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Research Article

Patients with COVID-19 Critical Illness Have a Significantly Higher Systemic Immune-Inflammatory Index on Admission

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ABSTRACT

The severity of Coronavirus Disease-2019 (COVID-19) has been correlated to the massive inflammatory response. Patients with COVID-19 have a higher inflammatory marker. The Systemic Immune-Inflammation Index (SII) can be considered as an indicator of the immune-inflammatory status. Many studies stated that SII could significantly indicate the severity of COVID-19. This research aimed to explore the admission SII score and its association with the severity of hospitalized patients with COVID-19. It was a cross-sectional observational study. Data were collected retrospectively from the electronic medical records (ERM) and Laboratory Information System (LIS). The severity of COVID-19 and laboratory data on admission were analyzed. There were 180 patients (49.4% males and 50.6% female) with COVID-19 included in this research. Of these 180 patients, 22. 8% were categorized as mild, 18.9 moderate, 37.2% severe, and 21.1% were critical cases. Patients with critical illness had significantly higher SII scores than other groups with a p-value < 0.05. SII on admission could be a noticeable predictor of the occurrence of critically ill COVID-19 patients.

INTRODUCTION

The Coronavirus Disease-2019 (COVID-19) has become a global health problem and has spreading rapidly, affecting all parts of the world. Based on data reported globally by the World Health Organization (WHO), there were more than 536 million confirmed cases of COVID-19 and more than 6.3 million deaths had occurred due to COVID-19 disease on June 19, 2022 (WHO, 2022). The COVID-19 case data in Indonesia, until July 29, 2022, showed 6,197,495 confirmed cases, with 5,992,539 cases recovered, and 156,970 cases died. The positivity rate was 9.1%, and the case fatality rate was 2.53%. Indonesia was ranked the second highest country with the most COVID-19 cases in ASEAN countries after Vietnam (Kementrian Kesehatan RI, 2022).

Based on the degree of severity, COVID-19 is divided into four degrees, namely mild and moderate or not severe, severe and critical clinical degrees. Putra's research (2022) stated that most patients with COVID-19 treated in hospitals had severe and critical illness degrees (57.29%). Another study by Guan *et al*. (2020) showed that 15.7% of COVID-19 patients after admission to the hospital developed severe COVID-19 disease, i.e., severe pneumonia. Male COVID-19 patients who were older and had comorbidities were more likely to experience acute respiratory distress syndrome (ARDS) (Chen *et al*., 2020).

There was an aggressive inflammatory response that underlies the pathophysiology of COVID-19 disease which had an impact on respiratory tract damage (Tay *et al*., 2020). The patients with severe COVID-19 typically had higher levels of inflammatory cytokines, known as "cytokine storms", which could release pro-inflammatory cytokines that caused organ failure

and death (Karimi *et al*., 2021; Merad *et al.,* 2020; Panigrahy, 2020).

The Systemic Immune-Inflammation Index (SII), obtained from peripheral blood examination, is the multiplication of the ratio of neutrophils to lymphocytes and the number of platelet counts. SII could be proposed to describe the immune-inflammatory status of a person. Xue *et al.* (2020) stated that SII could predict the degree of severity of COVID-19, which was better than the ratio of neutrophils to lymphocytes. Two other studies also found a significant correlation between SII scores and the severity of infection by SAR-COV-2 (Doganci *et al*., 2020; Fois *et al*., 2020). Accordingly, the SII marker is a simple, inexpensive, and feasible parameter associated with inflammatory status and might be useful in determining the severity of COVID-19 disease. This research aimed to explore SII on admission and its association with the degree of severity of hospitalized COVID-19 patients.

METHODS

This analytical observational study was conducted with a cross-sectional design and data sampling was collected retrospectively. Instruments in this study were electronic medical records (EMR) and Laboratory Information System (LIS), which included data from patients' hospitalization in Bethesda Hospital, Yogyakarta, who were confirmed with SARS-CoV-2 infection. The diagnosis of COVID-19 used the results of the examination with Real-Time Polymerase Chain Reaction (RT-PCR). A total of 180 COVID-19 patients at Bethesda Hospital, Yogyakarta, were included from June 2020 to June 2021. The exclusion criteria were: if the patient did not have complete medical records.

