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Can prognostic nutritional index and systemic immune-inflammatory index predict disease severity in COVID-19?

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Abstract

Background: Prognostic nutritional index (PNI) and systemic immune-inflammatory index (SII) are inflammation-based novel markers that predict the prognosis in various patient populations. We have investigated the relationship between the disease severity in COVID-19, and the PNI and SII scores in the present study.

Materials and Methods: This cross-sectional retrospective study included 118 hospitalised patients with a confirmed diagnosis of COVID-19. The patients were divided into two groups as those who were hospitalised at the intensive care unit (ICU) and those who had been internalised at the clinic (non-ICU).

Results: Of the 118 patients, 50.8% were male. The mean age was 57.7 ± 17.5 years in non-ICU patients and 70.3 ± 11.7 years in ICU patients and the difference was statistically significant ($P < .001$). The lymphocyte count and the albumin levels were significantly lower in ICU patients ($P < .001$, $P < .001$, respectively). The PNI score was significantly lower in ICU patients compared with non-ICU patients ($P < .001$). The SII score was found to be significantly higher in ICU patients compared with non-ICU patients ($P < .001$). The value of PNI and SII scores in prediction of the disease severity in COVID-19 was evaluated with the ROC analysis (PNI: AUC = 0.796, 95%CI: 0.715-0.877, $P < .001$; SII: AUC =0.689, 95% CI: 0.559-0.819, P=.004). When the cut-off value was taken as ≤36.7 for the PNI score, it was found to have 73.4% sensitivity and 70.8% specificity for predicting of the disease severity and ICU admission probability was 4.4 times higher. When the cut-off value was taken as ≥813.6 for SII score, it was found to have 70.8% sensitivity and 66.0% specificity for predicting of the disease severity and ICU admission probability was six times higher.

Conclusion: The PNI and the SII scores are independent predictors of the prognosis and the disease severity in COVID-19 patients who require hospitalisation at the ICU.

1 | INTRODUCTION

Lower respiratory tract infection cases with unknown etiology predicted to be of viral origin were reported in Hubei, Wuhan on 31 December 2019. Fever, non-productive cough, dyspnoea and bilateral pneumonic infiltration were reported in the patients.[1] However, studies have revealed that the clinical symptoms of Coronavirus disease-2019 (COVID-19) may vary between asymptomatic disease, non-specific symptoms, mild, self-limited respiratory disease and severe pneumonia, which may present with acute respiratory distress syndrome (ARDS), multi-organ dysfunction and death.[2,3] Death has usually occurred in patients with advanced age or have comorbid systemic conditions including hypertension, diabetes mellitus, cardiovascular, chronic obstructive lung disease, malignancy and other immune-suppressive conditions.[4]

An exaggerated, uncontrolled and severe inflammatory response is the most critical process that plays a role in disease

severity and a poor prognosis. Although many different molecules may play a role in the inflammatory response, elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), pro-inflammatory cytokines, ferritin, procalcitonin and hypoalbuminemia have been found to be the most correlated with severe disease and mortality.[5,6] Neutrophil, lymphocyte count and the neutrophil-to-lymphocyte ratio (NLR) and the platelet to lymphocyte ratio (PLR) are systemic inflammation markers.[7,8] The immunity and the nutritional status of the host play an important role in infectious diseases.[9] The Prognostic Nutritional Index (PNI) reflects the immune-nutritional status of the patients.[10] PNI is a predictor of severity and mortality in patients with inflammatory diseases, gastrointestinal surgery and cardiovascular disease (acute Stanford type A aortic dissection).[9-11] A poor nutritional status and immune dysfunction have been accepted to be the risk factors for severe infection caused by SARS-CoV-2.[12] There are very few studies, of which one is a pre-print, investigating the role of PNI in reflecting the inflammatory status and prediction of prognosis in COVID-19 patients.[13,14] Systemic immune-inflammatory index (SII) is another parameter that reflects the immune and inflammatory status of the organism.[15] SII is a predictor of disease severity and prognosis in patients with tumours, inflammatory diseases, obesity, pulmonary embolism and undergoing primary PCI for acute STEMI.[16-19] However, there are only a very few studies investigating the role of SII in reflecting the inflammatory status and prediction of prognosis in COVID-19 patients.[20] PNI and SII markers are helpful predictors for COVID-19 patients.

