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Correlation between HbA1C and D-dimer in Type 2 Diabetic with COVID-19 Patients

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Abstract:

Background. Coronavirus disease-19 (COVID-19) is the disease caused by 2019-nCoV/SARS-CoV-2, a novel β corona- virus of group 2B . COVID-19 has been reported to be associated with severe conditions with type 2 diabetes mellitus (T2DM). 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.

Methods: This study uses secondary data, which is obtained by looking at the contents of patient medical records at H. Adam Malik Medan Hospital between 2020-2021. The population of this study was all inpatients confirmed COVID-19 through an RT-PCR SARS-CoV-2 swab examination. The study sample was obtained by the total sampling method, where all populations that meet the criteria of inclusion and exclusion are used as research samples. Patients were triaged as per severity on basis of national guidelines: asymptomatic, Mild (respiratory rate < 24/min, SpO2 >94% at room air), moderate (respiratory rate: 24-30/min, SpO2 90-94% at room air) and severe (respiratory rate >30/min SpO2 < 90%), ARDS and septic shock [6]. HbA1c implementation using HPLC methods and D-dimer is measured by the ELISA method.

Result: One hundred and sixty-three patients of 92 men and 71 women, the average age was 56.9±10.3 years, and HbA1c, FPG, and PPG remained uncontrolled. There were no differences in age parameters of blood sugar profiles and D-dimers between men and women. D-dimers are significantly negatively correlated with PPG.

Conclusion: Age, blood sugar profile, and D-dimer did not differ significantly between men and women, and D-dimer had a correlation significantly with PPG on T2DM with COVID-19 patients.

Keywords: D-dimer, T2DM, COVID-19

Abstrak:

Latar belakang. *Coronavirus disease-19 (COVID-19) adalah penyakit yang disebabkan oleh 2019-nCoV/SARS-CoV-2, novel β corona-virus group 2B. COVID -10 dihubungkan dengan kondisi berat bila dengan komorbid Diabetes Melitus tipe 2 (DMT2). D-dimer adalah produk sampingan dari*

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degradasi fibrin. Ini secara luas diakui sebagai biomarker untuk tromboemboli dan sebagai penanda prognostik untuk pasien kritis.

***Metode**: Penelitian ini menggunakan data sekunder yang diperoleh dengan melihat isi rekam medis pasien di RS H. Adam Malik Medan antara tahun 2020-2021. Populasi penelitian ini adalah seluruh pasien rawat inap terkonfirmasi COVID-19 melalui pemeriksaan swab RT-PCR SARS-CoV-2. Sampel penelitian diperoleh dengan metode total sampling, dimana semua populasi yang memenuhi kriteria inklusi dan eksklusi digunakan sebagai sampel penelitian. Pasien diprioritaskan sesuai tingkat keparahan berdasarkan pedoman nasional: asimtomatik, Ringan (laju pernapasan <24/menit, SpO2 >94% di udara ruangan), sedang (laju pernapasan: 24-30/menit, SpO2 90-94% di kamar udara) dan berat (pernapasan >30/menit SpO2 < 90%), ARDS dan syok septik [6]. Implementasi HbA1c menggunakan metode HPLC dan D-dimer diukur dengan metode ELISA.*

***Hasil:** Ada 163 pasien yang terdiri dari 92 laki-laki dan 71 perempuan, usia rata-rata 56,9±10,3 tahun, dan HbA1c, FPG dan PPG tetap tidak terkontrol. Tidak ada perbedaan parameter usia profil gula darah dan D-dimer antara pria dan wanita. D-dimer secara signifikan berkorelasi negatif dengan PPG.*

***Kesimpulan:** Usia, profil gula darah dan D-dimer tidak berbeda secara signifikan antara pria dan wanita, dan D-dimer memiliki korelasi yang signifikan dengan PPG pada pasien DMT2 dengan COVID-19.*