Table 1. Demographic and Laboratory Findings on Admission of the COVID-19 Patients

Variable	n (%)
Age (years)	180 (100%)
18 - 49	47 (26.1%)
50 - 64	86 (47.8%)
> 64	47 (26.1%)
Gender	180 (100%)
Male	89 (49.4%)
Female	91 (50.6%)
Comorbidity	180 (100%)
Yes	112 (62.2%)
No	68 (37.8%)
Laboratory on Admission	Median (min - max)
Neutrophil (x10^3 /µL)	5.35 (0.9 – 34.3)
Lymphocyte (x10^3 /µL)	1.2 (0.5 – 7.6)
Platelet (x10^3 /µL)	223 (40 - 906)
SII (x10^3 /µL)	974.08 (147.37 - 19551)

Table 2. Comparison of the laboratory on admission between different degrees of COVID-19 patients

Laboratory on admission	Mild n:41	Moderate n:34	Severe n: 67	Critical n: 38	p-value
Neutrophil (x10^3 /µL)	4.9 (1.5 – 3.1)	4.75 (1.7 -34.3)	5.3 (0.9 – 20.5)	7.45 (1.9 – 18.5)	0.011*
Lymphocyte (x10^3 /µL)	1.5 (0.5 – 3.3)	1.35 (0.8 - 5)	1.3 (0.5 – 3.2)	1.1 (0.5 – 7.6)	0.03*
Platelet (x10^3 /µL)	223 (135 - 679)	211.5 (107.6 - 670)	224 (40 - 906)	239 (85 - 523)	0.667
SII (x10^3 /µL)	745.89 (161.19 – 17597.42)	653.04 (202.54 - 19551)	889.94 (147.37– 18425.63)	1718.50 (188.29– 6826.40)	0.004*

*p value < 0.05 indicating result as statistically significant.

Table 3. Post hoc test of neutrophil on admission between different degrees of COVID-19 patients

Degree	Mild	Moderate	Severe	Critical
Mild	-	0.848	0.334	0.013*
Moderate	0.848	-	0.182	0.005*
Severe	0.334	0.182	-	0.012*
Critical	0.013*	0.005*	0.012*	-

*p value < 0.05 indicating result as statistically significant.

Table 4. Post hoc test of lymphocyte on admission between different degrees of COVID-19 patients

Degree	Mild	Moderate	Severe	Critical
Mild	-	0.449	0.153	0.007*
Moderate	0.449	-	0.560	0.026*
Severe	0.153	0.560	-	0.063
Critical	0.007*	0.026*	0.063	-

*p value < 0.05 indicating result as statistically significant.

Table 5. Post hoc test of SII on admission between different degrees of COVID-19 patients

Degree	Mild	Moderate	Severe	Critical
Mild	-	0.632	0.438	0.007*
Moderate	0.632	-	0.187	0.003*
Severe	0.438	0.187	-	0.004*
Critical	0.007*	0.003*	0.004*	-

*p value < 0.05 indicating result as statistically significant.

Data on demographic characteristics and medical records of clinical information of COVID-19 patients (severity of COVID-19 and laboratory results, namely routine hematology results) at the time of hospital admission were taken and retrospectively analyzed. The severity of COVID-19 was determined by a doctor and was categorized as mild, moderate, severe, or critical. SII was calculated based on the following formula: SII = number of thrombocytes count × neutrophils/lymphocytes ratio (Karimi *et al.,* 2020).

This research was approved by the Health Research Ethics Committee of Bethesda Hospital Yogyakarta, Indonesia (No:55/KEPK-RSB/IV/22). All the results of the research data measured were presented as median (minimum-maximum). Kruskal-Wallis test was used to compare the difference in SII scores between groups based on the severity of the disease. Next, if there was a significant difference, the analysis was continued with the Mann-Whitney post hoc test. *P*-value < 0.05 was considered statistically significant.

RESULTS AND DISCUSSION

There were 180 COVID-19 patients (49.4% males and 50.6% female) finally included in this study. Most of them treated at the hospital were 50 to 64 years old. As many as 86 patients (47.8%) were in the age range >64 years and 18 to 49 years each was 47 patients (26.1%). Among them, 112 patients (62.2%) had one or more comorbidities (other diseases that coexisted with COVID-19). The median neutrophil count on admission was 5.35 x 10^3 /µL, lymphocyte count was 1.2 x 10^3 /µL, platelet count was 223 x 10^3 /µL, and SII was 974.08 x 10^3 /µL. The demographic and laboratory admission of 180 COVID-19 patients were shown in Table 1.

