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Effect of Glycemic Parameters on Mortality of Type 2 Diabetes Mellitus Patients with COVID-19 Infection in Haji Adam Malik Hospital Medan

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ABSTRACT

Introduction: Diabetes Mellitus Type 2 (DM T2) is a major health problem, especially in people in developing countries. DM T2 is the most frequently reported comorbid disease in patients with COVID-19. The relationship between DM T2 and poorer outcome in COVID-19 infection is thought to be because hyperglycemia and chronic inflammation impair control of viremia and inflammation by weakening the immune response. This research aim to determine the effect of glycemic parameters on the mortality of DM T2 patients with COVID-19.
Method: This research is a descriptive analytic study with a retrospective design which was carried out at the H. Adam Malik General Hospital in Medan. The data obtained was analyzed statistically and said to be statistically significant if $p < 0.05$.
Results: Based on the results of the study, there were significant differences in the values of inflammatory markers such as leukocytes, neutrophils, NLR, PCT, LDH, D-dimer, ferritin, SGOT, urea and creatinine in the severity of COVID-19 patients and there were significant differences in the mean fasting blood sugar, blood sugar 2PP, in moderate, severe and critical COVID-19 patients.
Conclusion: Glycemic parameters in patients who died were worse than patients who recovered, although the statistical results were not significantly different.

Keywords

Glycemic parameters, Diabetes mellitus type 2, COVID-19

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INTRODUCTION

Diabetes Mellitus Type 2 (DM T2) is a major health problem for the World Health Organization (WHO), especially in people in developing countries. This happens because the prevalence of DM T2 is increasing and it is a health threat in the world because of its involvement in the development of several diseases, including stroke, kidney failure, and heart disease.[1] Based on the International Diabetes Federation (IDF) the prevalence of T2 DM with a vulnerable age of 20-79 years is 10.5% of the total population equivalent to 536.6 million people and is expected to increase to 12.2% of people in 2045.[2] Meanwhile, in Indonesia itself the prevalence DM T2 is 2.0-2.1% in the population aged> 15 years.[3]

DM T2 is the most frequently reported comorbid disease in patients with COVID-19. This may be because DM T2 causes conditions that are more susceptible to infection in general and shows a worse prognosis after infection compared to the non-T2 DM population.[4] In the study by Guan et al, among patients with confirmed COVID-19, 19,2 % of 1,099 patients had comorbid DM T2.[5]

The relationship between DM T2 and worse outcomes in COVID-19 infection is suspected because hyperglycemia and chronic inflammation impair control of viremia and inflammation by weakening the immune response, namely T cells, thereby increasing the risk of excessive inflammatory responses and

cytokine storms, which in turn will exacerbate morbidity and mortality in patients with DM T2.[6] Patients with higher blood glucose values have a higher risk of ICU admission using mechanical ventilation.[7] Although many studies have shown that T2DM is an important risk factor for the severity of COVID-19, it is unclear whether effect of severity of COVID-19 infection on glycemic parameters, including blood glucose and glycated hemoglobin A1c (HbA1c). Because of this, DM T2 has become a major focus during the current COVID-19 pandemic.[6,8]

Research on this condition is very important, because of the high morbidity and mortality rates in DM T2 patients with COVID-19. This research has never been conducted at the H. Adam Malik General Hospital in Medan, so based on this background, the researchers wanted to see the effect of glycemic parameters on the mortality of DM T2 patients and COVID-19 patients at the H. Adam Malik Hospital in Medan.

METHOD

This research is a descriptive analytic study with a retrospective design to determine the effect of glycemic parameters on the mortality of T2 DM patients with COVID-19 infection at the Adam Malik Haji Center General Hospital in Medan and will be carried out from December 2021 to January 2022.

The research sample was obtained using the total sampling method, namely all DM T2 patients who were hospitalized with confirmed COVID-19 who were hospitalized at Haji Adam Malik General Hospital Medan from March 2020 to December 2021 who met the inclusion and exclusion criteria. The inclusion criteria included all inpatients with DM T2 who were confirmed to have COVID-19, via RT-PCR SARS-CoV-2 swab examination, at Haji Adam Malik Hospital in Medan, moderate, severe and critical COVID-19 patients, and aged $\geqslant$ 18 year. Exclusion criteria were patients diagnosed with anemia (Hb $\geqslant$ 10) and patients with incomplete medical record data.

