP falling below the normal level in patients in remission compared to those with active disease in IBD.[15] However, these markers are nonspecific and may elevate due to various factors such as obesity, smoking, and drug use.[1] CRP levels can be within the normal range in 30% of patients with active disease and elevated in 30% of patients without active disease, indicating that CRP alone may not be sufficient to evaluate disease progression.[16-18] In our study, we observed that ESR and CRP levels were higher in IBD patients with elevated FC levels compared to those with low FC levels. Ricanek et al. demonstrated that platelet count was higher in patients with a high IBD activity index.[19] Similarly, in our study, the platelet count, which tends to increase reactively in the presence of inflammation, was higher in patients with high FC levels compared to those with low FC levels. Albumin, a negative acute-phase reactant, was lower in patients with high FC levels than in those with low FC levels. Consequently, our study aligned with tests indicating acute inflammation in the group with high FC levels in IBD patients. In line with our findings, Abej et al. reported higher CRP levels and lower albumin levels in patients with positive FC compared to those with negative FC.[20]

Anemia is a common occurrence in 6-74% of patients with IBD, stemming from causes such as iron deficiency anemia, B12 and folic acid deficiency anemia, anemia of chronic disease, and malnutrition.[21] A study involving patients diagnosed with IBD demonstrated that Hb levels were lower in individuals with positive FC compared to those with negative FC.[20] Consistent with these findings, our study revealed lower Hb levels in patients with high FC levels than in those with low FC levels. In the subgroup analysis, Hb levels were lower in patients with high FC levels compared to those with low FC levels in patients with CD, but no significant difference was observed in patients with UC. Anemia in IBD can arise from deficiencies in iron, B12, and folate, as CD can involve the entire GIS. Furthermore, complications such as fistulas and abscesses that develop in CD may contribute to anemia of chronic disease.

In our study, we observed a higher utilization of corticosteroids, thiopurines, and biological agents in patients with high FC levels compared to those with low FC levels. This suggests that as disease activity and complications increase, there is a greater need for these treatments. The elevated usage of these therapeutic interventions in patients with higher FC levels may indicate a more pronounced disease severity, prompting the need for more frequent and potent medical interventions to control inflammation and address complications.

CONCLUSION

The statement highlights the substantive findings of the study, underscoring the ability of FC levels to predict the presence of complications during both the diagnosis and follow-up phases in individuals with IBD. The incorporation of FC alongside markers of acute inflammation is posited as a significant contributor to predicting disease trajectory and facilitating the development of risk models.

Firstly, it's important to note that this study is retrospective in nature, and furthermore, the number of patients is limited. Due to its retrospective design, the accurate scoring of the risk for IBD was challenging. Despite these limitations, we believe that this study can provide valuable insights for future research, offering a foundation to explore the relationship between FC and complications in patients with IBD.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Karadeniz Technical University Faculty of Medicine Ethics Committee (Date: 03.02.2022, Decision No: 24237859-70).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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Original Article / Orijinal Araştırma

Side Effect Profile of Meningococcal B Vaccine in Children

Çocuklarda Meningokok B Aşısının Yan Etki Profili

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Abstract

Aim: Invasive meningococcal infections have a clinical picture with a rapid onset and can lead to serious sequelae and death even in individuals who are treated early. The most common causes of related epidemics are serogroups A, B, C, W, Y, and X, and two different vaccines have been developed against serogroups A, C, W, and Y and serogroup B. The serogroup B-containing MenB-4C vaccine (Bexsero®) was licensed in Turkey in 2018 and is still being administered. In this study, the side effects of this vaccine in infants and children followed up in a tertiary pediatric clinic were questioned.

Material and Method: In our study, the local and systemic side effects of the MenB-4C vaccine doses, which were administered between March 1, 2019, and March 1, 2022, at the Child Health Follow-up Outpatient Clinic of Gazi University Faculty of Medicine, were evaluated retrospectively. All infants and children aged 0-18 years who were vaccinated at this clinic on the specified dates (n=102) were recruited, and a questionnaire was completed by calling their parents by telephone and questioning the side effects of the vaccine.

Results: It was determined that a total of 224 doses of the MenB-4C vaccine were administered to 102 children over the three-year study period, Of these vaccines, 21.6% were administered during the year before the pandemic and 78.4% during the two years after the pandemic. According to the total number of doses, the rate of local and systemic side effects was 30.8% (n= 69). It was found that among the 69 doses with side effects, 42 (60.8%) were systemic (fever), and 27 (39.1%) were local (stiffness, redness, and pain at the injection site). Side effects were observed in 41.3% of the patients after the first dose of the vaccine, 23.3% after the second dose, and 25.9% after the third dose.

Conclusion: In our study, no serious post-vaccine reactions, such as anaphylaxis and encephalopathy, were observed following vaccination with MenB-4C, and the most common side effects of this vaccine were fever and local pain, which were only transient and self-limiting, lasting only two to three days at most. Since the MenB-4C vaccine, which has been included in the vaccination schedule of most countries, is a strong tool to help prevent meningococcal infections, every parent presenting to a health institution should be informed by the physician about the necessity of this vaccine, and if possible, conjugated meningococcal vaccines containing not only serogroups A, C, W, and Y but also serogroup B should be added to the national vaccine scheme.

Keywords: Childhood, vaccination, meningococcal type B

Öz

Amaç: İnvazif meningokokal enfeksiyonlar hızlı başlangıçlı bir klinik tabloya sahiptir ve erken tedavi edilen bireylerde dahi ciddi sekellere ve ölüme yol açabilmektedir. İlgili salgınların en yaygın nedenleri serogrup A, B, C, W, Y ve X'tir ve serogrup A, C, W ve Y ile serogrup B'ye karşı iki farklı aşı geliştirilmiştir. Serogrup B'yi içeren MenB- 4C aşısı (Bexsero®) Türkiye'de 2018 yılında ruhsatlandırılmış olup halen uygulanmaktadır. Bu çalışmada üçüncü basamak pediatri kliniğinde takip edilen bebek ve çocuklarda bu aşının yan etkileri sorgulandı.

Gereç ve Yöntem: Çalışmamızda Gazi Üniversitesi Fakültesi Çocuk Sağlığı Takip Polikliniği'nde 1 Mart 2019 ile 1 Mart 2022 tarihleri arasında uygulanan MenB-4C aşı dozlarının lokal ve sistemik yan etkileri araştırıldı. Tıp Fakültesi retrospektif olarak değerlendirildi. Belirlenen tarihlerde (n=102) bu klinikte aşı olan 0-18 yaş arası tüm bebek ve çocuklar çalışmaya dahil edildi ve ebeveynleri telefonla aranarak aşının yan etkileri sorgulanarak anket dolduruldu.

Bulgular: Üç yıllık çalışma süresi boyunca 102 çocuğa toplam 224 doz MenB-4C aşısı uygulandığı belirlendi. Bu aşıların %21,6'sının pandemiden önceki yılda, %78,4'ünün ise iki pandemi döneminde uygulandığı belirlendi. salgından yıllar sonra. Toplam doz sayısına göre lokal ve sistemik yan etki oranı %30,8 (n= 69) idi. Yan etki görülen 69 dozun 42'sinin (%60,8) sistemik (ateş), 27'sinin (%39,1) ise lokal (enjeksiyon yerinde sertlik, kızarıklık, ağrı) olduğu belirlendi. Aşının ilk dozundan sonra hastaların yüzde 41,3'ünde, ikinci dozundan sonra yüzde 23,3'ünde, üçüncü dozundan sonra ise yüzde 25,9'unda yan etki görüldü.

Sonuç: Çalışmamızda MenB-4C aşılaması sonrasında aşı sonrası anafilaksi, ensefalopati gibi ciddi bir reaksiyon görülmedi ve bu aşının en sık görülen yan etkileri geçici ve kendiliğinden düzelen, en fazla iki ila üç gün süren ateş ve lokal ağrıydı. Çoğu ülkenin aşılama takviminde yer alan MenB-4C aşısı meningokok enfeksiyonlarını önlemeye yardımcı güçlü bir araç olduğundan, sağlık kuruluşuna başvuran her ebeveynin hekim tarafından bu aşının gerekliliği konusunda bilgilendirilmesi ve mümkünse sadece A, C, W ve Y serogruplarını değil serogrup B'yi de içeren konjuge meningokok aşıları ulusal aşı şemasına eklenmelidir.

Anahtar Kelimeler: Çocuk, Aşılama, Meningokok Tip B

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INTRODUCTION

Meningococci (*Neisseria meningitidis*) have caused endemics and epidemics in many parts of the world since the beginning of the 19th century. Invasive meningococcal infection has a clinical picture with a rapid onset and can lead to serious sequelae and death even in individuals who are diagnosed and treated early.[1] Despite the appropriate treatment, in addition to the mortality rate of 10-15%, one out of every five survivors faces long-term sequelae, such as limb loss, deafness, and problems with the central nervous system.[2]

Thirteen serogroups have been identified to cause meningococcal disease, with the most common being serogroups A, B, C, Y, W, and X. The distribution of these serogroups differs according to the geographical location and age of the evaluated populations.[3] The highest incidence of meningococcal disease across the world is found in the "meningitis belt" of sub-Saharan Africa. Major consequences occur in this region every five to 12 years, and the attack rate reaches 1,000 cases per 100,000 people. The measured annual attack rate, which is lower in other parts of the world, averages 0.3 to 3 per 100,000 people.[4] According to the meningococcal meningitis incidence, the World Health Organization classified countries as those having high endemic (>10 cases /100,000 persons/year), moderately endemic (2-10 cases/100,000 persons/year), and low endemic (<2 cases /100,000 persons/year) rates.[5] It is recommended that meningococcal vaccine be included in a routine immunization program in countries that are moderately endemic for meningococci. Turkey is also in this category. However, the epidemiology of meningococcus in Turkey differs from many other countries, and significant changes have been observed over time. In a multicenter study by Ceyhan et al., in which they evaluated bacterial meningitis agents in Turkey between 2005 and 2012, *N. meningitidis* was found to be the most common causative agent at a rate of 51.6%, and the W (38.1%) and B (26%) strains were mostly identified in the serotype distribution.[6]

Meningococcal infections are among the diseases that can be prevented by vaccination. It is possible to prevent invasive meningococcal infections with two types of vaccines: the first is the inactivated quadrivalent conjugate vaccine for serogroups A, C, W and Y, and the second is the serogroup B vaccine, which is an inactivated bacterial recombinant protein vaccine. Currently, there are two types of vaccines developed against meningococcal B serotype: the MenB-4C (Bexsero®) vaccine approved in Europe, Canada, Australia, and the USA and the MenB-FHbp (Trumenba®) vaccine approved in the USA.[7] In Turkey, the MenB-4C vaccine has been licensed for use after 2 months of age.[8]

The MenB-4C vaccine has been shown to be immunogenic in infants, adolescents, and adults.[9,10] In many clinical studies, the safety and undesirable effects of the MenB-4C vaccine have been investigated. While no problems were found in studies on its safety in adolescents, there are still concerns and a lack of knowledge among parents and even physicians due to the fever and systemic side effects observed in young children.[10,11] In our study, we planned to investigate the side effects and their frequency in pediatric patients who received the MenB-4C vaccine.

MATERIAL AND METHOD

The study was carried out with the permission of Gazi University Ethics Committee (Date: 27.07.2023, Decision No: 14).

In our study, the frequency of local and systemic side effects of the MenB-4C vaccine doses, which were administered between March 1, 2019, and March 1, 2022, at the Child Health Follow-up Outpatient Clinic of Gazi University Faculty of Medicine, Department of Social Pediatrics, was retrospectively evaluated.

All infants and children aged 0-18 years who were vaccinated at our clinic over the specified period (n=102) were included in the study. The names and telephone numbers of the vaccinated patients were obtained by screening the records. The parents were informed about the study by telephone, and those who provided consent were administered a questionnaire through a telephone interview to determine the side effects of the vaccine.

Using the questionnaire forms, sociodemographic characteristics, chronic disease history, drug use history, number of doses and age at MenB-4C vaccination (cross-checked through the vaccination records of the patients), side effects after vaccination, e.g., fever (body temperature of 38° and over, armpit or ear measurement), restlessness, swelling, redness, limitation of movement, pain, and stiffness at the injection site, duration of side effects, the vaccines included or not included in the national vaccination schedule (NVS) were questioned. In our department, for intramuscularly (IM) injections, in children younger than 1 years, the anterolateral aspect of the upper thigh is the preferred site. In older children, we preferred the deltoid muscle for IM injections.

Statistical Analysis

Data were analyzed using IBM SPSS V23. The conformity of the data to a normal distribution was evaluated with the Kolmogorov-Smirnov and Shapiro-Wilk tests. The Mann-Whitney U test was used to compare the data that were not normally distributed according to paired groups, and multiple comparisons were undertaken with Dunn's test. Pearson's chi-square, Yates' corrected chi-square, Fisher's exact, and Mc Nemar tests were used to compare categorical data. The results of the analyses were presented as mean ± standard deviation and median (minimum–maximum) for quantitative data, and as frequency and percentage for categorical data. The statistical significance level was taken as $p < 0.05$.

RESULTS

Of the total 1,972 patients who presented to the Child Health Monitoring Outpatient Clinic between March 2019 and March 2020 (before the COVID-19 pandemic), 22 (1.1%) received the MenB-4C vaccine. From March 2020, when the first COVID-19 case was reported in Turkey, to March 2022, a total of 2,853 patients presented to our outpatient clinic, and 80 (2.8%) of these patients were vaccinated against Meningococcal B. Accordingly, it was determined that 21.6% of the MenB-4C vaccine doses were administered during the year before the pandemic and 78.4% during the two years after the pandemic.

Demographic characteristics of vaccinated children and their families are given in Table 1. It was seen through the system that all the children included in our study were fully vaccinated according to their age and other vaccines in the NVS. It has been observed that 50% of the patients who received the MenB-4C vaccine were above 2 years of age when the first dose of vaccine was given. It was determined that 92.2% (n=94) of the children who received the meningococcal B vaccine had complete vaccine doses according to their age. It was observed that 7.8% (n=8) of them did not complete their vaccinations (**Table 1**). The families of the children whose vaccine dose was not completed were interviewed and the reason was asked. One of them stated that he did not have the other doses due to the high fever he experienced in the first dose, two families stated that they could not have it done due to financial reasons, while five families said that they delayed it due to the pandemic.

When the administration rates of other vaccines not included in the NVS were questioned, it was determined that 93.1% of the patients had received the meningococcal ACYW vaccine, 59.4% had received the rotavirus vaccine, 10.9% had received the influenza vaccine, and 6.9% had received the HPV vaccine. Of the parents, 19.4% stated that they also had their other children vaccinated with MenB-4C.

It was found that 95% of the parents had been informed about the vaccine and its possible side effects before vaccination. The MenB-4C vaccine was administered alone in 98% of the cases and simultaneously with the Men ACYW vaccine in two patients, and no side effects were observed in these two patients.

The 102 children received a total of 224 doses of the MenB-4C vaccine, and the rate of those with side effects according to the total number of doses was found to be 30.8% (n=69). It was determined that of the 69 side effects, 42 (60.8%) were systemic, and 27 (39.1%) were local. Only fever was seen as a systemic side effect and lasted two days in two of the 42 patients and three days in one patient. Fever was self-limiting and resolved within 24 hours in 92.8% (n=39) of the patients with this side effect. As a local reaction, stiffness, redness, and pain were observed at the injection

Table 1: Descriptive characteristics of the study group

	n	(%)
Gender		
Male	45	44.1
Female	57	55.9
Maternal education level		
Primary school	20	19.6
High school	15	14.7
University	67	65.7
Maternal working status		
Working	43	42.2
Not working	59	57.8
Paternal education level		
Primary school	12	11.9
High school	19	18.8
University	70	69.4
Paternal working status		
Working	3	3
Not working	98	97
Family Type		
Nuclear	99	97.1
Extended	3	2.9
Number of children		
1	45	44.1
2	34	33.3
≥3	23	22.5
Order of child who vaccinated		
1	70	68.6
2	21	20.6
≥3	11	10.8
Income level		
≤450$	11	10.8
450-900 $	46	45.1
≥900$	45	44.1
Chronic disease		
Absent	62	60.8
Present	40	39.2
Drugs		
Absent	90	88.2
Present	12	11.8
Immunosuppressive drug use		
Absent	9	75
Present	3	25
Hospitalization		
Absent	97	95.1
Present	5	4.9
Age at first dose		
2-5 months	5	4.9
6-12 months	33	32.3
13-24 months	13	12.7
2-10 years	25	24.5
>10 years	26	25.4
Vaccines in the national vaccination schedule		
Complete	102	100
Completed primary series for 4CMenB?		
No	8	7.8
Yes	73	71.6
Not vaccinated yet	21	20.6
	n / Medium ± S.deviation	**Median (min. - maks.)**
Maternal age	37.43 ± 6.74	38 (25 - 59)
Paternal age	40.18 ± 7.61	40 (26 - 65)

site, which regressed within 24-48 hours, except in one patient. Stiffness at the injection site, which was seen in only one patient, continued for seven to 10 days. Side effects occurred in 41.3% of the patients after the first dose of the MenB-4C vaccine, 23.3% after the second dose, and 25.9% after the third dose. When the relationship between the doses was examined in terms of side effects, statistically significant side effects were not observed at the second dose in patients who had not experienced any side effects after the first dose, but no such relationship was found for the third dose (**Table 2**). Of the 224 doses, 41.5% (n=93) were administered intramuscularly from the leg (to children under 1 year old) and the remaining 58.4% (n=131) from the arm (over 1 year of age) by the same nurse.

Considering the frequency of side effects according to the age of the children, fever was observed more frequently in those aged two years and younger (37.2%, 22,4% and 22%, after the first, second and third dose, respectively) compared to those aged over two years (5.8% after the first dose and 6.5% after the second dose) (**Table 3**).

The rate of antipyretic administration before the first dose of vaccination was 31.4% for the first dose, 26.6% for the second dose, and 27.6% for the third dose. When the effect of pre-vaccination antipyretic administration on the post-vaccination side effects status was examined, no statistically significant result was obtained (**Table 4**).

Table 3. Comparison of the second- and third-dose side effects according to the first-dose side effect status

	First-dose side effects		p*
	Absent	Present	
Second-dose side effects			
No	56 (96.6)	17 (45.9)	0.001
Yes	2 (3.4)	20 (54.1)	
Third-dose side effects			
No	14 (82.4)	6 (60)	0.508
Yes	3 (17.6)	4 (40)	

*McNemar test

Table 4. Evaluation of antipyretic effects before vaccination

	Pre-vaccination administration of antipyretics		p
	Absent n (%)	Present n (%)	
First-dose side effects			
Absent	38 (55.1)	22 (66.7)	0,369*
Present	31 (44.9)	11 (33.3)	
Second-dose side effects			
Absent	54 (79.4)	19 (73.1)	0,702*
Present	14 (20.6)	7 (26.9)	
Third-dose side effects			
Absent	16 (84.2)	4 (50)	0,145**
Present	3 (15.8)	4 (50)	

* Chi-square test with Yates correction, **Fisher's exact chi-square test

Table 2: Side effects by age groups

Age	Total number of children	Number of children with side effects	Systemic side effects		Local side effects		
	n	n (%)	Fever*	Restless	Redness at the injection site	Stiffness at the injection site	Pain at the injection site
First dose							
2-5 month	5	1 (20)	1				
6-12 month	33	17 (51.5)	15		1	1	
13-24 month	13	5 (38.5)	3			1	1
2-10 month	25	9 (36)	2			5	2
>10 month	26	9 (34.6)	1				8
	Total 102						
Second dose							
2-5 month	5	2 (40)	2				
6-12 month	31	9 (29)	8			1	
13-24 month	13	2 (15.3)	1				1
2-10 month	22	4 (18.1)	2				2
>10 month	24	4 (16.6)	1				3
	Total 95						
Third dose							
2-5 month	1	1 (100)	1				
6-12 month	18	5 (27.7)	5				
13-24 month	8	1 (12.5)					1
2-10 month	0	-					
>10 month	0	-					
	Total 27						

* Body temperature of 38° and over (armpit or ear measurement)

DISCUSSION

In our study, in which we retrospectively evaluated the local and systemic side effects of MenB-4C vaccines administered in the Child Health Follow-up Outpatient Clinic, no serious reactions such as post-vaccine anaphylaxis and encephalopathy were observed. It has been found that it has self-limiting features within 2-3 days at most.

Although local and systemic reactions are mostly self-limiting and transient after MenB-4C vaccination, fever has been reported more frequently in infants. But in adolescent pain at the injection site has been reported more frequently and, fever less frequently.[12] In the study with the largest adolescent cohort to date, 58,637 doses of 4CMenB vaccine were administered to 30,522 students (median age 16 years) during 2017–2018. Most common side effects were injection site reaction (126/193), headache (99/193) and nausea (61/193). Reported side effects declined with increasing age. It was found to be well tolerated in adolescent.[7] In a study conducted in Quebec, after the administration of a total of 43,000 doses of the MenB-4C vaccine, the incidence of fever was found to be higher in children under the age of two years (14-15%) than in those aged 2-4 years (12%) or five and over (6-8%).[13] Similarly, in our study, fever was observed more frequently in children aged two years and younger and less frequently in those over two years of age.

MenB-4C has been associated with increased rates of fever and other vaccine-related reactions, especially within the first 24-72 hours, when administered with other routine infant vaccines.[9] In vaccine side-effect studies, it can be very difficult to determine which vaccine is associated with the side effect that occurs due to the simultaneous administration of multiple vaccines.[14,15] Therefore, most studies have performed statistical analyses by attributing side effects to all vaccines in the presence of multiple vaccinations. In one of these studies, fever was detected at a rate of 26-41% when MenB-4C was administered alone, 23-36% after routine vaccinations alone, and 51-61% after the co-administration of MenB-4C and routine vaccines.[16] In our study, 98% of the patients having been administered the MenB-4C vaccine alone helped monitor the side effects specific to this vaccine in a more reliable manner.

England was the first country to include the MenB-4C vaccine in the national immunization program. In September 2015, the vaccine was started to be administered to infants to protect them from meningococcal B infections, and since then, studies have been published to prove the vaccine's safety and effectiveness.[9,17] In a meta-analysis conducted in 2018, it was reported that a high fever and local and systemic reactions were observed at a higher rate after the MenB-4C vaccine compared to other vaccines, but they were mild-moderate, short-term, and self-limiting.[18] Among the 43,000 doses of vaccine administered under the Quebec national immunization program, only two cases of bronchospasm were reported as serious vaccine-related reactions, and fever and local pain were the most common side effects.[13]

In a prospective cohort study conducted in the United Kingdom, approximately three million doses of vaccine were administered to 1.29 million children aged 0-18 months, and side effects were reported at a rate of 0.03% (n=902). The most common side effects were fever (41%, n=366), local reactions (40%, n=364), convulsions (6%, n=55), Kawasaki disease (<1%, n=3), and sudden infant death (<1 %, n=5).[19] In another study conducted in United Kingdom to investigate safety of 4CMenB, a total of 107,231 children aged 1–18 months received one doses of 4CMenB vaccination. Most 4CMenB exposure (93%) was on the same day as other vaccines within a complete national immunisation program stage. Adjusted incidence rate ratios including all 4CMenB exposures were 1.43 (95%CI: 1.02–2.02) for seizures and 1.72 (95%CI: 1.08–2.75) for febrile seizures. This study shows few cases of the outcomes after vaccination including 4CMenB with an increased risk of seizures and febrile seizures. But it is not possible to attribute the finding to one specific vaccination as the majority of 4CMenB was given with other vaccinations.[20] Such serious reactions were not observed in our study, and the vaccine side effects in our patients were acceptable, transient, and self-limiting.

