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Original Article

Predictors of Mortality in Sepsis Patients Resulting from Severe and Critical COVID-19

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ABSTRACT

Patients with severe and critical COVID-19 may exhibit sepsis and mortality resulting from multi-organ failure. Neutrophil-lymphocyte-ratio (NLR) values, C-reactive protein (CRP) levels, sequential organ failure assessment (SOFA), and acute physiology and chronic health evaluation II (APACHE-II) scores were used to assess the risk of mortality in sepsis patients resulting from severe COVID-19 infection. The adequacy of NLR, CRP, SOFA, and APACHE-II scores were evaluated as predictors of mortality in septic COVID-19 patients at Dr. Kariadi Hospital Semarang, Indonesia, between August 2021 and July 2022. The subjects included severe and critical COVID-19 patients who fulfilled the WHO interim guidelines and Sepsis-3 criteria. A total of 211 patients were included, which were divided into survivor (n = 116) and non-survivor (n = 95) groups. NLR values, CRP levels, SOFA, and APACHE-II scores were measured within 24 hours of patient admission. Univariate and multivariate logistic regression analyses were used to identify the risk factors for COVID-19 mortality. Receiver operating characteristic curve analysis was used to predict the mortality of severe COVID-19 patients. The results indicated that the APACHE-II score was an independent predictor of mortality in sepsis patients resulting from severe and critical COVID-19.

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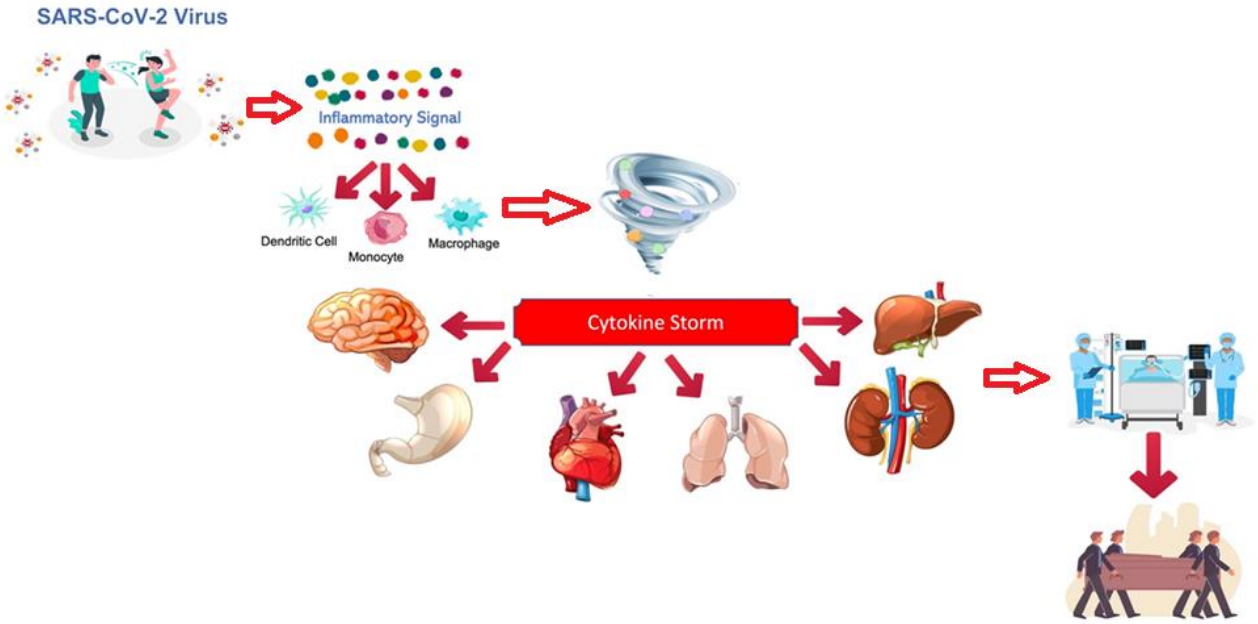
GRAPHICALABSTRACT