A search of medical record data was carried out to obtain demographic data consisting of patient's age, sex, body mass index and comorbid diseases. In addition, data related to comorbid diseases of DM T2 were also taken, namely a history of suffering from DM T2, newly diagnosed DM T2, and DM T2 therapy. Data on the degree of COVID-19 and steroid therapy in patients and length of stay included in the patient's outcome data were taken through medical record data. Medical records were also searched regarding laboratory data, namely glycemic parameters (KGDp, KGD 2PP, HbA1c), leukocytes, neutrophil-lymphocyte ratio, CRP, d-dimer, procalcitonin and ferritin.

The data obtained was processed using a computer device in the form of a statistical application, namely SPSS version 25. The normality test was carried out by the Kolmogorov Smirnov test. Differences between the two groups were analyzed using the independent T test if the data distribution was normal and using the Mann Whitney analysis test if the data distribution was not normal. Differences between the three groups were analyzed using the One Way Anova test if the data distribution was normal and using the Kruskal Wallis analysis test if the data distribution was not normal. The data is said to be statistically significant when $p<0.05$.

RESULT

Demographic characteristics of the 316 study subjects, consisting of 111 patients with moderate degree of COVID-19 where 60 (54.1%) were male and 51 (45.9%) female, 158 patients with severe degree of COVID-19 consisting of 98 (62%) male and 60 (38%) female and 47 critical degree COVID-19 patients with 32 (68.1%) male and 15 (31.9%) female. Patients with moderate and severe COVID-19 predominately had normal BMI (47.7%), while in critical COVID-19 patients more patients had excess body weight (46.8%). There was no statistically significant relationship between gender ($p=0.204$; $P>0.05$), comorbid CAD ($p=0.327$; $P>0.05$), comorbid HT ($p=0.353$; $P>0.05$) and number of comorbidities ($p=0.723$ $p>0.05$), length of stay ($p=0.056$; $p>0.05$), with degree of COVID-19. However, a statistically significant association was found between comorbid CKD ($p = 0.041$; $p <0.05$) and age $p = 0.02$ ($p <0.05$) and the degree of COVID-19 (Table 1).

Table 1. Demographic and Laboratory Characteristics of DM T2 Patients with COVID-19

Patient's Characteristics	Severity Degree of COVID-19			P value*
	Moderate (n=111)	Severe(n =158)	Critical (n=47)	
Sex				0,204
- Male	60 (54,1%)	98 (62 %)	32 (68,1%)	
- Female	51 (45,9%)	60 (38 %)	15 (31,9%)	
Type of Comorbid				
- CAD	25 (22,5%)	45 (28,5%)	9 (19,1%)	0,327
- CKD	2 (1,8 %)	3 (1,9 %)	9 (8,5%)	0,041
- Hypertension	56 (50,5%)	86 (54,4%)	20 (42,6%)	0,353
Number of Comorbid				0,723
- 0-1	86 (77,5%)	117 (74,1%)	37 (78,7%)	
- >1	38 (22,5%)	47 (25,9%)	12 (21,3%)	
Blood Pressure				
- Systolic	130 (100-160) [b]	140 (100-170) [b]	130 (100-160) [b]	0,215
- Diastolic	80 (60-100) [b]	80 (60-100) [b]	80 (60-100) [b]	0,077
BMI				0,679
- Obese	6 (5,4 %)	10 (6,3%)	2 (4,3%)	
- Overweight	49 (44,1%)	58 (36,7%)	22 (46,8%)	
- Normal	53 (47,7%)	87 (55,1%)	21 (44,7%)	
- Underweight	3 (2,7%)	3 (1,9%)	3 (2,5%)	
Age (years)	56 (25-82) [b]	57 (26-90) [b]	60 (31-89) [b]	0,02
Treatment (days)	8 (1-45) [b]	9 (1-45) [b]	6 (1-32) [b]	0,056

