Emergency Care Journal

Official Journal of the Academy of Emergency Medicine and Care (AcEMC)

eISSN 2282-2054

https://www.pagepressjournals.org/index.php/ecj/index

Emerg Care J 2024 [Online ahead of print]

To cite this Article:

Topal A,[1] Yarkaç A,[1] Babuş SB, et al. **Prognostic importance of the systemic inflammatory index and the systemic inflammatory response index in COVID-19 patients.** *Emerg Care J* doi: 10.4081/ecj.2024.12528

Prognostic importance of the systemic inflammatory index and the systemic inflammatory response index in COVID-19 patients

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Key words: COVID-19, systemic immune-inflammation index, systemic inflammation response index.

Contributions: literature search: AT, ÇSB, SB; data collection: ÇSB, SB, AY; study design: AT, AK, SE; analysis of data: SE, AY, ÇSB; manuscript preparation: AY, SBB, AK; review of manuscript: AK, SE.

Conflict of interest: the authors declare no potential conflict of interest, and all authors confirm accuracy.

Ethics approval: our study was conducted after the approval of Merin University Clinical Research Ethics Committee (28/09/2022 dated and 2022/646 numbered). The study is conformed with the Helsinki Declaration of 1964, as revised in 2013, concerning human and animal rights.

Informed consent: all patients participating in this study signed a written informed consent form for participating in this study.

Patient consent for publication: written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

Availability of data and materials: all data generated or analyzed during this study are included in this published article.

Abstract

COVID-19 can cause a wide range of effects on patients, from asymptomatic cases to mortality. Many factors can affect the prognosis of the disease. Our study aims to evaluate the predictive power of the Systemic Inflammatory Index (SII) and Systemic Inflammatory Response Index (SIRI) in determining prognosis and mortality in patients. Patients who tested positive for COVID-19 by polymerase chain reaction and presented to the emergency department of Merin Hospital between September 1, 2020, and August 31, 2021, were included in the study. The data of the patients were retrospectively analyzed. A total of 446 patients were included in our study. The rate of patients with severe disease was 55.6%, and the mortality rate was 30.5%. It was found that mortality increased with age ($p<0.001$). SII and SIRI levels were found to be higher in patients who died or had severe disease ($p<0.001$). It was determined that the severity level increased in COVID-19 patients when the SIRI value was above 1.648 ($p<0.0001$, AUC=0.689), and the mortality rate increased when the SIRI value was above 2.057 ($p<0.0001$, AUC=0.640). It was determined that the severity level increased in COVID-19 patients when the SII value was above 867.834 ($p<0.0001$, AUC=0.744), and the mortality rate increased when it was above 1370.353 ($p<0.0001$, AUC=0.682). In patients diagnosed with COVID-19, it was found that SII and SIRI parameters could predict the severity and mortality of the disease. Further comprehensive studies are needed to determine the future roles of these indices.

Introduction

The pathogenesis, clinical features, and pathological changes of Coronavirus Disease 2019 (COVID-19), characterized by diffuse inflammatory changes in the lungs in patients with severe disease status, are still under investigation.[1]

The World Health Organization has reported that 13.8% of infected people have severe infections and 6.1% have critical illnesses. It has also been reported that approximately 26.1-32.0% of confirmed cases may develop into severe or critical cases, with mortality rates of 4.3-11%.[2-4]

Given that markers of inflammation are so prevalent, identifying risk factors in the blood associated with disease severity and early intervention to improve mortality is vital. Biomarkers, together with some clinical factors, may help predict adverse outcomes among COVID-19 patients. Identifying early biomarkers of disease severity can facilitate early implementation of aggressive treatment, improve hospital resource utilization, and reduce mortality.[5-7]

A complete blood count is cheap and easy to perform. Hematologic markers, including platelets, lymphocytes, neutrophils, and monocytes, and their ratios to each other, have been proposed as indicators to aid in the diagnosis, early warning, and risk stratification of infectious diseases.[8] The Neutrophil-To-Lymphocyte Ratio (NLR), Platelet-To-Lymphocyte Ratio (PLR), and Systemic Inflammation Index (SII) have recently been shown to be useful for the assessment of the severity of COVID-19 patients. However, there are few studies evaluating the prognostic capacity of these indices, and these are limited to NLR and PLR.[9] In our study, we aimed to evaluate the prognostic effect of SII and the systemic inflammation response index (SIRI) in COVID-19 patients.

