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ANALYSIS OF SEVERITY LEVEL FACTORS IN COVID-19 PATIENTS WITH COMORBID DIABETES MELLITUS

Abstract

Background: There are several possibilities that patients infected with the SARS-CoV2/COVID-19 virus with comorbid diabetes mellitus type 2 will experience a worsening of their condition, resulting in increased levels of inflammatory mediators in the blood, including lipopolysaccharide, inflammatory cytokines and toxic metabolites that cause pulmonary fibrosis. This study aimed to determine the factors associated with the severity of COVID patients with comorbid Diabetes Mellitus Type 2. Design: non-experimental with a *sectional* approach *retrospective from* April to August 2021 who were treated in the Isolation Room. The sampling technique in this study used *Proportional Random Sampling* to obtain 142 medical records with logistic regression analysis as the multivariate test used in this study. Results: Selection of variables with p-value <0.25, namely random blood sugar variables (p=0.031), (SPO2), oxygen saturation (p=0.000) and d-dimer (p=0.034). The multivariate results show the results of the variables that affect the severity of COVID-19 with comorbid diabetes mellitus, namely blood sugar (p=0.417), SPO2 (p=0.095), D-dimer (p=0.890), which do not have a partial effect on severity, but together the three variables equally affect the severity. These three variables show a relationship with the severity of COVID-19 comorbid DM type 2 patients with a prediction rate of 93.7%.

Introduction

Diabetes mellitus is a metabolic disease often associated with the severity of the condition of patients infected with Covid 19. One of the mechanisms predicted to underlie the relationship between diabetes Mellitus, and COVID-19 is the mechanism of chronic inflammation, impaired immune response, increased blood coagulation activity, and the potential for direct damage to the pancreas by SARS-CoV-2. The correlation between Covid-19 and Type 2 Diabetes Mellitus is seen in metabolic inflammation, and excessive cytokine release and SARS-CoV2 infection can cause insulin resistance so that glycemic control decreases (requires insulin as much as 50-100 U/hour) and impaired insulin secretion causes complications form of diabetic ketoacidosis. The glycemic decrease that occurs in patients with type 2 DM shows the interesting observation that changes in ACE2 in mRNA and protein show a substantial increase in beta cells in response to inflammatory cytokines, thereby making beta cells more susceptible to infection (Muniangi-muhitu et al. ., 2020).

Some patients with type 2 diabetes mellitus at an older age, d-dimer levels greater than 1 μg/mL, and higher rates of organ failure experience worsening conditions when infected with the SARS-CoV2 virus; these factors are associated with severity and higher probability of death in hospital (Zhou et al., 2020). An increase in D-dimer concentration in serum indicates a process of intravascular coagulation. The mechanism of coagulopathy occurs when the SARS-CoV2 virus enters target cells through the activation of ACE2 receptors on the surface of epithelial cells of the lungs, arteries and veins. Infection with the virus induces prothrombotic gene injury and causes direct dysfunction that continues under conditions of endothelial injury (Heart & Vahdat, 2022).

SARS-CoV-2 infection also causes inflammatory mediators in the blood to increase, including lipopolysaccharide, inflammatory cytokine mediators and pulmonary fibrosis caused by toxic metabolites. Fibrosis or spots in the lungs cause impaired gas exchange in the lungs, which causes a decrease in oxygen saturation (Bae, 2021). A decrease in oxygen saturation causes the body to lose much oxygen, which can cause death. The lower the oxygen saturation the patient has, the higher the risk of death for the patient.

Type 2 DM is a degenerative disease; most people with this disease are old. Covid-19 patients with comorbid type 2 DM who are older have a higher risk of severity. The increased risk is due to aging of the immune system, which undergoes immunosenescence, changes in the diversity of T cells and chronic activation of the innate immune system known as inflammation. This aging of the immune system decreases the body's ability to fight the SARS-CoV-2 virus (Mueller et al., 2020).
Gender is thought to be a risk factor for mortality in COVID-19 patients, and more men die than women. Gender due to fundamental differences in the immune systems of men and women, differences in lifestyles, and the prevalence of smoking (Lewin & Rasmussen, 2020). In men, pro-inflammatory activity and deficiency of the adaptive immune response are one of the factors causing a cytokine storm that causes potential acute respiratory distress syndrome, multiple organ failure and death. This risk increases in older men (Qin et al., 2020).
COVID-19 patients with comorbidities are vulnerable and at risk of worsening their condition resulting in death. Based on the severity of the case, COVID-19 is divided into asymptomatic, mild, moderate, severe and critical (RI Ministry of Health, 2020). Critical conditions within the established criteria have manifestations of *Acute Respiratory Distress Syndrome* (ARDS) $PaO_2/FiO_2 \leq 100$ mmHg with PEEP ≥ 5 cmH_2O, or who is not ventilated).
Based on the phenomenon above, researchers want to know the factors that cause the severity of Covid 19 patients with comorbid DM Type 2.

