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Hyperglycemia and Obesity as Risk Factors for Severe Covid-19

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ABSTRACT

Background: Obesity and hyperglycemia are common in patients with COVID-19 and are associated with an aggravating risk of COVID-19. This study assesses hyperglycemia and obesity as risk factors for developing severe COVID-19. ***Method:*** Analytical observational research with the design used is a matched case-control study. This study divided subjects into two groups according to the dependent variable category of severe COVID-19 as a case and not as severe as a control group. In each group, a history of hyperglycemia and obesity was traced. The analysis includes descriptive tests, bivariate with Chi-Square and multivariate with linear logistic regression using Statistical Product and Service Solutions (SPSS) 26. ***Result:*** 126 subjects divided into two groups with 63 subjects each. By age, the COVID-19 group was found to be severe, with an average of 57.9±12.731, and the COVID-19 group was not severe, with an average of 57.53±12.589. Hyperglycemia was associated with severe COVID-19 with a p-result of 0.000 (OR 11.8; CI 95% 3.819-36.456). Obesity was associated with severe COVID-19 with a result of p 0.001 (OR 4.6; CI 95% 1.8 – 11.756). Another covariant factor related to the severity of COVID-19 is Diabetes mellitus (OR: 4.6; CI 95% 2.148–10.137; p=0.028)cardiovascular disease (OR:4.7; 95% CI 1.258-17600; P=0.013),chronic lung disease(OR: 14.5; CI 95% 1.835-115.999).The results of multivariate analysis of Adj Odd Ratio10.038 (95% CI 2.447 – 41.172; P<0.001)and the association with obesity with the Adj Odd Ratio 4.846 (95% CI 1.187 – 19.789; P=0.028). ***Conclusion:*** Hyperglycemia and obesity are risk factors for severe COVID-19.

Keywords: severe COVID-19; obesity; hyperglycemia; comorbid

INTRODUCTION

The clinical manifestations of COVID-19 range from asymptomatic or mild infection to severe, life-threatening illness. Among other risk factors, chronic conditions such as chronic lung disease, cardiovascular disease, diabetes mellitus, hypertension and obesity increase the risk of developing COVID-19 severity. Higher mortality compared to patients without the congenital disease.[1] Elijah et al. (2022) found the mortality rate of confirmed COVID-19 patients who had comorbidities in China, respectively, obesity at 13%, diabetes at 7.4%, hypertension at 9.5%, chronic pulmonary disease (COPD) at 7%, cardiovascular disease at 7.3%, liver disease 2.4%, kidney disease 0, 7%, and malignancy 2%.[2]Based on report data from the Indonesian COVID-19 acceleration task force until April 2022, it illustrates that type 2 diabetes mellitus is the most common comorbid or comorbid disease found in cases of death where a sample of 6203 cases of COVID-19 found 9.4% have comorbid diabetes.[3]

The ongoing COVID-19 pandemic has significantly affected blood glucose control in diabetes mellitus (DM) patients. DM is an endocrine disorder characterized by hyperglycemia, polyuria, polydipsia, and weight loss due to impaired insulin secretion and/or action.[4] DM is generally associated with metabolic, macrovascular and microvascular complications that increase morbidity and mortality in viral infections.[5]DM is a risk factor for poorer clinical outcomes in COVID-19 patients. However, the relationship between the two can be bidirectional.[6]Ceriello (2020) states that COVID-19 infection results in striking changes in the metabolism of patients with a significant increase in blood glucose[7].

This is associated with increased release of cytokines and inflammatory mediators, leading to increased insulin resistance and associated hyperglycemia. In addition, COVID-19 targets the ACE2 receptor on pancreatic beta cells, resulting in pancreas inflammation.[8,9]

LaRouche et al. (2021) explain that it is still unclear whether COVID-19-associated hyperglycemia and insulin resistance are more severe than non-COVID patients with similar disease severity.[9]

Obesity often occurs in patients with COVID-19 disease. The effect of obesity on the clinical outcome of COVID-19 requires systematic investigation to date. The study by Huang et al. (2020) explained that obesity increases the risk of hospitalization, ICU care, and death among COVID-19 patients.[10]The prevalence of obesity among hospitalized COVID-19 patients can reach 61.3%, according to a study in the United States (US).[10,11]In addition to the impact of obesity on the risk of hospitalization, this may also be due to the high prevalence of obesity in the American population. The majority of obesity among adults in the US is 42.4%. In 2016, obesity reached 27.8% in the UK, 19.9% in Italy, 6.2% in China, 4.7% in Korea, 3.9% in India, 22.1% in Brazil, 23 .8% in Spain, 21.6% in France, and 28.9% in Mexico.[12]