Kata Kunci: *D-dimer, DMT2, COVID-19*

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1 Introduction

Coronavirus disease-19 (COVID-19) is the disease caused by 2019-nCoV/SARS-CoV-2, a novel β corona- virus of group 2B.[1] The illness ranges from asymptomatic or mild infection to severe respiratory tract infections in humans such as those seen in severe acute respiratory syndrome (SARS) and the Middle East Respiratory Syndrome (MERS). Presentations include fever, coughing, dyspnea, watery diarrhea, myalgia, severe lymphopenia, prolonged coagulation profiles, cardiac disease, and sudden death.[2, 3]

Diabetes mellitus type 2 (T2DM) has in recent years become a frequently occurring disease with complications that can cause multisystem lesions, among which is microangiopathy, the main cause of death among diabetics. Glycated hemoglobin (HbA1c), a major marker of blood glucose control, primarily reflects the average blood glucose level of patients in the preceding two-to-three months and has become an internationally recognized gold standard for indicating long-term blood glucose monitoring for diabetes. In coagulation function examination, D-dimer can specifically reflect secondary hyperfibrinolysis and a hypercoagulable state in the body and serves as an index sensitive to reflecting thrombosis. Fibrinogen (FIB) concentration can indicate a prethrombotic state in the body. Existing studies suggested that monitoring coagulation function and HbA1c in patients with DM played a role in judging the progression of complications of the condition, particularly for microangiopathy.[4,5]

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, it is yet to be seen if D-dimer values in people with diabetes are any different from those without diabetes before we can assume it to be one of the causes of severe disease in COVID-19 showing increased susceptibility to thromboembolic disease in T2DM.

The study aimed to examine the relationship between D-dimer and age, gender, and blood sugar profile in Covit-19 with T2DM for hospitalization in H Adam Malik Medan.

2 Method

This study uses secondary data, which is obtained from medical records of H. Adam Malik Medan Hospital between 2020-2021. The population of this study was all inpatients confirmed COVID-19 through an RT-PCR SARS-CoV-2 swab examination. The study sample was obtained by the total sampling method, where all populations that meet the criteria of inclusion and exclusion are used as research samples. Inclusion criteria: all inpatients with T2DM confirmed COVID-19, and aged ≥ 18 years. Exclusion criteria of patients with incomplete medical record data. Patients were triaged as per severity on basis of national guidelines: asymptomatic, Mild (respiratory rate < 24/min, SpO2 >94% at room air), moderate (respiratory rate: 24-30/min, SpO2 90-94% at room air) and severe (respiratory rate>30/min SpO2 < 90%), ARDS and septic shock [6]. HbA1c implementation using HPLC methods and D-dimer is measured by the ELISA method.

2.1 Data Analysis

Data univariate analysis is presented descriptively, displaying average data and standard deviations. Test normality of data using the Shapiro Wilk test. The bivariate analysis uses a T-independent test if data is distributed abnormally. If data is not distributed normally used the Mann-Whitney test. Test Pearson correlation when distributed data is normal, and use spearman correlation if data is not distributed normally. Analysis using computer programs SPSS (Statistical Product and for Social Sciences) and confidence intervals of 95%, where $p< 0.05$.

3 Result

In table 1, 163 patients were consisting of 92 men and 71 women, the average age was 56.9±10.3 years, HbA1c, FPG, and PPG remained uncontrolled.

Table 1 Baseline data of study

Parameters	$\bar{x}$ **±SD, n=163**
Gender, m/f	92/71
Age, yr	56.9±10.3
FPG, mg/dl	241.6±122.2
PPG, mg/dl	286.0±123.4
HbA1c, %	9.4±2.4
D-dimer, μg/L	284.1±266.82

FPG : fasting plasma glucose; PPG: postprandial glucose

In table 2, there were no differences in age parameters of blood sugar profiles and D-dimers between men and women.

