TURKISH JOURNAL OF INTERNAL MEDICINE

ISSN:2687-4245

Infectious Diseases

Can the systemic inflammatory index be a prognostic indicator in COVID-19 patients presenting to the emergency department?

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A B S T R A C T

Background This study aimed to evaluate whether the systemic immune-inflammatory index (SII) can be used as a prognostic indicator in COVID-19 patients presenting to the emergency department. Given the high mortality and morbidity associated with COVID-19, identifying reliable prognostic markers is crucial for optimizing patient management.

Methods This retrospective observational study included 639 COVID-19 patients admitted to our emergency department between February 1, 2022, and February 1, 2023. Patients' SII was calculated using complete blood count parameters (neutrophil, lymphocyte, and platelet counts). Data on patient outcomes, including intensive care unit (ICU) admission and in-hospital mortality, were analyzed using statistical methods such as receiver operating characteristic (ROC) curve analysis to assess the predictive power of SII, neutrophil-to-lymphocyte ratio (NLR), and neutrophil-to-platelet ratio (NPL).

Results Among the 639 patients, 136 died during hospitalization. Significant differences in SII, NLR, and NPL were observed between patients admitted to the ICU and those with less severe outcomes. The highest AUC (area under the curve) value was observed for NLR, with a cut-off value of >4.87, predicting mortality with a sensitivity of 72.79% and specificity of 77.73%. SII also demonstrated significant prognostic value with a cut-off of >806.03, predicting mortality with a sensitivity of 75.74% and specificity of 66%.

Conclusion SII, NLR, and NPL are effective prognostic indicators in COVID-19 patients, particularly in predicting the need for intensive care and mortality risk. These findings suggest incorporating these markers into routine clinical practice could improve risk stratification and patient outcomes. However, further large-scale studies are needed to validate these results and refine the use of these markers in clinical settings.

Turk J Int Med 2024;6(4):155-162
DOI: 10.46310/tjim.1552501
Original Article

Keywords: *COVID-19, prognosis, systemic immune-inflammatory index, inflammatory markers*

Received: *September 18, 2024* ***Accepted:*** *October 15, 2024* ***Published Online:*** *October 29, 2024*

How to cite this article: *Efgan MG, Çınaroğlu OS. Can the systemic inflammatory index be a prognostic indicator in COVID-19 patients presenting to the emergency department? Turk J Int Med 2024;6(4):155-162. DOI: 10.46310/tjim.1552501*

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INTRODUCTION

COVID-19 emerged in December 2019 as a pneumonia outbreak caused by a novel coronavirus in Wuhan, Hubei province, China, and rapidly led to severe illness and death worldwide.[1-3] The virus's rapid global spread affected thousands of individuals across many countries, prompting the World Health Organization (WHO) to declare it a "Public Health Emergency of International Concern" on January 30, 2020, and subsequently a global "pandemic" on March 11, 2020.[1,2,4] Since the onset of the pandemic, emergency departments have experienced increased patient loads, resulting in higher hospital admissions and occupancy rates.[5] However, clear indicators to determine which patients are at higher risk of mortality and morbidity and who require intensive care have yet to be fully established. Therefore, reliable indicators are needed to predict mortality and intensive care needs in COVID-19 patients.

The systemic immune-inflammatory index (SII) is a laboratory test used to assess an individual's level of systemic inflammation. SII is calculated based on blood parameters such as neutrophil, lymphocyte, and platelet counts and helps determine the presence or severity of inflammation. SII is calculated using the formula: SII = platelet count x neutrophil count/lymphocyte count. High SII values indicate the presence of systemic inflammation and may also be used to monitor response to treatment.[6,7] Markers such as SII, NLR, and NPR are closely related to inflammation. Since COVID-19 is pathophysiologically based on inflammation, there is a close connection between the severity of the disease and inflammation markers. This suggests that inflammatory markers can be prognostic indicators in COVID-19 patients. Previous studies have suggested that SII can be a prognostic indicator in inflammation-related conditions such as liver malignancies, osteoporosis, sepsis, and COVID-19.[8-11] Previous studies suggested the usability of the SII value in severe COVID-19 patients with an area under the curve of 0.860, a sensitivity of 81.25% for a cut-off value of 88, and a specificity of 81.82%.[12] This study aimed to investigate whether SII, which can be easily calculated in COVID-19 patients diagnosed with pneumonia and presenting to the emergency department, can be used to predict the disease's prognosis.