Obese people tend to experience respiratory dysfunction of varying severity and may experience mild hypoxaemia. A study Palaiodimoset al. (2020) found that BMI ≥ 30kg/m2 was significantly associated with the risk of hypoxaemia among COVID-19 patients.[13]Obese patients diagnosed with hypoventilation syndrome experience typical hypoxemia and hypercapnia and are at high risk of infection with the more severe SARS-CoV-2. Therefore, obesity-related hypoxaemia could be an essential contributor to the severity of COVID-19.[14]

Our understanding of the pathophysiology of COVID-19 is still limited to cases of obesity and/or hyperglycemia. Data from various sources indicate that body mass index (BMI) and metabolic syndrome are independent solid risk factors for COVID-19.[15]

Therefore, this review aims to provide an overview of the potential relationship between hyperglycemia and obesity as a risk factors for the development of COVID-19.

METHODS

This research is an analytic observational study with a matched case-control study design. The match type used is a frequent or proportional match. This study divided subjects into two groups according to the dependent variable category of severe COVID-19 as a case and not severe as a control group. In each group, a history of hyperglycemia and obesity was traced. This research was conducted from August to February 2022. The study was conducted on COVID-19 patients who were treated at Prof Dr I.G.N.G Ngoerah Hospital Denpasar Hospital.

The inclusion criteria for this study were: 1) COVID-19 patients aged 18 years or over and patients being treated at Prof Dr I.G.N.G Ngoerah Hospital Denpasar from July to December 2021. Exclusion criteria were 1) incomplete medical records; 2) Malignant Diseases; 3) Requires a surgical procedure; 4) History of psychoactive drugs. The analysis includes descriptive tests, bivariate with Chi-Square and multivariate with linear logistic regression using Statistical Product and Service Solutions (SPSS) 26.

RESULTS

This research was conducted from July 2021 to December 2021, using a sample of 126 subjects consisting of 63 subjects who were COVID-19 patients with severe degrees (cases) and 63 subjects who were COVID-19 patients who were not severe (controls). The patient met the predefined inclusion and exclusion criteria. The results of patient data characteristics are obtained in Table 1.

TABLE 1: Characteristics of the research sample.

Variable	COVID-19 Degree		Total n(%)
	Severe n(%)	Not Severe n(%)	
Age			
Average	57,9±12,731	57,53±12,589	
< 65 years	21 (50)	21 (50)	42 (33.3)
≥65 years	42 (50)	42 (50)	84 (66.7)
Gender			
Man	34(50)	34(50)	68 (54%)
Woman	29(50)	29(50)	58 (46)
When blood sugar			
Average (mg/dl)	217.59±110,29	121.08 43.317±	
Hyperglycemia	28 (87.5)	4 (12.5)	32 (25.4)
Normal	35 (37.2)	59 (62.8)	94 (74.6)
Body mass index			
Average (mg/dl)	28,4±6.05	24.5 4.3±	
Obesity	23 (76.7)	7 (23,3)	30 (23.8)
Normal	40 (41.7)	56 (58.3)	96 (76.2)
Smoking History			
There is	26 (51)	25 (49)	51 (40.5)
There aren't any	37 (49.3)	38 (50.7)	75 (59.5)
History of Steroid Use			
There is	2 (33.3)	4 (66.7)	6 (4,8)
There aren't any	61 (50.8)	59 (49.2)	120 (95.2)
Diabetes mellitus			
There is	30 (62.5)	18 (37.5)	48 (38.1)
There aren't any	33 (42.3)	45 (57.7)	78 (61.9)
Hypertension			
There is	17 (63)	10 (37)	27 (21.4)
There aren't any	46 (46.5)	53 (53.5)	99 (78.6)

