Medical Journal of Bakırköy

Med J Bakirkoy 2022;18:52-58
DOI: 10.4274/BMJ.galenos.2022.2021.12-5

Research

The Relationship of Elevated Hepatic Fibrosis-4 Index Score with Pneumonia Severity Index and in Hospital Mortality Among COVID-19 Patients Admitted to Intensive Care Unit

Yoğun Bakıma Yatırılan COVID-19 Hastalarında Erken Dönemde Bakılan Yüksek Hepatik Fibrozis-4 Skoru ile Pnömoni Ciddiyet İndeksi ve Hastane İçi Mortalite Arasındaki İlişkinin Araştırılması

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ABSTRACT

Objective: We investigated the relationship hepatic fibrosis-4 (FIB-4) index score calculated in the early period and pneumonia severity index (PSI) and in-hospital mortality in patients hospitalized in the intensive care unit (ICU) due to new severe acute respiratory syndrome coronavirus-2 infection.

Methods: Seventy six consecutive patients diagnosed with coronavirus disease-2019 (COVID-19), hospitalized in the ICU due to hypoxemia, and selected consecutively were included. COVID-19 infection was diagnosed using real-time reverse transcription-polymerase chain reaction (RT-PCR) in nose and throat swab samples. The diagnosis of pneumonia was confirmed by showing typical ground-glass opacities and areas of subsegmental consolidation in lung computed tomography examinations of patients previously diagnosed with COVID-19 by RT-PCR. Hepatic FIB-4 index score and PSI score was calculated separately for each patient. In the statistical method, the independent samples t-test and Mann-Whitney U test were used to compare quantitative data. A chi-square test was used to compare qualitative data.

Results: The FIB-4 value and PSI value were significantly higher ($p<0.05$) in the mortality group than in the non-mortality group. Also, there was no significant statistical difference between the two groups in terms of the other laboratory parameters ($p>0.05$) FIB-4 value was significantly predictive [under the curve 0.835 (0.742-0.929)] in differentiating patients with and without mortality. For a cut-off value of 5.4, FIB-4 had a sensitivity of 60.6%, positive predictive of 95.2%, specificity of 97.6%, and negative predictive value of 75.9%

Conclusion: High FIB-4 index and PSI score detected in the early period in patients admitted to the ICU due to COVID-19 seem to be predictors of in-hospital mortality.

Keywords: Coronavirus infection, liver fibrosis, pneumonia, prognostic factors

ÖZ

Amaç: Yoğun bakım ünitesine (YBÜ) yatırılan, yeni şiddetli akut solunum yolu sendromu koronavirüs-2 enfeksiyonu nedeniyle yatırılan hastalarda erken dönemde hesaplanan hepatik fibrozis-4 (FIB-4) indeks skorunun, pnömoni ciddiyet indeksi (PSI) ve hastane içi mortaliteyle ilişkisinin araştırılması amaçlandı.

Gereç ve Yöntem: Koronavirüs hastalığı-2019 (COVID-19) tanısı konulan, hipoksemi nedeniyle YBÜ'ye yatırılan ve ardışık seçilen 76 hasta dahil edildi. Burun ve boğaz sürüntü örneklerinde gerçek zamanlı ters transkripsiyon-polimeraz zincir reaksiyonu (RT-PCR) kullanılarak COVID-19

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Cite as: Demir E, Güngör H, Erdoğan C, Olmuşçelik O, Çakmak R, Yıldırım A. The Relationship of Elevated Hepatic Fibrosis-4 Index Score with Pneumonia Severity Index and in Hospital Mortality Among COVID-19 Patients Admitted to Intensive Care Unit. Med J Bakirkoy 2022;18:52-58

Received: 10.12.2021
Accepted: 16.02.2022

enfeksiyonu tanısı konuldu. Daha önce RT-PCR ile COVID-19 tanısı almış hastaların akciğer bilgisayarlı tomografi incelemelerinde tipik buzlu cam opasitelerinin ve subsegmental konsolidasyon alanlarının gösterilmesiyle pnömoni tanısı doğrulandı. Hepatik FIB-4 indeks skoru ve PSI skoru her hasta için ayrı ayrı hesaplandı. İstatistiksel yöntemde, nicel verileri karşılaştırmak için independent samples t-testi ve Mann-Whitney U testi kullanıldı. Niteliksel verilerin karşılaştırılması için ki-kare testi kullanıldı

