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Prognostic Nutritional Index and Systemic Immune-inflammation Index: Possible New Parameters for COVID-19 Severity

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Abstract

Background: The prognostic nutritional index (PNI) parameter has been widely used in estimating the severity of COVID-19. In contrast, investigating the role of the systemic immune-inflammation index (SII) in determining the COVID-19 severity is prospective. This study aimed to investigate the potential of PNI and SII parameters to distinguish the severity of symptoms of COVID-19.

Methods: A retrospective observational study was conducted among 209 hospitalized patients with COVID-19. Data were collected from August 2021 to February 2022 in Indonesia's general COVID-19 referral hospital. Demographic and laboratory data, including PNI and SII, were analyzed and compared between the severe and non-severe symptoms of COVID-19 patients. The statistical analysis of the receiver operating characteristic curve (ROC) and area under curve (AUC) was conducted to predict the potential of these parameters in distinguishing the COVID-19 severity.

Results: More than half of this study's patients (54.55%) were non-severe COVID-19. The SII values in patients with severe symptoms were significantly higher than in those with non-severe symptoms (2,445.24 vs. 1,423.28, p=0.005). In contrast, the PNI value in patients with severe COVID-19 symptoms was significantly lower than those with non-severe symptoms (38.04 vs. 33.93, p<0.001). The area under the curve (AUC) value of PNI was 0.694, meanwhile the SII was 0.635. The optimum cut-off for the PNI was <35.407, whereas the SII was >2,212.787. PNI and SII were the potential new diagnostic parameters for COVID-19 severity.

Conclusion: PNI and SII parameters can potentially distinguish the severity of symptoms of COVID-19.

Keywords: COVID-19 severity, prognostic nutritional index, prognosis, systemic immune-inflammation index

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Introduction

The clinical manifestations of COVID-19 vary from mild to severe. Severe COVID-19 patients are often hospitalized for various reasons, including age and organ failure.[1] Approximately 20% of severe COVID-19 patients require treatment at the intensive care unit (ICU) due to respiratory failure, acute heart disease, acute kidney disease, and shock.[2] On the other hand, several parameters have been introduced to estimate the severity of the disease, both clinical and laboratory parameters. For instance, the neutrophil-to-lymphocyte ratio (NLR) measurement during COVID-19 hospital admission can be used to estimate the disease's severity and the treatment outcome.[3] Estimating the critical risk of illness can help identify the possible deterioration of a patient's condition, provide appropriate treatment, and optimize medical resources.[4]

Prognostic nutritional index (PNI) is a parameter that could be used to predict

the severity of COVID-19 symptoms. The PNI calculates albumin and lymphocyte parameters, reflecting nutritional and inflammatory status. This parameter was originally developed to evaluate the nutritional conditions before surgery and the risks of the surgical process.[5] A low PNI value indicates a higher severity of symptoms of the illness.[6] It is considered a novel independent prognostic factor for predicting the overall survival of malignant melanoma,[7] and other types of cancers.[5,8] Lately, this parameter has been used as an inexpensive and available biomarker to predict the severity of COVID-19.[9] Previous study found that the PNI value of critical COVID-19 patients is much lower than that of non-critical patients.[6] Lower PNI scores are associated with a worse prognosis in severe COVID-19 patients, where a PNI score of less than 33.4 was associated with higher risk of death among them.[10] Thus, PNI is considered an independent predictive factor in determining hospital deaths in cases of malignancy that experience COVID-19.[11]

Besides PNI, systemic inflammation index (SII) is an inflammatory parameter that can estimate the severity of symptoms of COVID-19. The SII is obtained by calculating the number of lymphocytes, neutrophils, and platelets. A higher score of SII indicated a poor prognostic marker in several malignancies.[12] The SII has been used as the prognostic role in tumors[12] or cancers.[13,14] During the COVID-19 pandemic, SII has been used to predict the in-hospital mortality of the disease.[15] It is a marker to predict the need for invasive ventilators and poor patient outcomes.[16] Patients suspected of being infected with SARS CoV-2 with high SII levels have a greater risk of SARS CoV-2 positive on a PCR test.[17] However, the study investigating the potential of both PNI and SII in distinguishing the severity of the patients with COVID-19 has been limited. This study aimed to explore the potential of the two parameters in determining the severity of COVID-19 symptoms.

