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Research Article

The Relationship Between HbA1c Levels and Severity of COVID-19 Patients with Diabetes Mellitus

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ABSTRACT

One of the factors influencing SARS-CoV-2 infection is comorbidity. Diabetes mellitus is a comorbidity with a high mortality rate. Poor glucose control in patients can affect cellular immune responses and increase morbidity and mortality associated with infections. The severity of COVID-19 is classified into 5 levels: asymptomatic, mild, moderate, severe, and critical. HbA1c is a good test for identifying the diabetes status of COVID-19 patients. According to the American Diabetes Association, HbA1c levels are considered controlled if $<7\%$ and uncontrolled if $\geq 7\%$. This study aims to analyze HbA1c levels in COVID-19 patients with diabetes mellitus from 2020 to 2022. This study uses the productive age category (15-64 years). To determine the relationship between HbA1c levels and the severity of COVID-19 patients with diabetes mellitus at Haji General Hospital, East Java Province, from 2020 to 2022. This research employs a cross-sectional, analytical observational method with a consecutive sampling technique involving 96 hospitalized COVID-19 patients. Data collection was conducted through medical record observation. The majority of the samples were male, with an average age of 53 years. The Fisher Exact Test yielded a p-value of 0.13, which is greater than the significance level (0.05), indicating no significant relationship between HbA1c levels and the severity of COVID-19 in diabetic patients. There is no significant relationship between HbA1c levels and the severity of COVID-19 in diabetic patients at Haji General Hospital, East Java Province.



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INTRODUCTION

COVID-19 is an infectious disease caused by the SARS-CoV-2 virus (Burhan et al., 2022). This virus has spread worldwide and was declared a pandemic by WHO in 2020. In Indonesia, the COVID-19 pandemic has gone through three waves due to various COVID-19 mutations (Bangsa, 2022).

SARS-CoV-2 infection is influenced by several factors, one of which is comorbidity. A survey conducted in China on 44,672 COVID-19 patients showed a diabetes mellitus prevalence of 5.3% as a comorbidity. A study in the United States (US) on 2,209 COVID-19 patients with diabetes mellitus reported a prevalence of 33.8%. In Indonesia, the prevalence of diabetes mellitus in COVID-19 patients is 10.1% among adults. Previous studies have shown that poor glucose control (hyperglycemia) can affect cellular immune responses and increase morbidity and mortality related to infections (Praptika, 2021). An imbalanced immune system can lead to cytokine storm, extensive lung injury, and inflammation. Cytokine storms are often associated with the severity of the disease (Cheng et al., 2020). Previous studies have shown that the older the patient, the higher the risk of COVID-19 infection (Team, 2022). Therefore, this study uses the productive age category (15-64 years).

HbA1c is considered the gold standard for long-term glucose control, providing an average value of the last 3 months. This test effectively identifies the diabetes status of high-risk COVID-19 patients compared to other parameters as HbA1c is readily available in daily practice (Zhu et al., 2021). In previous research, patients with poor glycemic control showed a risk of using assistive devices/ventilators compared to patients who had good glycemic control (B. Wang et al., 2021). However, research conducted in France

showed that long-term glycemia testing based on HbA1c levels had no impact on the severity of infection or mortality rates in patients treated in hospitals (Cariou et al., 2021). This study aims to determine the relationship between HbA1c levels and the severity of COVID-19 patients.

METHODS

This study is a quantitative analytical observational cross-sectional study using the consecutive sampling method. This study aims to determine the relationship between HbA1c levels and the severity of COVID-19 patients with Diabetes Mellitus at the Haji General Hospital, East Java Province. This study has obtained ethical permission from the ethics committee of the Haji General Hospital, East Java Province, No. 445/65/KOM.ETIK/2023. In this study, the proportion data used for the sample is an unknown sample population, so the sample size can be determined using the Lameshow formula, which is 96 samples. Data collection was carried out through observation of medical records of COVID-19 patients with diabetes mellitus from 2020 to 2022. The population data obtained were then selected based on inclusion and exclusion criteria. The inclusion criteria used were patients confirmed positive for COVID-19 with Diabetes Mellitus from RT-PCR examination, hospitalization, and productive age patients 15-64 years. The exclusion criteria used were patients with hypertension, kidney disease, heart disease, autoimmune disease, malignancy, anemia, and hyperbilirubinemia. The samples obtained were recorded in Microsoft Excel and then grouped based on the severity of COVID-19 cases according to WHO. After that, the data were analyzed using the Fisher Exact Test because it is a non-parametric test, where the data scale used in this research variable is ordinal and nominal. Data processing in this study used SPSS software.

RESULTS



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RESULTS

The research subjects were selected using consecutive sampling procedures and met the inclusion and exclusion criteria, totaling 96 patients at Haji General Hospital, East Java

Province. Below are the sample characteristics:

According to the American Diabetes Association (ADA), HbA1c levels are considered controlled if $<7\%$ and uncontrolled if $\geq 7\%$ (MRS Utomo, 2015).