Bulgular: FIB-4 değeri ve PSI değeri, mortalite olmayan gruba göre mortalite grubunda önemli ölçüde daha yüksekti (p<0,05). Ayrıca diğer laboratuvar parametreleri açısından da iki grup arasında istatistiksel olarak anlamlı fark yoktu (p>0,05) FIB-4 değeri mortalite olan ve olmayan hastaları ayırmada [eğri altında 0,835 (0,742-0,929)] anlamlı olarak prediktifti. 5,4'lük bir eşik değeri için, FIB-4'ün duyarlılığı %60,6, pozitif öngörü değeri %95,2, özgüllüğü %97,6 ve negatif prediktif değeri %75,9 olarak bulundu.

Sonuç: COVID-19 nedeniyle, YBÜ'ye yatırılan hastalarda erken dönemde saptanan yüksek FIB-4 indeksi ve PSI skoru hastane içi mortalitenin prediktörleri olarak gözükmektedir.

Anahtar Kelimeler: Koronavirüs enfeksiyonu, karaciğer fibrozisi, pnömoni, prognostik faktörler

INTRODUCTION

The novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic continues to threaten public health by being an important cause of mortality due to newly developing mutations and novel variants despite widespread use of vaccination worldwide (1-3). Among patients admitted to intensive care unit for pneumonia and hypoxemia, determining patients at high risk of death early in the infection and treating them more aggressively are particularly important. For this purpose, several risk scores have been developed to predict mortality, which are used in daily practice (4,5). However, some of those scores are too complex, difficult to calculate in daily practice, and time-consuming for clinicians. In this context, there is a need for developing novel risk scores that are relatively simple, inexpensive, and easy-to-calculate that use blood tests routinely studied in daily practice.

Elevation of liver enzymes is common in SARS-CoV-2 infection and has been related to a worse prognosis (6,7). In this regard, some hepatic risk scores predict long-term and short-term prognosis in SARS-CoV-2 infection (8,9). Hepatic fibrosis-4 (FIB-4) index score is one of those hepatic fibrosis scores that can be easily calculated with 4 simple parameters including age, alanine aminotransferase (ALT), aspartate aminotransferase (AST) levels, and platelet (PLT) count (9). Although some of the previous studies have provided important data suggesting that a high FIB-4 score predicts mortality in coronavirus disease-2019 (COVID-19) patients, their overall number is small; moreover, there is a limited number of studies on COVID-19 patients admitted to intensive care unit, necessitating new studies and data on this subject.

In our study, it was investigated the relationship of hepatic FIB-4 index score with pneumonia severity index (PSI) and in-hospital mortality among patients admitted to intensive care unit with SARS-CoV-2 infection.

METHODS

This study included 76 consecutive patients who were diagnosed with COVID-19 and admitted to intensive care unit because of hypoxia. SARS-CoV-2 infection was diagnosed by studying real-time reverse transcription-polymerase chain reaction (RT-PCR) test in nasal and throat swab samples. In COVID-19 patients previously diagnosed by RT-PCR, pneumonia was confirmed by showing the typical ground glass opacities and areas of subsegmentary consolidation in computed tomography (CT).

Among patients who were diagnosed with COVID-19 by showing the typical ground glass opacities and subsegmentary consolidation areas in CT, those with at least a finding given below, which were specified in the R.T. Ministry of Health General Directorate of Public Health, COVID-19 (SARS-CoV-2 infection) Adult Patient Treatment Guideline, were admitted to the intensive care unit (10):

Dyspnea and respiratory difficulty, respiratory rate ≥30/min, PaO_2/FiO_2<300, increased oxygen requirement at follow-up, SpO_2<90% or PaO_2<70 mmHg despite oxygen therapy at a rate of 5 lt/min, hypotension (systolic blood pressure <90 mmHg, and more than 40 mmHg drop in usual blood pressure and mean arterial pressure <65 mmHg, tachycardia >100/min, development of acute organ dysfunction such as acute kidney injury, acute liver dysfunction, confusion, and acute bleeding diathesis, immunosuppression, troponin elevation and arrhythmia, lactate >2 mmol, impaired capillary refill, and skin abnormalities such as cutis marmaratus.