Following the first dose of prophylactic paracetamol given immediately before or during MenB-4C vaccine administration, two additional doses four to six hours apart have been shown to reduce the frequency of post-vaccination fever and other related vaccine reactions without altering the immune response.[21] In a previous study, it was shown that while the use of the MenB-4C vaccine and prophylactic antipyretic in children under two years of age decreased the incidence of fever by 44%, there was a decrease of 22% in older children (five to 16 years old).[22] In our study, no statistically significant results were obtained when the effect of antipyretic administration before vaccination was examined according to the side effect status. This was attributed to our patients not using prophylactic paracetamol. Although the patients included in our study had received paracetamol before vaccination, they did not require any additional doses in the absence of side effects in the post-vaccination period.

In our Child Health Follow-up Outpatient Clinic before administration of MenB-4C, the parents were informed about common mild side effects of vaccination. For only one of the eight patients who did not complete their MenB-4C vaccine doses, the reason for discontinuation was related to the side effects experienced after the first dose. In a study conducted in 2016 to evaluate the views of parents and adolescents regarding the acceptability of the vaccine during the vaccination campaign initiated with the MenB-4C vaccine in Quebec, a serogroup B endemic region, a telephone interview was conducted with families. They reported that the main reasons for the refusal or discontinuation of vaccination were a lack of information about vaccination or time constraints. Negative perceptions of vaccine safety or the reporting of adverse events after the administration of a vaccine dose were not associated with vaccine rejection.[23]

In a study examining the attitudes of parents to vaccination in the United Kingdom, the majority of participants chose immunization with MenB-4C because they could not afford to risk invasive meningococci despite high fever rates.[24] In our study, it was observed that only one patient did not complete the vaccination schedule due to side effects, and that 92.2% (n=94) of the children received complete vaccine doses scheduled according to their age.

CONCLUSION

Similar to the literature, we determined that local and systemic reactions after MenB-4C administration were mostly self-limiting and transient. The MenB-4C vaccine, which is currently licensed in many countries and has also taken its place in the vaccination guidelines of most countries, will lead to significant progress in the fight against meningococcal B infections. Healthcare professionals have a significant role in increasing vaccine acceptance and the vaccination rates of vaccines that are not included in the NVC. Therefore, we believe that providing information about the vaccine and its side effects to every family presenting to a health institution, regardless of their income or the age of their children, will increase the vaccination rates.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Gazi University Ethics Committee (Date: 27.07.2023, Decision No: 14).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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Clinical Characteristics of Children and Adolescents Admitted with Chest Pain

Göğüs Ağrısı ile Başvuran Çocuk ve Ergenlerin Klinik Özellikleri

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Abstract

Aim: Chest pain is a common symptom in children. Chest pain is the second most common symptom referred to by paediatric cardiologists after cardiac murmurs. In this prospective study, we aimed to evaluate clinical characteristics and causes of chest pain in children admitted to our paediatric cardiology outpatient clinics.

Material and Method: We conducted this prospective study among 446 patients with chest pain in a tertiary care hospital from 1 June 2017 to 1 June 2020. The demographic data and clinical characteristics of the patients were analysed. All patients were evaluated with a medical history, physical examination, laboratory tests, electrocardiogram and echocardiogram and if necessary telecardiogram, 24-hour electrocardiogram monitoring, exercise stress test and psychological evaluation were made.

Results: The ratio of admissions with acute chest pain was 4% when 20% of the patients had chronic chest pain. The most common symptoms associated with chest pain were shortness of breath and palpitations. The non-cardiac causes were as follows: 25% musculoskeletal, 14% psychological, 9% respiratory, and 7% gastrointestinal, respectively. We found cardiac chest pain in 49 (11%) of patients. Idiopathic chest pain was found in 153 (34%) patients.

Conclusions: Our study showed that the aetiology of chest pain in children and adolescents admitted with chest pain is mostly due to non-cardiac causes. We found the slightly frequency of elevated rate for cardiac aetiologies of paediatric chest pain compared to the literature. We suggest that in addition to anamnesis and careful examination, further investigation, if necessary, is important in determining the aetiology of chest pain.

Keywords: Adolescent, aetiology, child, chest pain, echocardiogram

Öz

Amaç: Göğüs ağrısı çocuklarda sık görülen bir semptomdur. Göğüs ağrısı, pediatrik kardiyologlar tarafından kardiyak üfürümlerden sonra en sık belirtilen ikinci semptomdur. Bu prospektif çalışmada, çocuk kardiyoloji polikliniğimize başvuran çocuklarda göğüs ağrısının klinik özelliklerini ve nedenlerini değerlendirmeyi amaçladık.

Gereç ve Yöntem: Bu prospektif çalışmayı 1 Haziran 2017 - 1 Haziran 2020 tarihleri arasında üçüncü basamak bir hastanede göğüs ağrısı olan 446 hasta arasında gerçekleştirdik. Hastaların demografik verileri ve klinik özellikleri analiz edildi. Tüm hastalar anamnez, fizik muayene, laboratuvar testleri, elektrokardiyogram ve ekokardiyogram ile değerlendirildi ve gerekirse telekardiyogram, 24 saatlik holter elektrokardiyogram monitorizasyonu, egzersiz stres testi ve psikolojik değerlendirme yapıldı.

Bulgular: Akut göğüs ağrısı ile başvuru oranı %4 iken hastaların %20'sinde kronik göğüs ağrısı vardı. Göğüs ağrısı ile ilişkili en yaygın semptomlar nefes darlığı ve çarpıntı idi. Kalp dışı nedenler %25 kas-iskelet, %14 psikolojik, %9 solunum ve %7 gastrointestinal idi. Hastaların 49'unda (%11) kardiyak nedenli göğüs ağrısı bulduk. Yüz elli üç (%34) hastada idiyopatik göğüs ağrısı saptandı.

Sonuç: Çalışmamız göğüs ağrısı ile başvuran çocuk ve ergenlerde göğüs ağrısı etiyolojisinin daha çok kalp dışı nedenlere bağlı olduğunu göstermiştir. Literatüre kıyasla pediatrik göğüs ağrısının kardiyak etiyolojileri daha yüksek oranda bulduk. Göğüs ağrısı etiyolojisinin belirlenmesinde anamnez ve dikkatli muayeneye ek olarak gerekirse ileri tetkiklerin önemli olduğunu düşünüyoruz.

Anahtar Kelimeler: Adölesan, çocuk, ekokardiyogram, etiyoloji, göğüs ağrısı

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INTRODUCTION

Chest pain is a common symptoms in children. Chest pain is the second most common symptom referred to by paediatric cardiologists after cardiac murmurs.[1] It may be benign and non-cardiac reasons. In many cases, relatives become concerned due to the fear of cardiac disease. In spite of the fact that the number of severe cardiac conditions reported in childhood is relatively small, determining the aetiology of chronic or benign chest pain and convincing the family that the state is not life-threatening can sometimes take a long time. [1] Idiopathic and musculoskeletal causes of childhood chest pain are most commonly reported and do not require further investigation.[2] However, a meticulous physical examination and anamnesis are essential to rule out severe cardiac diseases. Although there were large sample retrospective studies about chest pain in children. [3] the number of prospective studies with a large cohort is limited in the literature.[4] There has yet no study in the literature comparing the characteristics and causes of chest pain in children and adolescence by gender. This study is also one of the most comprehensive prospective studies evaluating chest pain features in children and adolescents. In this prospective study, we aimed to evaluate clinical characteristics and causes of chest pain in children admitted to our paediatric cardiology outpatient clinics and to compare the results according to gender.

METHOD AND MATERIAL

Study Population

The present study was conducted prospectively between June 2017 and June 2020 in the Department of Paediatric Cardiology. There were approximately 10000 patients who visited the paediatrics department during the study period. 500 patients who applied to the pediatric cardiology outpatient clinic with complaints of chest pain were evaluated. The study included 446 outpatients who met the eligibility criteria. Children between the ages of 6 and 18, patients complaining of chest pain and patients with parental consent were included in the study. To evaluate whether there were differences in chest pain characteristics between age groups, patients were divided into three groups: 6-11 years old, 11-15 years old and 15-18 years old. Clinically unstable patients who presented to the emergency department and patients under 6 years of age who unable to describe the characteristics of chest pain were excluded from the study. The data of the patients who applied with the complaint of chest pain were recorded in the patient evaluation form prepared by us. Records of patients' complaints, physical examination findings, and personal and family histories were kept. All patients underwent an electrocardiogram and if necessary echocardiogram examination was performed. Haemogram, biochemistry, thyroid function tests, acute phase reactants, fasting lipid profile were also examined in patients with necessary indications. Cardiac enzyme levels were measured in patients with suspected heart-related chest pain based on anamnesis and physical examination. In the presence of abnormal anamnesis or family history, pathological physical examination, and electrocardiogram findings suggestive of cardiac pathology, telecardiogram was taken. 24-hour electrocardiogram monitoring was applied to patients with chest pain accompanied by palpitations and rhythm abnormalities. An exercise stress test was performed in patients with exertional chest pain that was not explained by other respiratory causes.

Test Interpretation

Electrocardiogram interpretation was based on documented findings in the paediatric cardiologist's clinic note. Echocardiogram and exercise stress test results were obtained from reports generated at the time of the study. Diagnoses that were considered potential cardiac causes of chest pain included coronary artery anomalies, cardiomyopathies, myocarditis, pericarditis, pulmonary hypertension, mitral valve prolapses with moderate-severe mitral regurgitation, aortic dissection, arrhythmia, and moderate or greater left ventricular outflow tract obstruction. Findings considered to be positive on the exercise stress test included ST-segment or T-wave changes concerning ischaemia or tachyarrhythmia. Arrhythmias on 24-hour electrocardiogram monitoring were considered to be positive findings.

Causes of chest pain were categorised mainly as cardiac-related causes and non-cardiac-related causes – musculoskeletal, respiratory, psychological, gastrointestinal, and miscellaneous disorders and idiopathic chest pain – as previously reported by Selbst (21). Chest pain lasting for 2 days or less was considered acute, intermittent chest pain for more than 6 months was considered chronic, 2 days to 6 months were subacute, and persistent for a long time was persistent chest pain.

Ethical approval was obtained for the study from the Local Ethics Committee on 17.01.2018 with the protocol number 2018/29. The recommendations of the Declaration of Helsinki for biomedical research involving human subjects were followed.

Statistical Analysis

Data were analyzed using tam SPSS 20.0 (SPSS Inc., Chicago, Illinois, USA). The data obtained by measurement were shown as mean ± standard deviation, data obtained by counting (%) and (n) in cases with normal distribution. Relationships between categorical variables according to age groups and gender were tested with the chi-square test. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 244 (54%) of the patients were boys. The mean ages of boys and girls were 12.4±3 and 12.6±3.2 years, respectively. The mean age of girls and boys was similar (p >0.05). The symptoms and characteristics of children and adolescents with chest pain comparing by gender were displayed in **Table 1**.

Table 1. Symptoms and characteristics of children and adolescents with chest pain according to gender

	Gender		χ^2	p*
	Boy (n:244) n (%)	Girl (n:202) n (%)		
Triggers of Chest Pain				
Exercise	108 (44.3)	78 (38.6)	4.742	0.448
Digestion	11 (4.5)	9 (4.5)		
Trauma	5 (2.0)	1 (0.5)		
Emotional stress	27 (11.1)	31 (15.3)		
Rest	90 (36.9)	81 (40.1)		
None	3 (1.2)	2 (1.0)		
Nature of Chest Pain				
Sharp	116 (47.5)	86 (42.6)	2.234	0.327
Pressure Feeling	48 (19.7)	36 (17.8)		
Jamming	80 (32.8)	80 (39.6)		
Location of Chest Pain				
Left of chest	90 (36.9)	92 (45.5)	5.070	0.535
Right of chest	5 (2.0)	3 (1.5)		
Bilateral	59 (24.2)	43 (21.3)		
Middle of chest	71 (29.1)	47 (23.3)		
Lower left chest	10 (4.1)	10 (5.0)		
Epigastrium	8 (3.3)	7 (3.5)		
Mastalgia	1 (0.4)	0 (0.0)		
Spread of Chest Pain				
Back	23 (9.4)	20 (9.9)	7.180	0.208
Shoulder	19 (7.8)	13 (6.4)		
Left arm	12 (4.9)	22 (10.9)		
Jaw	1 (0.4)	1 (0.5)		
None	189 (77.5)	146 (72.3)		
Duration of Chest Pain				
<1 Minutes	56 (22.9)	56 (27.7)	2.689	0.442
1-5 Minutes	114 (46.7)	91 (45.0)		
6-60 Minutes	59 (24.2)	48 (23.8)		
>60 Minutes	15 (6.1)	7 (3.5)		

Chest pain was most commonly localized on the left side of the chest in both genders (p:0.535). Sharp chest pain was the most common type of chest pain in both girls and boys (p:0.337). The duration of chest pain was similar in both sexes and was most frequently 1-5 minutes (p:0.448). The form of chest pain was non- spread type in both sexes (p:0.208). When compared to gender groups it was not found statistically significant in terms of significant triggering factors, nature, location, spread, and duration of chest pain. Symptoms accompanying chest pain, conditions that relieve pain, previous diseases and history of drug use were summarised in **Table 2.**

When compared in terms of gender, chest pain accompanied by dizziness and dyspnea was statistically significantly more common in girls than boys. There was no statistical difference between the two groups in terms of palpitations accompanying chest pain, stomach ache and conditions that relieve chest pain (p >0.05).

Table 2. Symptoms accompanying chest pain, conditions that relieve pain, previous diseases and history of drug use according to gender

	Gender		χ^2	p*
	Boy n (%)	Girl n (%)		
Is chest pain accompanied by dizziness?				
Yes	19 (7.8)	36 (17.8)	10.294	0.001
No	225 (92.2)	166 (82.2)		
Is chest pain accompanied by palpitation?				
Yes	64 (26.2)	69 (34.2)	3.320	0.068
No	180 (73.8)	133 (65.8)		
Is chest pain accompanied by dyspnea?				
Yes	71 (29.1)	87 (43.1)	9.429	0.002
No	173 (70.9)	115 (56.9)		
Is chest pain accompanied by stomach ache?				
Yes	29 (11.9)	30 (14.9)	0.847	0.357
No	215 (88.1)	172 (85.1)		
Have you received treatment for chest pain?				
Yes	7 (2.9)	8 (4.0)	0.405	0.524
No	237 (97.1)	194 (96.0)		
What conditions relieve chest pain?				
Rest	133 (54.5)	96 (47.5)	2.608	0.625
Massage	10 (4.1)	8 (4.0)		
Eating	3 (1.3)	2 (1.0)		
Sleep	5 (2.0)	6 (2.9)		
None	93 (38.1)	90 (44.6)		
Predisposition diseases				
Congenital heart disease	1 (0.4)	2 (1)	6.722	0.242
Acquired heart disease	5 (2)	2 (1)		
Previous cardiac surgery	1 (0.4)	1 (0.5)		
Infection	1 (0.4)	5 (2.5)		
Asthma	12 (4.9)	16 (7.9)		
None	224 (91.8)	176 (87.1)		

Comparison of findings of physical examination, electrocardiogram, telecardiogram and 24-hour electrocardiogram monitoring by gender were indicated in **Table 3**.

Table 3. Comparison of findings of physical examination, electrocardiogram, telecardiogram and 24-hour electrocardiogram monitoring by gender

	Gender		χ^2	p*
	Boy n (%)	Girl n (%)		
Heart sounds and murmurs				
Murmur	24 (9.8)	28 (13.9)	1.739	0.187
None	220 (90.2)	174 (86.1)		
Respiration system findings				
Ral	1 (0.4)	2 (1.0)	2.763	0.598
Wheeze	1 (0.4)	0 (0.0)		
Decreased breathing sound	2 (0.8)	1 (0.5)		
None	240 (98.4)	198 (98.0)		
Electrocardiogram				
Arrhythmias	6 (2.5)	2 (1.0)	3.236	0.357
Conduction Abnormalities	2 (0.8)	0 (0.0)		
Abnormal T and Q wave	2 (0.8)	1 (0.5)		
None	234 (95.9)	199 (98.5)		
Telecardiogarm				
Cardiomegaly	1 (0.4)	0 (0.0)	3.454	0.178
Normal	45 (18.4)	26 (12.9)		
None	198 (81.2)	176 (87.1)		
24-hour electrocardiogram monitoring				
SVE	0 (0.0)	1 (0.5)	7.742	0.459
Moderate often monomorphic VES	1 (0.4)	0 (0.0)		
Very often VES	0 (0.0)	1 (0.5)		
Normal	8 (3.3)	3 (1.5)		
None	235 (96.3)	197 (97.5)		

ECG: eleoctrokardiogram, SVE: supraventricular extrasystole, VES: ventricular extrasystole

Cardiac murmur was heard in 24 (9.8%) of boys and 28 (13.9%) of girls. The respiratory system examination revealed rales in 3 patients, wheezing in one patient, and decreased respiratory sounds in three patients. When gender groups were compared, no statistically significant difference was found in abnormal physical examination findings (p>0.05).

Arrhythmia was detected in six (2.5%) boys and two (1%) girls in the electrocardiogram. There were two patients with supraventricular tachycardia, three with frequent premature ventricular complexes, and three with Wolff Parkinson White Syndrome. In total, two patients have conduction abnormalities, three patients have abnormal Q-T waves. When gender groups were compared, no statistically significant difference was found in abnormal electrocardiogram findings (p>0.05). 24-hour electrocardiogram monitoring revealed arrhythmia in three patients with palpitation.

A telecardiogram was taken in 72 patients. Cardiomegaly due to cardiomyopathy was only detected in one boy patient on telecardiogram. When gender groups were compared, no statistically significant difference was found in abnormal echocardiogram findings (p>0.05). Echocardiogram was performed in all patients.

Thyroid function tests of 103 patients with chest pain accompanied by palpitation were within normal limits. We detected dyspidemia in two of 36 patients whose fasting lipid profiles were examined. Troponin I was studied in 43 (9.6%) patients. Troponin I level was found to be elevated in 9 of these patients who had seven pericarditis and two myocarditis.

The causes of chest pain in children and adolescents with chest pain were indicated in **Table 4**.

Table 4. The causes of chest pain in children and adolescents with chest pain

	n	%
Idiopathic	153	34.3
Musculoskeletal	112	25.11
Precordial Capture	44	9.86
Muscle Tension	32	7.17
Costochondritis	24	5.38
Trauma To the Chest	10	2.24
Cough-Related Muscle Pain	2	0.004
Psychogenic	60	13.45
Daily Stress	47	10.53
Depression	6	1.34
Conversion	4	0.89
Somatization	2	0.44
Hyperventilation	1	0.22
Cardiac	50	11.21
Ventricular Dysfunction	26	5.82
Inflammatory Conditions	19	4.26
Arrhythmias	5	1.21
Respiratory	41	9.19
Exercise-Related Asthma	38	8.52
Pneumonia	3	0.67
Gastrointestinal	30	6.72
GER	15	3.63
Gastritis	15	3.63

GER: gastroeusofagyal reflux

The chest pain was non-cardiac in 244 (55%) patients. The non-cardiac causes were as follows: 25% musculoskeletal, 14% psychological, 9% respiratory, and 7% gastrointestinal, respectively. We found cardiac chest pain in 49 (11%) of patients. We could not identify a cause that could explain chest pain in the remaining 152 (34%) patients. In this case, we classified it as idiopathic chest pain.

The proportions of patients according to age groups were 30.7% in the 6-11 age group, 37% in the 11-15 age group, and 32.3% in the 15-18 age group, respectively.

The patient's laboratory results determined that hemoglobin, creatine cinase (CK), and creatine cinase isoenzyme MB were higher in boy patients (p=0.001).

DISCUSSION

There is a high prevalence of chest pain among children that results in referrals to physicians. Some patients may experience recurrent or severe pain, affecting their daily activities. Currently, news and media reports about the sudden deaths of athletes have caused concern among families and physicians. Medical professionals have feared about missing cardiac pathology. In this prospective study, we assessed the demographic and clinical characteristics of a paediatric population with chest pain as well as the causes of chest pain in a paediatric cardiology outpatient clinic. Here we present one prospective of the most comprehensive studies that have been conducted on chest pain in the pediatric population.

Paediatric chest pain is most commonly seen between the ages of 10 and 21 and is associated with a wide variety of causes and symptoms.[2,5] Accordingly, the average age of the sample in our study was 12 years, and the frequency of chest pain did not differ significantly by gender. Our study showed the greatest prevalence of chest pain among 11 to 15-year-olds.

There has been a persistent finding in the paediatric population that chest pain occurs predominantly in the left hemithorax and is not diffuse.[5,6] The vast majority of patients in our study experienced chest pain primarily on the left side of the chest, and the pain did not spread widely. In our study most of the patients described the pain as sharp (45.2%), and the duration of chest pain was from 1 to 5 minutes in most patients, which was similar to the previous reports that paediatric chest pains last about one minute.[5,7] In our study, having chest pain for more than 1 month, and less than 6 months was prevalent among the cases (36% boy and 35% girls). Approximately 2% of the patients complained of persistent chest pain. Considering that the study included outpatient patients we expected that vast of the patients would complain of long-term pain. Studies including patients who were admitted to both the paediatric emergency room and paediatric cardiology department have reported a sharp and new beginning chest pain up to 70%.[8] Other studies reported chronic chest pain maintained over 1 and 3 months.[9,10]

A rate from 0 to 19% for the prevalence of cardiac abnormalities[11,12] and a rate of 4-6% for cardiac original chest pain was reported in the previous retrospective[2] and prospective studies.[9] Our results present a slightly elevated rate for cardiac aetiologies of paediatric chest pain compared to the literature. This may be due to the fact that the study was conducted in a tertiary hospital, resulting in a high rate of detecting the underlying cause.

The most common detected etiological causes of chest pain in our study were musculoskeletal disease, psychiatric disorders, respiratory diseases and GIS diseases, respectively. Patients with chest pain whose cause could not be identified constituted 34% of all patients. Previous studies report idiopathic chest pain rates of up to 45%.[7,8] We believe that diagnostically advancements and detailed examinations have led to a gradual increase in diagnosis rates and a decrease in idiopathic diagnosis.

According to previous study reports, the most common causes of chest pain among patients with heart-related chest pain were rheumatic heart disease, cardiomyopathy, postoperative closure of anatomical defects, and pericardial effusion.[7,14] We detected cardiac origin pain in 11% of all patients with chest pain. Chest pain in mitral valve prolapses leads to a palpitation sensation that can be perceived as pain due to microvascular perfusion defect associated with papillary and endocardial ischemia and could be accompanying ventricular and premature beats. In our study, patients with mitral valve prolapses comprised causes of 13% of cardiac chest pain. Chest pain due to mitral valve prolapses can be atypical and not triggered by effort, distinguishing it from anginal pain. Patients with mitral valve prolapses who were considered hemodynamically significant mitral regurgitation and had an electrocardiograpic sign of myocardial ischemia were included cardiac causes for chest pain but mild mitral valve prolapses did not. Six patients had moderate to severe mitral regurgitation and negative T wave on D2, D3 and AVF derivations. In our study, we detected pericarditis in 15 patients (3.3%) and myocarditis in 2 patients (0.04%). Girl patients had a 60% higher prevalence of the rheumatic heart disease. Most patients with pericarditis and myocarditis report chest pain at rest, which accounts for 64.7% of the cases. In 47.1% of cases, the chest pain was sharp and in 41.2%, it was accompanied by a pressure sensation. According to our study, structural cardiac disorders accounted for 3.5% of all cardiac causes of chest pain (aortic stenosis, pulmonary stenosis, cardiomyopathy), followed by 3.3% pericarditis, 1.3% mitral valve prolapses, 0.04% myocarditis, and 1.1% arrhythmias. The underlying diseases of the patients have been treated and followed.

