



# COMORBID AS RISK FACTOR FOR THE MORTALITY 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. Comorbidities can be a major risk factor for aggravating and dying in COVID-19 patients.

**Aim:** This study aims to assess the comorbid risk factors for the death of COVID-19 patients treated at Dr. M. Djamil Padang.

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

**Result:** Most patients were female (56.39%) and aged over 50 years (39.65%). Hypertension was the most common comorbidity (39.60%). Obesity is the most comorbid cause of death (35.00%). Cerebrovascular disease, immunodeficiencies (RR=1.885), and underweight BMI (RR=1.637) is the mortality risk factors for COVID-19.

**Conclusion:** COVID-19 patients treated at Dr. M. Djamil Padang General Hospital are mostly female and less than 50 years old. Cerebrovascular disease is the highest comorbid risk factor for COVID-19 mortality.

**Keywords:** Comorbidities, COVID-19, Risk Factor, patient, Mortality

## INTRODUCTION

Corona Virus Disease 2019 (COVID-19) was reported on December 31, 2019, in Wuhan, Hubei Province, China. The World Health Organization (WHO), on March 11 st, 2020, announced a global COVID-19 pandemic. As of July 19, 2020, COVID-19 has affected more than 200 countries, with 14 million cases, nearly 600 thousand deaths, and a mortality rate of 4.3%. Indonesia is ranked 3rd with the highest number of COVID-19 cases in Southeast Asia. Indonesia's position is under India and Bangladesh. The death rate due to COVID-19 in Indonesia is still relatively higher than the world average mortality rate set by the World Health Organization (WHO), which is 2% (1). COVID-19 cases in Indonesia in September 2022 were around 6,460,265 cases. A total of 158,345 cases died, and 6,285,790 cases were recovered. Data from the West Sumatra Provincial Health Office as of September 10, 2022, there were 104,592 cases of COVID-19, 2370 cases of which died, and 101,984 cases were declared cured (2–5). Risk factors for the degree of disease severity in several previous studies, namely smoking(6), obesity(7), body mass index, and longer waiting time for hospital admission(8,9), are lifestyle factors associated with a higher risk for disease severity(10–15). The most frequently cited demographic factors increasing the risk of developing severe disease were higher age followed by a male(15), postmenopausal(16), and higher age in women(16). Several publications mention an increased risk of the severity of COVID-19, namely at age > 65 years (6). Currently, data regarding comorbid risk factors for the mortality of COVID-19 patients in Indonesia and especially West Sumatra are still very limited. Therefore the authors are interested in studying comorbid risk factors for the mortality of COVID-19 patients at Dr. M. Djamil Padang.

**Methods****Study Populations**

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

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

**Statistical Analysis**

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

**Result**

The characteristics of the research subjects are presented in Table 1. The total sample in this study was 227 subjects. The most common age group was under 50, with as many as 90 subjects (20.70%). Based on gender, most subjects were female, with as many as 128 subjects (56.39%). Based on comorbidities in patients with COVID-19, hypertension was the most common comorbidity observed in 90 subjects (39.60%). Obesity's nutritional status is the most common in this study (52.90%). The mortality rate of COVID-19 patients in this study was high at 65.20%.

**Conclusion**

COVID-19 patients treated at Dr. M. Djamil Padang General Hospital are mostly female and less than 50 years old. Cerebrovascular disease is the highest comorbid risk factor for COVID-19 mortality.

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**Introductions**

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

Patient Characteristics	Total n= 227	%
<b>Ages</b>		
< 50 years	90	39,65
50 – 59 years	59	25,99
60 – 69 years	47	20,70
≥ 70 years	31	13,66
<b>Gender</b>		
Male	99	43,61
Female	128	56,39
<b>Comorbidities</b>		
Cardiovascular Disease	37	16,30
Hypertension	90	39,60
Diabetes Mellitus	88	38,80
Pulmonary Tuberculosis	7	3,10
Asthma	2	0,90
COPD	1	0,40
Chronic Kidney Disease	28	12,30
Cerebrovascular	4	1,80
Chronic Liver Disease	5	2,20
Immunodeficiency	2	0,90
Malignancy	14	6,20
<b>Nutritional Status</b>		
Obesity	120	52,90
<b>Treatment Outcome</b>		
Died	148	65,20
Recovered	79	34,80

Comorbidities with obesity were the most common cause of death, namely, 42 subjects (35.00%). Outcomes of recovered patients with the most sequelae were found in obesity in as many as seven subjects (5.83%). Comorbidities Obesity, uncontrolled diabetes mellitus, and moderate hypertension had the highest cure outcomes, namely 71 people (59.17%), 46 people (64.79%), and 27 people (50.94%, respectively).

