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Original Research

Predictive Value of Nutrition and Inflammation-Related Indices on Prognosis in Type 2 Diabetes Mellitus Patients with Coronavirus Disease-2019

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Abstract

Objectives: This study aimed to demonstrate how the prognostic nutritional index (PNI) and systemic immune-inflammatory index (SII) help predict the severity and prognosis of patients with type 2 diabetes (T2DM) and coronavirus disease (COVID-19).

Methods: This retrospective cohort study included 501 T2DM patients (male, 42.1%; female, 57.9%) who were hospitalized due to COVID-19 between April 2020 and December 2020. The patients were divided into survivors and non-survivors. After comparing demographic and laboratory data between the groups, the correlation of PNI and SII with clinical and laboratory data was evaluated.

Results: The median (interquartile) ages of the non-survivor and survivor groups were 74 (15) and 69 (14) years, respectively, and the difference was significant (p<0.001). The PNI was significantly lower in the non-survivor group than in the survivor group (p<0.001). The SII was significantly higher in the non-survivor group than in the survivor group (p<0.001). PNI was negatively correlated with glucose levels (r=-0.115, p=0.011). If the cut-off PNI value of 29.1 was used, it had a sensitivity and specificity of 76.2% and 76.3%, respectively, in predicting the severity of the illness and the risk of death in T2DM patients.

Conclusion: Consequently, the PNI and SII levels are effective in predicting survival and disease severity in patients with COVID-19 and T2DM.

Keywords: Coronavirus disease-2019, prognostic nutritional index, systemic immune–inflammatory index, type 2 diabetes mellitus

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Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has caused a pandemic. Over 270 million cases of coronavirus disease-2019 (COVID-19) have been diagnosed, and more than 5.2 million people died worldwide.[1] It has complications ranging from asymptomatic disease to life-threatening multi-organ failure and a non-specific clinical course leading to death. Type 2 diabetes (T2DM) is one of the most serious comorbidities in COVID-19 patients and is critical for disease severity and mortality.[2] The rate of T2DM in patients with COVID-19 varies from 5.7% to 68.7% globally.[2,3] The mortality rates in T2DM vary from 3% to 25%, depending on the studied country and geography.

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[4] The effects of poor glycaemic control and inflammatory parameters on morbidity and mortality were observed in patients with T2DM accompanied by COVID-19.[5,6] Inadequate nutritional status and immunological dysfunction (mainly decreased T lymphocytes) have been observed to be effective in the prognosis of SARS CoV-2 infection.[7,8] Inflammation was found to be associated with the clinical severity and mortality of COVID-19.[9]

Hypoalbuminemia, which develops due to inflammation and prolonged malnutrition, and lymphocytopenia, which usually occurs in viral infections, are two of the important findings of COVID-19. The prognostic nutritional index (PNI) is a parameter that reflects the patient's nutritional status and immune function. PNI is calculated using albumin and lymphocyte counts. PNI has been associated with prognosis in various patient groups, such as gastrointestinal surgery, cardiovascular diseases, and inflammatory diseases.[10,11] Another metric that represents immunity and inflammation is the systemic immune-inflammatory index (SII), which has been linked to the severity of numerous tumors and illnesses. SII is a new index that shows the patient's immune status and inflammation level. SII is calculated from the inflammatory parameters such as lymphocyte, neutrophil and platelet counts.[12] SII has been shown to be a marker of atherosclerosis that develops as a result of inflammation in cardiovascular diseases.[13] In addition, it has been revealed that it can be a prognosis indicator in respiratory system and urological cancers.[14] Thus, this single-centre retrospective study aimed to examine the effect of PNI and SII in determining the severity and prognosis of patients with T2DM and COVID-19.

Methods

Study Design

The study included 501 patients with T2DM who were hospitalized in Aksaray University Training and Research Hospital between 1 April 2020, and 31 December 2020, and diagnosed with COVID-19. Informed consent was obtained from all patients to be included in the study. COVID-19 infection was verified in throat and nose swab samples through a reverse-transcription polymerase chain reaction assay. The demographic and clinical outcomes of these patients were obtained from the hospital's digital database.