Materials and Methods

Study design

Patients aged 18 years and over who applied to the emergency department of Merin University Hospital between September 1, 2020, and August 31, 2021, and had a positive COVID-19 Polymerase Chain Reaction (PCR) test were included in the study. Information including age, gender, complaint at presentation, vital signs, comorbid diseases, laboratory and radiological examination results, emergency department (hospitalization, discharge, death), and hospital outcome (discharge, death) were recorded on a pre-prepared data form. Patient data were analyzed retrospectively through the hospital's electronic information management system.

Exclusion criteria

Patients younger than 18 years of age, patients with a negative PCR test at emergency department admission, patients with incomplete data, patients with a history of active malignancy, patients with hematological disorders (leukemia, lymphoma), patients who have received chemotherapy in the last month, and patients who received blood transfusions within the last 3 months before admission were excluded from the study.

Severity status

i) Oxygen saturation ≤ 93% at rest; ii) respiratory distress and a respiratory rate greater than 30/minute; iii) PaO2/FiO2 ratio ≤ 300 mmHg; iv) short-term (24–48 hours) >50% progression on lung imaging; v) cases with septic shock and/or multiple organ dysfunction were considered serious.[2]

Patients were categorized as severe if at least one of these criteria was present and non-severe if none was present. SII, SIRI, and other parameters were compared according to the severity of the disease, survival, and mortality.

Systemic inflammatory index (SII) was calculated as platelet count × neutrophil count/lymphocyte count,

Systemic Inflammation Response Index (SIRI) was calculated as (neutrophil count × monocyte count)/lymphocyte count).[9,10]

Our study was conducted after the approval of Merin University Clinical Research Ethics Committee (28/09/2022 dated and 2022/646 numbered).

Statistical analysis

Normality controls for continuous measurements were tested with the Shapiro-Wilk test. Differences between continuous measurements of mortality and severity parameters were tested with the Student t-test for normally distributed parameters and the Mann-Whitney U test for non-normally distributed parameters. As descriptive statistics mean and standard deviation values were given for normally distributed parameters, and minimum, maximum, median, and 25–75% percentages were given for non-normally distributed measurements. Pearson chi-square, Fisher Exact chi-square, and Likelihood Ratio chi-square tests were used for differences with categorical variables. Numbers and percentage values are given as descriptive statistics. Cut-off points for continuous parameters were obtained by using ROC analysis. Cut-off points, sensitivity, selectivity, and positive and negative predictive values are given as descriptive statistics. $P < 0.05$ was taken as statistical significance.

Results

Our study included 446 patients, 50.7% of whom were male. The mortality rate was 30.5%, and the rate of patients with severe disease was 55.6%. It was determined that 66.4% of the cases were hospitalized, 37.2% of which were in intensive care. The mean age of deceased and severely ill patients was found to be higher (p values $p<0.001$, respectively) (Table 1).

In terms of chronic diseases, hypertension (HT) ($p<0.001$), diabetes mellitus (DM) ($p<0.001$), coronary artery disease (CAD) ($p<0.001$), and heart failure (HF) ($p<0.001$, $p=0.006$) were found to be more common in deceased and severe COVID-19 cases (Table 1).

When analyzed in terms of laboratory parameters, it was found that leukocyte, neutrophil, C-reactive protein (CRP), troponin, SII, and SIRI values were higher in patients who were evaluated in the severe COVID-19 class and died (p values $p<0.001$) (Table 2).

Results of the ROC analysis of indices

SII and SIRI parameters were found to have predictive power for mortality. It was determined that the SIRI parameter had the power to distinguish between survivors and deceased patients ($p<0.0001$, AUC=0.640), and the mortality rate may be higher in patients with a value above 2.057. It was observed that the SII parameter had the power to distinguish between survivors and deceased patients ($p<0.0001$, AUC=0.682), and the mortality rate may be higher in patients with a value above 1370.353 (Table 3, Figure 1).