Feeling chest pain at rest was the most common type of pain among girls rather than boys (40.1%, and 36.9% respectively). Boys experienced exercise-induced chest pain more than girls (44.3% and 38,6% respectively). Chest pain following emotional stress was the second most common cause of chest pain (11.1% boy and 15.3% girl). Postdigestion (4.5%) and traumatic causes (2%) for chest pain followed.

Psychogenic aetiology for chest pain, psychosomatics with chest discomfort, and finally psychogenic cardiac diseases in children are widely evaluated.[15-17] The rates of chest pain related to gastrointestinal symptoms differ from 3-9%.[7,18] Gastroesophageal flux is reported as the most common cause of chest pain in children, both in the literature similar to our study.[19,21]

The strength of our study lies in the fact that it is a prospectively designed study with a large patient cohort. The present study's particular limitation is that we could not follow up with children with psychological problems after diagnosis and treatment.

CONCLUSION

Our study showed that the aetiology of chest pain in children and adolescents presenting with chest pain is mostly due to non-cardiac causes. We found the slightly frequency of elevated rate for cardiac aetiologies of paediatric chest pain compared to the literature. We suggest that in addition to anamnesis and careful examination, further investigation, if necessary, is important in determining the aetiology of chest pain.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Selçuk University Faculty of Medicine Ethics Committee (Date: 17.01.2018, Decision No: 2018/29).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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Original Article / Orijinal Araştırma

Although Diabetes is Not Obvious, its Complications May Be Obvious, Frequency of Nephropathy in Prediabetic Patients

Diyabet Aşikar Olmasa da Komplikasyonları Aşikar Olabilir, Prediyabet Hastalarında Nefropatinin Sıklığı

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Abstract

Aim: Prediabetes is considered a risk factor for diabetes mellitus (DM) and cardiovascular diseases. Complications are also detected during diagnosis in 10-40% of diabetes patients. Diabetic nephropathy is one of the critical microvascular complications of diabetes. Studies have shown that prediabetes is associated with the development of glomerular hyperfiltration and albuminuria, as in the early stages of diabetes. Identifying patients before overt DM occurs is important for early diagnosis and treatment of nephropathy and DM. The aim of our study is to investigate the presence and frequency of nephropathy in prediabetes patients.

Material and Method: Patients who applied to the outpatient internal medicine and endocrinology outpatient clinics and whose random fasting blood sugar was ≥100 mg/dl were evaluated. Oral glucose tolerance test (OGTT) was performed and HbA1C values were measured. 280 patients diagnosed with prediabetes and evaluated for nephropathy were included in the study.

Results: Nephropathy was detected in 81 (28.9%) of the patients. The average HbA1C value of the group with nephropathy was 6.28% (sd: 0.52) and the average HbA1C value of the group without nephropathy was 6.05% (sd: 0.29). The average HbA1C value was found to be significantly higher in the group with nephropathy (p=0.000).

Conclusion: The fact that nephropathy was detected in 28.9% of the patients showed once again the seriousness of prediabetes. Therefore, patients with prediabetes, especially those with higher HbA1C values, need to be evaluated more carefully in terms of nephropathy and CKD.

Keywords: Diabetes, prediabetes, nephropathy

Öz

Amaç: Prediyabet, diabetes mellitus (DM) ve kardiyovasküler hastalıklar için bir risk faktörü kabul edilmektedir. Tip 2 DM tanısı konduğu anda hastaların %10-40'ında komplikasyonlar vardır. Diyabetik nefropati diyabetin önemli mikrovasküler komplikasyonlarından biridir. Yapılan çalışmalar prediyabetin de diyabetin erken dönemlerinde olduğu gibi, glomerüler hiperfiltrasyon ve albüminüri gelişimi ile ilişkili olduğunu göstermiştir. Aşikar DM ortaya çıkmadan önce hastaların tespit edilmesi nefropatinin ve DM'ün erken tanı ve tedavisi için önemlidir. Çalışmamızın amacı prediyabet hastalarında nefropatinin varlığını ve sıklığını araştırmaktır.

Gereç ve Yöntem: Ayaktan İç Hastalıkları ve Endokrinoloji Polikliniğine başvuran, rastgele bakılan açlık kan şekeri ≥100 mg/dl olan hastalar değerlendirmeye alındı. Oral glukoz tolerans testi (OGTT) yapıldı ve HbA1C değerleri ölçüldü. Çalışmaya prediyabet tanısı konulan ve nefropati değerlendirmesi yapılan 280 hasta dahil edildi.

Bulgular: Hastaların 81'sinde (%28,9) nefropati saptandı. Nefropatisi olan grubun ortalama HbA1C değeri %6,28 (ss:0,52) nefropatisi olmayan grubun ortalama HbA1C değeri %6,05 (ss:0,29) düzeyinde saptandı. Nefropatisi olan grupta ortalama HbA1C değerinin anlamlı olarak daha yüksek olduğu görüldü (p=0,000).

Sonuç: Hastaların %28,9'unda nefropati saptanmış olması prediyabetin ciddiyetini bir kez daha göstermiş oldu. Bundan dolayı prediyabeti olan, özellikle de HbA1C değeri yüksek olan hastalarda nefropati ve KBY açısından daha dikkatli olunmalıdır.

Anahtar Kelimeler: Diyabet, prediyabet, nefropati

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INTRODUCTION

Diabetes Mellitus (DM) is one of the most common and important diseases all over the world. It constitutes one of the top five causes of death.[1] The number of prediabetic people predicted by the International Diabetes Federation (IDF) in 2035 is 473 million, and the number of patients diagnosed with DM in 2030 is 438 million.[2]

In order to solve Type 2 DM and its complications, extensive research is being carried out all over the world for early diagnosis, treatment and prevention of complications, and different criteria and treatment methods are emerging. It is essential to recognize patients and take early precautions, especially in the prediabetes period before overt Type 2 DM. If precautions are taken in the early period, the emergence of Type 2 DM and its complications can be prevented.

One of the most critical microvascular complications of diabetes is diabetic nephropathy and is the most common cause of end-stage renal failure.[2-4] According to the data of the Turkish Nephrology Association, the most common cause in end-stage renal failure patients receiving dialysis treatment was DM, with a rate of 39%.[5] Microalbuminuria has also been found to be associated with cardiovascular diseases.[1]

Since Type 2 DM often develops silently and insidiously, diabetic nephropathy can be detected at the time of diagnosis. In Type 2 DM, if nephropathy is detected at the time of diagnosis or even during the prediabetes period, the chance of preventing nephropathy will be higher.[3]

Diabetic nephropathy is diagnosed based on the albumin/creatinine ratio measured in the first morning urine.[4] In patients with high albumin/creatinine ratio (>30 mg/g), 2 more repeated measurements are performed at 3-month intervals. As a result of these measurements, if the low glomerular filtration rate (GFR) or the high albumin/creatinine level continues or if albuminuria is detected in 2 out of 3 measurements and if no other reason is found to explain the situation, the patient is considered to have diabetic nephropathy.[3]

Prediabetes is a term used for impaired glucose tolerance (IGT) and impaired fasting glucose (IFG), and both conditions are considered risk factors for DM and cardiovascular diseases.[3] Once type 2 diabetes is diagnosed, 10-40% of patients have complications.[6] Studies have shown that prediabetes is associated with the development of glomerular hyperfiltration and albuminuria, as in the early stages of diabetes.[7] Since patients are generally asymptomatic, it is difficult to catch the disease during prediabetes.

In this study, we aimed to investigate the presence and frequency of nephropathy in patients with prediabetes. Additionally, the relationship of nephropathy with HbA1C value and other variables was analyzed.

MATERIAL AND METHOD

An application was made to the Health Sciences University Erzurum Regional Training and Research Hospital Clinical Research Ethics Committee for the study. As a result of the application, approval was received on 19.03.2018 and with decision number KAEK 2018/06-40.

Patients who were admitted to the Endocrinology and Metabolic Diseases Polyclinic and Internal Medicine Polyclinic at Erzurum Regional Training and Research Hospital as outpatients and whose fasting plasma glucose was found to be between 100-125 mg/dl were included in the study. Afterwards, a 75-g OGTT test was performed. Height, weight, waist circumference, and body mass index (BMI) measurements of the patients were taken. Blood LDL-C (low density cholesterol), HDL-C (high density cholesterol), TG (triglyceride), HbA1C and albumin/creatinine ratio in spot urine were measured. 280 patients diagnosed with prediabetes and evaluated for nephropathy were included in the study.

The diagnosis of prediabetes was made if impaired glucose tolerance (IGT), impaired fasting glucose (IFG) or HbA1C value was detected between 5.7-6.4.[6]

Nephropathy evaluation in patients was made according to the protein, creatinine and total protein/creatinine values requested in the spot urine from the first morning urine. Accordingly, patients with proteinuria of 150 mg/dl and above were considered to have nephropathy. The patients' GFR values were also taken into consideration, and the presence of nephropathy was decided together with GFR and proteinuria. Those with diseases that may cause proteinuria, such as urinary system infection, glomerulonephritis or other active infective pathology, nephrolithiasis, heavy exercise, presence of rheumatic disease, diagnosis of hypertension, steroid use, menstrual bleeding, hemolysis, pregnancy, or heart failure, were not included in the evaluation.

RESULTS

Of the 280 patients included in our study, 36.4% were male (n=102) and 63.6% (n=178) were female. The average age of our patients was 54.15 (sd: 11.6).

The average HbA1C value of the patients was determined as 6.12% (sd: 0.38).

Nephropathy was detected in 81 (28.9%) of the patients. Nephropathy status was compared with other parameters. In the comparison made with HbA1C, the average HbA1C value of the group with nephropathy was found to be 6.28% (sd: 0.52) and the average HbA1C value of the group without nephropathy was 6.05% (sd: 0.29). The average HbA1C value was found to be significantly higher in the group with nephropathy (p=0.000). In addition, the LDL-C value of the group with nephropathy was significantly higher than the group without nephropathy (p=0.006). While the average LDL-C value of the group with nephropathy was 137.5 mg/dl (sd: 28.6), the average LDL-C value of the group without nephropathy was 125.6 mg/dl (sd: 33.9). No significant difference was observed in terms of HDL-C, TG, BMI and waist circumference.

Table 13. Comparative analysis of patients with and without nephropathy

	With nephropathy	Without nephropathy	p score
Number (n=280)	28.9% (n=81)	71.1% (n=199)	
HbA1C (%)	6.28 (sd:0.52)	6.05 (sd:0.29)	0.000
LDL-C (mg/dl)	137.5 (sd:28.6)	125.6 (sd:33.9)	0.006
HDL-C (mg/dl)	45.4 (sd:10.2)	47.5 (sd:11.3)	0.173
TG (mg/dl)	173.8 (sd:85.0)	153.7 (sd:79.5)	0.062
BMI (kg/cm²)	32.4 (sd:6.5)	31.3 (sd:6.3)	0.175
Waist circumference (cm)	88.4 (sd:8.9)	86.5 (sd:9.2)	0.125

Prediction of nephropathy by HbA1C was analyzed by ROC curve. In the analysis, AUC was found to be 0.642. Based on the HbA1C value of 6.05, it was observed that this value had 65% sensitivity and 50% specificity in predicting nephropathy (p=0.000).

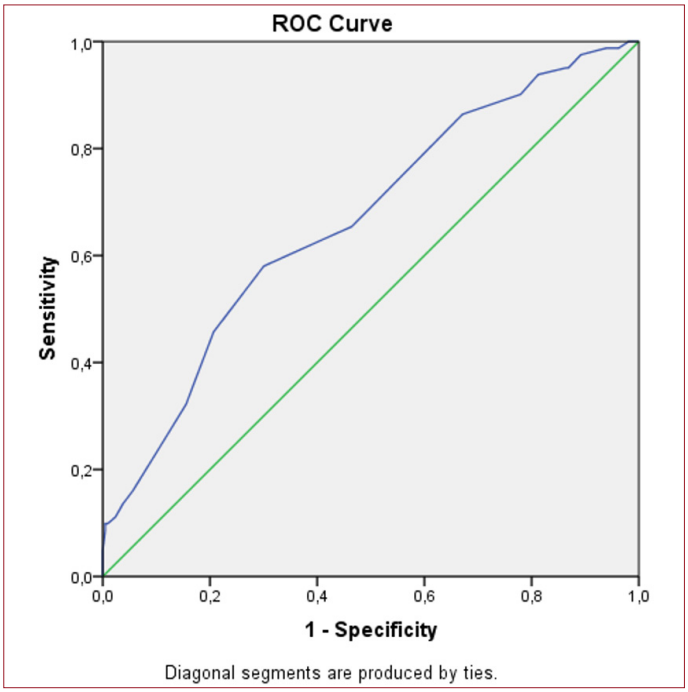

Figure 1. Analysis of HbA1C value predicting the presence of nephropathy with ROC curve

The relationship between OGTT results and nephropathy status was analyzed. It was observed that there was a significant difference between the groups (p=0.001). The highest rate of nephropathy was seen in patients with IFG and IGT together. The lowest rate was detected in the IFG group.

DISCUSSION

Studies show that prediabetes increases risk in many aspects. First of all, 5-10% of prediabetes patients are diagnosed with diabetes every year. Many problems and complications may arise in those who are not diagnosed with diabetes. On the other hand, lifestyle changes in prediabetes patients reduce the risk by 40-70%. This reveals the importance of detection and precautions to be taken at an early stage.[8]

In a study that included 46,911 prediabetes patients in the UK and examined data with a follow-up of 11.1 years, it was shown that the risk of atherosclerotic heart disease increased in those with an HbA1C value of >5.4% compared to those with an HbA1C value of <5%. It was also found that the risk of heart failure and chronic kidney disease increased in those with >6.2%. These results show that there is an increase in risk at HbA1C values below the Type 2 DM diagnostic limit.[9]

In our study, we obtained a result similar to this study. While the average HbA1C value of the patients with nephropathy was 6.28%, the average HbA1C value was 6.05% in the group without nephropathy. This result suggests that an HbA1C value of around 6.2% may be a threshold value in this regard.

In a large-scale review study, the risk of prediabetes in terms of all-cause mortality and complications of diabetes was examined. In this study, it was observed that prediabetes increased the risk of all-cause mortality, coronary heart diseases, stroke, heart failure, atrial fibrillation and chronic renal failure, ranging from 6% to 101%. At the same time, prediabetes has been found to be associated with hepatocellular cancer, breast cancer and dementia. The increased risk of all-cause mortality was found to be higher in those with impaired fasting glucose. As a result, it has been stated that prediabetes poses a significant increase in risk and that these data should be supported by detailed studies (for example, investigating the relationship between nephropathy and prediabetes).[10]

Based on the data of the 4C (China Cardiometabolic Disease and Cancer Cohort) study, which included 55,777 prediabetes patients in China, prediabetes patients were analyzed by dividing them into 6 groups. It has been observed that different risk increases and diseases occur in different clusters. This indicates that prediabetes patients should be examined in detail. For example, it was observed that the risk of cardiovascular disease was highest in the group with more common obesity and insulin resistance. The highest risk of chronic kidney disease was observed in clusters 4 and 6. While obesity and insulin resistance are common in cluster 4, high glycemic levels in multiple parameters are present in cluster 6. According to these data, we can say that if prediabetes is accompanied by obesity and there is a high glycemic level in more than one parameter, the risk of chronic kidney disease increases significantly.[11]

Cross-sectional studies show that prediabetes is associated with CKD. In a study, 1261 patients without diabetes were followed for 5.6 years, and it was shown that prediabetes was associated with the development of glomerular hyperfiltration and albuminuria, as in the early stages of diabetes.[7] Studies have shown that albuminuria increases significantly from normoglycemia to IFG, IGT, IFG+IGT and Type 2 DM, and that this occurs before the development of diabetes.[12-14]

Considering these studies, it is seen that prediabetes is a risk factor for nephropathy, and there is an increased albuminuria

and hyperfiltration state in prediabetes compared to the normal population, which predisposes to nephropathy and CKD.

In our study, 81 (28.9%) of 280 patients evaluated for nephropathy were found to have nephropathy. In the comparison made with HbA1C, the average HbA1C value of the group with nephropathy was 6.28% (sd: 0.52) and the average HbA1C value of the group without nephropathy was 6.05% (sd: 0.29). The mean HbA1C value was significantly higher in the group with nephropathy (p=0.000). Prediction of nephropathy by HbA1C was analyzed by ROC curve. In the analysis, AUC was found to be 0.642. Based on the HbA1C value of 6.05, it was observed that this value had 65% sensitivity and 50% specificity in predicting nephropathy (p=0.000).

As a result of these findings, we can say that there is a significant relationship between HbA1C and nephropathy. However, it does not seem possible to predict nephropathy status with HbA1C. It should be kept in mind that nephropathy may occur in patients with high HbA1C, even if it is at the prediabetes level. Patients should definitely be examined in this respect.

According to our study results, the highest risk of nephropathy was detected in the IFG+IGT, IGT and IFG groups, respectively. While there are data compatible with these results in the literature, there are also studies with different results.[11,15] As a result, it should be kept in mind that there is a significant increase in risk in all groups, but there may be differences between groups and this may be affected by side factors.

CONCLUSIONS

It was observed that prediabetes status and HbA1C value revealed a significant relationship with the presence of nephropathy. The fact that nephropathy was detected in 28.9% of the patients showed once again the seriousness of prediabetes. Therefore, early diagnosis and treatment of prediabetes is important in terms of nephropathy and CKD.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Health Sciences University Erzurum Regional Training and Research Hospital Clinical Research Ethics Committee (Date:19.03.2018, Decision No: KAEK 2018/06-40).

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

Referee Evaluation Process: Externally peer-reviewed.

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Original Article / Orijinal Araştırma

The Role of Clinical, Radiologic and Laboratory Markers in Distinguishing an Appendiceal Mucocele from Acute Appendicitis

Apendiks Mukoselini Akut Apandisitten Ayırmada Klinik, Radyolojik ve Laboratuvar Belirteçlerin Rolü

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Abstract

Aim: This study aims to assist the surgical treatment plan by increasing the rate of correct preoperative diagnoses through comparing the clinical, radiological, and laboratory findings of appendiceal mucocele (AM) and acute appendicitis (AA) before surgery.

Material and Method: The study included 63 patients with a histopathologic diagnosis of AM and AA among 4867 patients who underwent appendectomy with the diagnosis of acute appendicitis in the general surgery clinic between 2009 and 2020. The patients were separated into two groups: those with AM (21 patients) and those with AA (42 patients). Age, gender, physical examination (PE), Alvarado appendicitis score, ultrasonography (USG), computed tomography (CT), laboratory, preoperative diagnosis, intraoperative diagnosis, and pathological diagnosis results of both groups were compared.

Results: PE, abdominal pain, nausea, vomiting, fever symptoms, and Alvarado score were found to be significant between the two groups ($p<0.05$). In addition, WBC, NE, LYM %, and CRP were found to be high in group 2 ($p<0.05$), while there was no difference in radiological diagnosis (USG/CT) between the two groups ($p<0.05$). However, the appendix diameter was larger in group 1 ($p<0.05$). Patients with AM in 80% preoperatively, and 52% intraoperatively were operated on with a provisional diagnosis of AA. The second surgery was performed in Group 1 with a rate of 9.5% (2/21).

Conclusion: In our study, patients with AM who underwent surgery with a diagnosis of AA were found to differ in radiological, clinical, and laboratory findings from patients with AA.

Keywords: Appendiceal mucocele, acute appendicitis, differential diagnosis

Öz

Amaç: Bu çalışmanın amacı; cerrahi öncesi apendiks mukoseli(AM) ile akut apandisit(AA)'i klinik, radyolojik ve laboratuvar sonuçlarını karşılaştırıp ameliyat öncesi doğru tanı oranımızı artırarak cerrahi tedavi planına yardımcı olmaktır.

Gereç ve Yöntem: Çalışmaya 2009-2020 yılları arasında genel cerrahi kliniğinde akut apandisit tanısıyla apendektomi yapılan 4867 hastadan histopatolojik olarak AM ve AA tanısı alan 63 hasta dahil edildi. Hastalar AM'li olanlar (21 hasta) olmak üzere iki gruba ayrıldı. ve AA'lı olanlar (42 hasta). Her iki grubun yaş, cinsiyet, fizik muayene (PE), Alvarado apandisit skoru, ultrasonografi (USG), bilgisayarlı tomografi (BT), laboratuvar, preoperatif tanı, intraoperatif tanı ve patolojik tanı sonuçları karşılaştırıldı.

Bulgular: PE, karın ağrısı, bulantı, kusma, ateş semptomları ve Alvarado skoru iki grup arasında anlamlı bulundu ($p<0,05$). Ayrıca grup 2'de WBC, NE, LYM % ve CRP yüksek bulunurken ($p<0,05$), radyolojik tanı (USG/BT) açısından iki grup arasında fark yoktu ($p<0,05$). Ancak apendiks çapı grup 1'de daha büyüktü ($p<0,05$). AM'li hastaların %80'i ameliyat öncesi, %52'si ameliyat sırasında geçici AA tanısıyla ameliyat edildi. İkinci ameliyat ise %9,5 (2/21) oranında Grup 1'de yapıldı.

Sonuç: Çalışmamızda AA tanısıyla ameliyat edilen AM'li hastaların radyolojik, klinik ve laboratuvar bulgularının AA'lı hastalardan farklı olduğu görüldü.

Anahtar Kelimeler: Apendiks mukosel, akut apandisit, ayırıcı tanı

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INTRODUCTION

Appendiceal mucocele (AM) is a cystic disease caused by dilating the appendiceal lumen with mucopurulent fluid. It is a very rare and pathological condition of appendicitis, usually benign but sometimes malignant. It occurs due to complete or almost complete obstruction of the appendiceal lumen for many reasons, especially inflammation and defecation.[1] Acute appendicitis is the most commonly performed emergency abdominal surgery.[2] A negative appendectomy is performed in about 28% of these operations. In about 0.2% and 0.3% of patients operated on with a diagnosis of acute appendicitis (AA), the pathologic diagnosis is appendiceal mucocele.[2,3] While it is often found incidentally without causing symptoms, it sometimes produces an acute abdominal finding. Mucosal hyperplasia, mucinous cystadenoma, and mucinous cystadenocarcinoma are the four pathologic subgroups of AM retention cyst.[4] Mucinous cystadenoma is the most common of these pathological subgroups. Although AM generally occurs in all age groups and both genders, it is more common in women after the 5th decade. Although there is no common consensus on the surgical treatment option, appendectomy or right hemicolectomy is usually performed.[4] Despite the intensive use of radiological imaging equipment, it is unfortunately not possible in most cases to establish a definitive diagnosis before surgery.[5] Patients are usually operated on with a preliminary diagnosis of AA. Sometimes, patients are diagnosed by chance before surgery. Their complaints are mostly similar to AA. It can result in a second surgery and pseudomyxoma if misdiagnosed and treated. A correct preoperative diagnosis is very important to avoid such complications. For this purpose, the clinical prediction score, the Alvarado appendicitis score, ultrasonography (USG), and computed tomography (CT) should be used intensively.[6,7] Moreover, synchronous tumors, especially gastrointestinal tumors, may also occur in patients with AM.[8]

This study aims to compare the clinical, radiological, and laboratory results of AM and AA before surgery and support the surgical treatment plan by increasing our rate of correct diagnosis before surgery.

