Laboratory risk factors for mortality in severe and critical COVID-19 patients admitted to the ICU [version 1; peer review: awaiting peer review]

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Abstract

Background: Several studies have reported clinical characteristics and risk factors for predicting adverse outcomes in COVID-19.4–6 However, data exclusively from the ICU especially in the low- and middle-income countries (LMIC) remain lacking. This study aimed to explore risk factors associated with mortality based on laboratory parameters at hospital admission in severe and critical COVID-19 patients admitted to the ICU.

Methods: This study is a retrospective cohort study. Data from the electronic medical records were collected retrospectively from all severe and critical COVID-19 patients requiring ICU admission in two designated COVID-19 hospitals in Jakarta, Indonesia. A multivariate logistic regression analysis was used to identify the predictors associated with ICU mortality. The model performance was evaluated by the area under curve (AUC) from the receiver operating characteristic (ROC) analysis.

Results: There were 334 patients admitted to the ICU with COVID-19 included in the statistical analysis. The ICU mortality rate was 75.1%, with 251 patients died in the hospital. Independent risk factors associated mortality including white blood cell count >13.9 x109/L (OR=2.41; 95% CI, 1.15–5.06, p=0.02), neutrophil to lymphocyte ratio >10.7 (OR=2.20; 95% CI, 1.20 – 4.03, p=0.011), and creatinine >0.8 mg/dL (OR=3.55; 95% CI, 2.05 – 6.17, p<0.001). The model yielded an AUC of 0.72 (95% CI, 0.659-0.780, p<0.0001) for predicting ICU mortality in severe and critical COVID-19 patients.

Conclusions: White blood cell, neutrophil to lymphocyte ratio, and serum creatinine on hospital admission are significant predictors of mortality in severe and critical COVID-19 patients admitted to the ICU. The ICU mortality rate during the second wave of the pandemic in this study was high.
Keywords
covid, creatinine, ICU, NLR, prognostic, white blood cell

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Introduction
The coronavirus disease 2019 (COVID-19) has continued to be a global challenge since its first emergence in Wuhan, China, in December 2019. At the time of writing, more than 281 million cases have been recorded globally and have caused more than 5.4 million deaths worldwide. A total of 4,262,540 cases and 144,088 deaths (3.4% case fatality rate) was reported from Indonesia by December 30, 2021. Forty-three percent (1,848,565) of those cases were attributed to the spread of the Delta variant from June to August 2021. In July 2021, data from the Ministry of Health showed that the national bed occupancy rate (BOR) had reached 75%, with some COVID-19 referral hospitals in Java, including the capital city of Jakarta, reporting over 90% capacity. This surge was exacerbated by the shortage of medical oxygen in many regions, which had contributed to a level of crisis that had never been seen before in the country.

The sudden flood of patients during the second pandemic wave undoubtedly had overburdened the healthcare system. Thus, early prognostic measures would be valuable. Several studies have reported clinical characteristics and risk factors for predicting adverse outcomes in COVID-19. However, data exclusively from the ICU especially in the low- and middle-income countries (LMIC) remain lacking. The findings of those studies may also not be directly applicable in the LMIC, where there is a significant disparity in the socioeconomic status and quality of the healthcare services, which could affect the disease outcomes. The objective of this study was to explore laboratory risk factors associated with mortality in severe and critical COVID-19 patients admitted to the ICU.

Methods
Study design and participant
This retrospective cohort study was conducted in Pertamina Jaya Hospital and Pertamina Jaya Extension Hospital; both were tertiary referral hospitals for COVID-19 in Jakarta, Indonesia. Adult (18 years or older) patients with confirmed SARS-CoV-2 infection detected by reverse transcription-polymerase chain reaction (RT-PCR) less than seven days from hospital admission between June 1 and August 31, 2021, were included in the study consecutively. The pandemic in Indonesia peaked in July 2021 when the number of active cases driven by the Delta variant went over 50,000 cases in one day. Thus, the data was collected during the second wave of COVID-19 in Indonesia. The severity of the illness was categorized according to the WHO living guidelines for COVID-19. We only included data from patients requiring ICU admission. Cases with missing data at admission, without a definite outcome at the time of data collection, and patients who discontinued hospitalization against medical advice were excluded.

