

Factors Associated with Mortality in COVID-19 Patients Treated at Serui General Hospital, Papua Indonesia

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Abstract

Coronavirus Disease 2019 (COVID-19) has a high fatality rate and has caused around 4,771,408 deaths worldwide as of 30 September 2021. COVID-19 infection presents various severity levels, starting from asymptomatic to severe symptoms that lead to death. Mortality in COVID-19 patients is associated with multiple risk factors. This study aimed to analyze the risk factors associated with COVID-19 mortality in Serui General Hospital, Papua, Indonesia. A cross-sectional analytic observational study was performed in Serui General Hospital from September 2020 to September 2021. Subjects were COVID-19 positive inpatients who met the inclusion and exclusion criteria. The independent variables were demographic characteristics, clinical manifestations, comorbidities, and lab findings, while the dependent variable was mortality. Statistical analysis was performed using chi-square test and logistic regression. This study included sixty-nine patients with 21 of them were non-survivors. The multivariate analysis showed that an NLR of >3.13 (OR 7.49; $p=0.037$; 95% CI 1.63–34.35), hypertension (OR 4.71; $p=0.019$; 95% CI 1.28–17.29), and age (OR 4.26; $p=0.028$; 95% CI 1.17–15.52) were associated with mortality in COVID-19 patients. Thus, NLR >3.13 , hypertension, and age are considered to be the risk factors associated with the mortality caused by COVID-19 among patients in Serui General Hospital.

Keywords: COVID-19, mortality, risk factors

Introduction

Severe acute respiratory syndrome Coronavirus-2 (SARS-CoV-2) is the virus that causes widely known respiratory infectious disease known as Coronavirus disease 2019 (COVID-19).¹ As of October 1, 2021, globally, there were 233,136,148 confirmed cases of COVID-19 with 4,771,409 deaths worldwide as of 30 September 2021 with a case fatality rate (CFR) of 2%. Meanwhile, there were 4,215,104 confirmed cases of COVID-19 and 141,939 deaths in Indonesia, with case fatality rate (CFR) of 3.4%.² The characteristics of COVID-19 death in Indonesia mainly occur in the age group 60 years; male gender; has clinical manifestations including dyspnea, cough, and fever; and has comorbidities including hypertension, diabetes, and heart disease.³

The clinical manifestations of COVID-19 infection are varied, such as fever, fatigue, headache, cough, dyspnea, myalgia, sore throat,

nausea, vomiting, organ dysfunction, and even death.⁴ COVID-19 infection also causes laboratory changes, such as include an increased neutrophil-lymphocyte ratio (NLR), leukocytes, procalcitonin, D-dimer, liver transaminase enzymes, lactate dehydrogenase (LDH), creatinine levels, and C-reactive protein (CRP). COVID-19 also causes a decrease in platelets, lymphocytes, and albumin levels.⁵

Identifying the risk factors associated with the mortality of COVID-19 is critical thus clinicians can provide appropriate and adequate management, therefore improving patient prognosis and reducing the mortality due to COVID-19. Several studies report that there are multiple risk factors associated with the mortality of COVID-19, such as demographics (old age and male gender), clinical manifestations (fever, shortness of breath, and cough), comorbidities (heart disease, chronic kidney disease, COPD, hypertension, and diabetes), and laboratory results (an increase in leukocytes, neutrophil-lymphocyte ratio (NLR), creatinine, D-dimer, and thrombocytopenia).⁶⁻⁹

However, research on this topic is still underreported in Indonesia, and to date, the

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data on risk factors associated with the mortality of COVID-19 in the Eastern part of Indonesia is still not available, especially in Papua. Therefore, the authors are interested in conducting this research. This research aims to analyze the risk factors associated with COVID-19 mortality at RSUD Serui.

Methods

An observational analytic study with a cross-sectional design was performed at RSUD Serui. The research data were obtained from medical record data. The population of this study was all positive COVID-19 patients who were inpatients at RSUD Serui from September 2020 - to September 2021. The samples of this study were 69 patients who fulfilled the inclusion and exclusion criteria obtained using the purposive sampling technique. Thus, all subjects that fulfilled both inclusion and exclusion criteria were included. The inclusion criteria were COVID-19-positive patients who were inpatients at RSUD Serui aged ≥18 years old and had medical records. The exclusion criteria were pediatric patients, patients with incomplete medical records, patients referred to another hospital, and self-discharged patients. Ethical approval was approved by the Ethics Committee of RSUD Serui (No: 442/TU-351/RS/2021).