Surviving (n=400) and non-surviving (n=101) patients were evaluated as two different groups. Laboratory tests included blood counts (total count of leukocytes, lymphocytes, neutrophil, platelet and haemoglobin), glucose, haemoglobin A1c (HbA1c), creatine, creatine kinase (CK), lactate dehydrogenase (LDH), albumin, alanine aminotransferase (ALT), D-dimer and C reactive protein (CRP). The formula[10] shown was used to calculate the PNI=10×serum albumin (g/dL)+0.005×peripheral lymphocyte count (/mm^3). SII was also considered, which was determined using the formula: SII=neutrophil count×platelet count/lymphocyte count.[12]

All methods of our study took into account the ethical rules of the authoritative human experiments committee and the 2008 revision of the 1975 Declaration of Helsinki. The Aksaray University Clinical Research Ethics Committee examined and approved this study (Approval no. 25-SBKAEK, 2021/09-05).

Statistical Analysis

Descriptive statistics will be used to identify continuous variables. Parameters with normal distribution are presented as mean±standard deviation, whereas those that deviated from the normal distribution are presented as median and interquartile range (IQR). The Kolmogorov-Smirnov test was used to check for normal distribution in continuous data. According to the correspondence between categorical variables, the Chi-square or Fisher exact test was used. The relationship between two continuous variables that did not conform to a normal distribution was examined with the Mann–Whitney U test, and the relationship between two continuous variables that conformed to a normal distribution was examined by Student's t-test. The correlation between two continuous variables was calculated with the Pearson correlation coefficient (with the Spearman rho correlation coefficient if it does not meet the parametric assumptions). The receiver operating characteristic (ROC) curve was used to identify the best cut-off values of the PNI and SII for predicting COVID-19 mortality. Data were analyzed using SPSS software Version 20.0 (IBM Corp., Armonk, NY, USA). For all statistical analyses, $p<0.05$ was considered significant.

Results

Of the 501 patients, 42.1% were male and 57.9 % were female. Regarding gender, there was no difference between the groups (p=0.056). The median (IQR) ages of the non-survivor T2DM and survivor T2DM cohorts were 74 (15) and 69 (14) years, respectively, and the difference was significant ($p<0.001$). In terms of the comorbidities, the non-survival group had substantially higher rates of acute kidney damage (AKI), acute heart failure, septic shock, ARDS, and acute myocardial infarction (AMI) than the other group (Table 1).

The decrease in PNI levels in the non-survivor group was significant when compared to the other group (median [IQR], 21.6 (5.4) vs. 31.6 (5.4), $p<0.001$). The rise in SII levels was significant in the non-survivor group compared to

Table 1. Comparison of demographical characteristic, comorbid conditions and laboratory parameters of patients with T2DM with Coronavirus Disease-2019 on admission to hospital according to mortality

