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Original Research

Analysis Of Severity Factors In COVID-19 Patients With Comorbid Diabetes Melitus

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ABSTRACT

Background: *Patients infected with the SARS-CoV2/COVID-19 virus and 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.*

Methods: *A qualitative study, a cohort with secondary data from April to August 2021, sampling 142 medical records. Independent Variables are Age, Gender, Blood Glucose, Oxygen, Saturation (SPO2), D-Dimer Value, Other Comorbidities.*

Results: *The results of the selection of bivariate analysis showed that the variables that had no relationship were age (p = 0.262), gender (p = 0.340), and other co-morbidities (p = 0.962), while those having a relationship following the multivariate test were random blood sugar variables (p = 0.031), SPO2 oxygen saturation (p = 0.000), and d-dimer (p = 0.034). The multivariate results using the linear logistic regression test showed that the results of variables related to the severity of COVID-19 and co-morbid diabetes mellitus were blood sugar (p = 0.417), SPO2 (p = 0.095), and D-dimer (p = 0.890), which had no partial effect on the level of severity, but together these three variables equally affect the level of severity.*

Conclusion: *SAR-CoV2 patients with comorbid Type 2 DM, accompanied by decreased SPO2, increased d-dimer values, increased random blood sugar, with a predictive rate of 93.7%, experienced severe severity.*

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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 (requiring insulin as much as 50–100 U/hour) and impaired insulin secretion causes complications in the 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 greater severity and a 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-CoV-2 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).

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 the 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. 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) (Kemenkes RI, 2020).

Based on the phenomenon above, researchers want to know the factors that cause the severity of COVID-19 patients with comorbid DM Type 2. Research on factors that affect the prevalence rate in COVID-19 patients with comorbidities is still rarely carried out in Indonesia, generally, studies address the issue of survival rate analysis in COVID-19 patients. With reference to this phenomenon, the authors are interested in researching the "Analysis of Factors Influencing Severity in COVID-19 Patients with Comorbid Diabetes Mellitus at Ngudi Waluyo Wlingi Hospital".

MATERIALS AND METHOD

The study used a qualitative cohort with secondary data. Data research using the medical records of all patients diagnosed with COVID-19 and comorbid diabetes mellitus at the Ngudi Waluyo Wlingi Blitar Hospital from April to August 2021 was conducted in the isolation room. From April to August 2021, the population in this study included all patients with a medical diagnosis of COVID-19 and comorbid diabetes mellitus at the Ngudi Waluyo Wlingi Blitar Hospital, up to 219 of whom were treated in the isolation room.

The sampling technique in this study used the proportional random sampling technique by means of simple randomization based on the patient's medical record number, which was then drawn and taken according to a large number of research sample requirements through the wheelofnames.com randomization application on the computer. In proportional random sampling, each person in the population has the opportunity to be sampled. If the data in the medical record is incomplete, it is removed from the sample and replaced with new data.

Independent variables are age, gender, blood glucose, oxygen, saturation (SPO2), D-dimer value, and other comorbidities, while the dependent variable is the severity level. The instrument for severity is an instrument that hospitals have used to assess clinical symptoms and their onset: recent or worsening within one week. Chest imaging (thoracic CT scan or lung ultrasonography): bilateral opacity, unexplained pleural effusion, lung collapse, lobar collapse, or nodule. Cause of edema: respiratory failure not due to heart failure or fluid overload.

An objective echocardiographic examination is needed to rule out that the cause of the edema is not hydrostatic if no risk factors are found. $SpO_2/FiO_2 \leq 315$ indicates ARDS requiring a ventilator, categorized as severe severity. In the medical record, the screening results following the early detection of COVID-19 in the emergency room of Ngudi Waluyo Wlingi Hospital are adapted from the Indonesian Ministry of Health, (2020) in the mild, moderate, and severe categories.

Severity level using the criteria of patients who need breathing aids in the form of a ventilator is categorized as severe severity, while mild severity does not require a ventilator. A univariate statistical analysis of the variables from the research results will produce the distribution and percentage of each variable studied. The variable selection used the Chi-Square statistical test to test for differences in proportions.

If the results of the bivariate test have a $p < 0.25$, then these variables can be included in the multivariate model. Logistic regression analysis is a multivariate test to determine whether there is a probability that the dependent variable can be predicted by the independent variable.

RESULTS

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 1. Independent variable frequency distribution

Criteria	f	%
Age		
< 55 year	63	44,4
> 55 year	79	55,6
Gender		
Male	78	54.9
Female	64	45.1
Blood Glucose		
Normal	12	8,5
Abnormal	130	91.5
Oxygen Saturation (SPO2)		
95%-100%	25	17.6
< 94 %	117	82,4
D-Dimer Value		
Normal	59	41.5
Hypercoagulation	83	58.5
Other Comorbid		
No Comorbid	8	5.6
Another comorbid	134	94.4

Table 2. Dependent variable frequency distribution

Variable	Criteria	f	%
Severity Level	Severe severity	16	11,3
	Mild severity	126	88,7