The SII and SIRI parameters were found to be effective in determining the severity of the disease. It was determined that SIRI values above 1.6483 may increase the severity level of COVID-19 disease ($p<0.0001$, AUC=0.689). It was observed that the disease may be severe at values above SII 867.834, and the discriminative power of the SII parameter between severe and non-severe cases was high ($p<0.0001$, AUC=0.744) (Table 3, Figure 2).

Discussion

The COVID-19 disease is caused by a coronavirus called SARS-CoV-2 and has spread rapidly worldwide and affected the whole of humanity.[6] Early intervention has an important place in the course of the disease, and various biomarkers are being developed. SIRI and SII, which are among the biomarkers being developed, are parameters that can be easily reached with a simple complete blood count in emergency departments and hospitals.[9] Based on these data, we tried to determine the effectiveness of SII and SIRI in COVID-19 disease.

Like every disease, COVID-19 also shows different severity in people who are infected with the disease. The biggest reason for this is the difference in immune status between people. COVID-19 disease is more severe than other diseases that negatively affect the immune system. In a study of around 300,000 COVID-19 patients, it was found that the mortality rate of those with comorbidities was 12 times higher and the hospitalization rate was 6 times higher than that of those without comorbidities.[11] It has been reported that the risk factors that increase the rates of severe disease and mortality in COVID-19 are comorbidities such as advanced age (age > 65), HT, DM, cardiovascular disease, and kidney disease.[12] In our study, a significant relationship was found between comorbidities, mortality, and disease severity. It can be concluded that the mortality rate is increased, especially in patients with diabetes, as their immune system may be suppressed.

Since COVID-19 disease is a viral disease, systemic effects can be seen frequently. Certain laboratory features have been associated with poor outcomes in COVID-19 disease. Leukocyte counts may vary with diseases.[13] In our study, although the leukocyte count was within the normal range in both groups, it was found to be higher in deceased patients than in survivors and patients with severe disease than in patients with non-severe disease.

Lymphocyte count is directly related to immunity to the virus. Severely decreased lymphocyte count is associated with increased disease severity, morbidity, and mortality. In the study of Wang *et al.,* decreased lymphocyte count was associated with severe disease and death.[14] In our study, lymphocyte counts were lower in deceased patients compared to survivors.

Monocytes trigger inflammation through the production of cytokines and the activation of lymphocytes.[15] In the study conducted by Pan *et al.*, monocyte levels were found to be significantly low in COVID-19 patients.[16] In some studies, it has been reported that monocyte levels were low in patients with severe disease who were followed up in intensive care.[17] In our study, monocyte levels were found to be low in patients who were deceased and in the group with severe disease.

The COVID-19 disease affects neutrophil levels. Blood neutrophil levels usually increase in response to infectious agents and tissue damage. In a meta-analysis by Henry *et al.*, neutrophil counts were found to be higher in deceased patients than in survivors.[13]

Thrombocytopenia has been reported to be associated with a poor prognosis in COVID-19 disease.[18] In a study, a low platelet count was found in deceased patients and severe cases.[13] In a study by Lippi *et al.*, the presence of thrombocytopenia ($<31 * 10^9$/L) was found to be higher in individuals with severe disease, and it was reported that the rate of severe disease was five times higher in patients with thrombocytopenia.[19] In our study, unlike the studies reported in the literature, no significant difference was found between the two groups in platelet levels.

