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Predicting the Risk of Mortality for Patients Diabetic With Coronavirus Disease (Covid-19): a Retrospective Study

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ABSTRACT

Background. One of the biggest causes of mortality of patients diabetic with COVID-19 in the globe is diabetes mellitus. The study's goal was to examine the predicting the risk of mortality for patients diabetic with coronavirus disease (COVID-19).

Methods. This is a retrospective study of patients diabetic with COVID-19 on 22 June 2020 to 21 July 2021 in H. Adam Malik Hospital Medan from 22 June 2020 to 21 July 2021. We collected all the data from electronic medical records on diabetics with SARS-CoV-2 infection, including demographic, clinical, laboratory, and radiological characteristics, treatments, complications, and clinical outcomes. All patients had throat swabs taken from their upper respiratory tracts to determine whether they had SARS-CoV-2 infection. Diagnosis of diabetes mellitus used ADA criteria.

Results: There were 163 diabetic patients with COVID-19, consisting of mild (0%), moderate (39.8%), severe (44.2%), and critical (16.5%), and the most comorbid disease is hypertension. There was a significant age difference, length of stay, blood routine, and certain inflammatory markers between patients Diabetic with COVID-19 discharged from the hospital and died (all,

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p<0.05). The predicted death of patients diabetic with COVID-19 was D-dimer (OR: 4.069; p=0.008*;95% C.I: 1.43-11.55) and dexamethasone use (OR:4.769; p=0.007*; C.I: 1.54-14.71).

Conclusion. The use of dexamethasone and the increase of D-dimer values increase mortality predictions in treating diabetic patients with COVID-19 in hospitals. To prevent these harms, the management of inpatients diabetic with COVID-19 must be with good glucose consideration and monitoring.

Keywords: Diabetes Mellitus with COVID-19, Mortality

ABSTRAK

Latar belakang. *Salah satu penyebab kematian terbesar pasien diabetes dengan COVID-19 di dunia adalah diabetes melitus. Tujuan penelitian ini adalah untuk menguji prediksi risiko kematian bagi pasien diabetes dengan penyakit virus corona (COVID-19).*

Metode. *Ini merupakan studi retrospektif pasien diabetes dengan COVID-19 pada tanggal 22 Juni 2020 hingga 21 Juli 2021 di Rumah Sakit H. Adam Malik Medan dari tanggal 22 Juni 2020 hingga 21 Juli 2021. Kami mengumpulkan semua data dari rekam medis elektronik pada penderita diabetes dengan infeksi SARS-CoV-2, termasuk karakteristik demografis, klinis, laboratorium, dan radiologi, perawatan, komplikasi, dan hasil klinis. Semua pasien memiliki usap tenggorokan yang diambil dari saluran pernapasan bagian atas mereka untuk menentukan apakah mereka memiliki infeksi SARS-CoV-2. Diagnosis diabetes melitus menggunakan kriteria ADA.*

Hasil*: Terdapat 163 pasien diabetes dengan COVID-19, terdiri dari ringan (0%), sedang (39,8%), berat (44,2%), dan kritis (16,5%), dan penyakit komorbid terbanyak adalah hipertensi. Ada perbedaan usia yang signifikan, lama tinggal, rutinitas darah, dan penanda inflamasi tertentu antara pasien Diabetes dengan COVID-19 keluar dari rumah sakit dan meninggal (semua, hal<0,05). Prediksi kematian pasien diabetes dengan COVID-19 adalah D-dimer (OR: 4,069; p = 0,008*; 95% CI: 1,43-11,55) dan penggunaan deksametason (OR: 4,769; p = 0,007*; CI: 1.54-14.71).*

Kesimpulan. *Penggunaan deksametason dan peningkatan nilai D-dimer meningkatkan prediksi mortalitas dalam merawat pasien diabetes dengan COVID-19 di rumah sakit. Untuk mencegah bahaya ini, manajemen pasien rawat inap diabetes dengan COVID-19 harus dengan pertimbangan dan pemantauan glukosa yang baik.*

