IMPACT OF DIABETES MELLITUS AS A COMORBIDITY OF COVID-19 PATIENTS TREATED AT PANTI NIRMALA MALANG: REVIEWED FROM COAGULATION PARAMETERS

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ABSTRACT

Background: *Treatment of COVID-19 patients with comorbid like diabetes mellitus as more consequences such as greater mortality risk and prolonged hospitalization. One of the reasons is caused by a hypercoagulable state.* ***Aim****: To prove the difference in coagulation parameters of platelet count, C-Reactive Protein, and D-dimer between Covid-19 patients with diabetes comorbidity and without diabetes, and to analyze the correlation between coagulation parameters with the stage of pneumonia caused by Covid19.* ***Methods****: The design is a cross-sectional study. The sample was collected from patients registered whose hospitalized in an isolation ward at Panti Nirmala Hospital Malang from April to October 2021. Coagulation parameters (platelet counts, C-reactive protein (CRP), and D-dimer level) were measured from 134 patients, divided between 40 patients with diabetes mellitus and 94 patients without diabetes mellitus. Statistical analysis was performed by software SPSS 24, the version year 2016.* ***Results****: Among 134 COVID-19 patients who had diabetes and no diabetes comorbidity, there are results: no significant difference in average platelet counts between the two groups (p=0.763), and the difference in C-reactive protein is significant between the two groups (p=0.076), and the difference of D-dimer level is not significant between them (p=0.593). There is a positive correlation between CRP and D-dimer level with the stage of COVID19 pneumonia (r=0.000 and r=0.134), and on the other hand, there is a negative correlation between platelet counts with the stage of pneumonia (r=-0.126).* ***Conclusion****: COVID-19 patients hospitalized with diabetes mellitus tend to have more severe conditions marked by a higher level of coagulation parameters and correlate with the severity of pneumonia.*

Keywords*: COVID-19, , hypercoagulation, diabetes mellitus, pneumonia staging.*

ABSTRAK

Pendahuluan: Sejak tahun 2020, s emua negara di dunia diguncang pandemi Covid-**Latar belakang:** Perawatan pasien dengan infeksi COVID-19 akan memiliki konsekuensi lebih berat, seperti lamanya masa rawat dan risiko kematian yang lebih tinggi, apabila memiliki komorbid diabetes melitus (DM), karena hiperkoagulasi yang lebih sering terjadi. **Tujuan:** Membuktikan perbedaan parameter koagulasi antara kadar trombosit, C-reactive protein dan D-dimer pada penderita COVID-19 dengan atau tanpa komorbid diabetes melitus, dan melihat korelasi antara faktor koagulasi dengan derajat pneumonia COVID-19. **Metode dan material:** Studi ini menggunakan metode *cross sectional* dengan cara mengumpulkan data pasien rawat inap. Terdapat 40 pasien COVID-19 dengan DM dan 94

Jurnal Widya Medika Vol. 8 No. 2 Oktober 2022
https://doi.org/10.33508/jwm.v8i2.4321

penderita tanpa DM. Parameter koagulasi yang diperiksa adalah rerata kadar trombosit, C-reactive protein dan D-dimer. Analisis statistik dilakukan dengan *software* SPSS versi 24 tahun 2016. **Hasil:** Diantara penderita COVID-19 yang memiliki komorbid DM dengan yang tidak memiliki komorbid DM didapatkan hasil rerata kadar trombosit yang berbeda tapi tidak bermakna (p=0,763), kadar C-reactive protein yang berbeda bermakna (p=0,076) dan kadar D-dimer yang berbeda tetapi tidak bermakna (p=0,593). Didapatkan hasil korelasi positif antara kadar CRP dan D-dimer dengan derajat pneumonia (r=0,000 dan r=0,134) dan korelasi negatif antara kadar trombosit dengan derajat pneumonia (r=-0,126). **Kesimpulan:** Penderita COVID-19 yang dirawat dengan diabetes mellitus menunjukkan kondisi yang lebih berat, yang ditandai dengan tingginya kadar parameter koagulasi dibandingkan dengan yang tanpa diabetes dan berkorelasi dengan semakin beratnya pneumonia**.**

Katakunci: COVID-19, hiperkoagulasi, diabetes mellitus, derajat pneumonia.