MATERIAL AND METHOD

The study was conducted as a retrospective case-control study in the General Surgery Clinic of Hospital between 2009-2020. The study comprised AM patients with histopathological diagnosis among 4867 appendectomy patients. The study included twice as many patients with similar demographic features and histopathological diagnosis of acute appendicitis as the control group. The study was conducted in compliance with the Declaration of Helsinki, after approval by the Ethics Committee on 24.12.2020 under the number 2020/78.

The list of all appendectomy patients included in the study was obtained from our hospital's computerized electronic records system. In these patients, pathological diagnoses such as appendiceal lymphoma, neuroendocrine tumor of the appendix, adenocarcinoma of the appendix, granulomatous appendicitis, appendiceal mucocele were reached histopathologically, except AA. Patients with a diagnosis of non-AM and non-AA were excluded from the study. A total of 63 patients, 21 of whom were diagnosed with AM and 42 patients with AA as a control group, were included in the study. The patients' diagnoses were re-examined one by one in the pathology laboratory by an expert pathologist, and their diagnoses were confirmed following the new histopathological classification.

Patients who did not meet the criteria of our study, who were under 18 years of age, who were over 80 years of age, who had a laparoscopic appendectomy, and who had previously been diagnosed with colon and gastrointestinal stromal tumors were excluded from the study. Patients over 18 and under 80 years of age with open appendectomy diagnosed histopathologically with AM and AA were included in the study.

The Alvarado scoring system was used to evaluate the physical examination findings of the study's patients. In all patients, a diagnostic abdominal USG was performed. Diagnostic abdominal CT was additionally performed in patients in whom physical examination and abdominal USG failed to establish a definitive diagnosis.

The age and gender of patients who met study criteria and were enrolled in the study were recorded from their electronic files. The patients' physical examination, Alvarado appendicitis scores, USG, CT, laboratory results, and preoperative, intraoperative, and pathologic diagnoses were recorded individually. The recorded results were compared between the two groups.

Statistical Analysis

In the statistical analysis of the data, the SPSS 23.0 package software was used. Continuous measurements were summarized as mean, standard deviation, and minimum-maximum; categorical measurements were summarized as numbers and percentages. The conformity of the variables with the normal distribution was examined using the Shapiro-Wilk test. The Mann-Whitney U test was used for parameters that did not conform to the normal distribution, and independent Student t-tests were used for parameters that did conform to the normal distribution. The statistical significance level was taken as $p<0.05$ for all tests.

RESULTS

63 patients from 4867 appendectomies performed in our clinic for 10 years participated in the study. Group 1 consisted of 21 (0.04%) AM patients, and group 2 consisted of 42 AA control group patients. The gender distribution was similar in the groups (p:0.859). The mean age was 50 years for AM and 45 years for AA (p:0.285). 47% of AM patients were male, and 53% were female. 88% (56/63) of the operated patients were operated on urgently and 12% (7/63) electively. The number of patients who underwent urgent surgery was higher in the AA group than in the AM group (p:0.002). All from group

2 presented to the clinic with abdominal pain. Nausea (95% vs 83.3 p<0.001) and vomiting (95% vs 47.6% p:0.003) were more common in AA than AM. Fever AA was more frequent (9.5% vs. 42.9%, p:0.007). Other physical examination findings were not significant between the two groups (p>0.05) (**Table 1**). The Alvarado score was significantly higher in the AA group than in the AM group (p<0.001) (**Table 2**).

While 100% (21/21) USG and 47.6% (10/21) CT were performed radiologically in AM patients, (42/42) USG was performed in AA patients (100%) and CT in (17/42) (40.5%) patients. Radiological diagnosis of AM was 14.2% (3/21) and AA was diagnosed preoperatively in 92.8% (39/42) (p<0.05) . Pre-diagnosis of the AM group was rectal Ca in 4.7% (1/21), uterine myoma in 4.7% (1/21), intra-abdominal abscess in 4.7% (1/21), plastron appendicitis in 4.7% (1/21), and AA in 66% (14/21) of patients. Intraoperatively, AM has been diagnosed in 61.9% (13/21) cases, AA in 38% (8/21) cases and 4.7% (1/21) rectal Ca and 4.7% (1/21) uterine tumors were diagnosed together. In the control group, perforated appendicitis was diagnosed radiologically in 4.7% (2/42) of patients and ileus in 2.3% (1/42) (**Table 1**).

Table 1. Demographic and clinical data

	Group 1 Patients with Appendiceal Mucocele (n=21)	Group 2 Patients with Acute Appendicitis (n=42)	p
	n (%)	n (%)	
Gender			
Male	10 (47.6)	21 (50.0)	
Female	11 (52.4)	21 (50.0)	
Age (t)	50.3±17.1	45.76±15.2	0.879
Admission			
Emergency	15 (71.4)	41 (97.6)	0.002
Elective	6 (28.6)	1 (2.4)	
Physical Examination (Abdomen)			
Abdominal pain (+)	17 (81.0)	42 (100.0)	0.010
Nausea (+)	7 (33.3)	35 (83.3)	<0.001
Vomiting (+)	2 (9.5)	20 (47.6)	0.003
Constipation (+)	7 (33.3)	10 (23.8)	0.422
Diarrhea (+)	0 (0.0)	4 (9.5)	0.144
Fever (+)	2 (9.5)	18 (42.9)	0.007
Rebound and defense (+)	0 (0.0)	1 (2.4)	>0.05
Tenderness in the right lower quadrant (+)	2 (9.5)	9 (24.4)	>0.05
Mass in the right lower quadrant (+)	4 (19.0)	0 (0.0)	>0.05
Bottom right rebound (+)	0 (0.0)	31 (73.8)	<0.05
Rebound/defense in all quadrants (+)	0 (0.0)	1 (2.4)	<0.05
Radiological Diagnosis			
USG (+)	21 (100)	42 (100)	0.086
CT (+)	10 (47.6)	17 (40.5)	0.589
Surgical Method			
Open appendectomy (+)	21 (100)	42 (100)	
Secondary operation (+)	2 (9.5)	0 (0.0)	<0.05

* p<0.05, (t)=Independent Student's t-test, chi-square, and Fisher's exact test

Table 2: Alvarado score ratios between Group1 (AM) and Group2 (AA)

	Group1 (AM) (n=21) score (%)	Group2 (AA) (n=42) score (%)	p
Symptoms			
Abdominal pain (+)	17 (81.0)	42 (100.0)	0.010
Anorexia (+)	7 (33.3)	35 (83.3)	<0.001
Vomiting (+)	2 (9.5)	20 (47.6)	0.003
Clinical Findings			
Tenderness in the right lower quadrant (+)	4 (9.5)	18 (24.4)	>0.05
Bottom right rebound (+)	0 (0.0)	4 (9.5)	0.144
Fever (+)	2 (9.5)	18 (42.9)	0.007
Laboratory Results			
Increase in the number of leukocytes (+)	12 (35)	72 (85)	0.001
Left shift in neurophile (+)	6 (35)	33 (78.5)	0.001
Total Score	50	242	0.001

* p<0.05, (t)=Independent Student's t-test, chi-square, and Fisher's exact test

The mean appendix diameter was larger in AM (2 vs. 1 p < 0.001), and its size was larger in AA (6.6 vs. 7.1 cm). White blood cell count (10.8 vs. 15 p:0.001), neutrophil count (7.79 vs. 11.8 p:0.001), and CRP (9.6 vs. 55.5 p:0.001) were higher in AA, as shown in **Table 3**.

Table 3. Laboratory parameters

	Group 1 Patients with Appendiceal Mucocele (n=21)	Group 2 Patients with Acute Appendicitis (n=42)	p
	n (%)	n (%)	
Diameter (u) (USG/CT)	2 (1-7)	1 (0.5-2)	<0.001
Dimension (u) (USG/CT)	6.6±1.9	7.1±1.5	0.299
WBC (t)	10.8±4.8	15.0±4.4	0.001
EOS% (u)	0.55 (0-2.56)	0.64 (0-5.47)	0.759
NE (t)	7.79±4.7	11.8±4.3	0.001
LYM% (t)	22.7±13.9	15.6±7.1	0.010
BAS% (u)	0.4 (0.03-1.86)	0.32 (0-5.5)	0.321
CRP (u)	9.6 (0.3-367.01)	55.5 (2-436)	0.001
Hematuria (+)	7 (33.3)	10 (23.8)	0.422

* p<0.05, (t)=Independent Student t-test, (u)= Mann-Whitney u test, chi-square test

100%(42/42), one of which was perforated, were diagnosed intraoperatively as AA. All of these cases were histologically diagnosed as AA. 11.9% (5/42) of them were perforated. Open appendectomy was performed in all (**Table 2**). The rate of preoperative diagnosis of acute appendicitis in patients in group AM (81% vs. 97.6% p<0.05) was found in 52% of patients in group AM with intraoperative appendicitis mucocele. **Table 4** shows the intraoperative and postoperative variables.

Table 4. Preoperative and pathological variables

Diagnosis	Group 1 Patients with Appendiceal Mucocele (n=21)	Group 2 Patients with Acute Appendicitis (n=42)	p
	n (%)	n (%)	
Preoperative diagnosis			
Appendiceal mucocele	2 (9.5)	0 (0.0)	>0.05
Acute appendicitis	17 (81.0)	41 (97.6)	<0.05
Acute abdomen	0 (0.0)	1 (2.4)	>0.05
Rectum Ca	1 (4.8)	0 (0.0)	>0.05
Uterine tumor	1 (4.8)	0 (0.0)	>0.05
Pathological diagnosis			
No	0 (0.0)	42 (100.0)	<0.001
Mucinous adenocarcinoma (high-grade dysplasia)	2 (9.5)	0 (0.0)	<0.001
Low Mucinous cystadenoma (low-grade dysplasia)	14 (66.7)	0 (0.0)	<0.001
Mucocele, mucosal hyperplasia	2 (9.5)	0 (0.0)	<0.001
Mucocele, retention cyst	3 (14.3)	0 (0.0)	<0.001

* p<0.05, chi-square and Fisher's exact test

Histologically, 57.1% (12/21) of patients were diagnosed with low-grade appendiceal mucinous neoplasm (LAMN), 9.5% (2/21) with high-grade appendiceal mucinous neoplasm (HAMN), 14.2% (3/21) with mucocele retention cyst, and 9.5% (2/21) with mucocele mucosal hyperplasia. There was one case each of rectal Ca, uterine leiomyoma, and pseudomyxoma peritonei, synchronous with these diagnoses(**Table 4**). All operations (100%) were open, and the second operation was right hemicolectomy with a rate of 9.5% (2/21) (p<0.05) (**Table 1**).

DISCUSSION

In this study, when we compared AM patients' radiological, laboratory, and clinical data with those of patients who underwent appendectomy mainly because of AA, AM patients were found to have different findings than AA patients, and most of these data were statistically significant.

In their study, Akbaş et al. noted that the rate of correct diagnosis could increase by evaluating the preoperative radiological, physical examination, history, and laboratory data of the patients to be taken with the preliminary diagnosis of AA.[9] Beyrouti et al. reported that the clinical picture of AM patients overlapped by approximately 73% with the clinical findings of AA in their study.[10] Another study reported that many diseases of appendicitis, especially AM, can clinically and radiologically mimic acute appendicitis.[11] Sökücü and Balık (2010) noted that the signs and symptoms of AM patients are similar to those of AA, but sometimes they were diagnosed incidentally during an operation performed for another reason without symptoms .[12] Our two AM patients were also diagnosed during abdominal surgery, which was performed for a different reason.

In our study, the mean age and female gender were higher in the AM group than in the AA group, but this was not statistically significant. A study conducted in China found that the average age of patients with AM was generally high and that both groups were equally distributed in terms of gender. [13] Another study found that patients with AM were more common in women and older age, whereas patients with AA were more common in younger and older men.[14]

Preoperatively, all patients in group 2 had symptoms of abdominal pain, whereas only 81% of patients in group 1 had abdominal pain. Other clinical findings, nausea, vomiting, and fever, were statistically significant between the two groups. As a result of clinical studies, it was found that clinical symptoms were more likely to be observed in the AM patient group.[12,15] Another study found that patients with AA generally present to the clinic with symptoms of abdominal pain, nausea, vomiting, and fever.[16] Our study is compatible with the literature in this regard. In our study, the abdomen's physical examination (PE) was normal in 71% of the AM group, whereas 28.6% had pathologic findings. However, abdominal PE findings were pathological in 100% of the AA group. Senturk et al. discovered in their study that the clinical findings of AM patients, which differ from our results, are similar to the clinical findings of AA.[17] However, another study reported that only 50% of AM symptoms and clinical findings were similar to AA symptoms.[18] In recent years, the Alvarado appendicitis score has been applied to reduce the rate of negative appendectomies and increase the preoperative rate of correct diagnosis of acute appendicitis, and it has been reported to have a sensitivity of 54% to 70% in many scientific studies.[19,20] On the other hand, it has been reported that the Alvarado score alone is important but inadequate for a correct preoperative diagnosis. Therefore, radiologic diagnostic tools such as USG and, when appropriate, CT should be used to increase the rate of correct diagnosis. [21,22] Our study is compatible with the literature in this aspect.

Our study found no statistically significant difference between the two groups in the radiological evaluation of the patients' preoperative diagnosis. In most patients in the AM group, a radiological diagnosis of AA could not be established. The diagnosis was confirmed radiologically in the majority of AA patients. The literature indicates that the primary diagnosis in AM patients is radiologically low and is more likely to be established intraoperatively or histologically.[23,24] In our study, the correct diagnosis of AM patients was mostly established intraoperatively or histologically following the literature.

In many studies, it has been found that the diameter of the appendix can be an essential indication for preoperative diagnosis because the diameter of the appendix is larger in AM patients than in AA patients.[25,26] The appendix diameter of AM patients was found to be larger than that of AA patients in our study. Furthermore, Saylan et al. reported in their study that although the blood parameters between the two groups were not statistically significant, the number of patients with

erythrocytes in the urine was significantly higher in the AM group.[27] In our study, the values of blood parameters WBC, NE, LYM %, and CRP were statistically significantly higher in the group AA than in the group of AM patients, while hematuria was not statistically significantly higher in the AM group.

In all patients, the open surgical method was preferred. Right hemicolectomy was performed in the second surgery because of the pathologic diagnosis of mucinous cystadenocarcinoma in two patients in the AM group and the pathologic diagnosis of local pseudomyxoma peritonei in one of these patients. In clinical studies, open or laparoscopic appendectomy carefully performed to avoid AM pseudomyxoma peritonei is recommended, whereas cecal resection or right hemicolectomy is recommended if the diagnosis is cystadenocarcinoma.[27] On the other hand, it was observed in many studies that open surgery was recommended to AM patients instead of laparoscopy.[12]

The limitation of our study might be that it is a single-center retrospective study. Another limiting factor is that no intraoperative frozen section examination was performed in suspicious cases. Its strength is that it is the first study to compare AM and AA with preoperative radiological, clinical, and laboratory data.

CONCLUSION

In this study, it was found that radiological, clinical, and laboratory data differed among AM patients who were operated on with a diagnosis of AA and some of whom required surgery for the second time. This may contribute to the treatment plan to be applied by increasing the preoperative differential diagnosis rate for two different emergency surgical conditions of the same organ by noting the differences. However, there is a need for studies that include more patients and compare prospective AM with AA.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Niğde Ömer Halisdemir University Ethics Committee (Date: 24.12.2020, Decision No: 2020/78).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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Original Article / Orijinal Araştırma

The Impact of Age on Postoperative Outcomes in Plastic Surgery: Data Analysis and Inferences

Plastik Cerrahide Yaşın Ameliyat Sonrası Sonuçlara Etkisi: Veri Analizi ve Çıkarımlar

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Abstract

Aim: To investigate the effect of advancing age on postoperative outcomes in plastic surgery, focussing on patients 60 years and above.

Material and Method: A retrospective analysis of clinic data was conducted from January 1, 2020, to October 1, 2023. Data included demographic data from the patient, preoperative comorbidities, surgical details, and 30-day postoperative complications. Logistic regression models were used to evaluate the association between age and complication rates, adjusting for confounders such as comorbidities and surgery types.

Results: The study found a significant association between increasing age and higher complication rates within 30 days after surgery. It also revealed that older surgeons tend to have lower complication rates. Furthermore, factors like smoking, obesity, and gender were identified as influential in postoperative complications.

Conclusions: Increasing age is independently associated with an increased risk of postoperative complications in plastic surgery. The study highlights the need for a comprehensive approach to evaluate postoperative outcomes, considering various factors from the patient and the surgeon.

Keywords: Plastic surgery, postoperative outcomes, age, complication rates, patient care, surgeon age

Öz

Amaç: Plastik cerrahide, özellikle 60 yaş ve üzeri hastalarda, ilerleyen yaşın ameliyat sonrası sonuçları üzerindeki etkisini araştırmak.

Gereç ve Yöntem: 1 Ocak 2020'den 1 Ekim 2023'e kadar klinik verilerinin retrospektif analizi yapıldı. Veriler, hasta demografileri, preoperatif komorbiditeler, cerrahi detaylar ve 30 günlük postoperatif komplikasyonları içermektedir. Yaş ile komplikasyon oranları arasındaki ilişkiyi değerlendirmek için lojistik regresyon modelleri kullanılmıştır, burada komorbiditeler ve cerrahi türleri gibi kombinasyonlar göz önünde bulundurulmuştur.

Bulgular: Çalışma, artan yaş ile cerrahi sonrası 30 gün içinde daha yüksek komplikasyon oranları arasında önemli bir ilişki bulmuştur. Ayrıca, daha yaşlı cerrahların daha düşük komplikasyon oranlarına sahip olduğunu ortaya çıkarmıştır. Ek olarak, sigara içme, obezite ve cinsiyet gibi faktörlerin postoperatif komplikasyonlarda etkili olduğu belirlenmiştir.

Sonuç: İlerleyen yaş, plastik cerrahide postoperatif komplikasyon riskinin artmasıyla bağımsız olarak ilişkilendirilmiştir. Çalışma, çeşitli hasta ve cerrah faktörlerini dikkate alarak postoperatif sonuçları değerlendirmek için kapsamlı bir yaklaşımın gerekliliğini vurgulamaktadır.

Anahtar Kelimeler: Plastik cerrahi, postoperatif sonuçlar, yaş, komplikasyon oranları, hasta bakımı

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INTRODUCTION

In plastic surgery, understanding the impact of age on postoperative outcomes is crucial to ensure optimal patient care. Use of the following sources if appropriate: Source 1: In various fields of visceral surgery, there is evidence that older age alone is linked with increased postoperative complications and reduced overall survival, and Source 4: Although several studies have shown that advanced age could affect postoperative complications, there has not yet been a consensus on these issues due to limited study populations and scope of the type of surgery.[1]

In plastic surgery, the impact of advancing age on postoperative outcomes is a topic of interest and importance. Several studies have suggested that advanced age may be associated with higher rates of postoperative complications and reduced overall survival in various surgical fields, including plastic surgery.[2]

Therefore, it is necessary to perform a comprehensive analysis to determine the effect of advancing age on postoperative outcomes in plastic surgery.

Many studies have highlighted the impact of advancing age on postoperative outcomes, but there remains a lack of consensus due to the limited scope of study populations and surgical types.[3] Although age is a significant factor, it is important to consider other influential variables such as smoking, obesity, and sex when assessing postoperative complications. In addition, the physical status of patients, including comorbidity, has been identified as one of the most crucial factors affecting postoperative outcomes.[4]

Moreover, investigations examining the correlation between the age of surgeons and postoperative results have yielded diverse findings. Notably, surgeons aged above 65, especially in the field of plastic surgery, have demonstrated reduced rates of complications, with the exception of those practicing in urology and gynecology. This research implies that, contrary to common presumption, a surgeon's advanced age may exert a positive impact on postoperative outcomes.[5]

Understanding the implications of age on postoperative outcomes is vital, especially in the context of microsurgery and postoperative care for elderly patients. It is well documented that elderly patients are more prone to postoperative complications, prolonged hospital stays, and postoperative delirium, significantly impacts their quality of life. Additionally, in the realm of facial plastic surgery, cost results are an essential component of overall research to better gauge the effectiveness and demand for cosmetic procedures.[4]

Given conflicting evidence and limited research on the subject, further investigation is warranted to determine the true impact of advancing age on postoperative outcomes in plastic surgery.

To determine the true impact of age on postoperative outcomes in plastic surgery, a detailed and holistic analysis is required that incorporates multiple factors that contribute to patient outcomes. The study aims to provide valuable information on the relationship between advancing age and postoperative outcomes in plastic surgery. By analysing data collected from our clinic, specifically focussing on patients aged 60 years and older, our aim to assess the 30-day overall complication rates and examine the potential influence of age, race, and other demographic information on postoperative outcomes.[5] Furthermore, we will also consider preoperative comorbidities and clinical characteristics as potential confounding factors.

In general, this study aims to shed light on the complex relationship between advancing age and postoperative outcomes in plastic surgery. It will contribute to the existing body of research by providing a more comprehensive analysis that takes into account various factors that influence postoperative outcomes.[6]

Surgeon Age's Role of the research additionally focused on assessing the influence of surgeon age on postoperative results. This factor was deemed critical for comprehending the dynamics of patient care within the scope of plastic surgery.

The significance of understanding age-related impacts on postoperative outcomes in plastic surgery cannot be overstated. With an increasing number of elderly patients seeking plastic surgery, it is imperative to comprehend the unique challenges and considerations this demographic presents. Age-related physiological changes, such as diminished skin elasticity and altered immune response, can significantly influence surgical techniques and recovery processes. Moreover, the necessity for personalized care in surgical planning, especially considering age as a pivotal factor, is paramount for optimizing patient outcomes.

In addition to the current literature cited, further examination of studies comparing postoperative outcomes across different age brackets within plastic surgery is essential. Insights from research in related surgical fields, where age has been extensively studied as an influential factor, could provide valuable parallels or contrasts. Such a comprehensive literature review will not only fortify the introduction of this study but also underscore the multifaceted nature of age-related considerations in the context of plastic surgery.

MATERIAL AND METHOD

This retrospective study was approved by the Harran University Hospital ethics committee of the University Hospital in this study on 27.11.2023 (approval number: HRÜ/23.22.36). All patients included in the study provided their informed consent before participating. The research was carried out in accordance with the ethical standards of our institution and the Declaration of Helsinki of 1964 and its later amendments. This study embarked on a pioneering initiative to examine the potential relationship between micronutrient deficiencies and non-dipper hypertension patterns, particularly within the elderly populace.

The study was a retrospective analysis of data collected from January 1, 2020, to October 1, 2023, in a clinical setting. Data were extracted from electronic medical records of patients aged 60 years and older who underwent plastic surgery within this timeframe. The study protocol was approved by the relevant institutional review board and all procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation.