SII and SIRI are parameters that can be used to predict in-hospital mortality. In some malignancies, SII has been shown to strongly predict prognosis.[20] In another study, it was shown that it can be used to predict prognosis in pancreatitis patients.[21] There is a study in the literature showing an association between increased SII and poor prognosis in coronary artery disease.[22] Similarly, there are also studies conducted for SIRI. SIRI has been shown to predict poor prognosis in stroke and pancreatitis patients.[23,24] With these data, the power of SII and

SIRI in predicting prognosis and mortality in COVID-19 disease has aroused curiosity, and studies have been conducted. Eissa *et al.* found a correlation between an increase in SIRI and an increase in mortality rates, whereas no correlation was found between SII and mortality.[25] In the study by Fois *et al.*, both SII and SIRI were found to be significantly increased in COVID-19 patients who died.[26] In the study by Muhammad et al., the power of SII in predicting intubation and death in patients was emphasized.[27] In a study by Usul *et al.* on patients admitted to the emergency department, increased SII was found to be associated with poor prognosis and increased mortality.[5] In a study conducted on patients hospitalized in intensive care, it was emphasized that SII was an independent marker in determining the prognosis of COVID-19 patients. In the same study, SIRI (OR: 1.041, 95% CI: 1.006–1.078, p=0.021) was found to be the most effective factor in predicting hospitalization.[28] In another study conducted on patients hospitalized in intensive care, similar results were found, and a significant relationship was found between SII and SIRI and death, and the specificity of SII was found to be higher.[29] In our study, the mean SII and SIRI values in the deceased and severe groups were higher than the mean SII and SIRI values in the survivors and non-severe groups. increased inflammatory conditions, the neutrophil ratio increases as a product of natural immunity. Lymphocytes provide the main immunity against viruses. As the severity of the disease increases, immunity gradually decreases, with lymphocytes lost in this battle. Since SII and SIRI include both lymphocyte counts and neutrophil counts, they can be used to determine the state of immunity and inflammation. These indices indicate increasing inflammation, and as the rate of inflammation increases, the prognosis worsens. The association of increasing SII and SIRI with death is consistent in this respect. SII and SIRI are easily accessible markers and can be used independently to predict death and poor prognosis in patients with COVID-19.

Limitations

The most important limitation is that our study was conducted retrospectively at a single institution. Our study was performed with laboratory tests obtained at the time of presentation to the emergency department. No relationship was established with the time of symptom onset. There was no study on the stage of the disease at which the test was taken. Combining the indices with clinical findings and laboratory parameters such as blood gases may help to better predict the severity and prognosis of the disease.

Conclusions

In our study, SII and SIRI parameters were found to predict disease severity and mortality in patients with COVID-19. High SII and SIRI levels were found to be associated with a poor prognosis. We think that SII and SIRI parameters are easily accessible and inexpensive indices in the emergency department and can be used as auxiliary tests for prognosis prediction. Studies on these indices are limited, and more studies are needed.

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Table 1. Disease severity and its relation with death according to demographic characteristics of the patients.

		Survival n:310	**Death n:136**	**P**	**Non-Severe n:198**	**Severe n:248**	**P**
		Number (%)	**Number (%)**		**Number (%)**	**Number (%)**	
Gender	**Male**	147(47.4)	79 (58)	**0.038**	95 (47.9)	131(52.8)	0.309
	Female	163 (52.6)	57 (42)		103 (52.1)	117 (47.2)	
Age (average±sd)		59.3 ± 18.8	73.7 ± 11.2	**<0.001**	55.5 ± 19.5	70.3 ± 13.7	**<0.001**
Presence of chronic disease		167 (53.8)	119 (87.5)	**<0.001**	87 (43.9)	199 (80.2)	**<0.001**
DM		84 (27)	60 (44.1)	**<0.001**	36 (18.1)	108 (43.5)	**<0.001**
HT		114 (36.7)	83 (61)	**<0.001**	52 (26.2)	145 (58.4)	**<0.001**
HF		25 (8)	29 (21.3)	**<0.001**	14 (7)	40 (16.1)	**0.006**
CAD		55(17.7)	48 (35.3)	**<0.001**	29 (14.6)	74 (29.8)	**<0.001**
Arrhythmia		13 (4.2)	14 (10.3)	**0.023**	11 (5.5)	16 (6.4)	0.846
CKF		19 (6.1)	19 (13.9)	0.11	11 (5.5)	27 (10.8)	0.067
SVD		10 (3.2)	8 (5.8)	0.293	5 (2.5)	13 (5.2)	0.228
Asthma/COPD		25 (8)	11 (8)	1.000	7 (3.5)	29 (11.6)	**0.003**
Cirrhosis		1 (0.3)	0 (0)	1.000	1 (0.5)	0 (0)	0.444
Malignancy		6 (1.9)	8 (5.8)	**0.038**	3 (1.5)	11 (4.4)	0.138