Introduction

Coronavirus Disease 2019 (COVID-19) is an acute infection caused by the SARS-CoV-2 virus. Approximately 14% of COVID-19 patients progress to severe cases that require hospitalization and oxygen support [1]. Five percent are admitted to the intensive care unit (ICU) and develop acute respiratory distress syndrome (ARDS), sepsis, septic shock, multi-organ failure, and most ultimately die [1]. Sepsis is most commonly caused by bacterial and fungal infections, but it can also be caused by a viral infection. The World Health Organization (WHO) considers highly transmissible pathogens as global health issues. Examples include avian and swine influenza, coronaviruses, sepsis, and septic shock at the latest stage of infection [2]. Complex host immune dysregulation accompanies respiratory failure during severe COVID-19 infection [3]. Viral sepsis may sometimes occur through direct virus-induced tissue or cell injury [4]. Therefore, all aspects of the COVID-19 definition of Sepsis-3 may be applicable [5]. Karakike *et al.* conducted a systematic review and meta-analysis of COVID-19-related sepsis, evaluating the prevalence of organ failure, organ replacement, and the need for ICU admission as surrogate parameters for viral sepsis, based on Sepsis-3 criteria [6].

The scoring systems that are widely used to assess the severity of multi-organ failure and the prognosis of critically ill patients are SOFA and APACHE-II. The SOFA score for sepsis patients assesses the function of six organ systems, including respiratory, coagulation, cardiovascular, liver, central nervous system, and kidney function [7`]. The APACHE-II system scores disease severity and estimates mortality in critically ill patients based on age, reason for entering intensive care, an elective postoperative, emergency, or non-operative emergency condition, chronic disease, and 12 other physiological variables [8].

In addition to disease severity, inflammatory biomarkers are useful for assessing the prognosis of COVID-19 patients, such as the neutrophil-to-lymphocyte ratio (NLR) and C-reactive protein (CRP) levels [9, 10]. The neutrophil-to-lymphocyte ratio is an indicator of the systemic inflammatory response, which reflects lymphocyte sequestration in tissues along with massive granulocyte production [11]. C-reactive protein is an acute-phase protein that acts as an early indicator of inflammation or infection. [12]. In this study, we evaluated the NLR, CRP, SOFA, and APACHE-II scores as predictors of mortality in sepsis patients resulting from severe and critical COVID-19.

Materials and Methods

This prospective cohort study was conducted at Dr. Kariadi Hospital Semarang between August 2021 and July 2022. It included patients over the age of 18 with PCR-confirmed SARS-CoV-2 and severe and critical COVID-19 based on WHO interim guidelines [1]. Severe COVID-19 criteria included oxygen saturation of less than 90% on room air and severe respiratory distress symptoms (accessory muscle use, inability to finish complete sentences, and breathing rate higher than 30 breaths per minute). Critical COVID-19 criteria included acute respiratory distress syndrome (ARDS), sepsis, and septic shock, requiring life-saving therapy, such as invasive or non-invasive ventilation or vasopressor therapy [1]. Septic shock was characterized as sepsis with prolonged hypotension, which requires vasopressors to preserve MAP ≥65 mmHg and a serum lactate level >2 mmol/L (18 mg/dL) despite adequate resuscitation [3]. Pregnant women, hemophilia patients, and those suspected of having a bacterial infection were excluded. A research ethics clearance was obtained from the Health Research Ethics Committee (KEPK) RSUP Dr. Kariadi, No. 593/EC/KEPK-RSDK/2020.

Data extraction was performed using case record forms to collect baseline patient data. The logistic analyses included baseline data, such as demographics, history of illness, clinical symptoms, and laboratory variables, to assess their association with COVID-199 severity. Laboratory confirmation of COVID-19 was performed by the microbiology laboratory in Dr. Kariadi Hospital. Within 24 hours of admission, neutrophil-to-lymphocyte ratios, CRP levels, SOFA, and APACHE-II scores were determined.

Data are presented as means and standard deviations for continuous variables and as numbers and percentages for categorical variables. Differences between groups were analyzed using the Mann-Whitney U-test for continuous data or the Chi-squared test for categorical data. The risk factors for COVID-19 mortality were identified using univariate and multivariate logistic regression analyses. Variables with $p < 0.25$ in the univariate logistic regression analysis were included in the multivariate logistic regression analysis. The odds ratio (OR) and confidence interval (CI) were then computed. The receiver operating characteristic (ROC) curve was used to determine the optimal cut-off of variables for predicting COVID-19 mortality risk. IBM SPSS Statistics Version 22 was used for the statistical analysis.

Results and Discussion

The baseline characteristics of severe COVID-19 patients are listed in Table 1. From 211 patients of consecutive sampling, 95 patients died within 28 days. In the non-survivor group, more patients were males (69.5%; $p = 0.237$) and above 50 years old ($p = 0.017$). Comorbidities in the non-survivor group occurred in 87.4% of the patients and the most common comorbidity was hypertension in both groups.