This retrospective single-centre study aims investigates the role of PNI, SII and other inflammatory biomarkers in the predicting the severity and prognosis in COVID-19-positive patients and analysing biochemistry data.

What's known

- Wang et al first found PNI lower in critically ill patients.
- In the pre-print study of Doğancı et al showed that PNI can be used as a valuable predictor of hospital mortality.
- SII might be prognostic indicator to assess the in-hospital mortality (Li et al) and the requirement for invasive mechanic ventilator support (Muhammad et al) in patients with COVİD-19 patients.

What's new

- Our study was the first study to evaluate PNI and SII together.
- In ICU patients with COVID-19, the PNI score was lower and the SII score was higher compared with non-ICU patients.
- Taking the cut-off value ≤36.7 for PNI and cut-off as ≥813.6 for SII, the probability of ICU admission was 4.4 and 6 times higher, respectively.
- PNI and SII scores are important independent predictors in determining the need for intensive care unit (ICU), prognosis and disease severity in COVID-19 patients.
- The PNI and the SII scores may easily and rapidly be calculated from routine blood tests. Hence, it may be helpful for prediction of the ICU need during this period when mutant strains with the potential to spread the disease worldwide have emerged.
- Furthermore, these markers are of vital importance for the early diagnosis of potentially critical illness, providing medical care and improving the prognosis.

2 | METHODS

A total of 118 patients who had been hospitalised at the Sakarya University Research and Training Hospital from 1 April 2020 to 30 May 2020 and who had been diagnosed with COVID-19 were included in the study. Inclusion and exclusion criteria were shown as flow chart (Figure 1). Nasal and pharyngeal swabs were obtained from all patients. Isolated samples were tested with the Biospedy (Bioeksen, Turkey) real-time reverse transcriptase-polymerase chain reaction (rRT-PCR) kit that was provided by the Ministry of Health. The hospital records of the patients above 18 years of age were analysed retrospectively. The patients were divided into two groups hospitalised at the clinic and those hospitalised at the intensive care unit (ICU). Criteria for ICU were respiratory failure (requiring invasive oxygen support and monitored), ARDS, or multiple organ failure. Demographic/clinical data, laboratory parameters, and PNI and SII scores were compared between groups. Venous blood samples were drawn from all included patients at the time of hospitalisation in the ICU or non-ICU. Complete blood count (CBC) samples were studied at the biochemistry laboratory. The serum urea, creatinine, total cholesterol, triglyceride (TG), low-density lipoprotein (LDL), high-density lipoprotein (HDL), alanine transferase (ALT), aspartate transferase (AST) and the albumin values were tested with the alkaline picrate method using the Architect C 16000 (Abbott) device at the biochemistry laboratory of the hospital. The CBC parameters were tested with the Celldyn 3700 device. Neutrophil, lymphocyte, platelet, haemoglobin, CRP, procalcitonin and sedimentation values of all patients were recorded. The PNI was calculated according to the following formula[10]: PNI = 10 × serum albumin (g/dL) + 0.005 × peripheral lymphocyte count (/mm^3) and SII was calculated according to the following formula SII = neutrophil count × platelet count/lymphocyte count.[21] The ethics committee approval was obtained from the Sakarya University Medical School (Number: 71522473/050.01.04/131).

