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Research article

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Evaluation of hospitalized patients with a possible diagnosis of COVID-19

Derya Korkmaz, Petek Konya, Havva Tünay, Oğuzhan Dilek, Neşe Demirtürk

Afyonkarahisar University of Health Sciences Faculty of Medicine, Infectious Diseases and Clinical Microbiology Department, Afyonkarahisar, Turkey

ORCID ID of the author(s)

DK: 0000-0001-7236-2164
PK: 0000-0001-5055-1220
HT: 0000-0003-4333-082X
OD: 0000-0002-8996-3203
ND: 0000-0002-6186-2494

Corresponding Author
Derya Korkmaz
Afyonkarahisar University of Health Sciences Faculty of Medicine, Infectious Diseases and Clinical Microbiology Department, Afyonkarahisar 03200, Turkey
E-mail: drderya@ymail.com

Ethics Committee Approval
The study was approved by the Ethical Committee of Afyonkarahisar Health Sciences University, Faculty of Medicine (2020/14).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: The definitive diagnosis of COVID-19 disease is made by demonstrating the presence of SARS-CoV-2 in nasopharyngeal swab samples. In patients who present with COVID-19-like symptoms but are found to be PCR negative, lung tomography, physical examination, and specific laboratory findings can guide diagnosis and treatment. This study aims to retrospectively evaluate the clinical, laboratory, and radiological findings of patients who presented with Covid-19-like symptoms. but were found to be PCR negative.

Methods: This study was planned as a retrospective cohort study. Patients hospitalized in the pandemic service of Afyonkarahisar Health Sciences University between 19 March and 30 September 2020 - who were PCR negative and defined as possible cases through diagnosis, treatment, and follow-up guidelines of the Republic of Turkey Ministry of Health, were included. Of these patients, those without radiological pulmonary involvement were defined as group A, and those with radiological pulmonary involvement were defined as group B. Clinical and laboratory findings of both groups were evaluated and compared.

Results: In the lung tomographic examination of 238 patients in the study, 16.4% in group A without radiological lung findings and 83.6% in group B with signs of inflammation were identified. While common complaints were high fever and diarrhea in group A, cough and shortness of breath were significantly higher in group B. The most common comorbidities in both groups were hypertension and diabetes, respectively, while hypertension was found to be significantly higher in group B. There was no mortality in any patient without lung involvement, but there was no significant difference between groups in terms of mortality.

Conclusion: These techniques can be used in PCR-negative patients presenting with COVID-19, for an estimation of patients with a severe prognosis with pulmonary tomography findings, symptoms, laboratory results, and accompanying disease at the time of admission. Determining parameters that identify at-risk patients during the early period may contribute to improving patient management and the appropriate use of limited resources.

Keywords: COVID-19 pandemic, Diagnosis, SARS-CoV-2 virus

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Introduction

Coronavirus-related disease (COVID-19), a new beta coronavirus caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), having spread all over the world, causing a pandemic shortly after the first cases were seen in China in December 2019. The disease can cause different clinical pictures, ranging from mild upper respiratory tract infection to severe pneumonia, multi-organ failure, and thromboembolic complications [1]. The worldwide method for definitive diagnosis of COVID-19 is to assess for the presence of SARS-CoV-2 in nasopharyngeal swab samples by the reverse-transcribed polymerase chain reaction (RT-PCR) method. Sputum, tracheal aspirate, and bronchoalveolar lavage samples are used in cases with pneumonia from the second week of infection [2]. Although RT-PCR is a precise method, its sensitivity decreases when viral load in samples is low [2, 3].

Computed tomography (CT) is an essential diagnostic criterion as well as for follow-up of the disease, especially in RT-PCR negative patients, who typically present a bilateral ground-glass view in lower zones with multiple foci and peripheral or subpleural patch-like consolidation areas [3-5].

Determining parameters affecting the clinical course of PCR-negative patients with COVID-19 findings may contribute to reducing mortality rates by guiding clinicians in follow-up and treatment of patients. Retrospective evaluation of those who could not be diagnosed microbiologically, but were accepted as possible COVID-19 with clinical and non-specific laboratory tests; we aimed to investigate whether a difference exists between clinical and laboratory findings, and prognosis between patients with and without pulmonary involvement.

Materials and methods

This retrospective cohort study was conducted in the pandemic clinic of Afyonkarahisar Health Sciences University Medical Faculty Hospital between 19 March 2020 and 30 September 2020. All hospitalized patients defined as possible cases per COVID-19 diagnosis, treatment, and follow-up guides of the Republic of Turkey Ministry of Health, but RT-PCR did not detect SARS-CoV-2 in nasopharyngeal swab samples, were included in the study [6]. Our study was approved by the Ethical Committee of Afyonkarahisar Health Sciences University, Faculty of Medicine (2020/14).

The following criteria were used to define COVID-19, as its clinical picture could not be explained by another cause or disease, including:

A: At least one symptom of fever, cough, shortness of breath, sore throat, headache, muscle aches, loss of taste and smell, or diarrhea.

B: The presence of at least one symptom or finding of fever, cough, shortness of breath, sore throat, headache, muscle aches, loss of taste and smell, or diarrhea.

C: At least one of the signs and symptoms of fever and severe acute respiratory tract infection (cough and respiratory distress), and the presence of a hospitalization requirement, with Severe Acute Respiratory Infections-Severe Acute Respiratory Infections (SARI; fever, cough and dyspnea, tachypnea, hypoxemia, hypotension, common radiological findings with lung imaging, and a need for hospitalization due to changes in consciousness with acute respiratory tract infection that had developed in the last 14 days).

D: A combination of at least two of the findings or symptoms of fever, cough, shortness of breath, sore throat, headache, muscle aches, loss of taste and smell, or diarrhea [6].

The demographic findings of patients included in the study, whether they had suspicious contact, complaints at admission (fever, cough, shortness of breath, diarrhea), chest CT findings, hematological and biochemical blood findings, length of stay in the service, treatment responses, and prognoses were all assessed. Patient data were obtained from the hospital's automation system of file information.

Patients included in the study were also classified as to whether they had lung involvement or not. Patients without lung involvement were classified as group A, and those with lung involvement as group B. Those patients in group B were evaluated as mild/moderate (group B1), severe (group B2), and critical (group B3), using these criteria. Mild/moderate: patients with a cough, shortness of breath, tachypnea (SS: 24-30/min), hypoxia (Spo_2: 90 - 94%), fever, ground glass appearance in lower zones of lung CT. Severe patients: frequent cough and shortness of breath, tachypnea (SD > 30/min), hypoxia (Spo2 < 90%), high fever, diffuse bilateral involvement in lung CT. Critical patients: those who need mechanical ventilation, for organ dysfunction, sepsis, septic shock, and acute respiratory distress syndrome [7].

The pulmonary CT findings of patients were evaluated by dividing them into two groups, as typical involvement and atypical involvement in COVID-19. Criteria for typical involvement included peripheral bilateral ground-glass opacities with or without consolidation or visible intralobular infiltration, round morphology of multifocal ground-glass opacities with or without consolidation, or visible intralobular infiltration, an inverted halo sign, or other signs of organized pneumonia. Patients who did not meet these criteria but had signs of inflammation of lung CT were evaluated as having atypical radiological involvement [8].

Patients' clinical findings, treatment responses, and prognoses were compared based on clinical classification at the end of the study.

Statistical analysis

The IBM-SPSS Statistics v. 22 program was used for statistical analysis. Frequencies and percentages were given for categorical data, and median (minimum-maximum) values were given for quantitative data. Pearson and Fisher chi-square tests were used to evaluate the differences between categorical variables. $P < 0.05$ was considered significant.

Results

A total of 238 possible COVID-19 cases were hospitalized and followed in our pandemic service between March 19 and September 30, 2020. Of PCR negative patients, 129 (54.2%) were male and 109 (45.8%) were female.

Thirty-nine (16.4%) of 238 patients in the study were in group A, and 199 (83.6%) were in group B. Of patients in group B, 173 (86.9%) were classified as B1, 16 (8%) as B2, and 10 (5.1%) as B3. The mean age of group A was 54.49 (18.53), while the mean age of group B was 57.43 (18.45) There was no significant difference between the two groups in terms of age and gender ($P = 0.250$, $P = 0.689$). The demographic findings and admission symptoms of patients are based in groups and shown in Table 1.

High fever, malaise, and diarrhea were common symptoms at admission in group A, with cough, fever, and shortness of breath in group B. Eighteen patients had a family history of high-risk contact with patients with definitive diagnosis of COVID-19 (Table 1). When all patients were examined, the most common comorbidities were hypertension, diabetes, chronic obstructive pulmonary disease (COPD), and malignancy (29.8%, 20.2%, 12.2%, and 10.1%). It was observed that 4.2% with hypertension, 10.3% with COPD, and 20.8% with malignancy took a critical course. When group B patients were evaluated, hypertension (P = 0.017) and COPD (P = 0.016) were more common in group B2, and malignancy (P = 0.001) and heart failure (P = 0.032) in group B3. When patient laboratory parameters were examined, leukocyte count and neutrophil/lymphocyte ratio was significantly higher in group A, while lymphocyte count, ferritin, creatinine, LDH, and troponin levels were significantly higher in group B. Patient laboratory findings at admission are shown in Table 2.

Favipiravir was given to 36.9% of patients, and hydroxychloroquine was given to 61.7%, low molecular weight heparin to 47%, and steroids to 1.2%. Eleven patients (4.6%) required oxygen at discharge. While 10 patients (4.2%) whose oxygen requirement was above 5 L/min were group B patients, 92.3% of group A patients were followed without oxygen. Those without pneumonic involvement and 30% of critically ill patients were discharged in recovery status, but 5.8% of patients and 80% of those critically ill were transferred to the intensive care unit (ICU) (Table 3).

While no patients in group A faced mortality, its mean in group B was 5%. When patients in group B were evaluated, mortality was significantly higher (B1 P = 0.001, B2 P = 0.023, B3 P < 0.001): it was also significantly higher in patients receiving hydroxychloroquine in group B (P = 0.001). The rates of intensive care admission and mortality were higher in group B, but this difference was not statistically significant.

Table 1: Demographic findings and complaints at admission by group

Results	Group A	Group B n (%)				*P*-value *
	n (%)	B1	B2	B3	Total	
Gender						
F	19 (48.7%)	80 (46.2%)	8 (50%)	2 (20%)	90 (45.2%)	0.689
M	20 (51.3%)	93 (53.8%)	8 (50%)	8 (80%)	109 (54.7%)	
Fever	23 (59%)	70 (40.5%)	5 (31.2%)	5 (50%)	80 (40.2%)	0.030
Cough	13 (33.3%)	120 (69.4%)	9 (56.2%)	6 (60%)	135 (67.8%)	<0.001
Throat ache	7 (17.2%)	20 (11.6%)	1 (6.2%)	2 (20%)	23 (11.5%)	0.292†
Shortness of breath	3 (7.7%)	57 (32.9%)	12 (75%)	7 (70%)	76 (38.1%)	<0.001
Headache	5 (12.8%)	21 (12.1%)	1 (6.2%)	0 (0%)	22 (11.0%)	0.783†
Myalgia	12 (30.8%)	53 (30.6%)	4 (25%)	1 (10%)	58 (29.1%)	0.839
Abdominal ache	2 (5.1%)	12 (7%)	1 (6.2%)	0 (0%)	13 (6.5%)	1.000†
Diarrhea	14 (35.9%)	9 (5.2%)	1 (6.2%)	0 (0%)	10 (5.0%)	<0.001
Nausea-Vomiting	7 (17.9%)	28 (16.2%)	0 (0%)	0 (0%)	28 (14.0%)	0.532
Malaise	16 (41%)	67 (38.7%)	4 (25%)	2 (20%)	73 (36.6%)	0.608
Hypertension	5 (12.8%)	54 (31.2%)	9 (56.2%)	3 (30%)	66 (33.1%)	0.011
Heart failure	1 (2.5%)	13 (7.5%)	3 (18.7%)	3 (30%)	19 (9.5%)	0.353
COPD	3 (7.7%)	18 (10.4%)	5 (31.2%)	3 (30%)	26 (13.0%)	0.433†
Malignancy	2 (5.1%)	14 (8.1%)	3 (18.8%)	5 (50%)	22 (11.0%)	0.386†
Smoking	5 (12.8%)	5 (2.9%)	0 (0%)	0 (0%)	5 (2.5%)	0.012†
Renal failure	0 (0%)	5 (2.9%)	1 (6.2%)	1 (10%)	7 (3.5%)	0.603
Diabetes	4 (10.3%)	38 (22%)	5 (31.2%)	1 (10%)	44 (22.1%)	0.092
Liver insufficiency	1 (2.6%)	1 (0.6%)	0 (0%)	0 (0%)	1 (0.5%)	0.301†
Contact history	3 (7.7%)	13 (7.5%)	0 (0%)	2 (20%)	15 (7.3%)	1.000†

*The sum of group A and group B were compared. †Fisher's Exact Test

Table 2: Laboratory findings by groups

Parameters, (reference range)	Group A Median (Min-Max)	Group B n (%) B1 Median (Min-Max)	B2 Median (Min-Max)	B3 Median (Min-Max)	Total Median (Min-Max)	*P*-value *
WBC†	9,720 (2,280-18,000)	7,560 (700-35,750)	8,950 (4,390-29,010)	10,745 (3,400-24,060)	8,215 (700-35,750)	0.005
LYM†	970 (110-2,990)	1,300 (60-5,200)	1,100 (90-2,500)	465 (80-2,620)	1,245 (60-5,200)	0.048
N/L†	8.4 (1.54-123.91)	4.00 (0.70-47.96)	6.31 (2.08-116.56)	15.28 (2.17-137.75)	4.4 (0.70-137.75)	0.004
PLT†	237,000 (79,000-402,000)	213,000 (22,000-537,000)	210,000 (120,000-417,000)	195,000 (9,000-337,000)	218,500 (9,000-537,000)	0.571
CRP†	4.2 (0.1-17.0)	4.4 (0.0-41.9)	8.9 (1.5-37.2)	13.2 (0.80-31.3)	5 (0.0-41.9)	0.131
DD†	0.48 (0.00-77.28)	0.49 (0.00-7.74)	0.61 (0.10-1.96)	1.42 (0.20-8.77)	0.52 (0.0-8.77)	0.743
FERR†	104 (7-826)	245.2 (6-8,069)	490.35 (86.48-1,226)	745.9 (6.10-3,018)	224 (6-8,069)	<0.001
AST†	21 (10-155)	26 (8-271)	29.9 (13-103)	29 (14-50)	26 (8-271)	0.074
ALT†	17 (5-79)	20 (2-496)	17 (4-47)	30 (6-48)	20 (2-496)	0.145
Creatinine†	0.76 (0.37-1.60)	0.84 (0.37-7)	1.02 (0.32-2.90)	0.78 (0.49-8.28)	0.82 (0.32-8.28)	0.014
LDH†	199.5 (132-497)	249 (120-779)	278 (149-758)	256.5 (158-842)	245 (120-842)	<0.001
Troponin†	0.003 (0.00-0.04)	0.007 (0.00-0.25)	0.016 (0.00-1.75)	0.012 (0.01-0.04)	0.007 (0.00-1.75)	<0.001
Procalcitonin†	0.16 (0.02-6.40)	0.078 (0.00-17.90)	0.082 (0.06-8.04)	0.217 (0.06-24.58)	0.069 (0.00-24.58)	0.006

* The sum of group A and B were compared. † WBC: Leukocyte count (4000–1000 /µL), LYM: Lymphocyte (1200 – 4000 /µL), N/L: Neutrophil/Lymphocyte ratio, PLT: Platelet (160,000 – 370,000 /µL), CRP: C-Reactive Protein (0 – 0.5 mg/dL), DD: D-dimer (0 – 0.5 µg FEU/mL), FERR: Ferritin (30 – 400 ng/mL), AST: Aspartate amino transferase (5 - 40 U/L), ALT: Alanine aminotransferase (5 – 41 U/L), Creatinine (0.5 – 1.2), LDH: Lactate dehydrogenase (135-225 U/L), Troponin (0-0 -- 014 ng/mL), Procalcitonin (0.005 – 2 ng/mL)

Table 3: Treatment and prognosis

	Group A	Group B n (%)				*P*-value *
	n (%)	B1	B2	B3	Total	
Hydroxychloroquine	34 (87.2%)	96 (55.5%)	9 (56.2%)	8 (80%)	113 (56.7%)	<0.001
Favipiravir	1 (2.6%)	73 (42.2%)	8 (50%)	6 (60%)	87 (43.7%)	<0.001
Heparin	17 (43.6%)	82 (47.4%)	8 (50%)	10 (100%)	95 (47.7%)	0.635
Steroid	0 (0%)	1 (0.6%)	2 (12.5%)	0 (0%)	3 (1.5%)	1.000†
Oxygen-free follow-up	36 (92.3%)	111 (64.1%)	0 (0%)	0 (0%)	111 (55.7%)	<0.001
Oxygen < 3 L/min	2 (5.2%)	50 (28.9%)	1 (6.2%)	1 (10%)	52 (26.2%)	0.004
Oxygen 3-5 L/min	1 (2.5%)	10 (5.7%)	10 (62.5%)	6 (60%)	26 (13.1%)	0.092†
Oxygen > 5 L/min	0 (0%)	2 (1.1%)	5 (31.3%)	3 (30%)	10 (5.0%)	0.375†
Recovery	39 (100%)	168 (97.1%)	10 (62.5%)	3 (30%)	181 (90.9%)	0.050†
Transfer to ICU	0 (0%)	5 (2.9%)	1 (6.2%)	8 (80%)	14 (7.0%)	0.135†
ICU or Deceased	0 (0%)	2 (1.2%)	0 (0%)	5 (50%)	7 (3.5%)	0.603†
Mortality	0 (0%)	2 (1.2%)	3 (18.8%)	5 (50%)	10 (5.0%)	0.375†
O^2 requirement at discharge	1 (2.6%)	8 (4.6%)	1 (6.2%)	1 (10%)	10 (5.0%)	1.000†

*The sum of groups A and group B were compared. †Fisher's Exact Test

Discussion

The first case was seen in our country on March 19, 2020, but the number of cases increased rapidly, as patients admitted to hospitals were evaluated in accord with the COVID-19 guidelines prepared by the Ministry of Health, and upper respiratory tract samples were taken from patients with possible criteria for a preliminary diagnosis of COVID-19 and RT-PCR positive cases were evaluated, a definitive diagnosis made, and treatment started. Cases not found to be RT-PCR positive were managed with clinical, laboratory, and lung imaging, and in cases of high clinical suspicion, the patient was accepted as having COVID-19 and treated.

Definitive diagnosis of COVID-19 is made by RT-PCR tests of respiratory tract samples, especially in patients who develop pneumonia, as lower respiratory tract samples are more useful in diagnosis. The sensitivity of PCR tests decreases to 50-70% due to low viral load, problems in transfer of respiratory tract samples, and inappropriate sample collection [2]. Therefore, patients' symptoms, physical examination, and imaging findings should be considered when guiding treatment in patients for whom COVID-19 cannot be excluded.

Symptoms at admission are important during the pandemic period. In a study conducted by Rona et al. in our country, 338 RT-PCR negative patients followed with a preliminary diagnosis of COVID-19 were evaluated for cough, fever, and dyspnea (58.87%, 40.82%, 39.34%, respectively) were the most common presenting symptoms [9]. In our study, common symptoms were cough, fever, malaise, and shortness of breath. Fever and diarrhea were more common in group A without lung involvement on CT, and cough and shortness of breath were significantly higher in group B patients, along with CT findings.

Knowing potential risk factors that predict the course of the disease is crucial for patient triage, treatment management, mortality and morbidity prediction, and determining the need for intensive care. Preexisting cardiovascular disease, chronic renal failure, chronic lung diseases (especially COPD), diabetes mellitus, hypertension, immune suppression, and obesity predispose patients to a more severe clinical course and an increased risk of intubation and death [10, 11]. In a study of 35,583 patients with at least one comorbid disease in Mexico, obesity, diabetes, and hypertension were reported as risk factors for being infected and developing severe disease [12]. In our study, hypertension was more common in group B, but no difference was observed between groups A and B for other comorbidities. When group B was evaluated within itself, it was found that patients with heart failure and malignancy were significantly higher in the critically ill group. These findings confirm the literature data.

It is stated that the neutrophil-lymphocyte ratio (NLR), LDH, d-dimer, CRP, fibrinogen, and ferritin can be used in the early period to predict the severity of infection and prognosis at the first admission for SARS-CoV-2 infection [13, 14]. In the study conducted by Baştuğ et al., increases in d-dimer, NLR, and CRP were reported as the strongest laboratory predictors of severe prognosis [15]. When group A and B patients were compared in our study, ferritin, creatinine, LDH, and troponin values were significantly higher in group B patients with CT involvement. Yet, further studies will determine prognostic laboratory parameters related to the severity of the disease with COVID-19 and use them for triage at the time of admission.

The treatment of our patients was arranged in line with treatment recommendations of the Ministry of Health of the Republic of Turkey COVID-19 guidelines. In our study, 147 (61.7%) patients received hydroxychloroquine (87.2% and 47.4% in groups A and B, respectively), 88 (36.9%) patients received favipiravir (2.6% and 36.5% in groups A and B, respectively), and 112 (47%) patients received anticoagulant therapy (A and B groups; 43.6%, 42%, respectively). Although hydroxychloroquine, favipiravir, remdesivir, ivermectin, steroids, lopinavir/ritonavir, and immune plasma treatment are approaches used in the treatment of COVID-19 so far, there is an urgent need for effective and specific antiviral treatment against it [16, 17]. Hydroxychloroquine is not recommended for treating COVID-19 inpatients, but the hydroxychloroquine-azithromycin combination has been widely used in the first months of the pandemic as an attractive option for the immunomodulatory and antiviral effects of both drugs. However, hydroxychloroquine is not a preferred agent in daily practice, since patients treated with hydroxychloroquine were noted to have an increased intubation probability, increased QT prolongation due to combined use with azithromycin, and sudden cardiac death risks [7, 18]. Given the update of May 5, 2021, hydroxychloroquine treatment was removed from the Ministry of Health guidelines, although due to its possible side effects, its use was avoided in treating severe patients in our service prior to this date and favipiravir was preferred. In a multicenter randomized study, 96 patients using favipiravir and chloroquine were evaluated. In two groups who did not differ significantly for comorbidities, it was found that the hospital stay and need for mechanical ventilation were shorter in those on favipiravir [19]. In our study, it is notable that mortality rate was higher in patients receiving hydroxychloroquine in group B compared to other group B patients.

SARS-CoV-2 causes multi-organ failure by creating respiratory, gastrointestinal, cardiovascular, nephrological, and central nervous system involvement. In the patients, it is imperative to provide supportive treatment, such as hemodynamic support, IV fluid replacement, vasoactive agents, respiratory support, and adequate mechanical ventilation as necessary [20]. Hypoxia is a leading cause of multiple organ damage and death in COVID-19 patients [21]. In our study, 92.3% of group A patients and 64.1% of group B patients were followed without oxygen, while patients needing more oxygen than 5 L/min were in group B.

In a meta-analysis evaluating the COVID-19 mortality rates, overall mortality coincided with the rate we obtained: 4.9% in the U.S., 4.7% in Iran, and 4.3% in Brazil, while it was 1.4% in Russia, 3.02% in India, 13.9% in England, and 14.5% in Italy [22]. These rates, which vary by country, can be explained by the quality of the health service provided and differences in patients' clinical picture in the study. CT findings showing diffuse lung involvement were associated with increased mortality in the literature [10]. In our study, the rate of mortality among all patients was 4.2%. There was no statistically significant difference between A and B groups regarding mortality, yet all

of those who developed mortality were in group B with lung involvement, and mortality rates increased in tandem with increase in disease severity.

Limitations

An important limitation of this study is that we did not investigate SARS-CoV-2 in lower respiratory tract samples with the RT-PCR method. Another limitation is that we could not show microbiological evidence for other respiratory tract infectious agents. It will be informative to investigate these findings in other studies.

Conclusions

Determining the parameters predicting the clinical course in COVID-19 patients is important in assessing appropriate treatment and intensive care needs and using limited resources correctly. Although the clinical prognosis is better in PCR-negative patients with COVID-19-with findings but none in lung tomography, symptoms and lab findings at admission, accompanying comorbidities are striking as they guide the clinical approach for patients.

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The relationship between fragmented QRS and mortality in without reversible defects patients with scintigraphical myocardial infarction diagnosis

Ahmet Salan [1], Ekrem Aksu [2], Sedat Köroğlu [3], Adem Doğaner [4]

[1] Kahramanmaras Sutcu Imam University, Faculty of Medicine, Department of Nuclear Medicine, Kahramanmaras, Turkey
[2] Kahramanmaras Sutcu Imam University, Faculty of Medicine, Department of Cardiology, Kahramanmaras, Turkey
[3] Kahramanmaras Necip Fazıl City Hospital Hospital, Department of Cardiology, Kahramanmaras, Turkey
[4] Kahramanmaras Sutcu Imam University, Faculty of Medicine, Department of Statistics, Kahramanmaras, Turkey

ORCID ID of the author(s)

AS: 0000-0002-5022-1851
EA: 0000-0003-1939-1008
SK: 0000-0002-5138-0512
AD: 0000-0002-0270-9350

Corresponding Author
Ahmet Salan
Kahramanmaras Sutcu Imam University, Faculty of Medicine, Department of Nuclear Medicine, Kahramanmaras, Turkey
E-mail: asalan@hotmail.com

Ethics Committee Approval
This study was approved by Kahramanmaraş Sütçü İmam University Clinical Research Ethics Committee in session 2019-18 with no. 2 on 16.10.2019.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: Evidence of increased mortality in perfusion abnormalities on myocardial perfusion scintigraphy (MPS) can be found. However, electrocardiography (ECG) is a cheaper and more easily accessible examination than MPS. Fragmented QRS (fQRS) is also considered to be associated with mortality in some cardiological diseases. The present study aimed to analyze the relationship between fQRS based on electrocardiography (ECG) and mortality in patients without reversible defects whose fixed hypoperfusion/perfusion defects were diagnosed and associated with myocardial infarction (MI) based on myocardial perfusion scintigraphy (MPS).

Methods: Non-ischemic patients (2289 patients) with MI diagnoses based on scintigraphy were selected based on retrospective scintigraphy reports. The presence of fQRS was investigated in 85 patients whose 12-lead electrocardiographs could be accessed from the hospital archive, and their deaths due to all causes were questioned from the death information system. The relationship between left ventricular ejection fraction (LVEF), fQRS, type of exercise, number of leukocytes, other parameters, and mortality rates was analyzed.

Results: The numbers of living (n = 69) and deceased (n = 16) patients were obtained. They were divided into two groups: (1) surviving patients (n = 69, number of fQRS positive 42) and (2) deceased (n = 16, number of fQRS positive 11). No distributional differences were found between mortality rates and fQRS and demographic features between groups (P = 0.558). However, a statistically significant effect was observed between mortality rates and low LVEF levels, pharmacological stress, number of leukocytes, and a low HDL level.

Conclusion: The present study suggests that it may be useful to define benign features of fQRS. LVEF levels may be a very important parameter in decision-making for pharmacological stress, and its role in prediction of mortality may be higher than that obtained by fQRS.

Keywords: Myocardial perfusion scintigraphy, Fragmented QRS, Myocardial infarction, Reversible defects, Mortality rate

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Introduction

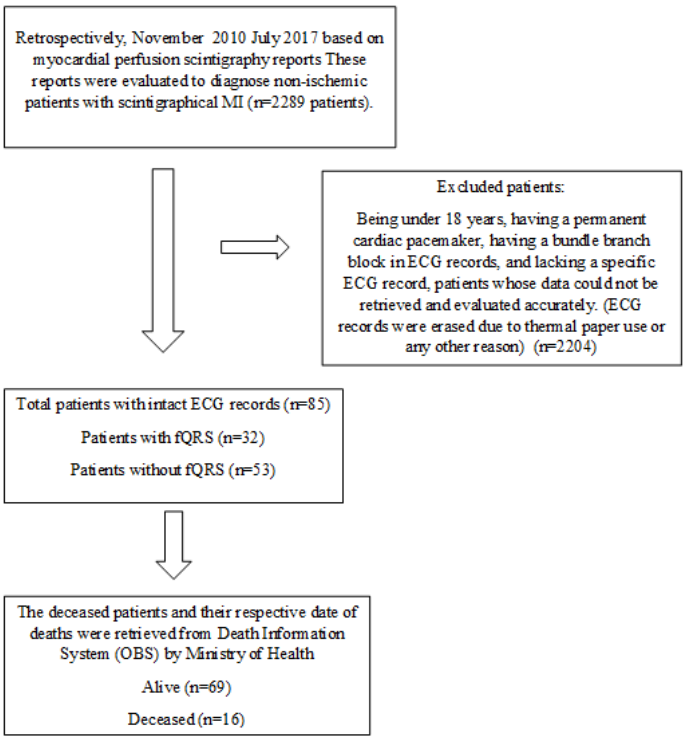
A significant correlation can be observed between non-sporadic fixed perfusion abnormalities and elevated all-cause mortality rate based on myocardial perfusion scintigraphy (MPS), which is used in the diagnosis and monitoring of coronary artery disease [1]. Ischemia and/or infarction interpretations can be made based on MPS reports by evaluating fixed perfusion abnormalities together with clinical data and functional findings. In MPS, fixed hypoperfusion is evaluated in favor of previous non-transmural MI and fixed perfusion defects are evaluated in favor of transmural MI under conditions that exclude chronic ischemia, whereas reversible defects are evaluated in favor of ischemia [2]. Myocardial fixed perfusion abnormalities are not peculiar to ischemic heart disease, and the distribution of mortality rates in patients with fixed perfusion abnormalities is heterogeneous. Therefore, diagnosis of patients with a higher mortality rate via monitoring their fixed hypoperfusion/perfusion defects based on MPS may contribute to the reduction of mortality rates. In this respect, new markers, which can be widely used in the diagnosis of patients with a higher mortality risk, are needed in present-day medicine. In recent years, in addition to fQRS, various hematological parameters have been used in the detection of patients with all-cause mortality risks [3]. fQRS can be defined as additional notching in the QRS complex and is caused by myocardial scarring/ischemia- or fibrosis-induced conduction abnormalities shown on the 12-lead ECG. The fQRS has attracted attention in the medical community as it offers advantages for predicting cardiac and all-cause mortality in patients with coronary artery disease [4–7]. It was reported that the presence of fQRS showed higher sensitivity in the diagnosis of MPS scars compared to pathological Q-wave in addition to being a specific marker for scar tissue [8]. In addition, it was demonstrated that some hematological markers correlated with both cardiovascular and elevated all-cause mortality rates [9]. The present study focused on the relationship between fQRS pattern and some hematological mortality markers and all-cause mortality rates in a group of acute non-ischemic patients with findings of MI based on MPS.

Materials and methods

The present study was conducted retrospectively at a nuclear medicine unit affiliated with a secondary healthcare institution between November 1, 2010, and July 31, 2017 based on MPS reports using a dual-headed E-Cam gamma camera (Siemens, Erlangen, Germany). These reports were evaluated to diagnose non-ischemic patients with scintigraphical-based MI (n = 2289 patients). The exclusion criteria for patients included several parameters: (1) less than18 years, (2) permanent cardiac pacemaker, (3) bundle branch block based on ECG records, and/or (4) lacking a specific ECG record. In addition, patients whose data could not be retrieved and evaluated accurately because ECG records were erased due to thermal paper use or any other reason were also excluded from the present study.