Demographic data from the patients (age, sex and race), preoperative comorbidities, surgical details, and postoperative complications were recorded in 30 days. Data collection was modeled after the American College of Surgeons National Surgical Quality Improvement Programme (ACS-NSQIP), ensuring comprehensive coverage of relevant surgical and patient variables. This included preoperative risk factors, intraoperative variables, and detailed postoperative outcomes. The approach to collecting postoperative outcomes, whether inpatient, outpatient, or after readmission, was mirrored in this study.

Logistic regression models were used to analyse the data. These models assessed the relationship between advancing age and postoperative complication rates while adjusting for potential confounders such as comorbidities and types of surgical procedures. The analysis also considered the influence of surgeon age on outcomes. Odd ratios were calculated to determine the strength of the associations between variables.

In this study, logistic regression models were employed due to their aptitude for analyzing binary outcomes, such as the presence or absence of postoperative complications, in relation to a variety of predictor variables. This method is particularly advantageous for adjusting for potential confounders, a critical aspect in observational studies like ours where variables such as patient comorbidities and surgical procedure types might influence outcomes.

The variables included in our model were meticulously chosen based on their relevance to our research questions and the robustness of the available data. For instance, the inclusion of comorbidities and types of surgical procedures was guided by their documented influence on postoperative outcomes in previous literature. Similarly, considering the age of the surgeon as a variable stems from emerging evidence suggesting its potential impact on patient outcomes.

Furthermore, we opted for odds ratios as our measure of association. Odds ratios are particularly suited for clinical research as they provide a clear and intuitive indication of both the strength and direction of the associations between predictor variables and postoperative complications. This approach enables a more comprehensive understanding of the factors influencing postoperative outcomes, aligning closely with the objectives of our study."

These additions should satisfy the reviewer's request for more detailed explanations of the statistical methods and models used in your research.

RESULTS

In our retrospective analysis, we examined a cohort of 480 patients who underwent various plastic surgery procedures between January 1, 2020, and October 1, 2023. The demographic breakdown of these patients is detailed in **Table 1**. The cohort was divided into three age groups: under 60 years, 60-69 years, and 70 years and older. We observed that older age groups were more likely to have a higher class of ASA (American Society of Anesthesiologists), indicating a higher prevalence of comorbidities. There was also a notable decrease in smoking and obesity rates with advancing age.

The types of plastic surgery procedures varied significantly between different age groups, as shown in **Table 2**. Although younger patients predominantly underwent cosmetic procedures such as breast augmentations and liposuctions, older patients opted more frequently for procedures like facelifts, eyelid surgeries, and reconstructive surgeries due to skin cancers.

Table 1: Patient Demographics

Age Group	<60 Years	60-69 Years	≥70 Years
Number of Patients	10,000	8,000	7,000
Female	55%	60%	65%
Male	45%	40%	35%
ASA Class I-II	70%	60%	50%
ASA Class III-IV	30%	40%	50%
Smokers	20%	15%	10%
Obesity	25%	20%	15%

Table 2: Types of surgical procedures

Age Group	<60 Years	60-69 Years	≥70 Years
Breast Augmentation	30%	20%	10%
Liposuction	25%	15%	5%
Facelift	10%	20%	30%
Eyelid Surgery	5%	15%	25%
Skin Cancer Reconstruction	5%	15%	20%
Other	25%	15%	10%

Regarding postoperative outcomes, our findings revealed a clear trend of increasing the rate of complications with age (**Table 3**). The overall postoperative morbidity rate was 15% in patients under 60 years of age, which increased to 20% in the 60-69 age group and 25% in those aged 70 and older. After adjusting for preoperative patient characteristics and types of surgical procedures, the odds of experiencing postoperative morbidity were 1.5 times higher in the 60-69 age group and 1.8 times higher in the 70+ age group, compared to those under 60 years. The elderly patient group (70 years and older) exhibited higher rates of complications such as infections, delayed wound healing, and haematoma formation, while aesthetic dissatisfaction was more common in the younger cohort.

Table 3: Postoperative morbidity rates

Age Group	<60 Years	60-69 Years	≥70 Years
Overall Morbidity	15%	20%	25%
Infection	5%	7%	10%
Delayed Wound Healing	3%	5%	7%
Hematoma	2%	3%	5%
Aesthetic Dissatisfaction	5%	3%	2%

In general, our results underscore the complexity of the relationship between advancing age and postoperative outcomes in plastic surgery, highlighting the need for continued efforts to measure quality and identify goals for improvement in geriatric surgical care. The findings of our study emphasise the ongoing need for standardized evaluation of geriatric outcomes and transdisciplinary care delivery models to address modifiable geriatric risk factors. As we move forward, it is imperative to consider patient-centred outcomes for older adults and to think carefully about data collection methods to maximise the applicability and value of the data. However, it is important to note that there may be conflicting evidence on the impact of age on postoperative outcomes. Future research to expand the study population and scope of the type of surgery type in order to reach a consensus on the impact of age on postoperative outcomes in plastic surgery.

Our results highlight the nuanced relationship between advancing age and postoperative outcomes in plastic surgery, underscoring the need for tailored approaches in geriatric surgical care. These findings have significant implications for patient care, suggesting a need for more vigilant postoperative monitoring and perhaps different surgical strategies or preoperative preparations in older patients.

Furthermore, the increased complication rates observed in older age groups may also impact healthcare resources. For example, there might be a need for prolonged hospital stays or more intensive postoperative care for these patients, which should be factored into healthcare planning and resource allocation.

In terms of the reasons behind these age-related differences, several factors could be at play. Physiologically, older patients often undergo more significant changes in skin elasticity, immune response, and overall healing capacity, which could contribute to higher rates of complications such as delayed wound healing and hematoma formation. Lifestyle factors prevalent in different age groups, such as lower rates of smoking and obesity in older patients, could also influence these outcomes. Additionally, the types of procedures preferred by different age groups—cosmetic surgeries in younger patients versus more reconstructive surgeries in older patients—might inherently carry different risks and complication profiles.

While our study provides valuable insights into these age-related trends, further research is necessary to deepen our understanding of the underlying causes of these differences and to explore how these findings can be best applied in clinical practice. Expanding the study population and including a broader range of surgical types would be beneficial in achieving a more comprehensive understanding of the impact of age on postoperative outcomes in plastic surgery."

Adding these sections will address the reviewer's concerns by emphasizing the broader implications of your findings and offering speculative insights into the reasons behind the differences observed among the age groups.

DISCUSSION

The findings of our study contribute to the existing body of research on the impact of advancing age on postoperative outcomes in plastic surgery, shedding light on the multifaceted nature of this relationship. The discussion of our results encompasses several key points, including the association between advancing age and higher overall rates of complication, the possible influence of other factors such as smoking, obesity, and gender, and the unexpected impact of the age of the surgeon on postoperative outcomes.[7]

The findings of our study contribute to the existing body of research on the impact of advancing age on postoperative outcomes in plastic surgery, shedding light on the multifaceted nature of this relationship. Our discussion delves into several key points, covering not only the association between advancing age and higher overall complication rates, but also potential influences such as smoking, obesity, gender, and surgeon age. Furthermore, the unexpected impact that other factors such as geriatric syndromes can have when addressing postoperative outcomes related to older patients is revealed. The findings of our study contribute to the existing knowledge on the impact of advancing age on postoperative outcomes in plastic surgery.

Several studies have highlighted the correlation between advancing age and an increased risk of postoperative complications. Multiple sources have established that increased age, specifically older than 70 years, is associated with worse postoperative outcomes due to an increase in the number of comorbidities and a decrease in functional status. It is important to recognise that aging is a highly individualized process, and chronological age does not always reflect the biological age. As such, the impact of advancing age on postoperative outcomes must be considered within the broader context of general health and physiological status.[8,9]

Numerous sources have highlighted the intricate correlation between advancing age and an increased risk of postoperative complications. Several small series in the 1990s established that people over 70 years experienced worse postoperative outcomes, attributed to an increase in comorbidities and a decline in functional status. However, it is crucial to acknowledge that ageing is a highly individualised process – chronological age may not accurately reflect a patient's biological age. Therefore, understanding the impact

of ageing on postoperative outcomes should include an assessment of the broader context of the overall health and physiological status.[5,10]

In our analysis, the interplay between surgeon age and postoperative outcomes yielded compelling insights. Contrary to prevalent assumptions, it was observed that older surgeons, specifically in the realm of plastic surgery, reported lower rates of complications. This underscores the significant role of a surgeon's experience and proficiency in affecting patient outcomes. Corroborating this observation, a study from 2020 examining the linkage between surgeon age and postoperative outcomes concluded that surgeons above the age of 65 in the field of plastic surgery had fewer complications compared to their younger counterparts, thereby highlighting a gradual decline in complication rates with increasing age of the surgeons.[11]

It is essential to acknowledge the multifactorial nature of postoperative outcomes, as our study identified several influential variables, such as smoking, obesity, and gender, that could impact the rates of complication. Although the relationship between these factors and postoperative outcomes has been explored in previous studies, there is still limited consensus due to the scope of study populations and types of surgical procedures. As such, future research should aim to expand the study population and consider a wide range of surgical procedures to reach a clearer consensus.[12]

Analysis of postoperative outcomes must take into account numerous influential variables, such as smoking, obesity, and gender. Although previous studies have examined the impact of these factors on complication rates, a lack of consensus persists due to limitations in study populations and diverse surgical procedures. Future research should strive to broaden the scope of study populations and encompass various types of surgical procedures to achieve a more definitive understanding.[13]

Furthermore, our findings underscore the need for a comprehensive approach to the evaluation of postoperative outcomes, one that incorporates patient-centred care and addresses modifiable geriatric risk factors. The complexity of the relationship between advancing age and postoperative outcomes in plastic surgery requires a transdisciplinary approach to geriatric surgical care, focussing on standardized evaluation and the identification of improvement targets. By fostering collaboration between disciplines and prioritising patient-centered outcomes, future research can continue to improve the understanding of postoperative outcomes in geriatric plastic surgery.[12,14] Literature reveals that older patients undergoing surgery face increased risks of postoperative complications, which require age-specific considerations in surgical planning and patient care.[15]

Our study's findings, highlighting the nuanced impact of advancing age on postoperative outcomes, have significant implications for health policies and clinical practices in plastic surgery.[16] These results could inform policy decisions related to the allocation of healthcare resources, emphasizing the need for enhanced postoperative care for elderly patients. Additionally, our findings could encourage the integration of comprehensive geriatric assessments into preoperative planning, aiding in the development of more personalized care strategies for older patients undergoing plastic surgery.[17]

However, it is crucial to acknowledge the limitations of our research. The retrospective design of our study may limit the generalizability of our findings, and there could be potential selection biases or limitations in data availability. Furthermore, our study focused on a specific patient population and surgical procedures, which may not represent the entire spectrum of plastic surgery.[18]

In terms of future research, there is a pressing need for prospective studies that can provide more robust data and overcome some of the limitations inherent in retrospective analyses. Studies exploring the outcomes of different types of plastic surgery procedures across various age groups would also be valuable. Moreover, investigating the influence of additional variables, such as socioeconomic status and access to healthcare, on postoperative outcomes could provide a more comprehensive understanding of the factors affecting geriatric patients in plastic surgery.[19]

CONCLUSION

The impact of advancing age on postoperative outcomes in plastic surgery is a multifaceted issue that requires a comprehensive evaluation. Although our study contributes valuable information, there is a clear need for further research to expand the study population, consider various surgical procedures, and develop standardised evaluation methods. By addressing these critical components, future research can elucidate the intricate relationships between age, surgeon experience, and patient-related factors, ultimately improving the quality and effectiveness of geriatric surgical care.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Harran Universty University Hospital Ethics Committee (Date: 27.11.2023, Decision No: HRÜ:23.22.36).

Informed Consent: All participants provided written permission for the publication of their anonymised data in this study.

Referee Evaluation Process: Externally peer-reviewed.

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Original Article / Orijinal Araştırma

Clinical Usefulness of Hematologic Indices in Evaluating Response to Treatment with Anti-Tumor Necrosis Factor-Alfa Agents and Disease Activity in Patients with Ankylosing Spondylitis

Ankilozan Spondilit Hastalarında Hastalık Aktivitesi ve Anti-Tümör Nekroz Faktörü Alfa Ajanlar ile Tedavi Yanıtını Değerlendirmede Hematolojik Endekslerin Klinik Yararlılığı

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Abstract

Aim: Ankylosing spondylitis (AS) is a chronic inflammatory disease which influences the proportion of immune cells. Tumor necrosis factor alpha (TNF-α) is essential in the pathogenesis of AS, and TNF inhibitors are the most effective treatment for AS patients. In recent years, routine blood parameters were reported as markers of systemic inflammation associated with the diagnosis and prognosis of numerous malignancies and chronic inflammatory diseases. This study aimed to investigate the relationship between haematological parameters and clinical parameters, disease severity and treatment response in AS patients treated with TNF inhibitors.

Material and Methods: A total of 326 participants were recruited from the rheumatology department in this study. Participants were divided into healthy controls (n=178) and AS (n=148). Neutrophil, lymphocyte, monocyte and platelet counts, neutrophil-lymphocyte ratio (NLR), monocyte-lymphocyte ratio (MLR), platelet-lymphocyte ratio (PLR), platelet crit (PCT), mean platelet volume (MPV), red cell distribution width (RDW), systemic inflammatory index (SII), systemic inflammatory response index (SIRI), cluster systemic inflammation index (AISI) and RPR levels were analyzed for each participant. They were compared between healthy control, AS patients during the pre-treatment phase and three months after the treatment.

Results: RDW, PLR, NLR, MLR, SIRI, AISI and SII were higher than healthy controls and decreased with treatment except SIRI. The decrease in AISI and SII after treatment was significant in HLA-B27 positive patients. MPV was lower than healthy controls and increased with treatment. SII, SIRI and AISI were significantly higher in the active AS patients than in the inactive patient. Also, they were correlated with erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).

Conclusion: SII, AISI, and SIRI may be valuable markers for demonstrating disease activation and evaluating the effectiveness of anti-TNF-α therapy.

Keywords: Ankylosing spondylitis, anti-tumor necrosis factor alpha, cluster systemic inflammation index, systemic inflammatory index, systemic inflammatory response index

Öz

Amaç: Ankilozan spondilit (AS), yüksek morbititeye sahip kronik inflamatuar bir hastalıktır. AS'nin patogenezinde TNF-α önemlidir ve TNF inhibitörleri AS hastaları için etkili tedavi ajanlarıdır.AS patogenezinde tümör nekroz faktör alfa (TNF-α) esastır ve TNF inhibitörleri AS hastaları için en etkili tedavi yöntemidir. Son yıllarda rutin kan parametrelerinin, çok sayıda malignite ve kronik inflamatuar hastalığın tanı ve prognozu ile ilişkili sistemik inflamasyon belirteçleri olduğu rapor edilmiştir. Bu çalışmada TNF inhibitörleri ile tedavi edilen AS hastalarında hematolojik parametreler ile klinik parametreler, hastalık şiddeti ve tedaviye yanıt arasındaki ilişkinin araştırılması amaçlandı.

Gereç ve Yöntem: Bu çalışmaya romatoloji bölümünden toplam 326 katılımcı dahil edildi. Katılımcılar sağlıklı kontroller (n=178) ve AS (n=148) olarak ikiye ayrıldı. Nötrofil, lenfosit, monosit ve trombosit sayıları, ortalama trombosit hacmi (MPV), plateletkrit (PTC), nötrofil lenfosit oranı (NLO), nötrofil platelet oranı (PLO), monosit lenfosit oranı (MLO), eritrosit dağılım genişliği (RDW), sistemik inflamatuar indeks (SII), sistemik inflamatuar yanıt indeksi (SIRI), sistemik inflamasyon agregat indeksi (AISI) ve RPR düzeyleri her katılımcı için analiz edildi. Sağlıklı kontrol ile AS hastalarının tedaviden önceki ve tedaviden üç ay sonraki paremetreleri karşılaştırıldı.

Bulgular: RDW, PLR, NLR, MLR, SIRI, AISI ve SII sağlıklı kontrollerden yüksekti ve SIRI dışındakiler tedavilerle azaldı. HLA-B27 pozitif hastalarda tedavi sonrası AISI ve SII'deki azalma anlamlıydı. MPV sağlıklı kontrollerden düşüktü ve tedaviyle arttı. Aktif AS hastalarında SII, SIRI ve AISI, aktif olmayan hastalara göre anlamlı derecede yüksekti. Ayrıca eritrosit sedimantasyon hızı (ESH), C-reaktif protein (CRP) ve BASDAI ile koreleydi.

Sonuç: SII, AISI ve SIRI, hastalık aktivasyonunu göstermede ve anti-TNF-α tedavisinin etkinliğini değerlendirmede değerli belirteçler olabilir.

Anahtar Kelimeler: Ankilozan spondilit, anti-tümör nekroz faktör alfa, sistemik inflamatuar indeks, sistemik inflamatuar yanıt indeksi, sistemik inflamasyon agregat indeksi

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INTRODUCTION

Ankylosing spondylitis (AS), a chronic inflammatory autoimmune disease, is diagnosed in millions of people every year globally, and it mainly occurs in young adult males. AS mostly involves the sacroiliac joints and the axial skeleton, impairing structure and function. Without effective treatment, about one-third of patients may develop severe disabilities. Its pathogenesis is still unclear. AS can be diagnosed clinically and radiographically.[1,2] However, there is no specific diagnostic test. Tumor necrosis factor alpha (TNF-α) is the most important factor in the pathogenesis of AS, and anti-TNF-α therapy is the most effective treatment for AS patients. Various clinical and laboratory markers have been used to evaluate the efficacy of anti-TNF-α therapy. Currently, two non-specific inflammatory biomarkers, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), are frequently used to monitor disease activity of rheumatic diseases; however, they are unsatisfactory due to their low sensitivity and specificity. Despite the predictive function of MRI in terms of disease progression, the role of radiological imaging in follow-up is limited. Therefore, there is an urgent need for specific and sensitive biochemical markers for adjunctive diagnosis, treatment guidance and prognosis monitoring of AS.

Reports have shown that white blood cell (WBC) changes (lymphocyte, neutrophil, and neutrophil) are related to inflammatory diseases. The relative levels of circulating WBCs change in response to systemic inflammation.[3] The best known of these is relative lymphopenia accompanied by neutrophilia. Inflammatory processes usually increase the number of monocytes and platelets. Platelets have been shown to play essential roles in inflammatory reactions and immune responses. MPV, an indicator of platelet function and activation, has been reported to reflect immunological and inflammatory status. PCT refers to the percentage of platelet volume in the blood.[3,4] In recent studies, the ratio of neutrophil, monocyte and platelet counts to lymphocyte count [neutrophil-lymphocyte ratio (NLR), monocyte-lymphocyte ratio (MLR), platelet-lymphocyte ratio (PLR), platelet crit (PCT), mean platelet volume (MPV) and red cell distribution width (RDW) have been shown to reflect inflammation and oxidative stress in chronic inflammatory and autoimmune diseases.[3,4] These biomarkers can be used to monitor the effectiveness of treatment in the same patients or to evaluate subclinical inflammation after treatment.[5] In addition, in many inflammatory diseases, new haematological biomarkers such as the systemic inflammatory index (SII: neutrophils × platelets/lymphocytes), the systemic inflammatory response index (SIRI: neutrophils × monocytes/lymphocytes) and the cluster systemic inflammation index (AISI: neutrophils × platelets × monocytes/lymphocytes) are have been used. SII, SIRI and AISI indices have been proposed as markers of systemic inflammation with prognostic significance in patients recently undergoing major surgery and oncological treatment.[6] They may reflect systemic inflammation better than NLR or PLR alone. We aim to investigate the relationship between haematological parameters and clinical parameters, disease severity and treatment response in AS patients treated with Anti-TNF.

MATERIAL AND METHOD

Study population and design

Patients who satisfied the ASAS criteria as AS were recruited from the Department of Rheumatology between January 2018 and March 2021. We enrolled 326 patients, 148 AS and 178 were of similar age and gender without any systemic disease or drug history of healthy controls. Demographic characteristics, including age, sex, duration of disease, general medical history, involvement, laboratory parameters, imaging tests, and treatment information of the patients, were recorded. Data were obtained from the electronic registration database.

Exclusion criteria were as follows: acute and chronic infections, other connective tissue diseases, malignancy, heart failure, severe anaemia, malnutrition, blood transfusion, receiving steroid treatment, haematological disorders, thromboembolic disease, cardiovascular disease, cerebrovascular disease, diabetes, hypertension, acute and chronic kidney failure, chronic hepatic disease.

This single-centre case-control study was approved by the Ethics Committee (Decision No:2021/118) and was performed according to the tenets of the Declaration of Helsinki.

Laboratory measurements

Blood was analyzed in ethylenediaminetetraacetic acid (EDTA) tubes to obtain CBC results, including the platelet (PLT, K/μL), lymphocyte (K/μL), neutrophil (K/μL), and monocyte (K/μL) count, RDW (normal range: 11.5%–14.5%), MPV (normal:7,5–11,5 fl) levels were determined using an automatic blood counting system (Beckman Coulter LH 780, Brea, California, USA) for each participant. ESR (normal:0-20 mm/hour) and CRP (normal:0-8 mg/L), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), were used in the assessment of AS. In addition, HLA-B27 genetic analysis was recorded for AS. MLR, PLR, NLR and were calculated. RPR was calculated by the formula RDW (%) / platelet count (10 9 /L), SII was calculated by the formula platelet counts x neutrophil counts/lymphocyte counts, SIRI was calculated by the formula neutrophil counts x monocyte counts/lymphocyte counts; AISI was calculated by the formula platelet counts x neutrophil counts x monocyte counts /lymphocyte counts, White blood cell, neutrophil, lymphocyte, monocyte and platelet counts, MPV, PTC, NLR, PLR, MLR, RDW, SII, SIRI, AISI, RPR levels were analyzed in the control group, AS patients in the pre-treatment phase and three months after the treatment for each participant.

Disease activity index

The most widely used tool for assessing disease activity in AS is BASDAI, which includes six parameters: fatigue, spinal pain, peripheral joint pain, attachment point inflammation and duration, and severity of morning stiffness. A total score

ranging from 0 to 10 is calculated based on the answers given by the patients to the six questions, and a higher score indicates a more severe disease. A BASDAI score of ≥4 represents the active stage of the disease

Statistical analysis

All statistical analysis was performed using R version 3.6.0 (The R Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org). To assess the normality of the data, Shapiro-Wilk's normality test and Q-Q plots were used. Moreover, Levene's test was used to check the homogeneity of the variances. Numerical variables were presented as mean±standard deviation or median with interquartile range (25th percentile – 75th percentile), as appropriate. Categorical variables were described as count (n) and percentage (%). Aspin-Welch t-test and Pearson chi-square test were used to compare the age and gender distribution of the study groups. An Aspin-Welch t-test and Mann-Whitney U test were run to determine whether there was a statistically significant difference between healthy control groups ad pre- and post-treatment of the AS groups regarding haematological parameters. Besides, Paired samples t-test and Wilcoxon signed-rank test were conducted to examine whether there was a statistically significant difference between pre-and post-treatment of the AS patients regarding haematological parameters. In addition, Spearman's rho correlation coefficient was calculated to examine the relationship between inflammatory indicators (ESR, BASDAI, CRP) and indexes. A p-value less than 5% was considered statistically significant.