Methods

This retrospective observational study was conducted on 209 people who were hospitalized due to being confirmed positive for COVID-19. Data was collected from August 2021 to February 2022 at Dr. Soedono Madiun Hospital, Indonesia. The criteria for patients with severe COVID-19 symptoms were based on guidelines for managing COVID-19 in Indonesia.[18] According to the guidelines, the severe symptoms of COVID-19 must include pneumonia (fever, cough, tightness, rapid breathing) plus one of >30 times/minute breathing frequency, severe respiratory distress, or SpO2 <93% in the room air.[18] Patients with critical symptoms, acute respiratory distress syndrome, sepsis, sepsis shock, or other condition that requires mechanical ventilation were also categorized as severe symptoms.[18]

The demographic and clinical data collected from the patients include gender, age, comorbidities, clinical symptoms, diagnosis, therapy, and duration of treatment, as well as outcomes of COVID-19 patients. The laboratory data collected include complete hematology, coagulation function, kidney function, liver function, albumin, electrolytes, C-reactive protein (CRP), and D-dimer. Diabetes mellitus was defined when the fasting blood sugar level was >126 mg/dL, two hours post prandial blood sugar was >200 mg/dL, or the HbA1C level was >6.5%. For obesity, if the body mass index (BMI) was >30 kg/m^2. Coronary heart disease was the condition of a patient diagnosed with coronary artery disease or congestive heart failure. Renal impairment if the level of glomerular filtration rate (GFR) <15 mL/min/1.73 m^2 or the patient has a history of hemodialysis and liver impairment if the marker of Hepatitis type B or C was positive.

Laboratory data were collected during the first examination. Neutrophil lymphocyte ratio (NLR) was obtained by dividing the number of neutrophils and the number of lymphocytes. Platelet lymphocyte ratio (PLR) was obtained by dividing platelet count and lymphocyte number. The PNI was calculated as 10 × serum albumin (gr/dL) + 0.005 × total lymphocyte count (per mm^3). The SII was obtained by the formula platelet number x (neutrophil/lymphocyte number).

Continuous variables such as hemoglobin, leukocytes, platelets, neutrophils, lymphocytes, NLR, lymphocyte-to-monocyte ratio (LMR), PLR, absolute lymphocyte count (ALC), serum glutamic oxaloacetic transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT), albumin, PNI, SII, prothrombin time (PT), activated partial thromboplastin time (aPTT), international normalized ratio (INR), D-dimer, CRP, creatinine, uric acid, and duration of treatment were reported using mean±standard deviation (SD) or median and interquartile (range). Categorical variables included age, gender, comorbidities, and clinical outcomes. Continuous variables were compared using the Student's t-test if the data

distribution was normal or the Mann-Whitney U test if the data distribution was skewed. Associations between categorical variables were tested using the Chi-square or Fisher's exact test.

The association between the severity of COVID-19 and the demographic, comorbid, laboratory, and clinical outcomes were examined. The PNI and SII variables were analyzed using the receiver operating characteristic (ROC) curve to determine the optimum value distinguishing the severe and non-severe COVID-19 symptoms. The area under the curve (AUC) analysis was performed for both variables. An AUC value above 0.60 indicates the potential for these parameters to distinguish the severity of COVID-19.

This study was approved by the Ethics Committee of RSUD dr. Soedono Madiun (Approval number: 070/23741/303/2021, approval date: June 8th 2021) and all participants or families provided written informed consent.

Results

COVID-19 patients with severe symptoms had a higher prevalence of comorbid kidney disease (13.7% vs 4.35%, p=0.017) and a higher risk of death compared to the group of COVID-19 patients with non-severe symptoms (64.2% vs 0.9%, p<0.001) (Table 1). Furthermore, severe COVID-19 patients had significantly higher levels of leukocytes, neutrophils, monocytes, blood ureum nitrogen (BUN), NLR, CRP, SII, and D-dimer than non-severe COVID-19 patients (p<0.05). Meanwhile, platelet, LMR, albumin, and PNI values were significantly lower in severe COVID-19 patients compared to non-severe patients (p<0.05;Table 2).

The AUC value for PNI was 0.694, while for SII it was 0.635. An AUC value greater than 0.60 indicated that both PNI and SII had potential to be diagnostic biomarkers for the severity of COVID-19. The optimum cut-off for PNI was <35.407, while SII was >2,212.787. The sensitivity and specificity values of PNI were 67.4 and 67.5, respectively. At the same time, the sensitivity and specificity values of SII were 40.0 and 86.0, respectively (Figures 1 and 2).