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

Table 3. Bivariate selection of severity factor variables

Variable	No Symptoms - Mild		Moderate-Severe-Critical		P-Value
	f	%	f	%	
Age					
< 55 year	5	3,5	58	40,8	0,262
> 55 year	12	8,5	68	47,9	
Gender					
Man	7	4,9	71	50	0,340
Women	9	6,3	55	38,7	
Blood Glucose					
Normal	2	1,4	10	7	0,031

Abnormal	14	9,9	116	81,7	
Oxygen Saturation (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
Hiperkoagulasi	10	7	73	51	
Other Comorbid					
No Comorbid	1	0,7	7	4,9	0,962
Another comorbid	16	11,3	118	83,1	

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

Table 4. Negelkerke R square Value

Cox & Snell R Square	Nagelkerke R Square
0,404	0,777

The table above gives a Nagelkerke R square value of 0.404 which means that the contribution of the three variables, random blood glucose, oxygen saturation (SPO2), and D-Dimer, can explain the accuracy of 77% and the other 40% explained by other factors.

Table 5. Chi-Square 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. Variables related to the severity

Variable	Coefisien	S.E.	Wald	df	Value p	OR	IK 95%	
							Min	Max
Blood Glucose	-0,981	1,208	0,660	1	0,417	0,375	0,035	3,999
Oxygen Saturation	22,100	3707,175	0,000	1	0,095	1,634	0,000	1,000
D-dimer	-0,134	0,967	0,019	1	0,090	0,875	0,132	5,819
Constant	-20,852	3707,176	0,000	1	0,000	0,000		

Showing the results of the variables that affect the severity of COVID-19 with comorbid diabetes mellitus are blood glucose (p=0.417), SPO2 (p=0.095), D-dimer (p=0.890) have no partial effect on severity (p>0, 05). However, these three variables affect severity with a constant p = 0.00 (<0.05). The magnitude of the effect showing 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.

Table 7. Predictions of research accuracy

Observed		Predicted		
		Severity Level		Percentage Correct
		No Symptoms – Mild	Moderate-Severe-Critical	
Severity Level	No Symptoms - Mild	15	2	88,2
	Moderate-Severe-Critical	7	118	94,4
Overall Percentage				**93,7**

The table above shows that the prediction accuracy in this study is 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 (Kemenkes RI, 2020). Handling positive COVID-19 patients who are asymptomatic or have mild symptoms will be encouraged to self-isolate at home. On the other hand, positive patients with COVID-19 who have moderate, severe, or critical symptoms need adequate treatment at the hospital.

These patients need independent isolation at home, in an emergency hospital, or in a COVID-19 referral hospital. Patients who test positive for COVID-19 with symptoms of severe illness will be isolated in a hospital or referral hospital (Kemenkes RI, 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 that many factors influence it.

Age, sex, oxygen saturation, the 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. Diabetes contributes to the severity of COVID-19 because of the global diabetes epidemic and the highly contagious nature of the coronavirus pandemic, making it critical to design tailored treatments and manage the clinical care of individuals affected by diabetes (Erener, 2020).

Identifying and validating factors that predict the development of COVID-19 disease is very important for 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 tests revealed that the majority of respondents had 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 and diabetes mellitus, it will result in a condition that causes high blood sugar.

Hyperglycemia and insulin resistance occur quickly after infection with a 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 or 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 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.

Diabetes mellitus can result in hyperglycemia, which can worsen the prognosis of patients infected with COVID-19. 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 saturations <94%. Oxygen saturation is the percentage of hemoglobin to oxygen that can be measured using pulse oximetry (Potter, Patricia A., Perry, 2006).

In COVID-19 patients, an inflammatory response triggers a cytokine storm, causing 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. When the lungs are damaged, the gas exchange process is disrupted, resulting in 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, 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 an oxygen saturation below 90% on admission strongly predicts in-hospital death in patients with COVID-19.

Patients with hypoxia had significantly higher severity scores. Both severity and oxygen saturation are important in 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 by low saturation, which can cause a lack of oxygen in the tissues, especially the brain. Reduced oxygen supply will worsen the patient's condition, leading 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 had 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 a higher risk of death in the hospital. D-dimer is one of the fragments formed 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 in 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. The 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 the overproduction of pro-inflammatory cytokines, increased patterns of molecular damage, mechanisms of stimulation of cell death, and 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 that are 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 defense, 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 are 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 worsen the condition and increase the 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 severity of the risk for 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).

CONCLUSION

Blood glucose, SPO2, and D-dimer affect the level of susceptibility. Although these factors do not directly affect the level of severity, they do influence it. The severity of COVID-19 patients with comorbid diabetes mellitus type 2 needs to be watched out for because the presence of blood glucose, SPO2, and D-dimer factors can push patients into a more severe condition. COVID-19 poses a considerable health hazard, especially for diabetes mellitus patients.

A treatment or vaccine for COVID-19 has not been found, and preventing infection in the first place is still the best solution. There is a relationship between blood glucose, SPO2, and D-dimer and the severity of COVID-19 patients with type 2 DM, with a prediction rate of 93.7%. In the study, other co-morbid factors besides diabetes mellitus have not been separated in detail, so in future studies, it is hoped that other co-morbid factors can be sorted out in detail. In addition, data on vaccine history and the history of diabetes do not need to be added to future studies.

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