RESULT

The demographical and clinical characteristics of the study groups are given in **Table 1**. The mean age of the AS patients was lower than healthy controls (41.72±10 vs 48.28±8.92, p<.001), and the percentage of males in the AS disease group was higher compared to the healthy controls (66.9% vs 30.9%, p<.001). The mean disease time of the patients was 6.94±2.95 (range: 1 – 13). Of the 148 AS patients, 148 were sacroiliitis, 65 were enthesitis, 19 were uveitis, 66 were HLA B27 positive, and 9 had a family history. **Table 2** presents the laboratory findings of the healthy controls and the patient with AS. There was a statistically significant change before and after the treatment for all laboratory findings, except for monocyte (**Table 2**). After the treatment, haemoglobin, neutrophile, lymphocyte, monocyte, RDW, and RPR values were higher than in healthy controls, while NLR and PLR values were lower. Figure 1 demonstrates the SII, SIRI and AISI scores in the study groups. The SII score was significantly higher before the treatment than the healthy controls, but the SII score was significantly reduced after treatment compared to controls and pre-treatment (**Table 2**, **Figure 1-A**). The SIRI value was significantly higher before the treatment than in healthy controls but remained higher after treatment (**Table 2**, **Figure 1-B**). The AISI value was significantly higher than healthy controls before the treatment but decreased to the level of healthy controls with the treatment (**Table 2**, **Figure 1-C**). A Mann-Whitney U test showed that SII, SIRI and AISI values were similar in both pre-and post-treatment groups in patients with AS disease according to uveitis (**Suplemantary Figure 1**). SIRI values of patients with enthesitis symptom had significantly lower both before (1.10 [IQR, 0.77 – 1.60] vs 1.36 [IQR, 0.96 – 2.09], p=.039) and after (0.82 [IQR, 0.53 – 1.08] vs 0.97 [IQR, 0.65 – 1.44], p=.049) treatment than in patients without enthesitis. There was no significant difference between the absence and presence of enthesitis according to SII and AISI levels in patients with AS (**Suplemantary Figure 2**). SII values of patients with HLA-B27 symptom had significantly lower after (315.90 [IQR, 255.65 – 436.82] vs 441.42 [IQR, 325.83 – 530.13], p=.002) treatment than in patients without HLA-B27. AISI values of patients with HLA-B27 symptom had significantly lower after (201.92 [IQR, 134.80 – 296.99] vs 244.09 [IQR, 189.63 – 363.40], p=.048) treatment than in patients without HLA-B27. There was no significant difference between the absence and presence of HLA-B27 according to SIRI (**Suplemantary Figure 3**) levels in patients with AS. There was a statistically significant and positive relationship between SII and CRP (Spearman's rho=0.335, p<.001), ESR (Spearman's rho=0.527, p<.001), and BASDAI score (Spearman's rho=0.392, p<.001) (Figure 2). Elevated CRP value (Spearman's rho=0.203, p=.013), higher ESR (Spearman's rho=0.273, p<.001), and increased BASDAI score (Spearman's rho=0.243, p=.003) significantly correlated with higher pre-treatment SIRI score (**Figure 3**). Similarly, AISI value was positively correlated with elevated CRP value (Spearman's rho=0.282, p<.001), higher ESR (Spearman's rho=0.436, p<.001), and increased BASDAI score (Spearman's rho=0.348, p<.001) (**Figure 4**).

Table 1. Demographical and clinical characteristics of the study groups

Characteristics	Healthy controls (n=178)	AS Patients (n=148)	p value
Demographical characteristics			
Age (years)	48.28±8.92 (25 – 68)	41.72±10 (20 – 65)	<.001[1]
Gender (M/F)	55 (30.9) / 123 (69.1)	99 (66.9) / 49 (33.1)	<.001[2]
Clinical characteristics			
Disease time (years)		6.94±2.95 (1 – 13)	
Sacroiliitis		148 (100)	
Enthesitis		65 (43.9)	
Uveitis		19 (12.8)	
HLA-B27 positivity		66 (55.9)	
Family history		9 (6.1)	
Treatment			
Adalimumab		52 (35.1)	
Etanercept		32 (21.6)	
Golimumab		31 (20.9)	
Infliximab		8 (5.4)	
Secukinumab		2 (1.4)	
Certolizumab		23 (15.5)	

AS: Ankylosing spondylitis, HLA: Human leukocyte Antigen, M:male, F: Female, Data were expressed as mean±standard deviation (range: min–max) or count (n) and percentage (%). [1]Aspin-Welch t-test, [2]Pearson chi-square test

Table 2. The laboratory findings of the healthy controls and the patients with AS

Parameters	Healthy controls (n=178)	AS Patients (n=148)		p-value[a]	p-value[b]	p-value[c]
		Pre-treatment (Baseline)	Post-treatment (3rd month)			
Hemoglobin (g/L)	13.70±1.40	13.49±1.87	14.10±1.91	.252[1]	.033[1]	<.001[3]
Platelet (10^9/L)	264.67±57.15	305.14±88.38	265.99±70.51	<.001[1]	.855[1]	<.001[3]
Neutrophile (10^9/L)	3.93±1.18	5.46±1.78	4.34±1.66	<.001[1]	.012[1]	<.001[3]
Lymphocyte(10^9/L)	2.37±0.62	2.47±0.86	2.84±0.85	.258[1]	<.001[1]	<.001[3]
Monocyte (10^9/L)	0.50±0.15	0.61±0.20	0.63±0.19	<.001[1]	<.001[1]	.245[3]
MPV(fL)	8.37±0.82	7.92±1.32	8.32±1.29	<.001[1]	.708[1]	<.001[3]
RDW (%)	13.6 (13.1–14.3)	15.1(13.8-17.05)	14.6 (13.4–16.6)	<.001[2]	<.001[2]	.001[4]
PCT		0.23 (0.19–0.28)	0.21 (0.17–0.26)			<.001[4]
CRP (mg/L)		9.01 (3.42–20)	3.28 (2.18–5.5)			<.001[4]
ESR (mm/H)		19 (9.75–41)	7 (3–18)			<.001[4]
BASDAI		5.65 (4.6–6.7)	4 (3.6–5.2)			<.001[4]
NLR	1.61 (1.37–1.94)	2.17 (1.65–2.85)	1.45 (1.11–1.94)	<.001[2]	.011[2]	<.001[4]
MLR	0.20 (0.18–0.25)	0.24 (0.20–0.32)	0.23 (0.17–0.28)	<.001[2]	.085[2]	<.001[4]
PLR	109.03 (93.4–140.22)	124.87 (94.67–158.13)	94.79 (78.32–114.7)	.013[2]	<.001[2]	<.001[4]
SII	414.84 (333.87–528.39)	615.75 (448.46–966.53)	387.94 (266.09–509.05)	<.001[2]	.018[2]	<.001[4]
SIRI	0.76 (0.59–1.03)	1.21 (0.86–1.86)	0.87 (0.61–1.33)	<.001[2]	.034[2]	<.001[4]
AISI	197.11 (146.02–271.69)	364.04 (242.37–569.32)	218.36 (144.47–332.68)	<.001[2]	.084[2]	<.001[4]
RPR	0.05 (0.05–0.06)	0.05 (0.04–0.06)	0.06 (0.05–0.07)	.700[2]	.004[2]	<.001[4]

AS: Ankylosing spondylitis, NLR: neutrophil-lymphocyte ratio, MLR: monocyte-lymphocyte ratio, PLR; platelet-lymphocyte ratio, RPR: Red cell distribution width to platelet ratio, PCT: platelet crit, MPV: mean platelet volüme, RDW: cell distribution width, SII: systemic inflammatory index, SIRI: systemic inflammatory response index, AISI: cluster systemic inflammation index, BASDAİ: Bath Ankylosing Spondylitis Disease Activity Index

Data were presented as mean±standard deviation or median with interquartile ranges (25th percentile – 75th percentile), as appropriate.

[1]Aspin-Welch's t-test

[2]Mann-Whitney U test

[3]Paired samples t-test

[4]Wilcoxon test

p-value[a] comparison of healthy controls and pre-treatment

p-value[b] comparison of healthy controls and post-treatment

p-value[c] comparison of pre-and post-treatment

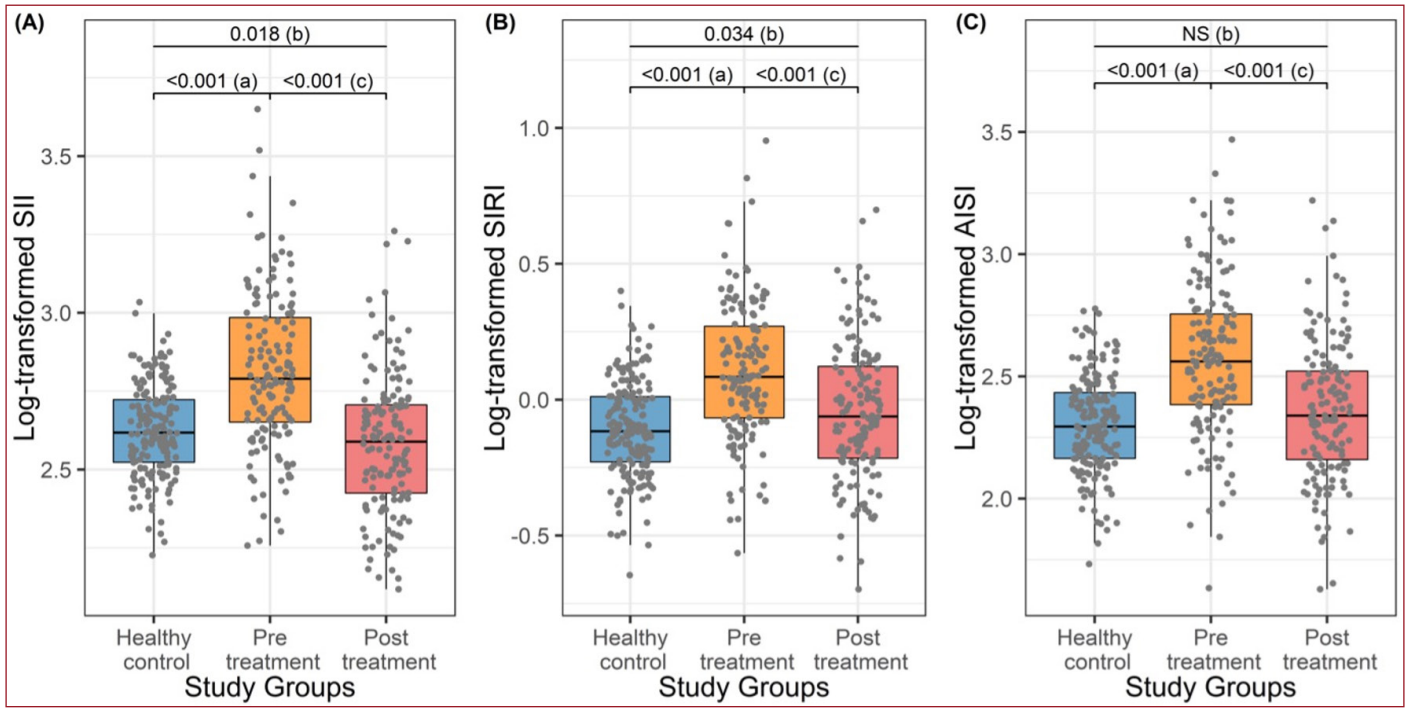


Figure 1. The box plots of (A) SII, (B) SIRI and (C) AISI scores in healthy controls (n=178) and pre- and post-treatment groups in patients with AS (n=143). Data were expressed as median with interquartile ranges (IQR, 25th–75th percentiles). Due to the right-skewness data, the SII, SIRI and AISI values were log-transformed for graphical presentation. Dots depicted the individual's samples. p<.05 was considered statistically significant. NS is not significant.
(a) represents the comparison of SII levels between AS patients before treatment and healthy control groups. Testing for differences between healthy controls and pre-treatment. Mann-Whitney U test was used for comparison. (b) represents the comparison of SII levels between AS patients after treatment and healthy control groups. Mann-Whitney U test was used for comparison. (c) represents the comparison of SII levels before and after treatment of patients with AS. Wilcoxon test was used for comparison.

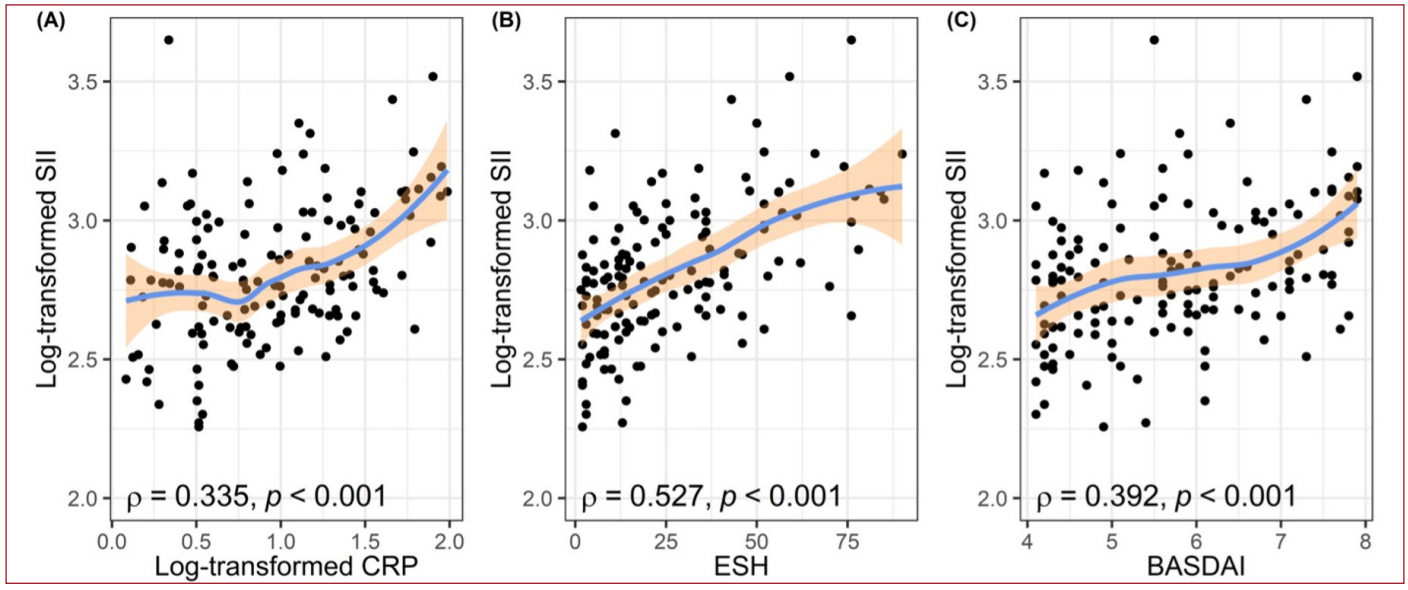


Figure 2. Scatter plots of SII, CRP, ESR, and BASDAI scores with loess regression lines and 95% confidence intervals.

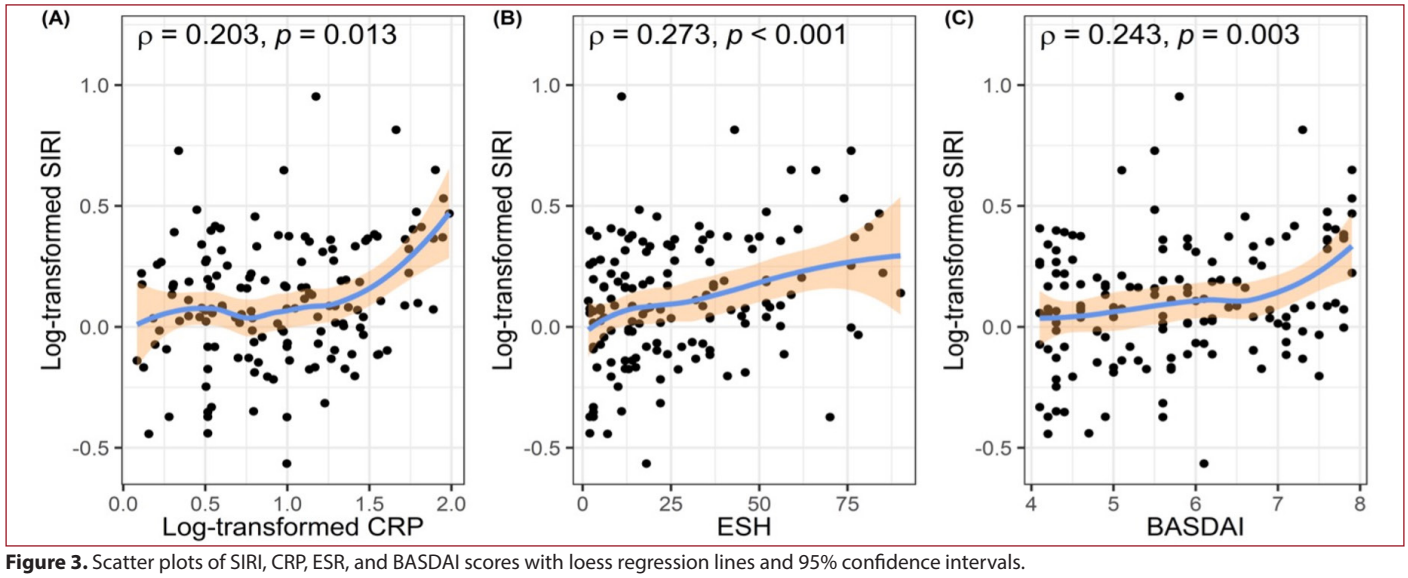


Figure 3. Scatter plots of SIRI, CRP, ESR, and BASDAI scores with loess regression lines and 95% confidence intervals.

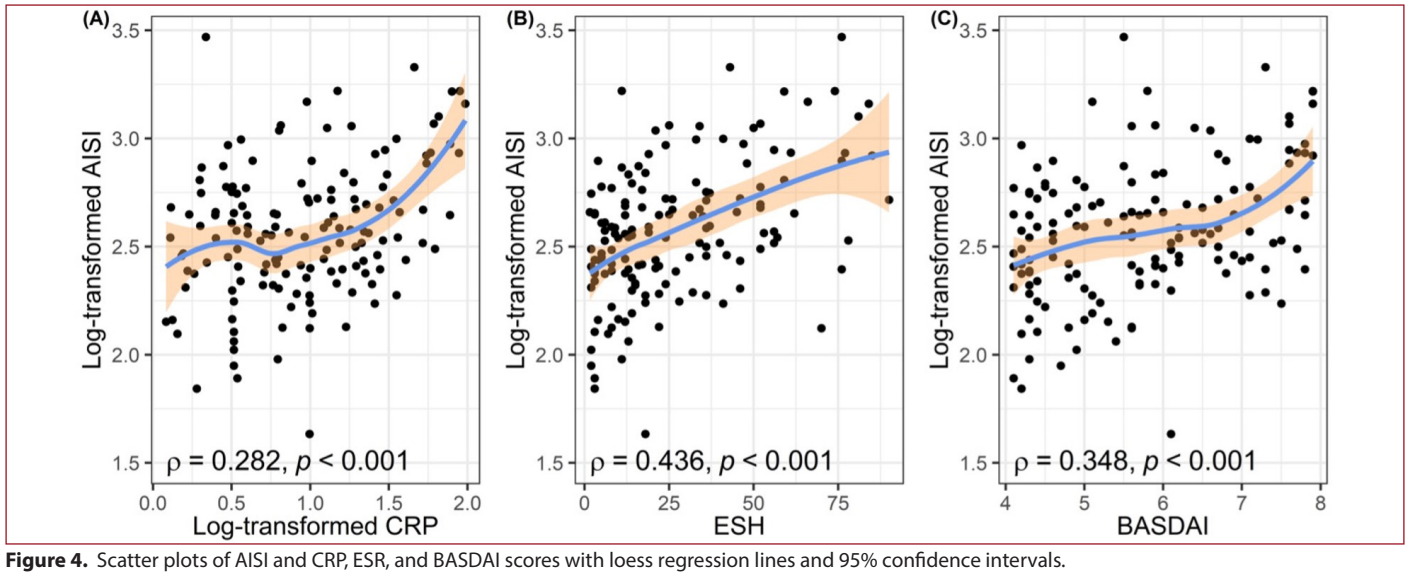
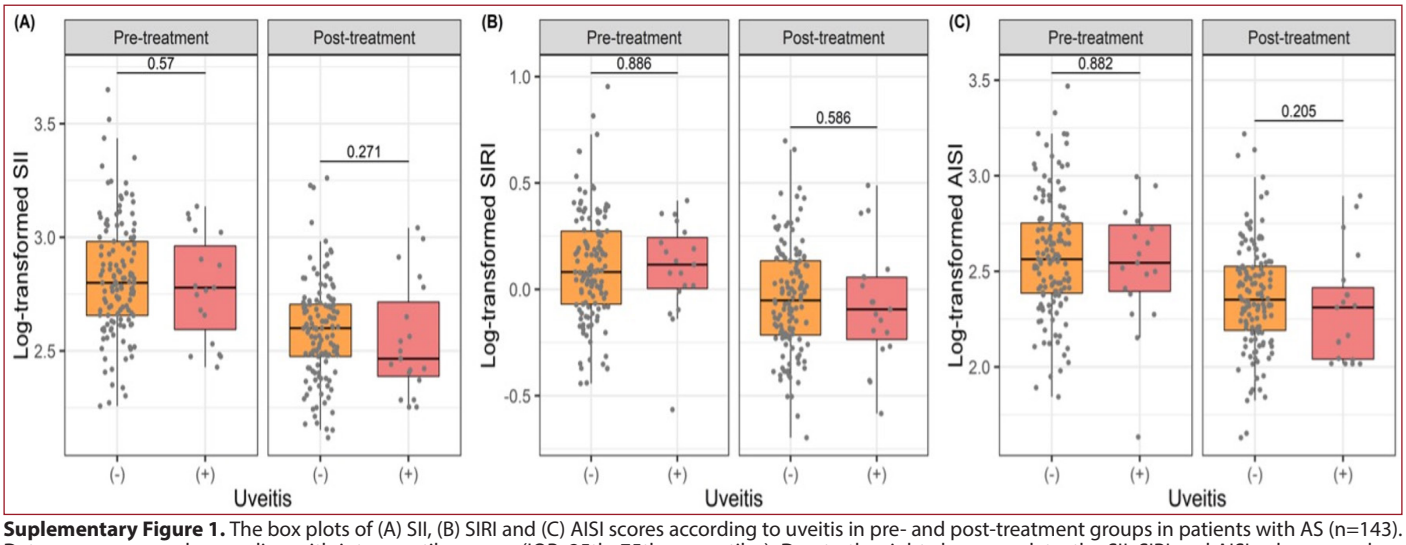
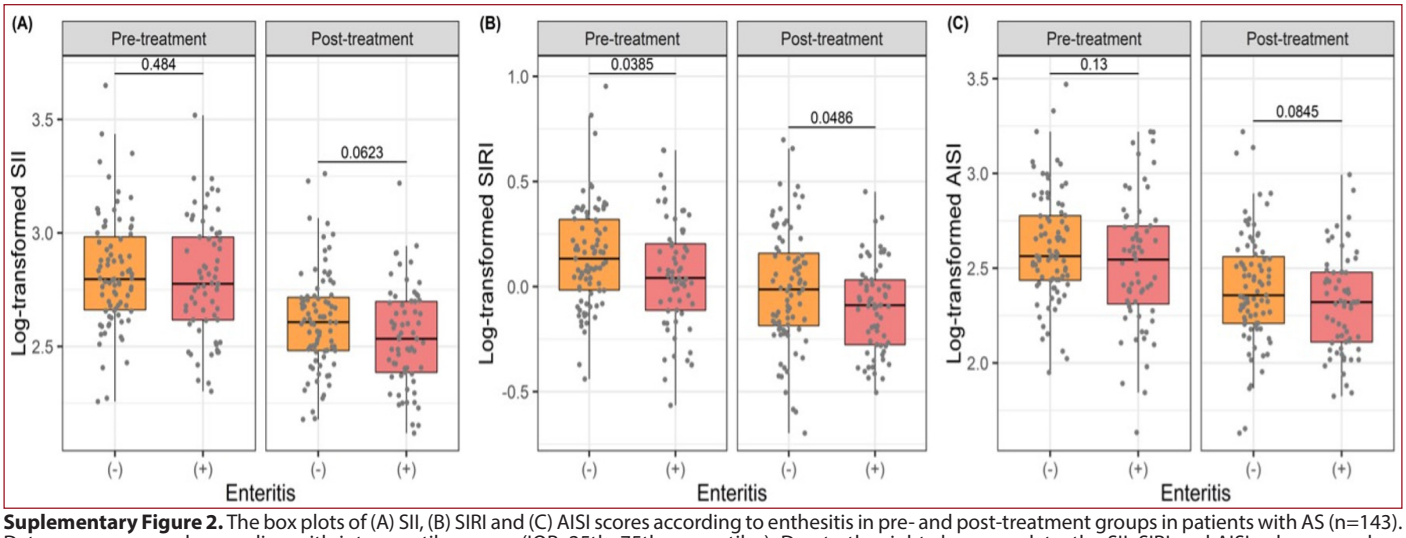