Kata Kunci*: Diabetes Melitus dengan COVID-19, Kematian*

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1 Introduction

One of the biggest causes of mortality in the globe is diabetes mellitus, and during the following few decades, it is expected to continue to climb. A substantial amount of research has shown that people with diabetes are more vulnerable to infectious illnesses.[1] Diabetes and high plasma glucose levels have both been linked to increased morbidity and mortality in SARS patients.[2] Patients with diabetes made up the first three SARS-CoV-2 infection deaths in Hong Kong. In a study conducted on a group of 52 ICU patients infected with SARS-CoV-2, the most common comorbidities between the 32 nonsurvivors of the group were diabetes (22%) and cerebrovascular disease (22%).[1] Diabetes is a pre-existing illness in the majority of individuals with COVID-19 disease, which has a high morbidity and death rate.[2] Diabetes was one of the most common comorbidities in COVID-19 patients, according to several retrospective investigations conducted in Wuhan. These studies also revealed that diabetics were likely more susceptible to SARS-CoV-2 and these patients would have a worse prognosis.[3] Diabetic patients were found to have a higher chance of developing diabetic nephropathy, ischemic heart disease, pneumonia resulting in, acute respiratory distress syndrome (ARDS), and multiorgan failure.[4] The most prevalent underlying disorders were hypertension, cardiovascular disease, history of smoking, and diabetes with incidences of 16.37 percent, 12.11 percent, 7.63 percent, and 7.87 percent, respectively.[5] The death rate for patients diabetic with COVID-19 ranges from 22% to 31% of all COVID-19 patients.[6] Severe hyperglycemia is a frequent finding in laboratory findings of COVID-19 in almost all critically sick patients, and this is frequently seen as a sign of illness severity.[7] The study's goal was to examine the predicting the risk of mortality for patients diabetic with coronavirus disease (COVID-19).

2 Material and Method

2.1 Data Collection

In this retrospective study, we included 163 patients diabetic with COVID-19 from 22 June 2020 to 21 July 2021 at H. Adam Malik Hospital, Medan, Indonesia which was also the designated hospital for the treatment of COVID-19. We collected all the data from electronic medical records on diabetics with SARS-CoV-2 infection, including demographic, clinical, laboratory, and radiological characteristics, treatments, complications, and clinical outcomes. Three separate researchers carefully examined the data. All patients had throat swabs taken from their upper respiratory tracts, which were then examined using either next-generation sequencing technology or reverse transcription polymerase chain reaction to determine whether they had SARS-CoV-2 infection. Diagnosis of diabetes mellitus must be met to one of the following criteria: 1) A fasting plasma glucose level of less than 7.0 mmol/L (126 mg/dL), and 2) A plasma glucose level of more than 11.1 mmol/L two hours following a 75-g oral glucose load in a glucose tolerance test;4) Glycated hemoglobin (HbA1c) 48 mmol/mol (casual plasma glucose level 11.1 mmol/L (200 mg/dL); (6.5 percent).[8] The

diagnosis, treatment, and Clinical classification of coronavirus disease 2019 (COVID-19) are according to Global Health & Medicine. 2020.[9] In the assessment of disease severity, critical illness was identified if satisfying at least one of the following criteria: 1) respiratory failure requiring mechanical ventilation; 2) shock performance; 3) multiple organ failure requiring intensive care unit (ICU) monitoring.[9] The presence of new abnormalities on an ECG or serum levels of the cardiac biomarkers high-sensitivity troponin I and creatine kinase-MB over the upper reference range were used to identify acute myocardial damage.[10] Acute kidney injury was defined based on the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines.[11]

2.2 Statistical Analysis

Independent variable grouping analysis and multivariate logistic regression analysis were used to determine the risk factors of mortality among diabetics with COVID-19. The prediction model was established according to the related risk factors. We presented the measure of association as odds ratios (ORs) and their corresponding 95% confidence intervals (CI). All statistical analyses were performed using SPSS software, and a p-value < 0.05 was considered statistically significant.

3 Results.

There were 163 diabetic patients with COVID-19, consisting of mild (0%), moderate (39.8%), severe (44.2%), and critical (16.5%), and the most comorbid disease is hypertension (Tabel 1).

Table 1 Baseline Characteristics of Patients Diabetic with COVID-19

Variable	n=163
Age year (%) < 40	0.5
> 40	93.9
Sex. F/M (%)	39.6/59.8
Severity of Covid-19 (%)	
Mild	0
Moderate	39.8
Severe	44.2
Critical	16.0
Comorbid (%)	
Diabetes	100
Hypertension	51.8
CAD	28.7
Dyslipidemia	36.0
AKI	35.4

Based on Table 2, there was a significant difference in age, length of stay, blood routine, and inflammatory marker between patients Diabetic with COVID-19 discharged from the hospital and died (all, p<0.05)

Table 2 The Comparison of Age, Laboratory Data, and Inflammation Marker between patients Diabetic with COVID-19 Discharged from the Hospital and Died

