ORIGINAL ARTICLE

Clinical Outcome of COVID-19 Infection on Chronic Diabetic Complications Patients

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ABSTRACT

Introduction: COVID-19 is an infectious disease resulting from the SARS-CoV-2 virus. The virus targets the respiratory system and leads to a significant number of fatalities worldwide. Consequently, it was officially classified as a pandemic in 2020. The Covid varians is now being monitored by the World Health Organization. Diabetes mellitus is one of the disorders that might deteriorate following an infection. Diabetes mellitus and its associated comorbidities continue to pose a significant health challenge in Indonesia, while it is also a focus of concern of the Sustainable Development Goals (SDGs). The study was aimed to assess the risks and outcomes associated with COVID-19 infection and the long-term consequences of diabetes mellitus.

Methods: This was a descriptive study using a retrospective design. Research data were taken from the medical records of patients confirmed positive for COVID-19 infection and also had chronic complications of diabetes mellitus who were treated at Dr Soetomo General Academic Hospital, Surabaya, Indonesia in 2021. There were 156 patients who met the criteria of this research.

Results: There were 156 patients (97 males, 59 females). The average age of the patients was 58, while most of the patients (84%) died and the rest of the patients (16%) survived. Most of the patients with fatality (55.8%) were those with critical severity level and complications of microangiopathy, while the patients who survived (10.3%) were those with moderate severity level and complications of microangiopathy.

Conclusion: COVID-19 patients with diabetes and comorbidities had a higher mortality rate than those who recovered, while most of the patients with fatality were those with significant COVID-19 and diabetic microangiopathy complications.

Keywords: COVID-19; diabetes mellitus; microangiopathy; macroangiopathy

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Article history: •Received 5 October 2023 •Revised 15 November 2023 •Accepted 3 December 2023 •Published 31 January 2024

INTRODUCTION

COVID-19 is a disease caused by a virus that has a primary clinical manifestation in the respiratory system. This virus originated from Wuhan, China in 2019 and was named SARS-CoV-2. This virus has caused many deaths around the world, The World Health Organization on January 30, 2020 announced that the COVID-19 outbreak was a public emergency of international focus or pandemic (Fatmaningrum et al., 2022). The manifestations of COVID-19 vary from asymptomatic to critical (Sulistyowati et al., 2021). This infection is known to attack the respiratory tract, so the patients mostly experience pneumonia symptoms. Like other viruses, COVID-19 also undergoes mutations. COVID-19 had spread variants that caused high rates of infection and death throughout the world. These variants result from the mutation of COVID-19. Currently, WHO is still classifying COVID-19 variants to find the variants at risk of causing subsequent health problems as early as possible (WHO, 2023b).

On the other hand, diabetes mellitus is a chronic disease characterized by increased blood sugar levels (CDC, 2023). Diabetes has two types of complications, acute complication and chronic complication. The chronic complication is divided into two, microangiopathy and macroangiopathy (Farmaki et al., 2020) Microangiopathic and macroangiopathic complications increase the possibility and risk of mortality in diabetes mellitus patients. Diabetes is a disease suffered by many Indonesian people and even in the world. WHO stated that in 2019 there were 1.5 million people in the world who died from diabetes mellitus (WHO, 2023a).

Meanwhile, diabetes mellitus is also a health problem in Indonesia because many Indonesian people are still diagnosed with diabetes mellitus. In 2017, Indonesia is the 6th place with most diabetes mellitus sufferers globally, with over 10,3 million people. Several cases of someone suffering from diabetes but undiagnosed have also been estimated by the International Diabetes Federation (IDF) where this is

Available at https://e-journal.unair.ac.id/CIMRJ ; DOI: 10.20473/cimrj.v5i1.51748

likely due to the wide rural areas, limited resources, and low priority diabetes screening. Indonesia has more than 73,7% of cases are undiagnosed (Ong, 2022). WHO said that the high rate of diabetic patients increased by 13% in countries with lower-middle income (WHO, 2023a). Meanwhile, a study revealed that 76.4% of diabetes mellitus patients suffered from at least one type of complication (Mao et al., 2019). The high rate of diabetic patients and complications certainly causes problems in the economic sector because the state and society have to pay quite a lot of money to treat this disease. According to the data, 4% of the 18.9 million people who used secondary and tertiary national health insurance services were identified as suffering from diabetes mellitus, and 57% of this number had complications, of which 24% were cardiovascular complications. So, the total need for diabetes patients with complications to undergo treatment would cost US $ 930 - $ 1480 or the equivalent of ± 14 million - 22 million per person per year (Hidayat et al., 2022).