sd, standart deviation, DM, Diabetes Mellitus, HT, Hypertension, HF, Heart Failure, CAD, Coronary Artery Disease, CKF, Chronic Kidney Failure, SVD, Cerebrovascular disease, COPD, Chronic Obstructive Pulmonary Disease.

Table 2. Association of laboratory values and indices with mortality and severity.

	Survival n:310	**Death n:136**	**P**	**Non-Severe n:198**	**Severe n:248**	**P**
Hgb (g/dL)	12.74±2.04	12.46±2.06	0.176	12.87±2.07	12.48±2.01	0.46
Rbc ($x10^3$/µl)	37.92±5.54	37.42±6.01	0.391	38.25±5.58	37.39±5.75	0.114
Leukocyte ($x10^3$/µl)	7.49±3.65	9.35±4.72	**<0.001**	6.86±3.27	9.02±4.42	**<0.001**
Lymphocyte ($x10^3$/µl)	1.33±0.81	1.03±0.64	**<0.001**	4.08±0.67	1.45±0.85	**<0.001**
Monocyte ($x10^3$/µl)	0.59±0.33	0.55±0.40	0.232	0.61±0.34	0.56±0.36	0.150
Neutrophil ($x10^3$/µl)	5.49±3.46	7.70±4.35	**<0.001**	4.70±2.92	7.33±4.16	**<0.001**
Platelet($x10^3$ /µl)	214.82±80.23	212.36±89.23	0.774	209.87±74.43	217.42±89.24	0.330
CRP (mg/L)	67.94±79.723	161.03±92.527	**<0.001**	35.42±45.71	144.95±94.51	**<0.001**
Troponin (ng/L)	34.60±227.31	313.63±2318.48	0.161	39.83±280.87	183.44±1720.54	0.246
SIRI	3.37±4.18	5.20±5.30	**<0.001**	2.77±3.41	4.86±5.22	**<0.001**
SII	1323.77±1856.37	2223.68±2542.62	**<0.001**	923.61±1162.99	2136.76±2533.72	**<0.001**

Rbc, Red blood cell, CRP, C-Reactive protein, SIRI, Systemic inflammatory response index, SII, Systemic inflammatory index.

Table 3. ROC analysis results of indices for predicting mortality and disease severity.

		Cut-off	AUC (p)	Sensitivity (CI)	Specificity (CI)	PPV (%)	NPV (%)
Death	**SIRI**	>2.057	0.640 (0.0001)	**72.06** (63.72 - 79.41)	50.97 (45.26 - 56.66)	39.20 (33.11-45.55)	**80.61** (74.37-85.90)
	SII	>1370.353	0.682 (0.0001)	55.15 (46.39 - 63.68)	**74.19** (68.94 - 78.97)	48.39 (40.30-56.54)	**79.04** (73.90-83.57)
Severity	**SIRI**	>1.648	0.689 (**0.0001**)	**78.63** (73.00- 83.56)	51.52 (44.32 - 58.66)	67.01 (61.28-72.39)	65.81 (57.77-73.23)
	SII	>867.834	0.744 (**0.0001**)	68.95 (62.79 - 74.65)	**70.71** (63.84 - 76.94)	74.67 (68.52-80.17)	64.52 (57.75-70.87)

SII, systemic inflammation index, SIRI, systemic inflammation response index, CI, confidence interval, AUC, area under curve, PPV, positive predictive value, NPV, negative predictive value.