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INTRODUCTION

Around December 2019, the emergence of the COVID-19 infection pandemic in Wuhan province, China, surprised the world. Until recently, this pandemic has infected approximately 450 million people worldwide, with a death toll of nearly 6 million.[1] In Indonesia, the disease caused by the SARS-CoV2 virus has affected about 5,5 million people and caused 148,000 deaths. One severe complication that often becomes a problem among COVID-19 patients is hypercoagulation. The pathophysiology of coagulation disorders in COVID-19 infection depends on a complex interaction between cytokine/proinflammatory factor secretion, platelet hyperactivation, and endothelial damage.[2,3]

The condition of patients infected with COVID-19 becomes more severe if the patient has comorbidities (such as hypertension, obesity, coagulation disorders, and diabetes), and Diabetes Mellitus (DM) comorbidity ranks second after hypertension in the COVID-19 cases.[4] The high prevalence of diabetes mellitus, around 10,7 million in 2019, causes the susceptibility of DM sufferers to COVID-19 disease.[5] Moreover, other data show that diabetes mellitus is the second most common comorbidity suffered by COVID-19 patients after hypertension. COVID-19 infection and Diabetes Mellitus can be related to one another. COVID-19 can predispose to infection in patients with hyperglycemia. Hyperglycemia can modulate inflammatory and immune response by interacting with other risk factors.[3,6,7] It means that a person with diabetes is more susceptible to COVID-19 infection because of weak immunity, and a person infected with COVID-19 can experience hyperglycemia due to sepsis or the use of steroid drugs; thus, triggering new-onset diabetes.[8,9] The relationship between diabetes and COVID-19 infection can be explained

through the influence of coagulation factors that cause hypercoagulation in DM patients infected with COVID-19.[10] One theory states that hyperglycemia will trigger coagulation due to increased procoagulant activity accompanied by inhibition of the fibrinolysis process, which is also caused by hyperinsulinemia conditions.[4,6,7] Inflammation and coagulation that happen in diabetic patients with COVID-19 infection is exacerbated by the release of glucocorticoids and catecholamines into the circulation. Several well-known coagulation parameters are the levels of platelets, C-Reactive Protein, D-dimer, Fibrinogen, Ferritin, and Interleukin-6.[12,13,14,15,16,17] Thrombocytes rich in thrombi and increased levels of megakaryocytes in the microvasculature be associated with obstruction and extensive damage, especially in the alveoli.[2] C-Reactive Protein is an inflammatory parameter that can be identified during acute infection. D-dimer is a fibrin degradation product (FDP) often used as a biomarker of the thromboembolism process and a prognostic marker.

This study aimed to identify the differences in coagulation parameters that increased in hospitalized COVID-19 patients with and without DM. The parameters examined were platelet levels, C-Reactive Protein, and D-dimer. From the results of this study, health workers are hoped to provide more intensive and aggressive treatment for COVID-19 patients who have diabetes mellitus comorbidity.

METHODS AND MATERIAL

This study was conducted using a cross-sectional method by collecting data from the medical record of patients hospitalized at Panti Nirmala Hospital, Malang, from April to October 2021. The patients criteria included in this study were patients who tested positive for COVID-19 through a PCR test, whether diabetic or non-diabetic. The inclusion criteria were all patients suffering from COVID-19 treated in isolation wards and who have diabetes equivalent to 7.5% as the case group and non-diabetic patients (HbA1c) levels below 7.5% as the control group. The exclusion criteria were patients who already had a history of coagulation or bleeding disorders and had received anticoagulant therapy.

The basic characteristics of the subjects included in this study were gender, age, length of stay, type of pneumonia, conditions at discharge, and the parameters examined were the levels of platelet, C-reactive protein (CRP), and D-dimer.