Discussion

Clinical indicators regarding the severity of the symptoms experienced by COVID-19 patients will significantly assist the doctors in planning appropriate treatment. In this study, it was found that the PNI value in patients with severe COVID-19 was lower than in non-severe patients. A low PNI value indicates a higher inflammation and poor nutritional status. Furthermore, the AUC of PNI score in our study (0.694) was lower than that reported by Wang et al.[6] (0.790), Wei et al.[10] (0.710), Nalbant et al.[19] (0.796), and Xue et al.[20] (0.760). The PNI value in our study was <35.407 with a sensitivity value of 67.4% and

Table 1 Socio-Demography, Clinical, Comorbid, and Outcome of the Study Respondents

Subject	Total (n=209)	Non-Severe (n=114), n (%)	Severe (n= 98), n (%)	P-value
Clinical data				0.129
Age (years), (mean + SD)	209	55.8±13.8	59.7±12.4	
Gender				0.578
Male	110	62 (54)	48 (50)	
Female	99	52 (46)	47 (49)	
Comorbid				
Diabetes mellitus	80	41 (35.9)	39 (41)	0.451
Obesity	3	1 (0.9)	2 (2.1)	0.592
Coronary heart disease	62	29 (25.4)	33 (34.7)	0.171
Renal impairment	18	5 (4.4)	13 (13.7)	0.017
Liver disorders	5	1 (0.9)	4 (4.21)	0.179
Outcome				<0.001
Death	62	1 (0.9)	61 (64.3)	
Recovered	147	113 (99.1)	34 (35.7)	
Duration of treatment (mean + SD)	209	12.22±4.52	12.57±8.996	0.732

Table 2 Analytical Statistic of Laboratory Data

Clinical Data	COVID-19										P-value	
	Severe					Non-Severe					Student's T-test	Mann Whitney U test
	Mean	SD	Median	Q1	Q3	Mean	SD	Median	Q1	Q3		
Laboratory												
Hb	13,411	2,1369	13,600	12,100	14,925	13,208	2,5431	13,800	11,100	15,300	0.540	
Leukocytes	7,8203	2,85685	7,3550	5,8100	9,4500	11,3489	5,80879	9,5500	7,1600	14,0700	**<0.001**	
Platelet	262,16	123,433	232,50	189,75	310,25	225,53	90,893	221,00	151,00	285,00	**0.017**	
Neutrophil	5,753	2,633	5,250	3,856	7,217	9,148	5,400	8,107	5,100	12,092	**<0.001**	
Lymphocytes	1,350	0,599	1,252	0,916	1,613	1,265	1,072	1,019	0,700	1,479	0.473	
Monocytes	0,618	0,286	0,583	0,399	0,778	0,762	0,601	0,622	0,466	0,877	**0.033**	
NLR			4,200	2,600	6,800			8,400	4,300	12,200		**<0.001**
LMR	2,605	1,469	2,315	1,578	3,291	1,882	1,139	1,716	1,233	2,234	**<0.001**	
PLR	224,722	150,671	168,935	131,270	282,050	236,942	159,488	198,873	126,219	308,151	0.570	
ALC	1351,667	601,582	1251,500	916,000	1625,750	1276,895	1064,352	1019,000	711,000	1479,000	0.524	
ALT			31,00	18,00	46,25			31,00	19,00	44,00		0.889
AST	44,29	44,022	32,00	22,00	51,00	50,74	29,716	46,00	27,00	63,00	0.226	
Albumin	3,8038	0,63534	3,7500	3,4150	4,0825	3,3925	0,56589	3,3900	3,0700	3,7000	**<0.001**	
PNI	38,045	6,353	37,508	34,156	40,831	33,932	5,659	33,908	30,707	37,000		**0.001**
SII			927,576	495,743	1672,844			1559,804	778,618	3080,000	**<0,001**	
PT	11,3885	1,90522	11,1000	10,4000	11,8000	11,5220	1,19274	11,3000	10,8000	12,2000	0.562	
aPTT	33,0927	8,33181	32,5000	28,4000	35,6000	32,8275	7,94954	31,5000	28,0000	35,3000	0.818	
INR	1,1400	0,86410	1,0400	0,9700	1,1000	1,0716	0,11761	1,0500	1,0000	1,1400	0.455	
D-dimer	1,575935	2,0740863	0,859210	0,506648	1,610413	3,616793	3,7270335	1,920000	0,980860	5,386800	**<0.001**	
CRP	105,4167	91,25843	98,0150	13,9075	146,7925	162,7249	101,33519	147,4400	79,8100	251,8100	**<0.001**	
BUN			15,7000	11,9250	24,4000			23,2000	13,0000	33,0000	**0.001**	
Creatinine			1,0900	0,7775	1,4025			1,1600	0,8600	1,9600		0.105
Uric Acid	7,4468	17,61408	5,1700	4,0200	6,4400	7,7980	12,68249	5,6900	3,8300	7,5750		0.204