The independent variables were demographic characteristics such as age and sex; severity such as severe and non-severe. Patients with clinically critical and severe illnesses were grouped into severe, while non-severe included groups with asymptomatic, mild, and moderate illness; clinical manifestations such as anosmia, malaise, fever, cough, headache, emesis, myalgia, diarrhea, dyspnea, and sore throat; comorbidities such as asthma, malaria, diabetes, tuberculosis, and hypertension; laboratory parameters such as platelets, hemoglobin, neutrophil-lymphocyte ratio (NLR), and leukocytes.

Age in this study was classified into two groups ≥52 years old and <52 years old. Fever was defined as having a temperature of >38°C. Anemia was defined as hemoglobin levels <13 g/dL for males and <12 g/dL for females. Leukocytosis is defined as a condition of blood leukocytes >11.000 u/L. Thrombocytopenia was defined as platelet counts <150.000/mm³. The neutrophil-to-lymphocyte ratio (NLR) is defined as elevated when NLR levels are >3.13. The dependent variable was the mortality of COVID-19.

The data analysis was performed with univariate, bivariate, and multivariate analysis tests. The univariate analysis describes the frequency of each independent and dependent variable. Bivariate analysis determines the association between independent and dependent variables using the chi-square test if the requirements are met, or the Fischer test was used as an alternative.

Furthermore, all independent variables with a p-value <0.25 were further analyzed multivariate using a logistic regression test. P-value <0.05 was considered statistically significant. Statistical analyses were conducted using SPSS for Windows version 26 (IBM Corp, Armonk, NY, USA).

Table 1 Demographic Characteristics of The Patients

Variables	n (%)
Age, median (IQR)	52 (37-62)
≥52 years	36 (52)
<52 years	33 (48)
Sex	
Male	45 (65)
Female	24 (35)
Comorbidity	
Yes	59 (85)
No	10 (15)
Asthma	
Yes	10 (14)
No	59 (86)
Malaria	
Yes	47 (68)
No	22 (32)
Diabetes	
Yes	22 (32)
No	47 (68)
Tuberculosis	
Yes	11 (16)
No	58 (84)
Hypertension	
Yes	20 (29)
No	49 (71)
Severity	
Severe	28 (41)
Non-severe	41 (59)
Mortality	
Severe	21 (31)
Non-severe	48 ()

IQR=interquartile range

Results

The 69 patients fulfilled both the inclusion and exclusion criteria included in the statistical analysis. Ten patients were excluded because seven patients had incomplete medical record data, and three were self-discharged. This study showed 48 (70%) survivors, while 21 (30%) were non-survivors. The median age of the patients was 52 years. Most of the patients were

from the age group of ≥52 years (52%).

Based on sex, most of the patients were male (65%). The majority of the patients had a non-severe illness (59%). The cough was the most commonly reported clinical manifestation (73%). The majority of the patients had comorbidity 59 (85%) with the most common comorbidities being malaria (68%), diabetes (32%), and hypertension (29%). Based on laboratory results, most patients have increased

Table 2 Clinical Characteristics of the Patients

Variables		n (%)
Dyspnea	Yes	24 (35)
	No	45 (65)
Malaise	Yes	36 (52)
	No	33 (48)
Headache	Yes	36 (52)
	No	33 (48)
Emesis	Yes	21 (30)
	No	48 (70)
Myalgia	Yes	12 (17)
	No	57 (83)
Fever	Yes	48 (70)
	No	21 (30)
Cough	Yes	50 (73)
	No	19 (27)
Diarrhea	Yes	23 (33)
	No	46 (68)
Sore throat	Yes	17 (25)
	No	52 (75)
Anosmia	Yes	7 (10)
	No	62 (90)
Anemia, median (IQR)		12.9 (10.3-13.7)
Leukocytosis, median (IQR)	Yes	27 (39)
	No	42 (61)
Thrombocytopenia, median (IQR)	Yes	25 (36)
	No	44 (64)
NLR, median (IQR)	Yes	24 (35)
	No	45 (65)
	>3,13	43 (62)
	≤3,13	26 (38)

