



Factors Affecting the Outcomes of COVID-19 Patients Treated at Dr. M. Djamil Padang General Hospital

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Abstract

Background: COVID-19 has spread rapidly throughout the world with high morbidity and mortality. This study aimed to determine the factors that influenced the outcomes of COVID-19 patients treated at RSUP. Dr. M. Djamil Padang.

Methods: This was an observational analytic study conducted with a retrospective cohort design on COVID-19 patients at RSUP Dr. M. Djamil Padang. Data were taken from medical records from January to March 2021. Association between comorbidities and the outcome of COVID-19 patients were analyzed using Chi-Square/Fisher Exact Test.

Results: Majority of the patients were female (56.4%) and aged above 50 years (64.3%). Hypertension was the most common comorbidity (41.1%). Diabetes mellitus affected the final outcome of treatment. The number of comorbidities the patients had was associated with a worse outcome for COVID-19.

Conclusion: Most of COVID-19 patients at RSUP Dr. M. Djamil Padang were male and more than 50 years old. There was a correlation between age, gender, and comorbidities in COVID-19 patients with the outcomes.

Keywords: Comorbidities, COVID-19, Outcome COVID-19

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INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is a new type of outbreak that is currently a global pandemic caused by Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2).^{1,2} Reports of COVID-19 cases in Indonesia at the end of February 2021 obtained that there was a decrease of 8.5% with increased mortality rate by 74.80%. The number of confirmed cases recorded on March 11, 2021 was around 1,403,722 cases, with 38,049 mortality cases and 611,097 cases were declared cured.³ Data in West Sumatra province as of March 11, 2021, there were 29,985 confirmed cases of COVID-19, 659 of them died and 28,297 were recovered, while in Padang City there were 14,820 confirmed cases of COVID-19, 288 of them died and 14,188 were declared cured.^{4,5}

The mortality rate due to COVID-19 in

Indonesia was still relatively higher than the world average mortality rate set by the World Health Organization (WHO), which was 2%.³ Several risk factors that have been studied as factors related to death include comorbidities, older age, and male gender. Signs and symptoms suggestive of respiratory failure or organ damage assessed from laboratory markers or radiological features are also considered potential risk factors for death in COVID-19. Izcovich et al. in their study concluded that laboratory values such as increased procalcitonin, increased D-Dimer, decreased lymphocytes, increased IL-6, and extensive infiltrates on chest X-ray could increase the risk of death in COVID-19.⁶

Currently, data regarding risk factors related to the outcome of COVID-19 patients in Indonesia and West Sumatra in particular were still very limited, therefore the authors were interested in

examining the factors that affect the outcome of COVID-19 patients at RSUP Dr. M. Djamil, Padang.

METHODS

This was an observational analytic study with a retrospective cohort design conducted in the COVID-19 isolation room at RSUP Dr. M. Djamil Padang. The study population was all COVID-19 patients treated in the COVID-19 isolation room of RSUP. Dr. M. Djamil Padang from January 1, 2021 to March 31, 2021.

The inclusion criteria were: COVID-19 patients treated in the COVID-19 isolation room, had complete medical record data, aged >18 years. Meanwhile, the exclusion criteria were subjects discharged at their own will and subjects with mild clinical degrees.

Data analysis was carried out descriptively and analytically. Bivariate analysis was used to find association between independent and dependent variables using Chi-square test (or Fisher's Exact Test if the data obtained did not meet the requirements for the test Chi-square).

RESULTS

The characteristics of the study subjects are presented in Table 1. The most common age group was found to be under 50 years old, as many as 35 subjects (35.6%). Based on gender, the majority of subjects were male for as many as 46 subjects (51.1%). Based on the presence of comorbidities in confirmed COVID-19 patients, hypertension was the most common comorbidity, which was observed in 37 subjects (41.1%).

The association between age and patient outcomes was found at a younger age that had a greater chance of recovering, namely at age <50 years with the prevalence of recovered patients of 75.7%, and aged 50-59 years of 47% ($P < 0.001$).