Note: Hb= hemoglobin, NLR= neutrophil-to-lymphocyte ratio, LMR= lymphocyte-to-monocyte ratio, PLR= platelet-to-lymphocyte ratio, ALC= absolute lymphocyte count , ALT= alanine aminotransferase, AST= aspartate aminotransferase, PNI= Prognostic nutritional index , SII= systemic inflammation index , PT= prothrombin time , aPTT= activated partial thromboplastin time, INR= international normalized ratio , CRP= C-reactive protein, BUN= blood urea nitrogen

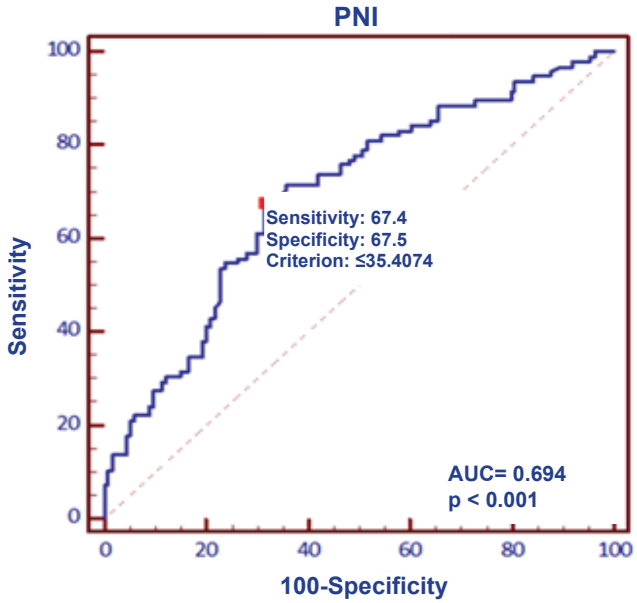

Figure 1 ROC Curve of Prognostic Nutritional Index (PNI)

specificity of 67.5%, which was also lower than Wang et al.[6] study, (<43, sensitivity= 85.7%, specificity= 60%), Nalbant et al.[19] (<36.7, sensitivity= 73.4%, specificity=70.8%), and Xue et al.[20] (34.05, sensitivity= 86.21%, specificity=60.71%. This difference could be due to the lower average albumin value of our study subjects, indicating poor nutritional status and more comorbidities compared to previous studies. Additionally, the PNI value of 33.41 in COVID-19 patients indicates their inability to survive, compared to the 37.2 value among COVID-19 patients who could survive. Therefore, the value of PNI below 33,405 is significantly associated with a high risk of death in COVID-19 patients.[10]

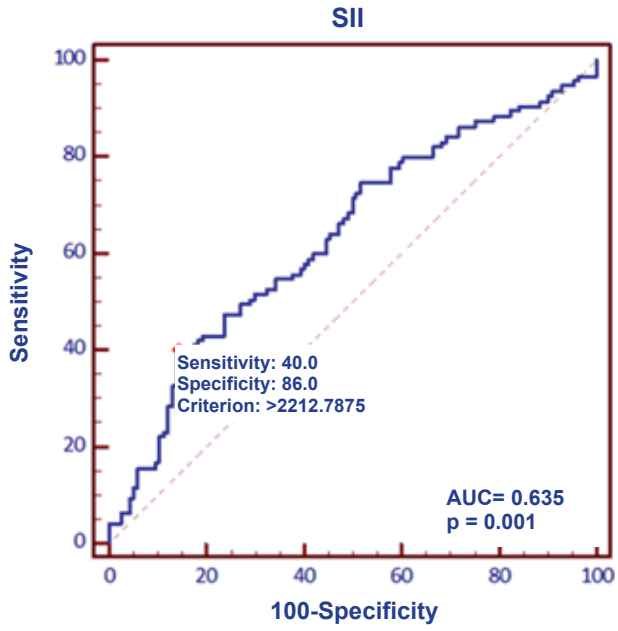

Figure 2 ROC Curve of Systemic Immune-Inflammation Index (SII)