Variable	COVID-19 Degree		Total n(%)
	Severe n(%)	Not Severe n(%)	
Heart disease			
There is	12 (80)	3 (20)	15 (11.9)
There aren't any	51 (45.9)	60 (54.1)	111 (88.1)
Chronic kidney disease			
There is	9 (75)	3 (25)	12 (9.5)
There aren't any	54 (47.4)	60 (52.6)	114 (90.5)
Strokes			
There is	3 (50)	3 (50)	6 (4,8)
There aren't any	60 (50)	60 (50)	120 (95.2)
Chronic lung disease			
There is	12 (92.3)	1 (7,7)	13 (10,3)
There aren't any	51 (45.1)	62 (54.9)	113 (89.7)

Variable hyperglycemia is categorized into 2 categories: with and without hyperglycemia. In this study, the assessment of hyperglycemia was determined when blood sugar was more than equal to 200 mg/dl. This study found that hyperglycemia had DM comorbid disease in 21 cases (65.6%). Meanwhile, 11 points (34.4%) did not have DM comorbidities. In addition, in 27 cases (56.3%) of patients with comorbid DM, the GDS value was average (no hyperglycemia).

This indicates that hyperglycemia is not only found in patients with comorbid DM, but not all patients with DM show hyperglycemia.

In the bivariate analysis between hyperglycemia and the degree of COVID-19, the results obtained were that in the case group, the majority of the sample 28 (87.5%) had hyperglycemia. While in the control group, most were without hyperglycemia 59 (62.8%) of the sample. The results of this analysis are listed in Table 2.

TABLE 2: Relationship betweenHyperglycemiawith the Degree of COVID-19 Patients.

Variable		COVID-19 degree		OR	CI 95%	p-value[a]
		Severe	Not Severe			
Hyperglycemia	There is	28 (87.5%)	4 (12.5)	11,8	3,819-36,456	0.000*
	There aren't any	35 (37.2%)	59 (62.8%)			

[a]analysis using chi-square
* Has a significant influence (p value< 0.05)

Results of bivariate analysis between obesity with the degree of disease of COVID-19 patients are listed in Table 3. Based on the table, it can be seen that in the case group, the majority of the sample 23 (76.7%) were obese. Meanwhile, in the control group, most of the samples 56 (58.3%) were without obesity.

TABLE 3: Relationship between Obesity with the Degree of Disease of COVID-19 Patients.

Variable		COVID-19 degree		OR	CI 95%	p-value[a]
		Severe	Not Severe			
Obesity	There is	23 (76.7%)	7 (23.3%)	4,6	1.8-11.756	0.001*
	There aren't any	40 (41.7%)	56 (58.3%)			

[a] analysis using chi-square
* Has a significant influence (p value< 0.05)

Confounding variables that influence the dependent variable are the history of smoking, history of steroid use, comorbid diseases, DM, hypertension, heart disease, chronic kidney disease, stroke and chronic lung disease.

Variables that have a significant relationship with the degree of COVID-19 patients are DM, history of heart disease and history of lung disease, presented in Table 4.

TABLE 4: Relationship between Confounding Variables with the Degree of Disease of COVID-19 Patients.

Variable	COVID-19 Degree		OR	CI 95%	p-value
	Severe n(%)	Not Severe n(%)			
Smoking History					
There is	26 (51)	25 (49)	1,068	0.524-2.176	0.856
There aren't any	37 (49.3)	38 (50.7)			
History of Steroid Use					
There is	2 (33.3)	4 (66.7)	0.484	0.085 – 2.741	0.403
There aren't any	61 (50.8)	59 (49.2)			

Variable	COVID-19 Degree		OR	CI 95%	p-value
	Severe n(%)	Severe n(%)			
Diabetes mellitus					
There is	30 (62.5)	18 (37.5)	4,667	2.148-10.137	0.028*
There aren't any	33 (42.3)	45 (57.7)			
Hypertension					
There is	17 (63)	10 (37)	1,959	0.816-4.700	0.129
There aren't any	46 (46.5)	53 (53.5)			
Heart disease					
There is	12 (80)	3 (20)	4,706	1,258-17,600	0.013*
There aren't any	51 (45.9)	60 (54.1)			
Chronic kidney disease					
There is	9 (75)	3 (25)	3,333	0.858-12.953	0.069
There aren't any	54 (47.4)	60 (52.6)			
Strokes					
There is	3 (50)	3 (50)	1,000	0.194-5.154	1,000
There aren't any	60 (50)	60 (50)			
Chronic lung disease					
There is	12 (92.3)	1 (7,7)	14,588	1,835-115,999	0.001*
There aren't any	51 (45.1)	62 (54.9)			