Table 1. Characteristics of COVID-19 patients with Diabetes Mellitus at Haji General Hospital

Characteristic	Year		
	2020	2021	2022
Gender			
Male	21	22	8
Female	29	10	6
Age			
26-35 tahun	1	2	0
36-45 tahun	9	5	2
46-55 tahun	17	11	2
56-65 tahun	23	14	10
Presence of Pneumonia from Radiology Results			
No Pneumonia			
Pneumonia	13	5	10
	37	27	4
Patient Outcome After Hospitalization			
Discharged alive	13	5	10
Deceased	37	27	4
Severity of COVID-19			
Mild	9	6	10
Moderate	30	13	3
Severe	3	6	0
Critical	8	7	1

Table 2. HbA1c Levels in COVID-19 Patients with Diabetes Mellitus

HbA1c Interpretation	Number	Percentage
Controlled	14	14.6%
Uncontrolled	82	85.4%
Total	96	100%

Table 3. Relationship Between HbA1c Levels and COVID-19 Severity with Diabetes Mellitus

HbA1c Interpretation	Mild	Moderate	Severe	Critical	Fisher Exact Test
Controlled	6	6	2	0	p-value = 0.13
Uncontrolled	19	40	7	16	
Total	25	46	9	16	



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Patients with controlled HbA1c levels totaled 14, mostly with mild and moderate COVID-19 severity. Patients with uncontrolled HbA1c levels totaled 82, mostly with moderate severity. The Chi-square test yielded a p-value of 0.17, greater than the significance level (0.05), indicating no significant relationship between HbA1c levels and COVID-19 severity in diabetic patients.

DISCUSSION

The patient characteristics by gender show that more males were affected than females. Factors influencing this include the immune system modulation by sex hormones, coagulation patterns, cardiovascular history, and habits such as smoking and alcohol consumption (Capuano et al., 2020). The sample with the highest age group was 61 years, with an average age of 53 years. From the research results, the higher the patient's age, the higher the risk factor for being infected with COVID-19. Age productive age is the age most at risk, due to mobility and social activities tall (Elviani et al., 2021).

Physiologically, HbA1c testing is more relevant for detecting hyperglycemia as it provides an average blood glucose level over the past three months. Hyperglycemia can lead to the accumulation of AGEs through non-enzymatic glycation driven by diffusion. Excessive AGE accumulation can result in lung function loss through decreased lung muscle strength and elastic recoil capacity (Wang et al., 2021).

Hyperglycemia impairs immune function, with increased angiotensin-converting enzyme-2 levels serving as the entry point for SARS-CoV-2 in COVID-19 patients with diabetes mellitus (Patel et al., 2020). A study in France showed that long-term glycemia testing based on HbA1c levels did

not impact infection severity or mortality rates in hospitalized patients (Cariou et al., 2021). In this study, the average time for HbA1c data collection was 2-3 days from hospital admission and COVID-19 diagnosis. While long-term glycemic management did not directly affect severity or mortality from SARS-CoV-2 infection, good glycemic management during hospitalization was associated with reduced mortality rates (Sardu et al., 2020).

In previous studies, HbA1c levels at hospital admission showed no relationship with COVID-19 severity. However, other studies indicated a significant relationship between HbA1c levels measured within 6 months and COVID-19 severity. Longer glycemic control periods (2-3 years) in patients with a history of diabetes mellitus successfully identified HbA1c as a significant risk factor for COVID-19 severity and served as a clinical parameter for assessing ICU use. It can be concluded that inadequate long-term glycemic control can lead to the development of comorbidities. The incidence of several diabetes mellitus comorbidities significantly correlates with longitudinal HbA1c levels over 2 years. Longitudinal HbA1c is related to the pathophysiology of COVID-19 progression and can be used to assess ICU admission risk for appropriate care and monitoring (Wang et al., 2021).

Among various medications for diabetes mellitus patients, the combination of glucose-lowering drugs with corticosteroids is associated with reduced COVID-19 severity risk. Metformin use is associated with a lower risk of ICU admission. In addition to glycemic control, metformin's beneficial effects include anti-inflammatory properties, virus entry inhibition, and prevention of critical diabetes mellitus cases. It suggests that metformin users potentially have a shorter diabetes history and lower severity of diabetes-related comorbidities



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but should also be adjusted for other comorbid conditions. Additionally, patients using a combination of metformin and insulin showed the best effects compared to metformin alone, indicating that more intensive glycemic control can reduce the severity risk of COVID-19 in diabetes mellitus patients (Wang et al., 2021).

Besides serving as a glycemic marker, HbA1c is also a marker of oxidative stress, where there is an imbalance between free radicals and antioxidants in the body. Critical COVID-19 patients requiring ICU intubation experience high oxidative stress. High HbA1c levels are associated with significant oxidative stress. Managing and monitoring hyperglycemia is crucial for targeted therapy in patients. HbA1c can be a clinical tool for early risk assessment of glycemic control. HbA1c impacts in-hospital glucose levels and can affect hospitalization factors such as insulin treatment, hospital interventions triggering hyperglycemia, disease severity during care, and mortality prediction (Zheng et al., 2020).

Risk factors related to the severity and poor health conditions apart from a history of comorbid diseases (hypertension and diabetes mellitus), namely old age and obesity. The severe course of the disease is associated with organ damage, especially the heart, liver, and kidneys. Apart from that, inflammation and coagulation can also affect the clinical condition of COVID-19 patients. Apart from that, smoking habits, long waiting times during infection to receive treatment in hospital, lifestyle factors, demographic factors, and post-menopausal women (Wolff et al., 2021).

CONCLUSION

Based on the HbA1c interpretation, the majority of patients had uncontrolled HbA1c levels with 82 samples, and 14 patients had controlled levels. Controlled HbA1c levels in

14 patients were mostly associated with mild and moderate severity. Uncontrolled HbA1c levels in 82 patients were mostly associated with moderate severity. The null hypothesis (H0) is accepted, and the alternative hypothesis (H1) is rejected, concluding that there is no significant relationship between HbA1c levels and COVID-19 severity in diabetes mellitus patients. It is different from the study known that Prolonged uncontrolled hyperglycemia increases the risk of adverse prognosis in COVID-19. Patients with higher HbA1c should be monitored strictly to minimize the risk of adverse prognosis in COVID-19.

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