Full blood count, ALT, AST, C-reactive protein, and creatinine levels were studied, and hepatic FIB-4 index score was calculated for each patient individually.

FIB-4 index was calculated using the formula: FIB-4= Age (years)×AST (U/L)/[PLT (10^9/L)×ALT1/2 (U/L) (9).

PSI was calculated by individually assessing and scoring 6 main headings including the demographic data of the patients, comorbidities, physical examination findings, laboratory findings, arterial blood gas analysis results, and radiological pulmonary findings, and 20 subheadings (11,12).

This study complied with the criteria of Helsinki Declaration and approved by Istanbul Medipol University Non-Invasive Clinical Research Ethics Committee (decision no: 91, date: 21.01.2021). Before study entry, written informed consent was obtained from the patients themselves when they could provide it, or their relatives when they were not.

Statistical Analysis

Study data were analyzed using SPSS 27.0 statistical software for Windows (SPSS Inc., Chicago, IL, ABD). Descriptive statistics included mean, standard deviation, median, minimum, maximum, frequency, and percentage. The normality of the distribution of continuous variables was tested using Kolmogorov-Smirnov test. Independent samples t-test and Mann-Whitney U test were used to compare quantitative data. chi-square test was used to compare qualitative data. Receiver operating characteristics curve was used to calculate the cut-off values to discriminate deceased patients with maximum sensitivity and specificity. A p value of less than 0.05 was considered statistically significant.

RESULTS

Demographic data, comorbidities and symptoms of patients are shown in Table 1. The age and gender distribution of the patients did not differ significantly between the groups with and without mortality ($p>0.05$). Cancer, congestive heart failure, stroke, chronic kidney disease, chronic liver disease, diabetes mellitus, chronic obstructive pulmonary disease, asthma, coronary artery disease and extracorporeal membrane oxygenation rates did not differ significantly between groups with and without mortality ($p>0.05$).

Laboratory results of patients are summarized in Table 2. Arterial PH in the mortality group was significantly ($p<0.05$) lower than the non-mortality group. The rate of mechanic ventilator use in the mortality group was significantly ($p<0.05$) higher than the non-mortality group. PaO_2 and SPO_2 values were significantly lower ($p<0.05$) in the mortality group than in the non-mortality group.

The FIB-4 value and PSI value were significantly higher ($p<0.05$) in the mortality group than in the non-mortality group (Table 2, Figure 1). Also, there was no significantly statistical diffence between two groups in terms of the other laboratovary parameters ($p>0.05$) (Table 2).

Additionally, ICU length of stay did not differ significantly ($p>0.05$) between groups with and without mortality.

FIB-4 value was significantly predictive [under the curve 0.835 (0.742-0.929)] in differentiating patients with and without mortality. For a cut-off value of 5.4, FIB-4 had a sensitivity of 60.6%, positive predictive of 95.2%, specificity of 97.6%, and negative predictive value of 75.9% (Figure 2).

DISCUSSION

Our study has two important results. Firstly, a high hepatic FIB-4 score calculated at the time of diagnosis appears to be correlated with in-hospital mortality. Secondly, a high PSI score calculated at the time of diagnosis was higher in a patient with mortality. The reason why mortality was higher in patients with higher FIB-4 score was probably that PSI score was also higher in the same patients.

SARS-CoV-2 infection is a disease characterized by a multi-organ involvement, and mild-to-moderate liver enzyme elevation is frequently encountered during its course (13). Elevated ALT, AST levels combined with mildly elevated bilirubin levels are usually observed (9). The plausible mechanisms for elevating liver enzymes include the direct cytopathic effect of the virus on hepatocytes and cholangiocytes, exaggerated immune response during infection, side effects of some antiviral drugs used to treat the infection, and the occurrence of septicemia during the infection (9,14). However, several studies have also shown that elevated liver enzymes have prognostic significance in SARS-CoV-2 infection (15,16). In this context, it is thought that some hepatic risk scores could be used to determine prognosis. Hepatic FIB-4 index is a useful risk score that can be readily calculated using several laboratory parameters that are widely used to diagnose and monitor COVID-19 patients in daily practice; additionally, many studies have shown that FIB-4 index has prognostic significance in patients with COVID-19 (8,17,18). There are several probable causes of an elevated FIB-4 index in COVID-19 infection. Among these, direct hepatocellular injury caused by the virus, systemic inflammation and cytokine storm, increased pulmonary artery pressure and right chamber pressures are the main ones (17). In a study that included 202 patients admitted to hospital due to COVID-19 infection, a high FIB-4 index was correlated with mortality; there were also positive correlations between a high FIB-4 index and viral load, and monocyte-related cytokines such as interleukin-6 (17). In a more comprehensive, retrospective, multi-center cohort study, Park et al. (18) showed that a high FIB-4 index score was a strong predictor of mortality. Similarly, Xiang et al. (19) demonstrated that FIB-4 index calculated at an early period was an important prognostic marker in patients hospitalized for COVID-19 infection. The authors found that patients with FIB-4 >3.25 had more than 12 times greater need for high-flow oxygen and 11 times greater rate of progression to severe disease, particularly at an early