[a]Analysis using chi-square
* Has a significant influence (p value< 0.05)

The multivariate analysis aims to assess or prove the strong relationship between each independent variable and confounding variable as a risk factor for the degree of disease in COVID-19 patients. The analysis used is binary logistic regression analysis with the enter method. In the multivariate analysis, the variables included in the analysis were variables that in the bivariate analysis had a p-value <0.25. In this study, the variables included in the multivariate analysis were hyperglycemia, obesity, comorbid diseases, steroid use, hypertension, diabetes mellitus, heart disease, chronic kidney disease and chronic lung disease. The variables of smoking history and stroke were not included in the multivariate analysis because they had a p>0.25. The results of the multivariate analysis are presented in Table 5.5.

Based on the results of the multivariate analysis, it was found that hyperglycemia and obesity were predictors independently related to the degree of disease in COVID-19 patients (p <0.05). The hyperglycemia variable is the variable that has the second largest OR value after comorbid pulmonary disease, which is equal to10.038 (IK 2.447-41.172) which means that patients with hyperglycemia have a 10.038 times greater risk of becoming severe degree of COVID-19 disease compared to no hyperglycemia. Obesity has a risk of 4.846 times more significant to be an extreme degree of COVID-19 disease compared to non-obese patients (CI 1.208-13.484). Meanwhile, the confounding variables related to the degree of COVID-19 are hypertension, heart disease, chronic kidney disease and chronic lung disease.

TABLE 5: Results of multivariate logistic regression multivariate analysis on independent variables and confounding variables on the degree of disease of COVID-19 patients.

Variable	Exp (B)	CI 95%	p-value*
Hyperglycemia	10, 038	2,447-41,172	0.001
Obesity	4,846	1,187-19,789	0.028
Hypertension	4,071	1.141-14.521	0.030
Diabetes mellitus	1,333	0.658-26.051	0.677
Heart disease	7,163	1.066-48.148	0.043
Chronic kidney disease	6,827	1.062-43.890	0.043
Chronic lung disease	20,631	1,779-239,204	0.015

* Has a significant influence (p value< 0.05)

DISCUSSION

The coronavirus disease 2019 (COVID-19) has severely threatened global public health.[16]In early 2020, the virus spread to many countries, and in March 2020, COVID-19 was declared a pandemic by the World Health Organization (WHO, 2020). COVID-19 has infected around 252.2 million people, with a mortality rate of 5.1 million worldwide.[12] In Indonesia, until June 2022, more than 6 million positive cases of COVID-19 and more than 156 thousand cases of death[12] have been confirmed.[12]

Several risk factors increase the risk of severe COVID-19 patients, including chronic lung disease, cardiovascular disease, diabetes mellitus, hypertension and obesity. COVID-19 patients with comorbid or comorbid diseases have a higher death rate than those without congenital diseases.[1]

Hyperglycemia conditions can occur with or without previous diabetes mellitus. In this study, overall hyperglycemia was found in 25.4% of cases.

In the case group, hyperglycemia was found as much as 87.5%.In addition, patients with a history of comorbid diabetes were 38%. Research conducted byAl Argan dkk., (2021)found that 75% of patients with hyperglycemia developed severe COVID-19, and 47.6% with diabetes mellitus[17]. A study that examined comorbid diseases in COVID-19 in Indonesia found that the prevalence of DM in COVID-19 in Indonesia was 33.6%[18]

Case characteristics based on BMI variables, this study found that the prevalence of obesity was 23.8%. In the obese case group, as much as 76.7%. A meta-analytic study conducted byHuang dkk., (2020) systematically reviewed 30 studies. The results obtained are the prevalence of obese patients of 16.3% -63%.[19]. The highest majority is found in the USA[19]. Characteristics of cases of smoking history were found in 40.4%. In the case group, 51% had a history of smoking.Clift dkk., (2022), who researched smoking and its relationship with COVID 19 found the prevalence of a history of smoking in COVID-19 patients who were hospitalized as much as 47.2%[20]

The history of steroid use is also one of the variables studied. There were 4.8% with a history of previous steroid use. Of all patients with a history of steroid use, only 33.3% have severe degrees of COVID-19. A higher prevalence was found byRana dkk., (2021), where the majority of a history of steroid use was found in 15.7% of cases[21]