The flowchart of patient selection is shown in Figure 1. A total of 933 patients who tested positive for COVID-19 were admitted to the hospital between June 1 and August 31, 2021. Three hundred sixty-four patients requiring ICU admission were included in the study. Twenty-seven patients with missing data at admission, two patients without definite outcomes (one was still hospitalized, the other was transferred to another hospital), and one discharged against medical advice were excluded from the study. Data from the remaining 334 patients were incorporated into the statistical analysis. This study was approved by the Ethical Committee of Pertamina Jaya Hospital (No.002/EC/RSPJ/2021-S0) and the requirement for informed consent was waived.

Data collection
All demographic, clinical, laboratory, and outcome data were extracted from the electronic medical record. Demographic characteristics of patients (age and sex), comorbidities (hypertension, diabetes, chronic obstructive pulmonary disease, coronary artery disease, heart failure, stroke history, chronic kidney disease, and liver disease), length of stay, hemoglobin, platelet, C-reactive protein, Neutrophil to Lymphocyte Ratio (NLR), D-dimer, ureum, and creatinine were recorded using a standardized data collection form and verified by two physicians. The comorbidities and previous medical history from the medical record were reviewed by the physicians in charge.

Laboratory testing
Blood samples were collected within 24 hours of ICU admission to perform routine laboratory tests (blood count, coagulation profile, renal and liver function). The routine blood test (including hemoglobin count, platelet count, white blood cell count, and leukocyte differential count) were measured with Mindray BC-6200 automatic hematology analyzer. D-dimer, CRP, AST, ALT, ureum, and creatinine were measured with TMS50i Superior automatic clinical analyzer. All measurements were done within two hours after blood sampling.

SARS-CoV-2 was identified by RT-PCR. The specimens were collected from nasopharyngeal and oropharyngeal swabs.

Outcomes
The primary outcome was in-hospital mortality from any cause. Patients who were admitted to the ICU met any one of the following criteria: (i) severely or critically ill patients according to WHO living guideline for COVID-19; (ii) patients who have another organ failure requiring ICU monitoring. The outcome was compared with the survivor group.
Categorical variables were described as frequencies and percentages and were compared using the Chi-squared test or Fischer's exact test. Normality test was performed for continuous variables to determine their distribution. Continuous variables were presented in median (IQR) due to their distribution and compared using the Mann-Whitney test. Univariable and multivariable logistic regression was used to explore the risk factors associated with ICU mortality. Variables with a p-value < 0.2 on the survivor vs. non-survivor group were selected for the multivariable logistic regression analysis. Three variables were subsequently removed to avoid model overfitting. We employed a backward selection method including seven variables (age, leukocyte, CRP, NLR, D-dimer, ureum, and creatinine). Only significant predictors (p<0.05) were kept in the final models.

We developed two models; we first examined the relationship between laboratory variables treated as continuous variables with ICU mortality. We then evaluated the relationship when the variables were converted into a dichotomous group based on the optimal cut-off value from the receiver operator characteristic (ROC) analysis to maximize sensitivity and specificity. The performance of the prediction models was evaluated by the area under curve (AUC) from the ROC analysis. Odds Ratio (OR) with 95% confidence interval (CI) were used to report the association between exposure to the risk factors and mortality. Statistical analysis was done using SPSS for Windows Version 26.0.

The protocol above is available on dx.doi.org/10.17504/protocols.io.kxygx9peog8j/v1.

Results
A total of 334 adults were enrolled in the study, among which 187 (56%) were male, and 147 (44%) were female. The median age was 57 years old, ranging from 18 to 87 years (Figure 2). Comorbidities were present in more than half of the patients (65%), with hypertension being the most common comorbidity (45.2%), followed by diabetes (31.4%) and chronic kidney disease (5.1%). The mortality rate was 75.1%, with 251 patients died during hospitalization. The length of
hospital stay was significantly shorter in the non-survivor group (8 days [IQR 5-13 days]) compared to the survivor group (14 days [IQR 6-15 days]).