[a]One Way Anova; [b]Kruskal Wallis

Based on the laboratory results of DM T2 patients with COVID-19, significant differences were found in the average leukocytes, neutrophils, lymphocytes, NLR, PCT, D-dimer, SGOT, LDH and ferritin based on the severity of COVID-19. The average D-dimer value in hospitalized patients who were confirmed to have moderate degrees of COVID-19 was 350 (80-4,000), severe cases of COVID-19 707 (80-4,000), and critical degrees of COVID-19 750 (116-4,000). From the Kruskal Wallis test, there was a significant difference in the mean D-Dimer in moderate and severe and moderate and critical COVID-19 patients ($p < 0.05$) (Table 2).

Outcomes in patients with severe degree of COVID-19 63.3% of patients recovered and 36.7% of patients died, while in patients with critical degree of COVID-19 patients who died with a percentage of 66% (Table 3). Meanwhile, there were no significant differences in fasting blood sugar, blood sugar 2PP, and HbA1C in patients with a history of T2DM and without a history of T2DM (Table 4).

A significant difference was found in the mean fasting blood sugar and blood sugar 2PP in DM T2 patients with moderate, severe and critical degrees of COVID-19. There were no significant differences in HbA1C in DM T2 patients with moderate, severe and critical COVID-19 degrees (Table 5).

A significant difference was found in the mean fasting blood sugar and blood sugar 2PP in DM T2 patients with moderate and severe degrees of COVID-19. There were no significant differences in the mean fasting blood sugar, blood sugar 2PP and HbA1C in DM T2 patients with moderate-critical and severe-critical COVID-19 (Table 6). Meanwhile, there were no significant differences in fasting blood sugar, blood sugar 2PP, and HbA1C in the group of DM T2 patients with COVID-19 infection who recovered and who died (Table 7).

Table 2. Characteristics of Laboratory Results of DM T2 Patients with COVID-19

	Severity Degree of COVID-19			
Laboratorium Parameters	Moderate (n=111)	Severe (n=158)	Critical (n=47)	P value*
Hemoglobin, g/dL	13,1 ± 1,77 [a]	13,21± 1,73 [a]	13,33± 2,03 [a]	0,750
Leukocyte, 10^3/µL	8,48 (2,77-27,06) [b]	12 (2,67-46,83) [b]	11,48 (3,36-34,3) [b]	0,00
Trombocyte, 10^3/µL	271(76-675) [b]	262 (18-784) [b]	242 (112-595) [b]	0,50
Neutrofil, %	69,7(25,9-95,4) [b]	83,8 (41,3-97,7) [b]	87,3(6,8-96,3) [b]	0,00
Limfosit, %	18,6 (25,9-95,4) [b]	9.75 (0.54-58) [b]	7.3 (0.60-31.80) [b]	0,00
NLR	3.99 (0,43-54.65) [b]	8.56(0.9-134.81) [b]	12.08 (0,88-160,5) [b]	0,00
Total Cholesterol, mg/L	157 ± 49 [a]	154 + 49 [a]	146 ± 54 [a]	0,471
Triglyceride, mg/L	106 (23-614) [b]	120 (25-660) [b]	108 (35-430) [b]	0,363
HDL, mg/L	32 (10-60) [b]	30.5 (7-140) [b]	30 (14-67) [b]	0,172
LDL, mg/L	104 ± 41[a]	101 ± 42 [a]	94,7± 48 [a]	0,469
PCT, ng/mL	0.06 (0.01-17.97) [b]	0.15 (0.01-73.73) [b]	0.16 (0.01-9.28) [b]	0,00
CRP, mg/L	0,70 (0.07-1,61) [b]	0.70 (0.07-3.40) [b]	0.70 (0.3-2,8) [b]	0,365
LDH, µ/L	257 (0,7-1.047) [b]	328 (100-3.000) [b]	430 (130-913) [b]	0,00
D-dimer, ng/mL	350 (80-4.000) [b]	707 (80-4.000) [b]	750 (116-4.000) [b]	0,00
Ferritin, ng/mL	500(51.32-2000) [b]	664 (12.57-2.000) [b]	760 (100-2.000) [b]	0,006
SGOT, µ/L	23(10-497) [b]	27(3-339) [b]	24(11-725) [b]	0,025
SGPT, µ/L	23(6-188) [b]	25(8-191) [b]	25(10-159) [b]	0,325
Ureum, mg/dL	26 (6-373) [b]	36 (9-26,8) [b]	38(19-268) [b]	0,00
Kreatinin , mg/dL	0,87(0,02-8,24) [b]	1,06(0,31-10,18) [b]	1,02(0,4-26) [b]	0,003
KGDP, mg/dL	176(27-568) [b]	208(65-651) [b]	190(86-682) [b]	0,007
KGD 2PP, mg/dL	233(40-552) [b]	260(56-800) [b]	258 (100-800) [b]	0,028
HbA1C,%	9(5-16,6) [b]	9(5-16) [b]	8,3(5,1-14,5) [b]	0,220