MATERIAL AND METHODS

Study design

This study is a retrospective observational study conducted on COVID-19 cases in a tertiary hospital between February 1, 2022, and February 1, 2023. Before the study began, the local ethics committee approved it.

Study population

The study included adult patients (aged 18 years and older) who presented to the emergency department with symptoms suggestive of COVID-19 pneumonia, such as shortness of breath, cough, fever, and altered mental status, and who had a positive PCR test result and a complete blood count (CBC) performed. Patients with incomplete data, those referred to another center, or those with conditions affecting hematological parameters (e.g., leukemia, lymphoma, anemia, primary coagulation disorders) were excluded.

Study protocol

Data on patients' presenting complaints, laboratory results, and medical histories were obtained from the hospital's electronic system and recorded on a data collection form. The patients' outcomes in the emergency department and mortality status were also noted. SII was calculated using CBC parameters (neutrophil, lymphocyte, and platelet counts) according to the formula (platelet count × neutrophil count) / lymphocyte count). The recorded data and SII values were then used for statistical analysis.

Statistical analysis

Data were analyzed using IBM SPSS Statistics Standard Concurrent User V 26 (IBM et al., USA) and MedCalc® Statistical Software version 19.6 (MedCalc et al., Belgium). Descriptive statistics were presented as counts (n), percentages (%), means, and standard deviations. The homogeneity of variances was checked using Levene's test, and normality was assessed with the Shapiro-Wilk test. Differences between the two groups were evaluated using the student's t-test for parametric data and the Mann-Whitney U test for non-parametric data. In our study, statistical methods were selected based on data distribution. The Mann-Whitney U test is a non-parametric test appropriate for comparing differences between two independent groups when the data do not follow a normal distribution. Therefore, we chose this test to ensure the analysis aligned with the characteristics of our dataset. The performance of SII, NLR (neutrophil-to-lymphocyte ratio), and NPR (neutrophil-to-platelet

Table 1. Descriptive statistics for categorical variables

Variables	n (%)	Responses	n (%)
Gender		Comorbidities	
Female	326 (51.0)	Fever	168 (16.9)
Male	313 (49.0)	COPD	103 (10.4)
Emergency department outcome		Diabetes mellitus	124 (12.5)
Home care	118 (18.5)	Hypertension	179 (18.0)
Hospital admission	372 (58.2)	Coronary artery disease	89 (9.0)
ICU admission	149 (23.3)	Heart failure	80 (8.1)
Hospital outcome		Malignancy	36 (3.6)
Discharge	503 (78.7)	Chronic kidney disease	67 (6.7)
Mortality	136 (21.3)	Alzheimer's disease	25 (2.5)
		Other chronic diseases	122 (12.3)
Total	639 (100.0)	Total	993 (100.0)

ICU: intensive care unit, COPD: chronic obstructive pulmonary disease.

ratio) in predicting outcomes such as discharge were assessed using receiver operating characteristic (ROC) curve analysis. Multiple response data were analyzed using the "multiple response" method. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 639 patients were included in the study, of which 326 were female. Among these patients, 136 resulted in death. For the multiple-response comorbidity questions, 993 responses were obtained from 639 individuals. The distribution of responses was as follows: fever (16.9%), chronic obstructive pulmonary disease (COPD) (10.4%), diabetes mellitus (12.5%), hypertension (18%), coronary artery disease (9%), heart failure (8.1%), cancer (3.6%), chronic kidney disease (6.7%), Alzheimer's disease (2.5%), and other chronic diseases (12.3%). Descriptive statistics for categorical variables are presented in Table 1.