Table 3 Result of Bivariate Analysis

Variables	Non-survivor n	Survivor n	P-value	OR (95% CI)
Age (years)				
≥52	16	20	0.008	4.48 (1.40–14.24)
<52	5	28		
Sex				
Male	15	30	0.474	1.50 (0.49–4.56)
Female	6	18		
Comorbidity				
Yes	19	40	0.438	1.90 (0.36–9.82)
No	2	8		
Dyspnea				
Yes	12	12	0.010	4.00 (1.35–11.8)
No	9	36		
Malaise				
Yes	10	26	0.616	0.76 (0.27–2.14)
No	11	22		
Headache				
Yes	9	27	0.305	0.58 (0.20–1.64)
No	12	21		
Emesis				
Yes	6	15	0.824	0.88 (0.28–2.71)
No	15	33		
Myalgia				
Yes	5	7	0.352	1.83 (0.50–6.61)
No	16	41		
Fever				
Yes	16	32	0.429	1.60 (0.49–5.15)
No	5	16		
Cough				
Yes	14	36	0.476	0.66 (0.21–2.03)
No	7	12		
Diarhea				
Yes	6	17	0.579	0.72 (0.23–2.22)
No	15	31		
Sore throat				
Yes	7	10	0.268	1.90 (0.60–5.96)
No	14	38		
Anosmia				
Yes	3	4	0.667	1.83 (0.37–9.02)
No	18	44		
Asthma				
Yes	1	9	0.263	0.21 (0.26–1.83)
No	20	39		
Malaria				
Yes	15	32	0.696	1.25 (0.40–3.83)
No	6	16		
Diabetes				
Yes	8	14	0.464	1.84 (0.61–5.52)
No	13	34		

Table 3 (continued)

Variables	Non-survivor n (%)	Survivor n (%)	P-value	OR (95% CI)
Tuberculosis				
Yes	4	7	0.725	1.37 (0.35–5.32)
No	17	41		
Hypertension				
Yes	11	9	0.005	4.76 (1.55–14.63)
No	10	39		
Severity				
Severe	10	18	0.602	1.51 (0.53–4.27)
Non-severe	11	30		
Anemia				
Yes	12	15	0.044	2.93 (1.01–8.45)
No	9	33		
Leukocytosis				
Yes	9	16	0.449	1.50 (0.52–4.29)
No	12	32		
Thrombocytopenia				
Yes	12	12	0.010	4.00 (1.35–11.8)
No	9	36		
NLR				
>3.13	18	25	0.008	5.52 (1.43–21.23)
≤3.13	3	23		

CI=confidence interval; IQR=interquartile range; NLR= neutrophil-to-lymphocyte ratio; OR=odds ratio

NLR >3.13 (62.3%). The demographic and clinical characteristics of the patients can be seen in Table 1 and Table 2 respectively.

The results of a bivariate analysis of various risk factors and mortality of COVID-19 are shown in table 3. Age >52 years (p=0.008), dyspnea (p=0.012), hypertension (p=0.010), anemia (p=0.044), thrombocytopenia (p=0.010), and NLR >3.13 (p=0.008) were found as risk factors with mortality of COVID-19 patients. The risk factors that showed association was analyzed further with a logistic regression test.

The results of multivariate analysis can be seen in table 4. The multivariate analysis showed that there were three risk factors for mortality of COVID-19 patients, including NLR >3.13 (OR 7.49; p=0.037; 95% CI 1.63–34.35), hypertension (OR 4.71; p=0.019; 95% CI 1.28–17.29), and age

>52 years (OR 4.26; p=0.028; CI 1.17–15.52).