Table 2 The difference in age parameters, D-dimer, and blood sugar profile between men and women of T2DM with COVID-19 patients

Parameter	**Man,** n=92	**Woman,** n=71	**p**
Age, yr	56.6±9.4	57.4±11.5	0.639
FPG, mg/dl	56.6±9.4	57.4±11.5	0.978
PPG, mg/dl	241.9±122.7	241.35±122.7	0.213
HbA1c, %	9.4±2.3	9.4±2.5	0.961
D-dimer, μg/L	275.4±252.0	295.2±284.6	0.640

FPG: fasting plasma glucose; PPG: postprandial glucose

In table 3, D-dimers are significantly negatively correlated with PPG

Table 3 Correlation between D dimer and Blood Sugar Profile

Parameters	**r**	**p**
Age, yr	-0.024	0.381
FPG, mg/dl	-0.088	0.134
PPG, mg/dl	-0.190	0.001*
HbA1c, %	0.019	0.403

FPG: fasting plasma glucose; PPG: postprandial glucose

4 Discussion

Abnormal coagulation function, including elevated D-dimer, has been demonstrated to be involved in the disease progression of COVID-19 [7]. In this study, we analyzed the association between elevated D-dimer levels and the disease severity of COVID-19 based on the evidence from our cohort study and meta-analysis. In our retrospective cohort study, the level of D-dimer was markedly increased in patients with severe COVID-19, and the meta-analysis further confirmed that odds of severe COVID-19 were associated with D-dimer greater than 0.5 μg/ml. D-dimer assays are commonly used in clinical practice to exclude a diagnosis of deep vein thrombosis or pulmonary embolism, and elevated D-dimer indicates an increased risk of abnormal blood clotting. Elevated levels of D-dimer were also found to be related to a higher mortality rate

of community-acquired pneumonia [8]. Patients with severe community-acquired pneumonia had significantly higher D-dimer levels, and D-dimer within the normal range indicated a low risk for complications [9]. The augmented activity of urokinase could cause hyperfibrinolysis, by increasing cleavage of plasminogen into the active plasmin, and finally led to diffuse alveolar damage and acute lung injury, in a mouse model of SARS-CoV disease [10]. In our cohort study, the level of coagulation function parameters, including prothrombin time, fibrinogen, fibrinogen degradation products, and D-dimer, were found elevated in patients with severe COVID-19. Presumably, the severity of COVID-19 might also be associated with coagulation dysfunction.

Recent studies documenting the laboratory changes of patients with confirmed COVID-19 have noted that elevated D-dimer might be associated with the disease progression of COVID-19. The level of D-dimer in patients with COVID-19 admitted to the ICU was reported to significantly increase. Clinical attention to venous thromboembolism risk should particularly be paid to those patients with severe COVID-19, who were often bedridden and present with abnormal coagulation function [11]. Rapid deterioration was observed in cases with significantly increased D-dimer during the disease progression. In this regard, pulmonary embolism after deep vein thrombosis detachment should be considered and immediately on the alert, especially when patients presented clinical manifestations such as a rapid drop in blood pressure, sudden deterioration of oxygenation, and respiratory distress. Four studies had paid to D-dimer in patients with COVID-19 and diabetes [12]. In the first study by Yang Zhang et al, 166 patients with COVID-19 were divided into three groups based on fasting plasma glucose (FPG). The first group was control (84 patients), the second group showed just one FPG increase (21 patients), and the third group displayed high FPG and hemoglobin A1c (61 patients), which was known as a diabetic group. The median D-dimer levels for these three groups were 0.8 and 1.8 (μg/ml), respectively. Overall, the two elevated FPG groups (82 patients) had 67 patients (81.7%) and the first group had 58 patients (69%) with an increase in D-dimer levels compared to standard values (< 0.5 μg/ml) [12]. In the second study conducted on 24 diabetic patients with COVID-19, without any other underlying disorders, the levels of D-dimer, CRP, and serum ferritin increased significantly. This result may indicate that patients with diabetes are more likely to become seriously ill [13]. The third study carried out on 193 COVID-19 patients, diabetic individuals (48 patients) had higher D-dimer levels than non-diabetic ones [14]. In last study of 28 COVID-19 patients with underlying diabetes, the level of D-dimer in patients admitted to the ICU was significantly different from that of the non-ICU patients.[15]

In this study, there were no significant differences in parameters of age, FPG, PPG, HbA1c, and D-dimer between men and women in T2DM with COVID-19 patients upon admission to the hospital. This means that hormonal influences have a small effect on T2DM and Covid-19 patients.

5 Conclusion

Age, blood sugar profile, and D-dimer did not differ significantly between men and women, and D-dimer correlated significantly with PPG.

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