Comorbidity with uncontrolled diabetes mellitus was the most often caused death, namely 35 subjects (56.5%). Outcomes of recovered patients with the most sequelae were found in stage 5 chronic kidney disease in as many as 4 subjects

(16.7%) and uncontrolled diabetes mellitus in 4 subjects (6.5%). Comorbidities of CAD, moderate hypertension, and uncontrolled diabetes mellitus had the highest recovery outcomes, namely 14 subjects (58.3%), 21 subjects (45.7%) and 23 subjects (37.1%) respectively.

Table 1. Characteristics of Confirmed COVID-19 Patients Treated at RSUP Dr. M. Djamil Padang

Patient Characteristics	Total n= 90	%
Ages		
<50 years	35	35.6%
50–59 years	25	27.8%
60–69 years	17	18.9%
≥70 years	14	15.6%
Gender		
Male	46	51.1%
Female	44	48.9%
Comorbidities		
Cardiovascular Disease	16	17.8%
Hypertension	37	41.1%
Diabetes Mellitus	30	33.3%
Pulmonary Tuberculosis	2	2.22%
Asthma	2	2.22%
Cerebrovascular Disease	2	2.22%
Chronic Liver Disease	3	3.33%
Chronic Kidney Disease	8	8.9%
Immunodeficiency	1	1.11%
Malignancy	6	6.7%
Nutritional Status		
Obesity	3	3.3%
Laboratory Finding		
NLR		
<3.13	36	40%
≥3.13	54	60%
ALC		
<500	26	28.9%
500–900	32	35.6%
>1000	32	35.6%
End of Treatment Outcome		
Died	26	28.9%
Recovered	64	71.1%

The correlation between the types of comorbidities and the outcome of COVID-19 patients was confirmed using statistical tests with the results of all comorbidities showing significant results ($P < 0.05$). Diabetes mellitus and chronic kidney disease had P -values of 0.0001 and 0.024 respectively, indicating that there was a correlation between each diabetes mellitus and chronic kidney disease with the outcome of confirmed COVID-19 patients.

Table 2. Association between Comorbidities Types and the End of Treatment Outcome of Confirmed COVID-19 Patients at RSUP Dr. M. Djamil Padang

Comorbidities Types	End of Treatment Outcome			P
	Recovered n (%)	Recovered with Sequelae n (%)	Died n (%)	
Cardiovascular Disease				
CAD	14 (58.33)	2 (8.33)	8 (33.34)	0.483
HHD	1 (20.00)	0	4 (80.00)	
CHF	5 (55.56)	1 (11.11)	3 (33.33)	
Hypertension				
Mild	20 (57.14)	2 (5.71)	13 (37.15)	0.315
Moderate	21 (45.65)	2 (4.35)	23 (50.00)	
Hypertensive Crisis	1 (50.00)	0	1 (50.00)	
Diabetes mellitus				
Controlled	8 (61.53)	0	5 (38.47)	<0.001*
Uncontrolled	23 (37.09)	4 (6.45)	35 (56.46)	
Chronic Lung Disease				
Pulmonary Tuberculosis	3 (42.85)	0	4 (57.15)	0.703
Asthma	2 (100.0)	0	0	
COPD	1 (100.0)	0	0	
Chronic Kidney Disease				
Stage I	0	0	1 (100.0)	0.101
Stage II	1 (50.00)	0	1 (50.00)	
Stage III	1 (100.0)	0	0	
Stage V	8 (33.33)	4 (16.67)	12 (50.00)	
Cerebrovascular Disease				
Yes	1 (25.00)	1 (25.00)	2 (50.00)	0.155
Chronic Liver Disease				
Yes	2 (50.00)	1 (25.00)	1 (25.00)	0.245
Immunodeficiency				
HIV	1 (50.00)	0	1 (50.00)	0.869
Obesity				
Severe (stage 3)	5 (35.71)	1 (7.14)	8 (57.14)	0.165
Malignancy				
Yes	8 (57.14)	2 (14.28)	4 (28.58)	0.352

DISCUSSION

In this study, the largest age group found was under 50 years old, for as many as 35 subjects (35.6%). Study from Verma obtained that the most common age group was in the range of 50-75 years (46.7%), followed by >75 years (32%) and <50 years (21.2%).⁷ Siordia in the study noticed that the highest COVID-19 cases were in the range of 30-79 years (87%).⁸ The elderly people suffering from COVID-19 are more susceptible to worsening clinical conditions, even death, due to decreased function of T and B cells, as well as excessive cytokine production resulting in a prolonged inflammatory response.⁹