Variable	Total (n=163)	Discharged (n=131)	Died (n=32)	p[a]-Value	95% C.I
Age (yr)	56.9±10.3	55.9±10.3	60.8±9.8	0.015*	8.82-0.87
Length of stay (days)	16.1±29.3	17.6±32.2	9.6±7.3	0.001*	3.28-19.44
Blood routine					
Hemoglobin, $x10^9$/L	13.0±2.3	13.1± 2.2	12.6±2.8	0.498	0.38-1.43
White blood cells, $x10^9$/L	11.1±6.2	10.0±5.6	15.6±6.7	0.001*	7.85-3.29
Platelets, $x10^9$/L	270.0±128.8	278.9±131.5	233.3±111.8	0.152	4.13-95.52
Neutrophils, x 10^9/L	75.5±14.5	74.0±13.6	81.9±16.7	0.001*	13.46-2.35
Lymphocytes, $x10^9$/L	15.4±10.8	17.1±11.0	8.8±6.6	0.001*	4.20-12.27
Blood Glucose					
HbA1c (%)	9.4±2.4	9.5±2.4	9.2±2.3	0.385	0.54-1.33
FPG (mg/dl)	241.6±122.2	240.4±125.1	246.5± 111.3	0.458	53.76-41.71
PPG (mg/dl)	286.0±123.9	290.8±126.4	266.1± 112.5	0.413	23.46-73.03
Lipid Profile					
TC (mg/dl)	166.3±45.4	165.9±45.9	167.9±43.8	0.643	19.74-15.75
TG (mg/dl)	164.6±100.4	162.8±102.2	172.2±93.5	0.581	48.55-29.81
HDL-C (mg/dl)	31.8±11.8	31.6±11.5	32.4±13.1	0.928	5.36-3.85
LDL-C (mg/dl)	107.0±38.2	107.2±38.7	106.2± 36.7	0.993	13.90-15.93
C-Reactive Protein, mg/L	0.9. ±0.5	2.4±15.1	1.0±0.4	0.345	0.22-0.16
D-dimer (ng/ml)	1067.5±1254.5	895.4±1164.2	1771.8±1379.7	0.001*	1347.08-405.70
Arum (mg/dl)	53.0±49.0	47.2±44.3	76.7±60.1	0.001*	0.22-0.16
Creatinin (mg/dl)	1.6±2.0	1.5±1.6	2.2±3.0	0.008*	1.47-0.09
LDH mU/ml	362.5±202.3	336.6±184.2	468.4±239.2	0.004*	208.10-55.43

Note:
- HbA1c: Hemoglobin A1c; FPG: Fasting Plasma Glucose; PPG: Postprandial Plasma Glucose; TC: Total Cholesterol; LDL-C: Low Density Lipoprotein Cholesterol; HDL-C: High Density Lipoprotein Cholesterol; TG: Triglyceride; LDH: Lactate dehydrogenase;
- p: Discharged VS Death; ***:** $p < 0.05$

Based on Table 3, the predicted death of patients diabetic with COVID-19 was D-dimer (OR: 4.069; p=0.008*;95% C.I: 1.43-11.55) and dexamethasone use (OR:4.769; p=0.007*; C.I: 1.54-14.71).

Table 3 Multivariate Logistic Regression Analysis of Death Patients Diabetic with COVID-19

Variable	OR	p-value	95% C.I
Comorbid			
AKI	0.089	2.068	0.89-4.78
CAD	1.155	0.736	0.49-2.67
Hypertension	1.211	0.673	0.49-2.94
Dyslipidemia	0.821	0.672	0.33-2.04
Diabetes			
HbA1c	0.610	0.369	0.283-1.58
FPG	2.016	0.508	0.208-1.79
PPG	0.610	0.369	0.208-1.79
Hypoglycemia	0.991	0.991	0.28-3.44
D-Dimer	4.069	0.008*	1.43-11.55
Dexamethason Use	4.769	0.007*	1.54-14.71
LDH	0.961	0.939	0.34-2.68

Note:
- AKI: Acute Kidney Injuri; CAD: Coronary Artery Disease; HbA1c: Hemoglobin A1c; FPG: Fasting Plasma Glucose; PPG: Postprandial Plasma Glucose; TC: Total Cholesterol; LDL-C: Low Density Lipoprotein Cholesterol; HDL-C: High Density Lipoprotein Cholesterol; TG: Triglyceride; LDH: Lactate dehydrogenase. p^a-value: discharged vs died
- ***:** $p < 0.05$