2.1 | Statistical analysis

Statistical analyses were performed using SPSS version 21 software. The suitability of the variables to normal distribution was examined

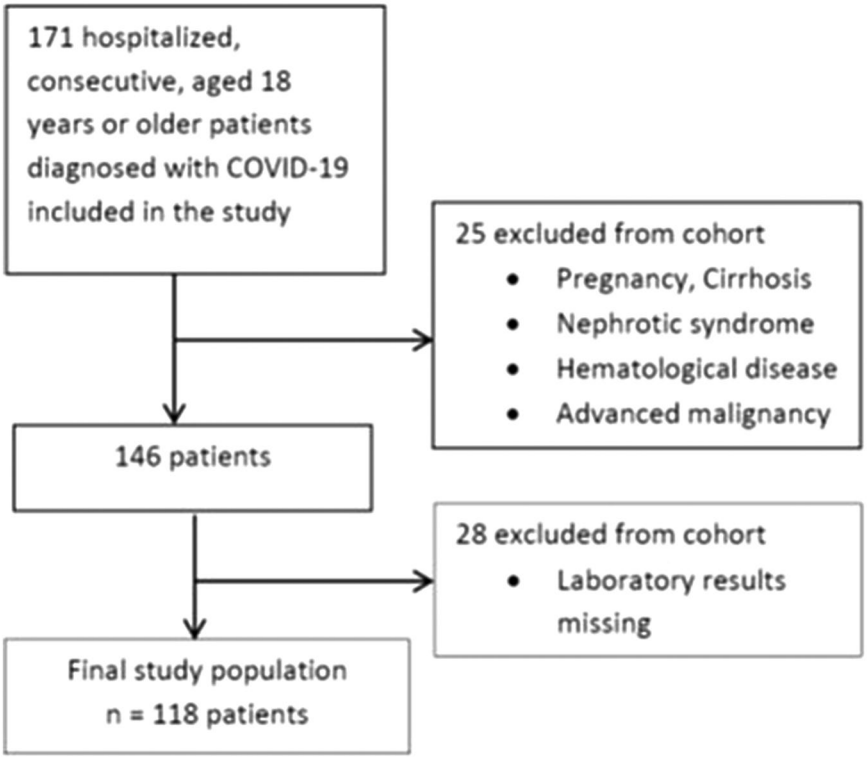


FIGURE 1 Study population inclusion/exclusion flow chart.

using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov). Categorical variables were described as frequencies and percentages. The chi-square test was used to determine whether there was any difference between the groups in terms of quality variables. The continuous variables were expressed as mean and standard deviation or as median and interquartile range, depending on the normality of their distribution. Whether there is a difference between the groups in terms of numerical variables; If parametric test conditions were fulfilled, independent groups were examined by *t*-test. If not, the Mann-Whitney *U* test was used. The effects of the patients PNI and SII scores on predicting mortality were analysed with the "Receiver Operating Characteristics (ROC)" curve analysis. The statistically significant two-tailed *P*-value was considered as <0.05.

3 | RESULTS

Of the 118 patients, 50.8% were males and 49.2% were females. The mean age was 57.7 ± 17.5 years in non-ICU patients and 70.3 ± 11.7 years in ICU patients and the difference was statistically significant (*P*<.001). No difference was found between the groups with regard to age (*P*=.301). The descriptive statistics for the demographic and the clinical characteristics have been displayed in Table 1. The presence of fever as the initial symptom was found to be significant in non-ICU patients (*P*=.021). There was a significant difference between the ICU patients and the non-ICU patients with regard to dyspnoea (*P*=.001). Hypertension and atherosclerotic cardiovascular disease (ASCVD) were found to be more frequent in ICU patients compared with non-ICU patients and the difference was statistically significant (*P*=.049, *P*<.001, respectively). The mortality rate was 24% in ICU patients (*P*<.001). LDH, procalcitonin, WBC, neutrophil count, D-dimer, CRP, ferritin and creatinine levels were significantly higher in ICU patients compared with non-ICU patients ($P < .001$, $P < .001$, $P = .002$, $P < .001$, $P < .001$, $P < .001$, $P < .001$, $P = 0.013$, respectively). There was no significant difference between the ICU and non-ICU patients with regard to the platelet count, although it was higher in ICU patients. The lymphocyte count, albumin, total cholesterol and the LDL levels were significantly lower in ICU patients ($P < .001$, $P < .001$, $P = .005$, $P = .005$, respectively) (Table 2).