Significant differences were observed in SII, NLR, and NPR variables across the emergency department outcome groups (p<0.05). The differences were primarily between patients admitted to the ICU and those in other groups. ICU patients had higher mean SII, NLR, and NPR values than other groups. These higher mean values are presented in Table 2. Significant differences were found in SII, NLR, and NPR variables across hospital outcome groups (p<0.05). The mean values in the mortality group were higher than those in the discharge group. These higher mean values are presented in Table 3.

ROC curve analysis was performed for SII, NLR, and NPR variables to predict hospital mortality. The highest area under the curve (AUC) was observed for NLR, while the lowest AUC was found for SII.

Table 2. Comparison of SII, NLR, and NPR variables across emergency department outcome groups

	Variable	Home care	Hospital admission	ICU admission	*P-value*
SII	1,309.4±2,192[a]	1,164.2±2,247.2[a]	2,672.4±3,117[b]	99.799	0.001€
NLR	5.1±6.5[a]	4.4±7.4[a]	11.5±15.5[b]	121.033	0.001€
NPR	0.04±0.2[a]	0.03±0.14[a]	0.05±0.05[b]	85.009	0.001€

Numerical variables were presented as mean±standard deviation or median (min-max). € Kruskal-Wallis test. [a]: There is no statistical difference between the same letters; [b]: there is a statistical difference between different letters.
SII: systemic immune-inflammatory index, NLR: neutrophil-to-lymphocyte ratio, NPR: neutrophil-to-platelet ratio, ICU: intensive care unit.

Table 3. Comparison of SII, NLR, and NPR variables across hospital outcome groups

	Discharge	Mortality	Test statistic	*P-value*
SII	1,225.6±2,218.8	2,715.7±3,236.7	-8.716	0.001†
NLR	4.7±7.2	11.9±16.1	-10.089	0.001†
NPR	0.04±0.15	0.05±0.05	-8.894	0.001†

Numerical variables were presented as mean±standard deviation, †Mann-Whitney U test.
SII: systemic immune-inflammatory index, NLR: neutrophil-to-lymphocyte ratio, NPR: neutrophil-to-platelet ratio.

Table 4. Cut-off scores, AUC values, sensitivity, specificity, and statistical significance of SII, NLR, and NPR variables for hospital outcome groups*

Test result Variables	*Cut-off*	AUC	S.E.	*P-value*	Asymptotic 95% CI		*Sensitivity*	*Specificity*
					Lower bound	Upper bound		
SII	>806.03	0.743	0.025	0.001	0.694	0.792	75.74	66.00
NLR	>4.87	0.782	0.022	0.001	0.738	0.826	72.79	77.73
NPR	>0.02	0.748	0.025	0.001	0.700	0.797	66.18	75.15

AUC: area under the curve, SE: standard error, CI: confidence interval.
SII: systemic immune-inflammatory index, NLR: neutrophil-to-lymphocyte ratio, NPR: neutrophil-to-platelet ratio.

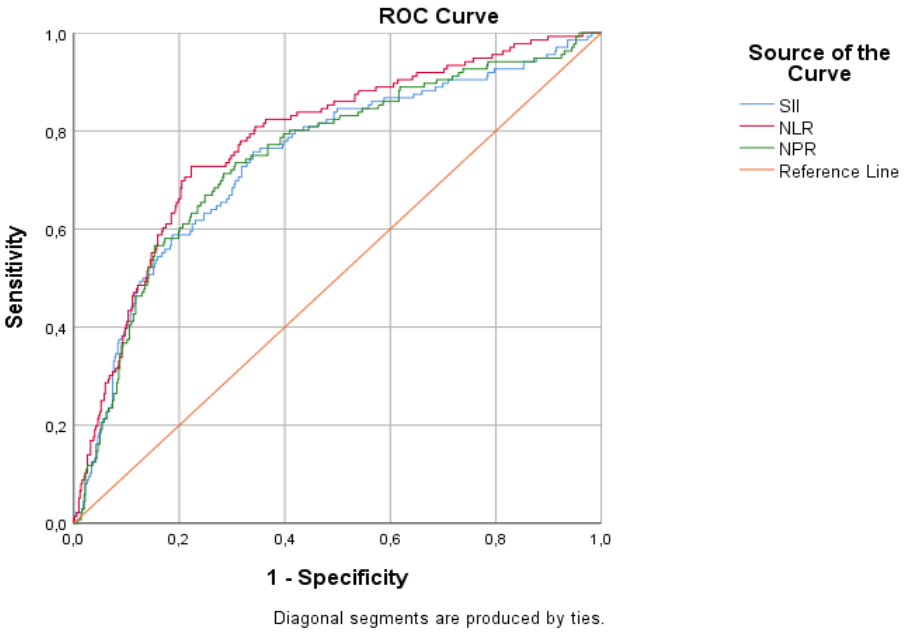
Table 5. Cut-off scores, AUC values, sensitivity, specificity, and statistical significance of SII, NLR, and NPR variables for ICU admission groups*