[a]One Way Anova; [b]Kruskal Wallis

Table 3. Outcome Description of DM T2 Patients based on the Degree of Severity of COVID-19 Infection

Outcome	Severity Degree of COVID-19			P value
	Moderate	Severe	Critical	0,00
- Recover	105 (94,6%)	100 (63,3%)	16 (34%)	
- Died	6 (5,4%)	58 (36,7%)	31 (66%)	

*Kruskal- Wallis

Table 4. Differences in the description of glycemic parameters in patients with newly diagnosed DM T2 and previously diagnosed DM T2 patients

Parameter	Previously Diagnosed DM T2 Patients	Newly Diagnosed DM T2 Patients	P value
Fasting blood sugar, mg/dL	196 (27-682)	261(127-651)	0.118
Blood sugar 2PP, mg/dL	250 (40-800)	305(194-552)	0.112
HbA1C, %	8,95 (5-16,6)	9,45(7-12,2)	0.664

*Mann-Whitney

Table 5. A significant difference was found in the average fasting blood sugar and blood sugar 2PP. Overview of Glycemic Parameters of DM T2 Patients with COVID-19 Based on the Severity of COVID-19

Glycemic Parameter	Severity Degree of COVID-19			P value
	Moderate	Severe	Critical	
Fasting blood sugar, mg/dL	176(27-568)[#]	208(65-651)	190(86-682)	0,007
Blood sugar 2PP, mg/dL	233(40-552)[#]	260(56-800)	258 (100-800)	0,028
HbA1C,%	9(5-16,6)	9(5-16)	8,3(5,1-14,5)	0,220

*Kruskal- Wallis; [#] significant difference with severe degree

Table 6. Comparison of fasting blood sugar, blood sugar 2PP and HbA1C in the moderate-severe, severe-critical and moderate-critical COVID-19 groups

Glycemic Parameter	P value*		
	Moderate-Severe	Severe-Critical	Moderate-Critical
Fasting blood sugar, mg/dL	0,001	0,154	0,648
Blood Sugar 2PP, mg/dL	0,008	0,119	0,946

* *Mann-Whitney U*

Table 7. Overview of glycemic parameters in DM T2 patients with COVID-19 infection who recovered and who died

Parameter	Recovered	Died	P value
Fasting blood sugar, mg/dL	190 (65-682)	200 (27-651)	0.169
Blood sugar 2PP, mg/dL	234 (56-741)	252 (40-800)	0.552
HbA1C, %	8 (5,10-15,50)	9,2 (5-16,6)	0.066

**Mann-Whitney U*

DISCUSSION

DM T2 is one of the main comorbidities that significantly contributed to adverse outcomes during the COVID-19 pandemic caused by Severe Acute Respiratory Syndrome - Coronavirus 2 (SARS-CoV-2).[9] DM T2, hypertension, and cardiovascular disease are comorbidities very commonly associated with COVID-19. Data from COVID-19 patients has shown that COVID-19 is associated with high blood glucose levels, especially in people with type 2 DM (DM T2). SARS-CoV combines with ACE2 in pancreatic islet cells and causes cell destruction, which increases blood glucose. This also contributes to an increase in mortality in patients with/without DM.[10]