Methods

The design in this study is non-experimental, namely quantitative research with a *retrospective* approach. The research was carried out in April-August 2021 while treated in the Isolation Room. The sampling technique in this study used *Proportional Random Sampling* to obtain 142 medical records that matched the needs of this study. *The checklist* records patient medical records starting from age, sex, blood sugar levels, oxygen saturation (SPO2), and D-dimer values. At the same time, the instrument for severity is based on instruments that the hospital has used to assess clinical symptoms documented in the record. Medically, the screening results following the early detection of Covid-19 in the emergency room at Ngudi Waluyo Wlingi Hospital adapted from the Indonesian Ministry of Health (2020) in the mild, moderate and severe categories. Univariate statistical analysis was carried out on the variables from the research results, and this analysis will produce the distribution and percentage of each variable studied. Test *Chi-Square* to test for differences in proportions. If the results of the bivariate test have $p < 0.25$, then the variable can be included in the multivariate model. However, if the p-value> 0.25, it can still be included in the multivariate if the variable is substantially important. Logistic regression analysis as a multivariate test was used in this study.

Results

Table 1. Frequency distribution of the independent

variable	**Criteria**	**f**	**%**
Age	≤ 55 years	63	44.4
	> 55 years	79	55.6
Gender	Male	78	54.9
	Female	64	45.1
Random Blood Sugar	Normal	**12**	**8.5**
	Abnormal	130	91.5
Saturation Oxygen (SPO2)	95%-100%	25	17.6
	< 94	117	82.4
D-Dimer value	Normal	59	41.5
	Hypercoagulation	83	58.5
Presence of other co	None	8	5.6
	Present	134	94.4

Table 1 shows that most respondents are elderly > 55 years, as many as 79 respondents (55.6%). Male respondents, with a total of 78 respondents (54.9%). Most random blood sugar levels were abnormal, namely 130 respondents (91.5%). The most oxygen saturation was <94%, namely 117 respondents (82.4%). The most D-Dimer lab value was hypercoagulation, with 83 respondents (58.5%). Most had comorbidities other than diabetes mellitus, amounting to 134 respondents (94.4%).

Table 2. Frequency distribution of the Dependent

Variable	Criteria	f	%
Severity Level	**Without Symptoms-Mild**	**16**	11.3
	Moderate-Severe-Critical	**126**	88.7

The severity level shows the moderate-severe-critical severity level of 126 respondents (88.7%) and 16 respondents (11.3%) without mild symptoms.

Table 3 Selection of variable factors related to the severity

Variable	Criteria	Asymptomatic-Mild		Moderate-Severe-Critical		P-Value
		F	%	F	%	
Age	**≤ 55 years**	**5**	**3.5**	58	40.8	0.262
	> 55 years	**12**	**8.5**	68	47.9	
Gender	Male	**7**	**4.9**	71	50	0.340
	Female	**9**	**6.3**	55	38.7	
Random Blood Sugar	Normal	**2**	**1.4**	10	7	0.031
	(Hypo/Hyperglycemia)	**14**	**9.9**	116	81.7	
Saturation Oxygen (SPO2)	95%-100%	**16**	**11.3**	9	6.3	0.000
	<94%	**0**	**0**	117	82.4	
D-Dimer Value	Normal	**6**	**4.2**	53	37.3	0.034
	Hypercoagulation	**10**	**7**	73	51	
Presence of other comorbidities	No existing	**1**	**0.7**	7	4.9	0.962
	16	**11.3**	**118**	83.1	Table	present

3 shows the results of bivariate selection; not all variables show a p-value <0.25 as a condition for entering into the multivariate test. Variables that will be included in the logistic regression analysis are variables that, in the bivariate analysis, have a p-value <0.25, namely random blood sugar (p=0.031), (SPO2), oxygen saturation (p=0.000) and d-dimer (p=0.034).