The PNI levels were significantly higher in non-ICU patients than in ICU patients (42 ± 6.1 vs 34.2 ± 5.3, $P < .001$) (Figure 2). When the groups were compared with regard to the SII, it was found to be significantly lower in non-ICU patients compared with ICU patients (median [IQR]; 543 [349-877] vs. 1227 [622-1958], $P < .001$) (Figure 3).

The values of PNI and SII in the prediction of the disease course and disease severity were analysed with the ROC curve and both were found to be statistically significant (PNI: AUC = 0.796, 95%CI: 0.715-0.877, $P < .001$), (SII: AUC = 0.689 95%CI: 0.559-0.819, $P = 0.004$) (Figure 4). When the cut-off value was taken as ≤36.7 for the PNI score, it was found to have 73.4% sensitivity and 70.8% specificity for prediction of the disease severity and ICU admission probability than non-ICU was 4.4 times higher. When the cut-off value was taken as ≥813.6 for the SII score, it was found to have 70.8% sensitivity and 66.0% specificity for prediction of the disease severity and ICU admission probability was six times higher.

TABLE 1 Descriptive statistics showing the clinical findings and demographic characteristics of the patients

	Non-ICU patients ($n = 78$)	ICU patients ($n = 40$)	*P* value
Age (year)	57.7 ± 17.5	70.3 ± 11.7	**<.001**
Gender, F/M (%)	41/37 (52.6/47.4)	17/23 (42.5/57.5)	.301
Systolic blood pressure (mm Hg)	122.02 ± 15.7	125.56 ± 19.9	.364
Diastolic blood pressure (mm Hg)	74.22 ± 8.9	76.54 ± 16.1	0.405
Initial symptom, yes (%)			
Cough	39 (50.0)	23 (60.5)	.286
Fever	38 (48.7)	10 (26.3)	**.021**
Sore throat	7 (9.0)	2 (5.3)	.483
Dyspnoea	22 (28.2)	26 (68.4)	**<.001**
Nausea and vomiting	3 (3.8)	2 (5.3)	.578
Loss of taste	3 (3.8)	-	.221
Headache	4 (5.1)	2 (5.3)	.975
Chronic diseases, yes (%)			
Diabetes mellitus	25 (32.1)	11 (27.5)	.611
Hypertension	30 (38.5)	23 (57.5)	**.049**
COPD	4 (5.1)	4 (10.5)	.282
ASCVD	5 (6.4)	14 (35.0)	**<.001**
Chronic renal failure	5 (6.4)	6 (15.4)	.117
Malignancy	1 (1.3)	2 (5.3)	.205
Mortality	0	24 (60.0)	**<.001**

Descriptive results for continuous variables were expressed as mean and standard deviation or as median and interquartile range, depending on the normality of their distribution. ASCVD, atherosclerotic cardiovascular disease; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit. Results are expressed as numbers and percentages (in parentheses). Values below $P < .05$ were shown bold.

4 | DISCUSSION

In the present study, we have reported a cohort of 78 non-ICU patients and 40 ICU patients with laboratory-proven COVID-19 infection. The rates of advanced age, WBC, neutrophil count, CRP, procalcitonin, D-dimer, ferritin, LDH and the creatinine levels were significantly higher in ICU patients. The lymphocyte count and the albumin level were significantly lower in ICU patients. The effect of the PNI and the SII scores in the prediction of the disease severity was statistically significant. While PNI was lower among ICU patients, SII was higher.