Test result Variables	*Cut-off*	AUC	S.E.	*P-value*	Asymptotic 95% CI		*Sensitivity*	*Specificity*
					Lower Bound	Upper Bound		
SII	>806.03	0.733	0.031	0.001	0.672	0.794	79.19	61.02
NLR	>4.87	0.754	0.030	0.001	0.695	0.813	71.14	72.03
NPR	>0.02	0.699	0.033	0.001	0.635	0.764	64.43	66.10

AUC: area under the curve, S.E.: standard error, CI: confidence interval.
SII: systemic immune-inflammatory index, NLR: neutrophil-to-lymphocyte ratio, NPR: neutrophil-to-platelet ratio.

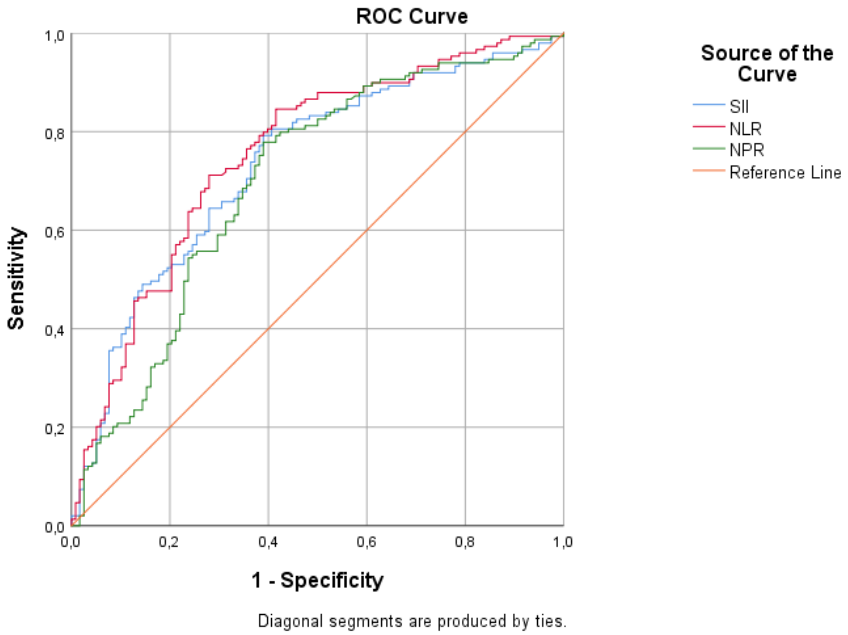
The optimal cut-off value for SII was >806.03, with a sensitivity of 75.74% and specificity of 66%. The optimal cut-off value for NLR was >4.87, with a sensitivity of 72.79% and specificity of 77.73%. The optimal cut-off value for NPR was >0.02, with a sensitivity of 66.18% and specificity of 75.15%. All results are presented in Table 4 and Figure 1. ROC curve analysis was also performed to evaluate the predictive power of SII, NLR, and NPR variables for ICU admission. The highest AUC value was observed for NLR, while the lowest was for NPR. The optimal cut-off value for SII was >806.03, with a sensitivity of 79.19% and specificity of 61.02%. The optimal cut-off value for NLR was >4.87, with a sensitivity of 71.14% and specificity of 72.03%. The optimal cut-off value for NPR was >0.02, with a sensitivity of 66.43% and specificity of 66.10%. The results are presented in Table 5 and Figure 2.

