Original Article

Prognostic Nutritional Index (PNI) and Systemic Immune-Inflammatory Index (SII) as markers of severity among patients having COVID-19 infection

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Abstract

Background: Prognostic nutritional index (PNI) and systemic immune-inflammatory index (SII) are two novel markers that have emerged as potential candidates as an early indication of the severity of the disease in coronavirus disease 2019 (COVID-19) patients. **Objective:** The objective of the study is to assess the utility of the prognostic nutritional index (PNI) and systemic immune-inflammatory index (SII) as markers of severity among patients with COVID-19 infection. **Methods:** This is a retrospective study conducted in a tertiary care centre in South India. A total of 80 patients diagnosed with COVID-19 were included in the study. The patients were divided into mild, moderate, and severe groups based on the clinical parameters as per Indian Council of Medical Research guidelines. Lab values taken at admission were obtained from patient records, using which the PNI and SII were calculated using standard formulae. These markers were correlated with the severity of the COVID-19 illness. **Results:** PNI and SII were significantly elevated in the patients with severe COVID-19 illness as compared with mild COVID-19 illness. The mean PNI among subjects with mild COVID-19 and severe COVID-19 being 46.62 ± 6.51 and 34.09 ± 5.81, respectively. The mean SII among subjects with mild COVID-19 was 9,52,287.2 ± 1,42,113, and among subjects with severe COVID-19 was 15,39,461 ± 8,04,285. The cut-off value for PNI and SII for predicting severity of COVID-19 illness was 35.93 and 5,82,400, respectively. The sensitivity for PNI was 87.5, and the SII was 95. **Conclusion:** The present study showed a significant correlation between the SII and PNI as markers used to determine the severity of COVID-19. Based on these findings, it can be effectively used independently of other markers to predict critical illness among COVID-19 patients.

Keywords: COVID-19, prognostic nutritional index, systemic immune inflammatory index

Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has caused a worldwide pandemic. The knowledge of the pathophysiology of the SARS-CoV-2 disease process is expanding daily. Dysregulated immune response and cytokine storms are the underlying mechanisms that can lead to multi-system involvement and the death of affected patients. Presentations of the disease are widely variable, ranging from asymptomatic cases to death, most often due to respiratory failure.[1]

Severe COVID-19 can have low serum albumin levels and lymphocytopenia compared with those with non-severe COVID-19. Poor nutritional status and immune dysfunction are known to be risk factors for severe infection.[2] Based on

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these observations, the prognostic nutritional index (PNI) and systemic immune-inflammatory index (SII) are two novel markers that have emerged as potential markers for early indication of the severity of disease.

PNI combines the serum albumin levels and the peripheral lymphocyte count and reflects the immune-nutritional status of the patients.[3] Critically ill patients usually suffer a reduction in food intake due of inflammation and anorexia and are predisposed to develop many adverse outcomes. Nutritional assessments with common tools can be difficult because of physical constraints, difficulties in collecting anthropometric and dietary information in patients with severe disease. PNI can be used as a tool for nutritional assessment as a predictor of the severity of illness. The systemic immune-inflammatory index (SII) is another parameter that reflects the immune and inflammatory status,[4,5] and its value is directly proportional to disease severity. The systemic immune inflammation index (SII) is calculated as neutrophils × platelets/lymphocytes and is a predictive parameter for various inflammatory states.[6-8]

This study aims to investigate the association between PNI and SII with the severity of COVID-19 infection in a tertiary care hospital in South India.

Materials and Methods

Study design: Retrospective study.

Study site: Tertiary Medical Care Centre in South India.

Study Population: A hospital based retrospective study was conducted in an urban tertiary medical care center for a period of six months, from January 2022 to June 2022, after obtaining due clearance from the Ethics Committee of the Institution (MSRMC/EC/SP-11/11-23).

