Original Article

Risk Factors Associated with 28-Day Mortality of COVID-19 Patients at RSUP Dr. M. Djamil Padang

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Abstract

Background: The COVID-19 mortality rate varies widely around the world. The COVID-19 death rate in Indonesia is currently relatively higher than the world average and is the highest in Southeast Asia. Data regarding risk factors of COVID-19 mortality in Indonesia, particularly West Sumatra, are still scarce. This study aims to determine the risk factors associated with the 28-day mortality of COVID-19 patients at RSUP Dr. M. Djamil Padang.

Methods: This was an observational analytic study with a retrospective cohort approach on confirmed COVID-19 inpatients who were treated at RSUP Dr. M. Djamil Padang between January 1 and March 31, 2021. A bivariate analysis using Chi square was calculated to see the correlation between clinical severity, and routine blood values, markers of inflammation, liver function, kidney function, blood gas analysis, the RALE score and comorbidities with a 28-day mortality outcome. To assess the dominant risk factors, multivariate analysis was performed using logistic regression.

Results: From 245 samples, patients aged >50 years and women were the most treated group of patients. Bivariate analysis obtained the following critical clinical grade factors: Hb <10 g/dl, leukocyte level >10.0x10^3/mm^3, monocyte level 8.0%, procalcitonin level >0.5 ng/ml, interleukin-6 level >7 pg/ml, ferritin >159/ml, D-Dimer level >500 ng/dl, SGOT level >38 µ/l, urea >50 mg/dl, creatinine >1.3 mg/dl, PO_2 <80 mmHg, SO_2 ≤90%, PO_2/FiO_2 ≤300 mmHg, high RALE score, comorbid of chronic renal failure, hypertension, type II DM; and comorbidities >1 were associated with 28 days of death. Multivariate analysis identified critical clinical severity as the dominant risk factor (OR=8.47; 95% CI=2.55–28.14; *P*<0.001).

Conclusion: Critical clinical severity was the dominant risk factor associated with the 28-day mortality of COVID-19 patients at RSUP Dr. M. Djamil.

Keywords: COVID-19, risk factors, 28-day mortality, clinical severity

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Submitted: November 20th, 2021
Accepted: December 25th, 2022
Published: January 28th, 2023

J Respirol Indones. 2023
Vol. 43 No. 1: 22–33
https://doi.org/10.36497/jri.v43i1.238

INTRODUCTION

Coronavirus Disease-19 (COVID-19) is caused by the new Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2). The World Health Organization (WHO) announced COVID-19 as a global pandemic on March 11, 2020.[1] Data from the Ministry of Health of the Republic of Indonesia as of October 5, 2021, recorded 4.2 million confirmed cases of COVID-19 with 142,338 deaths.[2]

The COVID-19 mortality rate varies widely around the world, from 0.5% to 10%. The mortality rate is 4.9% in Wuhan, and 2.1% overall in China. The mortality rate is higher in Europe than in Asia or America, which is more than 10%.[2] The current COVID-19 death rate in Indonesia is 2.7%, relatively higher than the world average mortality rate set by the WHO, which is 2%, so that is the highest in Southeast Asia based on data from the Center for Strategic and International Studies (CSIS).[3] Therefore, it is important to understand the risk factors associated with COVID-19 deaths in Indonesia.

Several risk factors have been studied and accepted by the scientific community as increasing the risk of death in COVID-19.[4] Izcovich et al in their study concluded that the prognostic factors for mortality doubled in the elderly (age increase per 10 years), and in men. In the same study, it was also concluded that comorbidities increased the risk of death from COVID-19 three times compared to those without comorbidities.[5] Vivas et al stated that factors which predict death within 30 days of patients with COVID-19 were age, Asian ethnicity,

immunodeficiency conditions, and increased body mass index (BMI).[6]

In addition, signs and symptoms indicating respiratory failure or organ damage assessed from laboratory markers or radiological features are also considered to be potential risk factors for death in COVID-19. Currently, data related to risk factors for 28-day mortality of COVID- 19 in Indonesia and West Sumatra in particular are still very limited. Therefore, the authors were interested in examining the risk factors for 28-day mortality of COVID-19 patients at Dr. RSUP. M. Djamil Padang, a type A referral hospital in West Sumatra.

METHODS

This was a retrospective cohort observational study of confirmed COVID-19 inpatients at Dr. M. Djamil Hospital Padang between January 1 and March 31, 2021. The sample was, population that met the inclusion criteria: confirmed COVID-19 from the results of RT PCR of SARS-CoV-2, aged >18 years, including the clinical severity of moderate, severe and critical illness. Exclusion criteria were patients with incomplete medical record data. The independent variables in this study were age, gender, clinical degree, laboratory values (complete blood count/CBC, markers of inflammation, liver function, kidney function, blood gas analysis), chest X-ray (CXR) RALE score and comorbidity. While the dependent variable was the outcome of 28-day mortality for COVID-19 patients.