The patients who were hospitalized and yielded a sufficient amount of data in the hospital archive were selected for the present study. Among these 85 patients, those with and without fQRS pattern based on their respective ECG records were selected. A positive fQRS pattern was defined as notches in at least two consecutive leads in the same coronary artery area as observed on the QRS complex. ECG records were also evaluated by two experienced cardiologists for final analysis. The deceased patients and their respective dates of death were retrieved from Death Information System (OBS) by the Ministry of Health. The flow chart regarding the selection criteria of the patients included in the study is in figure 1. The effects of all causes on mortality, scintigraphic data, fQRS patterns, hematological parameters (numbers of leukocytes, neutrophils, and lymphocytes, erythrocyte distribution width [RDW-CW], thrombocyte distribution width [PDW], mean thrombocyte volume [MPV]), lipid profiles, and liver transaminase levels were analyzed. MPS reports were used to obtain data about the date of scintigraphy scan and various patient-related data, such as age, height, weight, stress protocol (pharmacological stress test or Bruce protocol), duration of stress, basal systolic and diastolic blood pressure levels prior to exercise, basal heart rate, exercise metabolic equivalent of task (METs) value, the presence of left ventricular wall motion abnormality, LVEF levels, dilation of left ventricular cavity, the presence of transmural and/or non-transmural myocardial infarction, and lesion localization (apex, anterior/septum, lateral, inferior, and multiple zone).

Figure 1: Flow chart shows the patient selection process



Declaration of ethics

The present study was designed in accordance with the principles of the Helsinki Declaration and approved by Kahramanmaras Sutcu Imam University Medical Faculty Clinical Research Ethics Committee in session 2019-18 with no. 2 on 10.16.2019.

Statistical analysis

The data normality distribution was analyzed using the Kolmogorov–Smirnov test for data analysis. For group comparisons, the independent sample t-test was used to compare normally distributed variables, while the Mann–Whitney U test was used for non-normally distributed data. Logistic regression

analysis was used to identify variables affecting mortality. Cox regression analysis was performed in order to reveal the relationship between lifespan and independent variables. Chi-squares and exact tests were used for distributional differences for categoric variables. Receiver operating characteristic (ROC) curves were used to determine mortality cut-off values for left ventricular ejection fraction (LVEF) levels. The level of statistical significance was taken as $P < 0.05$. Statistical parameters were given in Mean, standard deviation, and median (range 25%–75%). IBM SPSS Statistics version 22 (IBM SPSS for Windows version 22, IBM Corporation, Armonk, New York, United States) software package was used for data analysis.

Results

Eighty five patients included in the present study were divided into two groups as deceased (n = 16) and alive patients (n = 69). The living patients were monitored for median (Q1-Q3) at 59.00 (47.00–70.00) months, whereas the deceased patients were monitored for median (Q1-Q3) at 35.00 (13.00–50.00) months. Their demographic features, basal blood pressure/pulse rate levels, hematological levels, durations of exercise, and a comparison of MET values and LEVF levels between surviving and deceased patient groups are given in Table 1. No statistically significant differences were observed between the groups in terms of MI type, basal blood pressure and heart rate, and MET levels in terms of age, sex, body mass index (BMI), and number of leukocytes ($P > 0.05$). However, a statistically significant difference was observed between mortality and pharmacological exercise, a low LVEF level, the number of leukocytes, and a low high-density-lipoprotein (HDL) level.

ROC analysis, which aimed to calculate the predictive power of statistically significant LVEF marker between patient groups, demonstrated that cut-off values for AUC, sensitivity, specificity, and *P*-value were 0.720, 0.889, 0.562, and 0.006, respectively (Figure 2). In addition, the positive and negative predictive values (PPV and NPV, respectively) and accuracy for LVEF were calculated as 58.8%, 91.2%, and 84.7%, respectively.

The surviving and deceased patients were compared in terms of sex, stress protocol, left ventricular wall motion, transmural and/non-transmural MI, dilation of cavity, localization of perfusion abnormality based on MPS, and presence of fQRS. It was found that only the type of stress was significantly different among these two groups (Table 2).

Figure 2: The calculation of cut-off values for mortality rates in LVEF levels

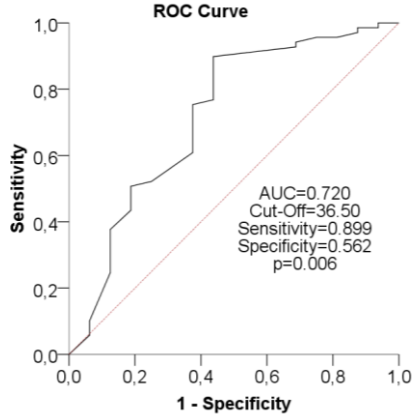


Table 1: Demographic, examination and laboratory data of the patients

		Deceased	Alive	*P*-value
Age (Years)	mean (SD)	65.19 (1.13)	62.94 (11.04)	0.474
Weight (Kilogram)	mean (SD)	81.5 (14.30	83.50 (14.38)	0.631
Height (Centimeter)	mean (SD)	161.69 (8.28)	163.4 (10.07)	0.468
Duration of stress (secs)	mean (SD)	443.00 (52.33)	465.00 (107.45)	0.661
Basal systolic blood pressure (mmHg)	median (Q1-Q3)	125.00(115.00-150.00)	130.00 (110.00–130.00)	0.598
Basal diastolic blood pressure (mmHg)	median (Q1-Q3)	80.00(70.00-90.00)	80.00 (70.00–80.00)	0.169
Basal heart rate (beats per minute)	mean (SD)	86.375 (22.665)	81.478 (15.182)	0.421
METs value	mean (SD)	9.150 (1.48)	9.142 (2.12)	0.995
LVEF (%)	median (Q1-Q3)	35.00 (28.50–50.50)	53.00 (45.00–59.00)	0.006*
Number of leukocytes (per microliter)	mean (SD)	9.78 (3.11)	7.95 (2.09)	0.038*
Hb (per deciliter)	median (Q1-Q3)	13.65 (12.15–14.70)	14.00 (12.40–15.10)	0.503
MPV (per microliter)	mean (SD)	9.60 (1.33)	10.03 (1.15)	0.245
LYM (%)	mean (SD)	2.37 (1.55)	2.23 (0.80)	0.737
RDW-CV (%)	mean (SD)	14.75 (1.99)	13.80 (1.68)	0.104
NEU (%)	mean (SD)	6.27 (3.10)	4.94 (2.13)	0.122
PDW (fL)	Median (Q1-Q3)	14.00(11.50-16.50)	12.60 (11.20–15.60)	0.381
AST (U/L)	mean (SD)	52.44 (83.99)	19.65 (6.10)	0.139
ALT (U/L)	mean (SD)	32.81 (59.76)	19.71 (9.88)	0.396
HDL (mg/dl)	mean (SD)	35.56 (9.84)	44.51 (11.98)	0.031*
LDL (mg/dl)	median (Q1-Q3)	100.50 (77.00–123.00)	96.00 (82.00–129.00)	0.992
NLR	median (Q1-Q3)	2.559 (1.624–4.666)	1.970 (1.653–2.909)	0.167
BMI	mean (SD)	31.111 (4.325)	31.36 (5.63)	0.846

Independent samples t test; Mann Whitney U test, α: 0.05, *Statistical significance, METs: metabolic equivalent of task, LVEF: Left ventricular ejection fraction, Hb: Hemoglobin, MPV: Mean thrombocyte volume, LYM: Number of lymphocytes, NEU: Number of neutrophils, RDW-CW: Erythrocyte distribution volume, PDW: Thrombocyte distribution width, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, HDL: High density lipoprotein, LDL: Low density lipoprotein, NLR: Neutrophil leukocyte ratio, BMI: Body mass index

Table 2: Comparison of surviving and deceased patient groups in terms of gender and scintigraphic characteristics

		Deceased		Alive		
		n	%	n	%	*P*-value
Sex	Female	5	20.0	20	80.0	0.858
	Male	11	18.3	49	81.7	
Type of stress	Pharmacological	14	26.9	38	73.1	0.019*
	Bruce	2	6.3	30	93.8	
Wall motion	Abnormal	12	21.1	45	78.9	0.497
	Normal	4	14.8	23	85.2	
MI type	Transmural	8	22.9	27	77.1	0.452
	Non-transmural	8	16.3	41	83.7	
	Unspecified	0	0.0	0	0.0	
Cavity width	Dilate	7	33.3	14	66.7	0.061
	Normal	9	14.1	55	85.9	
Lesion localization in MPS	Apex	3	25.0	9	75.0	0.298
	Anterior	1	9.1	10	90.9	
	Lateral	1	20.0	4	80.0	
	İnferior	3	10.0	27	90.0	
	Multiple zone	8	30.8	18	69.2	
fQRS	Yes	5	15.6	27	84.4	0.558
	No	11	20.8	42	79.2	

Chi-squared test; Exact test; α: 0.05; * distributional difference is statistically significant. MI: Myocardial Infarction, fQRS: fragmented QRS

In the logistic regression analysis, statistically significant effects were observed between the mortality and stress protocol, basal systolic blood pressure, LVEF level, number of leukocytes, and the neutrophil/leukocyte (NLR) ratio (Table 3).

The effects of the variables based on logistic regression analysis (leukocyte levels, basal systolic blood pressure, LVEF, stress protocol) and fQRS on survival were evaluated using a Cox regression analysis. While no statistically significant effect was found between fQRS and mortality rates, it was observed that other values were decisive variables for the lifespan of patients in the present study (Table 4).

Table 3: The effect of parameters on mortality with logistic regression analysis

	B	Wald	*P*-value	OR	95% CI	
					Lower	Upper
Stress protocol	-2.161	4.262	0.039*	0.115	0.015	0.896
Basal systolic blood pressure (mmHg)	-0.043	4.138	0.042*	0.958	0.919	0.998
LVEF (%)	0.124	7.552	0.006*	1.132	1.036	1.236
Number of leukocytes (per microliter)	-0.396	5.382	0.020*	0.673	0.481	0.940
NLR	-0.316	5.314	0.021*	0.729	0.558	0.954
Age (Years)		0.059	0.809			
Sex		0.339	0.560			
BMI		0.067	0.796			
Basal heart rate (beats per minute)		0.261	0.609			
Basal diastolic blood pressure (mmHg)		0.857	0.354			
Wall motion		4.021	0.134			
Cavity (Cavity width)		0.362	0.548			
MI type (MI type)		0.124	0.724			
Lesion localization in MPS		1.654	0.799			
Lesion localization in MPS						
Lesion localization in MPS (anterior)a		1.043	0.307			
Lesion localization in MPS (lateral)a		0.043	0.836			
Lesion localization in MPS (inferior)a		0.162	0.687			
Lesion localization in MPS (multiple zone)a		0.748	0.387			
fQRS		0.123	0.726			
Hb (per deciliter)		0.086	0.769			
MPV (per microliter)		0.094	0.759			
RDWCV (%)		0.928	0.335			
PDW (fL)		0.001	0.976			

Binary Logistic Regression: α: 0.05; Methods: LR; Nagelkerke's R^2: 0.498; Dependent Variable: Mortality; [a] Compared to reference group (Apex); * the effect is statistically significant, LVEF: Left ventricular ejection fraction, NLR: neutrophil leukocyte ratio, BMI: Body mass index, fQRS: fragmented QRS, Hb: Hemoglobin, MPV: Mean thrombocyte volume, RDW-CW: Erythrocyte distribution volume, PDW: Thrombocyte distribution width

Table 4: Parameters evaluated in cox regression analysis

	B	Wald	*P*-value	OR	OR 95% CI	
					Lower	Upper
fQRS	0.453	0.479	0.489	1.573	0.436	5.671
Number of leukocytes (per microliter)	0.312	5.722	0.017*	1.366	1.058	1.764
NLR	0.120	1.748	0.186	1.128	0.944	1.349
LVEF (%)	-0.052	4.280	0.039*	0.949	0.904	0.997
Basal systolic blood pressure (mmHg)	0.035	6.876	0.009*	1.035	1.009	1.062
Type of Stress	1.832	4.690	0.030*	6.249	1.190	32.816

OR; odds ratio, CI: confidence interval, Cox Regression: a: 0.05, * The effect is statistically significant; Dependent variables: Times, fQRS: fragmented QRS, NLR: neutrophil leukocyte ratio, LVEF: Left ventricular ejection fraction

Discussion

No statistically significant effect was observed between fQRS and all-cause mortality in the present study, which focused on non-ischemic patients with MI diagnoses based on scintigraphy. However, a negative correlation was found between LVEF levels and mortality. It has been reported in nuclear medicine practice that fixed lesions are likely to be correlated with poor prognosis based on non-sporadic MPS [6]. The presence of poor prognosis markers in patients with fixed perfusion defects has importance for reducing elevated cardiovascular mortality. fQRS is likely to become one of these markers as it is defined as additional notches on the QRS complex in at least two consecutive leads based on an ECG record and a display myocardial scar [4, 5]. Some studies have also reported that fQRS displays higher sensitivity in displaying scar tissue compared to the Q-wave [8]. In the existing literature, although the number of studies on the relationship between perfusion-induced mortality and fQRS is limited, many of these studies deal with its relationship with cardiovascular mortality [6, 10–13]. In a study monitoring MI and/or ischemia without any differentiation between transmural and non-transmural types on MPS in patients with coronary artery disease, fQRS was reported to be correlated with cardiac events (MI, need for revascularization, and cardiac death) [6]. Unlike the present study, another study which, due to cardiac events, excluded patients with scar tissue on MPS reports and included ischemic patients who underwent a coronary angiogram (CAG) reported that fQRS was a moderately sensitive and independent marker for ischemia diagnosis and showed a higher prognostic value compared to conventional risk factors [10]. Similarly, various studies showing that fQRS is likely to be an important marker for poor prognosis in ischemic patients have been published. For instance, a study on unstable patient groups without MPS in acute ischemic events indicated that fQRS was an independent predictor for all-cause mortality in patients with ACS [11]. Another study concerning acute ischemic patients who underwent a successful revascularization procedure found that unlike the conventional definition, fQRS was correlated with elevated in-hospital mortality even in a single lead in the same major cardiac area [12]. A similar study reported that the presence of fQRS during hospital admission can lead to an increase in mortality during cardiac events and long-term cardiovascular mortality in patients with non-ST elevated myocardial infarction. Based on these results in the existing literature, it is safe to assume a correlation between fQRS and poor prognosis in acute ischemic patients [13]. Therefore, the present study focused mainly on the predictive power of prognosis in patients with fixed hypoperfusion based on scintigraphical MI of fQRS.

In this study, fQRS morphology was found to have no prognostic value in patients with fixed perfusion anomalies. This result was not a surprising since the impact of fQRS on poor prognosis in ischemic patients has been reported in some previous studies. In addition, Das et al. reported that fQRS did not affect all-cause mortality, whereas it did affect cardiac events [6]. Because ischemic patients were excluded, the results of the present study also indicated that the presence of fixed defects did not play a prognostic role. Although they did not analyze its relationship with mortality, Ozdemir et al. [14] reported that the prevalence of ischemia and infarction in patients with fQRS in MPS was remarkably higher compared to the control group and that the probability of ischemia and/or infarction was both visually and quantitatively 10-fold higher compared to the patients without fQRS. In that study, fQRS in male patients was twice as high as in female patients. The presence of fQRS in normal MPS was associated with minimal fibrosis, inflammation, and/or early-stage CAD. Given that no effects were observed between fQRS and mortality in the present study and previously cited study, the results suggest the presence of probably benign fQRS with a higher level in male patients. It is widely known that fQRS patterns are not always malignant and do not occur at the same level for each lead. On the other hand, a study concerning patients with known and possible CAD reported that fQRS displayed a low sensitivity and specificity in terms of diagnosing myocardial scarring [15]. Although benign features of fQRS in anterior and lateral leads are relatively well-defined [16], the results of some studies suggest that some inferior leads are more likely to be benign. For instance, in a study on the prognostic importance of fQRS in inferior, anterior, and lateral leads, Terho et al. [17] reported that fQRS was prevalent in inferior leads, and the presence of fQRS without an

established heart disease did not indicate any cardiac event. fQRS in the lateral lead had the lowest incidence among these three leads; however, it had a higher risk of all-cause mortality. In a study comparing fQRS in inferior and anterior leads, Eyuboglu et al. [18] observed a correlation between fQRS in anterior leads and higher severity of multivessel disease. In particular, the presence of fQRS in lateral leads were found to be affected by cardiac events and all-cause mortality in patients with CAD [19]. Patients with fQRS in anterior leads had a 3.69-fold higher risk of abnormal MPS compared to those without fQRS in anterior leads, while the same levels were lower in inferior and lateral leads [20]. In the present study, it is likely that no effects would have been observed between fQRS and prognosis in patients with fixed hypoperfusion due to the dominant presence of fQRS morphology in the inferior leads. These results in the existing literature suggest that the relationship between fQRS and prognosis may differ depending on the selected patient groups and leads.

In this study, apart from fQRS, the demographic characteristics of the patients, MPS protocol, and the prognostic values of cardiovascular mortality markers obtained from laboratory tests were also investigated. These results also correlated with basal systolic blood pressure, leukocyte value, HDL levels, and NLR values. Another striking correlation was observed in patients who underwent pharmacological stress tests. The higher mortality rate in the patients who underwent pharmacological stress tests most likely resulted from their mobility limitations.

It was found that age, height, weight, body mass index (BMI), Bruce protocol stress test, duration of stress in Bruce protocol, (basal) diastolic blood pressure levels prior to exercise, basal heart rate, exercise METs values, left ventricular wall motion abnormality and dilation of cavity, type of MI (transmural/non-transmural), scintigraphic lesion localization, neutrophil, lymphocyte, RDW-CW, PDW, MPV, LDL cholesterol, ALT, and AST values were not correlated with mortality.

In the present study, it was observed that a higher NLR level and a lower LVEF level may have been correlated with elevated mortality in patients with fixed hypoperfusion/perfusion defects based on MPS. Similar to this finding, a study reported that the presence of fQRS was independently affected by a higher NLR in addition to elevated in-hospital mortality in patients with ST elevated myocardial infarction (STEMI). The presence of fQRS and the in-hospital mortality rate was higher in patients with NLR $\geq$ 5.47 in that study. In other words, it was suggested that NLR and fQRS were likely to offer additional prognostic clues in terms of diagnosing patients with a higher cardiac risk [21]. Similarly, despite no evidence of an association between fQRS and mortality, an association was observed between NLR and all-cause mortality in the present study. A similar study found an association between cardiac mortality and elevated NLR in patients with stabilized coronary artery disease. That study also analyzed the prognostic importance of LVEF level as a single variable predictor of mortality without focusing on the correlation between fQRS and mortality and observed a correlation between LVEF level and mortality in patients with LVEF $\leq$ 50, which overlaps with results related to LVEF in the present study [22]. In addition, the correlation between lower LVEF levels and all-cause mortality is a crucial result in the present study since decreased left ventricular systolic function may point to a higher-risk patient group [13]. Some studies concerning the prognostic role of LVEF levels can be found in the existing literature. For instance, similar to cut-off value in the present study (36.5%), a correlation was observed between low EF levels ($\leq$ 35%) and all-cause mortality rates in fragmented patients (including left bundle branch block, premature ventricular complex and paced QRS) with a QRS duration longer than 120 ms [7]. A study concerning patients with heart failure found a correlation between LVEF $\leq$ 45% and mortality [23]. Similarly, another study on patients with heart failure reported a higher cardiac death rate in patients with LVEF < 40% compared to those with a LVEF level higher than 40% [24]. In parallel with other studies in the existing literature, the present study found a negative correlation between LVEF levels and all-cause mortality rates in patients with fixed hypoperfusion/perfusion defects.

Limitations

The present study was designed based on a retrospective research model with limited duration of monitoring. The two most important limitations of the present study were the use of ECG records of hospitalized patients without any further automation records and the reliance on MPS reports without any MPS images in the automation system for the statistical analysis. Therefore, the number of patients included in the present study was fairly limited, which resulted in a relatively limited statistical analysis. Because the present study could not obtain MPS images and had to rely only on MPS reports for analysis, it was not possible to develop a model suitable to 17 different segments, resulting in a statistical analysis based on only five different segments.

Conclusions

Various studies in the existing literature have reported that fQRS is likely to be a marker associated with mortality and morbidity in cardiovascular diseases. However, no association was observed between fixed hypoperfusion in MPS and mortality and fQRS in the present study. It must be also noted that the patient group with fQRS morphology was a heterogeneous group in the present study. The results of the present study have importance in terms of indicating benign features of fQRS morphology in some patients, and it is evident that new markers are needed to diagnose such patients. In addition, future prospective studies must focus on the association between prognosis and fQRS and LVEF levels. A strong negative association was found between LVEF and mortality in the present study, which points to a correlation between LVEF levels and mortality. Another important result of the present study is the association between patients who underwent pharmacological stress tests and mortality. It can be suggested that in daily practice, LVEF level is likely to be a decisive factor for applying pharmacological stress tests. In conclusion, the present study demonstrated the need for larger volume prospective studies for the correlation between LVEF and prognosis in patients with fixed hypoperfusion/perfusion defects.

Nevertheless, the results of this study suggest that LVEF is a more useful predictor than fQRS for predicting all-

cause mortality in non-ischemic patients with fixed hypoperfusion/perfusion defects based on MPS.

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Dorsocaudal reconstruction of previous caudal septal resections with partial split spreader graft

Can Ekinci [1], Bilgen Can [2], Atacan Emre Koçman [3]

[1] Department of Plastic, Reconstructive and Aesthetic Surgery, Eskişehir Osmangazi University School of Medicine, Eskişehir, Turkey
[2] Department of Plastic, Reconstructive and Aesthetic Surgery, Balıkesir University School of Medicine, Balıkesir, Turkey
[3] Private Practice, Barbaros, Hoca Ahmet Yesevi Cd. No: 149, 34203 Bağcılar/İstanbul, Turkey

ORCID ID of the author(s)
CE: 0000-0002-5200-3305
BC: 0000-0001-7354-4015
AEK: 0000-0001-8196-1142

Corresponding Author
Can Ekinci
Department of Plastic, Reconstructive and Aesthetic Surgery, Eskişehir Osmangazi University School of Medicine, 26480, Meşelik, Eskişehir, Turkey
E-mail: canekinci234@gmail.com

Ethics Committee Approval
This study was approved by institutional ethical review board of Eskisehir Osmangazi University Medical School (02.09.2021, E-25403353-050.99-165875).
The written consent was obtained from the patients presented with images in the study. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: Nasal obstruction is caused mainly by nasal septal deviation, and submucosal resection is usually performed to treat this problem. However, if over-resected, nasal tip deprojection, deprojection of the dorsum, or pseudo-hump formation may be seen. Spreader grafts are used to restore the nasal septum in these cases, and different techniques have been described for this restoration; however, these techniques may not be the best fit for such restoration. This study presents a novel and effective method for septal reconstruction in patients with previous septal resections.
Methods: Between March 2012 and October 2014, a case series of 14 male patients with tip deprojection and pseudo-hump formation who had undergone corrective surgery in our clinic was retrospectively examined. Partial-split, caudal extension costal spreader grafts were used and were fixed to the dorsum of the remnant septum cranially to prevent warping while avoiding nasal dorsum widening. Pre- and post-operative comparisons were performed, and the Nasal Obstructive Symptoms Evaluation questionnaire for the functional results and subjective Esthetic Appearance test for the esthetic outcomes were administered.
Results: The mean age was 36.8 years (19–56 years), and the mean follow-up time was 14.6 months. Functional outcomes and esthetic appearance led to significantly improvements in all post-operative categories ($P < 0.05$) without any major complications. Common complaints were usually the same as seen in conventional rhinoplasty procedures, such as facial swelling, nasal stuffiness, pain, and/or epistaxis. None of the patients requested revision surgery.
Conclusion: Using partial-split, caudal extension costal spreader grafts in the reconstruction of dorsocaudal septum in patients with previous septal resections appears to provide favorable functional and esthetic results.

Keywords: Partial-split, Spreader grafts, Reconstruction of dorsocaudal septum, Nasal tip deprojection, Deprojection of dorsum

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Introduction

Nasal septum deviation is the most common cause of nasal obstruction [1], and submucosal septal resection is routinely performed as treatment [2]. Although removal of the deviated septum improves nasal airways in most patients post-operatively, over-resection without supportive reconstruction may cause further problems, including nasal tip deprojection and over-rotation, deprojection of the dorsum and pseudo-hump formation, columellar retraction or broad nasal tip [3, 4]. To prevent these deformities, preservation of the L-strut is crucial. Classically, at least 1 cm in width of dorsal and caudal septal cartilage is preserved as an L-shaped structure [5]. However, in severe caudal septal deviations, some surgeons may remove the deviated part without providing adequate support and reconstruction, leading to airway collapse that can cause nasal obstruction [6].

Besides the functional problems, esthetic appearance of the nose can change after removal of the deviated caudal part. Tip deprojection and pseudo-hump formation can be evident in patients who had prior septoplasties with caudal septal resection [7, 8]. In these types of nasal deformities, the nasal support solely depends on the nasal dorsum. If these patients request secondary septo-rhinoplasties, the surgeon should be aware that nasal support may weaken after further nasal hump removal. In these situations, the dorsal and caudal parts of the septum should both be restored and using support grafts is the mainstay of the treatment. Spreader grafts are commonly used for this purpose [9].

Although it is best to obtain spreader grafts from septal cartilages, patients who had previous septoplasties are usually devoid of adequate septal cartilage. Other sources of spreader grafts can be conchal or costal cartilages. Since conchal cartilage is usually inadequate, lacks strength, and can easily be twisted, costal cartilage grafts are often preferred as spreader grafts for reconstruction. The main disadvantage of using costal cartilage grafts is its potential to warp [3]. Although 90% of warping occurs within 1 h, warping may continue until a month after initial harvesting [10]. Besides, as has been suggested in some studies, a pair of spreader grafts customized from costal cartilage can cause widening of the nasal dorsum [3]. To prevent warping and preventing nasal dorsum widening with a pair of spreader grafts, a novel technique using costal cartilage as spreader grafts in a specially designed way is described.

Materials and methods

This study was approved by the Institutional Ethical Review Board of Eskisehir Osmangazi University Medical School (02.09.2021, E-25403353-050.99-165875). Informed consent was obtained from all patients for being included in the study. Additional written informed consents for patient information and images to be published were provided by the patients for whom identifying information is included in this article. A retrospective study of medical and personal records of 14 male patients who underwent corrective surgery with partial-split, caudal extension costal spreader grafts between March 2012 and October 2014 was conducted. All patients had undergone previous septoplasty or septorhinoplasty with caudal septal resection that caused tip deprojection and pseudo-hump formation.

Revision operations were performed by a single surgeon at a university tertiary care medical center. Inclusion criteria required at-least 1-year follow-up of the patients in the office, pre- and post-operative photographic documentation, and completion of a Nasal Obstructive Symptoms Evaluation (NOSE) questionnaire, which effectively evaluates the functional results [11]. Esthetic results, on the other hand, were assessed subjectively and were evaluated by the patients themselves. Medical records, including main pre-operative complaints and surgical indications, intra-operative surgical techniques and findings, and post-operative results, such as infection, graft extrusion and/or resorption and loss of the structural support over time were evaluated.

Surgical technique

All patients underwent surgery under general anesthesia. Nasal dorsum, lateral nasal walls, tip, and septum were infiltrated with 1% lidocaine hydrochloride and 1:100,000 epinephrine. An open rhinoplasty approach was used to provide wide exposure to nasal structures [12]. Transcolumellar and mucosal infracartilaginous incisions were made, and the nasal skin–soft tissue envelope was dissected. Septal exposure was started initially from the anterior septal angle and advanced between upper lateral cartilages and dorsal septum cranially. Bilateral mucoperichondrial flaps were created under the sub-perichondrial plane, and the remnant septum was exposed. The dissection was difficult in most instances because of previous surgeries. Maximum care was carried out not to perforate mucoperichondrial flaps. In case of residual dorsal hump, the cartilaginous and bony dorsum was reduced according to the component dorsal hump reduction technique [13].

Septal support was insufficient in all patients; therefore, the surgical area was switched to the chest wall to obtain costal cartilage graft. The fifth or sixth rib was marked and harvested as described by Marin et al. [14]. En bloc excision of the selected cartilaginous rib, approximately 4 cm in length, was performed. The central portion of the costal cartilage was reshaped in rectangular fashion. A spreader graft which has a size of 3 mm x 30 mm was obtained. Approximately two-thirds of the length (20 mm) of the graft was split horizontally from the midline, whereas, the other one-third of the graft remained intact (Figure 1). This partially split, caudally extended spreader graft was fixed with 5/0 Polydioxanone (PDS) sutures to the dorsum of the remnant septum cranially as it resides in the middle (Figure 2). Another rectangular graft was also sutured both to the anterior nasal spine and the partially split caudally extended spreader graft caudally in vertical fashion to restore the vertical part of the reconstructed L-strut (Figure 3). The nasal tip complex was fixed to the neo-septum in a tongue-in-groove manner. Routine medial and lateral osteotomies were performed if required. All incisions were closed properly. A plaster cast and intranasal Doyle splint was applied. The cast was removed after the first week; however, the intranasal splints were kept for two weeks to protect the integrity of the reconstructed septum.

Figure 1: Vertically split costal spreader cartilage graft

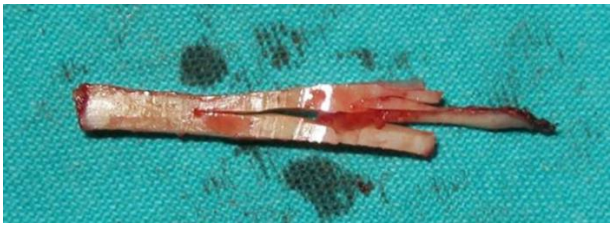


Figure 2: a. Patient with inadequate septal cartilage detected during secondary septorhinoplasty, b. Half-split, caudal extension costal spreader graft residing in the middle of the septal cartilage, c. Half-split, caudal extension costal spreader graft and caudal septal extension graft sutured together and to the septum

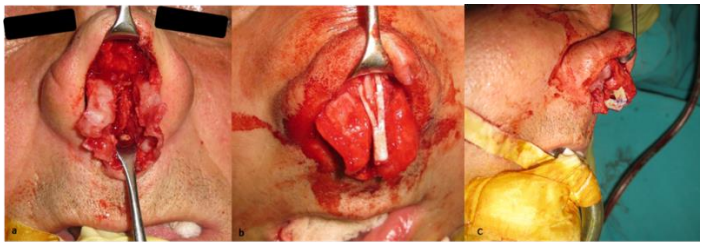
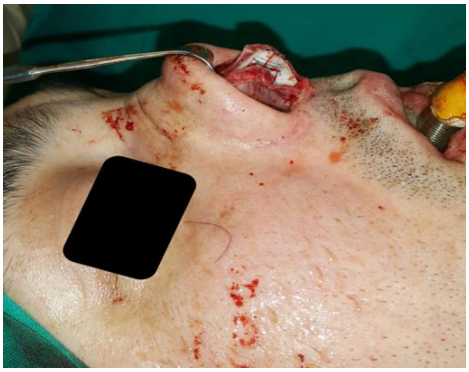


Figure 3: A rectangular graft is sutured both to the anterior nasal spine and the partially-split caudally extended spreader graft caudally in vertical fashion to restore the vertical part of the reconstructed L-strut



Statistical analysis

The data were analyzed using IBM SPSS 21.0 (IBM Corp., Armonk, NY, USA). The categorical variables were assessed both by numbers and decimals. The cross tabulations were generated according to the former and later score values. A marginal homogeneity test was used to analyze the cross tabulations. The significance level was set at $P < 0.05$.

Results

The youngest patient was 19 years old and the oldest was 56 years of age. The mean age was 36.8 years. The mean follow-up time was 14.6 months. All patients previously underwent septoplasty or septorhinoplasty (Table 1). They had breathing problems of varying degrees. Nasal tip dropping and exacerbation of the dorsal hump was evident in all cases due to previously over-resected caudal septum. When the amount of septal cartilage was inadequate, the graft for reconstruction was obtained from the fifth or the sixth costal cartilages. Improvement in the tip projection and elimination of the pseudo-hump became visually evident in all patients (Figures 4–6).