The comparisons between the survivor and non-survivor severe and critical COVID-19 groups were as follows: NLR value (8.73 ± 7.56 vs. 12.49 ± 13.05; $p < 0.008$), CRP levels 10.21 ± 9.29 vs. 11.76 ± 8.64; $p < 0.079$), SOFA score (2.85 ± 2.05 vs. 4.65 ± 2.97; $p < 0.001$), APACHE-II score (6.75 ± 4.66 vs 12.21 ± 6.09; $p < 0.001$), length of stay at hospital 19.69 ± 12.38 vs. 11.90 ± 5.56; $p < 0.001$), heart rate (93.4 ± 11.7 vs 100.37 ± 16.6; $p = 0.001$), and respiratory rate (25.79 ± 3.6 vs. 28.5 ± 5.05; $p < 0.001$), and SO_2% (92.71 ± 2.98 vs 89.61 ±7.16; $p < 0.001$). The values for the laboratory abnormalities were not significantly higher in the non-survivor group for WBC, urea, creatinine, total bilirubin, D-dimer, ferritin, and procalcitonin. Of these, 112 (53%) were admitted to the ICU, while the rest were in the isolation ward. There were 17 patients on ventilatory support and 15 patients died (88%).

Receiver operating characteristic (ROC) curve analysis (Figure 1) revealed that the area under the curve of NLR, CRP, SOFA score, and APACHE-II score were 0.570, 0.606, 0.704, and 0.777, respectively.

The cut-off values for NLR, CRP, SOFA, and APACHE-II scores for severe and critical COVID-19 patient mortality are summarized in Table 2. The cut-off value for NLR was 6.71. Elevated NLR was associated with a risk of mortality [OR= 1.50

(CI 95% 1.10–2.05); p = 0.008]. The cut-off value for CRP was 8.47. Elevated CRP was associated with an increased risk of mortality [OR = 1.24 (CI 95% 0.92–1.08); p = 0.079]. The cut-off SOFA score was 2.5 and the risk of mortality was [OR =1.91 (CI 95% 1.34–2.72); p = < 0.001]. The cut-off level for the APACHE-II score was 6.5 and the risk of mortality was [OR = 2.25 (CI 95%1.63–3.11); p < 0.001].

There was a significant relationship between the SOFA score (p < 0.001), APACHE-II score (p < 0.001), and NLR (p = 0.008) associated with 28-day mortality. There was no significant relationship between C-reactive protein levels (p = 0.079).

A multiple logistic regression analysis was performed to determine the impact of independent variables presumed to be mortality predictors of COVID-19 patients. Table 3 represents the independent variables that had p < 0.25 in the bivariate analysis.

Table 1: Characteristics of the enrolled patients

Variable	Survivor (n = 116)			Non-Survivor (n = 95)			*p-value*
	n (%)	Mean ± SD	Median IQR	n (%)	Mean ± SD	Median IQR	
Demography							
Sex							
Male	61 (52.6)	-	-	66 (69.5)	-	-	0.237
Female	55 (47.4)			29 (30.5)			
Age		49.66 ± 12,64	51.5 (41–59)		54.14 ± 12.59	55 (45–63)	0.017*
Comorbidities							
No Comorbid	36 (31)	-	-	12 (12.6)	-	-	0.015**
With Comorbid	80 (69)			83 (87.4)		-	
Type of comorbidity							
Diabetes Mellitus	24 (20.7)			18 (18.9)			0.640
Chronic Kidney Disease	8 (6.9)			3 (3.2)			0.553
Hypertension	31 (26.7)			23 (24.2)			0.997
Heart Failure	5 (4.3)			8 (8.4)			0.125
Malignancy	3 (2.6)	-	-	9 (9.5)	-		0.017*
Autoimmune Disease	4 (3.4)			5 (5.3)			0.840
Stroke	2(1.7)			7 (7.4)			0.104
Hepatitis	6 (5.2)			8 (8.4)			0.076
Tuberculosis	4 (3.4)			3 (3.2)			0.819
Number of comorbidities							
One	54(67.5)			55 (66.3)			0.867
≥ 2	26 (32.5)			28 (33.7)			
Length of Stay at Hospital	-	19.69 ±12.38	15 (11–25)	-	11.9 ±5.56	10 (6–15)	<0.001*
Type of room							
Ward	78 (67.2)	-	-	21(22)	-	-	<0.001**
ICU	38 (32.8)			77(78)		-	
Vital signs							
GCS		14.91 ± 0.68	15 (15–15)		13.76 ± 2.54	15(14–15)	<0.001**
Systolic BP (mmHg)	-	128 ± 21.39	122.5 (110–140)	-	123.51 ± 21.1	126 (110–135)	0.369
Diastolic BP (mmHg)		78 ± 11.8	80 (70–82)	-	76 ± 11.9	76 (70–82)	0.347
MAP (mmHg)	-	94.7 + 13.87	93 (87–102)	-	91.84 ± 13.66	91 (83–100)	0.223
HR (x/minutes)	-	93.4 ± 11.7	92 (66–130)	-	100.37 ± 16.6	100 (68–143)	0.001*
Respiratory Rate (x/minutes)	-	25.79 ± 3.6	25 (24–27.5)	-	28.5 ± 5.05	28 (25–30)	<0.001*
SO_2 (%)		92.71 + 2.98	92 (91–94)	-	89.61 ± 7.16	91 (88–98)	<0.001*

