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Association between blood glucose levels at admission and severity of COVID-19 patients

Nurul Asysyifa[1], Shinta Dewi Permata Sari[1]*, Dewi Martalena[1,2]

[1]Faculty of Medicine, Universitas Muhammadiyah Prof. DR. HAMKA, [2]Pondok Kopi Jakarta Islamic Hospital

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ABSTRACT

Hyperglycemia can be experienced by corona virus disease (COVID-19) patients due to the invasion of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) into pancreatic cells or other mechanisms such as insulin resistance, counter-regulatory, stress induction, and glucocorticoid therapy. Hyperglycemia can stimulate the production of reactive oxygen species (ROS) and pro-inflammatory cytokines leading to an increase in the disease severity. Based on the clinical and laboratory criteria, the severity of COVID-19 patients is classified into asymptomatic, mild, moderate, severe, and critical. This study aimed to investigate the association between blood glucose levels at admission and the severity of COVID-19 patients with and without diabetes mellitus (DM). It was a cross-sectional study using secondary data from COVID-19 patients in Pondok Kopi Jakarta Islamic Hospital from April to June 2021. This study involved 340 patients with comorbid DM (n=78) and without comorbid DM (n=262). The Mann-Whitney and Spearman correlation test were used. A significant difference between random blood glucose levels in comorbid DM patients and patients without comorbid DM ($p<0.05$). However, there is a weak correlation between random blood glucose levels and severity with comorbid DM ($r=0.112$) and without comorbid DM ($r=0.129$). In conclusion, a positive and weak correlation between blood glucose levels at admission and the severity of COVID-19. The severity increases as the blood sugar level increases. Further study needs to be performed considering other comorbid conditions.

ABSTRAK

Hiperglikemia dapat dialami oleh pasien *corona virus disease* (COVID-19) akibat invasi *severe acute respiratory syndrome coronavirus-2* (SARS-CoV-2) ke dalam sel pankreas atau mekanisme lain seperti resistensi insulin, kontra-regulasi, induksi stres, dan terapi glukokortikoid. Hiperglikemia dapat menginduksi produksi *reactive oxygen species* (ROS) dan sitokin pro-inflamasi yang menyebabkan peningkatan keparahan penyakit. Berdasarkan kriteria klinis dan laboratorium, tingkat keparahan pasien COVID-19 diklasifikasikan menjadi tanpa gejala, ringan, sedang, berat, dan kritis. Penelitian ini bertujuan untuk mengkaji hubungan antara kadar glukosa darah saat masuk rumah sakit dan tingkat keparahan pasien COVID-19 dengan dan tanpa diabetes melitus (DM). Penelitian ini adalah penelitian potong lintang dengan menggunakan data sekunder pasien COVID-19 di RSIJ Pondok Kopi pada bulan April hingga Juni 2021. Penelitian melibatkan 340 pasien dengan komorbid DM (n=78) dan tanpa komorbid DM (n=262). Uji analisis statistik menggunakan uji korelasi Mann-Whitney dan Spearman. Terdapat perbedaan bermakna antara kadar glukosa darah acak pasien komorbid DM dengan pasien tanpa komorbid DM ($p<0,05$). Namun terdapat korelasi lemah antara kadar glukosa darah acak dan derajat keparahan dengan komorbid DM ($r=0,112$) dan tanpa komorbid DM ($r=0,129$). Kesimpulannya, terdapat korelasi positif dan lemah antara kadar glukosa darah saat masuk rumah sakit dan tingkat keparahan COVID-19. Tingkat keparahannya meningkat seiring dengan meningkatnya kadar gula darah. Perlu dilakukan penelitian lebih dengan mempertimbangkan kondisi komorbid lainnya.