Laboratory data were obtained at the time of ICU admission. White blood cell (WBC), CRP, NLR, ureum, and creatinine were significantly higher in non-survivors. D-dimer and AST were higher in non-survivors but were not statistically significant. The demographics, comorbidities, and laboratory findings of the two groups are shown in Table 1.

**Table 1. Demographics, comorbidities, and laboratory findings of survivor and non-survivor group.**

| Variable                        | Total n=334 | Survive n=83 | Death n=251 | p-value  |
|---------------------------------|-------------|--------------|-------------|----------|
| Age (IQR), y                    | 57 (50–65)  | 54 (48–63)   | 58 (50–67)  | 0.039**  |
| Female, n (%)                   | 147 (44.0)  | 38 (45.8)    | 109 (43.4)  | 0.708*   |
| Comorbidities, n (%)            | 217 (65.0)  | 91 (65.0)    | 126 (64.9)  | 0.806*   |
| Hypertension, n (%)             | 151 (45.2)  | 37 (44.6)    | 114 (45.4)  | 0.894*   |
| Diabetes Mellitus Type 2, n (%) | 105 (31.4)  | 26 (31.3)    | 79 (31.5)   | 0.890*   |
| Stroke history, n (%)           | 12 (3.6)    | 5 (6)        | 7 (2.8)     | 0.181*   |
| Chronic kidney disease, n (%)   | 17 (5.1)    | 2 (2.4)      | 15 (6)      | 0.259*   |
| Coronary artery disease, n (%)  | 5 (1.5)     | 1 (1.2)      | 4 (1.6)     | 1.000*   |
| CHF, n (%)                      | 13 (3.9)    | 4 (4.8)      | 9 (3.6)     | 0.743*   |
| COPD, n (%)                     | 3 (0.9)     | 1 (1.2)      | 2 (0.8)     | 1.000*   |
| Asthma, n (%)                   | 2 (0.6)     | 0 (0)        | 2 (0.8)     | 1.000*   |
| Length of stay (IQR), d         | 9 (6–15)    | 14 (10–18)   | 8 (5–13)    | <0.001** |

**Laboratory tests on admission**

|                         | Total n=334 | Survive n=83 | Death n=251 | p-value  |
|-------------------------|-------------|--------------|-------------|----------|
| White blood cell, ×10^9/L (IQR) | 10.9 (7.4–16.3) | 9.5 (6.7–13) | 11.3 (7.8–16.9) | 0.003**  |
| Haemoglobin, g/dL (IQR)  | 13.7 (12.4–14.9) | 13.9 (12.4–15.2) | 13.6 (12.4–14.9) | 0.439*   |
| Platelet, ×10^9/L (IQR)  | 261 (194–357) | 270 (207–374) | 258 (189–340) | 0.122*   |
| CRP, mg/L (IQR)          | 86 (38–149)  | 71 (30–138)  | 92 (39–159)  | 0.038**  |
| NLR (IQR)                | 12.1 (6.2–23.2) | 8.7 (4.7–17.0) | 13.8 (6.8–25.9) | <0.001** |
| D-dimer, μg/mL (IQR)     | 1.79 (0.92–4.67) | 1.5 (0.7–3.3) | 1.9 (1.0–5.1) | 0.066*   |
| Ureum, mg/dL (IQR)       | 44 (29–66)   | 35 (26–46)   | 47 (29–75)   | <0.001** |
| Creatinine, mg/dL (IQR)  | 1.0 (0.8–1.3) | 0.8 (0.7–1.1) | 1 (0.8–1.4)  | <0.001** |
Table 1. Continued

| Variable          | Total n=334 | Survive n=83 | Death n=251 | p-value |
|-------------------|------------|-------------|-------------|---------|
| AST, U/L (IQR)    | 52 (32–87) | 49 (26–85)  | 54 (34–87)  | 0.240*  |
| ALT, U/L (IQR)    | 45 (26–77) | 49 (26–94)  | 43 (26–76)  | 0.417*  |

Notes: Continuous variables were presented in median (IQR), Categorical variables in n (%). p-values were calculated by *Mann-Whitney U test, †Chi-squared test, ‡Fisher exact test. *Significance.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransaminase; CHF, Congestive Heart Failure; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; NLR, Neutrophil to Lymphocytes Ratio; IQR, interquartile range.