In previous studies, advanced age and severe COVID-19 were found to be significantly correlated.[22] Similarly, in our study, the patients in ICU were of advanced age. COVID-19 is severe and potentially fatal in patients with comorbid conditions.[4] Hypertension was the most common comorbidity, followed by diabetes mellitus and coronary artery disease.[23] In our study, hypertension, ASCVD, diabetes mellitus and chronic renal failure were common in ICU patients. According to the Centre for Disease Control and Prevention, China, the mortality rate is ≤49% in critically ill patients.[24] Similarly, in our study, we found the mortality rate as 60% in ICU patients.

The uncontrolled and severe inflammatory response is the key process in the disease severity and poor prognosis in COVID-19. Many different molecules that play a role in this inflammatory response are related to severe disease and mortality. In a meta-analysis demonstrated that the WBC count, lymphocyte count, platelet count, interleukin-6 (IL-6) and serum ferritin were markers for critical illness.[25] In another meta-analysis, Ghahramani et al[26] found a significant reduction in lymphocyte count, haemoglobin, platelet count and albumin. The authors found a significant elevation in the neutrophil count, CRP, procalcitonin, LDH, D-dimer and the NLR in patients with severe COVID-19.[27] Elevated LDH, D-dimer, ferritin and creatinine levels were also found to be significantly correlated with severe COVID-19 in other studies.[22,28] Similarly, in our study, LDH, D-dimer, WBC, neutrophil count, CRP, procalcitonin, ferritin and the creatinine levels were significantly higher in ICU patients compared with non-ICU patients. Although the platelet count was higher in ICU patients, there was no statistically significant difference. In ICU patients, the lymphocyte count and the albumin level were significantly lower.

The prognostic nutrition index reflects the immune-nutritional status and chronic inflammation. A poor nutritional status and an immune dysfunction (particularly T lymphocyte) were accepted to be risk factors for severe infection caused by SARS-CoV-2.[12] We also investigated the predictive role of PNI and found that it was independently related with the disease severity and a poor prognosis. PNI is calculated using the peripheral lymphocyte count and serum

TABLE 2 Comparison of clinical and laboratory results according to the clinical severity of the disease

Variables	Non-ICU patients ($n = 78$)	ICU patients ($n = 40$)	*P* value
Lactatedehydrogenase (LDH) (U/L)	297 ± 100	473 ± 158	**<.001**
Procalcitonin (ng/mL)	0.06 (0.04-0.20)	0.23 (0.09-0.76)	**<.001**
White blood cell count ($10^3/mm^3$)	5.76 (4.88-7.93)	7.64 (5.69-10.7)	**.002**
Neutrophil count ($10^3/mm^3$)	3.63 (2.95-5.24)	5.64 (4.0-8.88)	**<.001**
Lymphocyte count ($10^3/mm^3$)	1.30 (0.91-1.90)	0.78 (0.49-1.18)	**<.001**
Platelet count ($10^3/mm^3$)	174 (150-231)	182 (144-219)	.998
Albumin (gr/L)	3.5 (3.2-3.8)	3 (2.7-3.3)	**<.001**
D-dimer (ng/mL)	550 (299-1080)	1260 (807-2080)	**<.001**
C-reactive protein (CRP) (mg/L)	32.2 (14.0-86.0)	113.0 (72.8-172.8)	**<.001**
Ferritin (ng/mL)	265 (122-606)	687 (426-1856)	**<.001**
Troponin (ng/L)	5.0 (2.1-7.9)	14.3 (6.0-52.6)	**<.001**
Creatinine (mg/dL)	0.78 (0.61-0.98)	0.91 (0.73-1.41)	**.013**
Total cholesterol (mg/dL)	158 ± 35	135 ± 44	**.005**
Low-density lipoprotein (LDL) (mg/dL)	100 ± 27	84 ± 32	**.005**
High-density lipoprotein (HDL) (mg/dL)	36 (27-42)	32 (23-38)	.115
Prognostic nutritional index (PNI)	42 ± 6.1	34.2 ± 5.3	**<.001**
Systemic immune-inflammation index (SII)	543 (349-877)	1227 (622-1958)	**<.001**

Continuous variables were expressed as means ± SD, or medians (interquartile ranges) and categorical variables as numbers with percentages (in parentheses). Values below $P < .05$ were shown bold.