The data were processed descriptively and analytically. A bivariate analysis with Chi square test was calculated to see the relationship between clinical severity factors, CBC, inflammation markers, liver function, kidney function, blood gas analysis, RALE scores and comorbidities with a 28-day mortality outcome. Multivariate analysis with logistic regression was calculated to assess the dominant risk factor.

RESULTS

Table 1 provides a description of the characteristics of COVID- 19 inpatients at Dr. M. Djamil Hospital Padang for the period January 1 to March 31, 2021. The COVID-19 patients being treated at Dr. M. Djamil Hospital Padang were mostly in the age group above 50 years for as much as 62.86% and the female patients (55.10%) were found to be more than the male. Moderate clinical severity accounted for the highest proportion of hospitalized patients (58.77%), followed by critical (37.14%) and severe (4.10%).

Table 1. Characteristics of COVID-19 Inpatients at Dr. M. Djamil Hospital (N=245)

Characteristics	N	%
Age		
<50 years	91	37.14
50–59 years	63	25.71
60–69 years	54	22.04
≥70 years	37	15.10
Gender		
Female	135	55.10
Clinical severity		
Moderate	144	58.77
Severe	10	4.10
Critical	91	37.14

For laboratory parameters, about 82.44% of patients were treated with Hb >10 g/dl, 66.93% with leukopenia, 65.71% with neutrophilia, 67.34% with monocytopenia, 95.51% with lymphopenia, and 86.53% with normal platelets count. On the inflammatory markers, almost 77.14% had procalcitonin <0.5 ng/ml, 86.53% had an increase in interleukin-6 level of >7 pg/ml, 69.38% had an increase in ferritin value >159 ng/ml, and 84.08% had an increase in D-Dimer of >500 ng/ml. According to the liver function profile, 58.36% of the patients had normal SGOT values (<38 µ/l) and 74.28% had normal SGPT values (<41 µ/l). On the renal function, about 74.69% had normal ureum level and 83.67% had normal creatinine level. For oxygenation, 66.5% of patients had normal PO_2 (>80 mmHg), 75.10% had SO_2% above 90% and 52.65% had PO_2/FiO_2 >300 mmHg.

The parameters of the CXR showed that the median RALE score was 2, with a minimum score of 0 and the highest score of 48. A total of 66.11% of treated COVID-19 patients had comorbidities, with hypertension and diabetes mellitus (DM) ranked as the most common, at 7.75% and 7.34%, respectively.

Table 2. Laboratory parameters of COVID-19 Inpatients at Dr. M. Djamil Hospital (N=245)

Parameters	N	%
Complete Blood Count		
Hemoglobin		
Hb <10 g/dl	43	17.55
Hb ≥10 g/dl	202	82.44
Leukocytes		
≤5.0–10.0 x 10^3/mm^3	164	66.93
>10.0 x 10^3/mm^3	81	33.06
Neutrophil		
≤50.0–70.0%	84	34.28
>70.0%	161	65.71
Monocyte		
≤2.0–8.0%	165	67.34
>8.0%	80	32.65
Lymphocytes		
≤20.0–40.0%	234	95.51
>40.0%	11	4.48
Thrombocytes		
<150 x 10^3/mm^3	33	13.46
>150 x 10^3/mm^3	212	86.53
Inflammation marker		
Procalcitonin		
≤0.5 ng/ml	189	77.14
>0.5 ng/ml	56	22.85
Interleukin-6		
≤7 pg/ml	33	13.46
>7 pg/ml	212	86.53
Ferritin		
≤9.3–159 ng/ml	75	30.61
>159/ml	170	69.38
D-Dimer		
≤500 ng/ml	39	15.91
>500 ng/dl	206	84.08
Liver function		
SGOT		
≤38 u/l	143	58.36
>38 u/l	102	41.63
SGPT		
≤41 u/l	182	74.28
>41 u/l	63	25.71
Kidney function		
Urea		
≤10–50 mg/dl	183	74.69
50 mg/dl	62	25.30
Creatinine		
≤0.8–1.3 mg/dl	205	83.67
1.3 mg/dl	40	16.32
Blood Gas Analysis		
PO_2		
<80 mmHg	82	33.46
80 mmHg	163	66.53
SO_2%		
≤90%	60	24.48
>90%	184	75.10
PO_2/FiO_2		
≤300 mmHg	129	52.65
300 mmHg	116	47.34

Based on the number of comorbidities, 34.28% of patients had >1 comorbidity A total of 31.83% of patients treated at Dr. M. Djamil Hospital Padang for the period January – March 2021 died, and another 68.16% recovered.