According to gender, the majority of subjects were male in as many as 128 subjects (56.4%). The result was similar to a study from Surendra in

Jakarta in line with this study which stated that the highest prevalence of COVID-19 was in men (52%).¹⁰ Males are more susceptible to infection associated with increased immune reactivation to viral infections compared to the females due to increased antibody production so that they are effectively resistant to infection.¹¹ Females are less susceptible than males related to innate immunity, steroid hormones and other factors associated with sex chromosomes. Immune regulatory genes encoded by the X chromosome in women will lead to decreased viral load and inflammation compared to men, in addition to higher CD4+ T cells and a better immune response. TLR7 levels in women are also higher while biallelic expression allows a better immune response and increases resistance to viral infections than in men.¹²

Comorbidities are conditions that are susceptible to infection due to a prolonged proinflammatory state and dysfunction of innate and adaptive immunity. Based on data from early 2020, this pandemic was associated with multiple comorbidities, many of which affected older age, hypertension, diabetes mellitus, coronary heart disease, obesity, and cerebrovascular disease. In patients with obesity, diabetes, or cardiovascular disease, an increased expression of ACE2 was found to increase the susceptibility to SARS-CoV-2 infection. In addition, lung function abnormalities and microangiopathy associated with obesity and diabetes might increase viral diversity and titer, as well as prolonged viral shedding (41.1%). Verma et al. observed comorbidities of CAD in 6.1% and CHF in 6.0%.⁷ Patients with mild hypertension were 15.4%, moderate hypertension of 20.3%, and hypertensive crisis of 0.9%. Studies conducted by Verma et al., Giannouchos et al., and Surendra et al. found that hypertension was 34.7%, 20.9%, and 19%; respectively.^{7,10,13}

Patients who had comorbidity of controlled diabetes mellitus were 5.7% while the uncontrolled were 27.3%. The results of the studies from Giannouchos et al. and Surendra et al., were almost close to the results of this study, which obtained that the number of COVID-19 patients with DM comorbidity of 17.5%; 12%.^{10,13} Diabetic patients are susceptible to infections including COVID-19.¹⁴ In diabetic patients there will be accumulation of activated innate immune cells in metabolic tissues resulting in the release of inflammatory mediators, especially IL-1 β and TNF- α which will lead to insulin resistance and damage. B cells and metabolic diseases can lower immune function by interfering with the function of macrophages and lymphocytes so that a person is susceptible to disease.

The percentage of patients with chronic lung diseases such as tuberculosis was 3.1%, asthma of 0.9%, and COPD of 0.4%. There was a total of 10.6% patients with stage 5 chronic kidney disease. Verma pointed out that patients with comorbidity of renal failure were about 20.6%, while on the other hand, Giannouchos et al. and Surendra et al., only

had 2.3% and 3% chronic kidney disease respectively.^{7,10,13}

Comorbidity of stroke in this study was found to be 1.8%. Phelps stated that the prevalence of stroke was around 9.5%.¹⁵ Only 1.8% of patients in this study had chronic liver disease. Study conducted by Surendra et al. discovered that the number of COVID-19 patients with liver disease was only 0.7%.¹⁰

There were 6.2% of patients with severe obesity. Surendra found 0.8% of obese patients in their study.¹⁰ A total of 6.2% of patients in this study had malignancy. COVID-19 patients with malignancy in the studies of Surendra et al., Siordia et al., Phelps et al. were 0.5%; 4.3%; and 10.3%, respectively.^{8,10,15} Only 0.9% of the patients in this study had HIV. Similar results were obtained in the studies of Giannouchos et al., Surendra et al., and Siordia et al. of 1.6%; 0.7%; and 0.2%, respectively.^{8,10,11}

Osibogun observed that more men died (4.79%) with an OR of 1.81 (95% CI=1.04-3.14; $P=0.036$).¹⁶ The results of the meta-analysis conducted by Biswas et al. pointed out that male gender significantly had increased mortality in COVID-19 patients compared to the female (RR=1.86; 95% CI=1.67-2.07; $P<0.00001$). Male patients have high ACE2 expression because ACE2 expression is encoded by the ACE2 gene on the X chromosome which can be regulated by male sex hormones so that they are more at risk and have poorer clinical outcomes. Hormonal factors also play a role, chemotactic factors on neutrophil and monocyte uptake such as CXCL1 and CCL20 are regulated by androgen receptors. On the other hand, the immune response to estrogen receptor regulation is to intensify interferon production and antiviral response.¹⁷