COVID-19, which infects patients with comorbid diabetes mellitus will worsen the patient's condition (Zhang et al., 2022). In a study, it was stated that in patients infected with COVID-19 and having type 2 diabetes mellitus, viral shedding was prolonged, while the duration of viral shedding is positively associated with the level of severity (Arfijanto et al., 2023). This is even worse if the patient has complications of diabetes mellitus. The study aimed to evaluate the risks and outcome caused by COVID-19 infection and chronic complications of diabetes mellitus.

METHODS

This research used a retrospective research design, in which the researcher used preexisting data to identify exposed and unexposed individuals in the past, and samples were taken from existing secondary data such as medical record (Klebanoff and Snowden, 2018). In this study, research data were taken from the medical records of the patients confirmed positive for COVID-19 with comorbid diabetes mellitus and diabetes complications between January – December 2021 and were treated in an isolation room at the Dr Soetomo General Academic Hospital, Surabaya, Indonesia. This research had obtained ethical clearance from the ethics committee of Dr. Soetomo General Academic Hospital (no 1124/LOE/301.4.2/XI/2022) on 11 November 2022.

The inclusion criteria were patients over 18 years old and confirmed positive for COVID–19 infection and diabetes comorbidities. They also had complications of cardiovascular disease or diabetic foot ulcers or diabetic kidney disease.

Patients with positive confirmation of COVID-19 infection was proved by positive RT–PCR examination results and serological tests. Then, the confirmed patients were divided into three groups based on severity according to NIH guidelines, namely patients with moderate COVID-19 severity (those who had SpO2 oxygen saturation ≥ 94% at initial diagnosis); patients with severe COVID-19 (those who had an oxygen saturation SpO2 < 94% at baseline; a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen PaO2/FiO2 < 300 mmHg; a respiratory rate >30 breaths/min or pulmonary infiltrates >50% at initial diagnosis); and patients with critical COVID-19 severity (those who experienced failure of respiration, multiple organ dysfunction and septic shock) (NIH, 2023). Whereas, patients with comorbid diabetes mellitus were proved by a history of diabetes from medical records or blood sugar examination results in accordance with ADA guidelines (those with GDA levels ≥ 200 mg/dl or HBA1C levels ≥ 6.5% or FPG levels ≥ 126 mg /dl) (Elsayed et al., 2023).

Diabetes mellitus complications regarded as macroangiopathy were those in the form of heart disease and diabetic foot ulcers. The heart disease was proved by the results of electrocardiography, CKMB, and troponin or confirmed based on the decision of the doctor in charge. Diabetic foot ulcers were taken from patients suffering from Wagner grade 3 – 5 ulcers. On the other hand, microangiopathy complications were taken from diabetic patients with kidney disease complications as evidenced by the results of urine tests or eGFR by using creatinine based estimated formula (Hendyatama and Mardiana, 2020), or confirmed based on the decision of the doctor in charge. Category data are displayed in the form of frequency and percent tables, while the numerical data are displayed with the average and standard deviation.

RESULTS

Data collection on patients infected with COVID-19 with co-morbid diabetes mellitus who also experienced diabetes complications at the Dr. Soetomo General Academic Hospital in 2021 revealed 156 patients. These patients have been selected and have met the research inclusion criteria, and having the characteristics can be seen in Table 1.

Table 1. General characteristics of patients with COVID-19 infection and comorbid diabetes mellitus with complications

Characteristics	N (%)	Mean ± SD
Age		57.9 ± 9.8
Gender		
Male	97 (62)	
Female	59 (38)	
Blood Glucose		
GDA		277 ± 138.85

From these data, it appears that the general characteristics of COVID-19 infection patients with comorbid diabetes mellitus who also have diabetes complications on average are those from the elderly age category of 58 years, with a standard deviation of 9.8. Characteristics based on gender showed that there were more male than female patients (97 vs 59 patients or 62% vs 38%). Laboratory results showed that random blood sugar levels in 156 patients had an average blood sugar level of 277 mg/dl with a standard deviation of 138.85.

Figure 1. Mortality presentation of COVID-19 infection with chronic complication among diabetic mellitus patients

Figure 1 shows that the surviving patients with COVID-19 infection and comorbid diabetes mellitus who also had chronic complications were 25 (16%), while those who died were 131 patients (84%).

Table 2 displays a total number of COVID-19 patients treated at Dr. Soetomo General Academic Hospital in 2021. Among them, there were 110 patients with a critical

severity level, 31 patients with a moderate severity level, and 15 patients with a severe level. The overall number of patients with complications of diabetes mellitus was 116 with microangiopathy, 21 with macroangiopathy, and 18 with both micro- and macroangiopathy.