Parameters (median [IQR])	All patients (n=501)	Non-survivors (n=101)	Survivors (n=400)	p
Age, years(median [IQR])	70 (14)	74 (15)	69 (14)	<0.001
Gender (male), n (%)	211 (42.1)	51 (50.5)	160 (40)	0.056
Comorbid conditions				
Hypertension, n (%)	424 (84.6)	89 (88.1)	335 (83.8)	0.277
Dyslipidaemia, n (%)	309 (61.7)	62 (61.4)	247 (61.8)	0.946
HF, n (%)	65 (13)	21 (20.8)	44 (11)	0.009
CAH, n (%)	278 (55.5)	64 (63.4)	214 (53.5)	0.075
Asthma, n (%)	98 (19.6)	15 (14.9)	83 (20.8)	0.178
COPD, n (%)	88 (17.6)	19 (18.8)	69 (17.3)	0.720
CVD, n (%)	65 (13)	16 (15.8)	49 (12.2)	0.337
CKD, n (%)	100 (20)	30 (29.7)	70 (17.5)	0.006
CLD, n (%)	5 (1)	1 (1)	4 (1)	0.993
Cancer, n (%)	12 (2.4)	5 (5)	7 (1.8)	0.060
Laboratory values				
Glucose (mg/dL)	200 (128)	224 (129)	175 (122)	0.051
HbA1c (%)	8.3 (2.7)	8.5 (2.9)	8.2 (2.6)	0.347
Creatine (mg/dL)	0.81 (0.51)	1.8 (3.1)	0.76 (0.31)	<0.001
TSH (mU/ml)	1.5 (1.3)		1.5 (1.3)	0.017
ALT (U/L)	27 (32)	25 (28)	27 (29)	0.531
Total bilirubin (mg/dL)	0.5 (0.3)	0.6 (0.9)	0.5 (0.3)	<0.001
Albumin (gr/L)	3 (0.6)	2.4 (0.6)	3.2 (0.5)	<0.001
D-dimer (ng/mL)	838 (849)	3890 (5074)	806 (715)	<0.001
CRP (mg/L)	20.1 (53.6)	152.4 (161)	14.5 (25.9)	<0.001
Uric acid (mg/dL)	6 (4.4)	8.4 (8)	5.1 (3.5)	<0.001
CK (U/L)	35 (46)	82 (99)	30 (25)	<0.001
LDH (U/L)	292 (149)	696 (340)	272 (103)	<0.001
Ferritin (ng/mL)	286 (510.8)	1071.6 (973.1)	226.9 (324)	<0.001
Leucocyte count ($10^3/mm^3$)	8.7 (5.7)	17.9 (11.4)	7.8 (4.9)	<0.001
Neutrophil count ($10^3/mm^3$)	6.7 (5.4)	17.1 (12.1)	5.6 (4.4)	<0.001
Lymphocyte count ($10^3/mm^3$)	1.1 (0.9)	0.6 (0.5)	1.3 (0.8)	<0.001
Platelet count ($10^3/mm^3$)	260 (151)	229 (127)	277 (166)	<0.001
Hgb (g/dL)	12.4 (2.6)	10.1 (5)	12.5 (2.4)	0.051
NLR	6.2 (8.4)	33.9 (24.5)	4.5 (5.7)	<0.001
PLR	227.4 (217.7)	360 (401.5)	212.9 (197.4)	<0.001
SII	1593 (2476.2)	8246.3 (9479.4)	1356.7 (1647.4)	<0.001
PNI	30.7 (6.2)	21.6 (5.4)	31.6 (5.4)	<0.001
Complications				
AKI, n (%)	110 (22)	59 (58.4)	51 (12.8)	<0.001
Acute heart failure, n (%)	4 (0.8)	3 (3)	1 (0.2)	<0.001
ARDS, n (%)	55 (11)	52 (51.5)	3 (0,8)	<0.001
AMI, n (%)	8 (1.6)	8 (7.9)	0 (0)	<0.001
Septic shock, n (%)	67 (13.4)	64 (63.4)	3 (0.8)	<0.001

p<0.05 statistically significant; HF: Heart failure; CAH: Coronary artery disease; COPD: Chronic obstructive pulmonary disease; CVD: Cerebrovascular disease; CKD: Chronic kidney disease; CLD: Chronic liver disease; HbA1c: haemoglobin A1c; TSH: Thyroid-stimulating hormone; ALT: alanine transaminase; CRP: C-reactive protein; CK: creatine kinase; LDH: Lactate dehydrogenase; Hgb: Haemoglobin; NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio; SII: Systemic immune-inflammation index; PNI: Prognostic nutritional index; AKI: Acute kidney injury; ARDS: Acute respiratory distress syndrome; AMI: Acute myocardial infarction.

the other group (median [IQR], 8246.3 (9479.4) vs. 1356.7 (1647.4), p<0.001) (Table 1). A significant correlation was found between PNI levels and age; duration of hospital stay; glucose; total bilirubin; levels of albumin, CRP, CK, LDH and ferritin; leucocyte count; neutrophil count; lymphocyte count; NLR; PLR; haemoglobin; and platelet count. A significant correlation was noted between SII levels and age; levels of albumin, D-dimer, CRP, LDH and ferritin; leucocyte count; lymphocyte count; neutrophil count; PLR; NLR; and platelet count (Table 2).

The ROC curve was used to analyze the PNI and SII values in the prediction of disease mortality in patients with T2DM and COVID-19, and both were significant (PNI: AUC=0.848, 95% confidence interval [CI] 0.801–0.895, p<0.001), (SII: AUC=0.198 95% CI 0.144–0.253, p<0.001). When the cut-off PNI value was set at 29.1, it demonstrated 76.2% sensitivity and 76.3% specificity for predicting disease severity and mortality risk in T2DM survivors (Fig. 1). When the SII level was set at 2270.3, the sensitivity and specificity for predicting disease severity and death were 26.7% and 26.5%, respectively, but this was not significant (Fig. 2).