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

Comorbidities Types	Treatment Outcome			P Value	
	Died n (%)	Recovered with Sequelae n (%)	Recovered n (%)		
<b>Cardiovascular Disease</b>					
CAD	9 (39,13)	0 (0,00)	14 (60,87)	0.186	<b>1.231</b>
HHD	0 (0,00)	0 (0,00)	5 (100,00)		0.000
CHF	3 (33,33)	1 (11,11)	5 (55,56)		0.934
<b>Hypertension</b>					
Mild	13 (37,15)	2 (5,71)	20 (57,14)	0.719	1.081
Moderate	24 (45,28)	2 (3,77)	27 (50,94)		<b>1.433</b>
<b>Diabetes mellitus</b>					
Uncontrolled	21 (29,58)	4 (5,63)	46 (64,79)	0.883	<b>1.365</b>
Controlled	4 (23,53)	1 (5,88)	12 (70,59)		
<b>Chronic Lung Disease</b>					
Pulmonary Tuberculosis	1 (14,29)	0 (0,00)	6 (85,71)	0.788	0.303
Asthma	0 (0,00)	0 (0,00)	2 (100,00)		0.000
PPOK	0 (0,00)	0 (0,00)	1 (100,00)		0.000
<b>Chronic Kidney Disease</b>					
Stage V	9 (64,29)	1 (7,14)	4 (28,57)	0.591	<b>1.387</b>
Stage III	1 (100,00)	0 (0,00)	0 (0,00)		0.000
Stage II	0 (0,00)	0 (0,00)	2 (100,00)		0.000
Stage I	1 (100,00)	0 (0,00)	0 (0,00)		0.000
<b>Cerebrovascular Disease</b>	2 (50,00)	1 (25,00)	1 (25,00)	0.155	<b>1.896</b>
<b>Chronic Liver Disease</b>	1 (20,00)	0 (0,00)	4 (80,00)	0.614	0.569
<b>Immunodeficiency (HIV)</b>	1 (50,00)	0 (0,00)	1 (50,00)	0.869	<b>1.885</b>
<b>Status Gizi</b>					
Obesitas	42 (35,00)	7 (5,83)	71 (59,17)	0.702	1.012
Normoweight	32 (32,65)	6 (6,12)	60 (61,22)		0.896

Underweight	5 (55,56)	0 (0,00)	4 (44,44)		<b>1.637</b>
<b>Malignancy</b>	5 (35,71)	0 (0,00)	9 (64,29)	0.632	1.044

The highest risk of comorbidities for COVID-19 mortality was cerebrovascular disease (RR=1,896). Statistical tests of all comorbidities in this study did not show significant results with the outcome of COVID-19 patients ( $P > 0.05$ ).

## Discussion

In this study, the most common age group was found under 50, with as many as 90 subjects (20.70%). This study's results align with the research of Soebandrio et al., who got the most age at <39 years(17). Hussein's study in Ethiopia also found the highest age at 25-34, 76.40% (18). Older people who suffer from COVID-19 are more susceptible to mortality due to low immunity due to decreased function of T and B cells. COVID-19 infection in the elderly is also susceptible to increased production of excessive cytokines, resulting in a prolonged inflammatory response.

The majority of the sexes in this study were women, with as many as 128 subjects (56.39%). This result differs from Singh's research in India; the highest percentage is male (66.60%) (19). Research Zhang et al. also got different results from this study, namely in the male gender group, the most were 71 patients (50.7%) and female as many as 69 patients (49.3%)(11). Men are susceptible to infection with SARS-CoV2, which is thought to be due to androgen hormone activity through the *Transmembrane protease serine 2* (TMPRSS2) pathway, which facilitates the binding of SARS-CoV2 to the ACE-2 receptor. Men also have several biological factors, such as hormones, immunity, and inflammatory responses. However, in theory, women have a lower risk of infection than men because women have innate immunity, steroid hormones, and factors related to sex chromosomes. This immune response becomes protection and increases when there is a viral infection (20).