The study included a total of 80 patients, more than 18 years of both genders, diagnosed with COVID-19 by reverse transcriptase-polymerase chain reaction (RT-PCR) testing of a nasopharyngeal swab, admitted to an urban tertiary medical care center. The exclusion criteria included patients with severe liver disease (Child-Pugh score > seven), chronic kidney disease, malabsorption syndrome, current malignancies, auto-immune diseases, and pregnant women. Clinical data, which included age, sex, height, weight, body mass index [BMI], complete blood counts, C-reactive protein, serum albumin, D-Dimer, and the high-resolution computerized tomography (HRCT) score, were retrieved from the patient's medical records. The patients were divided into mild, moderate, and severe based on the clinical parameters as per Indian Council of Medical Research (ICMR) guidelines.[9] The mild category included patients with symptoms of COVID-19 who were clinically stable and whose finger pulse oximetry revealed oxygen saturation of >95% in ambient air. The moderate category included patients with symptoms having oxygen saturation between 90% and 94% in ambient air or who had a respiratory rate of more than or equal to 24 cycles/min but less than 30 cycles/min. The severe category included patients with symptoms having oxygen saturation of <90% in ambient air or who had a respiratory rate of more than 30 cycles/min.

For the study, moderate and severe COVID-19 infections were categorized together. PNI and SII were calculated using standard formulae, with the lab values from patient records.

Assessment of PNI: PNI = 10 × serum albumin (g/dL) ± 0.005 × peripheral lymphocyte count (cells/mm^3)

Assessment of SII: SII = Neutrophil count × Platelet count/ Lymphocyte count.

Sample size estimation: As per the study conducted by Wang ZH *et al.*,[5] PNI with cutoff 43 was associated with severe COVID-19 illness. This study observed that the sensitivity of predicting disease severity based on PNI was 85.3. The present study expects similar results with a 95% confidence interval and 8% absolute precision. The study requires a minimum of 80 participants.

Statistical analysis: Data was entered into a Microsoft Excel data sheet and analyzed using SPSS 22 version software. Categorical data was represented in the form of frequencies and proportions. **The Chi-square test, or Fischer's exact test** (for two-by-two tables only), was used as a test of significance for qualitative data. Continuous data was represented as the mean and standard deviation. An **Independent t-test** was used as a test of significance to identify the mean difference between two quantitative variables**.** Correlations were performed with the **Pearson correlation coefficient.** Receiver operating characteristic curves (ROCs) were constructed for PNI and the severity of COVID-19. Receiver operating characteristic curves (ROCs) were constructed for SII and the severity of COVID-19. Receiver operating characteristic (ROC) and optimal cut-off points were chosen for the calculation of sensitivity, specificity, and positive and negative predictive values. A test that predicts an outcome no better than chance has an area under the ROC curve of 0.5. An area under the ROC curve above 0.8 indicated a good prediction. **P value** (probability that the result is true) of <0.05 was considered statistically significant after assuming all the rules of statistical tests.

Statistical software: MS Excel**,** SPSS version 22 **(**IBM SPSS Statistics, Somers NY, USA) was used to analyze the data.

Results

The medical records with data on 80 patients with mild and severe COVID-19 disease who had been admitted to the hospital for management of COVID-19 were assessed. PNI and SII were calculated at the time of admission. The study included 40 mild cases and 40 cases of severe COVID-19 illness. The demographic details and symptoms of the patients have been

summarized in Table 1. The mean age of patients in the mild illness category was 52 ± /- 7.5 years, and in the severe illness category was 64 ± /- 8.3 years. This difference was statistically significant (P = 0.002). The number of patients with type-2 diabetes was 22 (55%) in the severe illness group and 15 (37.5%) in the mild group. Hypertensives were 30 (75%) in the severe illness group and 16 (40%) in the mild illness group. These differences in comorbidities were statistically significant.

The inflammatory markers and HRCT severity scores of the patients have been summarized in Table 2. Mean C-reactive protein levels (CRP), D-Dimer levels, and mean neutrophil-lymphocyte ratio (NLR) levels were significantly elevated among the patients with the severe COVID-19 illness group. However, LDH levels were not found to be statistically elevated.

The mean PNI among subjects with mild COVID-19 was 46.62 ± 6.51, and the mean PNI among subjects with moderate-severe COVID-19 was 34.09 ± 5.81. There was **a statistically significant difference between PNI and the severity of COVID-19.** The mean SII among subjects with mild COVID-19 was 9,52,287.2 ± 1,42,113, and the mean SII among subjects with moderate-severe COVID-19 was 15,39,461 ± 8,04,285.3. There was **a statistically significant difference found between SII and the severity of COVID-19 [Table 3].** There was a strong negative correlation between PNI and CT severity score, which was statistically significant [Table 4, Figures 1 and 2]. There was a positive correlation between SII and the CT severity score, which was statistically significant. ROC was plotted for PNI and SII for predicting the severity of COVID-19 illness. The area under the curve for PNI for predicting the severity of COVID-19 illness was 0.905 and for SII was 0.768. Both were statistically significant. [Figures 3 and 4, Table 5]. The cut-off values for PNI and SII for predicting the severity of COVID-19 illness were 35.93 and 5,82,400, respectively. The sensitivity for PNI was 87.5, and the SII was 95. The positive predictive value and negative predictive value are summarized in Table 6.

