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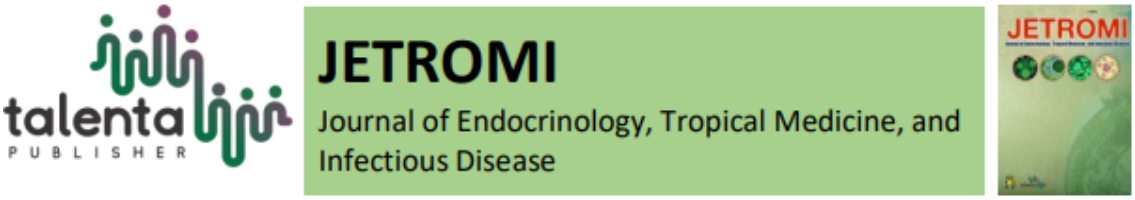

D-Dimer Levels of COVID-19 Patients with Diabetes Mellitus: a Retrospective Study

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ABSTRACT

Background: Diabetes is the commonest comorbidity in Coronavirus disease 2019 (COVID-19) patients, and D-dimer level assessment has reliable parameters for assessing and evaluating the prognosis of COVID-19 patients with comorbid. This study aims to compare D-dimer, FPG, and PPG levels between COVID-19 patients with comorbid.

Method: We conducted a retrospective descriptive and analytical study carried out at D-dimer, FPG, and PPG levels of COVID-19 patients with comorbid in a tertiary Hospital in Medan, Indonesia, from April 04, 2020, to November 22, 2020. The data were collected by cheek list, using electronic medical records. The data included age, gender, medical history, comorbidity disease inward, and ICU admission. All these cases of COVID-19 have been confirmed in the laboratory by Real-Time Reverse Transcription Polymerase Chain Reaction (RT-PCR).

Result: From 323 COVID-19 patients with comorbidities, there are significant differences in D-dimer, FPG, and PPG levels between all groups of COVID-19 patients with the comorbid disease ($p<0.05$), and there is a significant difference in D-dimer, FPG, and PPG level between severity of COVID-19 with comorbidities ($p<0.005$).

Conclusion: There is a significant difference between D-dimer, FPG, and PPG levels in COVID-19 patients with comorbidities in comorbid type and severity of COVID-19.

Keywords: COVID-19, Comorbid, Diabetes Mellitus, Severity

ABSTRAK

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***Latar Belakang**: Diabetes adalah komorbiditas paling umum pada pasien penyakit Coronavirus 2019 (COVID-19), dan penilaian tingkat D-dimer memiliki parameter yang dapat diandalkan untuk menilai dan mengevaluasi prognosis pasien COVID-19 dengan komorbid. Penelitian ini bertujuan untuk membandingkan kadar D-dimer, FPG, dan PPG antara pasien COVID-19 dengan komorbid.*

***Metode**: Kami melakukan studi deskriptif dan analitik retrospektif yang dilakukan pada tingkat D-dimer, FPG, dan PPG pasien COVID-19 dengan komorbid di Rumah Sakit tersier Medan, Indonesia, dari 04 April 2020 hingga 22 November 2020. Data dikumpulkan dengan cheek list, menggunakan rekam medis elektronik. Data tersebut termasuk usia, jenis kelamin, riwayat medis, penyakit komorbiditas, dan dirawat di ICU. Semua kasus COVID-19 ini telah dikonfirmasi di laboratorium dengan Real-Time Reverse Transcription Polymerase Chain Reaction (RT-PCR).*

***Hasil**: Dari 323 pasien COVID-19 dengan komorbid, terdapat perbedaan kadar D-dimer, FPG, dan PPG yang signifikan antara semua kelompok pasien COVID-19 dengan penyakit komorbid ($p<0,05$), dan terdapat perbedaan yang signifikan kadar D-dimer, FPG, dan PPG antara tingkat keparahan COVID-19 dengan komorbid ($p<0,005$).*

***Kesimpulan**: Terdapat perbedaan yang signifikan antara kadar D-dimer, FPG, dan PPG pada pasien COVID-19 dengan komorbid pada jenis komorbid dan tingkat keparahan COVID-19.*

***Kata Kunci**: COVID-19, Komorbid, Diabetes Melitus, Tingkat Keparahan*

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1 Introduction

Diabetes mellitus (DM) has been one of the most consistent risk factors for severe disease in patients with COVID-19 and uncontrolled hyperglycemia has been associated with poor outcomes and mortality. This could be due to diabetes being associated with other risk factors like age, hypertension, and obesity. This could be also due to people with diabetes having a dysregulated innate and adaptive immune response and they're already having chronic low-grade inflammation which makes them more susceptible to cytokine storm. People with diabetes could also be at higher risk for thrombotic events as diabetes is associated with an imbalance between clotting factors and fibrinolysis, which may be responsible for a higher risk of thrombotic events, which can lead to death. So far, studies have shown that DM has been one of the serious comorbidities in COVID-19 patients.[1]