The statistical analysis was done using SPSS version 24.0, 2016. The differences in the subjects' characteristics (gender, age, degree of pneumonia, length of stay, and conditions at discharge) were tested using chi-square. Differences in parameters of CRP, platelets, and D-dimer levels between the diabetic and non-diabetic groups were done using the Mann Whitney test. Meanwhile, the correlation between the platelet parameters, CRP, D-dimer levels, and the degree of COVID-19 pneumonia was analyzed using the Spearman rank correlation.

https://doi.org/10.33508/jwm.v8i2.4321

Table 1. Basic characteristics of research subjects

Characteristics of subjects	DM (n=40)	Non-DM (n=94)	P-Value
Gender n (%)			
Male	15(21.70%)	54 (78.30%)	0.039
Female	25 (38.50%)	40 (61.50%)	
Age (year) n (%)			
A (≤20 years old)	1 (25.00%)	3 (75.00%)	
B (21-40 years old)	2 (16.70%)	11 (83.30%)	0.751
C (41-60 years old)	19 (32.20%)	40 (67.80%)	
D (≥61 years old)	18 (30.50%)	41 (69.50%)	
Degree of Pneumonia n (%)			
Mild	4 (18.20%)	18 (81.80%)	
Moderate	2 (22.20%)	7 (77.80%)	0.338
Severe	34 (33.00%)	69 (67.00%)	
Length of stay (day) n (%)			
≤7 days	25 (%)	54 (%)	0.702
>7 days	15 (%)	40 (%)	
Discharge status n (%)			
Recovered	17 (23.60%)	55 (76.40%)	
Referred	4 (33.30%)	8 (66.70%)	
Passed away	19 (42.20%)	26 (57.80%)	0.078
Discharge against medical advice	0 (%)	5 (100%)	
Examination Result (Mean ± SD)			
Mean platelet level (mm/3)	216075±8796	210333±68208	0.763
Mean CRP level (mg/dL)	45.39±268.41	11.97±82.22	0.076
Mean D-dimer level (ng/dL)	80.19±73.42	66.31±66	0.593

DM; diabetes melitus; Non-DM: non diabetes melitus; CRP: C-reactive protein

RESULTS

The basic characteristics table shows that most respondents in the DM group were females (38.5%), but the non-DM group was dominated by males (78.3%). The chi-square test results showed a significant difference in the number of respondents based on gender (p <0.05). The mean age of DM patients was 60.18±16.84 years, while the average age of non-DM patients was 56.76±15.65 years. Most respondents in the DM group were aged 41-60 and >60 years, the same as in the non-DM group; the results of the chi-square test showed that the difference in the number of respondents based on age was not significant (p >0.05). In both groups, the majority had severe pneumonia, and the chi-square test results showed that the difference in the number of respondents based on the degree of pneumonia was not significant (p >0.05). In both groups, most patients were treated for less than seven days; the chi-square test results showed that the

difference in the number of respondents based on length of stay was not significant (p >0.05). Patients' conditions during hospital discharge showed different results between the DM and non-DM groups. The COVID-19 with DM comorbidity group showed that the highest outcome was passed-away (19 patients or 42.2%), but in the COVID-19 with a non-DM group, the highest condition was recovered (55 patients or 76.4%). However, the difference between the two groups was not significant (p >0.05).

Differences in Platelet, C-Reactive Protein, and D-dimer levels

Differences in coagulation parameters (platelet, D-dimer, and CRP levels) should be statistically tested. Before the difference test was carried out, the normality test was done using the Kolmogorov Smirnov test if it met the normality assumption (p-value >0.05); thus, an independent t-test was carried out, but if the normality assumption was not met, the Mann Whitney test was performed.

The results showed that the mean platelet level was 216075±8796.03 in DM patients, but it was at 210333±682.08 in the non-DM group, with a non-significant difference (p >0.05). The average CRP level was 45.39±268.41 in the DM group and 11.97±82.22 in the non-DM group, with a significant difference (p<0.05). Meanwhile, the mean of D-dimer was 80.19±73.42 in the DM group and 66.31±66 in the non-DM group, and the difference between the two was not significant (p>0.05).

The comparison of the mean coagulation parameters (platelets, CRP, and D-dimer) between DM and non-DM patients are presented in Figure 1, Figure 2, and Figure 3, respectively.