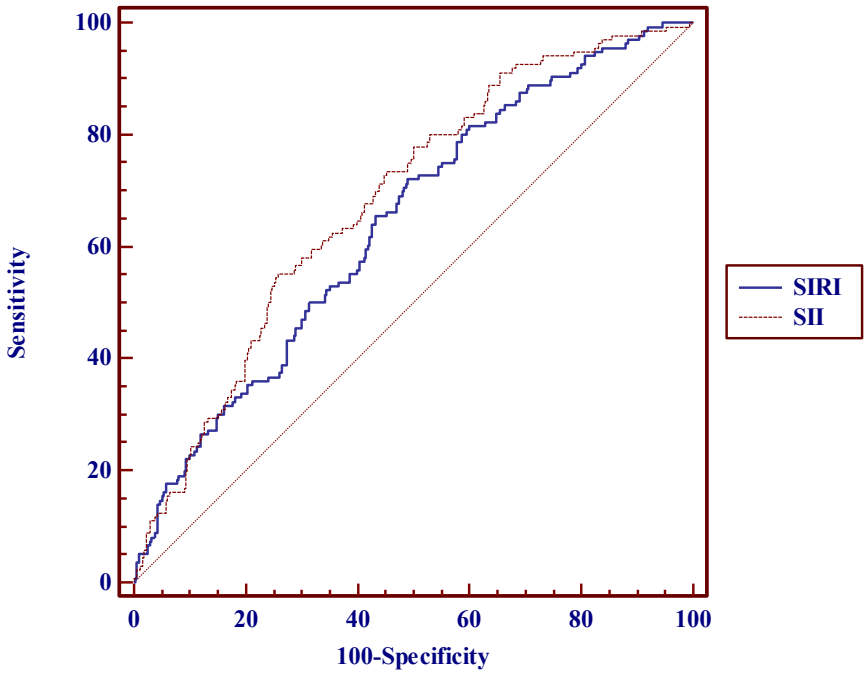

Figure 1. ROC analysis of indices for predicting death

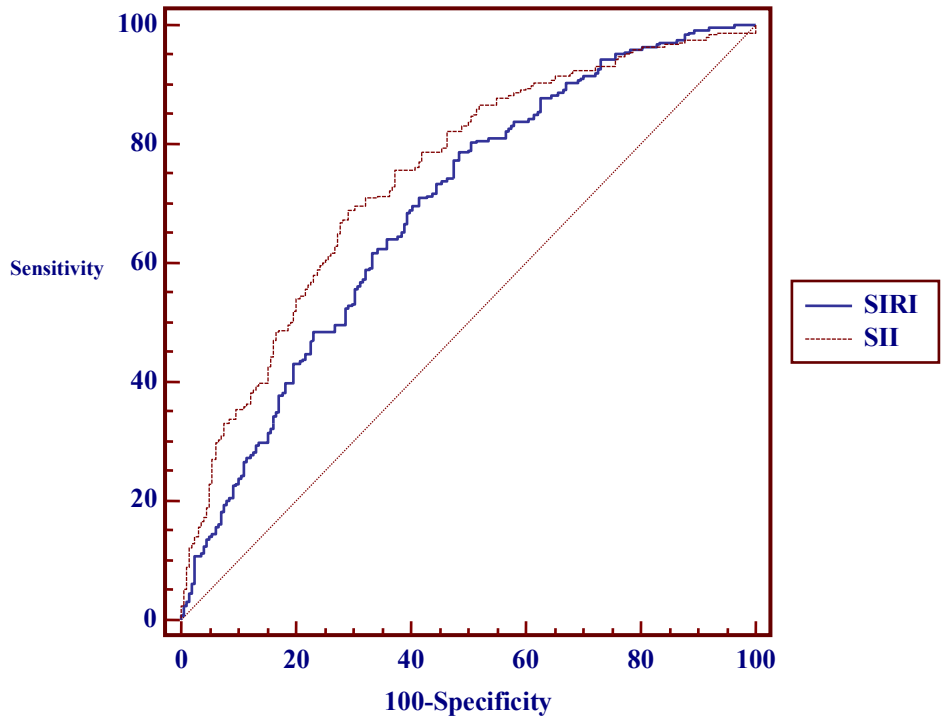

Figure 2. ROC analysis of indices for predicting disease severity