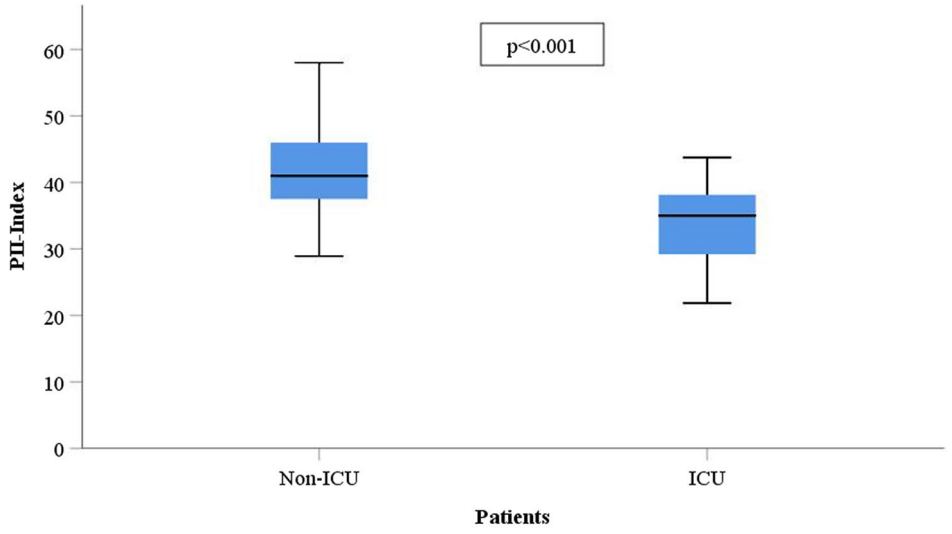


FIGURE 2 Comparison of Prognostic Nutritional Index (PNI) results between groups.

albumin level. It was first conceptualised and used by Buzby et al[10] for the prediction of the operative risk.

The albumin levels change in inflammation and malnutrition.[6] Albumin is an indicator of liver function status the body's and the body's nutritional status. Severe inflammation is related to hypoalbuminemia.[29] The hyperinflammatory status developing together with "cytokine storm" has revealed the potential predictive role of hypoalbuminemia in patients with COVID-19. Hypoalbuminemia results from reduced albumin synthesis due to hepatocellular damage in severe COVID-19. Increased capillary permeability may lead albumin to migrate to the interstitial space in many inflammatory diseases.[30] Lymphocytopenia has been shown to increase the COVID-19 severity.[28] SARS-CoV-2 may mainly act on lymphocytes, especially the T lymphocytes. The total lymphocytes, B cells, CD^{4+} T cells and CD^{8+} T cells were decreased in SARS-CoV-2 patients, and severe cases had a lower level than mild cases.[31] Immune dysfunction and immunological events caused by SARS-CoV-2 are the main mechanisms of progression of COVID-19 and this suggests that