Total duration of hospital stay among the patients with mild COVID-19 illness was 7.5 ± /- 2.5 days and severe illness was 15.3 ± /-4.5 days. A total of 4 (10%) patients who were included in the study died. The treatment given and the outcomes of the patients are summarized in Table 7.

Discussion

This study was conducted to assess the role of the prognostic nutritional index (PNI) and systemic immune-inflammatory index (SII) as markers for predicting disease severity among patients with COVID-19 infection. This is one of the first studies conducted in South India regarding PNI and SII in COVID-19 illness. These scores portray the effect of the immuno-nutritional status of patients on the severity of the COVID-19 illness.

The mechanism underlying the association between the PNI score and the severity of COVID-19 is not clear. PNI is a combination of peripheral lymphocytes and serum albumin levels. Hence, it links nutritional status and immune response. Nutrition plays an important role in the regulation of immunity and its responses. Malnutrition is known to have reduced immune responses like impairment of cell-mediated immunity, phagocytosis, complement function, and cytokine production. These processes,

Table 1: Demographics, symptoms, and comorbidities among the patients with COVID-19

Parameters	Mild COVID-19 illness (n=40)	Severe COVID-19 illness (n=40)	P
Mean Age (Years)	52 (S.D 7.5)	64 (S.D- 8.3)	0.002
Males	25 (62.5%)	28 (70%)	0.54
Females	15 (37.5%)	12 (30%)	0.42
Fever	35 (87.5%)	37 (92.5%)	0.32
Cough	22 (55%)	28 (70%)	0.09
Breathlessness	02 (5%)	30 (75%)	<0.001
Diabetes Mellitus	15 (37.5%)	22 (55%)	<0.001
Hypertension	16 (40%)	30 (75%)	<0.001
Ischemic Heart Disease	02 (5%)	07 (17.5%)	0.02