A cross-sectional study conducted by Alwafi et al. achieved that age was one of the risk factors associated and had a significant impact with a high risk of death and an increase in length of hospital stay.¹⁸ Mortality rates in study from Verma et al. were based on the age group <50 years, 50–75

years, and more than 75 years of around 5.1%, 13.5%, and 38.9%, respectively.⁷

Age was assessed to be significantly associated with mortality both without treatment and with treatment (OR=1.07; $P<0.0001$ and OR=1.06; $P<0.0001$). The increased risk of death at the age of 50 years and over was 15.4 times compared to the age of 50 years and under (RR=15.44; 95% CI=13.02-18.31; $P<0.00001$). Aging process will trigger an imbalance of functions in various systems including the immune system so that it is more susceptible to inflammation and death. Patients aged 50 years and over have a higher expression of ACE2 which is encoded by the ACE2 gene with other factors such as decreased immunity, low organ function or previous comorbidities that increase the risk of death.¹⁹

Based on the degree of severity, the more severe the disease, the more increasing the mortality rate. According to Osibogun, the mortality rate at critical level was 100%, severe level was 23.53%, moderate level was 2.67%, while mild was 0.37%.¹⁶ In this study, it was found that the comorbidity which had a significant correlation with the outcome was diabetes mellitus, while the length of stay did not have a significant correlation with each comorbidities.

COVID-19 patients who had cardiovascular disease in study from Fresan pointed out that cardiovascular disease was correlated with a statistically high risk of COVID-19 hospitalization and severity (OR=1.33; 95% CI=1.13-1.58; $P<0.001$ and aRR=1.61; 95% CI=1.13-2.30, $P=0.008$). Previous cardiovascular disease had a high risk of developing severe COVID-19 up to 5 times.²⁰ Meta-analysis showed that cardiovascular comorbidities were at high risk for severe COVID (OR=3.15; 95% CI=2.34-4.25), death (OR=3.23; 95% CI=2.28-4.57) and fatal outcome in patients at all age groups (OR=3.11; 95% CI=2.55-3.79).²¹ A history of cardiovascular disease becomes unstable with an increased incidence of coronary disease, heart failure, and arrhythmias in SARS-CoV-2 infection caused by an imbalance between metabolic demands and decreased cardiac work and is

associated with an inflammatory response and myocardial damage.¹²

As stated by Fresan, hypertension was associated with COVID-19 treatment (OR=1.22; 95% CI=1.06-1.41; $P=0.005$) and severity OR=1.53; 95% CI=1.11-2.10; $P=0.009$) but was not statistically significant.²⁰ Meta-analysis showed that hypertension was at high risk for severe COVID (OR=2.42; 95% CI=1.98-2.96), death (OR=2.60; 95% CI=2.11-3.20) and fatal outcome in patients at all age groups (OR=2.50; 95% CI=2.49-4.88).¹⁵ Immune system dysregulation in hypertensive patients is related to the severity of COVID-19. Monocytes in hypertensive patients are pre-active which produce more IL-6 after being stimulated by angiotensin II or lipopolysaccharide and found an increase in CD8+ T cells that produce TNF. These CD8+ T cells are unable to fight viral infections and result in the overproduction of cytokines.²²

Diabetics died in study of Wen et al. were as much as 11%, on the other hand, those who did not have diabetes experienced death as much as 3% with $P<0.001$. Patients with diabetes mellitus had 3.69 times the risk of death from COVID-19.¹¹ Meta-analysis showed that diabetes mellitus was at high risk for severe COVID (OR=2.47; 95% CI=1.86-3.27), death (OR=2.11; 95% CI=1.63-2.73) and fatal outcome in patients at all age groups (OR=2.25; 95% CI=1.89-2.69).²¹