Table 1: General patient features

Patient No.	Age	Gender	Type of Previous Surgery	Follow-Up Duration (Month)
1	32	M	Septoplasty	18
2	26	M	Septorhinoplasty	16
3	19	M	Septoplasty	12
4	44	M	Septoplasty	12
5	29	M	Septorhinoplasty	13
6	41	M	Septoplasty	16
7	56	M	Septorhinoplasty	18
8	48	M	Septorhinoplasty	14
9	33	M	Septorhinoplasty	12
10	41	M	Septoplasty	14
11	27	M	Septorhinoplasty	19
12	36	M	Septoplasty	13
13	52	M	Septoplasty	16
14	31	M	Septorhinoplasty	12

Figure 4: Pre- and post-operative results from patient No.3. a/b/c: Pre-operative, d/e/f: Post-operative six months

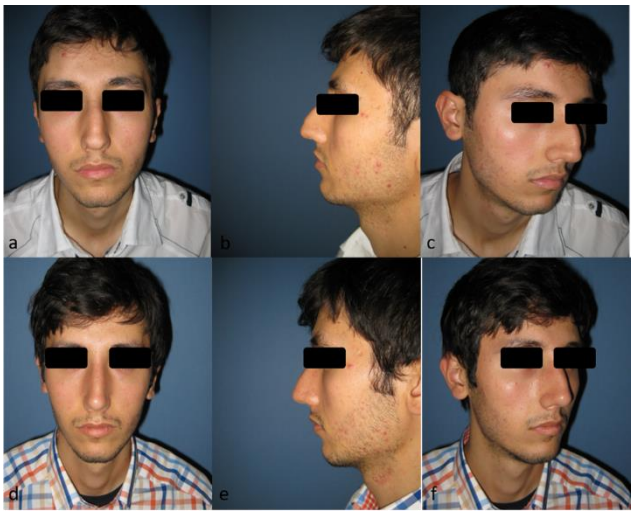


Figure 5: Pre- and post-operative results of patient No.7. a/b/c: Pre-operative, d/e/f: Post-operative four months

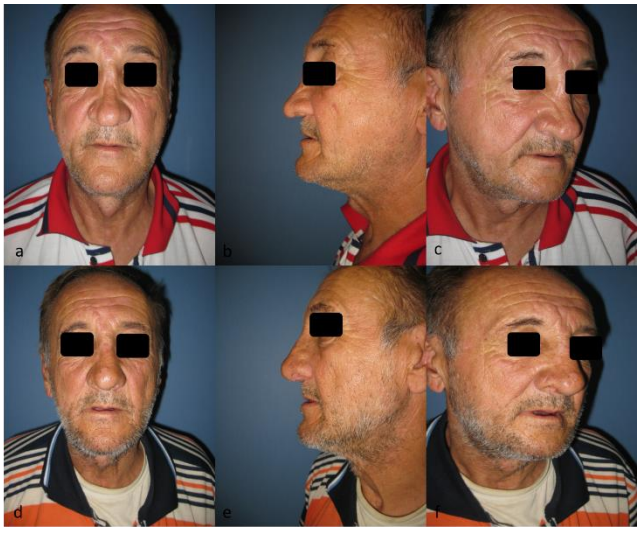
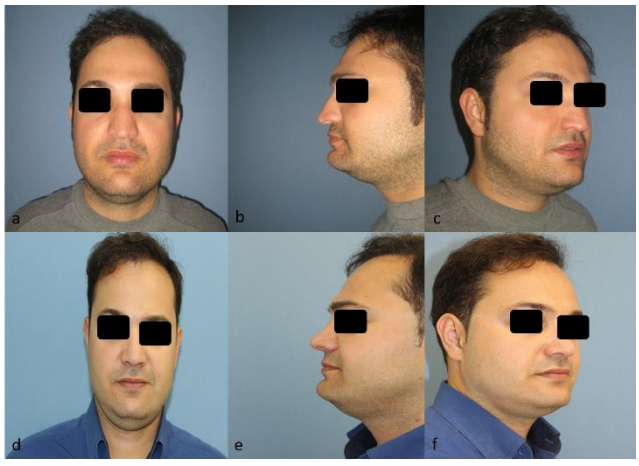


Figure 6: Pre- and post-operative results of patient No.9. a/b/c: Pre-operative, d/e/f: Post-operative nine months



Pre- and post-operative functional results were evaluated using the NOSE questionnaire [11] and showed statistically significant improvements in all categories with the smallest change occurring in trouble sleeping although this result was still significant (P = 0.012). Most improvement was seen in nasal breathing (pre-operative 2.79, post-operative 0.86, P < 0.001) as shown in Tables 2 and 3.

Table 2: Nasal Obstructive Symptoms Evaluation (NOSE) questionnaire [11]

	Not a problem	Very mild	Moderate	Fairly bad	Severe
1. Nasal congestion and stuffiness	0	1	2	3	4
2. Nasal blockage and obstruction	0	1	2	3	4
3. Trouble breathing through my nose	0	1	2	3	4
4. Trouble sleeping	0	1	2	3	4
5. Unable to get enough air through my nose during exercise and exertion	0	1	2	3	4

Table 3: Results of Nasal Obstructive Symptoms Evaluation (NOSE) questionnaire

	Nasal Congestion / Drainage		Nasal Blockage/ Obstruction		Breathing Through Nose		Trouble Sleeping		Nasal Obstruction During Exercise	
Patient	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	2	0	3	0	3	0	1	0	3	0
2	2	1	2	0	3	1	2	0	2	0
3	3	1	3	0	3	0	2	0	2	0
4	0	0	2	1	2	0	1	0	2	1
5	2	0	3	1	4	1	2	0	3	1
6	1	0	2	0	2	1	0	0	1	0
7	3	1	2	1	3	2	1	1	1	1
8	2	1	2	0	2	1	0	0	1	1
9	1	0	2	2	3	2	1	1	2	1
10	3	1	3	0	3	0	2	0	2	1
11	0	0	2	1	2	1	0	0	1	0
12	3	0	2	1	3	0	3	3	0	1
13	1	2	3	2	3	3	1	1	0	0
14	2	0	3	1	3	0	1	0	2	1

Overall satisfaction rate from the final appearance was high among the patients (P < 0.001) as shown in Table 4. No major complications occurred during the follow-up. Stable postoperative appearance of the nose indicated the maintenance of the structural support. No additional interventions were required or requested by the patients.

Table 4: Results of Subjective Esthetic Appearance (3 = Severe, 2 = Moderate, 1 = Mild, 0 = None)

	Deprojection		Pseudo-hump Appearance		Tip Definition		Unsatisfaction	
Patient	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	3	1	2	1	2	0	3	0
2	2	0	3	1	2	1	2	0
3	1	0	3	0	2	0	3	1
4	3	0	3	1	1	0	2	0
5	1	0	2	1	3	1	2	1
6	2	0	1	0	2	1	1	0
7	3	1	2	1	3	0	3	1
8	3	1	3	1	2	1	3	0
9	2	0	2	1	3	1	2	1
10	3	1	3	0	1	0	3	0
11	2	1	2	0	2	1	2	0
12	3	0	2	1	2	0	2	1
13	1	0	3	1	2	1	1	0
14	2	1	3	0	2	0	3	0

Postoperative complaints were usual as seen in conventional rhinoplasty procedures, facial swelling, nasal stuffiness, pain, and epistaxis being the most common. Almost all these complaints resolved during post-operative recovery. No infections or other complications at the donor sites were reported.

Discussion

It is not always possible to obtain septal cartilage grafts for secondary rhinoplasty procedures in patients who underwent previous septo-plasty/septo-rhinoplasty. In these patients, the septum is mostly over-resected, however; not further reconstructed with immediately obtained graft material. Septal support is lost with time, tip projection decreases, and the hump becomes more prominent. Therefore, the need for alternative sources of cartilage can arise during revision surgery due to an inadequate residual septum.

When the septal cartilage is not available in secondary operations, conchal or costal cartilages should be used as graft material [15]. Although conchal cartilage grafts are easier to obtain compared to costal cartilage grafts [16], conchal cartilage grafts lack the strength, can easily be twisted, and usually are inadequate for the reconstruction. Therefore, costal cartilage grafts are often preferred as spreader grafts in dorso-caudal reconstruction. The main disadvantage of costal cartilage grafts is the potential to warp. Different techniques have been described to overcome warping. The first principle to reduce cartilage warping was established earlier by Gibson and Davis when the struts are carved symmetrically [17]. Later internal stabilization with K-wires was proposed by Gunther et al. [18]. Farkas et al. [19] studied the warping effect on costal cartilages of fresh cadavers. They found carving in either anterocaudal or dorsocaudal central planes had no effects on prevention of warping. However, Taştan et al. [20] prepared costal cartilage grafts in a diagonal plane and used an oblique split method to prevent warping. The prepared cartilages were quite thin and could provide enough support for the dorso-caudal framework. Warping is prevented due to diagonal forces. This method was successfully applied to septal reconstruction in revisional cases [21]. Another method to prevent cartilage warping is opposite positioning of graft pieces [22]. Counterbalancing with two opposing costal cartilage grafts has been widely used in different studies [3, 23]. However, use of a pair of cartilage grafts can cause widening of the nasal dorsum. The one-piece frameworks used in dorsal augmentation provide narrower aesthetic dorsa, which are mostly used in patients with saddle-nose deformity [24, 25]. This type of reconstruction improves the appearance in case of near-total septal defects. However, if a septal remnant is available, fixation of cartilage grafts as spreaders ensures better stabilization and elongates the dorso-caudal septum. In the present study, a single unit of costal cartilage was split cephalically and fixed to the septum bilaterally. Therefore, a straighter nasal dorsum was achieved without warping or widening.

Two details deserve special attention in terms of our surgical technique. First, the loss of anterior septal support due to over-resection caused a relative hump formation. It can be defined as pseudo-hump (a relatively prominent hump) formation. This detail is important because one should pay attention to the incremental removal of the osteo-cartilaginous hump. Second, splitting the graft should be performed meticulously to prevent cutting the graft into two separate pieces although shaping the graft is otherwise very easy.

In the present study, the functional outcomes were also tested. It was demonstrated that nasal breathing improved significantly according to the NOSE questionnaire in all categories. The NOSE Scale was constructed by Stewart et al. [26] and published in February 2004. Each item in this survey was validated using a correlation and comparison analysis, and

items with low response sensitivity were removed from the survey composing the final version of NOSE scale. Although the scale and the answers to the items are still subjective, the scale has been used by many other authors and cited many times in the literature. The scale had been adapted and translated into many other languages and used actively in the literature suggesting that it is widely accepted and become quite an objective scale [27–30]. Therefore, our results based on this scale suggest that our method was quite effective in fixing functional problems arising from the deviated septum or unsupported nasal dorsum.

For the esthetic results almost all patients desired resolution for their breathing problems without radically changing their facial authenticity, and they were quite satisfied with their final appearances. Tip deprojection and pseudo-hump significantly improved after the surgery while better septal support was provided. Although the evaluation of the results was obtained via a subjective questionnaire, which is not as widely used as NOSE scale, it still yielded a an accurate reflection about the esthetic outcomes. A very significant decrease in the overall dissatisfaction compared to pre-operative appearances was a notable esthetic outcome. In summary, our technique not only ensures better functional results but also yields more satisfactory esthetic outcomes.

No major complications, such as infection, graft extrusion, resorption, or loss of structural support during follow-up were noted. The main complaints were similar to those seen in conventional rhinoplasty operations and included facial swelling, nasal stuffiness, pain, and epistaxis [31] which resolved within two weeks. Furthermore, no complications associated with the donor site were detected. Therefore, these results suggest not only the satisfying functional and esthetic results but also the safety of the surgical technique.

Although this technique is applicable for most revision cases that lack septal cartilage, its use may be limited in more extensive cartilage deficiencies, such as saddle nose. It may be also not be applicable for crooked nose cases that require stronger cartilage support to straighten the nasal dorsum. In cases of saddle and crooked noses, more enduring cartilage grafts may be necessary to ensure sufficient septal support [3, 16, 32]. In this case, providing thinner nasal dorsum may be sacrificed to ensure sufficient septal support.

Limitations

The limitation of this study includes small sample size, retrospective design, and subjective assessment of the esthetic results. Although the functional results were assessed with a more reliable scale, the NOSE questionnaire, it is almost impossible to assess the esthetic results with a more established method. Furthermore, no control group or comparison with another technique has been suggested by other authors were included. Therefore, conducting a prospective, larger sample study with a control or comparison group would yield more precise results.

Conclusion

In this study, a novel dorso-caudal septal reconstruction method was proposed to provide structural support for both the tip and the septum in patients with previous septal resections. With this method, in addition to the advantages described above, warping of costal cartilage grafts and widening of the dorsum with thick spreader grafts can be prevented. Using partial split costal spreader grafts is a reliable surgical technique that can be used safely for suitable indications.

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The role of immature granulocyte in the early prediction of gastrointestinal tract perforations

Dogukan Durak [1], Veysel Barış Turhan [2]

[1] Bursa Yüksek İhtisas Training and Research Hospital, General Surgery Clinic, Bursa, Turkey
[2] Hitit Univesity Corum Erol Olcok Training and Research Hospital, General Surgery Clinic, Corum, Turkey

ORCID ID of the author(s)

DD: 0000-0003-0693-5715
VBT: 0000-0001-5093-4993

Corresponding Author
Dogukan Durak
Bursa Yüksek İhtisas Training and Research Hospital, General Surgery Clinic, Bursa, Turkey
E-mail: dogukandurak404@hotmail.com

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All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: Gastrointestinal system (GIS) perforations cause acute abdomen an indication for emergency intervention. Early detection is very important in gastrointestinal perforations to prevent mortality and morbidity. This study aimed to examine whether immature granulocyte (IG) and IG percentages (IG%) can be used as a simple and easy marker for identifying gastrointestinal system perforations early on.

Methods: Between January 1, 2020, and January 1, 2022, 120 patients who presented to Hitit University Erol Olçok Training and Research Hospital's emergency service and underwent surgery on by the General Surgery Clinic with the diagnosis of the acute abdomen were investigated. The patients were divided into two groups. Patients in group 1 included those with peptic ulcers and bowel perforations. Group 2 was considered the control group. Of the 36 patients in group 2, 22 had acute appendicitis, 12 had ileus-related bridectomy or bowel resection, and two had acute cholecystitis. The common patient feature in this group was full-thickness or serosal iatrogenic bowel injury and repair. Pre-operative IG and IG% values were obtained from routine complete blood count values. IG and IG% values were compared between groups 1 and 2, and the predictive value of these biomarkers in the early diagnosis of GIS perforations was investigated.

Results: The mean age of the patients was 55.49 (19.58). The study consisted of 45 (37.5%) female patients and 75 (62.5%) male patients. Group 1 had 84 patients, whereas Group 2 had 36. When the two groups were evaluated, the IG value was higher in Group 1 ($P < 0.001$). In terms of the percentage value of immature granulocytes, a statistically significant difference was found between Groups 1 and 2 ($P = 0.001$). As a result, Group 1's IG and IG% values were much greater than those in Group 2.

Conclusion: IG and IG% values are inflammatory parameters that can be easily studied in routine hematology tests. According to this study, IG and IG% values were found to be higher in gastrointestinal tract perforations based on result blood tests taken at the time of admission to the emergency department.

Keywords: Gastrointestinal tract, Perforation, Percentage of immature granulocytes, Immature granulocytes

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Introduction

Gastrointestinal system (GIS) perforations cause acute abdomen, an indication for emergency intervention. Gastrointestinal tract (GIT) perforation occurs due to peptic ulcer disease, trauma, iatrogenic disease, foreign bodies, appendicitis, inflammation, and/or tumors, which require early diagnosis and timely surgical intervention [1]. Peptic ulcer perforation is the most common cause. The main treatment method for GIT perforation is surgery [2]. To plan the correct treatment, the presence, location, and cause of the perforation should be determined. Diagnosis is made by the presence of free air under the diaphragm on chest X-ray or intra-abdominal fluid or air on computed tomography (CT); in addition, the diagnosis is verified by elevated white blood cell (WBC) and C-reactive protein (CRP) levels. However, in the early stages of perforation, these examinations cannot provide a clear indication. Early diagnosis is significant for preventing mortality and morbidity in perforations. Therefore, a specific biomarker is needed for the early diagnosis of intra-abdominal organ perforation.

Immature granulocytes (IG) in peripheral blood are an indicator of increased bone marrow activation [3]. IG is a newly considered inflammatory marker that can be measured easily in a standard blood count [4, 5]. Studies have shown that IG counts and IG percentages (IG%) are higher than in healthy individuals in cases of sepsis and infection [6]. IG% count showed infection even without leukocytosis [7]. In the current study, the predictive value of IG count and IG percentage for the early diagnosis of GIS perforation was investigated.

Materials and methods

This research was planned as a retrospective cohort study. After receiving approval from Hitit University Faculty of Medicine's Clinical Research Ethics Committee in 2022 (Ethics Committee Decision No:2022-12), 120 patients who presented to the Emergency Service of Hitit University Erol Olçok Training and Research Hospital between January 1, 2020 and January 1, 2022 and underwent surgery in the General Surgery Clinic with the suspicion of the acute abdomen were examined. Inclusion criteria in included several parameters: (1) > 18 years old, (2) admission to the emergency department, and (3) underwent emergency surgery. Patients < age of 18, those who had a disease that may have affected their blood parameters (cirrhosis, chronic kidney failure), those who were scheduled for elective surgery, those who were pregnant or breastfeeding, those who were in a limited population (mental illness patients, soldiers, prisoners), and those whose data could not be accessed were excluded.

The study population was divided into two groups: (1) with GIS perforation during the operation (Group 1) and (2) those who did not (Group 2). Patients in group 1 included peptic ulcer and bowel perforations. Group 2 was planned as the control group. Of the 36 patients in group 2, 22 had acute appendicitis, 12 had ileus-related bridectomy or bowel resection, and two had acute cholecystitis. The common feature of the patients selected in this group was full-thickness or serosal iatrogenic bowel injury and repair

Patients' pre-operative hemogram parameters from the hospital's file system were scanned, and IG count and percentage IG% were recorded. Pre-operative IG and IG% values were compared between groups 1 and 2, and their value for predicting GIS perforations was statistically calculated.

Statistical analysis

Data analysis was performed using the IBM SPSS 22.0 software for Windows. The aim was to examine two separate clinical entities by retrospective analysis. The normality of the data was determined using the Shapiro–Wilk test. Continuous values are given as mean standard deviation (SD) or median and an interquartile range (IQR) of 25% to 75%. Non-parametric values were analyzed using the Mann–Whitney U test and parametric values using the Student's t-test. The optimum threshold values for IG and IG% were calculated by receiver operating curve analysis (ROC). *P*-values < 0.05 were considered statistically significant.

Results

One-hundred twenty patients who were admitted to the emergency department and underwent surgery were included in the study. Our sample had a mean age of 55.49 (19.58) years. Forty-five (37.5%) patients were female and 75 (62.5%) were male. Group 1 had 84 patients and, Group 2 consisted of 36. The mean age of group 1 subjects was 52 (21.19), and the mean age of group 2 was 63 (12.83). Group 1 consisted of 61 males and 23 females. Fourteen men and 22 women were in group 2. No statistical differences between the two groups in terms of the distribution of age and sex (P = 0.855 and P = 0.714, respectively) were found.

In the comparisons between the groups, the patients showed a non-normal distribution. When comparing the two groups in terms of IG, a statistically significant difference (P < 0.001) was observed. Group 1 had a median IG count of 0.07 (95% IQR 0.0836–0.1911) and Group 2 had a median IG count of 0.04 (95% IQR 0.0319–0.0936). Accordingly, the IG count was significantly higher in Group 1. Similarly, a statistically significant difference between the groups in terms of IG% (P = 0.001) was found. Group 1 had a median IG% of 0.5 (95% IQR 0.6630–1.0917) and Group 2 had a median IG% of 0.35 (95% IQR 0.3428–0.6961). Accordingly, the IG percentage was significantly higher in Group 1 than in Group 2.

In the ROC analysis (Figure 1), the area under the curve (AUC) for IG was 0.711 with 69% sensitivity and 63.9% specificity at a cut-off value of 0.045. The AUC value for IG% was 0.690 with 63% sensitivity and 72.2% specificity using a cut-off value of 0.45 (Table 1).

Our subgroup analysis demonstrated that the most common perforation in Group 1 (n = 84) was peptic ulcer perforation (n = 40) (Table 2). Other perforation areas were small bowel and large bowel perforations. In the evaluation made between them, no statistical difference was observed between IG and IG% values. However, in the examination between any perforation (Group 1) and no perforation (Group 2), IG and IG% values were found to be higher in Group 1 (P < 0.001). From these results, it was thought that the high IG and IG% values were not associated with the localization of the perforation but rather only with the perforation (Tables 3, 4).

Figure 1: ROC Curve for immature granulocytes and immature granulocytes (%)

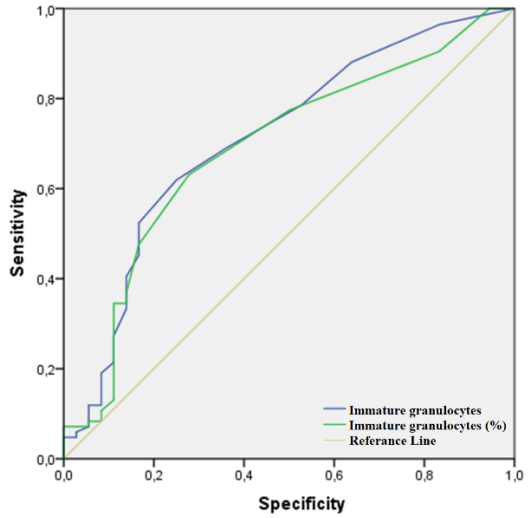

Table 1: Receiver operating characteristic (ROC) curves obtained for immature granulocytes (IG), and immature granulocytes percentages (IG%)

Variable(s)	AUC	*P*-value	95% CI Lower Bound	95% CI Upper Bound	Sensitivity	Specificity	Cut-off value
Immature granulocytes	0.711	<0.001	0.608	0.815	69%	63.9%	0.045
Immature granulocytes (%)	0.690	0.001	0.585	0.794	63%	72.2%	0.45

AUC: area under the curve; CI: confidence interval

Table 2: Percentages by perforated areas

	Frequency	Percent
Perforation (-)	36	30.0
Peptic ulcer perforation	40	33.3
Small bowel perforation	25	20.8
Colon perforation	19	15.8
Total	120	100.0

Table 3: Pairwise comparisons; Location of perforation for immature granulocytes

	Std. Error	*P*-value
Perforation (-) vs Peptic ulcer perforation	7.966	0.092
Perforation (-) vs Small bowel	9.932	0.011
Perforation (-) vs Colon	9.027	0.004
Peptic ulcer perforation vs Small bowel	9.661	1
Peptic ulcer perforation vs Colon	8.840	1
Small bowel vs Colon	10.553	1

Table 4: Pairwise comparisons; Location of perforation for immature granulocytes (%)

	Std. Error	*P*-value
Perforation (-) vs Peptic ulcer perforation	7.726	0.001
Perforation (-) vs Small Bowel	8.982	0.004
Perforation (-) vs Colon	9.793	0.001
Peptic ulcer perforation vs Small bowel	8.796	0.160
Peptic ulcer perforation vs Colon	9.312	0.984
Small bowel vs Colon	10.5	1

Discussion

IG and IG% are inflammatory parameters that can be easily examined by routine hematology tests. According to the current study, high IG and IG% values were significant for diagnosing GIS perforations early in the course of the disease.

Gastrointestinal (GI) perforation is defined as the disruption of tissue integrity in the GI canal wall due to an ulcer, trauma, foreign body, and/or cancer [8]. GIT perforation is a common medical emergency associated with considerable mortality, which ranges from 30% to 50% [9]. A subset of patients exhibits delayed symptoms, abscess formation that mimics an abdominal mass, and/or sepsis [10]. Diagnosing a GIS perforation can be difficult in cases presenting with nonspecific symptoms. Clinical findings vary based on the perforation site. Esophageal perforations may present with severe chest pain and vomiting, gastroduodenal perforations with acute severe abdominal pain, and colonic perforations with bacterial peritonitis with a slower course and abdominal examination findings due to localized abscess formation [11]. Physical examination, laboratory findings, and radiological chest and abdominal X-rays are used for the diagnosis of a GIS perforation. The presence of free intraperitoneal gas on a routine radiograph usually indicates bowel perforation. According to previous research, 1 mL of intra-abdominal air under the diaphragm on a chest X-ray suggests GIS perforation [12]. Multi-detector computed tomography (MDCT) is the modality of choice for evaluating a suspected perforation [13]. MDCT is quite useful for assessing extraluminal air [14]. Although the diagnosis of a GIS perforation involves both elevated white blood cell and C-reactive protein levels, these tests are nonspecific, and they are also elevated in other inflammatory conditions. Therefore, no specific hematological parameter for the early diagnosis of GIS perforations is available. In the present study, IG and IG% values were found to be significantly higher in patients with perforation, and it appears to be an effective, easy, and inexpensive biomarker for early diagnosis.

GIS perforations can be observed in either sex. Ilgar et al. [15] examined GIS perforations in both males and females and reported a rate of 57.4% for male patients. It was observed that male patients were more prevalent, constituting 67.5% of our sample. Still, no significant difference between the groups in terms of sex was found as shown in previous studies.

Today, with new analyzer systems, IG and IG% values can be calculated easily [16]. Research has proven that IG can be used as an inflammatory marker [17, 18]. Unal et al. [19] found that IG% was significant for the early diagnosis of acute necrotizing pancreatitis. Dogan et al. [20] demonstrated that acute appendicitis patients with higher IG levels could have a higher possibility of perforation. Senlikci et al. [21] revealed that IG and IG% values were significant for evaluating the presence of ischemic bowel in irreducible inguinal hernias.

In the current study, it was found that IG and IG% values were significantly predictive of GIS perforation. According to our ROC analysis, IG had 69% sensitivity and 63.9% specificity using a cut-off value of 0.045. IG% had 63% sensitivity and 72.2% specificity using a cut-off value of 0.45. As found in previous research, increases in IG and IG% values in inflammatory conditions were found. However, unlike previous studies involving inflammatory diseases, our research is the first in the literature to evaluate GIS perforations.

Ilgir et al. [15] reported that among GIS perforations, gastroduodenal perforations were the most common, and MDCT could detect the perforation site with 82.9% accuracy. In this study, gastric perforations (n = 40) were the most common type of perforation. Assessing the perforation sites as subgroups, it was found that IG and IG% values were again statistically higher in the perforated group. However, they were not effective in determining the perforation site.

Limitations

This study has certain limitations. The first is the small sample size, which could be understandable because this was a single-center study, and only patients diagnosed with a GIS perforation were include. Second, other inflammatory markers were not included. Our study is the first in the literature that evaluates GIS perforation in association with IG, and it could

pave the way for further research with larger and more comprehensive samples and other inflammatory markers.

Conclusion

IG and IG% values are inflammatory parameters that can be easily studied in routine hematology tests. According to this study, IG and IG% values were found to be higher in GIT perforations, such as peptic ulcer and small and large intestinal perforations based on the blood results obtained at the time of admission to the emergency department.

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Cholecystectomy after endoscopic sphincterotomy in elderly: A dilemma

Ahmed Ramiz Baykan [1], Serkan Cerrah [1], Levent Ogul [2], Ayetullah Temiz [3], Elmas Kasap [4]

[1] Erzurum Regional Training and Research Hospital, Gastroenterology, Erzurum, Turkey
[2] Erzurum Regional Training and Research Hospital, Internal Medicine, Erzurum, Turkey
[3] Erzurum Regional Training and Research Hospital, General Surgery, Erzurum, Turkey
[4] Celal Bayar University, Gastroenterology, Manisa, Turkey

ORCID ID of the author(s)

ARB: 0000-0001-6798-0240
SC: 0000-0002-9139-8039
LO: 0000-0001-8076-6134
AT: 0000-0003-2178-3369
EK: 0000-0002-4335-1156

Corresponding Author
Ahmed Ramiz Baykan
Erzurum Regional Training and Research Hospital, Gastroenterology, Erzurum, Turkey
E-mail: ahmedbaykan@hotmail.com

Ethics Committee Approval
Ethics Committee approval was taken from the Erzurum Training and Research Hospital ethics committee (approval number: 2021/07-150). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: Although cholecystectomy is recommended by many guidelines after endoscopic retrograde cholangiopancreatography (ERCP) for gallstones, the necessity of cholecystectomy in geriatric patients is a matter of debate. Here we compare the outcomes of new biliary events in cholecystectomized and non-cholecystectomized patients of geriatric age after ERCP for suspected choledocholithiasis.
Methods: Non-cholecystectomized patients who underwent ERCP for choledocholithiasis from 2015 to 2017 were included in this retrospective cohort study. Patients with other biliary pathologies, incomplete clearance of common bile duct stones, and those who could not be reached at follow-up were excluded from the study. Biliary events (cholecystitis, cholangitis, pancreatitis, re-ERCP) were evaluated by considering age groups in patients with and without cholecystectomy in their follow-up after sphincterotomy.
Results: A total of 284 patients were followed for an average of 69.77 (0.2) months. The cumulative incidence of biliary events in cholecystectomized patients was lower (16% vs. 21.5%; $P < 0.001$), and cholecystectomized patients had a longer time to the occurrence of events (mean 74.49 [0.27] months vs. 73.50 [0.33] months; $P = 0.03$). There was no significant difference in the frequency of biliary events between elderly patients with and without cholecystectomy ($P = 0.81$), and the cumulative incidence of biliary events in the in situ group was significantly lower than that in the geriatric group (17.5% vs 32.6%; $P = 0.03$)
Conclusion: Although cholecystectomy significantly reduces subsequent biliary complications in young patients, it does not provide a statistically significant benefit in geriatric patients. We believe that there may be no need for routine prophylactic cholecystectomy after endoscopic sphincterotomy in geriatric patients.

Keywords: Sphincterotomy, Endoscopic, Cholecystectomy, Aged, Geriatrics

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Introduction

Gallstone disease is very common. In Europe and America, approximately 20% of the population has stones in the gallbladder [1, 2]. The risk of significant complications (cholecystitis, cholangitis, pancreatitis) for symptomatic cholelithiasis is 0.5% to 3% per year. It is known that 55% or more of developed pancreatitis cases are of biliary origin [3].

After the widespread use of endoscopic retrograde cholangiopancreatography (ERCP) in the 1980s, many publications supported the conservative strategy, leaving the gallbladder in situ [4–7]. In the following period, with the loss of popularity of open surgery and the widespread use of laparoscopic cholecystectomy, the adequacy of the ERCP procedure for biliary tract stones started to be discussed again. Although laparoscopic cholecystectomy is currently recommended by many guidelines [8–10], because of regional differences in the frequency of post-ERCP biliary events [11] and the development of new techniques (e.g., large balloon dilation) that can be applied in the ERCP procedure, there is a need to reevaluate what the most appropriate method should be [12].

The necessity of cholecystectomy after sphincterotomy in patients of advanced age due to the longer life expectancy is another issue that has not been clarified. There are only a few studies that have been conducted in this direction. In a retrospective study, Mafalda et al. [13] compared 131 patients aged 75 years and older with and without cholecystectomy after ERCP. They reported that the group with cholecystectomy had fewer biliary events (cholecystitis, cholangitis, pancreatitis, re-ERCP), and there was no significant difference in mortality due to biliary tract diseases.

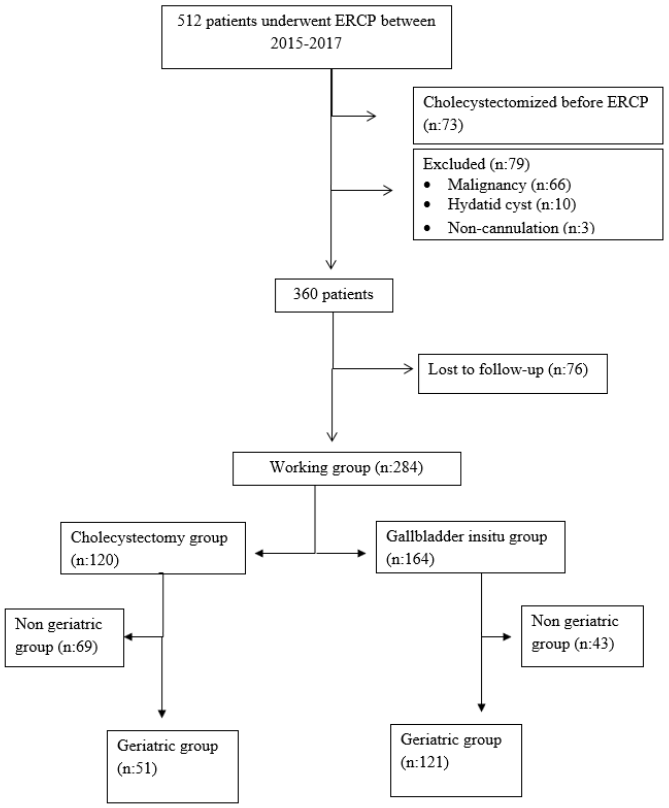
Patients aged 65 and over are referred to as the geriatric population by the World Health Organization (WHO). In this study, we aimed to compare the outcomes of new biliary events in cholecystectomized vs non-cholecystectomized patients of geriatric age after ERCP for suspected choledocholithiasis from 2015 to 2017.