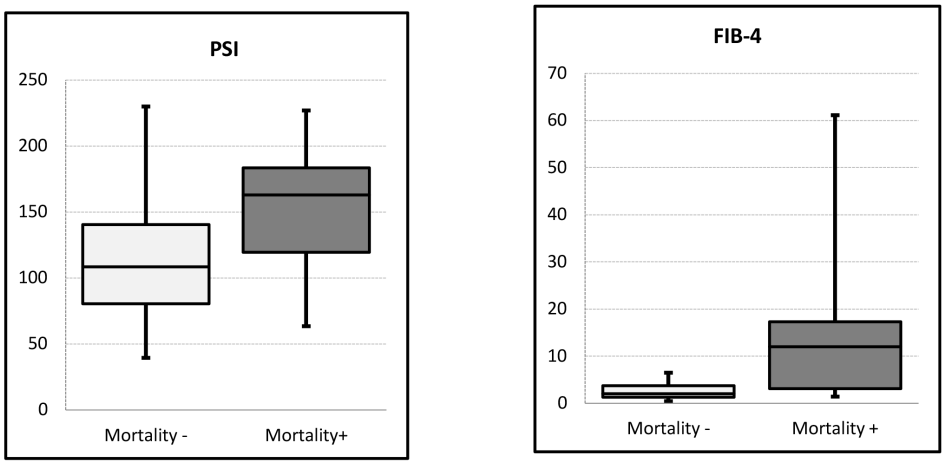

Figure 1. Comparison of FIB-4 index and PSI results between living and deceased patients
FIB-4: Fibrosis-4 index, PSI: Pneumonia severity index

disease period (19). Our results also support those previous observations. Intensive care unit patients who had a higher FIB-4 index early in the disease course suffered a worse prognosis a higher mortality rate.

Another important finding of our study is higher PSI score in patient with mortality. In fact, previous studies have shown that PSI index predicts mortality at the early period of COVID-19 (12,20). For example, Satici et al. (12) found that PSI more effectively predicted 30-day mortality in hospitalized patients than CURB-65, another risk score with proven effectiveness for predicting mortality in community-acquired pneumonia. Similarly, another retrospective study including 1,181 patients showed that PSI was superior than CURB-65 for predicting 30-day mortality (21). However, CURB-65 score was better in predicting patients who needed critical care (21). Hence, patients with a higher PSI score are older and have a higher number of comorbidities, worse vital signs, and a greater rate of multi-organ dysfunction. This makes the finding

	AUC	95% Confidence interval			p
FIB-4	0.835	0.742	-	0.929	**0.000**

ROC CURVE

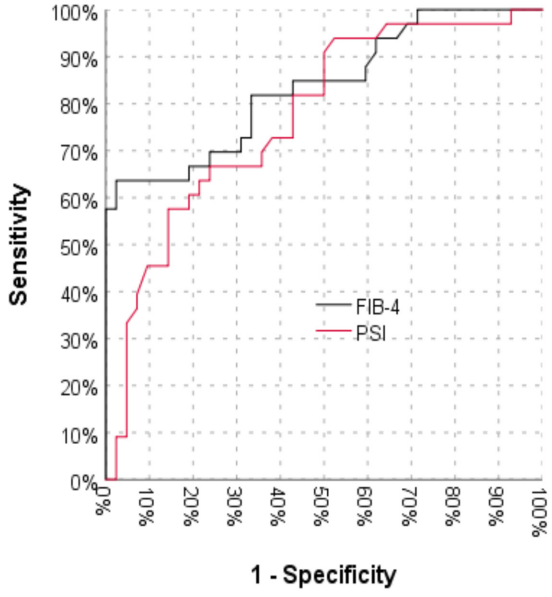

Figure 2. The result of receiver operating characteristic curve
ROC: Receiver operating characteristic, FIB-4: Fibrosis-4 index, PSI: Pneumonia severity index, AUC: Area under the curve