Discussion

Based on the results of this study shows that there are three significant risk factors associated with mortality of COVID-19, namely age, hypertension, and NLR >3.13. Age is one of the risk factors for mortality of COVID-19, especially in patients in the old age group. Results of the multivariate analysis in Table 3 show that there is a significant association between age with mortality of COVID-19 patients. These results are similar to the results of the meta-analysis conducted by Kim et al., which states that there is a significant association between old age with mortality in COVID-19 (OR 3.6; p <0.001; 95% CI

Table 4 Result of Multivariate Analysis

Variables	P-value	OR (95% CI)
NLR >3.13	0.037	7.49 (1.63–34.35)
Hypertension	0.019	4.71 (1.28–17.29)
Age	0.028	4.26 (1.17–15.52)

CI=confidence interval; NLR= neutrophil-to-lymphocyte ratio; OR=odds ratio

2.5–5.1).⁹

Another study by Rozaliyani et al.¹⁰ also showed that old age was associated with a higher mortality risk for COVID-19 patients (OR 1.03; $p < 0.001$; 95% CI 1.02–1.05). The increased risk of death in old age is caused by a decrease in the immune system so a non-optimal immune system can increase the likelihood of experiencing worsening clinical outcomes.

Comorbidities can affect clinical outcomes because they can worsen the patient's clinical condition, increasing the risk of death. Hypertension is one of the comorbidities believed to be one of the risk factors associated with mortality from COVID-19. Based on the results of the multivariate analysis in Table 3, there is a significant association between hypertension with mortality in COVID-19 patients. These results are in line with the research conducted by Surendra et al.,¹¹ which shows a significant association between hypertension and the risk of mortality in COVID-19 patients (OR 3.63; $p < 0.001$; 95% CI 2.97–4.44). Similar results were also obtained based on the meta-analysis results by Pranata et al., which show that hypertension is associated with an increased risk of mortality in COVID-19 patients (RR 2.21; $p < 0.001$; 95% CI 1.74–2.81).¹²

The association between hypertension and mortality of COVID-19 is probably due to increased activation of the RAS system due to COVID-19 infection; this condition causes a worsening of the inflammatory response and triggers a cytokine storm, which can affect the clinical outcome of patients and increase the risk of mortality of COVID-19 patients.¹³ Neutrophil-lymphocyte ratio (NLR) is one of the laboratory parameters that can act as a marker of inflammation consisting of neutrophils and lymphocytes. Neutrophils take part in the innate immune response. Meanwhile, lymphocytes take part in the adaptive immune response. In the case of COVID-19 infection, there may be an increase in NLR. An increase in NLR can describe an imbalance in the inflammatory response to indicate increasing disease severity.¹⁴

Based on the results of the multivariate analysis in Table 3, there is a significant association between NLR and mortality of COVID-19. This result is similar to Allahverdiyev et al.,¹⁵ which showed that NLR was associated with mortality in COVID-19 (OR 1.26; $p = 0.011$; 95% CI 1.05–1.50). Another study by Liu et al.¹⁶ also showed a similar result that an increase in NLR was significantly associated with mortality in COVID-19 patients (OR 1.10; $p = 0.016$; 95% CI

1.02–1.19).

SARS-CoV-2 infection can stimulate neutrophil production, thus increasing neutrophil counts and decreasing lymphocyte numbers. Various mechanisms can lead to this condition, including direct lymphocyte infection by SARS-CoV-2, lymphocyte sequestration in the lungs, immune response-mediated destruction of lymphocytes, bone marrow suppression, and apoptosis. Therefore, the imbalance in the number of neutrophils and lymphocytes causes an increase in NLR. Thus, the immune response imbalance plays an essential role in the severity of viral infection. Hence, the increase in NLR is probably a reflection of the degree of inflammatory severity and immune response.^{15,17,18}

This study has several limitations. The sample size in this study was relatively small. Followed by not all risk factors have been analyzed due to our hospital's limited laboratory and diagnostic capability. Lastly, low sample generalization because this was a single-centered study. Thus, the result of this study may not represent the entire population of all COVID-19 patients.

This study concluded that NLR > 3.13 , hypertension, and age were the risk factors associated with COVID-19 mortality at RSUD Serui. Thus, clinicians should pay more attention to and provide adequate treatment to patients with these risk factors to reduce the mortality rate of COVID-19.

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