Keywords:
COVID-19;
diabetes mellitus;
hyperglycemia;
severity;
comorbid

*corresponding author: shinta.dps@uhamka.ac.id

INTRODUCTION

The coronavirus disease (COVID-19) due to the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) spread rapidly to various countries and affected many sectors of life. It spreads mainly through direct contact in the form of droplets, as well as indirect communication.[1] Dry cough, fever, and shortness of breath are the most common symptoms. The severity of COVID-19 is divided into asymptomatic, mild, moderate, severe, and critical.[2]

Hyperglycemia conditions or elevated blood glucose also become one of the symptoms of COVID-19. This condition can occur when pancreatic β-cells can not produce insulin or the insulin does not work properly (insulin resistance). Hyperglycemia conditions are usually related to diabetes mellitus (DM). However, hyperglycemia can also occur in several circumstances, such as stress due to disease, one of which is infection. In addition, the occurrence of insulin resistance conditions that cause hyperglycemia can also occur due to endocrine system disorders in the form of a counter-regulatory hormone mechanism that is antagonistic to insulin action. Therefore, hyperglycemia does not only present in COVID-19 disease but also in other disease conditions.[3]

Age, comorbid diabetes, and other comorbidities are the most common predictors of COVID-19 morbidity and mortality. The condition of hyperglycemia due to the SARS-CoV-2 virus can elevate the severity in patients with comorbidities, especially DM. Studies showed new onset hyperglycemia in COVID-19 patients without DM and new onset DM related to severity.[4,5]secondary hyperglycaemia (group 2: no diabetes history, fasting plasma glucose levels of ≥7.0 mmol/L once and HbA1c values <6.5% Studies regarding these topics in COVID-19 patients in Jakarta related to the severity are still limited. This study aimed to investigate the association between blood glucose levels at admission and the severity of COVID-19 patients with and without comorbid DM.

MATERIAL AND METHODS

Design and subjects

It was an analytical-observational study with a cross-sectional design conducted at the Pondok Kopi Jakarta Islamic Hospital, Jakarta. The samples were patients hospitalized that confirmed COVID-19 by a reverse transcriptase–polymerase chain reaction (RT-PCR) test. The patient selection was from a list of medical records data from April to June 2021 with moderate, severe, and critical severity. The protocol of study was approved by the Research Ethics Committee of Universitas Muhammadiyah Prof. DR. HAMKA, Jakarta.

Protocol

The eligible data patients were selected based on the inclusion and exclusion criteria. The inclusion criteria consisted of the COVID-19 adult patients hospitalized from April to June 2021. The patients had the blood glucose data. The patients have no blood glucose data were excluded. Among 480 patients selected in this study, 140 patients were excluded. Therefore, 340 patients were involved in this study. They consisted of 78 patients with DM and 262 patients without DM (FIGURE 1),

Statistical analysis

Data were analyzed using SPSS Statistics 25. The blood glucose levels (BGL) of COVID-19 patients with comorbid DM were compared with those without comorbid DM using the Mann-Whitney test. The relationship between severity and BGL was analyzed using the Spearman correlation test. A p value <0.05 was considered significant.

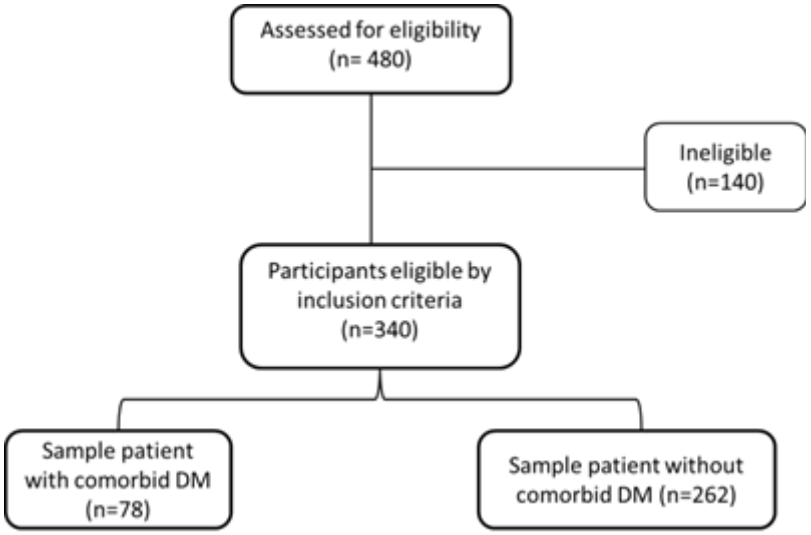

FIGURE 1. The recruitment flow of COVID-19 sample patients.