Laboratory tests							
Hemoglobin (gr/dl)	-	12.7 ± 2.45	13 (11.5–14.4)	-	12.5 ± 2.8	13.1 (11.3–14.7)	0.832
WBC ($10^3/mm^3$)	-	10.94 ± 6.96	8.95 (6.5–13.4)	-	12.63 ± 18.76	9.9 (6.9–12.4)	0.515
Platelet ($10^3/mm^3$)		262.3 ± 133.8	235 (170–340)		246 ± 125	228 (169–303)	0.428
Neutrophil (%)	-	78.08 ± 9.72	79.5 (71–86)	-	79.26 ± 16.23	82 (75–90)	0.013*
Lymphocyte (%)	-	13.9± 7.56	14 (8–18)	-	10.89 ± 6,71	11 (6–15)	0.002*
NLR	-	8.73 ± 7.56	5.79 (4–11)	-	12.49 ± 1.05	7.55 (5–15)	0.008*
Sodium (mmol/L)	-	135.5 ± 6.6	136 (132–139)	-	135.3 ± 6,1	136 (131–139)	0.806
Potassium (mmol/L)	-	4.0 ± 0.62	4.0 (3.6–4.4)	-	3.99 ± 0.96	3.9 (3.4–4.3)	0.209
Urea (mg/dL)	-	37.7 ± 31.8	32 (19–47.75)	-	60.7 ± 52.40	41 (26–68)	<0.001*
Creatinine (mg/dL)	-	1.43 ± 1.49	0.98 (0.86–1.3)	-	1.59 ± 1.19	1.2 (0.9–1.7)	0.010*
Total bilirubin (mg/dL)	-	0.82 ± 2.1	0.65 (0.48–1.14)	-	2.69 ±6.10	0.7 (0.49–1.52)	<0.001*
C-reactive protein (mg/dL)	-	0.21 ± 9.29	7.25 (3.2–15.75)	-	11.76 + 8.64	10.57 (05.09–17.49)	0.079
D-Dimer (ug/dL)	-	3396.6 ± 4852.4	1470 (680–3670)		5336.9 ± 6562.3	2340 (635–6835)	0.117
Ferritin (ug/L)	-	1313.37 ± 1890.48	676.8 (312–1304)		1929.1 ± 1584.48	1412.9 (909–2841)	0.050
Albumin (gr/dL)	-	3.32 ± 0.61	3.3 (3.0–3.8)		3.17 ± 0.44	3.15 (2.9–3.5)	0.184
Procalcitonin	-	2.51±9.28	0.18 (0.05–0.49)		3.59±8.97	0.19 (0.09–1.11)	0.075
PF ratio		284.4±171.9	253 (166–364)		175±130.6	136 (81–253)	<0.001*
Inotropic support							
No-Inotropic	114 (98.3)	-	-	88 (92.6)	-		0.089
Inotropic	2 (1.7)			3 (3.2)			
Ventilator support							
No-ventilator	114(98.3)	-	-	80 (84.2)	-		<0.001*
Ventilator	2 (1.7)			15 (15.8)			
Score systems							
SOFA score	-	2.85 ± 2.05	2 (2–4)	-	4.65 ± 2.97	4 (2–6)	<0.001*
APACHE-II score	-	6.75 ± 4.66	5.5 (3–9)	-	12.21 ± 6.09	11 (7–16)	<0.001*