Table 4 The value *of Nagelkerke R square*

Cox & Snell R Square	Nagelkerke R Square
0.404	0.777

Table 4 shows the value of *Nagelkerke R square* of 0.404, which means that the contribution of the three variables, namely, random blood sugar, oxygen saturation (SPO2), and D-Dimer, can explain the accuracy of 77% and the other 40% is explained by other factors.

Table 5 *Chi-Square* from *Hosmer and Lemeshow Test (goodness of fit)*

Chi-square	Df	Sig.
0.001	2	1.000

The table above is the *chi-square* from *the Hosmer and Lemeshow test* to determine the model's accuracy, correct if there is no significant difference (> 0.05) between the model and the observed value. With a significant p-value of 1.000 (> 0.05), then H0 is accepted that the model adequately explains the data, and a hypothesis test can be carried out because there is a significant difference between the model and the observations.

Table 6 shows that the prediction accuracy in this study was 81.0%.

Variable	Coefficient	SE	Wald	Df	P value	1,208	%	
							min	max
blood sugar	0.660	0	1	0.417	0.375	0.035	3,999	SPO2
22,100	3707,175	1	1,634	0.095	1,000	0000	1,000	1,000
1,634	0	.	-0.981	95	1,000	1,000	1,000	1,000
1,000	1,000	or176	0.000	1	0.000	0.000		

Shows the results of the variables that influence the severity of COVID-19 with comorbid diabetes mellitus are blood sugar (p=0.417), SPO2 (p=0.095), D-dimer (p=0.890) does not partially influence (alone) on severity (p>0.05). However, these three variables affect severity with a constant p = 0.00 (<0.05). The magnitude of the effect is indicated by the OR value where the SPO2 variable (OR = 1.634) means a decrease (> 94%) SPO2 is at risk of experiencing severe severity 1.634 times compared to people who have SPO2 95-100%. The positive SPO2 coefficient value is 22.100, so SPO2 has a positive relationship with the severity level.

Observed		Predicted		
		Severity		Percentage Correct
		Without Symptoms-Mild	Moderate-Severe-Critical	
Exacerbation	Without Symptoms-Mild	15	2	88.2
	Moderate-Severe-Critical	7	118	94.4
Overall Percentage				93.7

The table above shows that this study's prediction accuracy was 93.7%.

Discussion

In this study, moderate, severe and critical severity levels were the most common. Based on the severity of the case, COVID-19 is divided into asymptomatic, mild, moderate, severe and critical (RI Ministry of Health, 2020). Handling positive COVID-19 patients who are asymptomatic and have mild symptoms will be encouraged to self-isolate at home. On the other hand, positive patients with COVID-19 with moderate, severe and critical symptoms need adequate treatment at the hospital. These patients need independent isolation at home, Emergency Hospital, or in a COVID-19 Referral Hospital. Patients who are positive for COVID-19 with symptoms of severe illness will be isolated in a hospital or referral hospital (RI Ministry of Health, 2020). Patients with moderate and severe severity in this study need to be hospitalized because, in this study, Covid patients have comorbid diabetes mellitus. Several research articles show that the severity level does not stand alone, but many factors influence it. Age, sex, oxygen saturation, presence of comorbidities, and D-Dimer values are factors that affect the severity. Based on epidemiology, diabetes mellitus, which is not well controlled, is a risk factor for various infectious diseases due to a decreased immune system. The global epidemic of diabetes is very large, coupled with the highly contagious nature of the coronavirus pandemic, making diabetes contribute to increasing the severity of COVID-19, so it is very important to design tailored treatments and clinical management of individuals affected by Diabetes (Erener, 2020).

Identifying and validating factors that predict the development of COVID-19 disease is very important in improving health during the Covid-19 pandemic. Factors that are thought to increase the severity of Covid-19 patients are age, comorbidities, immune response, radiographic examination results, laboratory examination results, and indicators of organ dysfunction, which individually and collectively can predict a worse outcome. Identifying factors that predict complications of COVID-19 is very important as a basis for clinical care guidelines to improve the best outcomes for patients (Marin et al., 2021). Patients with severe severity will be more at risk of experiencing a worsening of the condition than patients with mild symptoms. Based on the experience of researchers, patients who come with a severe level of severity are more at risk of experiencing ARDS, so they are very vulnerable to ending in death.