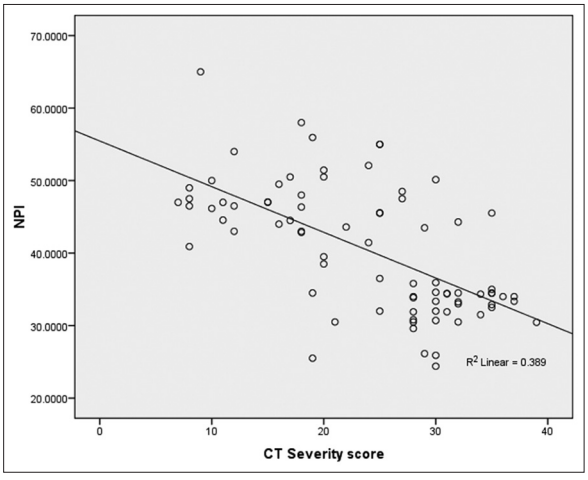

Figure 1: Scatter plot showing correlation between PNI and CT severity score

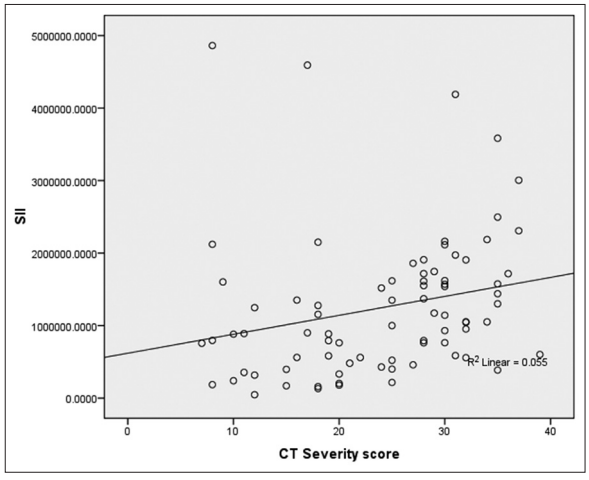

Figure 2: Scatter plot showing correlation between SII and CT severity score

Table 2: Inflammatory markers among the patients with COVID-19

Parameter	Mild COVID-19 illness	Severe COVID-19 illness	*P*
Mean CRP	6.4 ± /- 3.2	8.7 ± /- 4.2	<0.001
Mean D-Dimer	1.8 ± /- 0.2	2.2 ± /- 1.2	0.002
Mean NLR	4.7 ± /- 3.0	8.2 ± /- 3.2	<0.001
Mean LDH	210 ± /- 25	320 ± /- 32	0.6
Mean HRCT Chest-Severity score (Out of 22)	8.2 ± /- 2	16.6 ± /- 3.4	<0.001
Mean Neutrophil counts (cells/dL)	8755 ± /- 1223	9804 ± /- 1322	0.003
Mean Lymphocyte counts (cells/dL)	1703 ± /- 345	1187 + /- 124	0.001
Mean Platelet Count (cells/dL)	1,45.546 + /- 54,980	1,54,345 + /- 45,657	0.786

Table 3: SII and NPI among the patients admitted with COVID-19

Parameter	Mild COVID-19 illness	Severe COVID-19 illness	*P*
PNI	46.6 +/- 6.51	34.0 +/- 5.8	<0.001
SII	9,52,287.2 +/- 1,42,113.0	15,39,461 +/- 8,04,285.3	0.006

Table 4: Correlation of NPI and SII with CT severity score

Parameter	Pearson's coefficient	Value
PNI	Pearson Correlation	-0.624**
	P	<0.001
SII	Pearson Correlation	0.234*
	P	0.036

Table 5: ROC curve of SII and NPI in predicting severity of COVID-19

Parameter	Area under the curve	95% CI	*P*
PNI	0.905	0.819-0.959	<0.001
SII	0.768	0.661-0.855	<0.001

Table 6: Cut-off value, specificity, sensitivity, positive predictive value, and negative predictive value of PNI and SII in predicting severity

	Cutoff	Sensitivity	Specificity	PPV	NPV
PNI	35.93	87.5	95	94.6	88.4
SII	5,82,400	95	52.5	66.7	91.3

Table 7: Treatment given to the COVID-19 patients and the outcome parameters

Parameters	Mild COVID-19 illness	Severe COVID-19 illness
Duration of hospitalization (Days)	7.5+/- 2.5	15.3+/-4.5
Requirement of ventilatory support (No. of patients)	Nil	14 (35%)
Requirement of steroids and Remdesivir (No. of patients)	3 (7.%)	34 (85%)
Mortality (No. of patients)	Nil	4 (10%)

like decrease in lymphocyte counts and increased cytokines, are known to cause severe COVID-19 illness.[1,2]

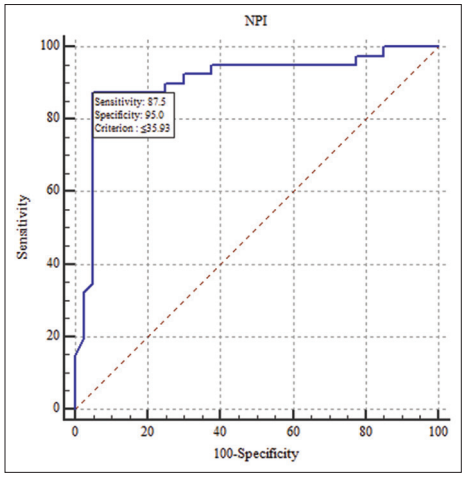

Figure 3: ROC curve for PNI in predicting severity of COVID-19

As per our results, the mean NPI among patients with mild COVID-19 illness was 46.6 ± /- 6.51 and among those with severe COVID-19 was 34 ± /- 5.8. This implies that patients with reduced serum albumin levels and with reduced lymphocyte levels are more likely to develop severe COVID-19 illness. These findings were concordant with the study conducted by Hu X *et al.*[10] where in the mean PNI among the patients with mild COVID-19 illness was 50, whereas in severe illness, it was 43.