Comparisons of the laboratory on the admission of 180 COVID-19 patients with different degrees of COVID-19 patients are presented in Table 2. Of the 180 patients with COVID-19, 41 (22.8%) were grouped as mild, 34 (18.9%) moderate, 67 (37.2%) severe, and 38 (21.1%) were critical cases. Compared with patients in the mild, moderate, and severe groups, COVID-19 patients in the critical clinic had higher levels of neutrophil count with a *p*-value < 0.05. The median total neutrophil count increased with increasing disease severity, although the severe disease did not significantly differ statistically compared with mild and moderate disease (Table 3). Meanwhile, COVID-19 patients with critical diseases experienced a significantly decreasing amount of lymphocyte counts compared to patients with mild, moderate and severe degrees (Table 4).

Peripheral blood cell count abnormalities on admission, such as neutrophilia and lymphopenia, were associated with the disease severity of the patients with COVID-19. A meta-analysis study conducted by Henry *et al.* found that neutrophilia on admission significantly increased the risk by 7.99-fold for severe disease, while admission with lymphopenia was significantly associated with 4.2-fold increased odds of developing the advanced disease (Henry *et al*. 2020).

Elevated blood neutrophil levels were an early sign of COVID-19 that predicted severe respiratory illness and poorer clinical outcomes. The neutrophil-lymphocyte ratio could be a simple parameter index to identify and differentiate between severe and non-severe COVID-19 patients (Zhang *et al*., 2020; Zuo *et al*., 2020). Our study showed that as the degree of COVID-19 disease increased, the absolute number of neutrophils also increased; conversely, the total number of lymphocytes would decrease. A study in Indonesia by Sukirman *et al.* (2020), indicated that absolute lymphocyte counts (ALC) also played an

important role in distinguishing between severe (median ALC: 1020 cells/ µL) and non-severe (median ALC: 1380 cells/ µL) cases of COVID-19. In our study, it was found that the median absolute lymphocyte counts at mild, moderate, severe, and critical degrees were as follows: 1500 cells/ µL, 1350 cells/ µL, 1300 cells/ µL, and 1100 cells/ µL, respectively.

This study showed no significant difference in the number of platelets in both the non-severe groups (mild and moderate) and the severe until critical groups. Our study's results differed from other studies on platelets and COVID-19. Lippi *et al.* (2020), conducted a meta-analysis of the relationship between platelet count and COVID-19 severity. Their study results suggested that lower platelet counts were found in more severe groups and were correlated with an increase in deaths of COVID-19 patients.

Thrombocytopenia in COVID-19 was more likely to experience critical illness (Barrett *et al.,* 2020). The admission platelet in our study showed no significant difference between both the severe and non-severe groups. The results of our study were in accordance with the study by Khave *et al.* (2021), but in their study, after seven days since the day of admission, there was a tendency to increase the platelet count in the non-severe group compared to the severe group.

Our study demonstrated that SII in critically ill patients scored significantly higher than in mild, moderate, and severe COVID-19 patients. The results of our study resemble those of the study by Nalbant *et al.* (2021). They found that the SII score in intensive care unit patients was significantly greater than in non-ICU patients. Li *et al.* (2020) stated that an elevated SII score in COVID-19 was a predictor of the development of ARDS and increased the risk of hospital mortality. A study by Muhammad *et al.* (2021) showed that the SII value at admission indicated a potential marker for estimating the need for invasive ventilator support and worse clinical outcomes in COVID-19

The limitation of this study was that the retrospective design of our study only took laboratory data and the clinical degree of COVID-19 disease at the time the patient was admitted to the hospital. We did not follow up until the outcome of the patient. However, the finding of our study added to the value of using SII on admission to the hospital as a possible marker of critical illness from COVID-19, so it could be helpful for quickly managing COVID-19 patients. This study also proved that increased neutrophils and reduced lymphocytes were associated with a critical degree of COVID-19 disease. These findings suggested that SII markers obtained from routine hematologic examinations could be helpful as clues to critically ill COVID-19. SII was very suitable for application in developing countries such as Indonesia because it was a simple and inexpensive marker.

CONCLUSION

SII on admission in critically ill patients had significantly higher scores compared with mild, moderate, and severe COVID-19 patients. SII markers might be a noticeable predictor of the occurrence of clinical severity in patients with COVID-19.

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