Table 6 analyzes the effect of the parameters on ICU hospitalization. This evaluation showed that an increase in the NPR variable increased the need for ICU hospitalization by 1.164 times, while an increase in the NLR variable decreased the need by 0.384 times. In Table 7, the effect of the parameters on mortality was analyzed. As a result of this evaluation, an increase in the SII variable increased the probability of mortality



ROC: receiver operating characteristic, SII: systemic immune-inflammatory index, NLR: neutrophil-to-lymphocyte ratio, NPR: neutrophil-to-platelet ratio.

Figure 1. ROC curves for SII, NLR, and NPR variables.



ROC: receiver operating characteristic, SII: systemic immune-inflammatory index, NLR: neutrophil-to-lymphocyte ratio, NPR: neutrophil-to-platelet ratio.

Figure 2. ROC curves for SII, NLR, and NPR variables.

Table 6. Logistic regression model for ICU admission

	B	S.E.	Wald	df	*P-value*	Exp (B)	95% CI for Exp (B)	
							Lower	Upper
Constant	-0.549	0.207	7.047	1	0.008	0.578		
SII	0.000	0.000	0.851	1	0.356	1.000	1.000	1.000
NPR	0.152	0.047	10.307	1	0.001	1.164	1.061	1.278
NLR	-0.957	1.321	0.526	1	0.468	0.384	0.029	5.108

β: regression coefficient, S.E.: standard error, Cl: confidence intervals, ICU: intensive care unit, SII: systemic immune-inflammatory index, NLR: neutrophil-to-lymphocyte ratio, NPR: neutrophil-to-platelet ratio.

Tablo 7. Logistic regression model for mortality

	B	S.E.	Wald	df	*P-value*	Exp (B)	95% CI for Exp (B)	
							Lower	Upper
Constant	-1.903	0.141	183.034	1	0.001	0.149		
SII	0.000	0.000	4.684	1	0.030	1.000	1.000	1.000
NPR	0.135	0.028	22.748	1	0.001	1.144	1.083	1.210
NLR	-0.124	0.839	0.022	1	0.882	0.883	0.170	4.575

β: regression coefficient, S.E.: standard error, Cl: confidence intervals, SII: systemic immune-inflammatory index, NLR: neutrophil-to-lymphocyte ratio, NPR: neutrophil-to-platelet ratio.

by 1 time. An increase in the NLR variable increased the likelihood of mortality by 1.144 times.

DISCUSSION

This study aimed to examine the role of inflammatory markers such as SII, NLR, and NPR in predicting disease severity and mortality in COVID-19 patients. These markers, especially SII and NLR, may be essential in assessing the prognosis of COVID-19 patients. SII, NLR, and NPR values showed statistically significant differences in ICU hospitalization and in-hospital mortality ($p<0.05$). These results indicate that SII, NLR, and NPR can be used to assess disease severity and possible mortality risk in COVID-19 patients.

COVID-19 is characterized by an intense inflammatory response, especially in patients with severe disease progression. This inflammatory response is closely related to the function of neutrophils, lymphocytes, and platelets. Increased neutrophil and decreased lymphocyte count have been associated with a worse prognosis in COVID-19 patients.[11,13] In previous studies, the area under the curve for NLR: 0.867 and the area under the curve for

SII: 0.860 were found, and the results were similar to this study.[13] In this context, it is noteworthy that NLR is used to indicate inflammatory response, especially in severe COVID-19 cases. A higher NLR indicates that patients have a more intense inflammatory response, possibly leading to a more severe disease course.[12,14]

As a marker of systemic inflammation, SII can be used in the follow-up of COVID-19 patients and evaluate their response to treatment. Higher SII values are associated with a worse prognosis in patients. Evidence in the literature shows that SII is used as a prognostic marker in various types of cancer, sepsis, and other inflammatory diseases.[15,16] The high levels of SII in patients with COVID-19 indicate that these patients may have a higher need for intensive care and an increased risk of mortality. The findings obtained in this study support that SII may be an effective tool in determining disease severity in COVID-19 patients.