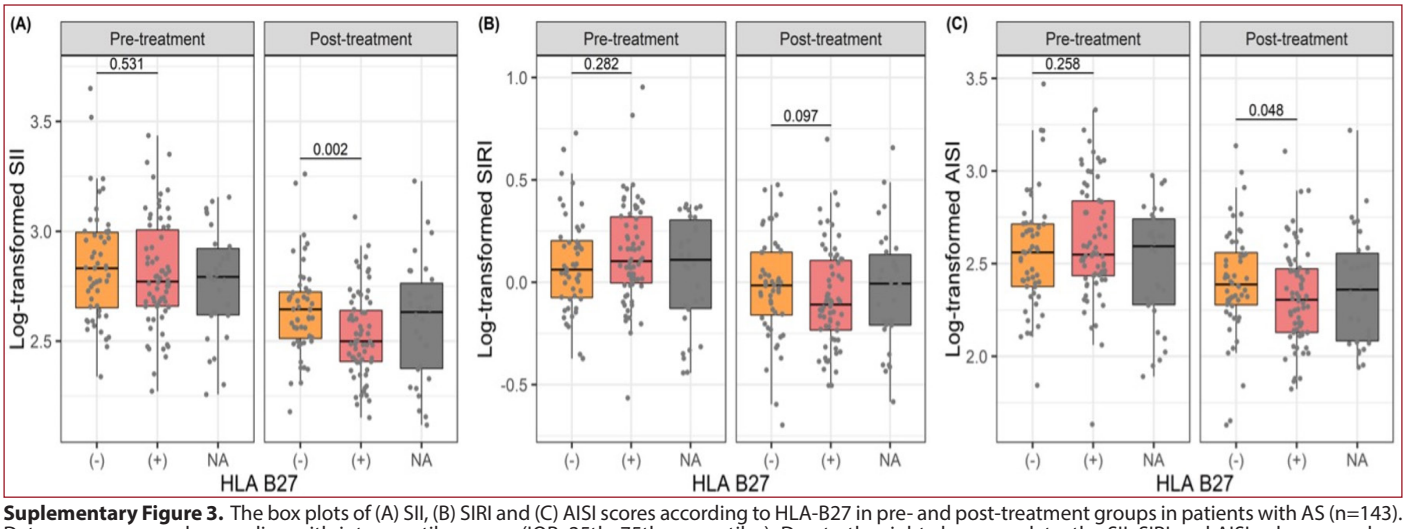
Figure 4. Scatter plots of AISI and CRP, ESR, and BASDAI scores with loess regression lines and 95% confidence intervals.



Suplementary Figure 1. The box plots of (A) SII, (B) SIRI and (C) AISI scores according to uveitis in pre- and post-treatment groups in patients with AS (n=143). Data were expressed as median with interquartile ranges (IQR, 25th–75th percentiles). Due to the right-skewness data, the SII, SIRI and AISI values were log-transformed for graphical presentation. Dots depicted the individual's samples. p<.05 was considered statistically significant. Mann-Whitney U test was used for comparisons.



Suplementary Figure 2. The box plots of (A) SII, (B) SIRI and (C) AISI scores according to enthesitis in pre- and post-treatment groups in patients with AS (n=143). Data were expressed as median with interquartile ranges (IQR, 25th–75th percentiles). Due to the right-skewness data, the SII, SIRI and AISI values were log-transformed for graphical presentation. Dots depicted the individual's samples. p<.05 was considered statistically significant. Mann-Whitney U test was used for comparisons.



Suplementary Figure 3. The box plots of (A) SII, (B) SIRI and (C) AISI scores according to HLA-B27 in pre- and post-treatment groups in patients with AS (n=143). Data were expressed as median with interquartile ranges (IQR, 25th–75th percentiles). Due to the right-skewness data, the SII, SIRI and AISI values were log-transformed for graphical presentation. Dots depicted the individual's samples. p<.05 was considered statistically significant. Mann-Whitney U test was used for comparisons. NA, not applicable, shows missing values.

DISCUSSION

AS is a common kind of autoimmune disease which influences the proportion of immune cells.[1] Therefore, identifying the immune status changing associated with AS can improve the diagnosis of AS. In recent years, routine blood parameters were reported as markers of systemic inflammation associated with the diagnosis and prognosis of numerous malignancies and chronic inflammatory diseases.[3,4] White blood cells (WBCs) and their counts change in systemic inflammation, including AS. This study aimed to investigate the differences in the complete blood count parameters, which incorporated easily accessible for the diagnosis, severity and response to Anti-TNF treatment of AS.

Studies have shown that patients with AS have a higher peripheral blood PLT count than healthy individuals. PLTs are important in inflammatory reactions and immune responses by releasing proinflammatory mediators such as chemokines and cytokines.[6] Although the specific mechanisms involving PLTs in the pathogenesis of AS are unclear, it has been reported that activation of PLTs by thrombin, histamine, TNF-α and interleukin (IL)-12 leads to adhesion between activated PLTs. Regulated with the aid of TNF and upon activation, normal T-cell expressed and possibly chemokine-secreting PLT factor 4 stimulates neutrophils and monocytes to release inflammatory mediators and participate in the inflammatory response. As a subgroup of leukocytes, neutrophils are an important line of cellular immune defence against external microbial inflammatory stimulation and invasion by exogenous pathogens. Studies have shown that many cytokines and chemokines play an important role in neutrophil recruitment, activation and survival in inflammatory sites, including IL-17, IL-8, interferon-γ, TNF-α and granulocyte-macrophage colonies. Abnormal lymphocyte signalling can lead to autoimmune diseases. In systemic inflammation, an increase in neutrophils is accompanied by a corresponding decrease in lymphocytes.[1] This is consistent with our findings showing that absolute neutrophil and platelet counts are higher in patients with AS than in healthy controls. Cellular components and blood ratios can provide insight into the extent of ongoing inflammation. In recent studies, MLR, NLR, PLR, RDW, MPV, and PCT have been shown to reflect inflammation and oxidative stress in chronic inflammatory and autoimmune diseases.[3,7] These parameters have been reported to reflect disease activity and prognosis in patients with systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), scleroderma, Behçet's disease (BD), and psoriasis.[4,8,9] These biomarkers can be used to monitor the effectiveness of treatment in the same patients or to evaluate subclinical inflammation after treatment.[5,10,11] NLR is predictive in general and cancer-specific surveillance of stomach, lung, breast, colorectal and kidney cancers.[12] Other inflammatory diseases such as acute pancreatitis, inflammatory bowel disease, and acute appendicitis, and systemic diseases such as hypertension, diabetes mellitus, chronic kidney failure, irritable bowel syndrome, Hashimoto's disease, the cardiovascular disease had higher NLR levels. In another study, bone loss and inflammation were associated with higher NLR levels in elderly patients with osteoporosis.[3] Recently, in studies conducted on patients with familial Mediterranean fever (FMF), the NLR was thought to be a valuable marker for demonstrating subclinical inflammation and for following the development of amyloidosis.[10] Similarly, PLR has been introduced as an inflammatory marker in thyroid conditions, DM, and liver fibrosis. Multiple studies have suggested that NLR and PLR can be considered markers of disease state in RA, SLE, Takayasu arteritis, ulcerative colitis, other autoimmune diseases, and infectious diseases. MLR is another parameter used as an inflammatory and prognostic marker in many autoimmune disorders, cardiovascular diseases, cancer and tuberculosis.[13] The efficacy and safety of PCT and MPV have been investigated in various dermatological diseases such as psoriasis, Behçet's disease, recurrent aphthous stomatitis and pemphigus vulgaris.[14] In recent years, NLR, PLR, and RDW have also been found to be associated with axial SpA disease activity.[15,16] Previous studies have demonstrated that NLR levels are related to CRP and ESR. Increased NLR was found in patients with high disease activity in axial SpA patients. In addition, different levels of NLR have been found in patients exposed to different treatments, such as anti-TNF-alpha therapy and nonsteroidal anti-inflammatory drugs.[17] PLR was identified as an independent factor for diagnosing AS and was associated with the severity of AS.[18,19] Peng et al. suggested that increased RDW is associated with AS and could be a potential marker to predict AS disease activity.[7] Consistent with the literature, our study showed significant differences between AS cases and healthy controls with increased RDW, PLR, NLR and MLR. Previous study found MPV to be lower than control in patients with rheumatoid arthritis, Behçet, AS.[20] They argued that this might be related to platelet utilization in inflammatory processes. Thus resulting in smaller, inactive platelets. Similar to the previous study, MPV was lower than healthy controls and increased with treatment. PCT decreased with treatment but was not significant.

Combined haematological indices of inflammation, especially NLR, MLR, PLR, SII, SIRI and AISI, are widely used with promising results in various diseases.[8,9,14,15] SII, SIRI, and AISI indices have been proposed as markers of systemic inflammation with prognostic significance in patients recently undergoing major surgery and oncological treatment.[21,22] SIRI was significantly higher in diseases such as cancer, infectious diseases and cardiovascular disease.[23] AISI has been found to be a prognostic factor in idiopathic pulmonary fibrosis.[24] SII has been widely used in oncology since 2014 with promising results. There are studies on gastrointestinal, bone, breast, kidney and gynaecological cancers and coronary artery diseases with SII.[25,26] A study showed that SII has a high diagnostic value for moderate/severe psoriasis. Another study showed that SII, NLR, and PLR were significantly elevated and associated

with endoscopic severity in ulcerative colitis patients.[27] In a study on Covid 19, significantly lower survival was found in patients with higher AISI, dNLR, MLR, NLPR, NLR, SII and SIRI.[28,29] In the field of rheumatology, there is an increasing interest in combined haematological inflammation indices, especially in SII.[30,31] In a study conducted on rheumatological diseases, the SII value was found to be significantly higher in the active BD group than in the inactive BD group.[32] Satis et al. previously evaluated SII and SIRI as a marker of inflammation in RA patients.[6] In a study evaluating SII in ANCA-related vasculitides, SII was found to be associated with disease activity and prognosis.[33] A study in adult-onset still disease (EBSH) demonstrated that laboratory inflammatory scores could be used as a practical tool to diagnose EBSH. The same study concluded that the combination of SII and ferritin was the most powerful assessment tool.[34] Similarly, it has been shown that osteoporosis can be an important marker in the evaluation of osteoporotic fractures.[35] There are studies concerned with AISI, SII and SIRI in some rheumatological diseases. However, there is no data in the literature on SII, SIRI and AISI indices, which are used as new and more comprehensive chronic inflammatory indicators based on monocyte, neutrophil, lymphocyte and platelet counts in AS. BASDAI, ESR, and CRP have commonly used measures to determine disease activity and patients' response to therapy. New biomarkers that can monitor AS disease activity need to be identified, and the accuracy of currently available disease activity assessment tools needs to be increased. In this study, NLR, PLR, MLR, RDW, SII, SIRI and AISI were higher in AS patients compared to the healthy control group. AISI, SIRI and SII levels were significantly higher in the highly active AS patient group than in the inactive patient. Also, they were correlated with ESR, CRP and BASDAI. Regarding AS, ROC analysis showed that SII, AISI, and SIRI had the best predictive performance for disease activity. Therefore, an estimator such as SII, AISI, and AISI may better reflect the inflammatory status in specific disease states. To our knowledge, this is the first study to show the relationship between AISI, SIRI, SII and disease activity in patients with AS. It was concluded that SII, AISI and SIRI could be new biomarkers to evaluate AS activity.

TNF-α plays an essential role in the pathogenesis of AS. It is also an important element in hematopoietic progenitor cell differentiation and maturation. Various clinical and laboratory markers have been used to evaluate the efficacy of anti-TNF-α therapy. Our study found that SII, AISI, SIRI, RDW, MLR, PLR, and NLR levels in patients with AS were significantly higher than in healthy individuals and decreased after treatment, except for SIRI. The decrease in PLR and RDW was less after treatment. MPV, which was low before treatment, increased with treatment. This may indicate that inflammation inhibits platelet maturation. In AS patients, the decrease in AISI and SII after treatment was more significant in HLA-B27 positive patients than in negative. It shows that SII, AISI, MLR, PLR, NLR, MPV, and RDW may be valuable markers to evaluate the efficacy of anti-TNF-α therapy in patients with AS. Given that SII, AISI, and AISI can be easily calculated from CBC, an inexpensive, easily accessible test, are promising markers for assessing disease activity in AS patients and aiding in treatment optimization.

The study has several limitations which should be reviewed. The first limitation was the single-centre, retrospective natüre of the study. Additionally, our small sample size limited the power of the statistical analysis. Another limitation was the complexity of relations between complete blood count parameters, and immune response. Furthermore, we believe that still there might be some unknown interactions. Thus, more investigations should be conducted to clarify these complex interactions.

CONCLUSION

SII, SIRI and AISI may be seen as valuable markers for demonstrating inflammation and disease activity. Besides, SII, AISI NLR, PLR, MLR, RDW, and MPV are valuable in evaluating the effectiveness of anti-TNF-α therapy.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Selçuk University Faculty of Medicine Hospital Ethics Committee (Decision No: 2021/118).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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Original Article / Orijinal Araştırma

The Analysis of Anesthesia Methods Used in Cesarean Section Through Data Mining Techniques

Sezaryen Ameliyatında Kullanılan Anestezi Yöntemlerinin Veri Madenciliği Yöntemleri İle İncelenmesi

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Abstract

Aim: The aim of this study is to examine and analyze new patterns of cesarean section anesthesia types and prediction performances of decision trees with data mining techniques.

Material and Method: Classification and clustering analysis were performed to analyze the data of 300 patients. Gini algorithm and C5.0 algorithm were applied to the data set with 24 parameters. These algorithms were also applied to the 16-parameter data set obtained after preprocessing. The estimation performances obtained were compared according to the accuracy criterion. Then, clustering analysis was applied to the 24 and 16 parameter data sets with the K-prototype algorithm.

Results: The study revealed that the prediction success of the Gini algorithm was determined as 96.61%, and the prediction success of the pruned decision tree obtained by the Gini algorithm was 94.91%. The prediction success of the C5.0 algorithm was determined as 98.87%.In the clustering analysis performed with the K-prototype algorithm, the number of clusters was determined as 4 and 5 for both data sets, based on expert opinion, and important patterns were observed with these cluster numbers.

Conclusion: As a result of the study, it was revealed that the C5.0 algorithm had the highest performance with an accuracy rate of 98.87As a result of the cluster analysis, it was concluded that the age of the patients, the duration of the operation, the type of previous anesthesia, the number of previous cesarean sections, the fear of anesthesia and the previous surgical operations were effective on the type of anesthesia in cesarean section cases.

Keywords: Data science, anesthesia types, cesarean section, k-prototype, classification

Öz

Amaç: Bu çalışmanın amacı, sezaryen anestezi tiplerinin yeni örüntülerini ve karar ağaçlarının tahmin performanslarını veri madenciliği teknikleri ile incelemek ve analiz etmektir.

Gereç ve Yöntem: 300 hastanın verilerini analiz etmek için sınıflandırma ve kümeleme analizi yapıldı. 24 parametreli veri setine Gini algoritması ve C5.0 algoritması uygulanmıştır. Bu algoritmalar, ön işlemeden sonra elde edilen 16 parametrelik veri setine de uygulanmıştır. Elde edilen tahmin performansları doğruluk kriterine göre karşılaştırılmıştır. Daha sonra K-prototip algoritması ile 24 ve 16 parametreli veri setlerine kümeleme analizi uygulanmıştır.

Bulgular: Çalışma, Gini algoritmasının tahmin başarısının %96.61, Gini algoritması ile elde edilen budanmış karar ağacının tahmin başarısının ise %94.91 olduğunu ortaya koydu. C5.0 algoritmasının tahmin başarısı %98,87 olarak belirlenmiştir. K-prototip algoritması ile yapılan kümeleme analizinde uzman görüşüne dayalı olarak her iki veri seti için küme sayısı 4 ve 5 olarak belirlenmiş ve bu küme sayıları ile önemli örüntüler gözlemlenmiştir.

Sonuç: Çalışma sonucunda C5.0 algoritmasının %98,87 doğruluk oranı ile en yüksek performansa sahip olduğu ortaya çıkmıştır. Kümeleme analizi sonucunda ise hastaların yaşı, operasyon süresi, önceki anestezi tipi, önceki sezaryen sayısı, anestezi korkusu ve önceki cerrahi operasyonların sezaryen olgularında anestezi türü üzerinde etkili olduğu kanısına varılmıştır.

Anahtar Kelimeler: Veri bilimi, anestezi türleri, sezaryen, k-prototip, sınıflandırma

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INTRODUCTION

Information technologies enable us to easily collect data in a great number of fields. However, data is meaningless unless it is processed and transformed into information. Therefore, data mining has an important role in discovering information in large amounts of data. It is an undeniable fact that solutions to problems produced by data mining provide significant benefits for every field. This also applies to medicine and healthcare.It is possible to define data mining as "the discovery of statistically significant patterns, relationships, changes, irregularities, rules and structures in data ".[1]

Research by WHO (World Health Organization) demonstrates that cesarean deliveries are increasing globally. Currently, cesarean section accounts for more than 1 in 5 (21%) births worldwide. It is estimated that this rate will increase in the next ten years and will reach 29% of all births by 2030. As in the rest of the world, the cesarean section rate is higher than the normal birth rate in Turkey.[2] According to OECD (Organization for Economic Cooperation and Development) data, 584 out of 1000 live births were performed by cesarean section in Turkey in 2021.[3] This situation has made the choice of anesthesia type in cesarean section operations more important.

Data mining studies focus on descriptive or predictive functions. The purpose of prediction-based functions is to build a prediction model using existing data, and the purpose of definition-based models is to identify patterns among data by observing available data, and to identify features and characteristics of different datasets[4] "Classification" and "Regression" are predictive models. "Clustering" "Association Rules" and "Sequential Models" are some examples of descriptive models.

The aim of this study is to determine whether there are new patterns about cesarean section anesthesia types decided by anesthetists using data mining techniques and to compare the prediction successes of decision tree algorithms in this regard.

This part of the study consists of two sub-sections. Firstly, data mining and machine learning studies in health sciences are mentioned. Secondly, the studies on the selection of anesthesia type in the cesarean section are explained.

Data mining methods are used in gynecological and obstetric studies, as in many branches of health. For example; Senthilkumar et al. in the study of it is aimed to determine risk factors for low birth weight by using data mining methods.[5] Similarly, Mehbodni et al. classified fetal health using machine learning methods.[6] In the studies of Abdar et al.[7] and Begum et al.[8] applied the data mining methods for internal diseases studied. Topaloğlu et al. used C5.0 and J48 as classification methods on infectional disease related data.[9] Moreover, Şatır et al., applied ID3, C4.5, CART and artificial neural network (ANN) methods on glokom data set.[10]

The selection of the most appropriate general or regional anesthesia method for cesarean sections takes into account various factors, such as the urgency of the procedure, the patient's preference, the patient's current health status and any comorbidities, as well as the expertise and experience of the surgeon and anesthetist.[11,12] Regional anesthesia is often preferred over general anesthesia due to lower maternal mortality rates associated with it compared to general anesthesia.[13,14] The safety of general anesthesia in cesarean section has improved greatly due to technological advances and advances in emergency algorithms. Maternal deaths due to anesthesia have gradually decreased, but it has been observed that, relatively speaking, the risk of maternal death in general anesthesia applications is higher than in regional anesthesia applications, although it is not statistically significant.[15] The decision on which anesthesia method to use depends on whether the case is urgent or elective.

Berrin et al., stated that the rate of spinal anesthesia in elective C / S increases because spinal anesthesia has a positive effect on the APGAR score.[16] In another study Okafor et al., suggested that spinal anesthesia was performed in 40% of emergency cases.[13]

When the indication for emergency cesarean section is realized by the obstetrician, the guidelines recommend consulting the anesthesiologist and making the evaluation at the earliest period.[17] According to the British and Irish Society of Anesthesiologists and Obstetrics and Anesthesiologists, the time allowed for preoperative anesthesia preparation and administration of spinal anesthesia is 30 minutes after an emergency cesarean section is reported to the anesthesiologist unless the life of the mother and baby is in danger.[18] Classification of urgency in cesarean sections is shown in **Table 1**.

Table 1. The urgency classification in cesarean sections[16,17]

	Identification (as soon as the operation decision is made)
Category 1	The lives of the mother or fetus are in danger; the operation is required as soon as possible.
Category 2	Some factors threaten the life of the mother or fetus, but there is no level of urgency that requires an immediate operation.
Category 3	Preterm birth is required, but the life of the mother and fetus is not in danger
Category 4	Delivery by cesarean can be planned for an appropriate time for the mother and birth team (planned elective)

In this classification, the time elapsed between cesarean delivery and the delivery of labor (Decision- To-Delivery Interval (DDI): in terms of maternal and infant health) is supposed to be under 30 minutes. In these cases, if cesarean delivery is not performed, the lives of the mother and fetus are at serious risk. General anesthesia is preferred in Category 1 cases. Guidelines and references for cases in Category 2, such as antepartum hemorrhage and progression of labor, suggest that this DDI duration should be <75 minutes, the anesthetic selection depends on the clinical situation of the mother and fetus at the time of the cesarean decision. Early membrane rupture in which maternal and fetus lives are not threatened, and non-progressive cases of fetal distress are not included in Category 3. In this category, the choice of anesthesia and the pace of the procedure performance are

determined by the clinical situations of the mother and fetus at the time of the cesarean decision. It has no difference from those in elective cesarean sections. Category 4 covers elective cesarean cases.[19, 20]

MATERIAL AND METHOD

In the model phase, C 5.0 and Gini algorithms as classification methods, k-prototype as clustering method used .For this purpose, data were collected from 300 participants who gave birth via cesarean section in a maternity hospital. Before data collection, the ethics committee approval was obtained from Atatürk University Medical Faculty (Date: 15/02/2018, Decision No: 2018/46). The data were collected via a data collection form including 24 parameters. While 239 of those participants were anaesthetized with spinal methods, remaining 61 of them were anaesthetized with general anesthesia method. Before the parameter selection, the data set is composed of the parameters specified in **Table 2**.