Blood sugar is related to the severity of Covid-19 patients with comorbid DM Type 2.

The results of blood sugar examinations showed that most respondents experienced abnormalities, both hyperglycemia and hypoglycemia. Adults with diabetes continue to have two to three times the risk of developing COVID-19 than adults without diabetes. Increased comorbid conditions of obesity, hypertension and dyslipidemia, as well as poor glucose control levels, can increase the potential risk (Jung et al., 2021). Patients with diabetes mellitus who experience hyperglycemia are susceptible to infections caused by decreased immunity (Berbudi et al., 2020), so people with diabetes are very susceptible to infection with COVID-19. In patients with COVID-19 with Diabetes mellitus, it will result in a condition that causes high blood sugar. Hyperglycemia and insulin resistance occur quickly after infection with pulmonary disease. The relationship between hyperglycemia and lung disease is less well-known but is thought to be due to insulin resistance rather than pancreatic beta-cell dysfunction (Mirzaei et al., 2021). Hyperglycemia contributes to the development of COVID-19 through dysregulation of the host immune response, with changes in immune cell function and the production of cytokines such as interleukin-6. Hyperglycemia also increases receptor glycosylation of angiotensin-converting enzyme 2, which facilitates the binding of the SARS-CoV-2 virus to the host, thereby exacerbating host cell infection by SARS-CoV-2 (Brufsky, 2020). From the analysis of the relationship between random blood sugar levels and survival in COVID-19 patients with Diabetes mellitus severity, it was found that there was a relationship between random blood sugar levels and severity in COVID-19 patients with comorbid diabetes mellitus. Wu et al. (2020) stated that blood glucose levels were an independent factor for predicting the development of critical cases/hospital death in COVID-19 patients.

In contrast, patients with higher average blood glucose values had worse clinical outcomes. In this study, hyperglycemia in diabetic and non-diabetic Mellitus patients with COVID-19 can increase the severity of the condition when these patients suffer from the covid disease. Hyperglycemia as an early marker of clinical deterioration in COVID-19 patients. Hyperglycemia increases the glycosylation of two angiotensin-converting enzyme receptors, which contributes to the binding of the SARS-CoV-2 virus to the host, which can exacerbate the degree of host cell infection by SARS-CoV-2. In patients with COVID-19 infection, hyperglycemia with diabetes mellitus can worsen the prognosis.

Oxygen saturation is one of the factors associated with the severity of Covid-19 patients with Comorbid DM Type 2.

In this study, most respondents had oxygen saturation <94%. Oxygen saturation represents haemoglobin to oxygen which can be measured by pulse oximetry (Potter, Patricia A., Perry, 2006). In COVID-19 patients, an inflammatory response triggers a cytokine storm, causing spots or spots to form in the lungs, which affects oxygen exchange in the lungs so that the oxygen saturation value also drops. Low oxygen saturation is a sign of ARDS. The lower the oxygen saturation the patient has, the higher the risk of death for the patient (Sittichanbuncha et al., 2015). Reduced oxygen saturation causes the body to lose much oxygen, which can cause death. Lung tissue injury is an inflammatory response to various causative factors and is characterized by inflammation, increased vascular permeability, and decreased lung tissue aeration. The lungs are the place where gas exchange occurs. If the lungs are damaged, the gas exchange process will also be disrupted, marked by a decrease in saturation. The decrease in saturation depends on the degree of lung damage. The lower the saturation, the greater the degree of lung damage.

There is a significant relationship between saturation oxygen severity in COVID-19 patients with comorbid diabetes mellitus. COVID-19 contributes in the form of microvascular complications that cause tissue hypoxia. Hypoxia at the cellular level in Covid-19 patients is caused by anaerobic respiration due to secondary infection by anaerobic bacteria in COVID-19, which can inhibit mitochondrial cytochrome oxidase (Premier et al., 2021). COVID-19 patients with oxygen saturation >90% have a very high probability of survival compared to patients with oxygen saturation <90%. Mejía et al. (2020) also stated that oxygen saturation below 90% on admission strongly predicts in-hospital death in patients with COVID-19. Patients with hypoxia had significantly higher severity scores. The severity and oxygen saturation contribute to clinical management. Moreover, it shows that previous medical history can also play an important role in assessing severity (Aalinezhad et al., 2021). According to researchers, oxygen transport to the body's organs will be disrupted with low saturation, which can cause a lack of oxygen in the tissues, especially the brain. Reduced oxygen supply will exacerbate the patient's condition, which leads to death.