Table 3 displays the distribution of patient deaths and survivals. Four individuals with moderate microangiopathy complications died and 16 survived. Eight severe patients died and one survived; 87 critical patients died and one survived. Three patients with moderate macroangiopathy complications died and six survived; three with severe levels died and none survived; and nine with critical levels died and none survived. For moderate microangiopathy and macroangiopathy complications, one patient died and one survived; for severe, three patients died and no patients recovered; and for critical, 13 patients died and no patients recovered.

Table 2. Severity level and the type of chronic diabetes complications among COVID-19 patients with comorbid diabetes mellitus

Variable	N (%)
COVID–19 Severity Level	
Moderate	31 (19.9)
Severe	15 (9.6)
Critical	110 (70.5)
Types of Chronic Complication	
Microangiopathy	117 (75)
Macroangiopathy	21 (13.5)
Microangiopathy + macroangiopathy	18 (11.5)

Table 3. The number of died and survive patients based on severity level and the type of chronic complications

Types of Chronic Complications	COVID - 19 Severity Level		
	Moderate n (%)	Severe n (%)	Critical n (%)
Microangiopathy			
Died	4 (2.6)	8 (5.1)	87 (55.8)
Survived	16 (10.3)	1 (0.6)	1 (0.6)
Macroangiopathy			
Died	3 (1.9)	3 (1.9)	9 (5.8)
Survived	6 (3.8)	0 (0.0)	0 (0.0)
Microangiopathy + macroangiopathy			
Died	1 (0.6)	3 (1.9)	13 (8.3)
Survived	1 (0.6)	0 (0.0)	0 (0.0)

DISCUSSION

This study showed that the average age of individuals with COVID-19 infection, comorbid diabetes mellitus, and chronic complications of diabetes was 58 years (table 1). The high incidence of diabetes mellitus in the aged population can be attributed to their increased susceptibility to the condition, as indicated by a recent study where the individuals experienced hormonal alterations, sarcopenic obesity, and a sedentary lifestyle as a result of advancing age. Therefore, elderly individuals experience an elevation in insulin resistance, which subsequently increase their susceptibility to developing diabetes (Kirkman et al., 2012). In addition, another study indicates that advancing age and prolonged uncontrolled hyperglycemia or diabetes mellitus significantly increase the likelihood of developing complications, including both microangiopathy and macroangiopathy, in patients with comorbid diabetes mellitus (Ong, 2022). Additional research also indicates that elderly individuals are more susceptible to experiencing issues related to diabetes. However, the likelihood of this danger will grow proportionally with the duration of the patient's diabetes diagnosis. According to this study, individuals who are diagnosed with diabetes at a young age are more likely to face difficulties in old age compared to those who are diagnosed with diabetes mellitus later in life. According to this study, the increased risk of diabetes complications is attributed to advancing age. Furthermore, individuals with a longer period of hyperglycemia or diagnosed with diabetes mellitus are more likely to experience a higher risk (Nanayakkara et al., 2021). The process of aging leads to physiological changes and a decline in organ function, resulting in a weakened immune system. Consequently, individuals become more susceptible to infections. Under these circumstances, an individual is more susceptible to contracting COVID-19 (WHO, 2020).

This study also found that male patients were the mostly affected by COVID-19 infection with comorbid diabetes mellitus and diabetes-related complications. Studies have indicated that males are at a larger risk of suffering from COVID-19, experiencing severe symptoms, and facing a higher likelihood of death compared to females. In fact, the risk of infection and mortality is approximately 1.7 times greater in infected males than in infected females. However, these are associated with health behaviors, occupational and lifestyle exposures, such as tobacco use, alcohol consumption, and disparities in physiological responses between the male and female immune systems (Kharroubi and Diab-El-Harake, 2022). The severity of this disease is determined by the cytokines and chemokines that are generated in response to the infection. An excessive synthesis of cytokines such as TNF, IL-6, and IL1β results in a cytokine storm, which in turn leads to increased infection severity (Jose and Manuel, 2020). Additionally, a separate study found that male patients with severe symptoms exhibited higher levels of IL-6, IL-8, and MCP-1 compared to female patients. Consequently, it was concluded that male patients are more likely to require hospitalization due to COVID-19 infection (Qi et al., 2021). Conversely, another study indicated that female patients were more prone to developing diabetes mellitus and its associated complications. These factors that impact the phenomenon include sexual hormones, pharmacokinetics, pharmacodynamics, plasma volume, and obesity, with a higher prevalence among women. Females in this scenario exhibit a higher susceptibility to diabetes with associated problems in comparison to males (Ciarambino et al., 2022). However, this present study indicated that the majority of individuals suffered from diabetes mellitus and its comorbidities, who were also infected with COVID-19, were males. This is related to the immune system, as previously discussed, and the occupational exposure of males, which tends to be higher than that of females. Consequently, males face a greater likelihood of encountering external sources, thereby increasing their susceptibility to COVID-19 infection.