Univariable analysis

Table 2 showed the result of the univariable analysis. Age (OR=1.02, 95% CI, 1.00–1.04, p=0.021), WBC (OR=1.07, 95% CI, 1.02–1.12, p=0.003), NLR (OR=1.04, 95% CI, 1.01–1.06, p=0.002), ureum (OR=1.01, 95% CI, 1.01–1.02, p=0.002), and creatinine (OR=1.48, 95% CI, 1.04–2.09, p=0.029) were associated with mortality. CRP >114 mg/L (OR=1.81, 95% CI, 1.06–3.08, p=0.029) and D-dimer >1.5 μg/mL (OR=1.82, 95% CI, 1.1–3.01, p=0.019) were associated with mortality. No comorbidities were significantly associated with mortality.

Table 2. The univariable logistic regression analysis.

| Variable     | Unadjusted OR (95% CI) | p-value |
|--------------|------------------------|---------|
| Model 1 (Continuous variable) |                        |         |
| Age (years)  | 1.02 (1.00–1.04)       | 0.021*  |
| WBC (×10^9/L) | 1.07 (1.02–1.12)       | 0.003*  |
| CRP (mg/L)   | 1.00 (1.00–1.01)       | 0.058   |
| NLR          | 1.04 (1.01–1.06)       | 0.002*  |
| D-dimer (μg/mL) | 1.03 (0.99–1.08)     | 0.146   |
| Ureum (mg/dL) | 1.01 (1.01–1.02)       | 0.002*  |
| Creatinine (mg/dL) | 1.48 (1.04–2.09)     | 0.029*  |

| Model 2 (Categorical variable) |                        |         |
| Age >65 years                 | 2.33 (1.19–4.56)       | 0.013*  |
| WBC >13.9×10^9/L              | 3.12 (1.63–5.94)       | 0.001*  |
| CRP >114 mg/L                 | 1.81 (1.06–3.08)       | 0.029*  |
| NLR >10.7                     | 2.53 (1.52–4.22)       | <0.001* |
| D-dimer >1.5 μg/mL            | 1.82 (1.10–3.01)       | 0.019*  |
| Ureum >44 mg/dL               | 3.39 (1.96–5.85)       | <0.001* |
| Creatinine >0.8 mg/dL         | 2.81 (1.68–4.70)       | <0.001* |

Abbreviations: WBC, White Blood Cell; CRP, C-reaction protein; NLR, Neutrophil Lymphocytes Ratio; OR, Odds Ratio; CI, confidence interval. *Significance.

Table 3. The multivariable logistic-regression analysis.

| Variable     | Adjusted OR (95% CI) | p-value |
|--------------|----------------------|---------|
| Model 1      |                      |         |
| NLR          | 1.04 (1.02–1.06)     | 0.001*  |
| Creatinine (mg/dL) | 1.50 (1.07–2.12)  | 0.020*  |

| Model 2      |                      |         |
| WBC >13.9×10^9/L | 2.41 (1.15–5.06) | 0.020*  |
| NLR >10.7    | 2.20 (1.20–4.03)    | 0.011*  |
| Creatinine >0.8 mg/dL | 3.55 (2.05–6.17) | <0.001* |

*Significance.
Multivariable analysis

Results for the multivariable analysis are shown in Table 3. NLR as a continuous variable was associated with a 4% increased risk of mortality (OR=1.04, 95% CI, 1.02–1.06, p=0.001). Creatinine >0.8 mg/dL was associated with mortality (OR=3.55, 95% CI, 2.05–6.17, p<0.001). WBC >13.9×10⁹/L was associated with mortality (OR=2.41, 95% CI, 1.15–5.06, p=0.02). The optimal cut-off value for WBC, NLR, and creatinine to predict mortality in this study were 13.9×10⁹/L, 10.7 and 0.8 mg/dL, respectively (Figure 3).