*** Mann–Whitney test, significant p <0.05 *Chi-square test, significant p <0.05.*

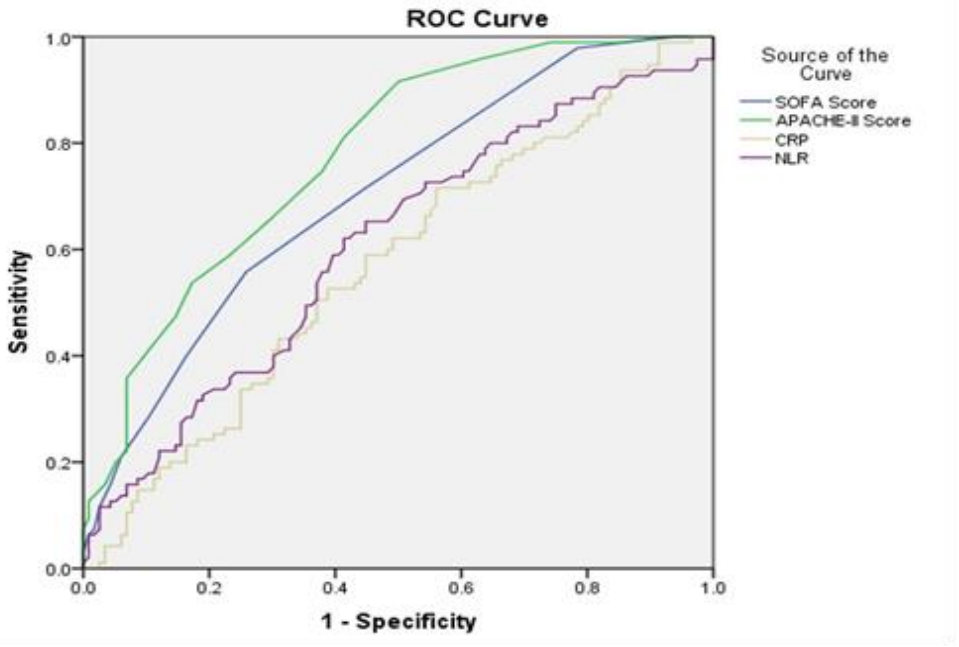


Figure 1: ROC curve analysis of NLR, CRP, SOFA scores, and APACHE-II score at 28-day mortality

Table 2: Cut-off levels for NLR, CRP, SOFA, and APACHE-II scores for severe COVID-19 patient mortality

Variable	Cut-off	Sensitivity	Specificity	OR (95% CI)	*P-value*
NLR	6.71	58.9%	59.5%	1.50 (1.10–2.05)	0.008*
CRP	8.47	54.7%	55.2%	1.24 (0.921.08)	0.079
SOFA	2,5	71.6%	44.8%	1.91 (1.34–2.72)	<0,001*
APACHE-II	6.5	65.3%	70.7%	2.25 (1.63–3.11)	<0.001*

OR: *Odd ratio*, **Chi-Square test.*

Table 3: Multiple logistic regression multivariate tests of CRP, NLR, SOFA, and APACHE-II scores

Variable	*P-value* OR	95% CI	
SOFA	0.077 1.801	0.938–3.461	Not significant
APACHE-II	<0.001 3.522	1.858–6.677	Significant
CRP	0.651 1.302	0.632–2.083	Not significant
NLR	0.402 1.143	0.703–2.412	Not significant

The results of multivariate analysis showed that the APACHE-II score had a *p*-value <0.001 for 28-day mortality. Therefore, the APACHE-II score is a good independent predictor of mortality in severe and critical COVID-19 patients [OR = 3.533 (CI 95% 1.858–6.677); *p* <0.001].

Indonesia is one of the Southeast Asian countries affected by COVID-19. Though several investigations have examined into the risk factors for mortality of COVID-19, the findings might differ since conditions vary by country, particularly in terms of diagnosis ability, supporting examinations, and facilities such as ICU for severe and critical patients. This study is intended to provide an overview of risk factors for mortality in patients with severe and critical COVID-19 in Indonesia.

In this study, the mortality rate of sepsis patients from severe and critical COVID-19 is high. The majority of severe and critical COVID-19 patients did not receive treatment in the ICU immediately because of the limited number of beds. The mortality rate is further associated with older age, male sex, and comorbidities [13-15]. The non-survivor group was relatively older in age, which was significantly associated with the risk of death. Older patients may have a lower immune response resulting from changes in the immune system (i.e. immunosenescence). In addition, older patients tend to have more comorbidity [13].