Table 2 shows that there are many patients in Dr. Soetomo General Academic Hospital in 2021, has come with critical Covid severity level. The high number of critical COVID – 19 severity levels in diabetic complication patients who are infected with COVID-19 could be due to patients with diabetes mellitus having a greater risk of developing severe pneumonia, an excessive uncontrolled inflammatory response because diabetes patients with COVID-19

infection have higher inflammatory biomarkers. Because of this, diabetes patients with COVID-19 infection experience worse conditions more quickly in COVID-19 (Guo et al., 2020). Patients with high glucose levels or hyperglycemia induce ROS, thereby causing oxidative stress (Bhatti et al., 2022). Meanwhile, COVID-19 infection also increases oxidative stress through ROMO1 (Amini et al., 2022). The level of oxidative stress caused by diabetes and COVID-19 affects the patient's severity level (Vollbracht and Kraft, 2022). Table 3 shows that the frequency of death patients was mostly in critical condition, 109 of 110 patients was death, but they came in critical condition. The high mortality rate caused by this critical level of severity is most likely related to the high level of organ damage. Meanwhile, the development of organ failure leads to a worse prognosis for the patient (Jain, 2020). Moderate and severe level severity. Moderate and severe severity levels have a lower mortality impact than critical severity levels due to the response to the inflammatory process, and the resulting oxidative stress is much lighter.

The chronic complication type variable shows that most patients came with microangiopathy complications, namely 116 patients suffered from microangiopathy complications. Table 3 shows that microangiopathy complications also have the highest frequency of patient deaths compared to other complications, namely 99 patients with microangiopathy complications died out of 116 patients who came with microangiopathy complications. In this study, patients with microangiopathy complications were measured based on the number of patients suffering from diabetic kidney disease. Diabetic kidney disease is a complication that takes a long time to develop into diabetic kidney disease due to high levels of glucose which must be filtered by the kidneys. The high incidence of microangiopathy complications in patients with diabetes in one study stated that this was due to hypertension impacts kidney damage by increasing intraglomerular pressure, microvascular disruption, inflammation and causing loss of kidney function. All of these processes increase triglyceride levels, which correlate with microangiopathic complications of diabetic kidney diseas. but, the complete mechanism is not yet known (Sutadji et al., 2023). However, these complications are likely to increase during the pandemic of COVID-19, which is most likely caused by COVID-19 infection of the ACE-2 receptor. These receptors are found in abundance in the kidneys, especially tubular epithelial cells. COVID-19 infection causes high levels of ROS, causing damage to lipids, proteins, and DNA. If this damage occurs to beta cells, it causes increasingly uncontrolled blood sugar levels in the body, which causes the workload on the kidneys to be much higher. Apart from that, lockdown conditions or restrictions on socializing cause early screening for patients with diabetes complications to be more hampered. This risks causing the patient to develop complications of diabetic kidney disease or microangiopathy complicationsn (Neumiller et al., 2022).

Macroangiopathy complications have a smaller number of sufferers than microangiopathy complications. in this study macroangiopathy were measured base on the number patient that suffered from diabetic foot ulcers and cardiovascular disease. In a study, it was stated that several things influence the occurrence of diabetic ulcer disease, that is, experience diabetes for more than 10 year and depend on ethnicity. but in that study explain that male and old age were not risk factors for diabetic foot ulcer, So the high age and male gender in this study did not have a big influence on the number of diabetic foot ulcer sufferers (Dewi et al., 2020).

CONCLUSION

The mortality rate for COVID-19 patients with comorbid diabetes mellitus who also experience complications is still high when compared to patients who successfully recover. Patients with critical COVID-19 severity and diabetes microangiopathy complications had the highest number of patients who died.

ACKNOWLEDGEMENT

The authors and supervisors involved in this research would like to express author's gratitude to the Faculty of Medicine, Airlangga University. The authors also would like to express gratitude to the supervisors who always gave suggestions and critical, feedback in the preparation of this manuscript and research.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest in this research.

ETHICS CONSIDERATION

Ethical clearance of this research was obtained from the ethics committee of Dr. Soetomo General Academic Hospital, Surabaya (no 1124/LOE/301.4.2/XI/2022) on 11 November 2022.

FUNDING DISCLOURE

This research did not receive any funding.

AUTHOR CONTRIBUTION

Designing, analyzing and drafting manuscripts: EPW, concept and reviewing manuscript: TPA, supervised result and discussion: TPA , IAM,HN. All authors reviewed and approved the final version of the manuscript.

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