Materials and methods

Study design

Our study was carried out with 512 patients who had MRCP images and underwent ERCP between 2015 and 2017 for choledochal stones. Follow-up data were obtained from examining hospitals, telephone calls, and outpatient records. Patients who underwent cholecystectomy before ERCP, those who had ERCP for reasons other than bile duct stones, those for whose common bile duct (CBD) cannulation failed in the procedure or those whose choledochal stones could not be completely removed, and those who could not be reached at follow-up were excluded from the study (Figure 1). The study was continued with the remaining 284 patients. Prophylactic cholecystectomy after ERCP was recommended for all patients after the procedure. During the follow-up period, those with and without cholecystectomy were evaluated in two groups. The ages of the patients were taken into account in the evaluation of the groups. Those aged 65 and over, as determined by the WHO, formed the geriatric age group.

Figure 1: Flowchart of patients



Ethics approval

The study design comprised a retrospective cohort study, in accordance with the Declaration of Helsinki, has been given a start upon approval of the Erzurum Training and Research Hospital ethics committee (ethics committee approval number: 2021/07-150).

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) program version 17.0 (IBM). Data are expressed as the mean (SD) or median with range. Categorical parameters were compared using the $\chi 2$ or Fisher's exact test when appropriate, and continuous variables were compared with Student's *t*-test. Survival and event-free survival were calculated using the Kaplan-Meier method. Categorical predictors of survival were compared using a log-rank test. *P*-values < 0.05 were considered statistically significant.

Results

The study was carried out with 512 patients. A total of 228 patients were excluded from the study because of a previous cholecystectomy (73 patients), nonbiliary causes (79 patients), and not being reachable during follow-up (76 patients). The study group consisted of 284 patients, with 79 (27.8%) males and 205 (72.2%) females. The mean age was 78.66 (8.3) years in patients aged 65 and over, which was considered the geriatric group. In the nongeriatric group, the mean age was 47.61 (11.64) years. The mean follow-up period was 69.77 (0.2) months. Endoscopic sphincterotomy was performed in all patients during the ERCP procedure.

Table 1: Characteristics of patients and details of complications

	Non geriatric group (n = 112)		Geriatric group (n = 172)		*P*-value
	Cholecystectomized	Gallbladder in situ	Cholecystectomized	Gallbladder in situ	
Gender (male/female) (%)	16 / 53 (14.3% / 47.3%)	11 / 32 (9.8% / 28.5%)	15 / 36 (8.8% / 20.9%)	36 / 85 (20.9% / 49.4%)	0.26
Age (mean (SD))	45.77 (11.62)	50.56 (11.19)	75.02 (7.26)	80.16 (8.35)	<0.001*
Indication for ERCP					
Choledocholithiasis	48 (17%)	29 (10.3%)	33 (11.7%)	83 (29.4%)	
Pancreatitis	16 (5.7%)	11 (3.9%)	12 (4.3%)	19 (6.7%)	
Cholangitis	5 (1.8%)	3 (1.1%)	5 (1.8%)	18 (6.4%)	
ERCP findings					
Stone size (mm) (mean (SD))	6.86 (3.72)	6.22 (2.8)	6.41 (3.29)	8.31 (5.31)	0.01*
Number of stone (mean (SD))	1.67 (0.96)	1.71 (1.06)	1.97 (1.49)	1.88 (1.52)	0.59
ERCP complications	9 (3.1%)		11 (3.9%)		0.54
Pancreatitis	2 (0.7%)	2 (0.7%)	1 (0.4%)	3 (1.1%)	
Bleeding	0	2 (0.7%)	1 (0.4%)	1 (0.4%)	
Perforation	1 (0.4%)	0	1 (0.4%)	1 (0.4%)	
Infectious	0	2 (0.7%)	1 (0.4%)	2 (0.7%)	
Hepatobiliary disease during follow-up	25 (8.8%)		29 (10.2%)		0.25
Pancreatitis	5 (9.1%)	7 (12.7%)	5 (8.8%)	12 (21.1%)	
Cholecystitis	0	4 (7.3%)	0	6 (10.9%)	
Re-ERCP	6 (10.9%)	3 (5.5%)	3 (5.5%)	3 (5.5%)	

*$P < 0.05$ is considered significant for statistical analyses.

One-hundred-nineteen (42.2%) patients underwent cholecystectomy after the ERCP procedure. While the rate of cholecystectomy in the non-geriatric group was 61.6%, cholecystectomy was performed in only 29.4% of the patients in the geriatric group ($P < 0.001$).

Considering all the patients, biliary events (cholecystitis, pancreatitis, or re-ERCP) occurred in 54 (19.1%) patients in post-ERCP follow-ups (Table 1).

The cumulative incidence rate for biliary events in cholecystectomized patients was lower (16% vs. 21.5%; $P < 0.001$), and cholecystectomized patients had a longer time to the occurrence of events (mean 74.49 [0.27] months vs. 73.50 [0.33] months; $P = 0.03$). In those who underwent cholecystectomy, ten (18.5%) patients developed pancreatitis, and nine (16.7%) patients required re-ERCP during follow-up. In those who had their gallbladder left in situ, 19 (35.2%) patients were admitted to the hospital with pancreatitis, ten (18.5%) patients were admitted with cholecystitis, and six (11.1%) patients needed re-ERCP (Figures 2 and 3).

Figure 2: Probability of developing biliary events in patients with and without cholecystectomy during follow-up

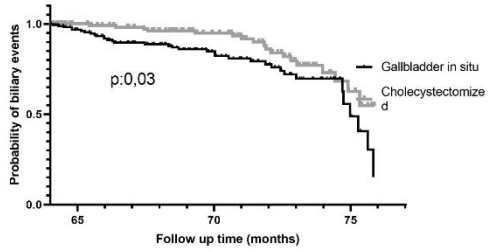
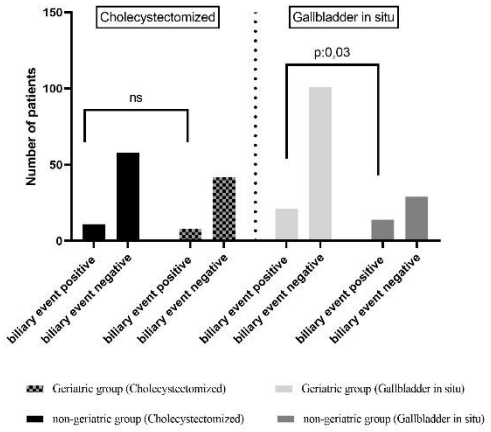


Figure 3: Significantly fewer biliary events were observed in the geriatric patient group with gallbladder in situ than non-geriatric gallbladder in situ group



Significantly fewer biliary events were observed in the younger patient group with cholecystectomy than in the young gallbladder in situ group ($P = 0.04$). There was no significant difference in the frequency of biliary events between elderly patients with and without cholecystectomy ($P = 0.81$).

When the groups were compared by age, the cumulative incidence rates of biliary events in cholecystectomized patients were similar between the geriatric and non-geriatric groups (15.9% in the non-geriatric group, 16% in the geriatric group; $P = 0.99$). However, the cumulative incidence rate of biliary events in the in situ group was significantly lower in the geriatric group (17.5% vs 32.6%; $P = 0.03$) (Figures 4 and 5).

Figure 4: Probability of developing biliary events in patient's groups during follow-up

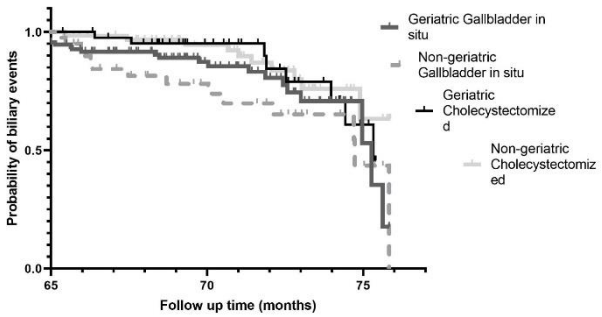
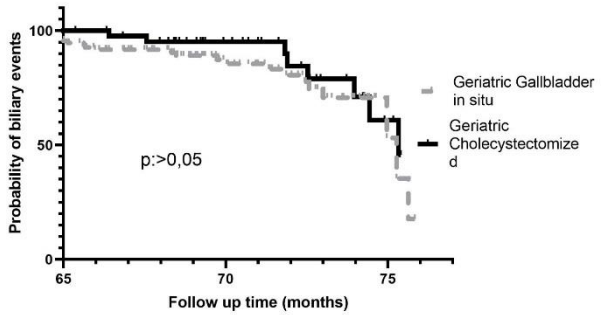


Figure 5: Probability of developing biliary events in geriatric groups



Discussion

In our study, we followed up with patients who underwent ERCP for choledocholithiasis for an average of 69.77 (0.2) months after the procedure and identified three important findings. The first of these is that a significant portion of the patients aged 65 and older, which is considered geriatric age, did not have a cholecystectomy operation after the ERCP procedure. Second, we observed that biliary events decreased significantly

after cholecystectomy in the younger age group, while cholecystectomy did not lead to a significant difference in biliary events in the elderly group. Third, we observed that the geriatric gallbladder in situ group developed fewer biliary events than the young gallbladder in situ group.

The decreased rate of cholecystectomy after ERCP in patients of advanced age may be due to concerns of increased mortality and postoperative complications. This situation was also emphasized in similar studies by Sousa et al. [13] and Lau et al. [14]. Indeed, Russell et al. [15], in their study including 30,145 patients, reported that male sex and age 65 and older were associated with increased serious morbidity and mortality for cholecystectomy patients. However, Lord et al. [16], in a recent meta-analysis including 366,522 patients, stated that cholecystectomy did not cause an increase in mortality even in patients over 80 years of age, but it was associated with prolonged hospitalization time and increased morbidity.

In a study by Sousa et al. [13] in 2018, the frequency of biliary events was reported to be higher in patients aged 75 and older who had their gallbladder left in situ compared to the control group (24%; 7%, respectively). But in their subgroup analysis, these authors stated that this significance disappeared if the patients were over 85 years of age. Similarly, in our study, biliary events were more common in the group in which the gallbladder was left in situ (16% vs 21.5%), and we observed that this significance was lost in patients aged 65 and older. A similar result was reported in Yasui's study [17]. These authors observed that during the 10-year follow-up period, cholecystectomized patients under 80 years old had fewer biliary events than patients with their gallbladder in situ (7.5% vs 21.7%). The groups were similar regarding biliary events in advanced age. In conclusion, they emphasized that it may not be necessary to recommend cholecystectomy in elderly patients who underwent endoscopic sphincterotomy due to common bile duct stones (CBDS).

The French study by Boytchev et al. [18] reports similar findings as reported here, but with a lower patient age limit. Boytchev reported that leaving the gallbladder in situ in 169 patients over 65 years of age who were followed up for 56.5 months did not make any difference for biliary events. However, it was unfortunate that 50% of the study's patients died during follow-up due to causes other than biliary diseases. Finally, in the comparative study of 43,338 patients over 60 years old and 45,295 younger patients, which was created using data collected by the Nationwide Inpatient Sample (Healthcare Utilization Project) from 2001 to 2014 and published in 2019, no statistically significant difference in hospital admission due to biliary tract diseases during the 4-year follow-up was detected between the ERCP group and the cholecystectomy group after ERCP [19].

Interestingly, the frequency of post-ERCP biliary events seems to vary regionally [11]. Two important randomized controlled studies addressed this issue. In a Dutch study [20], the frequency of biliary events was reported to be a high rate of 47% (32% morbidity, 81% of patients eventually underwent cholecystectomy, but with a conversion rate of 55%). This rate was reported as 7% in a Chinese study [14]. Lau et al. [14] explained that this difference, in addition to the regional characteristics, may also be caused by the age factor since the patients participating in the study were 75 years or older, and they emphasized the importance of cholecystectomy in young patients.

Our study observed pancreatitis (10.2%) as the most common biliary event in post-ERCP patients whose gallbladders were left in situ. The causes of biliary events in patients whose gallbladders were left in situ after ERCP also seem to be affected by this regional difference [14]. Cholangitis was the most common biliary event in patients whose gallbladders were left in situ in a Hong Kong-based study, while CBDS was reported to be the most common biliary event in patients whose gallbladders were left in situ in the studies of Schreurs et al. [21] and Yasui et al. [17]. In the study of Yasui et al., CBD stones were observed with a similar frequency between the group with and without cholecystectomy. It has been stated that this may be due to the scarcity of subgroup patients. As an argument supporting leaving the gallbladder in situ in geriatric patients, leaving the gallbladder in situ has no effect on mortality [17, 18, 21], and most biliary events after sphincterotomy are cholangitis or CBDS, which can be treated without the need for cholecystectomy [22]. In addition, some studies emphasized that cholecystectomy performed at advanced ages has increased mortality and biliary tract damage [23, 24].

Some studies have reported that cholecystectomy after ES reduces bile duct complications other than pancreatitis [25]. On the other hand, in a recent meta-analysis, Xu et al. [26] declared that the risk of pancreatitis, in addition to other biliary events, was lower in cholecystectomized patients after ES. In our study, we observed that the incidence of pancreatitis and other complications decreased in the group that underwent cholecystectomy, supporting this argument.

Limitations

Our study's strengths include its good follow-up period and the sufficient number of patients. Limitations of our study include its retrospective nature and the inaccessibility of some data during the follow-up period (especially the postoperative hospital stay and complication rate of some patients who had cholecystectomy in an external center).

Conclusion

Here, we evaluated the necessity of routine prophylactic cholecystectomy after endoscopic sphincterotomy in geriatric patients. No superiority of cholecystectomy was found in geriatric patients in preventing biliary complications in a mean follow-up period of 69.77 (0.2) months after endoscopic sphincterotomy. Further studies specifically focused on these issues are needed.

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Association of fear assessment in inflammatory rheumatic diseases (FAIR) questionnaire with ankylosing spondylitis quality of life and disease activity in patients with ankylosing spondylitis

Ayşe Bahar Keleşoğlu Dinçer, Serdar Sezer

Dışkapı Yıldırım Beyazıt Research and Training Hospital, Rheumatology Department, Ankara, Turkey

ORCID ID of the author(s)
ABKD: 0000-0001-8810-2869
SS: 0000-0001-5401-5599

Corresponding Author
Ayşe Bahar Keleşoğlu Dinçer
Dışkapı Yıldırım Beyazıt EAH, Mevki Hastanesi, Altındağ, Ankara, Turkey
E-mail: bdincer@ankara.edu.tr

Ethics Committee Approval
Ethics Committee approval was taken from the Dışkapı Yıldırım Beyazıt Research and Training Hospital, Number:1115/10, Date:12.07.2021. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: Fear against disease course, treatment, and limitations in family, work, and social life are commonly seen but mostly overlooked by physicians of patients with chronic inflammatory rheumatic diseases. Ankylosing spondylitis (AS) is a chronic inflammatory disease in young adults characterized by limitations in spinal mobility. The Fear Assessment (FAIR) Questionnaire was designed especially for patients with rheumatoid arthritis and spondyloarthritis to assess the level of fear from the patient's perspective. Here we evaluate the FAIR score in AS patients and its association with disease activity, AS quality of life (ASQoL), depression, anxiety, and fatigue levels.

Methods: This cross-sectional study included 79 patients with AS, and disease activity was assessed by Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), AS-Disease Activity Score-C reactive protein, and functional status was assessed by Bath Ankylosing Spondylitis Functional Index (BASFI). Patient global assessment of disease and pain were scored on 0–10 cm visual analog scores. All patients completed FAIR and ASQoL questionnaires. The depression and anxiety were evaluated by Hospital Anxiety and Depression Scale (HADS), and fatigue was assessed by Fatigue Severity Scale (FSS).

Results: The mean age of AS patients (62% male) was 41.7 (11.3) years. Most of the patients were on biological disease-modifying anti-rheumatic drugs (bDMARDs). The patients' median BASDAI, ASDAS-CRP, and BASFI were 5.4 (range, 3.8–7.4), 3.83 (1.4), and 4.0 (range, 2.3–6.2), respectively. The overall FAIR, ASQoL, FSS, HADS-depression, and HADS-anxiety scores were 75 (range, 52–91), 9.6 (5.2), 5.4 (range, 4.1–7), 7.7 (4.4) and 9.6 (5.2), respectively. There were statistically significant correlations between disease activity indices and FAIR, ASQoL, FSS, and HADS scores. The FAIR scores significantly correlated with ASQoL, FSS, and HADS scores. The patients with active disease (BASDAI ≥ 4) had significantly higher levels of FAIR, ASQoL, FSS, and HADS. The best cut-off value for the FAIR score of AS patients with moderate to severe disease activity was 50 (AUC: 0.734, 95% CI [0.599–0.870], $P = 0.002$), with a sensitivity of 89.8%, specificity of 55%, positive likelihood ratio of 1.99, and Youden index of 0.45.

Conclusion: This study shows that AS patients face a high level of fear which is associated with higher disease activity, higher risk of mood disorders, and lower quality of life. Physicians should not only focus on the physical improvement of the patient but also handle the fear of patients against their diseases and their treatment. This holistic approach will improve the dialogue between the physician and the patient, which will result in increased compliance with treatment and will raise the quality of care.

Keywords: Ankylosing spondylitis, Fear, Quality of life, Pain

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Introduction

Ankylosing spondylitis (AS) is a young-onset chronic inflammatory rheumatic disease (CIRD) that mainly affects the axial skeleton and is characterized by a progressive bony fusion of the vertebral column and hence, limitation of spinal mobility [1, 2]. It is a complex and debilitating disease that leads to chronic pain, stiffness, and disability [3]. These factors cause physical challenges and difficulties in participating in family, work, and overall social life [4]. Furthermore, the chronicity of the disease, unpredictable disease course, concerns about self-image, and long-term treatment are common in patients with CIRDs like AS [4]. Therefore, almost one-third of patients with a CIRD develop psychiatric disorders, most commonly depression and anxiety [4]. The relative risk of developing depression and anxiety was found in AS patients as 1.51 and 1.85 [2]. Due to decreased energy and reduced muscle capacity, fatigue is also very common in CIRDs [5]. Fatigue is defined as the sensation of generalized tiredness and exhaustion [6]. Physiological, psychological, social, and personal factors affect fatigue development, and more than half of the AS patients report fatigue.

Higher disease activity, pain, and functional disability are associated with a higher risk of mood disorders and fatigue [7]. Besides the mentioned concerns, patients with CIRDs face fear about dependence on others, limitations of daily life, and continuous need for treatment. The fear that the patients feel can trigger psychiatric disorders. Therefore, early recognition and handling of their fears give a chance to decrease the frequency of mood disorders and improve physician-patient communication [4]. The Fear Assessment in Inflammatory Rheumatic Diseases (FAIR) Questionnaire was developed in 2018 for patients with CIRD, such as rheumatoid arthritis (RA) and spondyloarthritis, with confirmed reliability and validity. This large cohort study revealed that almost 20% of patients had high fear scores [8]. Among all these psychiatric disorders, fatigue and fear result in poorer life quality in patients with AS. The AS quality of life (ASQoL) is an instrument to assess the disease severity, outcome and the impact of the disease from the patient's perspective [9].

This study aimed to evaluate the fear level of AS patients due to the disease itself and its treatment from the patient's perspective via a novel patient-reported measure of fear, namely the FAIR questionnaire, and to investigate its association with disease activity indices, ASQoL and, other psychological conditions.

Materials and methods

Study population

This cross-sectional study included 79 patients ≥ 18 years old diagnosed with AS according to 1984 Modified New York Criteria and admitted to the rheumatology outpatient clinic between September 2021 and April 2022 [10]. Exclusion criteria included concomitant rheumatic diseases other than AS, current or past history of malignancy, current or past history of drug and/or alcohol abuse and psychiatric disorder, mental retardation, pregnancy, and breast-feeding. The patients were included in the study consecutively according to inclusion and exclusion criteria.

The study was conducted according to the recommendations of the Declaration of Helsinki and was approved by the Ethics Committee of Dışkapı Yıldırım Beyazıt Research and Training Hospital (Number:1115/10, Date:12.07.2021). Written informed consents were obtained from all subjects.

Demographic characteristics and clinical assessment

The demographic characteristics, clinical, and treatment features were obtained during recruitment. Laboratory analysis included hepatic transaminases, serum creatinine, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and complete blood count (CBC) and was performed in the morning after 8 h of fasting.

Assessment of disease activity

The disease activity of AS patients was assessed using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Ankylosing Spondylitis Disease Activity Score-CRP (ASDAS-CRP), and Bath Ankylosing Spondylitis Functional Index (BASFI) [11-13]. The patient-reported global assessment of overall disease activity and pain severity were reported on a 0–10 cm Visual Analogue Scales (VAS). BASDAI ≥ 4 cm on a 0–10 scale was accepted as an "active disease". ASDAS-CRP levels below 2.1 show remission or low disease activity, whereas 2.1-3.5 high disease activity and levels above 3.5 indicate very high disease activity.

Measurement tools

The Hospital Anxiety and Depression Scale (HADS): HADS is an instrument for screening clinically significant anxiety and depression in patients at non-psychiatric outpatient clinics, which was first developed by Zigmond and his colleagues [14]. It consists of 14 items, of which seven items are related to anxiety, and the other seven items assess depression. Each item is scored on a 4-point scale (0–3) and ranges between 0 to 21 for each subscale. A score between 0 to 7 states a normal mental state, with 8–10 possibility of anxiety/depression, and a score above 11 points show definite anxiety or depression. The Turkish reliability and validity study was conducted [15].

The Fatigue Severity Scale (FSS): FSS is a nine-item instrument that measures the impact of fatigue on daily functioning, which is a simple and short self-assessment questionnaire [16]. Each item is scored between 1 (totally disagree) and 7 (totally agree), and a total score of ≥4 indicates severe fatigue. Its validation and translation to Turkish patients were performed in many diseases [17,18].

Ankylosing Spondylitis Quality of Life (ASQoL): ASQoL comprises 18 dichotomous items which assess patient-reported symptoms, functioning, and disease-related concerns. In each item, yes is scored as one point, and no is scored as 0 with a total score of 18 [19]. Higher scores of ASQoL indicate poor quality of life. Duruöz et al. [20] conducted a validity and reliability study of ASQoL.

Fear Assessment in Inflammatory Rheumatic Diseases (FAIR): FAIR is a self-reported measure to assess fear in AS and RA patients that includes 10 questions that are scored on a 10-point numerical scale ranging from 0 (no fear) to 10 (strong fear) and the total score is calculated by the sum of 10 individual item scores (0–100) [8]. The higher scores indicate more fear. The

translation and validation to the Turkish language are performed by a total of 115 patients (58 AS, 57 RA) [4].

Statistical analysis

IBM SPSS Statistics for Windows, version 25.0 (SPSS Inc, Chicago, IL, USA) was used for data analysis. Visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) were used to determine the data distribution. The normally distributed continuous variables were presented as mean (standard deviation), and skewed data were expressed as median (IQR). Categorical variables were summarized as frequency (%). Student's T-test and Mann-Whitney U test were used to compare normally distributed and skewed data, respectively. Chi-Square or Fisher tests were used for categorical variables when appropriate. The correlation analysis between scores was performed with Pearson correlation or Spearman rank correlation tests. We used receiver operating characteristics (ROC) analysis to determine the optimal cut-off score for FAIR patients with moderate to high disease activity. The Youden index was applied to select the best cut-off value. $P < 0.05$ was considered significant.

Results

In this study, 79 AS patients were included (62% male). The demographic and clinical characteristics of AS patients are shown in Table 1. More than half of the patients (50.6%) were on biological disease-modifying anti-rheumatic drugs (bDMARDs), which were adalimumab (42.5%), etanercept (22.5%), golimumab (20%), secukinumab (10%), and certolizumab pegol (5%), respectively. The majority of patients (74.7%) involved in the study had severe disease activity with a BASDAI of 5.4 (3.8–7.4) and ASDAS-CRP of 3.83 (1.4). The overall fatigue severity score was 5.4 (4.1–7), which indicates severe fatigue; while the majority of patients had higher anxiety scores (44.7%), most of the patients (50%) were within normal limits in terms of depression. The psychological status of AS patients are summarized in Table 1. The overall FAIR score was calculated as 75 (range, 52–91).

When the ROC analysis was used to determine the best cut-off value for a FAIR score of AS patients with moderate to severe disease activity, the optimal cut-off value was 50 (AUC: 0.734, 95% CI [0.599–0.870], $P = 0.002$) with a sensitivity 89.8%, specificity 55%, the positive likelihood ratio of 1.99, and Youden index of 0.45.

There were statistically significant positive correlations between AS disease activity scores and FAIR, ASQoL, HADS-D, and HADS-A scores, as summarized in Table 2. Additionally, FAIR scores correlated significantly with ASQoL, FSS, HADS-D, and HADS-A scores (Table 3).

Table 1: The demographic, clinical and laboratory characteristics of AS patients (n = 79).

Parameter	Value
Age (years)*	41.7 (11.3)
Male Gender+	49 (62)
Disease Duration (months) ¥	36 (12-96)
HLA-B27 status+ (known for 27 patients)	16 (59.3)
Treatment features+	
Concomitant NSAIDs	37 (46.8)
Concomitant c-DMARDs	23 (29.1)
b-DMARDs	40 (50.6)
Disease Activity Status	
VAS Pain¥ (0-10)	7.5 (5-9)
Pt-VAS¥ (0-10)	6 (5-8)
BASDAI¥	5.4 (3.8-7.4)
BASFI¥	4 (2.3-6.2)
ASDAS-CRP*	3.83 (1.4)
Laboratory Features	
ESR¥ (mm/h)	8 (3-18)
CRP¥ (mg/L)	5 (1.2-12.9)
Psychological Status	
Overall Fatigue Severity Score¥	5.4 (4.1-7)
< 4+	16 (20.5)
≥ 4+	62 (79.5)
ASQOL*	9.6 (5.2)
Overall FAIR score¥	75 (52-91)
< 50+	17 (21.5)
≥ 50+	62 (78.5)
HADS-Depression Score*	7.7 (4.4)
0-7+	38 (50)
8-10+	18 (23.7)
≥ 11+	20 (26.3)
HADS-Anxiety Score*	9.8 (4.9)
0-7+	22 (28.9)
8-10+	20 (26.3)
≥ 11+	34 (44.7)

NSAID: Non-steroidal anti-inflammatory drug, cDMARD: conventional disease modifying anti-rheumatic drug, bDMARD: biological disease modifying anti-rheumatic drug, VAS: Visual analogue score, ESR: Erythrocyte-sedimentation rate, CRP:C-reactive protein, Pt-VAS: Patient Visual analogue score, ASQoL: Ankylosing Spondylitis Quality of Life, FAIR: Fear Assessment in Inflammatory Rheumatic Diseases Questionnaire, HADS: Hospital Anxiety and Depression Scale, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, ASDAS: Ankylosing Spondylitis Disease Activity Score, * mean (SD), + n (%), ¥ median (Q1–Q3)

Table 2: The correlation between psychological status measurements and AS disease activity indices.

	BASDAI		BASFI		Pt-VAS		Pain-VAS	
	r_s/r	*P*-value	r_s/r	*P*-value	r_s/r	*P*-value	r_s/r	*P*-value
FAIR	0.357	0.001[a]	0.407	<0.001[a]	0.333	0.003[a]	0.367	0.001[a]
FSS	0.602	<0.001[a]	0.488	<0.001[a]	0.721	<0.001[a]	0.462	<0.001[a]
ASQoL	0.640	<0.001[b]	0.655	<0.001[b]	0.571	<0.001[b]	0.540	<0.001[a]
HADS-D	0.483	<0.001[a]	0.490	<0.001[a]	0.446	<0.001[a]	0.431	<0.001[a]
HADS-A	0.333	0.003[b]	0.373	0.001[b]	0.389	0.001[b]	0.337	0.003[a]

VAS: Visual analogue score, Pt-VAS: Patient Visual analogue score, ASQoL: Ankylosing Spondylitis Quality of Life, FAIR: Fear Assessment in Inflammatory Rheumatic Diseases Questionnaire, HADS: Hospital Anxiety and Depression Scale, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, [a] Spearman rank correlation test, [b] Pearson Correlation

Table 3: The association between FAIR scores and FSS, ASQoL, HADS-D, and HADS-A.

	r_s	*P*-value
FSS	0.490	<0.001
ASQoL	0.592	<0.001
HADS-D	0.577	<0.001
HADS-A	0.651	<0.001

ASQoL: Ankylosing Spondylitis Quality of Life, FAIR: Fear Assessment in Inflammatory Rheumatic Diseases Questionnaire, HADS: Hospital Anxiety and Depression Scale, Spearman rank correlation test.

The patients were grouped according to their BASDAI scores. The patients with BASDAI scores < 4 were categorized as "inactive disease activity" (n = 20), and patients with BASDAI ≥ 4 were accepted as "active disease activity" (n = 59). The demographic and clinical features of AS patients with BASDAI < 4 and ≥ 4 are shown in Table 4. Even though there were no differences between the two groups in terms of age, disease duration, and treatment features, the FSS, HADS-D, HADS-A, and ASQoL scores were significantly higher in the active group compared to the inactive group. The number of patients with severe fatigue (FSS ≥ 4) was significantly higher in the active group. Additionally, the FAIR score was statistically higher in the active group compared to the inactive group. Most active patients (89.8%) had FAIR scores above the estimated cut-off level of 50.

Table 4: The clinical, laboratory, and psychological features of AS patients with remission-to- low disease activity and moderate-to-high disease activity.

	BASDAI < 4 (n=20)	BASDAI ≥ 4 (n=59)	*P*-value
Age (years) *	39(14.5)	42.6(10)	0.30[a]
Male +	18 (90)	31 (52.5)	0.003[b]
Disease Duration¥ (months)	60 (12-96)	36 (12-84)	0.36[c]
Treatment features+			
Concomitant NSAIDs	10 (50)	27 (45.8)	0.74[b]
Concomitant cDMARDs	4 (20)	19 (32.2)	0.30[b]
bDMARDs	12 (60)	28 (47.5)	0.33[b]
Disease Activity Status			
VAS Pain¥ (0-10)	3.5 (2-5)	7 (6-9)	<0.001[c]
PtVAS¥ (0-10)	3 (2-4.8)	8 (7-10)	<0.001[c]
BASDAI¥	2.5 (1.53-3.45)	6.62 (4.8-7.8)	<0.001[c]
BASFI¥	1.6 (0.3-2.7)	4.9 (3.3-6.7)	<0.001[c]
ASDAS-CRP*	2.29(0.9)	4.38(1.1)	<0.001[a]
Laboratory Features			
ESR¥ (mm/h)	4 (2-8)	10 (3-19)	0.017[c]
CRP¥ (mg/L)	2.6 (1.2-7.1)	6.8 (1.2-14.8)	0.16[c]
Psychological Status			
Overall Fatigue Severity Score¥	3.2 (2.2-4.4)	6 (5-7)	<0.001[c]
< 4+	12 (60)	4 (6.9)	<0.001[d]
≥ 4+	8 (40)	54 (93.1)	<0.001[d]
ASQOL*	4.9(4.7)	11.2(4.3)	<0.001[a]
Overall FAIR score¥	48 (33-79)	78 (62-93)	0.002[c]
< 50	11 (55)	6 (10.2)	<0.001[d]
≥ 50	9 (45)	53 (89.8)	<0.001[d]
HADS-Depression Score*	4.1(3.5)	8.9(4)	<0.001[a]
0-7+	16 (84.2)	22 (38.6)	0.002[b]
8-10+	2 (10.5)	16 (28.1)	0.002[b]
≥ 11+	1 (5.3)	19 (33.3)	0.002[b]
HADS-Anxiety Score*	6.7 (4.4)	10.9 (4.6)	0.001[a]
0-7+	9 (47.4)	13 (22.8)	0.041[b]
8-10+	6 (31.6)	14 (24.6)	0.041[b]
≥ 11+	4 (21.1)	30 (52.6)	0.041[b]

NSAID: Non-steroidal anti-inflammatory drug, cDMARD: conventional disease modifying anti-rheumatic drug, bDMARD: biological disease modifying anti-rheumatic drug, VAS: Visual analogue score, ESR: Erythrocyte-sedimentation rate, CRP:C-reactive protein, Pt-VAS: Patient Visual analogue score, ASQoL: Ankylosing Spondylitis Quality of Life, FAIR: Fear Assessment in Inflammatory Rheumatic Diseases Questionnaire, HADS: Hospital Anxiety and Depression Scale, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, ASDAS: Ankylosing Spondylitis Disease Activity Score, * mean (SD), + n (%), ¥ median (Q1-Q3), [a] Independent-Samples T Test, [b] Chi-Square, [c] Mann-Whitney-U, [d] Fisher's Exact Test.