Prediction models for ICU mortality

The first model yielded an AUC of 0.69 (95% CI, 0.626–0.756, p<0.001), and the second model yielded an AUC of 0.72 (95% CI, 0.659–0.780, p<0.0001) (Table 4 and Figure 4).

**Table 4. Performance of prediction models.**

| Variable | AUC (95% CI)     | p-value         |
|----------|------------------|-----------------|
| Model 1  | 0.691 (0.626–0.756) | <0.001*         |
| Model 2  | 0.719 (0.659–0.780)  | <0.0001*        |

**Abbreviations:** AUC, Area Under Curve; CI, confidence interval.

*Significance.
Discussion

This study used data obtained on hospital admission to explore predictors associated with mortality in severe and critical COVID-19 patients admitted to the ICU. Our model yielded an AUC of 0.72 (95% CI, 0.659–0.780, p<0.0001) for predicting mortality in the severe and critical COVID-19 patients requiring ICU admission.

Prediction models for severity and disease outcome in COVID-19 patients have been reported in the previous studies. However, most of these studies were done in the upper-middle to high-income countries such as China, the UK, and the US with vastly different health profiles and disease burdens than those in the lower-middle income country (LMIC) counterpart. Like many other LMIC, Indonesia is still struggling with several communicable diseases, namely tuberculosis, HIV/AIDS, and malaria. These issues compounded by the inequality of social and healthcare services may magnify the severity and worsen the outcomes of COVID-19 patients in Indonesia.

The mortality rate of COVID-19 patients admitted to the ICU varies among the published studies, ranging from 0% to 84.6%, with values at both extremes arising from small case series. The ICU mortality rate across all studies included in the quantitative analysis was 35.5% based on one meta-analysis. In our study, the mortality rate was 75.1%, higher than reported by previous studies. This number (75.1%) was also substantially higher than one retrospective study conducted in 53 hospitals in Jakarta, with the overall mortality rate only reaching 12%. However, the population in the said study was not limited to the severe and critical patients admitted to the ICU. The higher mortality rate in our study could be explained by the ICU demand that was disproportionately higher than the ICU bed capacity during the second wave of the pandemic, as reported in a study involving 73 ICUs conducted in Spain.

Risk factors associated with COVID-19 severity and in-hospital mortality were varied among the published studies. Our study identified several risk factors for ICU mortality in adults with severe and critical COVID-19 cases in two designated COVID-19 hospitals in Jakarta during the peak second-wave outbreak in Indonesia. We found that WBC combined with NLR and creatinine on hospital admission were the strongest predictors for mortality. Multivariable analysis demonstrated WBC >13.9 × 10^9/L (OR=2.41; 95% CI 1.15–5.06, p=0.020), NLR >10.7 (OR=2.20; 95% CI 1.2–4.03, p=0.011), and creatinine >0.8 mg/dL (OR=3.55; 95% CI 2.05–6.17, p<0.001) were significantly associated with mortality.

Non-survivors had a significantly higher WBC count compared to survivors in this study. Elevated WBC counts in the severe COVID-19 patients may signify clinical worsening and increased risk of poor outcome. The optimum cut-off value for WBC to predict mortality in our study was 13.9 × 10^9/L with an AUC of 0.61, sensitivity 36.7% and specificity of 84.3% (p=0.001).