Table 2. Data set before parameter selection

Data Set 1	Parameters	Abbreviations
Demographic parameters of the patients		
	Age	AGE
	Height	
	Weight	WEIGHT
Parameters related to the pregnancies of the participants		
	Number of pregnancies	
	Gestational week	G.W
	Number of previous cesarean sections	CS. NUMBER
Parameters related to the caesarean condition of the participant		
	Caesarean section cause	CS. CAUSE
	Case type	CASE TYPE
	Fasting period	FASTING PERIOD
	Previous type of anesthesia	PTA
	Current anesthesia type	CAT
	Time of surgery	TIME SURGERY
Participant's health evaluation parameters		
	Comorbid disease history	
	Disease	
	Drug history	
	Drug	
	Laboratory values are suitable for spinal anesthesia	LSSA
	Anesthetist choice spinal anesthesia	ACSA
	Previous surgery	PREVIOUS SURGERY
	Asa	ASA
	Mallampati	MALLAMPATI
Anesthesia preference-related parameters		
	Patient's preference for general anesthesia	PPGA
	Patient's preference for spinal anesthesia	PPSA
	The patient's fear of general anesthesia	PFGA
	The patient's fear of spinal anesthesia	PFSA

Analyzes in the study were carried out using R software. With the Information Gain and Chi-Square methods, which are among the filtering methods, the number of 24 usable parameters has been reduced to 16. For the classification method applied to the data sets, 80% of the data was used as training data and 20% as test data with the hold out method.

Data analysis in the research was completed in 2 parts. The first part applied classification and clustering methods to the raw data containing all parameters. In the second part, Chi-square and Information Acquisition were used as parameter selection methods, classification, and clustering analyzes were performed on the reduced data set, and the results were compared.

RESULTS

In this part of the study, data mining results is presented. Although analysis conducted on all data including additional parameters such as education, BMI and normal birth number, only the findings representing the highest performance will be mentioned.

Classification Method Findings

It is observed that the same parameters are selected with the Information Acquisition and Chi-square methods used for parameter selection. Parameters selected in order of weight are ACSA, PPGA, PPSA, LSSA, PFGA, PFSA, CS. CAUSE, CASE TYPE, TIME SURGERY, FASTING PERIOD, PTA, PREVİOS SURGERY, CS. NUMBER, MALLAMPATI, WEIGHT.

Table 3 demonstrates that the performance value of the decision trees obtained through Gini algorithm based on the accuracy criterion is equal in both datasets. In addition, the decision tree obtained through the Gini algorithm, the pruned decision tree obtained through the Gini algorithm and the performance tree based on the accuracy criteria of the decision tree obtained by the C5.0 algorithm were determined as 96.61%, 94.91% and 98.87% respectively.

Table 3. Model Performance Evaluation

	Gini Algorithm	Pruned Gini Algorithm	C5.0 Algorithm
Accuracy	0.9661	0.9491	0.9887

Results Related to Cluster Analysis

Figure 1 and **Figure 2** indicate the histograms that were created to provide information about the clustering analysis performed before and after the parameter selection. **Figure 1** reveals that all the patients in the 4th cluster have the characteristics that require general anesthesia. Moreover, the cluster analysis after parameter selection suggests that the patients in the second cluster have the similar characteristics. The cluster analysis performed before the selection suggests that all the patients in the 5th cluster and almost all of the patients in the 4th cluster have characteristics that are suitable for general anesthesia. In addition, in the post-selection clustering analysis, it is determined that all the patients in the first cluster have tendency to general anesthetics.

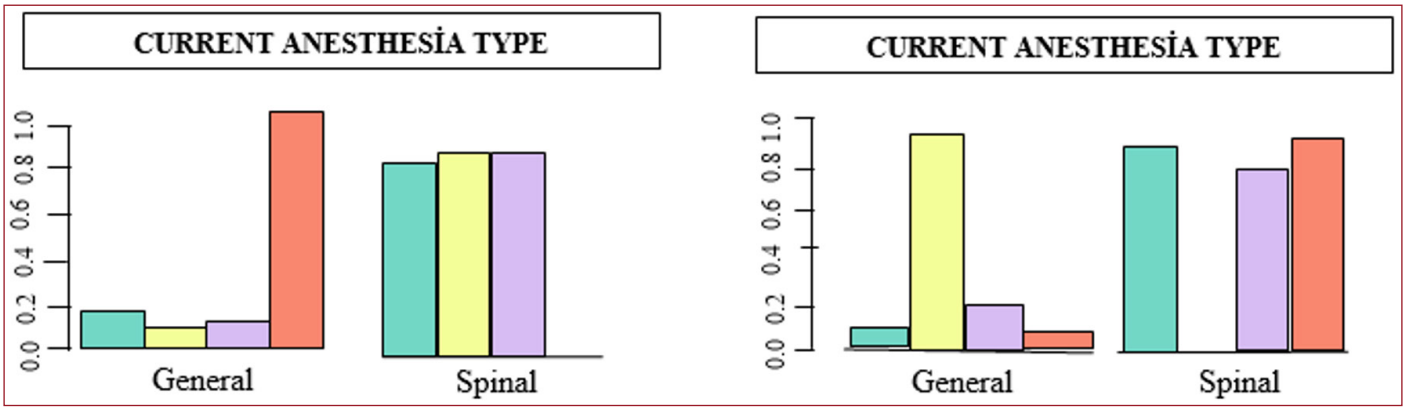

Figure 1. Pre-selection and post-selection clustering analysis for K=4

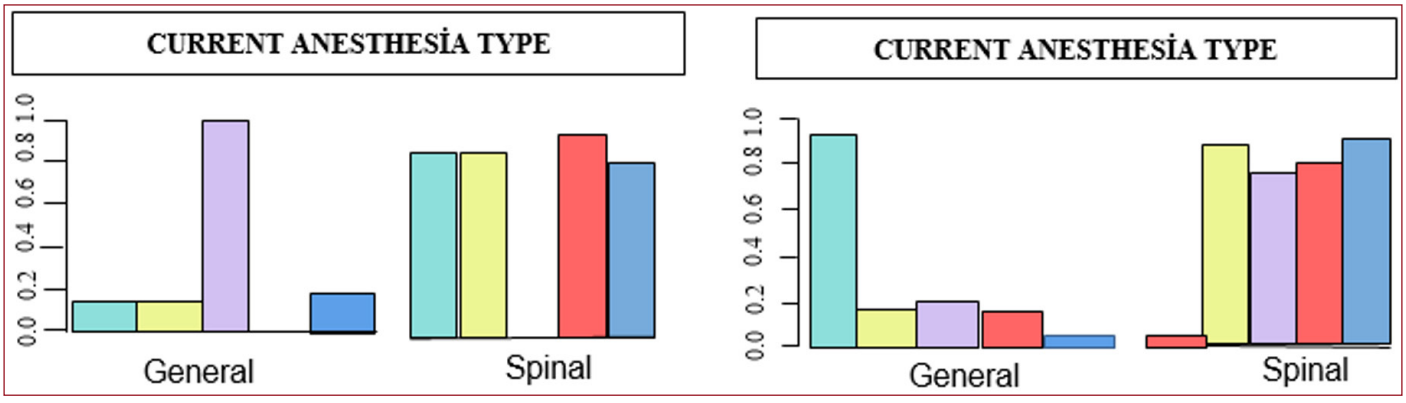

Figure 2. Pre-selection and post-selection clustering analysis for K=5

In addition, it was also concluded that case types of the patients were very urgent and the reasons for cesarean section were "3" (Fetal Distress) or "4" (Decollete Placenta) and the characteristics of mallampati class was 2. These findings were also in line with the clustering analysis conducted on the data that were obtained after parameter selection.

In addition to these characteristics, the clustering analysis conducted on the data that were obtained before parameter selection indicated that the majority of the patients in a cluster were between 20-40 years and their height varied from1.55 to 1.70. It was also observed that these patients were in the 35-40 weeks of gestation, had no concomitant diseases, no history of any drugs and their ASA classes were 2.

DISCUSSION

The purpose of this study is to extract the pattern from the previous data consisting of anesthesia decisions made by anesthetists for cesarean section and to investigate unpredictable or unusual relationships with the help of data mining methods. For this purpose, data were collected from 300 participants who gave birth by cesarean section in a maternity hospital. The ACSA attribute had the most significant importance in both methods. This also provides an evidence of how important it is for the patient to act with the advice of a physician in terms of having a healthy birth.

In cluster analysis, it was discovered that a pattern was formed in the selection of the data set into clusters 4 and 5 before and after parameter selection.

As a result of both clusters, it was found that the majority of the patients in one cluster were in the range of 55-80 kg and their fasting duration ranged between 5-12 hours and they were taken to the operation between 00:00-06: 00 a.m. In addition, it was argued that the majority of these patients had no previous surgery and received no anesthesia.

In this study, Gini and C5.0 algorithms were applied on the data sets as classification methods. According to the results, C5.0 algorithm had the highest performance. Decision trees were discussed with the anesthesiologists. They stated that although age parameter is effective in determining the type of anesthesia as a result of classification analysis, it is not effective in decision making. This may be due to the fact that age is already included in the biochemistry tests.

There is no previous data mining study on the type of anesthesia. However, the analysis of the data mining studies in the medical literature indicated that the study obtained similar values to the success performance of the decision trees created in the studies of Topaloğlu et al.[9] Abdar et al.[7] and Şatır et al.[10] Therefore, it seems that the decision trees mentioned above can be used by anesthesiologists or medical informatics specialists.

CONCLUSION

The study demonstrates that the C5.0 algorithm outperforms other algorithms in accurately predicting the type of anesthesia, achieving an accuracy rate of 98.87%.In addition, a notable result of the study is that the cluster analysis was found to be effective on the age of the patients, operation time, previous anesthesia type, number of previous cesarean sections, fear of anesthesia and previous surgical operations on the type of anesthesia in cesarean section cases.

In the light of the aforementioned results, it is recommended to use patient data to inform the patients before operation. Because it is notable that the field experts still have insufficient level of understanding many patterns obtained by data mining methods. In addition, infographics, brochures are necessary or events such as meetings are supposed to be organized in order to increase the awareness of patients. Future research could explore alternative data mining methods, such as deep learning approaches or ensemble models, to assess the generalizability of the findings. Furthermore, repeating the analysis with a larger dataset would enable comparison of the results.

On the other hand, the study has some limitations such as the sample size, the fact that it was carried out with a limited number of algorithms, and the data was collected in a limited time period of three months..

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Atatürk University Medical Faculty Ethics Committee (Date: 15/02/2018, Decision No: 2018/46).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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Case Report / Olgu sunumu

Forgotten Peser Ring in the Vagina: Case Report

Vajinada Unutulmuş Peser Halkası: Olgu Sunumu

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Abstract

An 88-year-old multiparous patient was brought to the clinic by her relatives because of vaginal bleeding and bad smell. There was no known condition in her medical history. A hard structure was observed during the examination. The speculum was observed on the deformed pessary ring attached to the surrounding vaginal tissue. The patient was hospitalized. The forgotten pessary ring was cut with an iron cutting tool without damaging the surrounding tissues and removed from the vagina without any complication. She was discharged with cure after intravenous antibiotic treatment. Pelvic examination should be performed carefully in elderly patient groups considering the possibility of forgotten pessary.

Keywords: Pessary, forgotten pessary, bad smell vaginal discharge

Öz

88 yaşında multipar hasta vajinal kanama ve kötü koku nedeniyle yakınları tarafından polikliniğe getirildi. Özgeçmişinde bilinen bir rahatsızlığı yoktu. Hastanın yapılan muayenesinde ele gelen sert bir yapı izlendi. Spekulum ile bakıda çevre vajen dokuya yapışık deforme olmuş peser halkası izlendi. Hasta kliniğe yatırıldı. Unutulmuş peser halkası çevre dokulara hasar vermeden demir kesici alet ile kesilip parçalanılarak vajenden komplikasyonsuz şekilde çıkarıldı. İntravenöz antibiyotik tedavisi sonrası şifa ile taburcu edildi. İleri yaş hasta gruplarında unutulmuş peser ihtimalini göz önünde bulundurarak pelvik muayenenin dikkatli yapılması gerekir.

Anahtar Kelimeler: Peser, unutulmuş peser, kötü kokulu vajinal akıntı

INTRODUCTION

Pelvic organs prolapse is a biopsychosocial health problem that affects nearly half of women.[1] Pessary ring is a frequently used non-surgical conservative treatment method for pelvic organ prolapse. In elderly cases where surgery is contraindicated, pessary treatment is a very advantageous treatment method, as it is non-invasive, economical and has immediate effect.[2] When follow-up and care is not regular, it may present with various complications that even lead to death. The most common complications are pelvic pain, bleeding, and bad odor. In our case, the complication of an infected pessary ring that had been forgotten for more than 5 years, causing isolation from social life, was reported.

CASE

An 88-year-old multiparous patient, who was isolated from social life due to vaginal bleeding and bad odor, was brought to the polyclinic by her relatives. She had no known illness in her history. During the examination of the patient, severe anaerobic foul-smelling purulent vaginal discharge, bleeding, and a hard palpable structure were observed. When examined with a speculum, a deformed pessary ring was observed attached to the surrounding vaginal tissue. When the patient and her relatives were questioned again, it was learned that they went to the gynecology and obstetrics clinic more than 15 years ago and had a pessary inserted due to uterine prolapse, and that they had not been to a doctor's examination since then. Body temperature is normal, no abdominal or adnexal tenderness was observed on physical examination. Serum leukocyte count was 15,400, C-reactive protein (CRP) was measured as 33 mg/L, and procalcitonin was measured as 0.202 ng/mL (>0.05). Although the pessary ring was highly adhesive, especially on the posterior wall, it was deeply infiltrated into the peripheral tissues.

The patient was admitted to the clinic. Since the patient had active vaginal bleeding, after the first dose of antibiotic therapy, the pessary ring was removed

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from the vagina under sterile conditions by blunt and sharp dissections, the aluminum ring inside was cut and fragmented with an iron cutting tool, without damaging the surrounding tissues **(Figure 1**). No urinary or gastrointestinal complications occurred during the procedure. The cervix could not be evaluated clearly. The vagina was washed with plenty of povidone-iodine and physiological saline. In antibiotic therapy, 3*500 mg intravenous Metronidazole was administered. After the procedure, the vagina was washed twice a day with plenty of povidone-iodine and physiological saline. During the patient's rectal examination, approximately 6 cm of hard tissue was palpated adjacent to the vagina. Because the patient's kidney function tests were high, non-contrast pelvic magnetic resonance imaging was performed, and when reported, the mass could not be fully identified. It was planned to take a biopsy, but the patient refused. He was discharged with full recovery after three days of hospitalization.

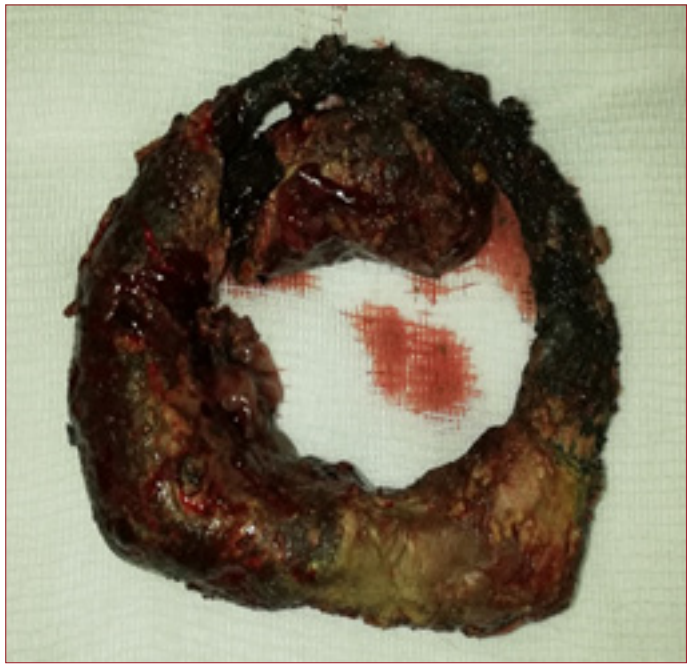

Figure 1. The metal ring inside the pessary ring can be seen at 12 o'clock.

CONCLUSION

Pessary rings in the treatment of uterine prolapse have been described in the literature since the time of Hippocrates. Rubber, plastic, silicone etc. It is made of different materials such as. Foreign bodies in the vagina can be present for a long time without any symptoms, but when deeply embedded they cause life-threatening complications.[5] Clinical symptoms in reported cases of pessary rings forgotten for a long time; These were foul-smelling vaginal discharge and irregular vaginal bleeding. Since the foreign body is covered with granulation tissue and pus, it is often difficult to separate it from other tissues.

Treatment with antibiotics and washing with antiseptic solution before removal have been shown to be helpful. Difficulties in removing an embedded pessary ring have been reported in almost all cases, and there is no specific technique described. Traction with various instruments has been described, along with dissection and rotation. In the present case, the tissue covering the metallic ring was gently dispersed and the ring was removed with traction. Forgotten pessary ring complications include chronic vaginitis, ulceration and metaplasia, and vaginal cancer.[3] Other complications include vesicovaginal, rectovaginal fistula formation, intestinal obstruction, urinary tract infection, and hydronephrosis.[4] In our case, it could not be ruled out whether the mass observed was a cervical malignancy with a possible infiltrative basis because the patient did not want further examination. We should not forget that if the follow-up and maintenance of the pessary ring, which is used safely as a conservative treatment in patients where surgical treatment cannot be performed, is not followed regularly, we may encounter various complications that can even lead to death.

ETHICAL DECLARATIONS

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

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Letter to the Editor/ Editöre Mektup

Ultrasound-guided Barbotage in the Treatment of Calcific Tendinitis

Kalsifik Tendinit Tedavisinde Ultrason Eşliğinde Barbotaj

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Dear Editor,

Calcific tendinopathy is one of the most common causes of shoulder pain. Deposition of calcium hydroxyapatite crystals in the rotator cuff tendons is seen.[1] Studies have shown that 7.5–20% of people without symptoms and 6.8% of those with shoulder pain have radiologically visible calcification.[1] It is more common in women and usually observed between the ages of 30 and 60.[1] It has been suggested that the pathology is caused by poor blood perfusion, which causes tenocytes to metaplastically change into chondrocytes and produce calcium hydroxyapatite. Three stages have been described to characterize the development of pathology: precalcific, calcific, and postcalcific.[2]

In this report, the approach to infraspinatus calcific tendinitis diagnosed by ultrasound (US) in a patient complaining of shoulder pain is presented.

A 51-year-old female patient presented with a four-month history of left shoulder pain. She previously used nonsteroidal anti-inflammatory drugs (NSAIDs), but her complaints increased, and the pain level was rated as 9/10 on the Visual Analogue Scale (VAS). The movements of the left shoulder joint were painful and limited in all directions. Neurologic evaluation of the upper limb was normal. Calcific deposits were visualized around the shoulder joint in plain radiograph. US showed a large calcification in the infraspinatus tendon. Laboratory tests were unremarkable. After that, the patient was diagnosed with calcific tendinitis, and was planned for barbotage under US guidance. After skin antisepsis, 1% lidocaine was used to provide local anesthetic. The 18G needle was advanced to the site of the calcifications by US-guided in-plane approach. A needle was used to penetrate the calcific region, and aspiration was tried. After that, 10 ml of an isotonic solution were injected gradually and aspirated. Calcium deposits were seen inside the syringe. Then, 1 mL triamcinolone acetonide (40 mg/1 mL) and 2 mL 1% lidocaine were injected in the subacromial/subdeltoid bursa. The procedure was completed without any complications. The patient's shoulder range of motion was complete in all directions at four weeks following the treatment, and her VAS pain score was a 2/10. US revealed a significant decrease in calcification in the infraspinatus muscle.

The use of US in the diagnosis of calcific tendinopathy of the shoulder has been shown to be reliable. It provides assessment of the rotator cuff and the long head of the biceps tendon and can also be used as a guide for interventional treatment.[3] Since the disease is usually self-limiting, it can be treated conservatively with rest, NSAIDs, and physical therapy. In patients who have severe or persistent symptoms, more invasive procedures such as calcium deposit needling and lavage (barbotage), subacromial corticosteroid injections, and extracorporeal shock wave therapy are recommended. However, if these approaches fail, surgical intervention can be required.[4]

Although calcific tendinitis is usually self-limiting, in cases of severe and long-term pain, it should be kept in mind that US-guided barbotage is a safe method with a high success rate. The limitation of the article is the lack of long-term follow-up of the patient.

Keywords: Calcific, shoulder, ınjection, ultrasound

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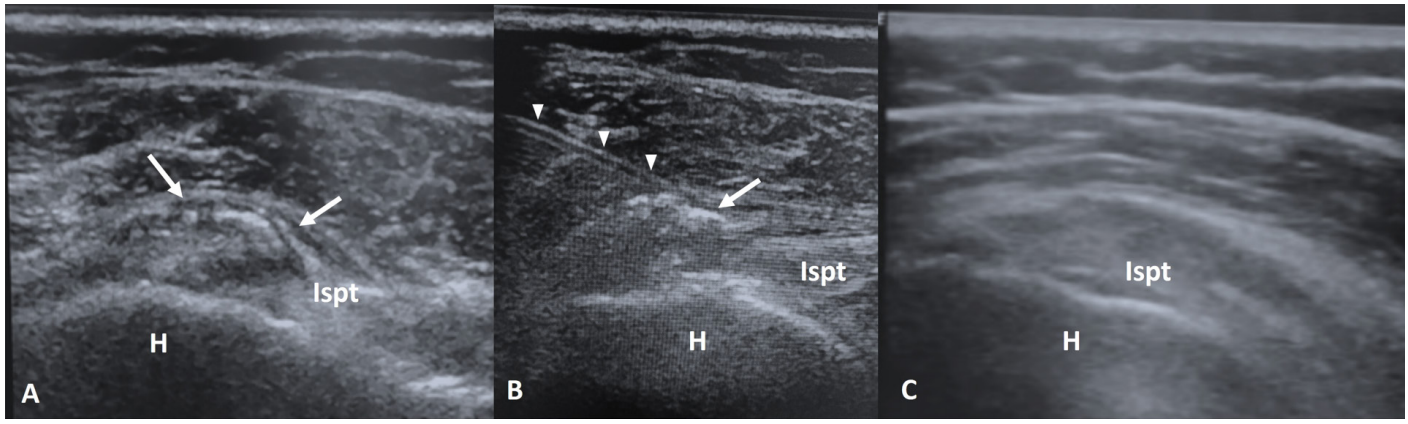

Figure. Axial US image shows calcification (arrows) within the infraspinatus tendon (Ispt) (A). The calcification is reached with a needle (arrowheads) for barbotage during an in-plane approach under US guidance. (B). Control image of the infraspinatus tendon (Ispt) after four weeks. H; humerus

ETHICAL DECLARATIONS

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