Discussion

In this study, we show that AS patients have high fear scores, which were well correlated with disease activity scores, and patients with a higher disease burden face a higher degree of fear. Additionally, patients with higher disease activity have significantly increased fatigue, anxiety, depression, and lower quality of life. Fear scores were not only significantly correlated with disease activity indices but also with fatigue, anxiety, depression, and quality of life scores.

Due to their chronic and unpredictable course, patients with CIRDs, such as RA and spondyloarthritis, encounter psychological distress as well as fear about the prognosis of the disease, limitation in daily activities, risk of dependence on other people, and their roles in work, family and social life [8, 21]. Understanding the level and the reasons for fear in these patients and counseling towards it allows for optimizing treatment adherence and improving the quality of care given via advanced patient-physician dialogue [21]. Until recently, there was no measure to specifically assess the CIRD-related fear even though there are many patient-reported outcome measures to evaluate psychological states like anxiety and depression. Gossec et al. [8] developed and validated the patient-reported outcome measure of fear assessment in patients with CIRD, namely the FAIR questionnaire, in 2018. This study included a total of 432 RA patients and 240 axial spondyloarthritis patients to whom a 10-item questionnaire was applied. In this study, patients were classified due to their fear scores as high (mean score: 87.0 [7.9], n = 116; 17.2%), moderate (mean score: 65.8 [11.4], n = 276; 41.1%) and low (mean score: 31.1 [14.7], n = 280; 41.7%) in which the distinguishing cut-off level for high and low fear was found as 77 and 51, respectively [8].

In our study, the optimal cut-off level distinguishing high and low fear levels in patients with AS was 50 out of 100 points. However, we showed that AS patients with active disease (BASDAI ≥ 4) had a median fear score of 78 (62–93), which is in the group of high fear in the study stated above. The other study that assessed the utility of FAIR in CIRD is the validation study of the FAIR questionnaire in the Turkish language which included 58 AS and 57 RA patients [4]. In this study by Küçükakkaş et al. [4], the authors found that the mean FAIR score of AS patients was 49.3 (22.7), which was similar to our study. In both studies, no correlations were found between BASDAI and FAIR scores; however, Gossec et al. [8] stated that people with severer perceived disease activity were mostly in the high fear group. Our study showed significant correlations in patients' visual analog scores of global assessment and pain and in objective disease activity scores of BASDAI and BASFI. We also confirmed that patients with higher BASDAI scores have significantly higher FAIR scores compared to the low disease activity group and that they can be classified as the high fear cluster group based on Gossec et al. [8] study. One of the reasons why we showed a correlation between disease activity indices and fear degree may be due to the larger number of patients recruited, and secondly, we involved only patients with radiographic axial spondyloarthritis (i.e., AS), whereas the study of Gossec et al. [8], included patients also non-radiographic axial spondyloarthritis patients. Similar to the other two studies, our results showed a significant correlation between fear levels with HADS anxiety and depression scores [4, 8]. As a result, it is noteworthy that our study is the first study to assess the magnitude of fear in AS patients and its good relationship with disease activity indices, quality of life, and psychiatric status.

ASQoL is an 18 dichotomous questionnaire first developed in 2002 to assess the impact of the disease and treatment from the patient's perspective [19]. It was translated and validated in the Turkish language in 2013 by Duruöz et al. [20]. ASQoL evaluates the pain, energy, physical mobility, emotional status, sleep, and social interactions, which are all components of quality of life. Our study showed a statistically significant correlation of ASQoL with BASDAI, BASFI, patient assessment of disease activity, and pain. Duruöz et al. [20] also found a mild to moderate correlation between ASQoL and BASDAI, BASFI, and VAS-Pain. In the study of Bodur et al. with a total of 962 AS patients, the mean ASQoL was 7.1 (5.7), and ASQoL was strongly associated with BASDAI, BASFI, pain, and fatigue [22]. In our study, the mean ASQoL level was 4.9 (4.7) in AS patients with BASDAI < 4 and 11.2 (4.3) in patients with BASDAI ≥ 4, similar to our results, in the study of Bodur et al. [22], mean ASQoL in patients BASDAI < 4 was 4.56 (4.32) whereas mean ASQoL was 11.19 (5.13) in patients with BASDAI ≥ 4. Likewise, in other studies evaluating the association of ASQoL with BASDAI, BASFI, and total pain, strong correlations between the mentioned parameters were shown [23-25]. Our study is the first to evaluate the association between ASQoL and fear levels in AS patients and demonstrated that higher fear levels were associated with higher ASQoL, which results in poorer quality of life.

Several studies focused on the psychological status of patients with AS and found an increased risk of depression and anxiety [26]. In a recent meta-analysis, Park et al. [2] showed a 51% higher risk of depression among AS patients compared to a healthy population. Zhang et al. [27] found the prevalence of depression in AS patients ranges from 3% to 66%, and the prevalence of major depressive disorder was 13%. Increased disease activity, sleep problems, fatigue, and poorer quality of life are more common in AS patients with depression.

Indeed, studies showed that BASDAI, BASFI, ASQoL, and ASDAS-CRP were independent factors for depression [2, 26]. Additionally, an 85% increased risk of anxiety was demonstrated in AS patients compared to healthy controls [28]. Similarly, in our study, we found overall depression and anxiety scores of 7.7 (4.4) and 9.8 (4.9), respectively. Moreover, HADS-D and HADS-A scores were not only correlated with BASDAI, BASFI, and pain assessments but also with FAIR scores. Furthermore, the prevalence of fatigue ranged from 53 to 65% in AS patients [29, 30]. Zhou et al. [29] reported an incidence of fatigue in Chinese AS patients of 48.7% and showed BASDAI as an independent risk factor for fatigue severity. Likewise, in our study, AS patients had higher fatigue levels on the FSS scale, and FSS scores correlated positively with BASDAI, BASFI, and pain scores. Besides, FAIR scores correlated significantly with fatigue severity.

Limitations

The study's cross-sectional design restricted the interpretation of psychological status change after successful treatment. The second limitation was the relatively small number of AS patients included, hence, a lower number of patients with inactive disease activity. On the other hand, the current study is unique as it is the first study evaluating the association of fear by using the FAIR questionnaire, which specifically assesses the fear level in AS patients with disease activity indices as well as depression, anxiety, and fatigue status. Prospective studies are needed to evaluate more thoroughly the fear degree in spondyloarthritis patients and also the change in fear scores after especially bDMRD initiation with a larger cohort.

Conclusion

This study shows that the FAIR and ASQoL scores are associated with disease activity and depression, anxiety, and fatigue scores. Also, patients with higher disease activity face more fear about their disease, physical disability, and social life. As a result, physicians should adopt a holistic approach when treating patients with inflammatory rheumatic diseases, focusing on controlling disease activity and handling psychological status.

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Comparison of hematological and biochemical parameters in COVID-19 pneumonia patients before and after convalescent plasma (CP) treatment

Esra Polat [1], Fatma Yekta Ürkmez [2]

[1] Department of Cardiology, Fethiye State Hospital, Fethiye, Muğla, Turkey
[2] Department of Infectious Diseases and Clinical Microbiology, Kirikkale Yüksek Ihtisas Hospital, Kirikkale, Turkey

ORCID ID of the author(s)

EP: 0000-0002-2330-2816
FYÜ: 0000-0002-5438-4623

Corresponding Author
Esra Polat
Department of Cardiology, Fethiye State Hospital, Fethiye, Muğla, Turkey
E-mail: esrapolat-1907@hotmail.com

Ethics Committee Approval
The study was approved by the Health Science Ethics Committee of Muğla Sıtkı Koçman University (14.04.2021- 61) and the Ministry of Health (2021-02-01T_15-_26_43).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: Convalescent plasma (CP) therapy, which includes processing and administering antibody-rich plasma from recovered patients to sick patients, is used for passive immunity in COVID-19 pneumonia patients in addition to antivirals and antibiotics. This study aimed to assess whether CP treatment significantly affects hyperviscosity and COVID-19 prognosis-related blood parameters.
Methods: This study was a single-center retrospective cohort study. Ninety-seven patients with COVID-19 polymerase chain reaction (PCR)-positive results and pneumonia observed on thoracic computed tomography (CT) were included. Patients' ferritin, d-dimer, C-reactive protein (CRP), and complete blood count levels before and after CP administration were compared.
Results: Ferritin, d-dimer, white blood cell (WBC), neutrophil, and plateletcrit (PCT) levels and the platelet distribution width (PDW) were significantly higher and there was a significant decrease in the CRP level after CP treatment compared to before CP ($P < 0.05$). Ferritin, d-dimer, and CRP values measured after CP were higher in deceased patients than in survivors ($P = 0.001$, $P = 0.007$, and $P < 0.001$, respectively)
Conclusion: Ferritin, d-dimer, WBC, and neutrophil levels, which we expected to decrease on the basis of the COVID-19 prognosis, unfortunately increased, and only CRP levels decreased. However, we found that these increases were more pronounced in patients who died. Considering these prognostic factors, the findings of our study suggest that CP treatment has no effect on the COVID-19 disease course and may lead to a worse prognosis.

Keywords: COVID-19, Convalescent plasma, CRP, d-dimer, WBC

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Introduction

The Coronavirus Disease 2019 (COVID-19), which first appeared in China, was declared a pandemic by the World Health Organization (WHO) in March 2020 [1]. As drug research continues for COVID-19, passive immunotherapies have come to the forefront in treatment. Convalescent plasma (CP) therapy, which was previously used for passive immunity in treating severe acute respiratory syndrome coronavirus (SARS-CoV), has also been used to treat COVID-19 [2]. It was first used in China in February 2020 for a patient with COVID-19 [3]. Shortly thereafter, the United States Food and Drug Administration (FDA) approved an emergency use recommendation in March 2020 [4].

CP is plasma collected from individuals who have recovered from a particular infection and have developed antibodies. In addition to neutralizing antibodies, other proteins such as anti-inflammatory cytokines, coagulation factors, natural antibodies, defensins, pentraxins, and other unidentified proteins are obtained from donors during apheresis [5].

In research on the use of CP in COVID-19, Shen et al. reported that the clinical condition in five critically ill patients improved after receiving CP and undergoing extracorporeal membrane oxygenation (ECMO) and mechanical ventilation [6]. However, a randomized controlled trial by Li et al. showed that CP in addition to the standard treatment did not make a significant difference in mortality [7]. Many studies on COVID-19 and CP have been published, but there are few studies on hyperviscosity associated with COVID-19 and CP. In the study conducted on six patients with COVID-19-related hyperviscosity, there was a decrease in the d-dimer, C-reactive protein (CRP), and fibrinogen levels [8].

This study aimed to observe whether CP treatment significantly affects hyperviscosity and COVID-19 prognosis-related blood parameters.

Materials and methods

Study design and settings

This retrospective cohort study was approved by the Health Science Ethics Committee of Muğla Sıtkı Koçman University (14.04.2021- 61) and the Ministry of Health (2021-02-01T_15-_26_43). The study was performed in the COVID-19 intensive care unit and COVID-19 services in a secondary care hospital in Muğla, Turkey. Between April 2020 and February 2021, patients with SARS-CoV-2 polymerase chain reaction (PCR)-positive results and pneumonia who received at least one unit of CP were included in the study. The following information was collected and examined: patients' demographic information, comorbidities, blood groups, the number of plasma units administered, ferritin, d-dimer, CRP, white blood cell (WBC) count, lymphocyte levels, neutrophil count, mean platelet volume (MPV), platelet distribution width (PDW), and plateletcrit (PCT) before and after plasma.

Participant selection

Sample size calculations were performed using G*Power 3.0 (Franz Faul, University of Kiel, Germany) before starting the study. A study with 80% statistical power that allowed 5% Type I error required at least 78 participants.

Patients over 18 years of age who were hospitalized with COVID-19 pneumonia between April 2020 and February 2021 were included in the study. The COVID-19 pneumonia diagnosis was made based on COVID-19-positive results by PCR and the presence of ground-glass opacities on a thorax computed tomography (CT). Patients with incomplete file information were excluded from the study. Pediatric patients, pregnant people, and patients who were immunosuppressed or who had IgA deficiency were excluded from the study. The in-hospital treatment protocol was as follows: all patients received supportive treatment including oxygen and fluid therapy and, if necessary, vasopressor treatment. All patients received favipiravir (2×1600 mg loading and 1200 mg/day, orally), ciprofloxacin (400 mg/day parenterally), methylprednisolone (80 mg/day parenterally), and enoxaparin (4000–6000 IU twice a day).

Measurements and Outcomes

Patients with COVID-19 pneumonia, who received CP with a plasma therapy indication of at least one 200-mL unit at that time, and who were followed-up were included in the study. Only the first CP treatment was considered in patients who received more than one plasma unit, and at least 24-hours were required between two plasma treatments. Ferritin, d-dimer, CRP, WBC, lymphocyte, neutrophil, MPV, PDW, and PCT tests were analyzed before and after CP. The duration of hospitalization, the hospitalization day when the plasma was administered, and their discharge status were also examined.

Statistical analysis

Descriptive statistics were tabulated as the mean (standard deviation) or median, minimum, and maximum depending on the distribution of continuous variables in the data summaries obtained from the study. Categorical variables were summarized as the number and percentage. The normality test of numerical variables was assessed using the Shapiro–Wilk, Kolmogorov–Smirnov, and Anderson–Darling tests. On the basis of the patient's discharge, the Mann–Whitney U test was used for numerical variable comparisons when the variables were not normally distributed. To compare some blood parameters before and after CP, a paired *t*-test was used when numerical variables showed a normal distribution, and the Wilcoxon test was used when the data were not normally distributed. Statistical analyzes were performed using Jamovi Project (Version 1.6.13.0, Sydney, Australia) and JASP (Version 0.14.1.0, JASP Team, Amsterdam, the Netherlands). The level of significance in the statistical analysis was accepted as 0.05.

Results

Ninety-seven patients were included in the study, with a mean age of 53.9 (13.7) years. Fifty-seven patients were men and 40 patients were women. The most common blood group was A+ (37 patients, 38.1%). The most common comorbid disease was hypertension (32 patients; 33%). The mean length of the hospital stay was 13.1 (6.5) days. Thirty-eight (39.2%) patients were treated in the intensive care unit. The median number of plasma units administered to patients was 1. Twenty (20.6%) patients were discharged from the hospital (Table 1).

The ferritin level after CP treatment was higher than before CP treatment (367.6 vs. 266.5, $P < 0.001$). The d-dimer

level was higher after CP than before CP (0.4 vs. 0.3, $P = 0.043$). The CRP level was lower after CP than before CP (13.5 vs. 32.7, $P = 0.035$). The WBC count was higher after CP than before CP (10,300 vs. 5900, $P = 0.001$). The neutrophil level was higher after CP than before CP (8100 vs. 3600, $P < 0.001$). PDW was higher after CP than before CP (0.3 vs. 0.2, $P = 0.011$) (Table 2).

Table 1: Demographic and clinical characteristics of the patients with COVID-19 patients given plasma

	Mean (SD) / n (%)	Median (Min- Max)
Age	53.9 (13.7)	52.0 (20.0- 83.0)
Gender		
Male	57 (58.8)	
Female	40 (41.2)	
Blood type		
0-	6 (6.2)	
0+	30 (30.9)	
A+	37 (38.1)	
AB+	7 (7.2)	
B+	17 (17.5)	
Diabetes Mellitus	21 (21.6)	
Hypertension	32 (33.0)	
Coronary Artery Disease	10 (10.3)	
Chronic Obstructive Pulmonary Disease	4 (4.1)	
Asthma	1 (1.0)	
Chronic Kidney Disease	2 (2.1)	
Cancer	2 (2.1)	
Stroke	1 (1.0)	
Length of hospital stay	13.1 (6.5)	11.0 (5.0- 34.0)
Intensive care unit admission	38 (39.2)	
Unit of plasma		1.0 (1.0- 4.0)
Day of plasma administration		4.0 (1.0- 24.0)
Exitus		
None	77 (79.4)	
Yes	20 (20.6)	

SD: Standard deviation

Table 2: Changes in laboratory parameters of patients before and after plasma treatment

Variable	Before	After	*P*-value
Ferritin (ng/ml)	266.5 (5.6- 2000.0)	367.6 (9.4- 4309.0)	<0.001**
D dimer (ng/ml)	0.3 (0.0- 10.2)	0.4 (0.1- 13.8)	0.043**
CRP (mg/l)	32.7 (0.8- 395.9)	13.5 (0.2- 222.8)	0.035**
WBC ($x10^3$)	5.9 (1.2- 56.7)	10.3 (4.5- 25.3)	<0.001**
Lymphocyte ($x10^3$)	1.3 (0.4- 8.4)	1.1 (0.2- 13.6)	0.952**
Neutrophil ($x10^3$)	3.6 (0.2- 18.9)	8.1 (0.6- 23.5)	<0.001**
MPV (fl)	10.6 (1.5)	10.8 (1.0)	0.075*
PDW (fl)	12.7 (2.4)	13.1 (2.5)	0.011*
PCT (%)	0.2 (0.1- 0.7)	0.3 (0.1- 0.6)	<0.001**

*: Independent Samples T-Test, **: Mann Whitney U Test, CRP: C-reactive protein, WBC: White blood cell, MPV: Mean platelet volume, PDW: Platelet distribution width, PCT: Plateletcrit

The ferritin level before and after CP in non-survivors was higher than in survivors ($P = 0.010$ and $P = 0.001$, respectively). In patients who died, the d-dimer level after CP was higher than in patients who survived (1.4 vs. 0.4, $P = 0.007$). The CRP level after CP in patients who died was higher than in patients who survived (76.1 vs. 9.1, $P < 0.001$). WBC counts were higher in patients who died before and after CP than in those who survived ($P = 0.002$ and $P < 0.001$, respectively). In patients who died, the lymphocyte count after CP was lower than in patients who survived (900 vs. 1200, $P = 0.019$). Neutrophil levels were higher in patients who died before CP and after CP than in patients who survived ($P = 0.004$ and $P < 0.001$, respectively). The MPV level in patients who died was higher in patients who survived (11.2 vs. 10.5, $P = 0.003$) (Table 3).

While the CRP level increased after CP (54.4% increase) in non-survivors, it decreased (69.6% decrease) in survivors ($P < 0.001$). The change in the MPV level was also different in patients who died and in those who survived ($P = 0.035$) (Table 4).

Table 3: Comparison of laboratory parameters between the patient who survivor and non-survivor after plasma administration

	Survivor (n = 77)	Non-survivor (n = 20)	*P*-value
Ferritin (ng/ml)			
Before plasma	214.0 (5.6- 2000.0)	483.0 (60.6- 2000.0)	0.010
After plasma	320.5 (9.4- 4309.0)	846.8 (134.2- 2000.0)	0.001
D dimer (ng/ml)			
Before plasma	0.3 (0.0- 7.9)	0.5 (0.1- 10.2)	0.154
After plasma	0.4 (0.1- 13.8)	1.4 (0.1- 10.0)	0.007
CRP (mg/l)			
Before plasma	27.7 (0.8- 186.9)	51.4 (3.6- 395.9)	0.09
After plasma	9.1 (0.2- 176.1)	76.1 (17.7- 222.8)	<0.001
WBC ($x10^3$)			
Before plasma	5.4 (1.2- 56.7)	7.7 (3.5- 20.1)	0.002
After plasma	9.4 (4.5- 24.4)	14.1 (6.8- 25.3)	<0.001
Lymphocyte ($x10^3$)			
Before plasma	1.4 (0.4- 3.4)	1.1 (0.5- 8.4)	0.397
After plasma	1.2 (0.2- 8.7)	0.9 (0.3- 13.6)	0.019
Neutrophil ($x10^3$)			
Before plasma	3.5 (0.2- 13.5)	5.0 (1.6- 18.9)	0.004
After plasma	7.9 (2.7- 20.7)	12.7 (0.6- 23.5)	<0.001
MPV (fl)			
Before plasma	10.4 (0.2- 12.4)	11.0 (9.3- 14.2)	0.101
After plasma	10.5 (8.7- 12.9)	11.2 (9.9- 13.3)	0.003
PDW (fl)			
Before plasma	12.3 (9.7- 18.4)	12.8 (10.3- 22.9)	0.081
After plasma	12.4 (8.9- 18.0)	13.8 (11.4- 22.2)	0.007
PCT (%)			
Before plasma	0.2 (0.1- 0.7)	0.2 (0.2- 0.5)	0.169
After plasma	0.3 (0.1- 0.6)	0.3 (0.2- 0.5)	0.895

Mann Whitney U test. The variable that does not show normal distribution is shown as [min-max]. CRP: C-reactive protein, WBC: White blood cell, MPV: Mean platelet volume, PDW: Platelet distribution width, PCT: Plateletcrit

Table 4: Comparison of percentages of change before and after plasma administration in survivor and non-survivor patients

	Survivor (n = 77)	Non-survivor (n = 20)	*P*-value
Δ Ferritin	-26.7 (-1101.4- 62.7)	-54.4 (-498.7- 4.8)	0.126
Δ D dimer	-30.8 (-3629.7- 84.6)	-72.7 (-7584.6- 74.2)	0.355
Δ CRP	69.6 (-1283.5- 99.1)	-54.4 (-1104.1- 56.4)	<0.001
Δ WBC	-70.7 (-1740.3- 73.0)	-64.5 (-210.7- 30.2)	0.880
Δ Lymphocyte	-2.1 (-328.6- 80.8)	24.5 (-78.5- 80.2)	0.130
Δ Neutrophil	-113.7 (-8525.0- 66.0)	-92.5 (-323.5- 63.0)	0.950
Δ MPV	0.0 (-5300.0- 15.9)	-5,9 (-18.8- 7.1)	0.035
Δ PDW	-3.6 (-34.1- 22.0)	-7,7 (-72.1- 8.1)	0.143
Δ PCT	-38.4 (-176.5- 73.1)	-29,4 (-200.0- 43.4)	0.275

Mann Whitney U test. The variable that does not show normal distribution is shown as [min-max]. CRP: C-reactive protein, WBC: White blood cell, MPV: Mean platelet volume, PDW: Platelet distribution width, PCT: Plateletcrit

Discussion

When laboratory differences before and after CP were examined in patients who received CP due to COVID-19 pneumonia, ferritin, WBC, neutrophil, PDW, and PCT values increased statistically after CP. Considering the differences in blood parameters according to the survival and death status of the patients who received plasma, the ferritin level in patients who died was higher. After CP, d-dimer and CRP were more elevated in patients who died than in those who survived.

Although the efficacy of CP in COVID-19 pathogenesis is controversial, its rapid availability has allowed its emergency use in epidemics such as Spanish flu, SARS-CoV, West Nile virus, and recently Ebola [9-11].

In this study, we wanted to investigate the effect of CP on blood parameters. A recent study showed that platelet indices were not useful parameters to determine the prognosis of COVID-19 patients [12]. In our research, we found that blood parameters did not improve after CP treatment.

In a study by Abolghasemi et al. [13] that included 115 COVID-19 pneumonia patients who received CP, the most common comorbidities were hypertension and diabetes mellitus, which is consistent with the results of our study.

A study conducted in our country evaluated patients who received CP, and it showed that patients with blood group A received CP most often and had a high follow-up rate in the

intensive care unit [14]. Similarly, in our study, blood group A was the most common blood group among patients who received CP [14]. This may be because COVID-19 patients with blood group A have a high risk and a poor prognosis [15, 16] and plasma is given to patients with a poor prognosis.

In a randomized study, no improvement was observed in the clinical condition after 28 days in patients with COVID-19 who received CP, but there was a decrease in mortality [17]. In the PlasmAR Study, which is a double-blind study comparing CP and placebo that compared 228 CP patients and 105 placebo patients with COVID-19 pneumonia, there was no significant difference in the clinical status and mortality between the CP group and the placebo group [18]. Similarly, the CONCOR-1 study was a multi-center, open-label, randomized trial that showed no decrease in 30-day mortality in hospitalized CP patients with COVID-19 [19]. In a randomized study by Li et al. [7], 103 patients with severe or life-threatening COVID-19 received CP in addition to standard treatment, but CP treatment did not show a clinical improvement within 28 days. In our study, 77 of the patients treated with CP recovered, while 20 died. However, it is not possible to draw a firm conclusion on the effect of CP treatment on mortality because no comparison was made with a control group.

While other studies showed that CP does not have a significant positive contribution to mortality and clinical status, its effects on hematological and biochemical parameters show that lymphocyte counts increased and CRP level decreased after ten patients with severe COVID-19 received CP [20]. In a clinical study conducted by Huang et al. [3], a decrease in WBC and CRP values and an increase in lymphocyte values were reported after CP. In contrast to their study, we observed an increase in WBC levels after CP, and we did not observe a significant increase in the lymphocyte count. Similarly, a significant decrease in the CRP level was observed. These differences may be because they evaluated the results of 14 patients who benefited from CP, and we evaluated patients who died and who did not benefit from CP treatment.

Truong et al. [8] investigated six patients with COVID-19-associated hyperviscosity and showed a decrease in the d-dimer level after CP, but we found an increase in d-dimer after CP in our study. This difference may be because the six patients studied had a disease associated with hyperviscosity, and this was not the case in our patients.

Another study conducted with 26 intensive care unit patients in our country showed no difference in CRP levels between patients who died and those who survived, whereas, in our study, the CRP level was initially high and then increased in patients who died [21]. The reason for this difference may be the high number of patients and because only patients in the intensive care unit were included in the other study while patients in both the intensive care unit and the pandemic clinic were included in our study.

When the patients who died and survived in our study were compared, d-dimer, CRP, MPV, and PDW values were similar in both groups before CP, but they showed a significant increase in patients who died after CP. Additionally, ferritin, WBC, and neutrophil values were significantly higher in deceased patients compared to survivors before CP, but increased more after CP. In our study, only the lymphocyte value was found to be significantly lower in patients who died after CP. Although these data were not calculated for every patient, they suggest that the neutrophil-to-lymphocyte ratio increased in patients who died. Atlas et al. investigated COVID-19 patients who were followed-up in the intensive care unit, and they showed that an increase in the neutrophil-to-lymphocyte ratio, d-dimer, and CRP levels was associated with an adverse outcome [22]. In our study, an increase in neutrophils, d-dimer, and CRP and a decrease in lymphocyte levels were observed after CP in patients who died, which is consistent with Atlas et al.'s results. Thus, CP treatment may not have a positive effect on patient prognosis. Although CP treatment was initially recommended in the COVID-19 treatment guideline from the Ministry of Health of the Republic of Turkey, the recommendation for use was later removed from the guideline [23]. This is consistent with the results of our study.

Limitation

There are some limitations to our study. First, at the time of the study, there were no clearly defined CP indications. Second, the time elapsed between the disease diagnosis and CP administration was not similar. Additionally, including patients who did not receive CP treatment in studies of patients who received CP would have provided more explanatory results. The inability to measure the anti-SARS-CoV-2 antibody levels in our patients is a critical limitation of our study. Furthermore, the retrospective nature of the study is a limitation of our research.

Conclusion

In patients with COVID-19 pneumonia who received CP and were followed-up, values such as ferritin, d-dimer, WBC, neutrophil, PDW, and PCT values, which were expected to decrease based on the COVID-19 prognosis, unfortunately increased after CP. Only the CRP level decreased, which reflected positively on the prognosis. When patients who died were compared with the survivors, increased ferritin, d-dimer, CRP, WBC, neutrophil, MPV, and PDW values and a decreased lymphocyte count were evident in those who died. Because the neutrophil-to-lymphocyte ratio, d-dimer, and CRP values were associated with a negative outcome, administering CP was suggested to have no effect on the COVID-19 prognosis, and it may lead to worsening of the prognosis. However, additional studies are needed to clearly evaluate the effect of CP therapy on the prognostic factors for COVID-19.

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Effects of Algan hemostatic agent foam in rat femoral artery injury model: A randomized animal trial

Dila Şener [1], Atakan Aydın [2], Ekin Cücü [2], Taylan Adademir [3], Deniz Mukaddes Türet [4], Mehmet Karadağ [5]

[1] Department of Histology and Embryology, Bahcesehir University, Faculty of Medicine, Istanbul, Turkey
[2] Department of Medicine, Bahcesehir University, Faculty of Medicine, Istanbul, Turkey
[3] Department of Cardiovascular Surgery, Kartal Kosuyolu Heart and Research Hospital, Istanbul, Turkey
[4] Marmara University, Medical School, Experimental Animal Implementation and Research Centre, Istanbul, Turkey
[5] Department of Biostatistics, Mustafa Kemal University, Faculty of Medicine, Hatay, Turkey

ORCID ID of the author(s)

DŞ: 0000-0001-9496-7324
AA: 0000-0001-7145-7954
EC: 0000-0002-4093-8285
TA: 0000-0003-1643-3751
DMT: 0000-0003-1989-9637
MK: 0000-0001-9539-4193

Corresponding Author
Dila Şener
Department of Histology and Embryology, Faculty of Medicine, Bahcesehir University, Sahrayıcedit Mahallesi, Batman Sokak, No: 66-68, 34734, Göztepe-Kadıköy, Istanbul, 34000, İstanbul, Turkey
E-mail: dila.senerr@gmail.com

Ethics Committee Approval
This study was conducted at Marmara University, Medical School Experimental Animal Implementation and Research Centre and ethical approval for this study was obtained from Local Animal Experiments Ethics Council of the Marmara University (No: 65.2021, Dated: 09.08.2021).

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Abstract

Background/Aim: Nowadays, many deaths are related to vessel injury-induced blood loss. Failure to control bleeding also increases the risk of death. This study aimed to investigate the hemostatic effects of the Algan Hemostatic Agent (AHA) foam application in a rat model in which severe femoral artery bleeding was induced.

Methods: Fourteen rats were randomly assigned to two groups: (1) control (physiological saline) (n = 7) and (2) AHA foam (n = 7). The left femoral artery of the rats was incised and when the bleeding started, and the area was pressed with another sponge for 10 s in all rats. Afterwards, physiological saline solution impregnated gauze or AHA foam was placed over same area. A chronometer was started and area was checked after 2 min. If no bleeding occurred during the first 2 min of application, it was recorded as "successful". If bleeding occurred, the same procedure was repeated up to three times. If hemostasis could not be achieved even after the third application, it was considered a failure, and "failed" was recorded. All animals were sacrificed under high anesthesia for least 10 min after the experiment.

Results: Application of AHA resulted in complete (100%) control of bleeding in all rats within the first 2 min. In control group, hemostasis was achieved in 1 out of 7 (14.3%) rats by the third application. Failure was recorded for the remaining six rats. The hemostatic success rate of the AHA foam was significantly higher than the rates of control group ($P = 0.005$).

Conclusion: AHA foam is a very effective hemostatic agent and can be applied easily on vascular trauma models. Further studies are needed to elucidate hemostatic features of AHA.