Comorbidities can exacerbate the underlying disease condition. Exacerbation is due to inflammation and dysfunction of innate and adaptive immunity. This study found cardiovascular diseases such as CAD, hypertension, and CHF in 37 subjects (16.30%). Verma et al.'s study found that the comorbidity of CAD was 6.10%, and CHF was 6.00%(21). This study's risk of CAD mortality was 1.231x compared to having no CAD comorbidities. This study is in line with Liu's study, where the risk ratio of CAD to mortality is 1.92x (22). Similar results were also obtained in Huang's study with a Risk Ratio of CAD mortality of 1.83x (11). COVID-19 will cause changes in endothelial homeostasis and coagulation so that it can predispose to thrombosis in all layers of arteries(23). Viral infection upsets the balance between relaxation and vascular contraction and reduces the number of platelet aggregation inhibitors, coagulation inhibitors, and fibrinolytic activators that support clotting factors. Common complications of COVID-19, such as venous thrombosis and pulmonary embolism, result from disorganized endothelial homeostasis triggered by a storm of inflammatory or infectious cytokines (24,25). This process causes intracellular oxidative stress. Acute myocardial injury and CAD with thromboembolic events may be associated with impaired endothelial function, as SARS-CoV-2 infects cells responsible for vascular homeostasis (23). Vascular endothelial cell dysfunction leads to a prominent procoagulant state due to the rapid release of high levels of cytokines associated with infection, with patients with CAD and COVID-19 presenting a higher risk of death in this patient population (26).

Comorbid hypertension in this study obtained as many as 90 subjects (39.60%). This result is lower than other studies. Wang's research in China found that hypertension in COVID-19 patients was 44.60% (27). Grasselli's research on COVID-19 patients with hypertension was 48.80% (28). This study's risk ratio of moderate hypertension to the mortality of COVID-19 patients was 1,433x. Wang's research also got the same result: the Risk Ratio for comorbid hypertension was 1.471x (29). This result is lower than Clark's study in 2020, where the Risk Ratio for hypertension was 2.49x (27). Hypertension is a high-risk factor for cardiovascular disease. Risk Ratio cardiovascular is because hypertension plays an important role in regulating the RAAS, inflammation, immune response, and the gastrointestinal tract, partly explaining the poorer outcomes in COVID-19 patients. The coexistence of hypertension and SARS-CoV-2 infection can strongly predict mortality in these patients (30).

Patients who had comorbid diabetes mellitus were 88 subjects (38.80%), of which 17 subjects were controlled (7.49%), and uncontrolled were 71 subjects (31.28%). This result is much higher than Harbuwono's study in Indonesia on comorbid diabetes mellitus, which was obtained at 3.40% (31). Muryanto's study with comorbid diabetes mellitus was 26.40% (32). The risk Ratio of comorbid diabetes mellitus to mortality of COVID-19 patients is 1.365x. This result is lower than other studies. Corrao's study in 2021 found that diabetes mellitus had a risk ratio of 3.62x to mortality compared to no comorbid diabetes mellitus (33). Higher results were also found in Du's study in 2022, where the risk ratio of comorbid diabetes mellitus in COVID-19 was 3.16x (34). Diabetic patients tend to be prone to infections, including COVID-19 infection. COVID-19 infection with comorbid diabetes mellitus will stimulate the accumulation of activated innate immune cells in metabolic tissues. This process causes the release of inflammatory mediators, especially IL-1 $\beta$  and TNF- $\alpha$ , which will cause insulin resistance and damage. B cells and metabolic diseases can reduce immune function by interfering with the function of macrophages and lymphocytes, making a person susceptible to disease.

Comorbid chronic lung disease in this study was obtained in as many as ten subjects (4.41%), consisting of pulmonary tuberculosis in seven subjects (3.10%), asthma in two subjects (0.90%), and COPD in 1 subject (0.40%). This study found no increased risk of death in comorbid chronic lung disease. Research data on the number of TB epidemiology in COVID-19 is still very limited because the focus of treatment is more directed to COVID-19, which is acute. Hence, tuberculosis cases have the potential to be neglected. The disease COVID-19 doubles the growth of tuberculosis in humans. Several studies show that TB cases in COVID-19 patients range from 0.37-4.47% (35). COVID-19 and TB share an immune response imbalance based on unique immunological mechanisms. The case suggests that coinfection may increase the risk of progression in both diseases. In TB and COVID-19 patients, the combination of malnutrition and low BMI is a major risk factor for premature death (35).