Table 3. Chest X-Ray parameters of COVID-19 Inpatients at Dr. M. Djamil Hospital (N=245)

Parameters	N	%
Chest X-Ray [Median (Min – Max)]	2.00 (0–48)	
RALE SCORE		
Comorbidities		
Cerebrovascular disease	1	0.40
Hypertension	19	7.75
Cardiovascular disease	8	3.26
Chronic lung disease	4	1.63
Chronic liver disease	1	0.40
Chronic kidney disease	8	3.32
Diabetes mellitus	18	7.34
Malignancy	7	2.85
Immunodeficiency (HIV)	1	0.40
Obesity	12	4.89
No comorbid	83	33.87
Number of comorbidities		
No. comorbid	83	33.87
1 comorbid	78	31.83
>1 comorbid	84	34.28
Outcome		
Survived	167	68.16
Death	78	31.83

The correlation of demographic factors, clinical degrees, laboratory values, chest radiographs and comorbidities with the 28-day mortality of COVID-19 patients at Dr. M. Djamil Hospital can be seen in Table 4. There was a relationship between age and 28-day mortality of COVID-19 patients (P<0.05), where, based on the greatest risk opportunity, it is known that age 70 years was associated with OR=4.44 (95% CI=1.92–10.29). It was also found that there was a relationship between clinical severity and 28-day mortality in COVID-19 patients (P<0.05), and the probability of 28-day mortality in COVID-19 patients was found in patients with critical clinical severity with OR= 31.92 (95% CI=14.81–68.81).

Based on the parameters of the laboratory description, it was observed that there was a correlation with 28-day mortality of COVID-19 patients at hemoglobin <10 g/dl (P<0.05) with OR=2.43 (95% CI=1.24–4.75).

Table 4. Correlation of Demographic Factors, Clinical Severity, Laboratory Values, Chest X-Rays and Comorbidities with 28-Day Mortality of COVID-19 Patients at Dr. M. Djamil Hospital

Variables	Survived (n = 167)	Death (n = 780	*P*	OR (95% CI)
Age, f (%)				
<50 years	75 (82.4)	16 (17.6)		Reff.
50–59 years	40 (63.4)	23 (36.5)	0.002*[a]	2.69 (1.28–5.68)*
60–69 years	33 (61.1)	21 (38.9)		2.98 (1.38–6.43)*
≥70 year				
Gender, f (%)				
Male	71 (64.5)	39 (35.5)	0.337	1.35 (0.79–2.32)
Female	96 (68.2)	39 (28.9)		0.74 (0.43–1.27)
Clinical severity, f (%)				
Moderate	133 (92.4)	11 (7.6)		Reff.
Severe	9 (90.0)	1 (10.0)	<0.001*[a]	1.34 (0,16–11.60)
Chritical	25 (27.5)	66 (72.5)		31.92 (14,81–68.81)*
Laboratory finding, f (%)				
Hemoglobin				
Hb <10 g/dl	22 (51.2)	21 (48.8)	0.014*[a]	2.43 (1.24–4.75)*
Hb ≥10 g/dl	145 (71.8)	57 (28.2)		Reff.
Leukocytes				
≤5.0–10.0 x 103/mm^3	129 (78.7)	35 (21.3)	<0.001*[a]	n/a
>10.0 x 103/mm^3	38 (46.9)	43 (53.1)		
Neutrophil				
≤50.0–70.0%	80 (95.2)	4 (4.8)	<0.001*[a]	n/a
>70.0%	87 (54.0)	74 (46.0)		
Monocytes				
≤2.0–8.0%	99 (60.0)	66 (40.0)	<0.001*[a]	n/a
>8.0%	68 (85.0)	12 (15.0)		
Lymphocytes				
≤20.0–40.0%	156 (66.7)	78 (33.3)	n/a	n/a
>40.0%	11 (100.0)	0 (0.0)		
Thrombocytes				
≤150 x 103/mm^3	21 (63.6)	12 (36.4)	0.690	n/a
>150 x 103/mm^3	146 (68.9)	66 (31.1)		
Inflammation markers				
Procalcitonin, f (%)				
≤0.5 ng/ml	152 (80.4)	37 (19.6)	<0.001*[a]	n/a
>0.5 ng/ml	15 (26.8)	41 (73.2)		
Interleukin-6				
≤7 pg/ml	31 (93.9)	2 (6.1)	0.001*[a]	n/a
>7 pg/ml	136 (64.2)	76 (35.8)		
Ferritin				
≤9.3–159 ng/ml	67 (89.3)	8 (10.7)	<0.001*[a]	n/a
>159 ng/ml	100 (58.8)	70 (41.2)		
D-Dimer				
≤500 ng/ml	37 (94.9)	2 (5.1)	<0.001*[a]	n/a
>500 ng/ml	130 (63.1)	76 (36.9)		
Liver function, f (%)				
SGOT				
≤38 u/l	110 (76.9)	33 (23.1)	0.001*[a]	n/a
>38 u/l	57 (55.9)	45 (44.1)		
SGPT				
≤41 u/l	130 (71.4)	52 (28.6)	0.088[a]	n/a
>41 u/l	37 (58.7)	26 (41.3)		

Table 4. Correlation of Demographic Factors, Clinical Severity, Laboratory Values, Chest X-Rays and Comorbidities with 28-Day Mortality of COVID-19 Patients at Dr. M. Djamil Hospital (Cont.)