D-dimer is a by-product of fibrin degradation. It is widely recognized as a biomarker for thromboembolism and as a prognostic marker for critical patients. COVID-19 is a procoagulant state thus D-dimer has been studied as a biomarker for predicting disease severity. Studies have shown people with diabetes especially as well as those with macrovascular and microvascular

complications have higher levels of D-dimer. Since diabetes has been identified as a strong predictor of disease severity in COVID-19.[2]

Evidence is showing that hyperglycemia can influence the prognosis of COVID-19.[3] Interestingly, in people with hyperglycemia and COVID-19 increased D-dimer levels have been found. Moreover, it has been shown that reducing hyperglycemia is followed by a decrease in the D-dimer level.[4] Thrombosis affects the prognosis of people with COVID-19,[5] Therefore, clarifying the possible link between hyperglycemia and thrombosis might be very useful for better management of COVID-19 with comorbid, especially DM.

This study aims to compare D-dimer, FPG, and PPG levels between COVID-19 patients with comorbid to its comorbid type and severity.

2 Methods

2.1 Study Population

This is a retrospective descriptive and analytical study carried out at D-dimer, FPG, and PPG levels of COVID-19 patients with comorbid in a tertiary Hospital in Medan, Indonesia, from April 04, 2020, to November 22, 2020. The data were collected by cheek list, using electronic medical records. The data included age, gender, medical history, comorbidity with diabetics, and ward and ICU admission. D-dimer, FPG, and PPG level. All these cases of COVID-19 have been confirmed in the laboratory by Real-Time Reverse Transcription Polymerase Chain Reaction (RT-PCR). Exclusion criteria were age <18 years, patients who were on anticoagulants or had a history of venous thromboembolism and pregnancy, and only patients who received a D-dimer assay were included in this study. 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. COVID-19 severity disease divided by 4: 1). Mild; 2). Moderate; 3). Severe; and 4). Critical,[5] and Guidelines for The Prevention and Control of Coronavirus Disease (COVID-19) of The Indonesian Ministry of Health.[6] Examination of D-dimer values with ELFA (Enzyme-Linked Fluorescent Assay)

2.2 Statistical Analysis

The data were entered and analyzed into SPSS software by first performing a descriptive analysis of the various data; Quantitative variables were described by means, and counts and percentages described qualitative variables. We used the Kruskal-Wallis test to compare more than two quantitative variables in an abnormal distribution, and the Mann-Whitney Test is used to test the significance of the difference between the two variables. The difference is considered to be statistically significant when $p < 0.05$. The Institutional Ethics Committee gave its approval to this report.

3 Result

In this study, there were 323 COVID-19 cases, and based on the medical records, cases were classified into 4 groups: G1: COVID-19 group; G2: COVID-19 with DM group; G3: COVID-19 with all comorbid group; G4: COVID-19 with comorbid non-DM, and the highest severity of COVID-19 was mild 130 (40.2%) and moderate 115 (35.6%) cases (table 1).

Table 1 Baseline data of COVID-19 patients

Variable	n=323 (%)
Sex	
Woman	133 (4.4)
Male	188 (58.6)
Comorbid	
Non-DM	138 (42.7)
DM	32 (9.9)
DM+ other comorbid	59 (18.3)
Non-DM	94 (29.1)
COVID-19 Severity:	
Mild	130 (40.2)
Moderate	115 (35.6)
Severe	75 (23.2)
Critical	3 (0.9)
Cases	
G1	138 (42.7)
G2.	32 (9.9)
G3.	59 (18.3)
G4.	94 (29.1)

Note: G1: COVID-19 group; G2: COVID-19 with DM group; G3: COVID-19 with all comormid group; G4: COVID-19 with comormid non DM group

Based on Table 2, there are significant differences in D-dimer, FPG, and PPG between all the groups of COVID-19 with comorbid ($p < 0.05$).

Table 2 Comparison of D-dimer, FPG, and PPG between Groups of Covid-19 with Comorbidities.

Variable	**Group 1 (n=138) Mean Rank**	**Group 2 (n=32) Mean Rank**	**Group 3 (n=59) Mean Rank**	**Group 4 (n=95) Mean Rank**	**p**
D-dimer mg/L	169.06	165.77	136.59	166.30	0.001*
FPG mg/dL	115.84	231.69	259.77	144.68	0.001*
PPG mg/dL	116.47	247.28	261.80	137.18	0.001*

Note: - Kruskal-Wallis Test
- G1: COVID-19 group; G2: COVID-19 with DM group; G3: COVID-19 with all comormid group; G4: COVID-19 with comormid non DM group; FPG: fasting plasma glucose: PPG: postprandial plasma glucose
- *: $p < 0.05$

Based on Table 3, there is a significant difference in D-dimer, FPG, and PPG between subgroups of COVID-19 with comorbidities ($p<0.05$).