In the present study, both the T2DM and new-onset hyperglycemia groups showed higher levels of inflammatory markers, namely white blood cell (WBC) count, C-reactive protein (CRP), D-dimer, and interleukin-6, except for plasma fibrinogen concentrations. The mean difference in D-Dimer was found to be significant in moderate and severe and moderate and critical COVID-19 patients ($p < 0.05$). Previous studies have shown that there is an increased incidence of venous thromboembolism (VTE) in patients hospitalized for COVID-19 pneumonia ($p = 0.004$). In the ROC analysis, the peak D-dimer level >2000 ng/mL (AUC 0.703; 95% CI 0.572–0.834; $p = 0.004$) is the most accurate threshold value capable of predicting DVT (RR 3.74; 95%CI 1.27- 10, $p = 0.016$).[11]

Patients with a history of DM had three times higher mortality (6/67, 9%) than patients without DM (10/309, 3,1%). A similar pattern was observed from Wuhan where mortality (20.2% vs 8.0%, $P = 0.001$) in the DM T2 group was significantly higher than in the non-DM T2 group.[12] Severe COVID-19 infection and hyperinflammation occurred , contributes to hyperglycemia through indirect negative effects on insulin target tissues and potential direct negative effects on pancreatic β-cells. Maintaining good glycemic control during the COVID-19 pandemic is very important for T2DM patients.[13]

The glycemic parameters were worse in the mean fasting blood sugar, blood sugar 2PP and HbA1C in the newly diagnosed DM T2 patient group but no significant difference was found after statistical analysis was carried out. In a study by Ghosh et al, 2021 it was found that new onset DM T2 during COVID-19 (NOD)

had worse glycemic parameters and higher C-peptide levels compared to NOD; however, there were no differences in other clinical, anthropometric, behavioral, or biochemical parameters.[10]

A significant difference was found in the mean fasting blood sugar, blood sugar 2PP in DM T2 patients with moderate, severe and critical COVID-19 degrees. This is in line with a study conducted by Kumar et al., random plasma glucose values increased progressively from asymptomatic patients to patients with severe COVID-19 disease (asymptomatic 124 ± 70 (114–134), mild 105 ± 29 (100–111) , moderate 169 ± 85 (141–196), and severe disease 255 ± 110 (221–289) mg/dL; $P < 0.0001$ according to MoHFW severity criteria.[12] Hyperglycemia on day 1 has been shown to be the best predictor of SARS -CoV2, regardless of past medical history of DM T2. In this study there was no significant difference in HbA1C in DM T2 patients with moderate, severe and critical degrees of COVID-19. This is in line with research that was previously conducted on 75 DM T2 patients with COVID-19, which also showed statistically insignificant results.[14]

This study is in line with research conducted by Patel et al., there was no significant relationship between hba1c and mortality in these patients with a p value of 0.08. So this study shows that long-term glycemia as measured by HbA1C cannot be an indicator in determining outcome in COVID-19 patients who are hospitalized. This is because long-term management of glycemia may not have a direct effect on death in COVID-19, optimal management during hospitalization has a direct effect on reducing mortality rates.[15]

This research is a comprehensive study and has a large sample size so that it can be used as basic data for further research. This study also has the drawback that this research is a retrospective study and is influenced by many confounding factors.

CONCLUSION

Based on the results of the study it can be concluded that there are significant differences in the values of inflammatory markers such as leukocytes, neutrophils, NLR, PCT, LDH, D-dimer, ferritin, SGOT, urea and creatinine on the severity of COVID-19 patients. In this study, significant differences were found in the mean fasting blood sugar, blood sugar 2PP, in moderate, severe and critical COVID-19 patients. Glycemic parameters in patients who died were worse than patients who recovered, although the statistical results were not significantly different.

DECLARATIONS

Ethics approval and consent to participate. Permission for this study was obtained from the Ethics Committee of Universitas Sumatera Utara and Haji Adam Malik General Hospital.

CONSENT FOR PUBLICATION

The Authors agree to publication in Journal of Society Medicine.

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COMPETING INTERESTS

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTIONS

All authors significantly contribute to the work reported, whether in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas. Contribute to drafting, revising, or critically reviewing the article. Approved the final version to be published, agreed on the journal to be submitted, and agreed to be accountable for all aspects of the work.

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