RESULTS

Among 480 COVID-19 patients selected in this study, 340 patients met the inclusion and exclusion criteria. The clinical characteristics of patients are presented in TABLE 1. The patients consisted of 78 patients with comorbid DM and 262 patients with non-DM. There were 180 male (52%) patients and 160 female (47%) patients. Productive age (<50 years) is the largest population in this study. No significant difference between gender and severity was observed (p>0.05). However, a significant difference between patient with comorbid DM, non-DM, and severity was observed (p<0.05).

TAThis study showed that only 11 (3.2%) patients had BGL <70 mg/dL and dominated by patients without comorbid DM with moderate severity (n=6). Most patients (266 patients or 78%) had BGL between 70-200 mg/dL, dominated by the patients without comorbid DM with moderate severity (n=204). Meanwhile, there were 63 (18%) patients with BGL above 200 mg/dL, dominated by patients with comorbid DM with moderate severity (n=27) (TABLE 1). No significant difference in BGL at admission among severity of COVID-19 patients was observed (p>0.371). However, significant difference in BGL at admission

No significant correlation between the BGL at admission in COVID-19 patients with comorbid DM and the patient's severity (r=0.112; p=0.327) was observed (TABLE 2). In contrast, significant correlation between the BGL at admission in COVID-19 patients without comorbid DM and the patient's severity (r=0.129; p=0.037) was observed (TABLE 3).

BLE 1. The clinical characteristics of COVID-19 patients

Variable	Total [n (%)]	Moderate		Severe		Critical		p
		DM	Non-DM	DM	Non-DM	DM	Non-DM	
Total patients	340 (100)	53	226	4	8	21	28	0.001
Male	180 (52)	23	119	2	7	11	18	0.167
Female	160 (47)	30	107	2	1	10	10	
Age (y.o.)								
• <50	154 (45)	12	125	23	55	18	45	
• 50-60	100 (29)	1	2	1	3	2	3	0.034
• >60	86 (25)	5	9	8	11	6	11	
BGL (mg/dL)								
• <70	11 (3.2)	1	6	0	0	2	2	
• 70-200	266 (78)	28	204	2	6	4	22	0.371
• >200	63 (18)	27	16	2	1	14	3	
Length of stay	8.2±2.6*	10	7	3	10	11	8	0.001
Death	42 (12)	2	4	2	2	12	20	0.781

Note: *: data presented as mean ± standard deviation

TABLE 2. The Spearman correlation test analysis between the BGL in COVID-19 patients with comorbid DM and patient's severity

		BGL in COVID-19 patients with comorbid DM	Patient's severity
BGL in COVID-19 patients with comorbid DM	r	1	0.112
	p		0.327
Patient's severity	r	0.112	1
	p	0.327	

TABLE 3. The Spearman correlation test analysis between the BGL in COVID-19 patients without comorbid DM and patient's severity

		BGL in COVID-19 patients without comorbid DM	Patient's severity
BGL in COVID-19 patients without comorbid DM	r	1	0.129*
	p		0.037
Patient's severity	r	0.129*	1
	p	0.037	

DISCUSSION

Various factors, included comorbidities, can cause the severity of COVID-19 patients. Diabetes mellitus is one of the most common risk factors that cause the worsening of the COVID-19 patients. Paolo *et al.*[6] reported that the new-onset of hyperglycemia in patients without comorbid DM increased the risk of admission to the ICU. Furthermore, Li *et al.*[7]453 patients were admitted to Union Hospital in Wuhan, China, with laboratory-confirmed severe acute respiratory syndrome coronavirus 2 infection. Patients were classified into four categories: normal glucose, hyperglycaemia (fasting glucose 5.6-6.9 mmol/L and/or HbA1c 5.7%-6.4% reported the risk of death is two time compared to patients with comorbid DM. Therefore, new-onset hyperglycemic patients without a previous history of DM can also cause worsening of the disease.