Variables	Survived (n = 167)	Death (n = 780	*P*	OR (95% CI)
Kidney function, f (%)				
Urea				
≤10–50 mg/dl	147 (80.3)	36 (19.7)	<0.001*[a]	n/a
>50	152 (80.4)	42 (67.7)		
Creatinine				
<0.8–1.3 mg/dl	151 (74.0)	53 (25.9)	<0.001*[a]	n/a
>1.3 mg/dl	16 (39.0)	25 (62.5)		
Blood gas analyses, f (%)				
PO_2				
<80 mmHg	31 (37,8)	51 (62.2)	<0.001*[a]	8.29 (4.51–15.22)*
≥80 mmHg	136 (83,4)	27 (16.6)		Reff.
SO_2%				
≤90%	22 (36,1)	39 (63.9)	<0.001*[a]	6.59 (3.51–12.39)*
>90%	145 (78,8)	39 (21.2)		Reff.
PO_2/FiO_2				
≤300 mmHg	58 (45,0)	71 (55.0)	<0.001*[a]	19.06 (8.24–44.12)*
>300 mmHg	109 (94.0)	7 (6.0)		Reff.
Chest X-ray, Median (min-max) RALE SCORE	0 (0–48)	16.0 (0–48)	<0.001*[a]	1.09 (1.06–1.12)*
Comorbidities				
Cerebrovascular disease	2 (40.0)	3 (60.0)	0.330	3.30 (0.54–20.16)
Hypertension	45 (58.4)	32 (41.6)	0.039*[a]	1.89 (1.07–3.32)*
Cardiovascular disease	24 (63.2)	14 (36.8)	0.595	1.30 (0.63–2.68)
Chronic lung disease	6 (66.7)	3 (33.3)	1.000	1.07 (0.26–4.41)
Chronic heart disease	4 (80.0)	1 (20.0)	1.000	0.57 (0.06–4.82)
Chronic kidney disease	10 (35.7)	18 (64.3)	<0.001*[a]	4.71 (2.06–10.78)*
Diabetes mellitus	33 (49.3)	34 (50.7)	<0.001*[a]	3.14 (1.74–5.65)*
Malignancy	11 (68.8)	5 (31.3)	1.000	0.97 (0.33–2.89)
Immunodeficiency (HIV)	1 (50.0)	1 (50.0)	0.536	2.16 (0.13–34.92)
Obesity	17 (63.0)	10 (37.0)	0.692	1.29 (0.57–2.98)
No comorbidity	70 (84.3)	13 (15.7)	<0.001*[a]	0.28 (0.14–0.54)*
Number of comorbidities				
No comorbidity	70 (84.3)	13 (15.7)	<0.001*[a]	Reff.
1 comorbidity	51 (65.4)	27 (34.6)		2.74 (1.29–5.82)*
>1 comorbidity	46 (54.8)	38 (45.2)		4.65 (2.23–9.69)*

Also, there was leukocytes >10.0x10^3/mm^3 with OR=4.17 (95% CI=2.35–7.41), neutrophils >70.0% with OR=17.01 (95% CI=5.95–48.66), monocytes 8.0% with OR=3.78 (95% CI=1.89–7.52), procalcitonin >0.5 ng/ml with OR=11.23 (95% CI=5.62–22.43), interleukin-6 >7 pg/ml with OR=8.66 (95% CI=2.02–37.19), ferritin >159/ml with OR=5.86 (95% CI=2.65–12.97), D-Dimer >500 ng/dl with OR=10.82 (95% CI=2.54–46.14), SGOT >38 u/l with OR=2.63 (95% CI=1.52–4.57), ureum >50 mg/dl with OR=8.58 (95% CI=4.49–16.35), and creatinine >1.3 mg/dl with OR=4.45 (95% CI=2.21–8.96).

There was a relationship between 28-day mortality of COVID-19 patients and each of blood gas analysis parameters, namely PO_2 levels <80 mmHg with OR=8.29 (95% CI=4.51-15.22), SO_2 90% with OR=6.59 (95% CI=3.51–12.39), and PO_2/FiO_2 300 mmHg with OR=19.06 (95% CI=8.24–44.12). Based on the CXR description with RALE scores, there was a correlation between RALE scores and 28-day mortality of COVID-19 patients (*P*<0.05) with OR=1.09 (95% CI=1.06–1.12).