To distinguish the severity of COVID-19 symptoms, our study obtained the optimum SII cut-off value >2,212.78, AUC=0.635, sensitivity=40% and specificity=86%. Higher SII values indicate the presence of more inflammation, as illustrated by the lymphocyte, neutrophil, and platelet values. A previous study found the SII value of 2087 as a predictor of intubation use in COVID-19 patients,[16] meanwhile, another study suggested the SII score of 1227 as an indicator of patients requiring ICU care.[19] Furthermore, a study in Turkey[19] found an SII value of >813.6 with an AUC of 0.689, sensitivity of 70.8%, and specificity of 66.0% for predicting the severity COVID-19, whereas Xue et al.[20] suggested the cut-off of SII of 809.2, with an AUC of 0.72, the sensitivity of 72.41% and a specificity of 67.86% for estimating the severity of COVID-19. Our study found a higher SII cut-off with a lower AUC than previous studies. The higher SII cut-off could be due to the higher average NLR and CRP values in our study showing more severe inflammation in the subjects of our study compared with previous research. Comorbidities in research subjects also influence the AUC value of the SII.

PNI and SII values as inflammatory markers can be used to determine the severity of COVID-19.[21] PNI defines the nutritional and inflammatory status of a patient. Inadequate nutritional status and pre-existing diseases such as diabetes, chronic lung disease, cardiovascular disease, and various other diseases make patients immunocompromised and affect the severity of COVID-19. Low nutritional status and an unhealthy lifestyle are also associated with inflammation and increased oxidative stress.[22] Furthermore, hypoalbuminemia is a poor prognosis in COVID-19.[23] Hypoalbuminemia results from inflammation and reflects a severe inflammatory state, which can interfere with the response to administered therapy and is associated with poor quality of life and decreased age.[24] During COVID-19 infection, the virus activates APCs, macrophages, and dendritic cells, introducing SARS-CoV2 antigens to T cells, leading to the activation, differentiation, and release of inflammatory cytokines. Decreased lymphocyte levels, infiltration of monocytes and macrophages, and high levels of inflammation result in poor outcomes and death.[22] Thus, low lymphocyte count is a predictive factors of in-hospital mortality, organ damage, and severe pneumonia in COVID-19.[25]

SII is an inflammatory marker based on lymphocyte, neutrophil, and platelet count. Neutrophils are the largest type of white blood cell and play an important role in innate immunity. During infection, neutrophis migrate to infected organs and contribute to the death of pathogens. Neutrophils also play an important role in thromboinflammation and activate thrombus formation. In the case of COVID-19 infection, neutrophil activation stimulates the formation of neutrophil extracellular trap (NET), platelet aggregation, and cell damage.[26] In addition, lymphopenia is a major immunological disorder in most severe COVID-19 patients, and is significantly associated with mortality. Lymphopenia can cause immunosuppression and trigger a cytokine storm, which plays an important role in viral persistence, viral replication, multi-organ failure, and eventually death.[27]

The role of platelets is also crucial in the severity of the development of COVID-19. Platelets are responsible for hemostasis and thrombus formation; thus, platelet hyperreactivity induced by the pro-inflammatory microenvironment contributes to the "cytokine storm" that characterizes the more aggressive course of COVID-19.[28]

The SII value can also predict death due to COVID-19 infection in hospitals. The SII values between 1,854[15] and 2,828[29] were often found in patients who died due to COVID-19 infection. Therefore, the cut-off SII >1,835, AUC 0.628, the sensitivity of 55%, and specificity of 75% can be used as prognostic parameters for mortality in COVID-19 patients.[15] Meanwhile, PNI can also be used as a predictive factor for in-hospital mortality with a cut-off of 287, AUC of 0.70, a sensitivity of 88%, and specificity of 55%.[11]

Furthermore, it was also found that the count of leukocytes, neutrophils, NLR, D-dimer, CRP, and creatinine values were higher in patients with severe symptoms of COVID-19 compared to the non-severe patients. These findings are consistent with previous studies showing higher values in COVID-19 patients with severe symptoms.[19,29,30] We also found significantly lower albumin levels and platelet counts in severe COVID-19 patients than in patients with non-severe symptoms. This corresponds to a severe inflammatory state in severe COVID-19 and previous studies.[24,28,29]

This study revealed that the PNI and SII values, obtained from routine blood tests, can be straightforwardly used to predict the severity of COVID-19 patients. Thus, it strengthens the role of PNI and SII as parameters to predict the severity of COVID-19. Nevertheless, this study

has several limitations, including the relatively small sample size, differences in sick days, the study was conducted in one setting only, the retrospective design, and the presence of comorbid factors that might affect the results. Further studies could consider a longitudinal approach, considering comorbidity factors and multiple settings.

In conclusion, PNI and SII values can be used as prognostic parameters for death in COVID-19.

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