In the non-survivor group, 69.5% were male. Galbadage *et al.* found that male sex was a consistent risk factor in both Asia and Europe for COVID-19 mortality [14]. In general, women have an innate or adaptive immune system, which is superior to men for the same age range [16]. Meanwhile, the presence of aberrant methylation of the ACE2 gene promoter was found to be higher in males, which may explain why the risk of COVID-19 infection in males is higher compared with that in females [17].

In the present study, hypertension, diabetes mellitus, cancer, heart failure, hepatitis, stroke, autoimmune disease, tuberculosis, and chronic renal disease were the most common comorbidities in the cohort. Comorbidities were also considered to affect the mortality of severe COVID-19 patients. Gold *et al.* reported that severe COVID-19 cases had higher rates of hypertension, diabetes mellitus, and respiratory diseases [15]. Surendra *et al.* found that hypertension, diabetes mellitus, heart disease, chronic obstructive pulmonary disease, chronic renal disease, immunocompromised condition, liver disease, malignancy, and obesity were the most common comorbidities associated with COVID-19 patients [18].

C-reactive protein is linearly related to the inflammation degree according to the immune response of each patient. The elevated CRP levels in early stages is correlated with disease severity [19, 20]. In the present study, although serum CRP was not correlated with COVID-19 mortality, CRP levels were higher in the non-survivor group. Castelli *et al.* reported that CRP was high during

less severe stages of systemic inflammation and organ dysfunction. However, the values did not increase further during the more severe stages of the disease [21].

In this study, NLR values >6 had a significantly positive correlation with mortality in severe and critical COVID-19. Ciccullo *et al.* also found that severe COVID-19 cases exhibited a considerably higher NLR compared with mild or moderate cases [22]. Severe cases of COVID-19 tend to have high neutrophil counts and lower lymphocyte counts [11]. Absolute lymphopenia is a hallmark of severe and critical SARS-Cov-2 infection and is a significant feature of the clinical phase immediately preceding decreased respiratory function and the need for additional oxygen or ventilation [23].

Koo *et al.* reported that an animal model may also be used to observe interactions for both SARS-CoV-2 and the immune response. Macaques lost a large number of total lymphocytes during the early stages of infection, including CD4+ and CD8+ T cells, B cells, and NK cells [24]. Lymphopenia was identified in 83.2% of SARS-CoV-2-hospitalized patients [25]. In addition, alterations in the subsets of peripheral lymphocytes appear to be linked to severe cases [26].

In this study, a cut-off SOFA score >2.5 had a significantly positive correlation with mortality in severe and critical COVID-19 cases. Zhou *et al.* found that severe COVID-19 patients with higher SOFA scores were significantly correlated with an increased mortality rate [27]. According to a study by Liu *et al.*, the SOFA score is a fairly sensitive marker for risk stratification of mortality in hospitalized COVID-19 patients, with a cut-off of 3 [28]. The SOFA score is used as a diagnostic marker for sepsis and septic shock, and also can describe the severity of multi-organ disorders [29].

We found that an APACHE-II score >6.5 was significantly correlated with mortality and was a good independent predictor of mortality in severe and critical COVID-19 patients within 28 days. Wilfong *et al.* reported that the APACHE-II score had the best performance for predicting the mortality of severe COVID-19 patients that required intensive care [30]. Zou *et al.* found a similar result, in which the APACHE-II score was better at predicting hospital mortality for COVID-19 patients [31]. In the present study, the APACHE-II score was an independent predictor of mortality in sepsis patients caused by severe and critical COVID-19. The APACHE-II score measures several important components that are strongly associated with the risk of patient mortality [8].

This study had limitations. First, we did not evaluate the various treatments for the patients and several important variables, such as other biomarkers, may have an impact on the mortality of severe and critical COVID-19 cases. Second, we did not perform serial blood cultures because of patient overcapacity and the limited healthcare workforce available during the study period.

Conclusion

In this study, the APACHE-II score was a good independent predictor of mortality than NLR, CRP, and SOFA score in sepsis patients as a result of severe and critical COVID-19 within 28 days. Besides, many other factors, such as various treatments and biomarkers may have an impact on the mortality of severe and critical COVID-19.

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No potential conflict of interest was reported by the authors.

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Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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