Sunjaya's study in 2022 found that the prevalence of asthma with COVID-19 was 8.08% (36). The results of Sunjaya's research are higher than those in this study. In a meta-analysis study, the prevalence of asthma in COVID-19 also found a higher outcome of 7.46% (37). Uncontrolled asthma will worsen asthma exacerbations. Studies have reported that asthmatics have impaired epithelial cells and leukocytes' function in producing antivirals such as pulmonary IFN- $\alpha$ , IFN- $\beta$ , and IFN- $\lambda$ . This IFN deficit can inhibit the ability of the patient's innate immunity to prevent the spread of the virus to the lower respiratory tract, thereby increasing the severity of asthma exacerbations so that it can be a risk factor for the severity of COVID-19 (35,38). In addition, SARS-CoV-2 uses the



angiotensin-converting enzyme 2 (ACE2) as its cellular receptor, and it has been shown that ACE2 receptor expression is reduced in asthmatic patients (39). The increase in eosinophils in asthma may be beneficial in COVID-19-infected lungs. Eosinophils are reduced in the peripheral blood of patients infected with COVID-19. The increased number of eosinophils in the airways of asthmatic patients may protect against the exaggerated inflammatory response of the severe COVID-19 phenotype (11).

Bonato's research in 2021 found that COPD with COVID-19 occurred at 5.90% [40]. Research in Italy found the co-existence of COVID-19 with COPD of 2.80% (41). The results of both studies are higher than this study. Susceptibility to SARS-CoV-2 infection in COPD patients focuses on ACE2 and protease expression. COPD has a generally increased susceptibility to viral infection due to decreased production of interferon type 1 (IFN) or immunosenescence, which is characterized by an increase in the number of depleted T cells and a decrease in the number of memory T cells. Increased ACE2 levels in COPD patients increase susceptibility to SARS-CoV-2 infection (42).

In this study, 28 subjects (12.30%). This result is higher than the Gibertoni study in 2021, where the incidence of COVID-19 in CKD patients was 4.09% (43), and Tang's study was 8% (44). The Risk Ratio of comorbid Chronic Kidney Disease to the mortality of COVID-19 patients is 1.387x. These results are in line with other studies. Alberto's research in 2021 stated that the risk ratio for the mortality of Chronic Kidney Disease in COVID-19 was 1.59 (45). Dashtban's research also found that the risk ratio for mortality in COVID-19 with Chronic Kidney Disease was 2.08 (46). Chronic Kidney Disease is associated with inflammation and dysregulation of immune function that increases the risk of death in COVID-19. Dysregulation of immune function due to the overexpression of tubular cells in Chronic Kidney Disease. It was characterized by elevated serum creatinine and urea nitrogen (47).

This study found the cerebrovascular disease in COVID-19 in 4 subjects (1.80%). This study is much lower than Spence's, which received 5% (48). The risk ratio of cerebrovascular comorbidities to the mortality of COVID-19 patients is 1,896x. Cerebrovascular comorbidity has the highest risk of mortality compared to other comorbidities. The Bekelis study is much higher than this, where the risk ratio in patients with cerebrovascular disorders to COVID-19 mortality is 10.50. There are three main mechanisms for cerebrovascular disorders: hypercoagulable states, vasculitis, and cardiomyopathy (48). In addition, SARS-CoV-2 can also cause direct nerve damage or vascular events such as stroke and an increase in proinflammatory cytokines. The process will damage the vascular endothelium and increase blood coagulability (49).

Comorbid Chronic Liver Disease in this study amounted to 5 subjects (2.20%). There was no increase in the risk ratio for mortality in this comorbid. The results of this study were higher than the study of Surendra et al., where comorbid Chronic Liver Disease in COVID-19 patients was only 0.70% (50). Liver tissue damage has been reported as a common manifestation with unclear clinical significance. Potential mechanisms of liver tissue damage in COVID-19 are caused by direct viral damage (based on the presence of ACE2 receptors in the liver), psychological stress, systemic inflammatory response, drug-induced liver tissue damage, and the development of pre-existing diseases such as fatty liver to steatohepatitis (51).