Our finding was in line with previous study, which stated that patients with increased WBC count were more likely to develop critical illness and had a higher mortality rate when compared with those without increased WBC count. Leukocytosis was speculated to reflect excessive inflammation, which is also reflected in the much higher C-reactive protein levels among patients with severe COVID-19 admitted to the ICU.
NLR was a significant predictor for mortality, as demonstrated by the multivariable analysis in this study. This finding is consistent with the result previously reported by several studies. A retrospective cohort study in China conducted by Liu et al. reported that NLR was an independent risk factor of the in-hospital mortality for COVID-19 patients, with an 8% higher risk of death with each unit increase in NLR (OR=1.08; 95% CI 1.01 – 1.14; p= 0.0147).28 Another prospective cohort study conducted by Zeng et al. involving 352 patients in China also reported the prognostic value of NLR measured at hospital admission for predicting subsequent disease deterioration and death.29 The median NLR between the death vs. survival group in that study was 7.19 vs. 2.25 (p <0.001) respectively, a cut-off value of 2.69 to 7 with a sensitivity of 92% (95% CI 66.0–100) and specificity of 63.9% (95% CI 58.7–69.5) for predicting mortality.29 One meta-analysis reported NLR was found to have an independent predictive value for death in COVID-19 with a relative risk (RR) of 2.74 (95% CI: 0.98–7.66) regardless of the cut-off values used.30 In our study, the median NLR between the death vs. survival group was 13.8 vs. 8.7, respectively (p<0.001). The optimum cut-off value of NLR to predict mortality was 10.7 with an AUC of 0.64, sensitivity 60.2% and specificity of 62.7%.

We also found elevated creatinine on admission as a significant predictor for ICU mortality (OR=3.55; 95% CI, 2.05–6.17, p<0.001). The optimum cut-off value in this study for creatinine to predict mortality was >0.8 mg/dL with an AUC of 0.655, sensitivity 73.3%, and specificity of 50.8% (p<0.001). Our finding was consistent with a large prospective cohort study including 701 patients in China that reported a significantly higher in-hospital death rate in patients with elevated baseline serum creatinine.31 Those with elevated baseline serum creatinine were also more likely to be admitted to the intensive care unit and undergo mechanical ventilation, suggesting that kidney disease on admission represented a higher risk of deterioration.31 However, the study did not specify the cut-off value used for the baseline serum creatinine level.

Interestingly, age and comorbidities were not significant predictors for mortality in our model, which differs from previous literature.32 The possible explanation of this finding is that most of our study population (75.1%) was already in the susceptible age of ≥50 years old, which might also explain the higher mortality rate in this study.31 Comorbidities and past medical history were self-reported, making it partly subjective and which might led to underdiagnosis and underestimation of its effect.

Limitations
This study has several limitations. First, being a tertiary referral hospital for COVID-19, patients were sometimes transferred late during the illness. The data was also obtained during the second wave of the pandemic when many ICUs in Jakarta were overridden and exceeded 90% of their capacity, which might explain why the mortality rate in this study was very high (75.1%) and caused the actual mortality rate of severe and critical COVID-19 cases to be underestimated. Comorbidities were self-reported as currently there is no integrated data on patient’s history and medication between the referring and accepting hospitals, which might cause underdiagnosis and lead to an underestimation of its effect. Obesity was not explored owing to the unavailability of the data in the electronic medical records.

Conclusion
The ICU mortality rate during the second wave of the pandemic in this study was very high. This study showed that elevated white blood cell count, NLR, and serum creatinine at admission were independent predictors for mortality in severe and critical COVID-19 patients admitted to the ICU. Future prospective studies should be performed to confirm the predictive ability of these laboratory parameters and their utility to identify the progression and prognosis of the disease early, conduct early triage and initiate optimal treatment strategies in time, which may reduce the overall mortality COVID-19.

Informed consent
The requirement for informed consent was waived from our IRB because this study used secondary data from medical records.

Data availability
Zenodo: Raw dataset for ‘Laboratory risk factors for mortality in severe and critical COVID-19 patients admitted to the ICU’, https://doi.org/10.5281/zenodo.7127161.34

Zenodo: Data Legends dataset for ‘Laboratory risk factors for mortality in severe and critical COVID-19 patients admitted to the ICU’, https://doi.org/10.5281/zenodo.7152260.35

Data are available under the terms of the Creative Commons Attribution 4.0 International license (CC-BY 4.0).
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