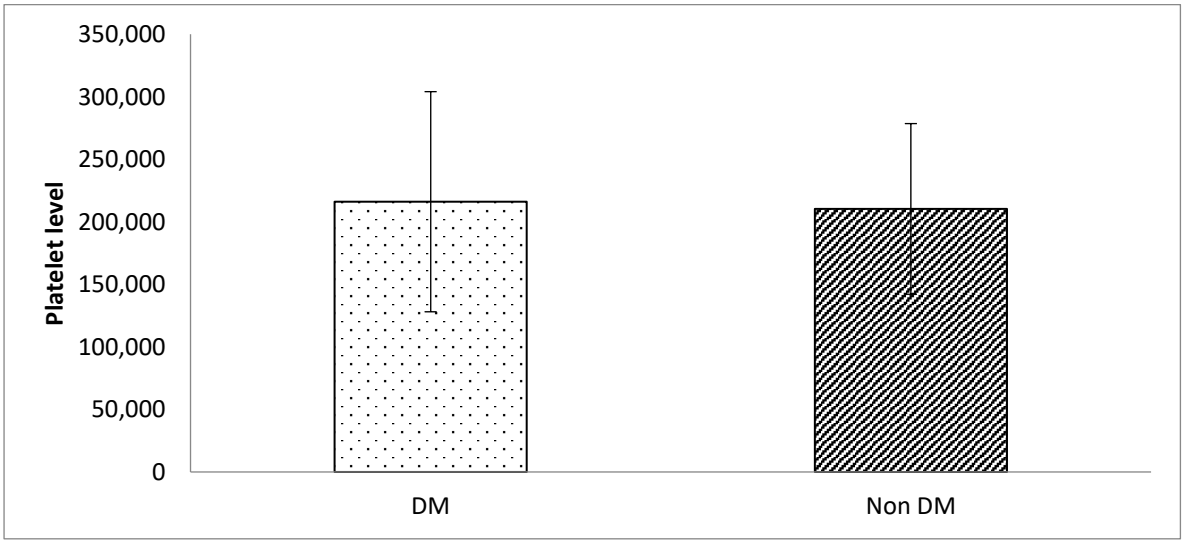

Figure 1. Comparison of Mean Platelet level between DM groups and non DM groups. The mean platelet level in DM groups is 216075± 8796.03/mm3 compared with non DM groups is 210333±68208/mm3. DM: diabetes mellitus non DM: non diabetes mellitus

https://doi.org/10.33508/jwm.v8i2.4321

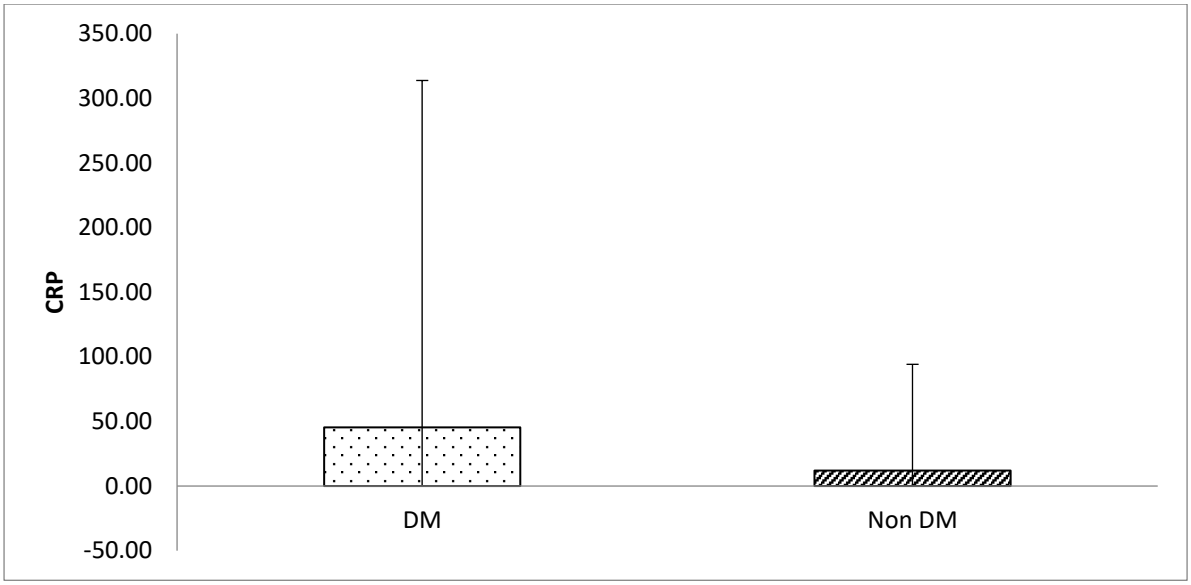

Figure 2. Comparison of Mean C-reactive protein (CRP) level between DM groups and non DM groups. The mean CRP level in DM groups is 45.39±268.41 mg/dL compared with non DM groups is 11.97±82.22 mg/dL. DM: diabetes mellitus non DM: non diabetes mellitus