Based on comorbidities, it was known that both chronic kidney disease and DM were associated with 28-day mortality of COVID-19 patients (*P*<0.05), and the OR=4.71 (95% CI=2.06–10.78) and OR=3.14 (95% CI=1.74–5.65), respectively. Furthermore, hypertension was also associated with 28-day mortality in COVID-19 patients (*P*<0.05), and the OR=1.89 (95% CI=1.07–3.32).

Table 5. Dominant Risk Factor for 28-Day Mortality of COVID-19 Patients at Dr. M. Djamil Hospital

Variables	B	SE	*P*	OR (95% CI)
Age				
50–59 years	0.956	0.731	0.191	2.60 (0.62–10.89)
60–69 years	0.458	0.681	0.501	1.58 (0.42–6.01)
≥70 years	0.665	0.779	0.393	1.95 (0.42–8.95)
Clinical Severity				
Severe	-0.771	1.317	0.558	0.46 (0.04–6.12)
Critical	2.136	0.613	<0.001*	8.47 (2.55–28.14)*
Hb ≥10 g/dl	0.999	0.679	0.141	2.72 (0.72–10.27)
Leukocytes 10.0 x 10^3/mm^3	0.619	0.507	0.222	1.86 (0.69–5.02)
Neutrophil >70.0%	1.621	0.933	0.082	5.06 (0.81–31.49)
Monocytes ≤2.0–8.0%	-0.415	0.705	0.557	0.66 (0.17–2.63)
Procalcitonin >0.5 ng/ml	0.829	0.539	0.124	2.29 (0.79–6.59)
Interleukin-6 >7 pg/ml	-0.332	1.002	0.740	0.72 (0.10–5.12)
Ferritin >159/ml	0.539	0.776	0.487	1.71 (0.38–7.84)
D-Dimer >500 ng/dl	-0.818	1.152	0.478	0.44 (0.05–4.22)
SGOT >38 u/l	0.361	0.536	0.500	1.44 (0.50–4.11)
SGPT >41 u/l	0.161	0.602	0.789	1.18 (0.36–3.82)
Urea >50 mg/dl	1.119	0.697	0.109	3.06 (0.78–12.02)
Creatinine >1.3 mg/dl	-0.798	0.886	0.368	0.45 (0.08–2.56)
PO_2 <80 mmHg	0.799	0.624	0.200	2.22 (0.65–7.55)

Patients without comorbidities had protective factors to prevent adverse outcomes in COVID-19 patients with an OR=0.28 (95% CI=0.14–0.54). The number of comorbidities was associated with 28-day mortality in COVID-19 patients (*P*<0.05). Patients with more than one comorbidity had the highest risk factor for 28-day mortality with an OR=4.65 (95% CI=2.23–9.69), followed by patients with only 1 comorbidity with an OR=2.74 (95% CI=1.29–5.82).

However, there was no relationship between gender, platelet count, SGPT, cerebrovascular disease, cardiovascular disease, chronic lung disease, chronic liver disease, malignancy, immunodeficiency and obesity with 28-day mortality of COVID-19 patients (*P*>0.05).

The analysis was continued with a multivariate analysis by first selecting candidate variables based on the previous bivariate analysis. Based on bivariate analysis, the variables that passed the selection were those with *P*<0.25. These variables were age, clinical grade, hemoglobin level, leukocyte count, neutrophil count, monocyte count, procalcitonin, interleukin-6, ferritin level, D-Dimer, SGOT, SGPT, ureum, creatinine, PO_2, SO_2, PO_2/FiO_2, Rale score, comorbidities of hypertension, chronic kidney disease, DM, without comorbidity, and the number of comorbidities. The most dominant factor in the 28-day mortality of COVID-19 patients was critical clinical degree with an OR=8.47 (95% CI=2.55–28.14), as can be seen in Table 5.

DISCUSSION

The results showed that COVID-19 patients who were treated at Dr. M. Djamil Hospital Padang were mostly in the age group less than 50 years (37.1%), followed by the age group 50–59 years (25.7%) and the age group 60–69 years (22%). This result was in line with the study by Islam, which had the highest age range in the 25–39 years group (39.4%) followed by 40–59 years group (34.3%).[7] This age range is a productive age group that is active in outdoor activities, thereby increasing the risk of exposure to the SARS-CoV-2 virus.

Based on the gender of the hospitalized patients, women were found to be more than men (55.1% compared to 44.9%). Similar findings were obtained in study from Mardewi in Bali, where women with COVID-19 outnumbered men (53.9% vs 46.1%).[8] The higher number of women treated compared to men in this study could be influenced by

the data on the distribution of COVID-19 in West Sumatra, where the number of COVID-19 female patients was higher than that of male patients (54.9% vs. 45.1%).[9] An earlier study in China also found that in East Asian women, ACE2 expression was higher, so they were more likely to get COVID-19.[10] This factor could be one of the factors causing the high number of female patients compared to men in this study.