Keywords: Algan hemostatic agent, Femoral artery, Hemostasis, Bleeding, Rat, Coagulation

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Introduction

Injury of the major vessels is one of the significant reasons of death caused by trauma [1]. Moreover, hemostatic balance can be easily disturbed even after common surgeries, such as cardiopulmonary bypass [2]. Therefore, stopping the bleeding during a surgical process or during emergencies after injury can be a lifesaving process. The need for methods to minimize hemorrhage-derived blood loss problems that are caused by trauma, such as an injury, fracture, cleft, or surgery, are necessary [3]. Direct pressure can be applied to the bleeding area to suspend the circulation after trauma [1]. Besides direct pressure, fast acting and effective procedures and products are needed to expedite hemostasis. Agents that are locally used for this purpose have been reported and include chitosan linear polymer (Celox®), poly-N-acetylglucosamine (Chitin®), fibrin glues, microporous hydrogel-forming polyacrylamide (BioHemostat®), microporous polysaccharide hemosphere (TraumaDEX®), oxidized cellulose (Bloodcare®), and Ankaferd Blood Stopper® (ABS) [4]. However, inflammation and/or infection risks have also been reported in various studies through the use of most of these materials [5–9], and no consensus on which product is the ideal one has been reached. Hence, studies in the literature report a continuous search for an optimal hemostatic agent.

Algan Hemostatic Agent (AHA) Foam is a class III starch-based absorbable hemostatic agent (Certificate number: EC Design-Examination Certificate 1783-MDD-216). It is used to stop all minor and major bleeding, such as internal and external bleeding, bleeding that emerges during surgeries, surgical interventions and operations, rupture, fragmentation, traumatic cuts, and others.

Recently, the hemostatic effects of AHA foam have been reported [10–12]. In addition, the effectiveness and safety of the different forms of AHA have been studied [13–16]. AHA foam generates a polymer network throughout its application area, creating a passive barrier that stops blood from leaking. It is also advantageous in terms of its low cost and ease of handling. Based on recent studies that showed the effects of this new herbal product in various tissues with different surgical models, the study aimed to investigate the effectiveness of AHA foam in a rat femoral artery bleeding model.

Materials and methods

Animals

All animal experiments were performed in accordance with the ethical norms approved by the Local Animal Experiments Ethics Council of Marmara University Istanbul, Turkey (Ethics Committee Approval No: 65.2021, Dated: 09.08.2021). Fourteen adult 8–10-week-old, Wistar Albino rats with weights between 230 and 280 g were used, and animals were randomly divided into two groups of seven animals in each group: (1) control (physiological saline solution impregnated gauze) and (2) AHA foam. All animals were housed in an air-conditioned animal room in standard clean polypropylene cages under standard vivarium conditions with 12-h light/dark cycles. All animals were fed with a standard pellet diet and water *ad libitum*. All experiments were performed after one week-long of adaptation period.

Study design

All rats were sedated with 100 mg/kg ketamine hydrochloride (Ketalar, Eczacıbaşı, İstanbul, Türkiye) and 10 mg/kg xylazine hydrochloride (Rompun, Bayer, İstanbul, Türkiye) intraperitoneally. Anesthetic depth was monitored by examining skin or finger nipping response, palpebra or corneal reflex, heartbeat, respiratory rate, and other physiological parameters. The surgical procedure of our study was performed according to methods described in the literature [4]. After wiping and shaving the left inguinal area of the rats, layers of the skin and subcutaneous tissues were cut open to reveal the left femoral vessels. Femoral arteries were injured with the injector tip to initiate bleeding. Immediately after the bleeding had started, a standard sponge was pressed over the incised area for 10 s in all rats. Immediately after removing the sponge, physiological saline-impregnated gauze and AHA foam were applied to the same injured area in control and AHA foam groups, respectively (Figure 1A, B). Chronometer was started to measure time and the area was checked after two minutes. If there was no bleeding, first 2 minutes application was recorded as “successful”. If the bleeding had not stopped, same application was repeated for 2 additional min, and the bleeding was checked again. If the bleeding had stopped, it was recorded as “second 2-min successful” application and on the contrary, same procedure was repeated for the third time if there was bleeding. If the bleeding had stopped at the third application, it was recorded as “third 2-min successful”. Hemostasis that could not be achieved even after the third application was considered a failure and recorded as “failed" (Table 1). All animals were sacrificed under high anesthesia for at least 10 min after the hemostasis.

Figure 1: Femoral artery in the left inguinal region (A), Algan Hemostatic Agent (AHA) foam application on the injured area (B). Visible hemostasis and adherence of AHA foam to the area after 2 min of pressure (C). Bleeding control after removal of AHA foam in another rat from the same group (D).

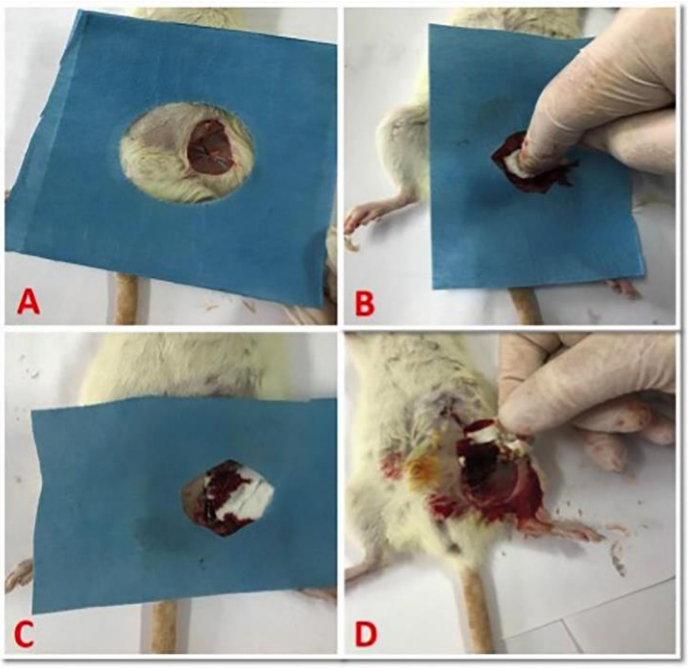

Table 1: Bleeding control interval recordings

	First application success (2 min)	Second application success (2 min)	Third application success (2 min)	Failed
Algan Hemostatic Agent (AHA) foam	7 (100%)	0 (0%)	0 (0%)	0 (0%)
Control (saline impregnated gauze)	0 (0%)	0 (0%)	1 (14.20%)	6 (85.7%)

Statistical analysis

An exact chi-squared test was used for the comparison between control and AHA results. Numbers and % data were assigned to categorical variables as demonstrative statistics. Statistical analysis is performed with Statistical Package for the Social Sciences (SPSS) software version 24.0 (SPSS Inc., Chicago, IL) and $P < 0.05$ was considered statistically significant.

Results

Application of AHA foam to the bleeding area resulted in complete control of bleeding in 7 out of 7 rats after the first application (within the first 2 min) as shown in Figure 1C, D. None of the rats had stopped bleeding after the first or second application in the physiological saline solution group. Nonetheless, hemostasis was received only in 1 out of 7 rats by the third application (within 6 min) in the saline group. For the other 6 out of 7 rats, the bleeding could not be stopped even after 6 min (Table 1). In conclusion, AHA foam resulted in 100% success compared to physiological saline solution (only 14.3%). It has been found that the success of the AHA foam over control physiological saline's success in terms of hemostasis was statistically significant ($P = 0.005$) as shown in Table 2.

Table 2: Bleeding control statistics between study groups

	+	-	Total	*P*-value
AHA foam	7 (100)	0 (0)	7 (100)	0.005
Control group (saline-impregnated gauze)	1 (14.3)	6 (85.7)	7 (100)	
Total	8 (57.1)	6 (42.9)	14 (100)	

AHA: Algan Hemostatic Agent, +: successful application, −: hemostasis that could not be achieved after third application

Discussion

This study compared the hemostatic effects of AHA foam and physiological saline solution-impregnated gauze on a rat femoral artery incision model. The results showed that AHA foam was significantly more effective for causing a cessation of bleeding. Although many hemostatic materials were compared in different studies, no agreement on which one of them is the better hemostatic agent [17–20]. Hanks et al. [21] compared the hemostatic effectiveness of oxidized cellulose and fibrin glue and concluded that fibrin glue was more effective. Ersoy et al. [22] studied the hemostatic effects of microporous polysaccharide hemospheres and observed that they accelerated hemostasis. Abacıoğlu et al. [4] studied the hemostatic effects of Ankaferd Blood Stopper (ABS) and showed hemostasis had occurred by 2 min in 40% of all the rats and by 4 min in 60% of rats. In our study, all rats in the AHA foam group had reached hemostasis within the first 2 min, and no need for a second application of AHA foam was required. Wang et al. [23] compared chitosan sponges, chitosan fibers, and standard bandages in a rat femoral artery incision model and found a significant difference in hemostatic effectiveness between chitosan sponge and standard bandage and concluded that the chitosan sponge was more effective. Köksal et al. [24] showed the preeminence of Celox compared to compression in a rat femoral artery injury model in which Celox caused a significant decrease in the amount of time it took to reach hemostasis. In all groups with hypothermia, normothermia, and warfarin, Celox was found to be more effective than compression. Bertram et al. [25] analyzed the effect of intravenous synthetic platelet injections on rat femoral artery incision models and reported that synthetic platelets led to a reduction in bleeding nearly to half that of the control group. Studies have found no significant contribution from administration of extra amounts of physiological hemostatic substances to hemostasis when they were administered intravenously [26, 27]. In studies conducted to test the effectiveness of AHA in heparinized/non-heparinized rat splenectomy and heparinized/non-heparinized rat hepatectomy models, AHA was found to lead to a decrease in the average time to achieve hemostasis by 97.7% and 98%, respectively [13, 16].

In this study, AHA foam was applied directly to the bleeding area using light pressure. And after 2 minutes, pressure was removed, and the area was observed to detect local bleeding. AHA was found to be quite successful in controlling bleeding due to femoral artery injury, and similar results with AHA have been shown in previous studies. [13–16, 28, 29]. AHA provides hemostasis by creating a local polymer web that binds to the tissue and acts as a mechanical barrier. Its detachment from the application site can create trauma to tissues and vessels; thus, detachment may trigger re-bleeding. Consequently, it is suggested to leave AHA on the application site to prevent rebleeding.

Even though bleeding duration under the effect of compression was found to be 4 minor femoral artery incision [4, 22] and approximately 6 min for tail incision [17], no successful hemostasis could be observed to occur spontaneously. In our study, the bleeding from femoral artery incision was stopped for every rat (100%) in the AHA group within the first 2 min. In the saline group, however, hemostasis was achieved solely in 1 rat (14.3%) within 6 min and for the other 6 rats (85.7%) the bleeding failed to stop. This difference of at least 4 min on bleeding durations supports the significantly positive effect of AHA on severely damaged arteries. Although the supplements were not compared directly, results have shown that AHA is a quick effective agent in vascular damage models.

Limitations

This study had some limitations. The bleeding area was directly approachable, which is unlikely to be encountered in real life, clinical situations. Thus, this controlled situation can make the application and the effect of the AHA easier to detect compared to real life settings. Second, as a potential source of bias in the study, the time to reach normal hemostasis could have differed independently from AHA due to the genetic structure of the rat genus used in this study, and a 1-sec margin of error in measuring the exact moment of hemostasis in all animals could have been present.

Conclusions

Treatment with AHA application versus physiological saline solution-soaked gauze was more effective at the bleeding femoral artery incision sites of rats. AHA was more efficient in terms of causing a decrease in bleeding duration and acceleration of hemostasis. Although the application was performed in a controlled environment with limitations, this situation simulated

a real-life situation well enough. The importance of AHA is incontrovertible when considering how bleeding time may change the outcome of a medical emergency. Hence, AHA has great potential among hemostatic agents, and it can be used as a rapid and beneficial tool in the field and on vascular damage models. Moreover, further studies are required to investigate the effects of AHA in animal models of blood-related dysfunctions and to compare its effects with several local hemostatic agents.

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A cohort study on use of the spot urine calcium-creatinine ratio for prediction of antepartum preeclampsia among high-risk pregnant women in Delta State, Nigeria

Lloyd Jagu [1], V. Peter Orugbo [2], Patrick Okonta [1]

[1] Department of Obstetrics and Gynecology, Delta State University, Abraka, Delta State, Nigeria
[2] Department of Chemical Pathology, Delta State University, Abraka, Delta State, Nigeria

ORCID ID of the author(s)
LJ: 0000-0002-2290-5316
VPO: 0000-0001-6391-5732
PO: 0000-0001-6209-7336

Corresponding Author
V. Peter Orugbo
Department of Chemical Pathology, Delta State University, Abraka, Delta State, Nigeria
E-mail: drorugbopeter@gmail.com

Ethics Committee Approval
Ethical approval (Reference number, HREC/PAN/2019/006/0304; dated March 18, 2019) was sought and obtained from the Health Research Ethics Committee of CHW and DELSUTH and formal consent from the other centers.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: Preeclampsia is a multisystemic disorder, which significantly contributes to maternal and fetal morbidity and mortality, especially in developing countries where it accounts for about one-third of maternal mortality cases. Predicting its occurrence will reveal a sizeable population of pregnant women who will undoubtedly benefit from prevention. The ideal screening marker for the disease is still being investigated. The urine calcium-creatinine ratio (CCR) is an inexpensive, simple, and easily assayed biomarker. This study determined the accuracy of the spot urinary calcium-creatinine ratio in predicting the occurrence of preeclampsia.

Methods: This was a prospective cohort study conducted in Delta State, which involved four healthcare facilities in Nigeria. A total of 138 pregnant women between 8 and 18 weeks gestation were recruited. Urine samples were obtained at 18 weeks to assay their CCR, and patients were followed up weekly for blood pressure measurement and dipstick urinalysis until delivery.

Results: The mean spot urine CCR in this study was 0.225 (0.101). It was significantly lower in women who developed preeclampsia compared to normotensive women ($P < 0.001$). Multiple logistics regression analysis showed that the association between urine CCR and occurrence of preeclampsia was statistically significant. At a receiver operating characteristic cutoff of ≤ 0.1065, CCR had a sensitivity of 75%, specificity of 91.3%, positive predictive value (PPV) of 35.3%, and negative predictive value (NPV) of 98.3%. The low PPV of 35.3% can be explained by the low prevalence of preeclampsia (5.78%) in the study population.

Conclusion: In conclusion, the poor PPV of the urine CCR was due to the low prevalence of preeclampsia in the study. However, in considering all women at risk, urine CCR may be a good prognostic marker when the illness prevalence is substantial.

Keywords: Preeclampsia, Urine calcium-creatinine ratio, Preeclampsia, Screening High-risk women, Significant proteinuria

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Introduction

Preeclampsia is a significant cause of maternal morbidity and mortality. It is defined as blood pressure ≥ 140/90 mmHg on two occasions at least 4 h apart, in the presence of significant proteinuria (≥ 300 mg in 24 h) or after 20 weeks of gestation [1–3]. According to the World Health Organization, preeclampsia is the second leading cause of maternal mortality globally with 76,000 maternal deaths estimated annually [4]. Its incidence is seven times higher in developing countries (2.8% of live births) than in developed countries (0.4%) [5, 6]. In Nigeria, the prevalence ranges between 2% to 16.7% [7–9]. While 10–15% of maternal deaths in developing nations are attributed to preeclampsia and its complications, the prevalence is 0–1.3% in industrialized nations [10–12]. The fetuses are not spared the numerous complications. In fact, about 500,000 neonatal deaths reported annually are a result of this disease [4]. It is estimated that 20 other women suffer from severe morbidity or disability from preeclampsia for every maternal death recorded. Near-miss cases are eight times more frequent in women with preeclampsia and 60 times more frequent if eclampsia occurs compared to women without these conditions [13]. These severe complications are multisystemic involving the central nervous, respiratory, and cardiovascular systems [5, 14, 15]. The fetus suffers from morbidities including intra-uterine growth restriction, oligohydramnios, placental abruption with evidence of fetal compromise, stillbirth, and prematurity [14, 16]. Long-term complications occur in both the mother and neonate and can be cardiovascular- or endocrine-related such as chronic hypertension, thromboembolism, and diabetes mellitus [5, 12]. Although its etiology is unknown, several theories have been proposed [16, 17]. One postulate is that distortion occurs during formation of the utero-placental unit in early pregnancy (8–18 weeks), resulting from a failure of trophoblastic invasion [1] and causing impaired placental perfusion with the generation and build-up of oxidative stress. Subsequent events are the development of systemic endothelial dysfunction leading to multisystemic disease [17-19], and possibly an imbalance between pro-angiogenic and anti-angiogenic factors [17]. There has been less reported about the prediction and prevention of preeclampsia than about the diagnosis and management of the disease. Nonetheless, prevention remains a core component in addressing this issue of public health relevance [1].

Biomarker analyses (clinical, biophysical, and biochemical) have been the focus of several research projects. Despite abundant research investigating the predictive accuracy of biomarkers, less has been done to identify the ideal biomarker. For most studies, outcomes appear unrealistic or have low replicability; other studies have poor validity indices or results that are too ambiguous to interpret [5, 6, 20]. Therefore, there is an urgent need for a marker that can predict preeclampsia in asymptomatic women in early pregnancy. In this study, the urine calcium-creatinine ratio (CCR) of pregnant women between 8 and 18 weeks gestation was analyzed in four healthcare centers in Delta State Nigeria.

Austdal et al. [21] showed that urine metabolomic profiles are better predictive markers than serum equivalents. Urine is an excretory product from which several biochemical analytes have been researched, many of which have been linked to disease processes. Normal urinary calcium concentration is 100 to 300 mg/24 h, which increases to 350–620 mg/dL in pregnancy., and normal urinary creatinine concentration is 1500 to 3000 mg/24 h [22]. The urine calcium concentration in women with preeclampsia is lower than that in their normotensive counterpart even when serum calcium levels are not significantly different [23–25]. Urine calcium is measured either from 24 h urinalysis or random spot samples. Urine calcium has a diurnal pattern that peaks at about midday [26]. The 24 h estimation is a more reliable estimate of total calcium; however, it has a number of drawbacks. Early morning spot urine samples correlate well with 24 h collection [27]. Estimation of early morning spot urine sample is time saving, convenient, and less cumbersome than 24 h estimation, which is error prone from contaminants arising mostly at the collection point. Random urine calcium is expressed as the ratio of calcium to creatinine called the CCR or fractional excretion of calcium [28-30]. Creatinine serves as a reference standard due to its relatively constant excretion rate throughout a 24 h period [29, 31-33].

The predictive value of urine CCR in preeclampsia has been shown in some studies; however the biomarker was mostly employed at ≥ 20 weeks gestation where it represented an early diagnostic tool rather than a predictive marker for the pathology [28-36]. Preeclampsia tends to develop between 8 and 18 weeks gestation, triggered by failure of trophoblastic invasion with resultant clinical manifestations occurring mostly after 20 weeks of gestation. Accordingly, certain preventive measures such as low-dose aspirin are recommended in the first trimester for women at high risk of preeclampsia. Therefore, the need to identify early in pregnancy, those likely to develop the disease cannot be overemphasized. Studies evaluating urine CCR as a predictive marker for preeclampsia in the African population were not found during our literature search. Thus, studies are needed to determine if the urine metabolome will be effective as a predictive biomarker for preeclampsia among asymptomatic Negroid women in early pregnancy (between 8 and 18 weeks). The results of this study will not only provide knowledge on the CCR of high-risk women in Nigeria but will also ascertain its relevance as a predictive marker of preeclampsia. Accurate prediction of preeclampsia will allow better counseling and closer monitoring of 'at risk pregnant' women and will facilitate prevention, early detection, and timely intervention, which will minimize the complications associated with the disease.

Therefore, this study investigated the predictive value of urine CCR among high-risk women in early pregnancy in hospitals in Delta State Nigeria.

Materials and methods

Study design

This was a prospective cohort study that determined the indices of validity of the spot urine CCR ratio for the prediction of preeclampsia in high-risk pregnant women. Participants included consecutively recruited women with risk factors for preeclampsia at the antenatal clinic or in the ward. All recruits were followed up for four times weekly with blood pressure measurement and dipstick urinalysis conducted at each antenatal visit until delivery to monitor the development of preeclampsia.

A spot urine sample, which is the first morning urine, was obtained from each recruit at 18 weeks and analyzed for urine CCR.

Study location

This study took place between November 2019 and September 2020 and involved the following four healthcare facilities in close proximity to one another in Delta State: Delta State University Teaching Hospital (DELSUTH), Oghara; Central Hospital, Warri; General Hospital, Oghara; and Central Hospital, Sapele. DELSUTH and Central Hospital, Warri have accreditation for residency training in Obstetrics and Gynecology by the National Postgraduate Medical College of Nigeria. There is a memorandum of understanding between hospitals that are part of the Hospital Management Board and Delta State University Teaching Hospital. They all have similar protocols for the diagnosis and management of preeclampsia. As at the time of this study, the Department of Obstetrics and Gynecology at DELSUTH had 9 consultants and 23 resident doctors at different stages of postgraduate training. The Department of Obstetrics and Gynecology in Central Hospital, Warri has 4 consultants and 10 resident doctors also at different stages of training. Central Hospital, Sapele has two consultants. Together, the institutions have a combined annual delivery rate of 7,500, and residents rotate among the hospitals. They collaborate in the training of medical students of DELSUTH and the training of resident doctors at all levels. DELSUTH and Central Hospital, Warri are located about 40 km apart, along the federal east-west highway and provide specialist Obstetrics and Gynecological care to patients. They are the major referral centers to Delta State as well as neighboring towns/villages in Edo and Bayelsa States. Patients are usually referred from private medical centers, government-owned healthcare centers, and general hospitals as well as from other departments in these hospitals.

Recruitment of study participants

The study population consisted of pregnant women attending antenatal clinics in the study centers who had risk factors for preeclampsia. The sample size was calculated using the formula for the cohort Study [37], using a previous study by Rashmi and Indu [35], which share similar characteristics as the study references. With an attrition rate of 20%, an additional 12 women were recruited per group, yielding a total of 72 women per study group. Thus, a total of 144 participants were recruited for the study. Research assistants assisted resident doctors and nurses in recruiting women from antenatal clinic and wards and following up with them until delivery in all four centers. Study personnel also included a chemical pathologist at DELSUTH and Central Hospital, Warri. Training sessions were held to demonstrate how participant recruitment, follow-up, sample collection, handling, and processing were done.

Selection of cases

Consecutive sampling technique was employed for the selection of participants who met the inclusion criteria. Following counseling, those who provided written informed consent were enrolled.

Inclusion criteria

The inclusion criteria were women between 8 and 18 weeks gestation who had at least one preeclampsia risk factor including maternal age ≥ 40 years, obesity (pre-pregnancy or first trimester body mass index [BMI] > 35 kg/m²), family history of preeclampsia (mother or sister), interpregnancy interval of more than 10 years, multiple gestation, and admission systolic blood pressure (SBP) > 130 mmHg but < 140 mmHg or diastolic blood pressure (DBP) > 80 mmHg but < 90 mmHg; or those who had two or more of risk factors such as primigravidity, family history of early-onset cardiovascular disease, interpregnancy interval of less than 2 years, use of assisted reproductive technologies, and a new partner.

Exclusion criteria

Women were excluded from the study if they were of gestational age (GA) > 18 weeks; had a previous history of early onset preeclampsia (< 34 weeks); were hypertensive; had diabetes mellitus; had a history of renal disease, vitamin D deficiency, autoimmune disease, or coagulation disorders; were on calcium supplementation or medications other than iron and folic acid supplementation that altered or interfered with serum calcium or its metabolism or excretion (e.g., thiazide diuretics, lithium, anti-epileptic drugs); were on drugs that affect the bioavailability of creatinine such as antibiotics (e.g., cephalosporins and aminoglycosides, cisplatin, phenytoin, deriphyllin, levofloxacin) that affect alkaline picrate methods; or refused to provide informed consent.

Follow-up study procedure

A detailed medical and obstetric history was obtained from each participant. Their weight (in kilograms) and height (in meters) were measured with the adult analogue weight-measuring scale fitted with height-measuring stadiometers (ZT-160®; Techmel, Los Angeles, CA, USA). The BMI was calculated. Blood pressure was measured with mercury sphygmomanometer using the appropriate sized cuff. General and systemic examinations were conducted. Participants were followed up four times weekly until delivery. Blood pressure measurements and urinalysis were done at each visit.

At 18 weeks gestation, participants were given universal bottles to take home. They were instructed to void the first morning urine into the bottles after normal washing of the genitals; the midstream urine specimen was collected at least 2–3 s from the start of urination. The bottle cover was tightly sealed and returned to the hospital the same day. Research assistants received samples at the clinics and wards and sent them to the laboratory for analysis. Samples retrieved at the Central Hospital, Warri were analyzed there, whereas those retrieved from other centers were analyzed at the DELSUTH laboratory.

Quality assurance measures were taken at all times through the pre-analytic, analytic, and post-analytic phases [38]. In the pre-analytic phase, participants were given all necessary instructions from recruitment to sample collection. They were instructed to avoid medications that could alter serum calcium levels, its metabolism and excretion such as calcium supplements and diuretics. The first morning urine was collected. The samples were returned to the laboratory same day as collection. Participants and research assistants were instructed to avoid exposing the sample to extreme weather conditions at all times. Then one milliliter of 6 M hydrogen chloride was added and the mixture was thoroughly stirred to dissolve any sediment and keep the calcium in solution. Samples were analyzed upon return. Those that could not be analyzed on that day were stored

at 4°C. They were analyzed the following day. Urine calcium is stable in solution for up to 3 days at temperatures ≤ 4°C and for at least 3 or more weeks at ≤ -20°C. Samples were thoroughly stirred before they were analyzed. During analysis, laboratory standard operating procedures and/or quality assurance plans were adhered to. Reagent kits were stored in their ideal environment at all times. Universal safety measures and laboratory guidelines were followed.

Preeclampsia was diagnosed when blood pressure was ≥140/90 mm Hg on two occasions at least 4 h apart in the presence of a dipstick test showing at least 1+ protein in a random clean catch urine sample [20, 28, 32]. Participants who had only one of either finding of hypertension or proteinuria were excluded from the analysis, whereas those who developed preeclampsia were managed according to departmental protocol. Those diagnosed with mild preeclampsia were conservatively managed on oral antihypertensives for blood pressure control and seen more frequently at antenatal visits for fetomaternal monitoring. This was terminated when the disease progressed despite conservative management. Those with severe preeclampsia were admitted for stabilization (blood pressure control, seizure prophylaxis, judicious intravenous fluid, management of clinical and laboratory findings) and then delivery through the most expeditious route.

The midstream urine dipstick for protein assessment was done using the Multistix 10SG urinalysis strip. The following were the grades of proteinuria and the corresponding protein concentration provided by the manufacturers: 0, trace (10–20 mg/dL), 1+ (30 mg/dL), 2+ (100 mg/dL), 3+ (300 mg/dL), and 4+ (1000 mg/dL). A 1+ of midstream clean catch urine protein by dipstick was considered significant proteinuria [28].

Laboratory analysis

Samples collected from participants were sent to the laboratory where analyses were carried out under the supervision of the chemical pathologists.

Spot urine calcium assay

Urine calcium was analyzed using the colorimetric method in which under alkaline conditions, the metal-complexing dye, orthocresolphthalein, formed a purple-red chromophore with calcium. The color intensity was directly proportional to the total calcium concentration. Total urinary calcium was quantified using spectrophotometry to measure the color intensity of the reaction at 340 nm [39].

Spot urine creatinine assay

The principle of analysis of creatinine was based on Jaffe's alkaline picrate reaction in which picric acid reacts with creatinine in alkaline medium to produce a red complex, the absorbance of which is proportional to the creatinine concentration. Urine creatinine was quantified using spectrophotometry to measure the color intensity from the reaction at 520 nm [41].

Spot urine CCR calculation

CCR was calculated as: urine calcium (mg/dL)/urinary creatinine (mg/dL).

Statistical analysis

Participants' sociodemographic data, blood pressure, dipstick urine protein, and urine CCR results were collated using specially designed data collection proforma. At the end of the study, data were entered into the computer and analyzed using SPSS statistical software (version 22; IBM Inc., Chicago, IL, USA). Descriptive statistics were used to calculate mean, standard deviation, and minimum and maximum values. A multiple linear regression model was used to analyze effects of age, BMI, and parity on spot urine CCR. The receiver operating characteristic curve for urine CCR was generated from the data entered into the SPSS statistical software (version 22; IBM Inc., Chicago, IL, USA), and the optimal cutoff was determined. This was used to estimate the indices of validity of urine CCR in this study. This was possible by comparing with a cutoff ≤ 0.04 [20, 27, 33], which is used in many studies.

Ethical approval

Ethical approval (Reference No. HREC/PAN/2019/006/0304; dated March 18, 2019) was obtained from the Health Research Ethics Committee of Community Health Workers and DELSUTH, and formal consent was obtained from the other centers. Informed consent was obtained from study participants after counseling. Patient participation in the study was voluntary and those who declined to participate in the study were not penalized and received the care that was due to them. There was no added cost to the participants for their participation in the study.

Results

A total of 183 women were recruited from four healthcare centers. Their data were collected through questionnaires, and they were given clean plastic bottles to take home and return at 18 weeks with their first morning urine. They were all followed up through phone calls. Seventeen of the women did not return with their samples and were reminded on the phone to do so. Some said they were traveling; others could not be reached by phone. An additional three declined to continue with the study due to their spouse's refusal. The remaining participants were followed up until delivery. Forty-seven women delivered outside their primary facility; seventeen of whom could not be contacted due to their phone being unreachable, turned off, or the wrong phone number. Another eight women did not provide the needed data concerning their delivery such as their blood pressure or protein in urine. Complete data were obtained from 138 women; the others were excluded. Among the 138 women followed up with complete data, 127 (92%) remained normotensive, 3 (2.17%) had gestational hypertension, and 8 (5.78%) developed preeclampsia. The three women with gestational hypertension were excluded from the analysis. Table 1 summarizes the anthropometric and clinical characteristics of the women. It showed a statistically significant difference in maternal age, GA at delivery, and SBP and DBP at delivery. The GA at the time of recruitment (P = 0.393), parity (P = 0.198), BMI (P = 0.558), SBP (P = 0.119), and DBP (P = 0.173) at the time of entry into the study did not significantly differ. The significant majority of the women (97%) were between 18 and 39 years old, with only 3% aged ≥ 40 years old. The majority of women were primigravida (44.2%) followed by primipara (37.7%) and multipara (25%).

Table 1: Anthropometric and clinical characteristics (means)

	Normotensive (n = 127)	Preeclamptic (n = 8)	*P*-value
Age	26.23 (4.79)	33.25 (7.29)	0.030*
Parity	1.00 (1.00)	1.00 (2.00)	0.198
GA (at recruitment)	14.19 (2.33)	14.75 (1.67)	0.393
BMI (at recruitment)	27.60 (4.26)	28.99 (6.23)	0.558
SBP (mm Hg upon joining the study)	114.20 (10.61)	119.88 (8.84)	0.119
DBP (mm Hg upon joining the study)	66.06 (7.65)	70.25 (7.67)	0.173
SBP (mm Hg at delivery)	121.22 (9.89)	163.13 (8.89)	0.000*
DBP (mm Hg at delivery)	71.63 (7.76)	100.38 (7.21)	0.000*
GA (at delivery)	37.65 (2.20)	34.50 (2.07)	0.003*

*statistically significant

The mean urinary calcium, urinary creatinine, and urinary CCR of the cohort (n = 135) were 21.74 (14.36) mg/dL, 103.3 3(48.89) mg/dL, and 0.225 (0.101) mg/dL, respectively. Table 2 illustrates the urinary levels of the analytes in both arms of the study. The urinary levels of calcium and CCR were significantly lower in the preeclamptic group than the normotensive group. On the other hand, the normotensive group had higher urine creatinine levels, although not statistically significant.

Table 2: Biochemical characteristics (mean)

	Normotensive (n = 127)	Preeclamptic (n = 8)	*P*-value
Urinary calcium (mg/dL)	22.37 (14.56)	11.73 (3.60)	< 0.001*
Urinary creatinine (mg/dL)	99.63 (40.42)	166.34 (107.36)	0.122
Urinary CCR	0.233 (0.099)	0.100 (0.065)	< 0.001*

*statistically significant

The ROC curve plotted for the CCR produced a cutoff value of 0.1065 (Youden's index) with an area under the curve of 0.885 (P < 0.001). This produced a sensitivity of 0.75 and specificity of 0.08 (Figure 1).