NPR is a parameter that reflects the effect of platelet and neutrophil functions on the inflammatory response in COVID-19 patients. Platelets play an essential role in inflammatory processes, and high values of NPR may be a marker of thromboinflammatory response, especially in severe COVID-19 cases.[17] High NPR is associated with mortality risk in COVID-19 patients, and this parameter can be used to predict the need for intensive care.

The findings of this study emphasize the importance of inflammatory markers in prognosis assessment in COVID-19 patients. In particular, parameters such as SII and NLR may play an essential role in determining the severity of COVID-19 and guiding the treatment process. These markers may be critical to optimizing the clinical management of patients and achieving better outcomes. Studies on the role of inflammation markers in COVID-19 patients show that these parameters are increasingly finding a place in clinical practice.[18]

However, large-scale, prospective studies are needed to increase the accuracy of the findings obtained in our research and to understand the clinical use of these markers better. In particular, studies on different populations may help to determine whether these markers are universally valid. Furthermore, whether inflammatory markers such as SII, NLR, and NPR can be used as prognostic markers in respiratory infections and inflammatory diseases other than COVID-19 should be investigated.

Finally, this study's findings help us better understand the effects of inflammatory response on disease severity and mortality in COVID-19 patients. High values of SII, NLR, and NPR are associated with poor prognosis and high mortality risk in these patients. Therefore, the routine use of these markers in clinical practice may offer an essential innovation in managing COVID-19 patients. Future studies should test the accuracy of these markers in a larger patient population and investigate how these parameters can be used more effectively in COVID-19 treatment processes.

LIMITATIONS

This study was conducted with data from a single center, and the generalizability of the findings is limited. Furthermore, the study population is relatively small, so the results must be validated in a more extensive and diverse group of patients. There may be technical variations in the measurement of inflammatory markers such as SII, NLR, and NPR, which may affect the accuracy of the results. Measuring inflammatory markers and changes in reference values in different hospitals may produce different results. Observations of missing data in the study may have limited the scope of some analyses. Furthermore, as the study had a retrospective design, it took more work to identify causal relationships. Finally, as long-term outcomes were not assessed, the long-term prognostic value of these markers should be investigated in further studies.

CONCLUSIONS

This study revealed that inflammatory markers such as SII, NLR, and NPR could be powerful tools for predicting disease severity and mortality in COVID-19 patients. Our findings suggest that high values of these parameters are particularly predictive of the need for intensive care and the risk of death in COVID-19 patients. SII, NLR, and NPR stand out as essential biomarkers not only in managing COVID-19 but also in evaluating inflammatory processes in general. The decision for hospitalization can be made using these parameters. It can also be effective in the initiation and revision of treatment. This study argues that with the routine use of these markers in the emergency department, patients can be stratified into

risk groups early, optimizing intervention strategies and thus improving patient outcomes. However, more large-scale, long-term studies are needed to integrate these ambitious findings fully into clinical practice. In conclusion, SII, NLR, and NPR are powerful enough indicators to revolutionize the management of COVID-19 potentially.

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding Sources

This manuscript received no specific grant from any funding agency in the public, commercial, or non-profit sectors.

Ethical Approval

The protocol of the study was approved by the Medical Ethics Committee of İzmir Katip Çelebi University, İzmir, Turkey. (Decision number: 0436, date: 26.10.2023).

Authors' Contribution

Study Conception: MGE, OSÇ; Study Design: MGE, OSÇ; Literature Review: OSÇ; Critical Review: MGE, OSÇ; Data Collection and/or Processing: MGE, OSÇ; Analysis and/or Data Interpretation: MGE; Manuscript preparing: MGE, OSÇ.

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