Moderate clinical severity accounted for the highest proportion of hospitalized patients (58.8%), followed by critical clinical severity (37.1%) and severe clinical severity (4.1%). This result was higher than in Wuhan (17.7%) and Hubei (10.4%).[11] The majority of clinical cases had been treated at Dr. M. Djamil Hospital due to comorbidities or accidents that required specialized management.

These specialties cannot be carried out in regional hospitals, such as hemodialysis, sectio caesarea or other surgical procedures, so even though the clinical severity was moderate, they still required treatment at a referral hospital.

The CBC revealed that 17.6% of patients had Hb below 10 g/dl, 66.9% had leukopenia, 65.7% had neutrophilia, 67.3% had monocytopenia, 95.5% had lymphopenia, and 13.5% had thrombocytopenia. Zhou et al in Wuhan also concluded that lymphopenia, leukopenia, and thrombocytopenia were the most common laboratory abnormalities found in COVID-19.[12] Cytotoxic lymphocytes, such as cytotoxic T lymphocytes and Natural Killer cells, play an important role in viral infection control by maintaining immune homeostasis and the inflammatory response. The occurrence of apoptosis or functional exhaustion of cytotoxic lymphocytes causes lymphopenia, monocytopenia, and leukopenia.[13]

According to the description of inflammatory marker parameters, 77.1% of patients had procalcitonin level below 0.5 ng/ml, 86.5% had an increase in interleukin-6 of more than 7 pg/ml, 69.4% had an increase in ferritin level >159 ng/ml, and 84.1% had an increase in D-Dimer level of more than 500 ng/ml. Zhou et al in Wuhan concluded that the most frequent laboratory abnormalities found in patients with COVID-19, besides lymphopenia, leukopenia, and thrombocytopenia, were elevated inflammatory markers.[12]

An irregular and exaggerated immune response to SARS-CoV-2 infection activates several complex pathways involved in cytokine storm pathogenesis, which are the Renin-Angiotensin-Aldosterone System (RAAS), Janus kinases (JAK), the Signal Transducer and Activator of Transcription (STAT) pathway, and the complement activation pathway. Furthermore, there is also a cytokine release syndrome (CRS), which is a state of immune dysregulation and hyperinflammation thought to be due to T cell activation and characterized by an increase in inflammatory markers.[14]

The parameters of the chest radiograph showed that the median RALE score was 2, with a minimum score of 0, and the highest was 48. These results were in line with study from Sensusiati at Universitas Airlangga Hospital, which gained the median RALE score of 3. The Borghesi study in the United States also concluded that a high RALE score (>3) increased the risk of requiring ICU care or mortality.[15]

Furthermore, COVID-19 patients who were treated had the most common comorbidities of hypertension (7.8%) and DM (7.3%). This result was similar to the finding of Surendra's study in Jakarta, where hypertension was the most common comorbidity (19%), followed by DM (12%).[9] In Indonesia, the epidemiological transition resulted in an increase in noncommunicable diseases. The burden of hypertension and DM in Indonesia is high, with a national prevalence of 34.1% and 11.3%, respectively.[16]

Based on the number of comorbidities, 34.3% of patients have >1 comorbidity. The Leulseged study in Ethiopia found that 43.8% of COVID-19 patients had a history of one or more comorbidities.[17] Surendra in Jakarta found 69% patients without comorbidity, 20% with 1 comorbid, and 11% with >1 comorbidity.[9] A total of 31.8% of patients admitted to Dr. M. Djamil Hospital for the period January – March 2021 died, and the rest 68.2% survived. This result was not much different from the study by Ramatillah

in Jakarta which observed 27.8% of patients treated in hospitals could not survive.[18]

In this study, it was found that age significantly affected the outcome of COVID-19 patients (*P*<0.002), and that the risk of mortality increased with age. These results were consistent with the study of Signescosta et al, who concluded that old age was associated with increased mortality in COVID-19.[19] The same conclusion was also obtained by Borghesi et al, Huang et al, and Zhou et al.[12,15,20] Borghesi stated that men >50 years and women >80 years were the highest age groups at risk of suffering from severe COVID-19 symptoms.[15]

Increasing age is associated with physiological changes as part of the aging process, such as immunosenescence, which alters pathogen recognition and clearance due to a decrease in T cells and accumulation of memory T cells.[21] The aging process will trigger an imbalance of functions in various systems, including the immune system, making them more susceptible to inflammation and death. Patients over the age of 50 have higher ACE2 expression encoded by the ACE2 gene, which is associated with other risk factors such as decreased immunity, por organ function, or previous comorbidities that increase the risk of mortality.[22]