Figure 1: ROC curve of urine CCR at 18 weeks

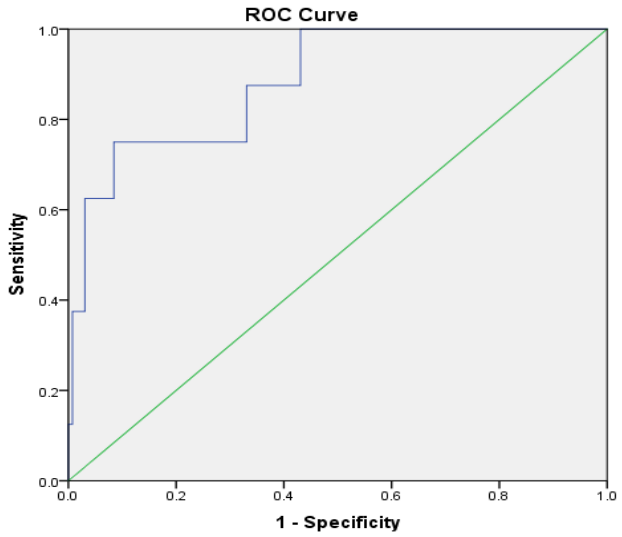

Table 3 depicts the logistic regression of the association between preeclampsia (categorical dependent variable) and a set of independent or explanatory variables (maternal age, parity, BMI, and urine CCR). For the outcome (preeclampsia), there was a statistically significant difference between CCR < 0.1065 and CCR > 0.1065 (P = 0.001), adjusted for parity, BMI, and maternal age. It can be inferred that a unit change in the value of CCR caused an inverse change in preeclampsia by log (0.018), and all other factors and covariates were constant. It also showed that there was a statistically significant difference between maternal age ≥ 40 years and less than, in predicting preeclampsia, all other factors, that is, parity, BMI and urine CCR, being adjusted for.

Table 3: Multiple logistics regression analysis

Outcome; Preeclampsia	Regression Coefficient (B)	Chi-Square	*P*-value	Odds Ratio (95% Confidence Interval)
Intercept	6.184	0	0.042	0.8 (0.098–6.739)
Nulliparity	-0.21	0.038	0.846	0.05 (0.000–0.195)
Age > 40 years	-1.941	1.394	0.005*	0.144 (0.06–3.20)
CCR < 0.1065	-3.933	15.491	0.001*	0.018 (0.002–0.207)
BMI	0.073	0.385	0.537	1.076 (0.853–1.357)

*statistically significant

Table 4 shows the distribution of the outcome with CCR ≤ 0.1065 being a positive test and CCR > 0.1065, a negative test. Of the 135 women administered the test, 17 tested positive (CCR ≤ 0.1065), 6 (4.34%) of whom had preeclampsia (true positive), and 11 (8.14%) who did not (false positive). Of the remaining 118 (85.5%) with CCR > 0.107 (test negative), 2 (1.45%) had the disease (false negative) and 116 (84.1%) did not (true negative).

Table 4: Distribution of patients according to urinary CCR = 0.1065

	Preeclamptic	Normotensive	Total
CCR ≤ 0.1065	6	11	17
CCR > 0.1065	2	116	118
Total	8	127	135

R = 0.1065; X^2 = 31.09; P < 0.001

Table 5 analyzed the distribution of test outcome, taking the common CCR cutoff ≤ 0.04 as positive test. As shown above, two women had a positive test, one of whom had preeclampsia and the other was normotensive. A CCR > 0.04 indicated a negative test. In all, 133 women had a negative test result, 7 of whom had the disease and 126 of whom were normotensive.

Table 5: Distribution of patients according to urinary CCR = 0.04

	Preeclamptic	Normotensive	Total
CCR ≤ 0.04	1	1	2
CCR > 0.04	2	126	133
Total	8	128	135

X^2=7.274, P = 0.026

Measures of validity of CCR for predicting preeclampsia

Table 6 compares the measures of validity between the tests CCR ≤ 0.1065 and CCR ≤ 0.04. At CCR ≤ 0.1065, urine CCR is a more sensitive test. It is by far a better diagnostic test among those who have the disease. On the other hand, CCR > 0.1065 and CCR > 0.04 are equally as good in screening out those not likely to have preeclampsia.

Table 6: Measures of validity of CCR for predicting preeclampsia

	Sensitivity	Specificity	PPV	NPV
CCR ≤ 0.1065	75.0	91.3	35.3	98.3
CCR > 0.04	12.5	99.2	50.0	90.0

Discussion

This was a prospective cohort study that investigated spot urine CCR as a tool for predicting the occurrence of preeclampsia among gravid women in south southern Nigeria. The sensitivity, specificity positive predictive value, and negative predictive values were the measures assessed to determine the validity of CCR as a predictive modality.

In this study, preeclampsia had a prevalence rate of 5.78% among women at risk who were recruited. These women had significantly lower urine calcium and CCR assayed at 18 weeks gestation compared to their normotensive counterparts. Few studies have explored this biomarker in early gestation among those at risk. Additionally, they are rare in the Negroid population. Mandira et al. [26] investigated the predictive validity of urine CCR of serial assays from 16 weeks using 24 h urinary samples. In their findings, urine calcium and CCR were

lower significantly among women who developed preeclampsia compared to their normotensive counterpart at the various times of urine calcium and creatinine assay from 16 weeks. Urine CCR progressively declined with advancing GA to 0.26, 0.21, 0.14, and 0.12 at 28, 32, 36, and 40 weeks, respectively. Most studies on the predictive validity of this biomarker were conducted in women at or beyond 20 weeks gestation, when failure in utero-placental trophoblastic invasion had already occurred and the pathology was already activated in those who will develop the disease. The findings of reduced urine CCR among women, who developed preeclampsia compared to their normotensive counterparts, have nonetheless been consistent [22, 27, 33-35]. The changes are thought to be due to alterations in calcium homeostasis in its microenvironment among those who have developed preeclampsia [40]. Mechanisms such as decreased distal tubular reabsorption, decreased glomerular filtration rates, and decreased intestinal calcium absorption have been postulated to explain this phenomena [41, 42].

In this study, the mean GA of women who developed preeclampsia was 14.19 (2.33) weeks at the time of recruitment and 14.75 (1.67) weeks for those who remained normotensive. However, as was the methodology of the study, urine CCR was assayed at 18 weeks gestation in all participants. This was to avoid confounding the value of urine CCR attributed to differences in GAs in women at recruitment. We achieved the desired sample size; however, difficulty was envisaged due to the late booking nature of women in the study area. The drawback was the limited benefit in starting aspirin prophylaxis at 18 weeks. In most studies investigating CCR as a predictive marker for preeclampsia, the spot urine biomarker assay was studied over a wide range GAs. While a ready cohort of women would be recruited with ease, the drawback is that the relevance of the predictive biomarker at a given GA is blurred.

The aim of having a predictive marker is to detect early disease as evidenced by altered urine CCR levels in large numbers of apparently healthy women who had risk factors as a basis for commencing prophylaxis. Urine CCR assayed at 18 weeks had a sensitivity of 75%. This indicates that CCR ≤ 0.1065 is good at establishing the presence of preeclampsia among those who developed the disease excluding those who remained normotensive despite being positive. However, the positive predictive value (PPV) of the test was low (35.3%). This seemingly indicates that the probability of a woman with a positive test (CCR ≤ 0.1065) developing preeclampsia is low, after excluding those with preeclampsia who tested negative (CCR > 0.1065). On the other hand, the screening test (CCR > 0.1065) had a specificity of 99.2% and NPV of 90%. This indicated that CCR > 0.1065, which represented a negative test at 18 weeks, was a good marker in predicting that women will not develop preeclampsia at delivery excluding normotensive women whose CCR ≤ 0.1065 and represented a probability of 9 of 10. Prevalence however impacts the PPV and NPV of a test such that as the prevalence decreases, the PPV decreases while the NPV increases [43]. The poor PPV in this study can thus be attributed to the low preeclampsia prevalence rate of 5.78% in this study. Again, the low prevalence in this study is likely the result of the exclusion of women with high-risk factors such as a previous history of early onset preeclampsia, histories of hypertension, diabetes, renal and autoimmune diseases. Thus, it is likely that if these cohorts of women were factored in, the PPV value of the test would be high.

When a CCR ≤ 0.04 was applied as a predictive marker, its sensitivity, specificity, PPV, and NPV were 12.5%, 99.2%, 50%, and 90% respectively. This cutoff has been widely used in studies assessing the predictive accuracy of CCR. A CCR ≤ 0.04 was a poor predictor of the disease among those who had preeclampsia (screened population) but among those with positive results, it had a performance of 50% in identifying those with preeclampsia. Again, the relatively higher PPV at CCR ≤ 0.04 is attributed to the low prevalence rate of disease in this study. However, it performed well in identifying those without preeclampsia who had a negative test as did a CCR ≤ 0.1065. The poor sensitivity of CCR ≤ 0.04 compared to CCR ≤ 0.1065 emphasize the fact that urine CCR cutoff is an entity defined by the ethnic and sociodemographic characteristic of populations and is thus is not generally applicable to other populations with different characteristics. The cutoff of urine CCR = 0.04 ,which gave high diagnostic accuracies in studies by David [27], Sheela [33] and Rashmi [35], were due to similarities in the sociodemographic features of the study populations in those communities in India.

The accuracy measures of urine CCR at 16 weeks using Youden's index with cutoff point > 220 mg in the study by Mandira et al. [26] were sensitivity, specificity, PPV, and NPV of 73%, 97%, 96%, and 78%, respectively. In their analyses, orthocresolphthale and Jaffe's alkaline picrate reactions were used for calcium and creatinine estimation as was done in this study. Although assaying the calcium and creatinine from 24 h urinary samples is the gold standard, the more suitable reason for the high values in validity measures in their study, especially the PPV and NPV, was the high preeclampsia prevalence of 16.6%.

This study was carried out in four centers in Delta State with the analysis of the urine biomarkers done in two laboratories, unlike other studies that involved just one facility where the bioassays were likely done. Although standards and protocols were similar and quality control measures were followed as much as possible, the subtle deficiencies and errors attributable to laboratory and personnel in different laboratories is possibly a limitation as this may affect the measurements and thus predictive validity measures of the assayed biomarker. Again, in the centers where the participants had delivered outside the four antenatal care facilities, the outcome variables assessed such as blood pressure and dipstick proteinuria could have been error prone, as standard techniques that were taught to the research assistants in the four centers would not have been followed. These may be a source of bias in the results. Others factors that would have produced bias are faulty instruments and use of instruments without correct calibrations, among others.

Although the urine CCR had a seemingly low PPV in this study, is still likely to be a good predictive marker of preeclampsia when utilized in populations where all at risk women are screened.

Conclusion

At 18 weeks, the urine CCR was significantly lower in those who developed preeclampsia compared to those who remained normotensive. The low PPV of urine CCR is

attributable to the low prevalence of preeclampsia in the study. Urine CCR is still capable of being a good predictive marker when all women at risk are factored in, at which time the disease prevalence is high.

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Comparison of thiol disulfide values in the cord blood of patients undergoing cesarean section under spinal or general anesthesia

Çağanay Soysal [1], Yalçın Soysal [2], Cihan Döğer [3], Elif Yılmaz [1], Oğuz Özdemir [1], Tuncay Küçüközkan [1], Özcan Erel [4]

[1] Department of Obstetrics and Gynecology Dr. Sami Ulus Women's and Children's Health Teaching and Research Hospital, Ankara, Turkey
[2] Turkish Medicines and Medical Devices Agency, Ministry of Health, Ankara, Turkey
[3] Department of Anesthesiology and Reanimation, Ankara City Education and Research Hospital, Ankara, Turkey
[4] Department of Medical Biochemistry, Ankara City Education and Research Hospital, Ankara, Turkey

ORCID ID of the author(s)

ÇS: 0000-0002-4381-6099
YS: 0000-0002-1160-2950
CD: 0000-0003-3071-5181
EY: 0000-0001-5107-6492
OÖ: 0000-0001-9328-8047
TK: 0000-0003-4280-3883
ÖE: 0000-0002-2483-1939

Corresponding Author
Elif Yılmaz
Obstetrician and Gynecologist, Dr. Sami Ulus Women's and Children's Health Teaching and Research Hospital, Department of Obstetrics and Gynecology, Alparslan Turkes Street, Bestepe, Ankara, Turkey
E-mail: elifakkasyilmaz@gmail.com

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Ethics Committee approval of the study was obtained from Yıldırım Beyazıt University Faculty of Medicine Clinical Research Ethics Committee on 26/10/2016 and it was approved with the number 26379996/252.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: Oxidative stress is known to increase in patients receiving anesthesia before undergoing surgery. Since newborns are more sensitive to oxygen-free radicals, the effects and characteristics of anesthesia methods that are used for pregnant women require analysis. This study aimed to evaluate the effects of spinal and general anesthesia on oxidative stress by investigating thiol disulfide and ischemia modified albumin (IMA) concentrations in the cord blood of patients undergoing cesarean section (C-section) via spinal or general anesthesia.

Methods: This cross-sectional prospective study included 60 patients who were indicated for elective cesarean section. Patients with chronic disease, pregnancy complications and/or required emergency cesareans were not included. Group 1 (n = 30) underwent general anesthesia, and Group 2 (n = 30) underwent spinal anesthesia during their C-sections. Thiol–disulfide levels were evaluated concurrently in all blood samples taken from the umbilical artery remaining on the placental side.

Results: The mean age (SD) of the mothers was 30.6 (4.4) years and the mean gestational age (SD) was 39.0 (0.9) weeks. Gestational age, birth weight, and first and fifth min Apgar scores of the two groups were similar. The mean (SD) native thiol (362.4 [63.8]; 323.2 [45.8]), total thiol (409.6 [70.2]; 363.5 [46.1]), and disulfide values (23.6 (5.4); 20.2 (4.3)) were significantly higher in group 1 than group 2, while the median (interquartile range [IQR]) values of IMA (0.89 (0.85-max 0.92); 0.85 (min 0.82-max 0.879) were significantly higher in group 2 than group 1 ($P < 0.05$).

Conclusions: As general anesthesia may cause a higher degree of oxidative stress, selecting the appropriate anesthetic technique may be especially important for risky pregnancies in which increased oxidative stress in the mother and baby may be critical for the outcome.

Keywords: Thiol disulfide, Ischemia modified albumin, Cesarean section, Anesthesia

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Introduction

Free oxygen radicals appear during normal metabolism. The levels of these substances are balanced by the action of various antioxidant systems present in the body. Disruption of this balance in favor of oxygen free radicals, which is called "oxidative stress" can causes cellular damage [1]. Thiols are among the molecules that are used for prevention of oxidative stress [2]. After oxidation, thiols form disulfide bonds called disulfide bridges. The formation of these bonds is reversible and when broken, provide thiols. The result is a dynamic thiol–disulfide homeostasis, which plays an important role in antioxidant protection against oxidative stress [3]. Since free radicals have an extremely short half-life, indirect markers are generally used for the determination of the levels of reactive oxygen species (ROS) and oxidative stress. Ischemia-modified albumin (IMA) has been suggested as a marker of nonspecific ischemia. Although recent studies suggest that various other mechanisms are involved in the formation of IMA, it is accepted that ischemic damage causes an alteration in the N-terminus of albumin, leading to increased IMA levels [4]. The levels have been shown to correlate with the degree of oxidative stress [5].

Oxidative stress is known to increase in patients receiving anesthesia before undergoing surgery [6]. Since newborns are more sensitive to oxygen free radicals, the effects and characteristics of anesthesia methods that are used with pregnant women require analysis. Previous studies have evaluated the relationship between thiol disulfide homeostasis and oxidative stress in cord blood [7]. Although no study on the effect of the type of anesthesia used at birth on the levels of oxidative stress in cord blood, it has been reported that general anesthesia has a considerably stronger negative effect on thiol disulfide homeostasis than does spinal anesthesia [8].

Therefore, the quantification of markers of oxidative stress in cord blood may be important in determining the extent of oxidative stress suffered by newborns during cesarean section surgery. It was hypothesized that umbilical cord thioldisulfide concentrations may be important in determining neonatal well-being and in ruling out suspected perinatal asphyxia. Tis study aimed to evaluate the effects of spinal and general anesthesia on oxidative stress by investigating thiol disulfide and IMA concentrations in the cord blood of patients undergoing cesarean section via spinal or general anesthesia.

Materials and methods

This cross-sectional prospective study was conducted in the Obstetrics and Gynecology Department of a hospital that is one of the primary maternity hospitals in Ankara, Turkey, between January 2019 and January 2020. The study included 60 patients between 18 and 40 years with an American Society of Anesthesiologists (ASA) group of I-II. Using the G-Power program, in the case in which the effect size was taken as moderate and bidirectional and $\alpha = 0.05$, power $(1-\beta) = 0.80$, the smallest sample size for each group was calculated as a minimum of 30 patients. Patients with diabetes mellitus, hypertension, chronic obstructive pulmonary disease, allergies to local anesthesia, bleeding-clotting time abnormality, liver disease, renal failure (creatinine levels ≥ 2.5 mg), preeclampsia, eclampsia, those who had children with metabolic disorders, patients who underwent emergency surgery, and/or those who refused to participate were excluded from the study. To prevent oxidative stress, emergency cesarean indications and additional systemic diseases were excluded.

The Ethics Committee approved the study. All individuals were informed about the study, and informed written consent was obtained.

All cesarean section procedures were performed by experienced obstetricians. Premedication was not used in any cases. All patients were allowed to lie on their left side while being transported to the operating room until the end of the operation. Electrocardiography, noninvasive mean arterial pressure, and peripheral oxygen saturation monitoring were performed for all patients after admission. The study patients were informed about spinal and general anesthesia and underwent cesarean section according to their preference. Because all patients had planned cesarean section, they were summoned to the hospital on the morning of surgery and hospitalized on the same day. The patients were followed in the hospital for 48 h post-operatively, and all patients were discharged 48 h later. Patients did not develop infections or complications.

Anesthesia protocols

Group 1 (n = 30) received spinal anesthesia, and Group 2 (n = 30) received general anesthesia. Spinal anesthesia was administered while the patient was in the left lateral position after appropriate antiseptic practice. Local anesthesia was performed with 1 cc 2% lidocaine in the L3-4 or L4-5 range. Spinal needle (22 G Quincke) advancement from the same level was continued until free cerebral spinal fluid (CSF) flow was observed. Spinal anesthesia was performed with previously prepared 2–2.2 ml 0.5% hypertonic bupivacaine (Marcain Heavy®). The sensory block level was evaluated with a pin-prick test, and motor block level was evaluated via the Bromage scale. When the sensory block reached a sufficient level (T10), the operation was started. From the beginning of the operation until the end, 100% oxygen support (3 L/min) was provided with a mask. Group 1 patients received 2 mg/kg propofol and 0.6 mg/kg rocuronium for anesthesia induction. After muscle relaxation, endotracheal intubation was performed by cricoid compression. Controlled ventilation (with Datex-Ohmeda S/5 Avance device) was achieved by adjusting tidal volume to 8 to 10 ml/kg and respiratory frequency to 10 to 12 /min. Anesthesia was maintained with 50% O_2 + 50% N_2O and included 1–1.5% sevoflurane.

Measurements

In both groups, maternal hemodynamic parameters (heart rate, mean arterial blood pressure) were recorded every 5 min for 45 min after anesthesia induction. In all cases, 5 ml blood samples were taken from the umbilical artery remaining on the placental side of the cord immediately after the cord was clamped and cut after delivery, and serum / plasma samples were separated and stored at −80 ºC. Thiol–disulfide levels were evaluated concurrently by spectrophotometric methods in all blood samples using a new technique developed by Erel [9]. Routine caesarean section and anesthesia procedures were performed during the operation; however, blood samples were also taken during the procedure. Blood samples were collected from the placental cord, which was discarded as medical waste after birth. Evaluation of

the newborn was performed by a pediatric health and disease specialist and the Appearance/Pulse/Grimace/Activity/Respiration (APGAR) scores were recorded at the first and fifth minutes post-birth.

Statistical analysis

In the presentation of descriptive statistics, central and prevalence measures, such as number, percentage, median, mean, and standard deviation were used, and Pearson's chi-squared test was used to determine the difference between categorical variables. The distribution of continuous variables was evaluated using the Shapiro–Wilk test and histogram. An independent t-test was used for comparison of independent continuous variables with a normal distribution, and the Mann–Whitney U test was used for variables not having a normal distribution. Pearson's correlation analysis was used to determine the relationship between continuous variables. Data were analyzed using SPSS software (version 24, IBM, Chicago, IL, USA). *P*-values < 0.05 were considered statistically significant.

Results

In this study, 60 pregnant women (30 general anesthesia and 30 spinal anesthesia) who delivered their baby via elective cesarean section were evaluated. The mean age (SD) of the mothers was 30.6 (4.4) years, and the mean gestational age (SD) was 39.0 (0.9) weeks. The mean neonatal birth weight (SD) was 3230 (468.3) grams. No significant differences between characteristics of the mothers or newborns who comprised each group ($P > 0.05$, Table 1) were noted. APGAR scores at 1 and 5 min were similar between the two groups (Table 1).

Table 1: Maternal and neonatal characteristics

	General anesthesia (Group 1) (n = 30)	Spinal anesthesia (Group 2) (n = 30)	*P*-value
Maternal age (Years, Mean (SD)	30.7 (4.5)	30.5 (4.3)	0.815
Parity (Median [IQR])	1.0 (1.0-2.0)	1.0 (1.0-2.0)	0.677
Gender N (%)			
Female	19 (63.3)	17 (56.7)	0.598
Male	11 (36.7)	13 (43.3)	
Gestational age (Weeks, Median [IQR])	39.1 (38.7–39.6)	38.9 (38.6–39.3)	0.306
Birth weight (Grams, Mean (SD))	3188.2 (504.8)	3272.2 (433.3)	0.492
1 min Apgar score (Median [IQR])	8.0 (8.0–9.0)	9.0 (8.0–9.0)	0.354
5 min Apgar score (Median [IQR])	9.0 (9.0–10.0)	10.0 (9.0–10.0)	0.235

SD: standard deviation; IQR: interquartile range

When cesarean indications of the patients included in the study were evaluated, among those who underwent spinal anesthesia, the reason for non-urgent planned cesarean section was previous cesarean section for 28 patients and breech presentation in two patients. In the general anesthesia group, 29 patients underwent non-emergency planned cesarean section due to previous cesarean section, and one patient due to breech presentation. Among the patients who received general anesthesia, 24 (80%) had at least one living child, three (10.0%) had one miscarriage, and 24 (80%) had delivered by cesarean section. In the group receiving spinal anesthesia, 23 (76.7%) had at least one living child, 7(23.3%) had at least one miscarriage, and 22 (73.3%) had undergone a previous cesarean section.

Thiol–disulfide homeostasis values from cord blood are shown in Table 2. Albumin, disulfide/native thiol ratio, disulfide/total thiol ratio, and native thiol/total thiol ratio values were not statistically different between the two groups ($P > 0.05$). The mean native thiol value (SD) of the spinal anesthesia group was significantly higher than that of the general anesthesia group (362.4 (63.8); 323.2 (45.8); $P = 0.009$). Similarly, mean total thiol (SD) (409 (70.2); 363.5 (46.1); $P = 0.004$) and mean disulfide values (SD) (23.6 (5.4); 20.2 (4.3); $P = 0.008$) of the spinal anesthesia group were significantly higher than the corresponding values of the general anesthesia group. The median (IQR) values of IMA in the general anesthesia group were significantly higher than for those receiving spinal anesthesia (0.89 [0.85–0.92] versus 0.85 [0.82–0.87]; $P = 0.046$, Table 2). Finally, it was also found that disulfide and native thiol values ($r = 0.27$; $P = 0.036$), and disulfide and total thiol values ($r = 0.45$; $P < 0.001$) were positively correlated.

Table 2: Values of thiol–disulfide homeostasis in cord blood

	General anesthesia (Group 1) (n = 30)	Spinal anesthesia (Group 2) (n = 30)	*P*-value
Native thiol (μmol/Lt, Mean [SD])	323.2 (45.8)	362.4 (63.8)	0.009
Total thiol (μmol/Lt, Mean [SD])	363.5 (46.1)	409.6 (70.2)	0.004
Disulfide (μmol/Lt, Mean (SD))	20.2 (4.3)	23.6 (5.4)	0.008
Albumin (g/dL, Median [IQR])	4.02 (3.78–4.21)	4.23 (3.97–4.30)	0.084
Ischemia modified albumin (ABSU, Median [IQR])	0.89 (0.85–0.92)	0.85 (0.82–0.87]	0.046
Disulfide/ native thiol ratio (%, Mean [SD])	6.38 (1.69)	6.57 (1.41)	0.624
Disulfide/ total thiol ratio (%, Mean [SD])	5.62 (1.30)	5.78 (1.09)	0.594
Native thiol/ total thiol ratio (%, Mean [SD])	88.8 (2.6)	88.4 (2.9)	0.594

SD: standard deviation, IQR: interquartile range

Discussion

Thiols are involved in the neutralization of ROS that are formed normally (or abnormally) in the body. Therefore, a decrease in serum thiol levels in the event of oxidative stress is often observed [10, 11]. Thiol levels have been shown to decrease in diseases that demonstrate increased inflammatory activity, including many disease types of the renal, cardiovascular, and neurological systems, in addition to those that progress with elevated oxidative stress, such as diabetes mellitus, atherosclerosis, Alzheimer's disease and cirrhosis [10]. In our study, it was found that both native and total thiol levels of patients receiving general anesthesia were significantly lower than those receiving spinal anesthesia. The oxidative stress enhancing effect of various drugs used in general anesthesia may have led to this result, and therefore, the decrease of thiols in the general anesthesia group could be associated with this property of the drugs. Furthermore, considering that the oxidative balance of the body is not only associated with thiol concentration, IMA levels were also measured as an indirect marker of oxidation in cord blood. The increased levels of IMA in those receiving general anesthesia supported initial findings with thiol values. Overall, our results suggest that general anesthesia may lead to an increase in oxidative stress to a higher degree compared to spinal anesthesia.

In a recent and similarly planned study, the authors investigated the effect of anesthesia technique during cesarean section on thiol–disulfide homeostasis in maternal and cord blood. The authors showed that native thiols, total thiols, disulfide levels, disulfide / total thiol and native thiol/disulfide ratios were higher in the blood of mothers who delivered with general anesthesia compared to spinal anesthesia. In the cord blood of the patients under general anesthesia, native thiol and total thiol levels were significantly lower than those receiving spinal anesthesia, and

other measurements were similar between the groups [8]. However, in contrast, Karabayırlı et al. [12] evaluated the oxidative stress index in the cord blood of women who underwent cesarean section using the same groups and found that oxidative stress was lower in recipients of general anesthesia. In contrast to our results, these authors suggested that general anesthesia should be preferred in cases in which lower fetal oxidative stress is desired. In the current study, cord blood native thiol, total thiol, and disulfide levels were found to be significantly higher in the spinal anesthesia group.

However, it appears to important to note that since thiols values were not measured in the cord blood before anesthesia, direct conclusions in regard to the nature of the differences found between the groups cannot be drawn. It is possible that the native thiol, total thiol, and disulfide values increased in the spinal anesthesia group or quite conversely, they may have decreased in the general anesthesia group. Despite this limitation, it is also apparent that it would be unreasonable to assume that patients undergoing any type of surgery with anesthesia would benefit from the procedure in terms of oxidative stress and/or antioxidant levels; thus, the differences found in our study seem to show that general anesthesia has significantly more adverse effects on the oxidative balance of women undergoing cesarean section.

In our study, disulfide values were significantly higher in the spinal anesthesia group compared to the general anesthesia group (23.6 [5.4]; 20.2 [4.3]). In the literature, disulfide values have been shown to increase in proliferative conditions, such as various cancer types [9, 13]. Factors, such as ongoing cell proliferation and development in newborns, may cause an increase in disulfide levels [13]. The mechanism leading to higher cord blood disulfide levels in the general anesthesia group could not be determined based on the available data; however, a positive correlation between the increase in disulfide level and the increase in native and total thiol levels directed us to the conclusion that this increase was mainly due to alterations in thiol levels and subsequent changes in oxidative homeostasis.

In studies evaluating the effect of anesthesia technique on oxidative stress by measuring different oxidative stress markers, it was found that various cytokines increased to a greater degree in cases in which general anesthesia was applied compared to those receiving local and spinal anesthesia [14, 15]. Another early indicator of hypoxia, ischemia, and oxidative stress is an increase in IMA levels, which was also evaluated in our study [16, 17]. Several studies have shown that IMA values rapidly increase immediately after the onset of surgery [16, 18]. In a study that compared the levels of IMA in the cord blood of women undergoing normal and cesarean deliveries without specifying anesthesia method, it was found that values were higher for those undergoing normal delivery [19]. In another study evaluating the effect of anesthesia technique on oxidative stress during cesarean section using IMA, a statistically significant difference was found between pre-operative and 30-min post-operative blood values of the mothers who received general anesthesia. This difference was not detected in the spinal anesthesia group. In the same study, it was stated that no statistically significant difference between general and spinal anesthesia groups in both maternal and cord blood could be found [20]. In contrast to this study, IMA values in the cord blood were found to be significantly higher in patients who underwent general anesthesia than those who underwent spinal anesthesia (0.89 versus 0.85). Although the number of variables assessed was low, our results appear to demonstrate that general anesthesia may be associated with higher oxidative stress compared to spinal anesthesia as determined by high IMA and low thiol levels in the cord blood of patients who received general anesthesia.

Thiol disulfide balance reacts rapidly and is affected by instant changes. Thiol and disulfide levels from cord blood were measured to determine intra-operative oxidative stress status. Since thiol–disulfide equilibrium shows the instantaneous state, it is not considered significant to evaluate any post-operative parameter or to use it as an indicator of surgery after the effect of anesthesia has disappeared. Oxidative stress can be confirmed by blood gas from the umbilical artery for the newborn, but blood gas was not examined in our study since in previous studies conducted for this purpose, the relationship between umbilical arterial blood gas and oxidative stress has already been investigated [21]. Although the newborn was not evaluated, in our study, it was found that under general anesthesia, the mother was exposed to greater oxidative stress. This finding may indicate that spinal anesthesia could be the preferred anesthesia technique for cesarean section since the mother is exposed to less oxidative stress.

Limitations

The cross-sectional nature of the study, the small number of participants, and the study being conducted with a homogeneous group can be considered as limitations of the study. Since levels of the related blood values in the cord blood before anesthesia were not measured, conclusive data regarding the influence of anesthesia type could not be provided. Furthermore, the mechanisms by which the anesthesia techniques affect thiol–disulfide homeostasis could not be evaluated. In addition, although the first and fifth minute APGAR scores of the newborns were determined, the lack of long-term well-being assessments can be considered as a limitation.

Conclusions

In conclusion, in our study, it was found that the values of native thiol, total thiol, and disulfide in cord blood were lower and IMA values were higher in the general anesthesia group. Based on these results, it can be said that general anesthesia may cause a higher degree of oxidative stress compared to spinal anesthesia. Deciding on the appropriate anesthetic technique may be especially important for risky pregnancies in which increased oxidative stress suffered by the mother and baby may be critical. In line with the results of this study, it would be important to determine the anesthesia approach for select groups through studies involving a higher number of patients and an extensive set of parameters associated with oxidative stress.