In this study, two subjects (0.90%) of COVID-19 patients had comorbidities with Immunodeficiency (HIV). This study obtained a risk ratio of Immunodeficiency (HIV) to COVID-19 mortality of 1,885x. This result is in line with the Sentongo study, which found that the risk ratio for mortality of immunodeficiency patients in COVID-19 was 1.78 times compared to HIV-negative (52). An irregular immune system generally characterizes 53 PLWHA. The rapid and well-coordinated innate immune response provides a vital defense against viral infections. In COVID-19 patients, there is evidence of high levels of proinflammatory cytokines and chemokines leading to increased severity of COVID-19 infection, higher consumption of CD4+ and CD8+ T cells, decreased regulatory T cells, and altered innate immune environment leading to cytokine storm and tissue deterioration. The damaged one. In addition, some data suggest that COVID-19 may suffer from a hyperinflammatory syndrome called secondary hemophagocytic lymphohistiocytosis (sHLH). This syndrome is often triggered by a viral infection or underlying sepsis. The condition can cause fulminant and fatal hypercytokinemia with multiorgan failure. Although the incidence of sHLH among patients with HIV may be rare, coinfection of HIV patients with COVID-19 can lead to sHLH leading to increased disease severity and high mortality (52). Patient nutritional status was dominated by overweight as many as 120 subjects (52.90%) and underweight as many as nine subjects (7.09%). The results of this study are lower than Huang's study, where the prevalence of overweight COVID-19 patients reached 61.30% (53). Different results were found in Kompaniyets' research; the study found a higher percentage of underweight than this study, which was 20%. However, the results of this study are almost the same as the underweight of Ye's research, which is 5.70%. Overweight in Ye's study was 36.27% (54).

The risk ratio of overweight and normoweight BMI to mortality in COVID-19 patients is insignificant. However, research such as Huang's study found that the risk ratio for overweight BMI mortality in COVID-19 patients was 1.35 (53). This study obtained the highest mortality risk ratio based on nutritional status, namely underweight (1,637). The results align with Nagila's research that 1,83 (51). Obesity is associated with an increased risk of diabetes mellitus, hypertension, and cardiovascular disease. The greater the number of co-morbidities in obese patients, thus increasing the severity of COVID-19. The respiratory system also changes in obese people. Changes in the respiratory mechanism, increased airway resistance, and decreased lung volume can impair gas exchange (55). Obesity may be associated with COVID-19 severity through metabolic dysregulation, impaired immunity, and adiposopathy. The condition can alter adipokine levels, such as increased leptin and decreased adiponectin concentrations (54). Being underweight is associated with death from COVID-19. Immune disorders due to protein malnutrition can increase the risk of viral infections. This condition can lead to more severe infections with higher mortality rates, reduced antiviral antibody responses, and levels of specific CD8+ cell proteins. The antiviral response is impaired in underweight patients and is associated with a severe risk of COVID-19 (56).

Comorbid malignancy in this study amounted to 14 subjects (6.20%) with a risk ratio that was not significantly significant. COVID-19 patients with malignancy in the study of Surendra et al., Siordia et al., and Phelps et al. is 0.5%; 4.3%; and 10.3%, respectively (50,57,58). Immunodeficiency in patients with hematological malignancies will stimulate the occurrence of severe infections. This process can occur by humoral immunodeficiency. Delayed or reduced seroconversion and prolonged viral shedding or cellular immunodeficiency. T cell exhaustion leads to long-term reduced immunity. This process increases the severity of COVID-19 and the risk of reinfection (59).

## Conclusion

COVID-19 patients treated at Dr. M. Djamil are mostly female and less than 50 years old. Cerebrovascular disease is the highest comorbid risk factor for COVID-19 mortality.

## Acknowledgment

We want to thank the director of Dr. M. Djamil Padang General Hospital, who has assisted in supporting and providing data and information to achieve the objectives of this research.

## Ethics of Study

Ethical approval was obtained from the Ethical Dr. M Djamil Padang General Hospital, where the main research from, number. 146/KEPK/2021 with the title: Hubungan Komorbid dengan luaran Pasien COVID-19 di RSUP Dr. M Djamil Padang.

## Conflict of Interest

The authors agree that this research was conducted in the absence of any self-benefits, commercial or financial conflicts and declare the absence of conflicting interests with any organization.

## Funds

This work was supported by the Departement of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Andalas, Padang Indonesia

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