Although more men were hospitalized in this study than women, the percentage of men who died was higher (35.5%) than that of women (28.9%), but the difference was not statistically significant (*P*=0.337). Jin et al concluded that although the susceptibility of men and women to be infected with COVID-19 was the same, however, male sex was an important clinical risk factor for severity and death (*P*=0.016).[23] Women were less susceptible than men for reasons associated with innate immunity, steroid hormones, and other factors associated with the sex chromosomes. Immune regulatory genes encoded by the X chromosome in women will cause a decrease in viral load and a decrease in inflammation compared to men, in addition to higher CD4+ T cells and a better immune response. TLR7 levels in women are also higher, allowing a better immune response and increased resistance to viral infections than in men, so they have a better prognosis.[24]

Critical clinical severity showed a significant relationship with the risk of mortality in COVID-19 (*P*<0.001), with OR=31.92 (95% CI=14.81–68.81). Gau et al also observed a significant relationship between clinically critical severity and 28-day mortality of COVID-19 patients (*P*<0.05).[25] Oliveira stated that the mortality rate in critical COVID-19 in the ICU ranged from 50–65%, and in patients requiring mechanical ventilation, the mortality rate is 97%.[26] Critical severity is characterized by dysregulation of cytokine release, pneumonia, and acute lung injury, which can rapidly progress to acute respiratory distress syndrome (ARDS), disseminated intravascular coagulation (DIC), multisystem failure, and death.[27]

Based on the parameters of the laboratory description, there was a relationship between hemoglobin and 28-day mortality of COVID-19 patients (*P*<0.05), the chance of 28-day mortality risk of COVID-19 patients in patients with Hb levels below 10 g/dl had an OR=2.43 (95% CI=1.24-4.75). Oh et al revelaed the same conclusion, that anemia at admission was an independent risk factor for death (OR=1.523; 95% CI=1.008-2.303; *P*=0.046). Anemia is independently associated with an increased likelihood of death in hospitalized patients with COVID-19.[27,28]

There was a relationship between leukocytes, neutrophils and monocytes with 28-day mortality of COVID-19 patients (*P*<0.05). The increase in total leukocyte count and neutrophil count had a significant correlation with the severity of the disease. One mechanism underlying this increase is bacterial or fungal comorbidity in a large number of patients infected with SARS-CoV-2 with poor outcomes.[28]

There was an association between 28-day mortality of COVID-19 patients (*P*<0.05) with; procalcitonin (PCT) >0.5 ng/ml (OR=11.23; 95% CI=5.62-22.43), interleukin-6 >7 pg/ml (OR=8.66; 95% CI=2.02–37.19), ferritin >159/ml (OR=5.86; 95% CI=2.65–12.97), and D-Dimer >500 ng/dl (OR=10.82; 95% CI=2.54–46.14). Similar findings were obtained by Zare et al and Deng et al.[28,29] Increased PCT levels were observed in severe SARS-CoV-2 infections that had bacterial

complications or higher levels of proinflammatory cytokines.[28] Excessive cytokine production can activate the coagulation pathway, induce DIC and multi-organ failure, with IL-6 and TNF- serving as the primary mediators of Cytokine Release Syndrome (CRS) in COVID-19. Deng et al obtained significantly higher amounts of ferritin in the critical group compared to the moderate and severe groups. Other inflammatory cytokines, such as interleukin (IL)-8, IL-10, C-reactive protein (CRP), and tumor necrosis factor (TNF)-α, were found to be positively correlated with ferritin and D-dimer concentrations.[30]

Based on the parameters of liver function and kidney function, there was a correlation between SGOT, ureum and creatinine with the 28-day mortality of COVID-19 (*P*<0.05). Higher risk was found in patients with SGOT levels >38 u/l with an OR of 2.63 (95% CI 1.52–4.57), in ureum >50 mg/dl with an OR8.58 (95% CI=4.49–16.35), and in creatinine >1.3 mg/dl with an OR=4.45 (95% CI=2.21–8.96). Potential mechanisms of liver dysfunction in COVID-19 include: (a) immune-related impairment due to a severe inflammatory response to infection, (b) direct cytotoxicity due to viral replication in ACE-2-expressing bile duct epithelial cells, (c) hypoxic hepatitis due to anoxia, and (d) drug-induced liver damage.[30]

Bao et al stated that the SGOT/SGPT ratio examination could be a strong predictive factor for early detection of liver damage and was positively correlated with COVID-19 patient mortality.[30] Acute kidney injury (AKI) in COVID-19 is causally related to the cytopathic effect of the virus or to the systemic inflammatory response and cytokine storm. These results were in line with study conclusion by Arikan which stated that AKI affected the increasing morbidity and mortality of COVID-19.[31]