Comorbid illnesses are widely recognized as risk factors for COVID-19. This study found that 71.4% had comorbid diseases. The comorbid diseases were DM (33.6%), hypertension (21.4%), heart disease (11.9%), chronic kidney disease (9.5%), stroke (4.8%) and chronic lung disease. (10.3%). Research conducted byKaryono & Wicaksana, (2020) found slightly different results, the prevalence of a history of hypertension was 52.1%, cardiovascular disease was 20.9%, kidney disease was 4.9%, and chronic lung disease was 15.1%.[18]

Hyperglycemia is a condition when the body's blood sugar increases above normal. Reasonable blood sugar control is a significant factor in determining the prognosis of hyperglycemia. Complications of hyperglycemia are the leading cause of poor patient prognosis because it can be life-threatening. If hyperglycemia has caused complications, the condition is generally irreversible.[22]Complications often occur in patients with uncontrolled hyperglycemia, including microvascular complications (retinopathy, neuropathy, and nephropathy) and macrovascular complications (cardiovascular disorders, coronary artery disease, etc.).[23]

Hyperglycemia induces inflammatory changes and oxidative stress, compromising cardiovascular and endothelial function. Insulin resistance, one of the 2 main contributors to type 2 diabetes, is essential in chronic cardiovascular risk. Insulin resistance, inflammation, and atherogenesis are linked by a standard range of metabolic defects, including dyslipidemia and hypercoagulability. With insulin resistance, especially in patients with 4 or 5 aspects of the metabolic syndrome, deregulation of pro-inflammatory and anti-inflammatory cytokine production will lead to oxidative stress (ROS). The resulting impact of ROS, combined with hypercholesterolemia and insulin resistance, contributes to endothelial dysfunction.[24]

In COVID-19, several conditions cause hyperglycemia, including COVID-19 induced Diabetes, stress hyperglycemia related to COVID-19, hyperglycemia caused by COVID-19 therapy and comorbid DM. This study found that hyperglycemia had DM comorbid disease in 21 cases (65.6%).

Meanwhile, 11 points (34.4%) did not have DM comorbidities. In addition, in 27 cases (56.3%) of patients with comorbid DM, the GDS value was average (no hyperglycemia). The hyperglycemia induced by COVID-19 caused by SARS-CoV-2 can directly damage beta cells in the pancreas, so there is interference with insulin secretion.[25] SARS-CoV-2 can also bind to the ACE2 receptor, which causes impaired insulin secretion.[26]Stabilization of insulin function due to damage to pancreatic cells and binding of the virus to the ACE2 receptor causes an increase in blood sugar in the body above standard limits, or hyperglycemia.[27]

Hyperglycemia is associated with a poor prognosis and can cause death because it increases the progression of SARS-CoV-2 infection in the body.[28]Regardless of the presence of diabetes or not, hyperglycemia has been shown to play a role in worsening the prognosis of COVID-19.[29]The pathogenesis associated with the effect of hyperglycemia on the poor prognosis of COVID-19 is in hyperglycemic conditions, the occurrence of non-enzymatic glycosylation, especially at the ACE2 receptor. This glycosylation process is the bridge needed by the SARS-CoV-2 virus to be able to bind to human body cells. Therefore, increased glycosylation under conditions of hyperglycemia also facilitates the invasion of the SARS-CoV-2 virus into cells.[29,30] Hyperglycemia also interferes with the function of proteins in the body, one of which is the antithrombin protein.[29]When there is an increase in oxidative stress when antithrombin is disturbed, endothelial dysfunction and thrombosis can occur, which leads to multi-organ complications.[7,29]

In this study, it was found that hyperglycemia was associated with COVID-19 (p=0.000). Hyperglycemia conditions have an 11.8 times greater risk of developing severe COVID-19 disease than those without hyperglycemia (95% CI)3,819-36,456). In addition, this study also analyzed differences in average blood sugar during the case and control groups. The results obtained mean blood sugar when patients with severe degrees of COVID-19 were significantly higher than those with mild COVID-19 (p=0.000). Similar results were found in several studies where hyperglycemia was associated with adverse conditions in COVID-19, both with comorbid DM and no comorbid DM.[31]In the case group, 75% (24 cases) of patients with hyperglycemia died, and 25% (8 cases) lived. While in cases without hyperglycemia, 64 cases (68%) lived, and 30 cases (31.9%) died. Other research also states that hyperglycemia has a relationship with a higher risk of death.[15]