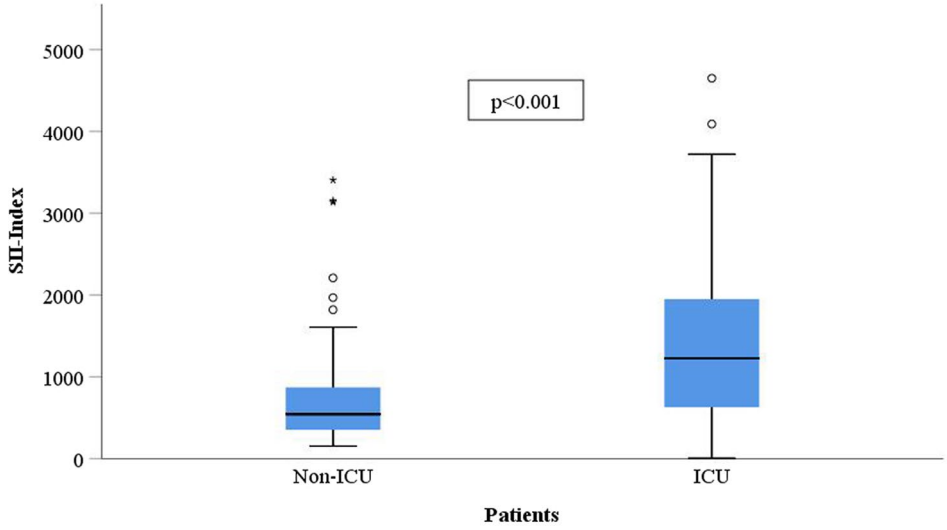
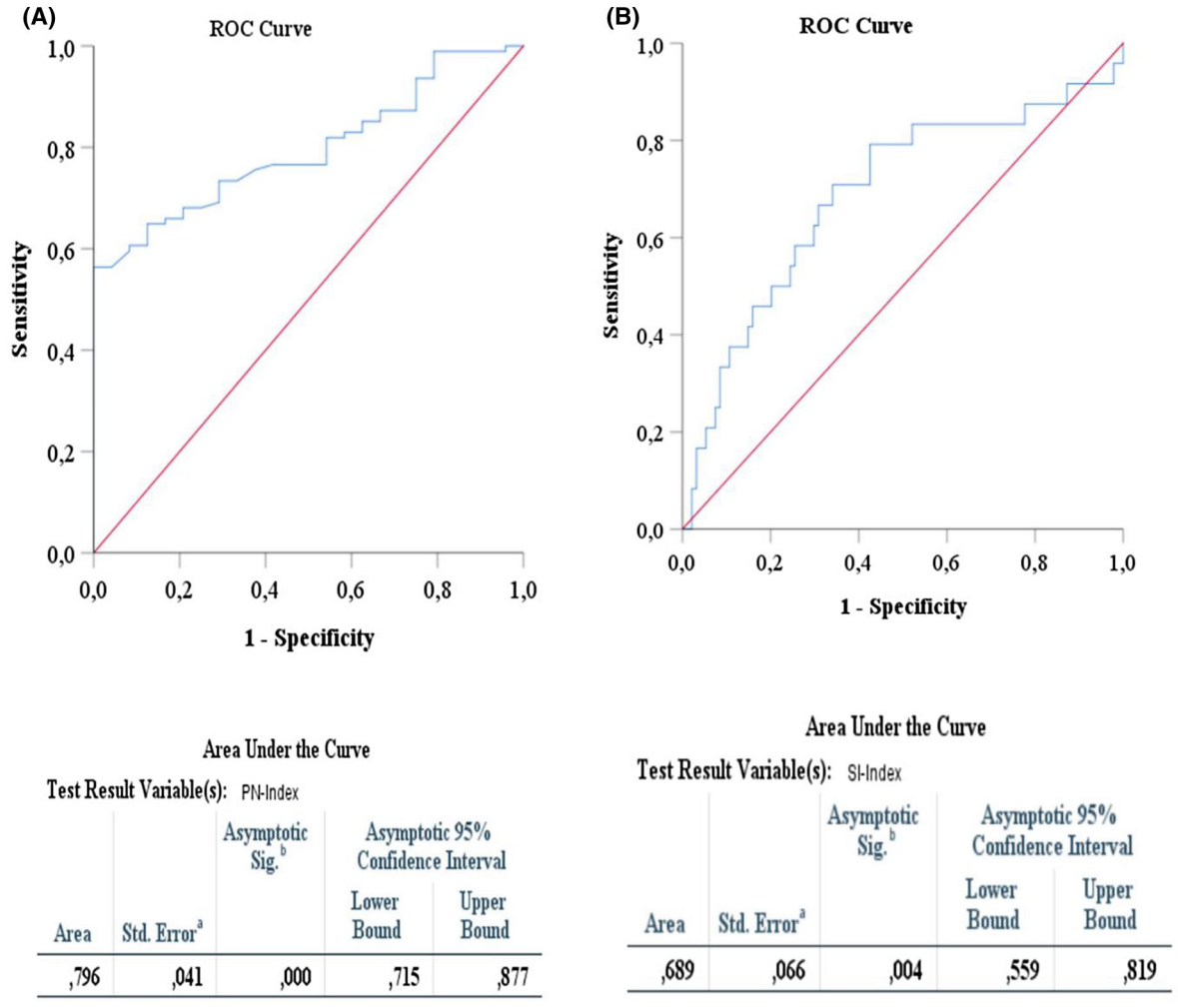