This study showed that the proportion of male COVID-19 patients was higher than female. These results are in line with previous studies conducted at Pondok Kopi Jakarta Islamic Hospital in 2020,[8] in North Kalimantan,[9] and in China.[10] Furthermore, there were variations in patients' age, dominated by patients aged <50 yr. These results were in line with previous studies in Jakarta that the highest age group of COVID-19 patients is 31-45 y.o. Pepople <50 y.o. are productive people with many activities outside, thus making them susceptible and easily infected with COVID-19.[11] Meanwhile, most elderly patients tend to experience decreased natural immunity and organ function caused by degenerative processes, accompanying comorbid conditions, and taking drugs for medications. These can cause elderly patients to experience a higher mortality risk than younger-aged groups.[12,13]

This study showed that most patients are without comorbid DM with normal BGL (70-200 mg/dL). A study in the United States also reported that patients with normal BGL at admission in patients without comorbid DM are higher than patients with hyperglycemia (>200 mg/dL). Meanwhile, most patients with higher BGL at admission (> 200 mg/dL) were patients with comorbid DM.[14] However, no significant difference between BGL at admission in comorbid DM patients and without comorbid DM was observed in this study.

In this study, most critical patients with high BGL (>200 mg/dL) were observed in patients with comorbid DM. Meanwhile, critical patients with normal BGL (70-200 mg/dL) were mostly present in patients without comorbid DM. This result follows a study in Spain that reported comorbid DM could increase the severity and mortality of patients, especially patients with uncontrolled DM. COVID-19 patients with hyperglycemia (blood sugar at admission >180 mg/dL) with or without previous comorbid DM can elevate the risk of complications and mortality.[15] Another study also reported that patients with hyperglycemia and hypoglycemia induce a worsening condition of COVID-19.[16]

Diabetes mellitus is one of the risk factors that can elevate the severity and mortality in COVID-19 patients. In COVID-19 patients, elevated glucose levels is caused by an increased in pro-inflammatory cytokines and decreased immunity. These conditions usually occur in elderly patients, as well as a decrease in ACE-2 regulation. Patients with a history of comorbid DM have an increased expression of ACE-2 in several tissues; increased BGL alone can lead to replication of the SARS-CoV2 virus.[17] Patients with comorbid DM are also more susceptible to infection. The laboratory results from comorbid DM showed a greater incidence of decreased lymphocyte count, increased number of neutrophils, CRP, and LDH, accompanied by higher BGL, compared with patients

without comorbid DM. In addition, hyperglycemia can also impair the control process of viremia and inflammation. These conditions can cause worsening in patients with a history of comorbid DM and tend to have a higher risk of severity and mortality than patients without a history of comorbid DM.[18]

The BGL at admission in COVID-19 patients without comorbid DM have significant positive correlation with patient's severity, but not in patients with comorbid DM (TABLE 2 and 3). A positive correlation between BGL at admission and patient's severity in COVID-19 patients with comorbid DM[19] and without comorbid DM[20] were reported in the previous studies. A previous study in the Pondok Kopi Jakarta Islamic Hospital in 2020 also stated a significant relationship between comorbid DM and the severity of the disease.[8]

Hyperglycemic do not only occur in patients with a history of comorbid DM, but patients without comorbid DM can also experience hyperglycemia called new-onset hyperglycemia. It is associated with the binding of SARS COV-2 with ACE2 on the surface of the pancreatic cell membrane. There are classifications of new-onset hyperglycemia, such as stress-induced hyperglycemia, hyperglycemia leading to new-onset DM in previously unknown prediabetes, hyperglycemia due to SARS-CoV-2 invasion of pancreatic islets, and hyperglycemia following corticosteroid use.[21]especially exploring the gender difference existing in PTSS. One month after the December 2019 COVID-19 outbreak in Wuhan China, we surveyed PTSS and sleep qualities among 285 residents in Wuhan and surrounding cities using the PTSD Checklist for DSM-5 (PCL-5 Hyperglycemia in patients without comorbid DM can also cause worsening by the mechanism as patients with comorbid DM. In addition, patients without comorbid DM may have other comorbid conditions such as hypertension, dyslipidemia, and obstructive pulmonary disease. Chronic cardiovascular disease can also increase severity through different mechanisms. Therefore, COVID-19 patients without comorbid DM may also have a high risk of severity.[22]

CONCLUSION

In conclusion, there is a weak positive correlation between the BGL at admission and the severity of COVID-19 patients without comorbid DM. Initial screening of BGL in COVID-19 patients are needed to predict the clinical outcomes.

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