Table 1. Comparison of demographic data, comorbidities and symptoms of patients

		Mortality (-)		Mortality (+)		p
		Mean ± SD/n-%	Median	Mean ± SD/n-%	Median	
Age		62.8±16.2	63.0	65.1±13.2	65.0	0.525[m]
Gender	Female	13/31.0%	-	12/36.4%	-	0.622[X²]
	Male	29/69.0%	-	21/63.6%	-	
Cancer		5/11.9%	-	7/21.2%	-	0.275[X²]
Congestive heart failure		7/16.7%	-	7/21.2%	-	0.616[X²]
Stroke		4/9.5%	-	0/0.0%	-	0.126[X²]
Chronic kidney disease		7/16.7%	-	9/27.3%	-	0.266[X²]
Chronic liver disease		2/4.8%	-	0/0.0%	-	0.501[X²]
Hypertension		21/50.0%	-	15/45.5%	-	0.696[X²]
DM		14/33.3%	-	11/33.3%	-	1.000[X²]
COPD		2/4.8%	-	1/3.0%	-	1.000[X²]
Asthma		3/7.1%	-	4/12.1%	-	0.462[X²]
Coronary artery disease		1/2.4%	-	1/3.0%	-	1.000[X²]
ECMO		0/0.0%	-	2/6.1%	-	0.190[X²]
Symptoms						
High fever		19/45.2%	-	14/42.4%	-	0.807[X²]
Cough		13/31.0%	-	11/33.3%	-	0.826[X²]
Dyspnea		31/73.8%	-	24/72.7%	-	0.916[X²]
Myalgia		4/9.5%	-	5/15.2%	-	0.457[X²]
Headache		1/2.4%	-	4/12.1%	-	0.093[X²]
GIS symtoms		3/7.1%	-	1/3.0%	-	0.626[X²]
Loss of taste and smell		0/0.0%	-	0/0.0%	-	1.000[X²]
Pleural effusion		9/21.4%	-	9/27.3%	-	0.556[X²]
Lung involvement		34/81.0%	-	25/75.8%	-	0.586[X²]

SD: Standard deviation, DM: Diabetes mellitus, COPD: Chronic obstructive pulmonary disease, ECMO: Extracorporeal membrane oxygenation, GIS: Gastrointestinal system, [m]Mann-Whitney U test, [X²]chi-square test

of a higher mortality rate among COVID-19 patients with a higher PSI score more understandable. Additionally, one must expect that FIB-4 index, which is calculated using age, PLT count, and basic liver function tests ALT and AST, will be particularly higher in older patients who more commonly have multi-organ failure and liver injury, and a higher PSI score. In conclusion, high FIB-4 index and PSI score calculated early during SARS-CoV-2 infection indicates that these two parameters may independently predict mortality at an early stage. Furthermore, the combined use of these two scores, particularly when both of them are elevated, can allow physicians to diagnose SARS-CoV-2 infection requiring critical care at an early period, and to lower mortality by more aggressively treating such patients.

Study Limitations

Our study has some limitations. A relatively small number of patients is an important limitation. Other important limitations include the lack of having a basal abdominal ultrasonography and not excluding underlying liver diseases that could have increased FIB-4 index. Moreover, the lack of using other hepatic FIB scores such as AST-to-PLT ratio index, aminotransferase