Obesity is a condition where the body mass index (BMI) is 30 kg/m2. State≥ Obesity is an accumulation of abnormal fat that can increase the risk of diabetes mellitus, cardiovascular disorders, hyperlipidemia, and hypertension. Several studies have shown that weight loss in obese patients can significantly impact an individual's health condition and quality of life.[32–36]

In COVID-19, obesity is one of the causes of poor prognosis, both in the form of a severe degree of disease and an increased risk of mortality. The mechanisms that explain obesity in increasing the severity of COVID-19 are inflammation, impaired immunity, and disturbances in glucose metabolism.[37]

The influence of obesity on the inflammatory process is the enlargement of adipocyte cells which causes an increase in levels of pro-inflammatory chemokines and cytokines.[38]Repeated stimulation will cause changes in macrophages M2 to M1 (pro-inflammatory), leading to hyperactivity of the immune response, known as a cytokine storm.[39]

Components that play a role in this include IFN-gamma, IL-6, and several other pro-inflammatory cells, which overall worsen the prognosis of COVID-19.[40]

The second mechanism is a decrease in the immune response. Obesity conditions generally have a lower immune response characterized by decreased lymphocytes, such as CD4+ and CD8+ T cells, B cells, and NK cells. Obesity with COVID-19 will exacerbate the condition of the body's immune response.[41]The weak immune system can increase the severity of COVID-19 due to increased viral replication, faster distribution of the virus, and increased number of viruses in the body.[42,43]

The third mechanism is that obesity can interfere with glucose metabolism. This is thought to be due to the attack of SARS-CoV-2 infection on the islet cells in the pancreas.[44]Hyperglycemia due to COVID-19 will worsen when it occurs together with obesity, which is one of the leading causes of hyperglycemia and type 2 diabetes mellitus.[45]All these complications due to hyperglycemia are collectively associated with worsening the prognosis of COVID-19.[46] Another mechanism is that in obesity, there is a disturbance in lung function. There are mechanical changes and airway resistance that cause interference with the exchange of oxygen and carbon dioxide. Disturbances in lung function will, of course, worsen the condition of COVID-19[47].

In this study, it was found that there was a statistically significant relationship betweenobesitywithdegree of disease of COVID-19 (p=0.001). In the odds ratio analysis, it was found that obesity has a risk 4,6 times more likely to develop severe COVID-19 disease than those who are not obese (95% CI: 1.8-11.756). In addition, this study also analyzed the differences in average BMI in the case and control groups. The results showed that the average BMI of patients with a severe degree of COVID-19 was significantly higher than that of patients with a mild degree of COVID-19 (p=0.000), 28.4 ± 6.05 mg/dl compared to 24.5 4.3. Similar results were found in research ± conducted in France also found that obese COVID-19 sufferers (BMI > 30) had 7.36 times the risk (95%CI 5 1.63-33.14; P=0.02) of developing severe COVID and required intensive care.[48] BMI>30 kg/m2 was one of the causes of mortality in COVID-19 patients, so special attention is needed in obese individuals.[37]

Factors that influence the severity of COVID-19 are hypertension, diabetes, cardiovascular disease, cerebrovascular disease, chronic obstructive pulmonary disease and chronic kidney disease.[49]In addition, in research conducted at the Robert Koch Institute, other risk factors were found to influence the emergence of severe COVID-19, which is the influence of smoking and the use of immunosuppressive drugs, including steroids.[50]

The confounding variable risk factors examined in this study were a history of smoking, a history of steroid use, and comorbid diseases such as DM, hypertension, heart disease, chronic kidney disease, stroke and chronic lung disease. Variables that have a significant relationship with the degree of COVID-19 patients are the history of steroid use, comorbid conditions such as DM, history of heart disease and lung disease. Meanwhile, variables that are not significantly related to the severity of COVID-19 are smoking history, hypertension, chronic kidney disease and stroke.