Table 2. Correlations between prognostic nutrition index, systemic immune-inflammatory index and laboratory parameters of patients with T2DM with Coronavirus Disease-2019 on admission to hospital

Parameters	PNI		SII	
	r	p	r	p
Age	-0.313	<0.001	0.116	0.009
Hospital stay	-0.330	<0.001	0.026	0.562
HbA1c	-0.114	0.110	-0.083	0.244
Glucose	-0.115	0.011	0.065	0.149
Total bilirubin	-0.194	<0.001	0.039	0.394
Albumin	1.000	<0.001	-0.343	<0.001
D-dimer	-0.109	0.107	0.139	0.039
CRP	-0.424	<0.001	0.379	<0.001
Uric acid	0.163	0.063	-0.071	0.420
CK	-0.155	0.001	-0.008	0.861
LDH	-0.422	<0.001	0.253	<0.001
Ferritin	-0.454	<0.001	0.344	<0.001
Leucocyte count	-0.374	<0.001	0.598	<0.001
Neutrophil count	-0.438	<0.001	0.670	<0.001
Lymphocyte count	1.000	<0.001	-0.394	<0.001
Platelet count	0.217	<0.001	-0.121	0.007
Hgb	0.269	<0.001	-0.107	0.017
NLR	-0.446	<0.001	0.846	<0.001
PLR	-0.228	<0.001	0.783	<0.001

p<0.05 statistically significant; HbA1c: haemoglobin A1c; CRP: C-reactive protein; CK: creatine kinase; LDH: Lactate dehydrogenase; NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio; Hgb: Haemoglobin, SII: Systemic immune-inflammation index; PNI: Prognostic nutritional index.

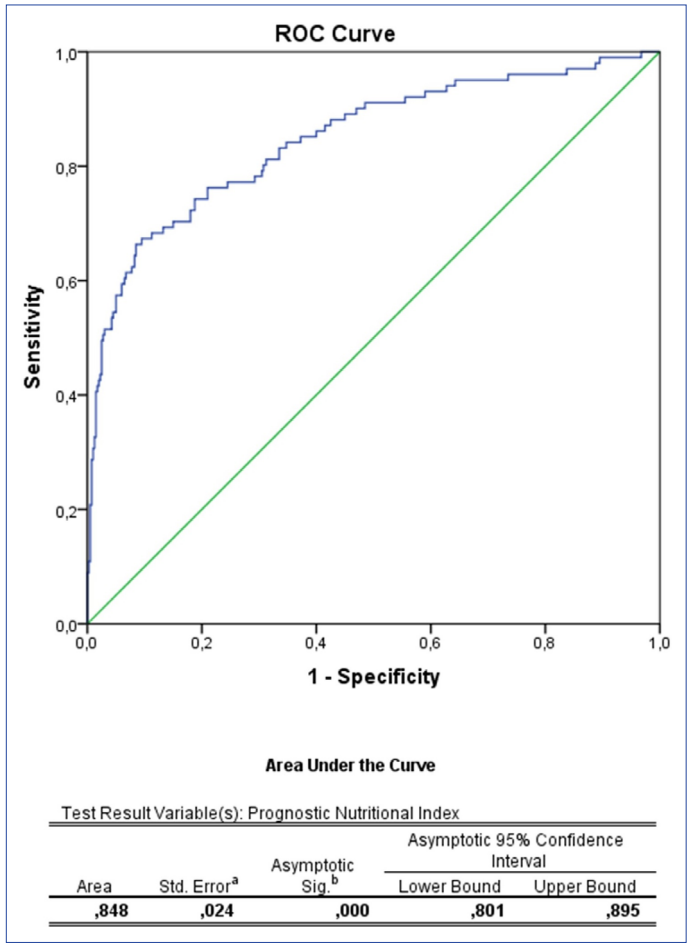
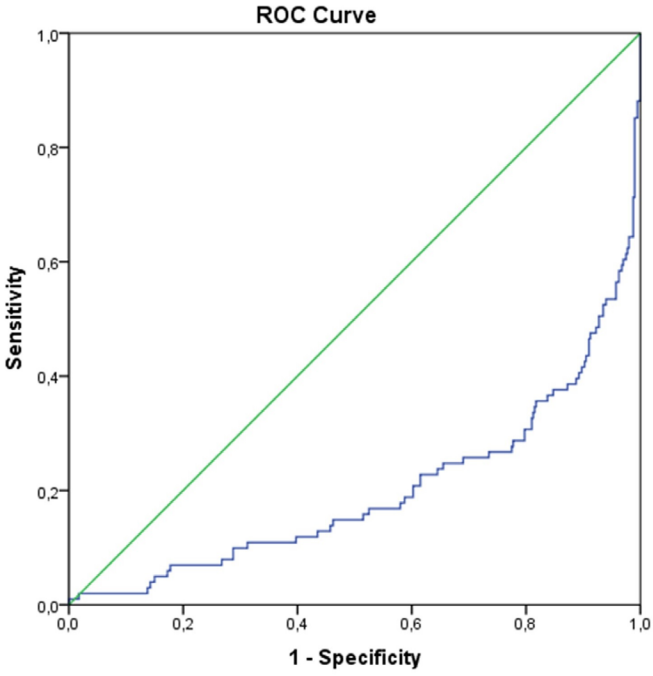