It was seen in the current study that PNI had a statistically negative correlation with the HRCT severity score. This demonstrates that the PNI value can reflect the severity of the COVID-19 illness.

There was a statistically significant difference found between PNI values among severe and non-severe cases, with a cutoff of less than 36. These findings were like the study conducted by Wang *et al.*[5] which showed that PNI was found to be lower in critically ill patients compared to non-critically ill patients with an optimal cutoff value of 43. In a study conducted by Hu *et al.*,[10] PNI was independently and inversely associated with the severity of COVID-19 among patients regardless of age, sex, and BMI, with PNI <49 defined as a cutoff value as a predictor of severe forms. As per Song *et al.*,[11] patients with less PNI had a higher risk of in-hospital deaths. Patients with a lower geriatric nutritional risk index (GNRI) and higher Controlling Nutritional Status (CONUT) scores were also found to have a

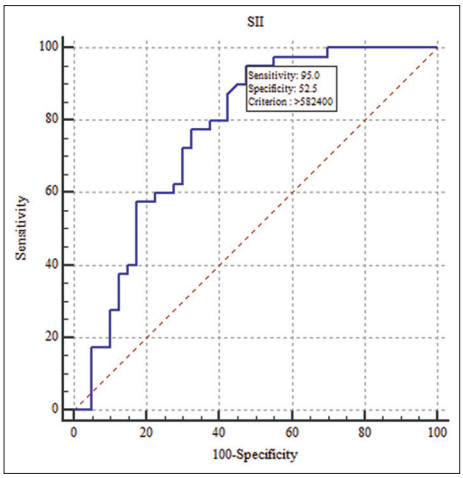

Figure 4: ROC curve for SII in predicting severity of COVID-19

higher risk of adverse outcomes among COVID-19 patients. The study by Wei *et al.*[6] showed that the baseline PNI score was an independent predictor of mortality, and a score of less than 33.4 was associated with a higher mortality risk in severe COVID-19 patients. A study by Bilge *et al.*[7] demonstrated that PNI is an independent predictor of in-hospital health in COVID-19 patients with malignancies. It was found to be significantly lower in non-survivors as compared to survivors. Al-Shami *et al.*[8] that ICU admitted patients had significantly lower PNI scores as compared to non-ICU patients.

Similarly, Shao *et al.*[12] found that PNI, GNRI, and CONUT scores at admission were independent predictors of both in-hospital and one-year mortality rates among critically ill patients.

It was observed in the current study that the mean SII among patients with mild COVID-19 was 9,52,287 and severe COVID-19 was 15,39,461. The findings of the study were concordant with the study by Nalbant *et al.*,[13] where SII scores are independent predictors of prognosis and disease severity in COVID-19 patients. SII cutoff was taken as >813.6 were critically ill and required intensive care admissions.

There was a statistically significant difference found between SII values and the severity of COVID-19 patients, with a cutoff of >582400. Li *et al.*[4] found that SII might be a good marker to predict the development of acute respiratory distress syndrome and death among COVID-19 patients. Karaaslan *et al.*[14] studied the role of SII in determining mortality in COVID-19 patients and observed that a cutoff value of >618.8 was associated with a 4.68-fold higher mortality and could be used as an independent predictor.

According to the study by Xia *et al.*,[15] SII was significantly higher in severe cases of COVID-19 compared to non-severe cases, with a cutoff of 887.20. Muhammad *et al.*[16] concluded in the study that SII was a strong marker to predict the requirement of invasive ventilation and adverse clinical outcomes in patients with COVID-19.

The present study does have its own limitations, such as the single-center study design. The parameters used in the calculation of PNI and SII are simple and available even in resource limited settings. Hence, these markers can be of immense use in the prognostication of patients and in effectively utilizing the resources for the better management of COVID-19 illness. The study demonstrates that patients with low PNI at admission had adverse clinical outcomes. Hence, such patients can benefit from aggressive nutritional support and vigilant monitoring. The findings of the study pave the way for further larger multicentric trials to confirm the findings and improve the care of COVID-19 patients.

Conclusion

PNI and SII are reliable markers of the severity of the COVID-19 infection. PNI, which represents immuno-nutritional status, and SII, which represents the inflammatory status of the body, can be used to identify patients who are likely to acquire a severe COVID-19 illness.

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Conflicts of interest

There are no conflicts of interest.

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