Diabetes is one of the most common and most dangerous metabolic diseases characterized by chronic inflammatory conditions that lead to metabolic and vascular abnormalities which affect the response to pathogens.²² Type 2 diabetes mellitus is associated with chronic inflammation produced by excess visceral adipose tissue. This inflammatory condition affects glucose homeostatic regulation and peripheral insulin sensitivity. Chronic hyperglycemia and inflammation can cause an abnormal and ineffective immune response by stimulating the synthesis of proinflammatory cytokines and oxidative markers that create tissue inflammation. In addition, diabetic patients are at high risk of developing an uncontrolled hypercoagulable state and inflammatory response.²⁴

Potential mechanisms that make diabetic patients more susceptible to the risk and severity of COVID-19 include the role of hyperglycemia, high cellular affinity binding, efficient viral entry, decreased viral clearance, impaired T cell function, hyperinflammation, cytokine storm syndrome, and the presence of cardiovascular disease.

Pulmonary disease can be a strong predictive comorbidity predictor of poor outcome and death with ORs 4.17 (95% CI=2.67-6.50) and 3.23 (95% CI=2.55-4.32).²³ In opinion of Alwafi et al. and published reports of similar studies, it was known that patients with chronic lung diseases, particularly COPD were found to be a high-risk factor for the outcome of more severe COVID-19 patients. This was because the patient's lung function has decreased.¹⁸

On a report of Fresan, it was stated that chronic kidney disease was associated with a high risk of hospitalization and severity of COVID-19 (OR=1.52; 95% CI=1.21-1.91; $P<0.001$ and OR=1.78; 95% CI=1.14-2.76, $P=0.010$).²⁰ Osibogun noticed that patients with kidney disease were 12.53 times more likely to die from COVID-19.¹⁶ Chronic kidney disease is associated with inflammation and dysregulation of immune function which increases the risk of mortality in COVID-19. This is due to overexpression of tubular cells in COVID-19 patients with kidney disease characterized by elevated serum creatinine and urea nitrogen.¹⁷

Fresan argued that cerebrovascular disease was associated with a high risk of hospitalization and severity of COVID-19 (aRR=1.41; 95% CI=1.04-1.92; $P=0.025$ and aRR=1.91; 95% CI=1.13-3.25; $P=0.016$).²⁰ This is due to cerebrovascular disease which can produce disability, SARS-CoV-2 can generate direct nerves damage or vascular events such as stroke, and an increase in proinflammatory cytokines which will damage the vascular endothelium and increase blood coagulability.²⁴

Previous studies have described high mortality rates in chronic liver disease infected with COVID-19. The results of the logistic regression analysis in study from Alwafi et al. revealed that the odds ratio of death was 1.92 with 95% CI 1.65-

8.63.¹⁸ According to Zhou et al. there were no significant associations between chronic liver disease and the severity of COVID-19 (OR=1.54; 95% CI=0.95-2.49).²³ COVID-19 patients with chronic liver disease are prone to adverse outcomes such as death or longer hospitalization compared to patients without chronic liver disease. Laboratory findings emphasize the negative impact of SARS-CoV-2 infection on liver function.¹⁷

Patients with obesity had a mortality of 7% and those without obesity had a mortality of about 4% with $P<0.001$.¹⁶ Obesity is associated with impaired lung function that occurs due to decreased lung compliance, expiratory reserve volume and functional capacity, as well as an increase in cytokines.¹²

Alwafi et al denoted that mortality rate was high and the hospital stay period was longer in COVID-19 patients with malignancy. The nature of cancer and the therapeutic use of antineoplastic agents which attack the immune system will escalate fatal outcomes and more severe COVID-19 infections.¹⁸

Patients with HIV are 12.21 times at risk of dying from COVID-19.¹⁸ The study found that the incidence of COVID-19 living with HIV was 0.9% of cases, 14% of cases became severe and 4% of cases reported death.²⁵ Patients with HIV have decreased TCD4+ cells and develop T-cell dysfunction and inflammation, which increases the risk of severe outcomes in viral infection.²⁶

LIMITATION

There were several limitations in this study, including the retrospective cohort design, data collection using medical records, and some of the obtained data still required manual categorization.

CONCLUSION

Most of COVID-19 patients at RSUP Dr. M. Djamil Padang were male and more than 50 years old. There was a correlation between age, gender, and comorbidities in COVID-19 patients with the outcomes.

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Conflict of Interest

None.

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