Comorbid disease is widely known to be a risk factor for the severity of COVID-19. COVID-19 patients with comorbid or comorbid conditions have a higher death rate than those without congenital diseases.[1]

A study in Mexico determined that among 32,583 patients (12,304 cases and 20,279 controls), having at least one comorbidity was a risk factor for getting COVID-19 or increasing the degree of severity of COVID-19. Comorbidities that occur, cardiovascular disease, chronic kidney disease, chronic lung disease (especially COPD), diabetes mellitus (DM), and hypertension, are said to affect the worsening of the clinical course of COVID-19 patients, increasing the risk of intubation events and increasing the risk of death in patients with COVID-19. -19.[51]

Based on report data from the Indonesian COVID-19 acceleration task force until April 2022, type 2 diabetes mellitus is the most common comorbid or comorbid disease found in cases of death where a sample of 6203 patients of COVID-19 found that 9.4% have comorbid diabetes.[3]In a study conducted in India, the results obtained a significant relationship between a history of comorbid diabetes mellitus and the severity of COVID-19 with a consequence of p <0.01.[52] This study found an association between diabetes mellitus and the severity of COVID-19 (p=0.028). Patients with diabetes mellitus have a 4.7 times greater risk of developing severe COVID-19 (95% CI 2.148-10.137).

Research at Prof. Dr. I.G.N.G. Ngoerah Hospital in 2021 found that more severe COVID-19 patients had heart comorbidities (21% vs 6% ; p = 0.022) and kidney disease (17% vs 9% ; p = 0.037) compared to mild-moderate COVID-19.[53] The results of another study were study conducted by Moreno-pérez et al. (2021) with the results of COVID-19 found to have cardiovascular disease in 18 people (6.9%) out of 261 people and a risk of 1.03 times becoming severe COVID-19 (95% CI) 1.01-1.06; P=0.04).[54]In this study, it was found that there was a relationship between heart disease and the severity of COVID-19 (p=0.013). Patients with heart disease have a 4.7 times greater risk of developing severe COVID-19 (95% CI 1,258-17,600).

Covid-19 affects the respiratory tract, leading to pneumonia and acute respiratory failure. The morbidity and mortality related to Covid-19 are due to complications, especially ARDS, which occurs in up to 15% of cases.[55–57]Patients with comorbid chronic lung disease certainly have lower lung function than regular patients. Research conducted by Xiao et al. (2020) found that comorbid chronic lung disease had a significant relationship with the severity and mortality of COVID-19 patients, with a hazard ratio of 2.681 (p = 0.002).[58] In this study, it was found that there was a relationship between chronic lung disease and the severity of COVID-19 (p=0.001).

In multivariate analysis, hyperglycemia and obesity were consistently associated with the severity of COVID-19 (p=0.01 and p=0.028). Hyperglycemia conditions have a 10 times greater risk of developing severe COVID-19 disease (95% CI 2.447-41.172). Meanwhile, DM comorbidities did not show a significant relationship with the severity of COVID-19 (p=0.677). The condition of hyperglycemia causes does not always appear due to DM. As previously explained, 4 conditions cause hyperglycemia in COVID-19. ComplicationsSymptoms that appear in DM patients are caused by uncontrolled hyperglycemic conditions that lead to microvascular complications (retinopathy, neuropathy, and nephropathy) and macrovascular (cardiovascular disorders, which are comorbid for COVID-19 of lousy degree.[59] Therefore reasonable blood sugar control will prevent complications. Blood sugar control can be done through a healthy diet, diligent exercise, and anti-hyperglycemia drugs; patients can achieve euglycemia (normal sugar levels) with a good prognosis.[60]

Obesity risk factors have a risk of 4.8 times becoming a severe degree of COVID-19 (95% CI 1,187-19,789).

Besides that, hypertension, heart disease, chronic kidney disease and chronic lung disease are independent risk factors for the severity of COVID-19. The incidence of decreased kidney function in Covid-19 patients is relatively high, especially in critical cases, so AKI has been recognized as a common complication in Covid-19 patients. Besides causing AKI, SARS-Cov-2 infection can also affect various pre-existing chronic kidney diseases (CKD), including hemodialysis (HD) patients and kidney transplants, and various CKD-related conditions, including hypertension.[61–64]