Based on the parameters of blood gas analysis, there was a relationship between each PO_2, SO_2 and PO_2/FiO_2 with 28-day mortality in COVID-19 patients (*P*<0.05). The higher risk was found in patients who had PO_2 <80 mmHg with OR=8.29 (95% CI=4.51–15.22), SO_2 90% with OR=6.59 (95% CI=3.51–12.39), and PO_2/FiO_2 300 mmHg with OR=19.06 (95% CI=8.24–44.12). Gao et al also reported that SpO_2 <90% was strongly associated with mortality (OR=47.41; 95% CI=6.29–357.48) and concluded that PaO_2/FiO_2 <200 mmHg was associated with a higher 28-day and 60-day mortality risk (*P*<0.05).[25]

Based on the chest X-ray with RALE scores, we found a correlation between RALE scores and 28-day mortality in COVID-19 patients (*P*<0.05) with an OR=1.09 (95% CI=1.06–1.12). It was in line with study from Sensusiati that also obtained significant relationship between RALE scores and outcomes of COVID-19 patients (*P*<0.05); the risk of mortality for patients with high RALE scores increased 6.826 times compared to patients with lower scores (95% CI=2.076–22.444).[32] Cozi et al also concluded a significant correlation between RALE scores and patient outcomes. A RALE score of more than 15 points was associated with a higher risk of ICU admission.[33]

Chronic kidney disease, DM and hypertension were found to have association with 28-day mortality of COVID-19 patients (*P*<0.05), with each OR=4.71 (95% CI=2.06–10.78), OR=3.14 (95% CI=1.74–5.65) and OR=1.89 (95% CI=1.07–3.32), respectively. These results were similar to the study findings from Guan et al, which stated that comorbidities such as chronic renal failure, hypertension, and DM, were correlated with poor COVID-19 outcomes.[9,14]

Patients with hypertension exhibit endothelial dysfunction and immunometabolic modifications that contribute to high serum levels of inflammatory cytokines. Diabetes mellitus is prone to experience poor COVID-19 outcomes because of chronic inflammation in DM increases the risk of hyperinflammation and cytokine storms. The IL-6 and CRP were found to be significantly higher in patients with DM. In addition, hyperglycemia can interfere with immune responses and increase oxidative stress.[25,26] Meanwhile, chronic kidney disease is associated with an increased risk of pneumonia, increased ACE2 expression and increased susceptibility to hyperinflammation and cytokine storms in SARS-CoV-2 infection, resulting in an increased risk of mortality.[34]

The number of comorbidities was associated with 28-day mortality of COVID-19 patients (*P*<0.05).

Patients with comorbidity >1 had the highest risk factor, with an OR=4.65 (95% CI=2.23–9.69). Study by Surendra reported that the mortality rate for patients with no comorbidities was 38%, while patients with 1 comorbidity had a mortality rate of about 30%, and patients with more than 1 comorbidity had a mortality rate of about 32%.[9] Khedr et al pointed out that the number of comorbidities significantly increased the risk of death; patients with one comorbidity had HR=2 (95% CI=1.1–3.7), patients with two comorbidities had HR=2.6 (95% CI=1.4–4.7) while those with 3 or more comorbidities had HR=2.9 (95% CI=1.5–5.6).[35]

Critical clinical severity was found to be the most important risk factor for 28-day mortality of COVID-19 patients, with an OR= 8.47 (95% CI=2.55–28.14; *P* <0.001). Gao et al also concluded that critical clinical severity was an independent risk factor for 28-day and 60-day mortality of COVID-19 patients in China.[25] These findings supported previous studies that obtained critical clinical severity of COVID-19 pneumonia to be associated with a high mortality rate. The mortality rate in ICUs due to COVID-19 worldwide and in the United States range from 20–62%. In mechanically ventilated patients, mortality ranges from 50-97%. Patients classified as having critical clinical severity on admission have a much greater risk of mortality, because they have a higher indication of increased inflammation, a more serious risk of organ dysfunction, and a higher SOFA score, which can caused septic shock, followed by ARDS and multiorgan failure.[25,35]

LIMITATION

The limitations of this study are that this study did not assess the influence of therapeutic factors as one of the factors that can influence mortality.

CONCLUSION

Risk factors associated with 28-day mortality of COVID-19 patients at Dr. M. Djamil Hospital Padang were age >70 years, critical clinical severity, laboratory values: Hb <10 g/dl, leukocyte count >10.0x10^3/mm^3, neutrophil count >70%, monocyte count ≤8.0%, procalcitonin >0.5 ng/ml, interleukin-6 >7 pg/ml, ferritin level >159/ml, D-Dimer >500 ng/dl, SGOT level >38 u/l, ureum >50 mg/dl, creatinine >1.3 mg/dl, PO_2 <80 mmHg, SO_2% <90%, PO_2/FiO_2 300 mmHg, high RALE score, comorbidities: chronic renal failure, hypertension, type II DM and the number of comorbidities >1. The critical clinical severity was the most important risk factor for the 28-day mortality of COVID-19 patients at Dr. M. Djamil Hospital Padang.

ACKNOWLEDGMENTS

None.

CONFLICT OF INTEREST

None.

FUNDING

None.

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