Figure 1. Receiver operating characteristic (ROC) curve of PNI in COVID-19 mortality.

Discussion

This study demonstrated that PNI and SII are independent predictors of COVID-19 mortality in patients with T2DM. A PNI <29.1 was the optimal cut-off for risk assessment. Advanced age was reported as an important factor in the prognosis and severity of COVID-19.[15] Similarly, the non-survivors were of advanced age. Consistent with the literature, hypertension was the most common comorbidity in addition to DM.[2] Heart failure, chronic renal failure and cancer occurred more frequently in the non-survivor group than in the survivor group.

Various parameters have affected COVID-19 morbidity and mortality. Especially, parameters showing immune system status and inflammation are important in demonstrating the disease process of COVID-19. There may be a significant increase in neutrophil count, leukocyte count and ferritin, D-dimer, LDH, CRP and fibrinogen levels in patients with critical COVID-19 in relation to their severity. On the contrary, a decrease in lymphocyte count, platelet count, ferritin, haemoglobin and albumin levels were associated with



Area Under the Curve

Test Result Variable(s): Systemic immune-inflammatory index (SII)

Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
,198	,028	,000	,144	,253

Figure 2. Receiver operating characteristic (ROC) curve of SII in COVID-19 mortality.

COVID-19 severity.[6,9,16] Albumin is a serum protein and its plasma level may vary depending on inflammation and nutritional status. Hypoalbuminaemia was found to be associated with prognosis in severe diseases.[17] Hypoalbuminaemia can be observed in patients with critical COVID-19 following an increase in vascular permeability and deterioration of liver and kidney functions. COVID-19 morbidity and mortality were found to be associated with a decrease in albumin levels.[18] Lymphocytopaenia, an immunological indicator in viral infections, was observed to be associated with COVID-19 severity and mortality.[19] A decrease in the number and activity of CD4 and CD8 T-cells, natural killer cells and B cells was observed in severe COVID-19. Therefore, hypoalbuminaemia and lymphocytopaenia are early markers in predicting the severity of COVID-19.[20]