Table 3 Comparison of D-dimer, FPG, and PPG between Subgroups of Covid-19 with Comorbidities

Variable	Group	Mean Rank	p
D-dimer (ng/mL)	G1 vs G2	85.82 vs 84.11	0.859
	G1 vs G3	88.42 vs 123.75	0.001*
	G1 vs G4	122.53 vs 107.65	0.001*
	G2 vs G3	38.20 vs 50.23	0.038*
	G2 vs G4	65.69 vs 62.76	0.695
	G3 vs G4	96.47 vs 64.78	0.001*
FPG (mg/dl)	G1 vs G2	75.74 vs 127.59	0.001*
	G1 vs G3	72.84 vs 160.18	0.001*
	G1 vs G4	106.26 vs 131.54	0.001*
	G2 vs G3	48.02 vs 44.91	0.592
	G2 vs G4	89.08 vs 54.79	0.001*
	G3 vs G4	114.69 vs 53.35	0.001*
PPG (mg/dl)	G1 vs G2	73.33 vs 138.00	0.001*
	G1 vs G3	72.79 vs 160.31	0.001*
	G1 vs G4	109.35 vs 126.99	0.001*
	G2 vs G3	45.92 vs 46.04	0.983
	G2 vs G4	89.08 vs 54.79	0.001*
	G3 vs G4	115.45 vs 52.87	0.001*

Note: - Mann-Whitney Test
- G1: COVID-19 group; G2: COVID-19 with DM group; G3: COVID-19 with all comormid group; G4: COVID-19 with comormid non DM group
- *: $p < 0.05$

Based on Table 4, there is a significant difference in D-dimer, FPG, and PPG between subgroups severity of COVID-19 with comorbidities ($p<0.05$).

Table 4 Comparison of D-dimer, FPG, and PPG between groups of Covid-19 severity

Variable	Mild (n=130) Mean Rank	Moderate (n=115) Mean Rank	Severe (n=75) Mean Rank	Critical (n=3) Mean Rank	p
D-dimer	145.63	163.61	187.15	180.67	0.022*
FPG	130.17	168.02	204.27	253.67	0.001*
PPG	131.94	163.24	208.68	249.83	0.001*

Note: - Kruskal-Wallis Test
- FPG: fasting plasma glucose:PPG: postprandial plasma glucose
- *: $p < 0.05$

Based on Table 5, there is a significant difference from D-dimer in the mild vs severe of COVID-19 ($p < 0.003$). FPG and PPG differ significantly in all severe COVID-19 groups ($p < 0.01$) except in the critical group ($p > 0.05$)

Table 5 Comparison of D-dimer, FPG, and PPG between Subgroups of Covid-19 severity

Variable	Group	Mean Rank	P
D-dimer (ng/mL)	Mild vs Moderate	116.35 vs 130.52	0.118
	Mild vs Severe	93.56 vs 119.37	0.003*
	Mild vs Critical	66.73 vs 78.67	0.620
	Moderate vs Severe	89.71 vs 104.38	0.072
	Moderate vs Critical	59.38 vs 64.00	0.838
	Severe vs Critical	39.40 vs 42.00	0.864
FPG (mg/dl)	Mild vs Moderate	109.80 vs 137.92	0.002*
	Mild vs Severe	85.65 vs 133.07	0.001*
	Mild vs Critical	65.72 vs 122.67	0.005*
	Moderate vs Severe	87.34 vs 108.01	0.011*
	Moderate vs Critical	58.77 vs 87.67	0.159
	Severe vs Critical	39.19 vs 47.33	0.570
PPG (mg/dl)	Mild vs Moderate	112.55 vs 134.81	0.014*
	Mild vs Severe	84.63 vs 134.83	0.001*
	Mild vs Critical	65.76 vs 120.83	0.007*
	Moderate vs Severe	85.63 vs 110.63	0.002*
	Moderate vs Critical	58.80 vs 86.33	0.181
	Severe vs Critical	39.21 vs 46.67	0.604

Note:- Mann-Whitney Test
- FPG: fasting plasma glucose: PPG: postprandial plasma glucose
- *: p , 0.05

4 Discussion

Hyperglycemia can cause a pro-thrombotic status,[7] according to two distinct pathways: the first path is oxidative stress, which improves thrombin production during acute hyperglycemia, and the second pathway is non-glycation. Furthermore, enzymatic reduces the function of antithrombin III and heparin co-factor II;[8] thus, persistent hyperglycemia may contribute to inflammation and endothelial dysfunction, leading to thrombus formation.