The D-Dimer Lab value is one factor related to the severity level of Covid-19 patients with Comorbid DM Type 2.

The D-Dimer value found that the majority of respondents with D-Dimer values above normal or hypercoagulable. A higher D-dimer level indicates hypercoagulability, and a d-dimer value is examined to predict the severity of the disease and the incidence of death. Increased D-dimer values can inform future prognostic results for predicting disease progression in COVID-19 (Varikasuvu et al., 2021). Patients diagnosed with COVID-19, with increased d-dimer values on admission, are common; it is associated with increased disease severity and risk of death in the hospital. D-dimer is one of the fragments when plasmin cleaves fibrin to break up clots. Laboratory examination of d-dimer values is routinely used as a diagnostic algorithm, except for the diagnosis of thrombosis. However, increased fibrin production or breakdown also increases plasma d-dimer levels of any pathological or non-pathological process (Yao et al., 2020). Inflammation forms the basis of the pathogenesis of COVID-19 when SARS-CoV-2 triggers an inflammatory response that initiates the influx of neutrophils and monocytes as a result of infection with pulmonary capillary endothelial cells. COVID-19 infection is associated with coagulation factor abnormalities such as increased pro-coagulant factors, one of which is the d-dimer value, which is associated with higher patient severity and mortality.

The results of the analysis of the relationship between d-dimer and severity in COVID-19 patients with comorbid diabetes mellitus showed that there was a significant relationship. The pathogenesis of coagulopathy in COVID-19 has yet to be fully elucidated. The mechanism of septic coagulopathy induced by bacteria is one of the pathogenesis mechanisms of COVID-19. The main causes of coagulation disorders in any severe infection are 1) overproduction of pro-inflammatory cytokines, 2) increased patterns of molecular damage, 3) mechanisms of stimulation of cell death, and 4) vascular endothelial damage. Compared to coagulopathy/DIC induced by bacterial sepsis, in COVID-19, an increase in 1) levels of fibrin-related biomarkers and 2) prolonged PT (prothrombin time) and 3) aPTT (activated partial thromboplastin time) is not the main level. Clinical signs and outcomes are determined by viral virulence and host reaction. In more severe viral infection conditions, virus-induced cytotoxic effects directly or indirectly mediated by the host response are collaboratively deleterious to the host, and coagulopathy exacerbates the condition. In the case of COVID-19, the involvement of pro-inflammatory cytokines recruits immune cells to infected tissues, primarily for host defence, but also results in host damage. The response of the lymphatic system is more pronounced in viral infections, but the mechanism is the same as in bacterial infections.

Severe lymphoid depletion in the lymph nodes and lymphopenia is a frequent findings in Covid-19 patients. Severe lymphoid depletion is caused by increased apoptosis-inducing ligands that stimulate lymphocyte apoptosis. Immune activation stimulates the expression of tissue factors on monocytes/macrophages and vascular endothelial cells (Iba et al., 2020). Increased pro-coagulant factors, including D-dimer, were associated with higher patient severity and mortality. Higher D-dimer levels at admission increase the severity and higher risk of death. Acute respiratory distress syndrome (ARDS) and thromboembolic and hemorrhagic complications are clinical features of COVID-19. Symptoms vary from asymptomatic to rapid progression to worsening to death. The risk for the severity of a Covid-19 patient can be seen or measured based on the d-dimer level. During an emergency, segregation of risk severity is as important as diagnosis, especially if it is impossible to test all patients suspected of having COVID-19 (Gungor et al., 2021).

Conclusions

Random blood sugar results, SPO2 and D-dimers, influenced this study's severity level. Although these factors partially do not directly affect the level of severity, these three variables influence the severity. The severity of COVID-19 patients with comorbid diabetes mellitus type 2 needs to be watched out for because the presence of blood sugar, SPO2 and D-dimer factors can push patients to a more severe condition. COVID-19 poses a considerable health hazard, especially for diabetes mellitus patients. A definitive treatment or vaccine for COVID-19 has not yet been found. Therefore, preventing the infection in the first place is still the best solution. Blood sugar, SPO2 and D-dimer show a relationship with the severity of COVID-19 patients with type 2 DM with a prediction rate of 93.7%.

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