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Predictors of eligibility for reimbursement of antiviral treatment in HBe-Ag negative chronic hepatitis B patients with high ALT levels

İsmail Engin [1], Ali Erkan Duman [2], Hayriye Esra Ataoğlu [3], Aslı Çifçibaşı Örmeci [4], Şule Poturoğlu [5]

[1] Department of Endocrinology and Metabolism, Sultan II. Abdulhamid Han Hospital, İstanbul, Turkey
[2] Department of Internal Medicine, Division of Gastroenterology, Kocaeli University, Kocaeli, Turkey
[3] Deparment of Internal Medicine, Haseki Training and Research Hospital, İstanbul, Turkey
[4] Department of Internal Medicine, Division of Gastroenterology, İstanbul Faculty of Medicine, İstanbul University, İstanbul, Turkey
[5] Department of Gastroenterology, Başakşehir Çam ve Sakura Hospital, İstanbul, Turkey

ORCID ID of the author(s)
İE: 0000-0002-6559-2575
AED: 0000-0002-7093-2503
HEA: 0000-0002-6493-9194
AÇÖ: 0000-0001-6297-8045
ŞP: 0000-0002-2722-9636

Corresponding Author
Ali Erkan Duman
Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine, Kocaeli University, 41100 Kocaeli, Turkey
E-mail: dralierkanduman@hotmail.com

Ethics Committee Approval
The study was approved by the local ethical committee of Haseki Training and Research Hospital (approval date / number: 22.02.2017/455)
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: A liver biopsy is required for the reimbursement of antiviral therapy in Hepatitis B e-antigen (HBe-Ag) negative chronic hepatitis B patients. Liver biopsy is an invasive procedure with potential complications, such as bleeding, pain, pneumothorax, and even death. The study aimed to evaluate simple and non-invasive parameters that may help predict histological criteria that would be eligible for antiviral treatment reimbursement.

Methods: HBeAg-negative chronic hepatitis B patients with alanine transaminase (ALT) levels > upper normal limit (40 IU/L) and HBV DNA viral load > 2000 IU/ml who underwent liver biopsy were enrolled in this retrospective cohort study. ALT, aspartate aminotransferase (AST), alpha-fetoprotein (AFP) values, hepatitis B virus (HBV) DNA levels, platelet count, and hepato-steatosis grade based on ultrasonography were used to predict the eligibility for antiviral therapy reimbursement. Eligibility for reimbursement of antiviral treatment regarding histological criteria defined by National Social Security Institution is based on the hepatitis activity index (HAI) score ≥ 6 and/or fibrosis score ≥ 2 according to Ishak's scoring system.

Results: One hundred and fifteen patients were included in the study; 79 patients (68.7%) were male. The mean age of patients was 46.51 (11.39). Sixty-two patients (53.9%) had a fibrosis score ≥ 2, and 80 (69.6%) patients had an HAI score ≥ 6. Ninety-two (80%) of the patients fulfilled histological criteria for antiviral treatment reimbursement. Multivariate analysis revealed that age and platelet count were independent predictors of eligibility for antiviral treatment reimbursement. The platelet count cut-off point was 198 x 10^9 /L for predicting eligibility for antiviral treatment reimbursement.

Conclusion: Most patients (92/115, 80%) with high ALT and DNA viral load were eligible for antiviral treatment reimbursement. Platelet count and age may be used as simple non-invasive parameters for predicting the eligibility for antiviral treatment reimbursement in terms of histological findings.

Keywords: Chronic hepatitis B, HBeAg-negative, High ALT, Reimbursement

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Introduction

Chronic hepatitis B is still a high burden for public healthcare systems. In 2015, it was estimated that 257 million people worldwide were infected with chronic hepatitis B virus (HBV) [1]. The prevalence of HBS Ag positivity is 4% in Turkey [2].

Cumbersome complications such as cirrhosis and hepatocellular carcinoma may develop as a consequence of chronic HBV infection [3]. Regular follow-ups and timely initiation of antiviral treatment is crucial to prevent those unfavorable outcomes. The European Association for the Study of the Liver (EASL) guidelines recommend that all patients with HBeAg-positive or -negative chronic hepatitis B, HBV DNA level > 2,000 IU/ml, alanine transaminase (ALT) > upper limit of normal (ULN), cut-off value ~ 40, and/or at least moderate liver necroinflammation or fibrosis, should be treated [4]. In our country, HBV DNA levels ≥ 2000 IU/ml with an HAI score ≥ 6 or fibrosis score ≥ 2 based on results from a liver biopsy is required for reimbursement of antiviral treatment in HBe Ag-negative patients.

Liver biopsy is the gold standard for assessing the histology of liver in patients with chronic hepatitis B. Owing to its invasive nature, liver biopsy has cumbersome complications, such as bleeding, pneumothorax, vasovagal reactions, and death [5]. It is uncomfortable and undesirable for a patient as it is associated with pain and anxiety [6]. Therefore, non-invasive methods have gained popularity for assessing hepatic fibrosis. Fibroscan and Fibrotouch are ultrasound imaging techniques that help to assess the degree of fibrosis in liver. However, these pieces of equipment are not widely available. Biochemical markers, such as aspartate aminotransferase (AST)-to-platelet ratio index (APRI) and the fibrosis index based on four factors (FIB-4) are also used in the assessment of hepatic fibrosis [7, 8]. APRI and FIB-4 are not practical as they require the combination with other indexes and increase the workload. Therefore, this study aimed to evaluate simple and non-invasive parameters in HBeAg-negative chronic hepatitis B patients with high ALT level that may help to predict histological criteria eligible for reimbursement of antiviral treatment.

Materials and methods

This single-center retrospective cohort study was conducted as a thesis study with the approval of Haseki Training and Research Hospital Ethical committee (Approval date/ number: 22.02.2017/455). Medical records of 283 chronic hepatitis B patients with HBV DNA levels ≥ 2000 IU/ml who underwent liver biopsy were reviewed. Of those 283 patients, 115 HBeAg-negative chronic hepatitis B patients with ALT levels > ULN were taken for statistical analysis. 40 IU/L was accepted as ULN of ALT according to the EASL guidelines.

Patients younger than 18 years old, with HCV and/or HIV co-infections, delta virus (HDV) infection, liver comorbidities (such as auto immune hepatitis, Wilson disease), and chronic alcohol consumers were excluded from the study.

ALT, AST, and alpha-fetoprotein (AFP) values, hepatitis B virus (HBV) DNA levels, platelet count, and hepato-steatosis grade based on ultrasonography were recorded. HBV DNA was measured quantitatively using commercially available kits (Realtime PCR Rotor-Gene Q, QIAGEN, Hamburg/GERMANY). FIB-4 and HAI were scored using the Ishak scoring system [9].

Eligibility for reimbursement of antiviral treatment regarding histological criteria defined by National Social Security Institution was an HAI score ≥ 6 and/or fibrosis score ≥ 2.

Statistical analysis

All statistical analyses were performed using IBM SPSS for Windows version 20.0 (SPSS, Chicago, IL, USA) and MedCalc 14. Kolmogorov–Smirnov and Shapiro–Wilk's tests were used to assess the assumption of normality. Numeric variables were presented with or median (25^{th}–75^{th} percentile). Categorical variables were summarized as counts (percentages). Comparisons of numeric variables between groups were carried out using independent sample t-test or Mann–Whitney U test, whichever was appropriate. The association between two categorical variables was examined using the chi-squared test. Logistic regression analysis was used to determine the factors affecting the outcome variable. Receiver operator characteristic (ROC) analysis was used to determine the area under the curve (AUC), sensitivity, specificity, and cut-off values. A *P*-value < 0.05 was considered statistically significant.

Results

One hundred and fifteen patients were included in the study; 79 patients (68.7%) were male. The mean age of patients was 46.51 (11.39). Baseline characteristics of the study population are shown in Table 1.

Table 1: Baseline parameters of the study population

		Patients (n = 115)
Age, years	mean (SD)	46.51 (11.39)
Sex, n (%)	Male	79 (68.7)
	Female	36 (31.3
ALT (IU/l)	median (25^{th}–75^{th} percentile)	80 (56–140)
AST(IU/L)	median (25^{th}–75^{th} percentile)	56 (40–96)
AFP(ng/ml)	median (25^{th}–75^{th} percentile)	2.78 (2.02–3.85)
Platelet count, $x10^9$/L	median (25^{th}–75^{th} percentile)	193 (152–254)
HBV DNA (log_{10}IU/ml),	mean (SD)	6.15 (1.36)
HAI	mean (SD)	7.49 (3.08)
Fibrosis stage	mean (SD)	2.06 (1.42)
Hepato-steatosis, n (%)	Grade 0	79 (68.7)
	Grade 1	24 (20.9)
	Grade 2	12 (10.4)

ALT: alanine aminotransferase, AST: aspartate aminotransferase, AFP: alpha-fetoprotein, HAI: histological activity index, HBV: hepatitis B virus, SD: standard deviation

All patients had HBV DNA levels > 2000 IU/ml. The mean HBV DNA level was 6.15 (1.36) log 10 IU/ml. Sixteen patients (13.9%) had HBV DNA levels < 4.27 log 10 (20000) IU/ml, 19 patients (16.4%) had HBV DNA levels between 4.27 and 5.38 log10 (20000–200000) IU/ml, 80 patients (69.7%) had DNA levels > 5.38 log10 (200000 IU/ml).

Histopathological findings are given in Table 2. Sixty-two patients (53.9%) had a FIB-4 score ≥ 2 and 80 (69.6) patients had an HAI score ≥ 6. Ninety-two (80%) patients fulfilled histological criteria for reimbursement of antiviral treatment (HAI ≥ 6 or F ≥ 2).

Table 2: Histopathological findings in liver biopsy specimens of chronic hepatitis B patients with high alanine aminotransferase, according to the Ishak scoring system

Histopathological findings	n (%)
Fibrosis stage (F)	
0	12 (10.4)
1	41 (35.7)
2	17 (14.8)
3	26 (22.8)
4	12 (10.4)
5	6 (5.2)
6	1 (0.9)
HAI	
1–5	35 (30.4)
≥ 6	80 (69.6)
HAI ≥ 6 or F ≥2	
Negative	23 (20)
Positive	92 (80)

HAI: Histological activity index

Univariate and multivariate analysis of factors associated with eligibility for reimbursement

The association of age, sex, AST, ALT, AFP, platelet count, HBV DNA (log_{10}IU/l), and hepato-steatosis with reimbursement eligibility was analyzed (Table 3). In univariate analysis, platelet count was associated with reimbursement eligibility. Patients eligible for treatment had lower mean platelet counts (195.37 [74.09] x 10^9/L versus 234.35 (62.45) x 10^9/L; *P* = 0.007).

Multivariate analysis revealed that age (odds ratio [OR] 1.070, 95% confidence interval CI 1.016–1.1126; *P* = 0.010) and platelet count (< 193 x 10^9/L; OR 4.448, 95% CI 1.476–13.401) were independent predictors of eligibility for reimbursement of antiviral treatment (Table 4).

Table 3: Univariate analysis of factors associated with eligibility for reimbursement of antiviral treatment

		Eligible for reimbursement		
		None	Yes	*P*-value
Age, years	mean (SD)	42.61 (11.67)	47.49 (11.18)	0.066[i]
Sex	Female	9(25.0)	27(75.0)	
	Male	14(17.7)	65(82.3)	0.366[ii]
ALT	min–max(median)	41–335 (67)	41–412 (81)	
	mean (SD)	97.35 (71.24)	111.12 (78.54)	0.206[iii]
AST	min-max(median)	25–434 (39)	26–250 (59)	
	mean (SD)	77.43 (87.63)	77.33 (51.10)	0.060[iii]
AFP	min-max(median)	1–8 (2.89)	1–56 (2.77)	
	mean (SD)	3.04 (1.80)	4.53 (7.24)	0.531[iii]
Platelet count,	min-max(median)	115–386 (223)	113–504 (182.5)	
x10^9/L	mean (SD)	234.35 (62.45)	195.37 (74.09)	0.007[iii]
HBV DNA	min-max(median)	3.70–8.77(5.37)	3.47–8.23(6.51)	
(log_{10}IU/ml),	mean (SD)	5.83 (SD)	6.23 (0.13)	0.213[iii]
Hepatosteatosis,	Grade 0	15 (19.0)	64 (81.0)	
n (%)	Grade 1	4 (16.7)	20 (83.3)	0.509[ii]
	Grade 2	4 (27.3)	8 (72.7)	

[i] Student's t-test, [ii] Pearson chi-squared test, [iii] Mann–Whitney U test

Table 4: Multivariate analysis for eligibility of treatment reimbursement

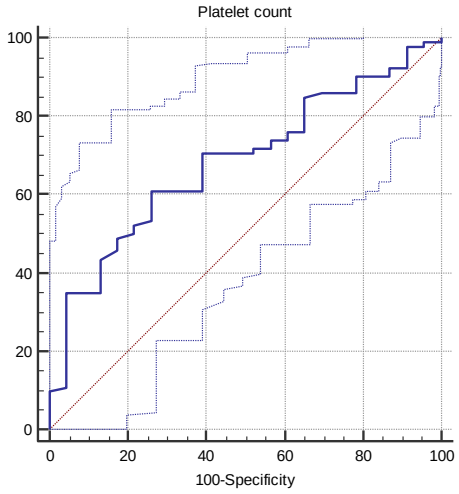
Reimbursement criteria	Multivariate analysis		
	OR	95% CI	*P*-value
Age	1.070	1.016–1.1126	0.010
Sex	0.552	0.187–1.631	0.282
Platelet group	4.448	1.476–13.401	0.008
HBV DNA(log_{10}IU/ml) group	1.757	0.454–6.801	0.415

OR: odds ratio, CI: confidence interval, HBV: hepatitis B virus, HBV DNA(log10IU/ml) group: 3.30-4.30 vs > 4.30

AUC for the association of platelet count with eligibility for reimbursement

Platelet count was used to predict the probability of being eligible for antiviral therapy reimbursement in HBe Ag-negative patients with high ALT. The cut-off point for platelet count was 198x10^9 /L. The AUC of the platelet value associated with eligibility for reimbursement of antiviral treatment was 0.682 (95% CI 0.589–0.766; sensitivity = 60.87%, specificity = 73.97%; *P* = 0.001) as shown in Figure 1.

Figure 1: ROC curve of platelet value associated with eligibility of reimbursement of antiviral therapy in HBeAg-negative patients with hih-ALT levels. (AUC = 0.682, 95% CI 0.589–0.766; sensitivity = 60.87%, specificity = 73.97%, *P* = 0.001)



Discussion

In the present study, the association of laboratory and demographic parameters with eligibility for antiviral treatment reimbursement in HBeAg-negative chronic hepatitis B with high ALT levels was analyzed. Platelet count and age were found to be statistically significant independent parameters for predicting eligibility for reimbursement of antiviral treatment.

Age is an important parameter that affects the degree of liver damage. Older patients probably have a longer duration of disease, and their immune-tolerance and immune clearance phases are relatively longer which predispose them to more severe liver damage [10]. Papatheodoridis et al. [11] found that histological indication for treatment was more likely in patients older than 45 years old compared to ones younger than 45 years. In two previous studies from our country, the age cut-off for age in predicting the requirement of treatment in HBeAg negative chronic hepatitis B patients was 46 years [10, 12]. Parallel with previous studies, patients in our study who were eligible for reimbursement of antiviral treatment were older compared to non-eligible patients which did not reach statistical significance (47.49 [11.18] versus 42.61 [11.67]). However, logistic regression analysis showed that age could predict eligibility for reimbursement (OR: 1.070, 95% CI 1.016–1.126).

Thrombocytopenia is a well-known feature of liver cirrhosis, usually resulting from portal hypertension and hypersplenism that leads to splenic sequestration [13]. Besides splenic sequestration, a decrease in platelet production due to diminished synthesis of thrombopoietin and/or other humoral factor(s) by the liver also contributes to thrombocytopenia in cirrhosis [14]. However, before the development of cirrhosis, platelet count may begin to gradually decline during the course of chronic hepatitis as fibrosis progresses. Studies have shown a negative correlation between platelet count and FIB-4 score [15, 16]. In this present study, it was also found that patients eligible for antiviral treatment reimbursement had lower mean platelet counts compared to non-eligible patients.

HBV DNA viral load is also an important determinant of the requirement for antiviral treatment. Papatheodoridis et al. [11] found that histological indications for treatment increased as HBV viral loads increased. A similar result was found in a study

from our country [12]. On the other hand, Ormeci et al. [10] reported an opposite finding. In contrast to the previously described studies, patients requiring treatment were more likely to present HBV DNA levels between 2000 and 20000 IU/ml compared to levels > 20000 IU/ml. In our study, the difference in HBV viral loads between eligible and non-eligible patients for antiviral treatment was not statistically significant. As a high percentage of patients (80%, 92/115) patients were eligible for reimbursement of antiviral treatment, the difference might not have reached statistical significance. The first two studies included patients with high and normal ALT values. In a study by Ormeci et al., only patients with normal ALT values were included, whereas our study consisted of patients only with high ALT levels. This difference may explain the discrepancy in the results.

Limitations

Some limitations of the study should be mentioned. The retrospective nature of the study is an important limitation. A small sample size is also an important limitation. Thus, it is necessary to design a multicenter study with a larger study population to obtain more definite results.

Conclusion

In conclusion, platelet count and age may be used as non-invasive parameters for predicting the eligibility for reimbursement of antiviral treatment in terms of histological findings.

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The association of fibrocystic breast disease with endometrial histopathological results in abnormal uterine bleeding

Selahattin Vural [1], Oğuz Özdemir [2], Meryem Sağır [2], Çağanay Soysal [2], Zehra Yılmaz [2]

[1] Giresun University Faculty of Medicine, Department of General Surgery, Giresun, Turkey
[2] Dr. Sami Ulus Women's and Children's Health Teaching and Research Hospital, Department of Obstetrics and Gynecology, Turkey

ORCID ID of the author(s)

SV: 0000-0003-1706-3799
OÖ: 0000-0001-9328-8047
MS: 0000-0003-3074-277X
ÇS: 0000-0002-4381-6099
ZY: 0000-0002-8719-1879

Corresponding Author
Selahattin Vural
Giresun University Faculty of Medicine, Department of General Surgery, Giresun, Turkey
E-mail: drselahattinvural@hotmail.com

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Abstract

Background/Aim: Fibrocystic breast disease (FBD) is the most frequent benign breast disease. Increased estrogen and decreased progesterone concentrations are thought to be involved in the pathogenesis of FBD. But there is insufficient data on benign breast disease and endometrial pathology. This study evaluates the association between FBD and endometrial pathology in women complaining of abnormal uterine bleeding.

Methods: This study was designed as a retrospective case-control study. The medical records of women who had endometrial sampling for abnormal uterine bleeding between 2018 and 2020 were evaluated. Patients with FBD were included in the study group, while the first patients who had endometrial sampling after patients with FBD and without breast disease were recruited as the control group. Demographic, laboratory data, and endometrial histopathological results were obtained from hospital records and compared between the groups.

Results: In total, 250 women (106 women with FBD and 144 without breast disease) were recruited for the study. There was no statistically significant difference in mean age, gravidity, parity, and BMI between FBD and control groups. Endometrial hyperplasia without atypia (19.8% versus 10.5%, respectively, P = 0.037) and endometrial polyp (12.2% versus 4.8%, respectively, P = 0.033) were found to be significantly increased in patients with FBD than women without the disease. There was no statistically significant difference in terms of other histopathological results between the groups.

Conclusion: Evaluation of the endometrium for abnormal uterine bleeding is essential for early diagnosis and treatment of endometrial pathology, especially for endometrial cancer. In this study, we found that women with FBD have an increased risk for endometrial hyperplasia and endometrial polyp. As endometrial hyperplasia is a precursor lesion for endometrial cancer, clinicians should pay attention to and investigate menstrual bleeding abnormalities of women with FBD and should not delay the evaluation of the endometrium.

Keywords: Fibrocystic breast disease, Endometrial pathology, Hyperplasia, Polyp

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Introduction

Benign breast disease represents a spectrum of disorders, and fibrocystic breast disease (FBD), recently termed fibrocystic changes, is the most frequent benign breast disease. The incidence of FBD is approximately 7% in the general population and is mostly seen between 20 and 50 years of age [1]. It has been suggested that the balance of estrogen and progesterone affects the mammary gland [2]. The exact etiology of FBD is unknown. However, an imbalance in steroid ovary hormones with relatively increased estrogen and decreased progesterone concentration during the menstrual cycle may be involved in the etiology of FBD [2, 3].

Abnormal uterine bleeding (AUB) is used for uterine bleeding outside the normal menstruation pattern. It is the most common gynecological complaint and occurs in 9–14% of women, accounting for two-thirds of all hysterectomies [4-5]. Uterine pathologies (myomas, polyps, endometrial hyperplasia or cancer) and ovulatory disorders are common causes of AUB [6]. Endometrial hyperplasia (EH) is a precursor lesion of endometrial adenocarcinoma (EAC), so evaluation of the endometrium for endometrial pathologies and treatment of AUB in women is important. Chronic estrogen stimulation without progesterone is considered a major risk factor for both pathologies [7].

Although an association between gynecological cancers such as ovarian and endometrial cancer with breast cancer is known, there is insufficient data on benign breast disease and endometrial pathology. In the present study, we aimed to investigate if there is an association between FBD and endometrial pathology results in women with AUB.

Materials and methods

This retrospective case-control study was conducted at the Dr. Sami Ulus Women's Health Education and Research Hospital. The medical records of all patients who had endometrial sampling for AUB between 2018 and 2020 were systematically evaluated. Women who had endometrial sampling for AUB with FBD were taken to the study group, and the first patients who had endometrial sampling after patients with FBD and without breast disease were recruited as the control group. Patients with postmenopausal status, malignant disease, women on hormone treatment and women with chronic disease (e.g., diabetes mellitus, hypertension, thyroid disease) were excluded from the study. This clinical study was approved by Dr. Sami Ulus Women's Health Education and Research Hospital, Clinical Research Ethics Committee (Number: 2020-KAEK-141/086, Protocol Number: E-21/02-85).

AUB was defined as bleeding abnormal in frequency, prolonged menstrual bleeding (>8 days), heavy menstrual bleeding (bleeding that affects women's physical and social life), or intermenstrual bleeding.

All women were examined with a speculum for cervical lesions, and a cervical smear was taken from all patients. Serum human chorionic gonadotrophin (hCG) was measured to exclude pregnancy. Serum complete blood count, prolactin (PRL), and thyroid-stimulating hormone (TSH) concentrations were measured for all women. Transvaginal ultrasonography was performed, and endometrial sampling was done with all women. Women with organic pathology (such as myoma, cervical or vaginal lesion) and women using an intrauterine device were excluded from the study. Endometrial pathological results were classified as proliferative endometrium (PE), secretory endometrium (SE), endometrial polyp (EP), chronic endometritis (CE), endometrial hyperplasia (EH) without atypia, endometrial hyperplasia with atypia, and endometrial adenocarcinoma (EAC). FBD was defined as anechoic cystic lesions or the presence of diffuse micronodular or microcytic changes of breast tissue on breast ultrasound or mammography [8, 9]. All women in the study population had breast ultrasound examinations.

Demographic data were recorded from patients' files, including all patients' age, parity, BMI, and laboratory data. Endometrial histopathological results were obtained from the patient hospital records. The patients in the study population were classified into two groups: Group 1, patients with FBD (n = 106) and Group 2, patients without breast disease (n = 144). Endometrial histopathological results were compared between the two groups.

Statistical analysis

Statistical Package for Social Sciences, Windows version 20.0 (SPSS, Chicago, IL, USA), was used for study data analyses. Mean, and standard deviation (SD) were used for descriptive data. Normality of the data distribution and variance homogeneity were evaluated with the Kolmogorov-Smirnov test. The student's t-test was used to compare groups with normal distribution. The Chi-square test was used to compare categorical variables. Non-parametric tests, such as Mann–the Whitney U test or Fisher Exact test, were used to compare parameters with non-normal distribution. *P*-values < 0.05 was considered statistically significant.

Results

Two-hundred-fifty patients were included in the study. The mean age of the study population was 46.1 (4.7). The predominant histopathological result was PE+SE in 144 (57.6%) patients. DPP was reported in 11 (4.4%), EH without atypia was reported in 36 (1.4%), and EH with atypia was reported in 18 (7.2%) women. One patient had a diagnosis of endometrial adenocarcinoma. The endometrial histopathological results of the study population are presented in Table 1.

Table 1: Endometrial histopathological results of the study population

Variable	Study population (n = 250) n (%)
Proliferative endometrium + Secretory endometrium	144 (57.6%)
Disordered proliferative pattern	11 (4.4%)
Endometrial polyp	20 (8%)
Chronic endometritis	20 (8%)
Endometrial hyperplasia without atypia	36 (14.4%)
Endometrial hyperplasia with atypia	18 (7.2%)
Endometrial adenocarcinoma	1 (0.4%)
Total	250 (100%)

Mean age, gravidity, parity, and BMI values were similar between FBD and control groups. In terms of laboratory characteristics, serum TG levels were significantly higher in the FBD group than in the control group (146.1 [73.9] vs. 120.7 [40.5] respectively; *P* = 0.03), while there was no difference in other parameters. The demographic and laboratory data of the study are presented in Table 2.

Endometrial hyperplasia without atypia (19.8% vs 10.5%, respectively, P = 0.037) and endometrial polyp (12.2% vs 4.8%, respectively, P = 0.033) were significantly more frequent in patients with FBD than women without the disease. Proliferative endometrium+secretory endometrium was significantly less reported in the FBD group than the control group (47.2% versus 65.3 %, respectively, P = 0.004). Other histopathological results were similar between the groups. A comparison of endometrial histopathological results of the FBD and control groups is presented in Table 3.

Table 2: Comparison of demographic and laboratory findings of FBD and control groups

Variable	FBD group (n = 106)	Control group (n = 144)	*P*-value
Age (year)	46.1 (4.5)	46.08 (5.1)	0.90
Gravidity	2.7 (1.4)	2.5 (1.2)	0.29
Parity	2.3 (1.2)	2.08 (1.04)	0.09
BMI (kg/m^2)	30.3 (3.8)	30.4(3.5)	0.90
Hemoglobin(gr/dL)	11.9 (1.3)	11.7 (1.4)	0.80
Glucose (mg/dL)	99.7 (19.7)	103.5 (34.9)	0.37
ALT (U/L)	14.2 (7.2)	15.1 (4.1)	0.80
AST (U/L)	16.7 (8.1)	18.2 (5.6)	0.60
TC (mg/dL)	219.8 (41.3)	211.0 (41.4)	0.27
TG (mg/dL)	146.1 (73.9)	120.7 (40.5)	0.03*
LDL (mg/dL)	137.6 (36.8)	133.7 (38.7)	0.60
HDL (mg/dL)	53.1 (10.6)	56.0 (22.7)	0.37
HT (n, %)	26 (24.5%)	29 (20.1%)	0.40
DM (n,%)	10 (9.4%)	15 (10.4%)	0.79

BMI: Body Mass Index, WBC: White Blood Cell, Plt: Platelet, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, TC: Total Cholesterol, TG: Triglyceride, LDL: Low-Density Lipoprotein, HDL: High-Density Lipoprotein, HT: Hypertension, DM, Diabetes Mellitus. Data are expressed as mean (standard deviation), * indicates statistical significance

Table 3: Comparison of endometrial histopathological results of FBD and control groups

Variable	FBD group (n = 106)	Control group (n = 144)	*P*-value
Proliferative endometrium + Secretory endometrium	50 (47.2%)	94 (65.3%)	0.004
Disordered proliferative pattern	4 (3.8%)	7 (4.8%)	0.76
Endometrial polyp	13 (12.2%)	7 (4.8%)	0.033*
Chronic endometritis	7(6.7%)	13 (9.1%)	0.48
Endometrial hyperplasia without atypia	21 (19.8%)	15 (10.5%)	0.037*
Endometrial hyperplasia with atypia	10 (9.4%)	8 (5.5%)	0.24
Endometrial adenocarcinoma	1 (0.9%)	0	-
Total	106 (100%)	144 (100%)	

Data are given as n (%), FBD; Fibrocystic Breast Disease, * indicates statistical significance

Discussion

In this study, we found that endometrial hyperplasia without atypia and endometrial polyp were more frequently observed in women who complained of AUB with FBD than those without breast disease. To our knowledge, our study is the first clinical study to report a relationship between endometrial histopathological findings and FBD in women with AUB.

Hormones play a critical role in the function of the breast and gynecological tissues, and most of the pathologies, including cancer in these organs, are related to excess exposure or relative imbalance in the levels of these hormones. FBD is the most common benign breast disease, and its incidence is approximately 7% in the general population. It is a hormone-dependent disease with lobular and diffuse increases in glandular tissue [10, 11]. Small cysts, large cysts, and diffuse micronodules may be seen, and pain, tension, and tender nodes in the breast are the most common complaints in women with FBD [12].

The balance between estrogen and progesterone is significant in the growth of the mammary gland, and hyperestrogenism and anovulation are suggested to be involved in the pathogenesis of FBD [2]. Inappropriate estrogen stimulation causes proliferation in the breast tissue and is thought to be responsible for the pathogenesis of FBD [13]. Mauvais-Jarvis et al. also verified this hypothesis [14]. Furthermore, in their study, Marchesoni et al. [15] showed that luteal phase progesterone levels were significantly lower in women with mastodynia and breast micronodularity than in women without breast disease. Wypych et al. [16] showed decreased progesterone levels in women with gross breast cysts and suggested that decreased progesterone activity can be a hormonal reason for the pathogenesis of benign breast disease. Some studies have also found a statistically significant relationship between polycystic ovary syndrome (PCOS) and FBD [17, 18]. Ozkaya et al. [19] found that FBD risk is increased in women with anovulation, and PCOS patients with hyperandrogenemia had a decreased risk of FBD when compared with anovulatory and normoandrogenemic PCOS patients. In their study, they found that hyperandrogenemia is protective for FBD.

Abnormal proliferation of endometrial glands causes EH, and its incidence is approximately 133 per 100,000 women-years [20]. Endometrial cancer (EC) is the most common gynecological malignancy affecting women in developed countries [21]. Chronic stimulation of the endometrium by estrogens unopposed by a progestin is responsible for both EH and EAC, so the risk factors are similar for both diseases. EH is a precursor lesion of EC, and the presence of cytological atypia is the main histological finding for its malignant potential, so early diagnosis and treatment of EH are important [7, 21].

Breast cancer (BC) is the most common malignancy and the first common cause of cancer death in women worldwide, and benign breast disease is also known to be a risk factor for BC [22]. Probably due to common risk factors (such as age, obesity, high endogenous estrogen levels, and higher insulin levels, and reproductive factors (such as earlier menarche or later menopause, nulliparity, and infertility), breast cancer patients have an increased risk of endometrial pathology [23]. The association between endometrium cancer and breast cancer is clear in the literature. However, the relationship between benign breast disease and endometrial pathology is unknown. Our study found that endometrial hyperplasia without aypia was significantly higher in women with FBD than in women without breast disease. There was no difference in endometrial hyperplasia with atypia between groups, and one patient was diagnosed with endometrial adenocarcinoma in the FBD group.

Endometrial polyp is one of the most common pathologies of abnormal genital bleeding in both premenopausal and postmenopausal women [24]. Hyperplastic overgrowth of the endometrial gland and stroma causes the formation of endometrial polyps. Endometrial polyps have estrogen and progesterone receptors, as in normal endometrial tissue, and progesterone has an antiproliferative role in the pathogenesis of endometrial polyps [25]. Age, obesity, postmenopausal hormone therapy, and tamoxifen treatment are known risk factors for the disease [25, 26]. Although the prevalence of endometrial polyp is not known exactly, in one study, it was found to be 23.8% among symptomatic women undergoing endometrial biopsy [27]. In their study of asymptomatic gynecological patients with breast cancer, Lopez et al. found a hysteroscopic diagnosis of endometrial polyp in 28.5% of all patients in their study group [28]. To our knowledge, this study is the first to investigate the prevalence of endometrial polyp in women with benign breast disease. In our study, we found that 12.2% of women with FBD and 4.8% of women without the disease had a diagnosis of

endometrial polyp, and the difference reached statistical significance. The histopathological results of CE and DPP were similar between the groups.

Limitations

Our study's limitations include its retrospective design and the low number of cases of endometrial carcinoma. Prospective large-scale studies are needed to better define the association between FBD and endometrial pathologies.

Conclusions

According to our knowledge, our study is the first preliminary study to report the association of FBD and endometrial pathology in women with abnormal bleeding. We showed that endometrial hyperplasia without atypia and endometrial polyps were more often diagnosed in women with FBD than without the disease. As endometrial hyperplasia is a precursor lesion for endometrial carcinoma, clinicians should pay attention to menstrual bleeding abnormalities in women with FBD and should not delay evaluation of the endometrium.

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