PNI is a parameter that indicates malnutrition and immunity status calculated from albumin and lymphocyte count. PNI has been found to be associated with prognostic clinical outcomes in many infectious diseases. Wang et al.[21] were the first to identify the association of PNI with COVID-19 severity. Some subsequent studies have observed that PNI is associated with mortality, need for intensive care and serious clinical outcomes in COVID-19.[20,21] It can predict the severity of COVID-19 much more precisely than albumin and lymphocyte levels.[11] In the study of Anzo et al.,[22] PNI was found to be associated with both the severity and mortality of COVID-19. The predictive threshold value of PNI for severe COVID-19 was calculated as 44.81, with specificity and sensitivity similar to our study. In addition, a PNI level of 42.49 was found to be a significant threshold in predicting mortality of COVID-19. In the multiple inflammatory parameter analysis conducted by Çelik et al.[23] on hospitalized patients with COVID-19, PNI was found to be the most powerful parameter in predicting mortality of the disease. PNI provides 80% sensitivity and 64.1% specificity at a threshold value of 40.71. In the large-scale study of Cakirca et al.[24] with 827 COVID-19 patients, low PNI was found to be an important determinant of mortality, independent of other parameters. In this study, the threshold value of PNI of 40.03 predicts mortality with 90.43% sensitivity and 77.63% specificity. In addition, this study showed that PNI was the index with the highest AUC in ROC analysis and was the most valuable indicator compared to other indices in predicting mortality. Studies on PNI in COVID-19 subgroups are insufficient, such as in those with diabetes. Although it has been observed in the literature that glycemic regulation negatively affects mortality in diabetic patients in severe COVID-19, this effect was not observed in our study, but PNI showed very serious effects on mortality. Poorly controlled hyperglycaemia can suppress the patient's immune system and worsen COVID-19 severity,[25] similar to a decrease in PNI. However, poor glycaemic regulation is associated with mortality, need for intensive care and poor clinical outcomes in COVID-19.[7,26] This relationship has not been fully observed in our study. This may be because all patients participating in our study were diagnosed with T2DM and our study did not include a comparison with non-diabetic patients. Basal high glycemic levels (especially HbA1c) may not have shown sufficient change in the acute infection due to COVID-19. Since PNI is calculated with parameters that can change more rapidly in case of acute infection, it may be a more prognostic indicator than glycemic parameters. Although no significant difference was found between the two groups in terms of HbA1c and glucose levels, PNI was negatively correlated with serum glucose levels. Moreover, PNI demonstrated significant associations with inflammatory parameters and was a significant early predictor of mortality in patients with T2DM and COVID-19. In addition, a significantly negative correlation was observed between PNI and age, duration of hospital stay and laboratory parameters related to inflammation in our study.

The systemic index is associated with clinical outcomes in many tumors and infectious diseases. A few studies have shown association between mortality and severity in COVID-19.[11,27] In these studies, SII was higher in patients who developed ARDS, needed intensive care and died. Only a few publications regarded SII in diabetics with COVID-19. In this study, it was significantly higher in non-survivors. The significant cut-off value could not be observed because of the small sample size. It was positively correlated with inflammatory parameters and age, independent of glycaemic control.

In a meta-analysis of 39 articles by Mangoni et al.,[28] high SII was found to be associated with the severity of COVID-19 and mortality due to COVID-19. In a multicenter COVID-19 study conducted by Hamad et al.,[29] SII (>1346) was found to be the inflammation marker with the highest specificity (95.6%) in indicating the severity of the disease. In the study of Karaaslan et al.,[30] SII was found to be significantly higher in patients who died due to COVID-19 than in patients who survived. In this study, it was shown that when the cut-off value of SII was accepted as 618.8, COVID-19 mortality could be predicted with 80% sensitivity and 61.5% specificity.

This study has several limitations. First, it is a single-center cohort study with a retrospective design. Second, some data on the patients such as height, weight, blood pressure and fibrinogen levels at admission were lacking because of the epidemic urgency. Finally, nutritional data that will affect the malnutrition status of patients were missing. Therefore, more prospective studies on patients with DM are needed, but due to pandemic conditions, this may be difficult to do.

Conclusion

PNI and SII levels are determinants of COVID-19 mortality and disease severity in patients with T2DM. A PNI level <29.1 indicates COVID-19 mortality in T2DM patients with high sensitivity and specificity. Similarly, SII level >2270.3 is an important indicator in predicting COVID-19 mortality. The results obtained in this study may provide guidance for early recognition and close treatment of COVID-19 patients with T2DM with poor prognosis.

Disclosures

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Ethics Committee Approval: The Aksaray University Clinical Research Ethics Committee examined and approved this study (Approval no. 25-SBKAEK, 2021/09-05).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – A.B., M.E., T.S.M.; Design – A.B., M.E., T.S.M.; Supervision – D.Y.; Materials – M.E., T.S.M., R.C.; Data collection &/or processing – A.B., M.E., T.S.M.; Analysis and/or interpretation – A.B., M.E.; Literature search – R.C., D.Y.; Writing – A.B., M.E., T.S.M.; Critical review – R.C., D.Y.

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