Table 2. Comparison of laboratory findings between living and deceased patients

	Mortality (-)		Mortality (+)		p
	Mean ± SD/n-%	Median	Mean ± SD /n-%	Median	
Heart rate (beats per minute)	98.5±21.7	98.0	99.4±19.7	96.0	0.902[m]
Respiration rate (breaths per minute)	27.0±7.9	26.0	25.4±8.6	24.0	0.330[m]
Systolic blood pressure (mmHg)	136.3±24.7	140.0	124.1±26.2	120.0	**0.034**[m]
Diastolic blood pressure (mmHg)	77.1±15.8	80.0	72.3±14.8	73.0	0.110[m]
Arterial pH	7.4±0.1	7.4	7.3±0.1	7.3	**0.000**[m]
Use of ventilator	13/31.0%	-	31/93.9%	-	**0.000**[X²]
Use of high flow oxygen	36/85.7%	-	14/42.4%	-	**0.000**[X²]
PaO_2 (mmHg)	86.0±19.2	87.5	54.5±8.7	55.0	**0.000**[m]
SPO_2 (%)	95.5±3.4	97.0	79.1±12.5	78.0	**0.000**[m]
FIB-4	2.6±1.6	2.0	14.7±15.9	12.0	**0.000**[m]
PSI	114.2±43.3	108.5	155.2±39.1	163.0	**0.000**[m]
Sodium (mEq/L)	137.0±5.7	137.0	134.9±6.3	136.0	0.096[m]
Glucose (mg/dL)	163.8±81.9	131.1	167.7±93.5	131.8	0.728[m]
Hematocrit (L/L)	34.9±7.3	35.8	33.0±5.6	33.1	0.182[m]
ALT (U/L)	61.3±126.0	37.9	183.9±766.6	23.4	0.144[m]
AST (U/L)	64.4±63.8	47.3	334.0±1510.2	40.6	0.873[m]
Platelet (10^9/L)	245.8±99.8	228.0	250.6±135.3	205.0	0.823[m]
LDH (U/L)	412.8±190.9	359.0	659.5±1230.9	420.0	0.188[m]
CRP (mg/L)	134.1±108.8	92.1	161.3±87.8	163.0	0.147[m]
D-dimer (ng/L)	2900±2870	1852	5173±9897	1992	0.361[m]
Troponin (ng/L)	0.07±0.19	0.01	0.48±1.39	0.01	0.526[m]
Lymphocyte (cells/mm^3)	1.04±0.56	0.84	1.83±5.42	0.82	0.279[m]
Neurophil (cells/mm^3)	8.74±5.25	7.51	9.70±4.89	9.64	0.245[m]
NLR	12.7±13.3	8.2	12.8±9.1	10.6	0.245[m]
PLR	337.8±329.7	288.5	321.3±212.3	276.3	0.777[m]
Ferritin (ng/L)	1335,7±2557,7	596	4382,6±1631,3	946,6	0.036[m]
IL-6 (pg/mL)	227.8±348.2	94.7	763.3±1353.9	151.1	0.097[m]
Time of stay in ICU	8.9±6.5	7.0	9.6±7.9	8.0	0.563[m]

SD: Standard deviation, PaO_2: Partial Pressure of oxygen, SPO_2: Blood oxygen saturation, FIB-4: Fibrosis-4, PSI: Pneumonia severity index, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, LDH: Lactate dehydrogenase, CRP: C-reactive protein, NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio, IL-6: Interleukin-6, ICU: Intensive care unit, [m]Mann-Whitney U test, [X²]chi-square test

ratio to alanine in addition to FIB-4 index may also be considered a limitation. Another important limitation is that other risk scores predicting mortality in COVID-19 infection, such as Severe Community-Acquired Pneumonia, COVID-GRAM score, and CURB-65 score, were not calculated and thus their correlation to FIB-4 was not analyzed (22,23).

CONCLUSION

FIB-4 index, and PSI score calculated at an early period among patients admitted to intensive care unit for COVID-19 appears to be good predictors of in-hospital mortality. More extensive, randomized studies are needed on this subject.

ETHICS

Ethics Committee Approval: This study complied with the criteria of Helsinki Declaration and approved by Istanbul Medipol University Non-Invasive Clinical Research Ethics Committee (decision no: 91, date: 21.01.2021).

Informed Consent: Informed consent form was filled out by all participants.

Authorship Contributions

Surgical and Medical Practices: C.E., H.G., A.Y., Concept: E.D., O.O., Design: E.D., Data Collection or Processing: A.Y., R.Ç., H.G., Analysis or Interpretation: E.D., O.O., H.G., Literature Search: E.D., R.Ç., A.Y., Writing: E.D.

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

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

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