Hypertension is one of the most common comorbidities in COVID-19 cases. A Cox regression analysis that adjusted for age and smoking history found that hypertension is associated with a poor prognosis and incidence of ICU admission, ventilator use and risk of death. Hypertension increases the patient's severity risk by as much as 6%. Long-lasting hypertension will cause target organ damage, including myocardial infarction. Apart from that, COVID-19 also causes an exacerbation of cardiac damage. The pathogenesis of hypertension in the severity of COVID-19 is complex and related to other comorbidities. Several potential mechanisms that explain the role of hypertension in the severity of COVID-19 include regulation of the RAAS system, systemic inflammation, immune response and ACE2-related gastrointestinal dysfunction.[65]

Patients with pre-existing coronary heart disease are more likely to have more severe COVID-19 than those without coronary heart disease. As the primary receptor for SARS-CoV-2 to enter target cells, angiotensin-converting enzyme 2 (ACE2) is found in lung cells, heart cells, kidney epithelial cells, intestinal mucosal cells, immune cells, cerebral nerve cells, etc. SARS-CoV-2 can invade human cells through interactions between the spike protein and the extracellular domain of ACE2 and induce a cytokine storm by downregulating ACE2 on infected cellular surfaces in various ways. However, an imbalance between ACE and ACE2 in lung and myocardial tissue, manifested as increased ACE activity and decreased ACE2 activity, can cause myocardial inflammation and acute respiratory distress syndrome. In patients with heart disease, high ACE2 expression in pericytes may be a target for cardiac cells that attack SARS-CoV-2, which can cause capillary endothelial cell dysfunction and lead to microcirculation disorders. The myocardial inflammation and microvascular dysfunction caused by SARS-CoV-2 will exacerbate the imbalance between the cardiac reserve and metabolic demand in patients with coronary heart disease, further promoting coronary plaque rupture. This may be why COVID-19 patients with coronary heart disease are more likely to have a poor prognosis which can cause capillary endothelial cell dysfunction and cause microcirculation disorders. The myocardial inflammation and microvascular dysfunction caused by SARS-CoV-2 will exacerbate the imbalance between the cardiac reserve and metabolic demand in patients with coronary heart disease, further promoting coronary plaque rupture. This may be why COVID-19 patients with coronary heart disease are more likely to have a poor prognosis [66].

Cronic kidney desese is the most common risk factor for prognostic morbidity and mortality of COVID-19 worldwide. The risk increases with the higher stage of CKD. Patients who receive replacement therapy/hemodialysis at the centre have a much higher risk of COVID-19 than those who receive dialysis therapy at home. This can be caused by an increased risk of exposure to SARS-CoV-2 both in and on the way to the hospital. The reason why CKD is related to the degree of severity in COVID-19 patients is still poorly understood. Several opinions state that CKD is a vital risk factor for AKI in patients with COVID-19, and AKI is strongly associated with increased severity in patients with COVID-19. Besides that, people with CKD are also at higher risk of bacterial infection and poor outcomes after infection than those who do not have CKD. Patients with CKD also have a poor immune response, and several types of antiviral drugs are not recommended for patients with eGFR <30 mL/min/1.73 m 2. Therefore, several studies have found a relationship between chronic kidney disease and COVID-19 degree disease.[67,68]

Chronic obstructive pulmonary disease (COPD) occurs in older people due to persistent inhalation of harmful particles, usually from smoking. Lung disease includes inflammation and airway remodelling, with variable alveolar destruction (emphysema). COPD patients suffer from dyspnea, cough and sputum production and may experience sudden exacerbations (exacerbations) often caused by respiratory tract infections. In addition, COPD is associated with a high prevalence of comorbidities such as cardiovascular disease and diabetes, which is not surprising in an older population with a significant smoking history. Therefore COPD and COVID-19 have many potentially damaging interrelationships, which can lead to worse outcomes from COVID-19, including impaired pulmonary function, older age, and the presence of comorbidities in COPD patients. In addition, COPD patients may also be more susceptible to contracting viral infections, including SARS-CoV-2. This causes patients with COPD to tend to develop severe COVID-19[69].

CONCLUSION

1. Hyperglycemia is a risk factor for severe COVID-19, with a risk of 10 times compared to no hyperglycemia.
2. Obesity is a risk factor for severe COVID-19, with a risk of 4.8 times compared to without obesity.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest related to the publication of this research article.

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ETHICS IN RESEARCH

This research has received approval from the research ethics committee of the Prof Dr I.G.N.G Ngoerah Hospital Denpasar/ University of Udayana with No. 265/UN 14.2.2VII.14/LT/2023

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