FIGURE 3 Comparison of systemic immune-inflammation index (SII) results between groups.



Area Under the Curve

Test Result Variable(s): PN-Index

Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
,796	,041	,000	,715	,877

Area Under the Curve

Test Result Variable(s): SI-Index

Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
,689	,066	,004	,559	,819

FIGURE 4 Receiver operating characteristic (ROC) curve of PN-index (A) and SI-index (B) in predicting disease severity.

surveillance of the lymphocyte count is valuable for early screening of COVID-19-related critical illness.[32] Wang et al[14] first defined PNI as an independent biomarker for the COVID-19 severity. In the pre-print study of Doğancı et al,[13] it showed an association between the prognosis and mortality of COVID-19. Our study found the PNI to be lower in ICU patients than non-ICU patients (ICU

PNI = 34.2 ± 5.3; non-ICU PNI = 42 ± 6.1). When the cut-off value was taken as ≤36.7, the PNI was found to have 73.4% sensitivity and 70.8% specificity for the prediction of the disease severity.

SII is another parameter that reflects the immune and inflammatory status of the organism.[15] SII is estimated based on the lymphocyte, neutrophil and the platelet counts. Previous studies have shown that SII is important for the prediction of the prognosis of tumours and other inflammatory diseases.[16,17] However, there are a few studies investigating the predictive role of SII in the prognosis of COVID-19.[20,33] In those studies, the SII levels were high in patients who died at the hospital and who developed ARDS. In our study, SII was significantly higher in ICU patients compared with non-ICU patients [ICU SII = 1227 (622-1958); non-ICU=543 (349-877)]. This elevation is related to elevated neutrophil count and decreased lymphocyte count. When the cut-off value was taken as ≥813.6, SII had 70.8% sensitivity and 66.0% specificity for prediction of the disease severity in COVID-19.

The PNI and the SII scores may easily and rapidly be calculated from routine blood tests. Hence, it may be useful for prediction of the ICU need during this period when mutant strains with the potential to spread the disease worldwide have emerged. Furthermore, these markers are of vital importance for the early diagnosis of potentially critical illness, providing medical care and improving the prognosis.

This study has some limitations, including the small sample size, being a single-centre cohort study, having a retrospective design and lacking anthropometric data due to the urgency of epidemic disease. Hence, more extensive prospective studies are required.

In ICU patients with COVID-19, the PNI score was lower and the SII score was higher compared with non-ICU patients. Taking the cut-off value ≤36.7 for PNI and cut-off as ≥813.6 for SII, the probability of ICU admission was 4.4 and 6 times higher, respectively.

In conclusion, the PNI and the SII scores are useful for the prediction of the ICU need and the disease severity in COVID-19. Our findings may be useful for early detection of the ICU need in COVID-19 patients.

DISCLOSURE

All authors declare no conflict of interest

AUTHORS CONTRIBUTION

AN, AA, EG and TK did data collection and manuscript writing. AN, TD and MA conceived, designed and did statistical analysis and editing of manuscript. AN did review and final approval of manuscript. AN takes the responsibility and is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

ETHICAL APPROVAL

The ethics committee approval was obtained from the Ministry of Health and Sakarya University Medical School (Number: 71522473/050.01.04/131).

DATA AVAILABILITY STATEMENT

The datasets analysed during the current study are available from the corresponding author on reasonable request.

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