From Sixteen systematic reviews investigating the possible associations of comorbidities with severity or death from COVID-19 disease, hospitalization was associated with age > 60 years, smoking habit, and chronic pulmonary disease. Chronic pulmonary disease, cerebrovascular disease, and cardiovascular disease were likely to be associated with an increased risk of critical COVID-19. The highest risk of mortality was associated with cardiovascular disease, cerebrovascular disease, and chronic renal disease.[9 In the association between the D-dimer level and the severity of COVID-19, it was found that a higher D-dimer level was associated with higher disease severity (i.e. ICU patients).[2]

In COVID-19 patients with diabetes, poorly-controlled blood glucose (>11 mmol/L) may be associated with poor outcomes. Admission hyperglycemia, elevated d-dimer, and high HRCT score are potential risk factors for adverse outcomes and death.[10]

D-dimer levels were statistically higher in diabetic patients compared to non-diabetic patients. D-dimer level > 2885 ng/mL was a significant predictor of mortality in diabetic patients with a sensitivity of 71,4% and a specificity of 70,7%.[11] D-dimer value on admission is an accurate

biomarker for predicting mortality in patients with COVID-19 and 1.5 μg/ml is the optimal cutoff value of admission D-dimer for predicting mortality in COVID-19 patients, with good sensitivity and specificity. D-dimer can thus be an easy-to-perform and inexpensive laboratory indicator for COVID-19 prognosis.[12]

Overall, high D-dimer and DM are indicators of a poor prognosis. Still, the combination of the two will be worsening and aggravates the prognosis with progression to high-risk complications and death, which requires proper treatment and strict supervision. In addition, compared with non-diabetic patients, it is found that some inflammation-related biomarkers are elevated in diabetic patients, this can also be attributed to diabetic patients who already have baseline low-grade chronic inflammation and their innate and adaptive immune systems are deregulated, making them more vulnerable to the cytokine storm, responsible for the rapid deterioration and poor prognosis of COVID-19.[13]

In this study, the comparison of D-dimer, FPG, and PPG between groups and subgroups of COVID-19 patients with comorbidities differed significantly (all, $p<0,05$), while the comparison of D-dimer between (COVID-19) patients and (COVID-19) + DM patients (G1 vs G2) is not significant ($p>0.05$). FPG and PPG were different significantly in each group ($p<0.05$) except in (COVID-19) + DM compared (COVID-19) + all comorbid (G2 vs G3; $p>0.05$).

For the severity of COVID-19 disease, there is increased significant D-dimer, FPG, and PPG associated increased severity of COVID-19 disease ($p<0.05$), and In subgroups, D-dimer only increased significantly compared to others severity ($p<0.05$). Meanwhile, FPG and PPG increased significantly according to the increase in the severity of COVID-19 disease ($p<0.05$), except in the critical COVID-19 subgroup.

COVID-19 causes hyperglycemia in an individual with diabetes which may be related to insulin resistance and destruction of β-cells during SARS-CoV-2 infection.[14] Early observations also suggest a correlation between oral hypoglycemic agents and the risk of COVID-19. In conclusion, D-dimer, FPG, and PPG increased significantly concerning the increase in comorbid diseases especially DM in COVID-19. The increase in D-Dimer is highest at severe COVID-19 severity, while FPG and PPG increase significantly according to the increase in the severity of COVID-19 disease. D-dimer during hospital stay had the highest C-index to predict in-hospital mortality in COVID-19 patients. D-dimer value ≥ 2.01 mg/mL can effectively predict in-hospital mortality in patients with COVID-19.[15] A significant association between increased D-dimer levels has been found with diabetes mellitus and elderly age.

The strength of the study is comprehensively analyzing the comparison between D-dimer, FPG, and PPG in COVID-19 disease with comorbid including DM as risk factor morbidity and mortality of the cardiovascular disease.

The study has several limitations, it is an observational retrospective study conducted during an outbreak, so there may be residual or unmeasured laboratory examination, confounding factors, no HbA1c measurement, and a limited number of subgroup G4 patients

5 Conclusion

Comorbid diseases especially DM often coincide with COVID-19 patients, D-dimer, FPG, and PPG level assessment have reliable parameters for assessing and evaluating the prognosis of COVID-19 patients as well as an accurate and practical coagulation parameter and blood glucose level for predicting mortality. In our study, D-dimer, FPG, and PPG increased significantly concerning the increase in comorbid diseases especially DM in COVID-19. The increase in D-Dimer is highest at severe COVID-19 severity, while FPG and PPG increase significantly according to the increase in the severity of COVID-19 disease.

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