4 Discussion

Stress hyperglycemia, a disease marked by hyperglycemia, insulin resistance, and glucose intolerance, can be brought on by the body's protection mechanisms during an acute sickness.[12] Hospitalized patients may endure additional stress on their bodies due to intubation and other therapies like glucocorticoids, on top of the severe illness they already have from COVID-19. In patients receiving treatment in intensive care units, stress hyperglycemia is frequently observed. [13] According to numerous studies, patients with admission hyperglycemia and no known diabetes fared worse than patients with previously diagnosed diabetes and patients with normoglycemia in terms of the severity of their illnesses and fatality rates.[14,15] It has been documented in various acute care scenarios, such as heart failure, that admission of hyperglycemia without diabetes and its effects on mortality.[15] A nationwide analysis conducted on 1,590 laboratory-confirmed patients in China had a mean age of 49 years, with 399 (25.1%) patients having at least one comorbid disease.[16] In the investigation, the most common comorbidities in patients with DM on Covid-19 were hypertension (51,8%), CAD (28.7%), dyslipidemia (36.0%), and AKI (35.4 percent). To understand the possible causal association between chronic untreated hyperglycemia and higher death rates in COVID-19 patients, certain biological pathways have been suggested. The primary cause of mortality in COVID-19 patients with diabetes is an inadequate immune response to viral infections.[17] The increased blood sugar level is expected to substantially affect the intracellular degradation of bacteria, neutrophil chemotaxis, and phagocytosis, thus improving viral binding affinity and entry and

decreasing virus clearance.[18] In addition, it has significant effects on the proteins by inducing glycosylation and altering the composition of complements,[19] and glycosylation renders cells susceptible to viral inflammation and damage.[20] In addition, endothelium may be a potential pathway that triggers organ dysfunction that causes essential COVID-19 disease, aggravated by endothelial dysfunction coupled with chronic hyperglycemia.[21] In this study, white blood cells, neutrophils, and lymphocytes were significant differences between discharge from the hospital and death of diabetic with COVID-19 patients (all, p= < 0.05).

The main fibrin breakdown product, D-dimer is a biomarker for both fibrin synthesis and degradation.[22] D-dimer is a useful marker of activation of coagulation and fibrinolysis, according to numerous studies. D-dimer levels are typically low in healthy people, however, they are increased in disorders linked to thrombosis.[23] To diagnose, monitor, and treat venous thromboembolism (VTE), for which it is frequently employed, D-dimer has undergone substantial research.[24] In chronic inflammatory disorders such as active cancer, rheumatoid arthritis, sickle cell disease, and asthma, D-dimer levels are also increased.[25] D-dimer levels are greater in COVID-19 participants who are seriously ill or who died.[26,27] However, the incidence of outcomes across different D-dimer levels both at clinical presentation and during hospitalization are not well characterized. In addition, the trajectory of D-dimer in subjects with COVID-19 remains unexplored. Given that widespread microthrombi have been observed in COVID-19 in multiple organ systems.[28] In this study, the multivariable-adjusted odds ratio showed significantly higher odds of death in patients with elevated D-dimer than in those without (OR: 4.069; p=0.008*; 95% C.I: 1.43-11.55).

Corticosteroids and COVID-19 show severe negative effects on diabetics. They can be found in numerous medications that are used for both short-term and long-term treatments. They are mostly utilized for their anti-inflammatory and immunosuppressive properties, which might have unfavorable side effects including osteoporosis, hypertension, hyperglycemia, and steroid-induced diabetes.[29] The risk of getting steroid-induced diabetes increases with the dose of steroid medication. Steroid use in diabetic people raises their risk of being admitted to the hospital for uncontrolled blood sugar.[30] Following the warning, numerous institutions began observational studies and randomized controlled trials (RCT) on steroid therapy for COVID-19. The largest study, known as The RECOVERY trial was conducted in the UK and demonstrated that dexamethasone, compared to standard care, decreased 28-day mortality in patients needing steroid therapy or mechanical ventilation.[*31]* Mortality increased in association with the level of D-dimer. The association between elevated D-dimer and mortality was consistent across multiple subgroups, including age, sex, body mass index, hypertension, atrial fibrillation, and kidney disease. Individuals with a presenting D-dimer >2000 ng/mL had the highest risk of all-cause mortality (48.3%). D-dimer trajectory by all-cause mortality is presented [32]. In this study, the multivariable-adjusted odds ratio

showed significantly higher odds of death in patients with dexamethasone use than in those without (OR: 4.769; p=0.007*; 95% C.I: 1.54-14.71).

This study has several limitations, it is an observational retrospective cohort study conducted during an outbreak, so there may be residual or unmeasured confounding factors, most patients did not have an HbA1c measurement only fasting blood sugar and postprandial blood sugar, the registry is missing data on some relevant inflammatory variables such as D-dimer and serum ferritin and time from hospital admission to ICU admission was not available.

5 Conclusion

Diabetes is one of the most common comorbidities linked to COVID-19, and there is consistent evidence that diabetes increases the risk of severe COVID-19 disease, including admission to the intensive care unit and death. Elevation of blood glucose level predicted worse outcomes in hospitalized patients diabetic with COVID-19. The use of dexamethasone and the increase in D-dimer values increase mortality predictions in treating diabetic patients with COVID-19 in hospitals. To prevent these harms, the management of inpatients diabetic with COVID-19 must be with good glucose consideration and monitoring.

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