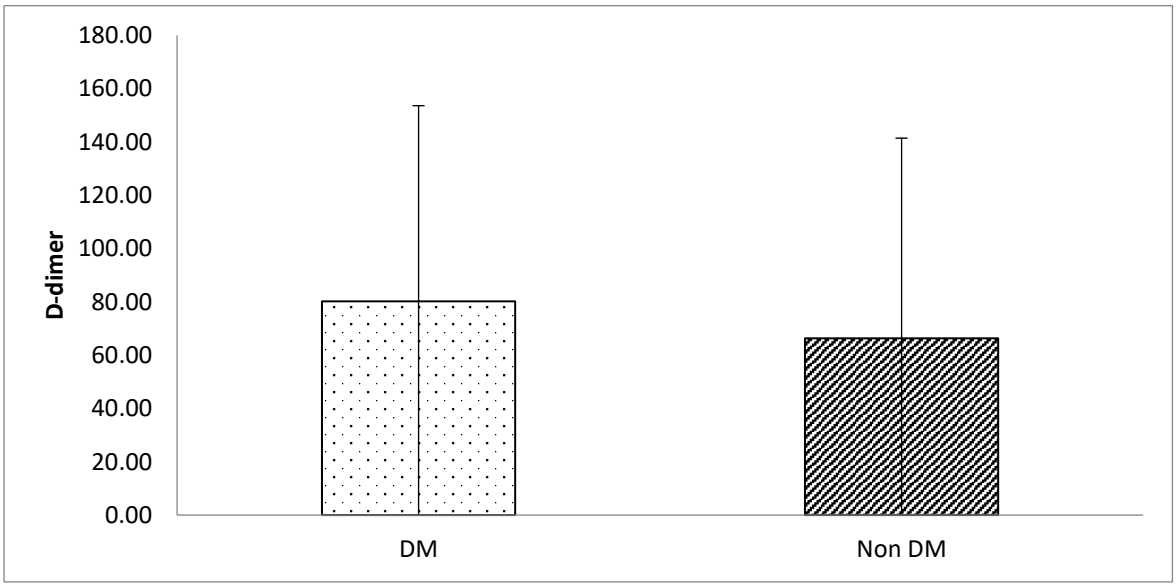

Figure 3. Comparison of Mean D-dimer level between DM groups and non DM groups. The mean D-dimer level in DM groups is 80.19±73.42 ng/dL compared with non DM groups is 66.31±66 ng/dL. DM: diabetes mellitus non DM: non diabetes mellitus.

Correlation between degree of pneumonia with the levels of platelets, CRP, and D-dimer

This study also aims to determine the correlation between platelet, D-dimer, CRP levels and the degree of pneumonia (mild, moderate, severe). The degree of pneumonia was mild (code 1), moderate (code 2), and severe (code 3) (ordinal scale). The Spearman's Rank correlation test results are presented in Table 2.

Table 2. Spearman's Rank Correlation Test Results

Variable 1	Variable 2	Correlation Value	P-Value
Platelet count	Degree of Pneumonia	-0.133	0.126
CRP level	Degree of Pneumonia	0.448	0.000
D-dimer value	Degree of Pneumonia	0.214	0.134

CRP**; C-reactive protein**

Based on Table 4, the correlation value between the number of platelets and the degree of pneumonia is 13.3%; thus, the correlation is negative, meaning that the higher the platelet count, the lower the degree of pneumonia. With a p-value of 0.126 >0.05 can be concluded that the correlation between the number of platelets and the degree of pneumonia is not significant. The correlation value between CRP level and the degree of pneumonia is 44.8%; thus, the correlation is positive, meaning that the higher the CRP level, the more severe the pneumonia degree. With a p-value of 0.000 <0.05 can be concluded that the correlation between CRP level and the degree of pneumonia is significant. The correlation value between the D-dimer with the degree of pneumonia is 21.4%; thus, the correlation is positive, meaning that the higher the level of the D-dimer value, the more severe the pneumonia degree. With a p-value of 0.134 >0.05 can be concluded that the correlation between the D-dimer value and the degree of pneumonia is insignificant

The graph below shows the correlation between platelet, C-Reactive Protein, D-dimer levels and the degree of pneumonia due to COVID-19.

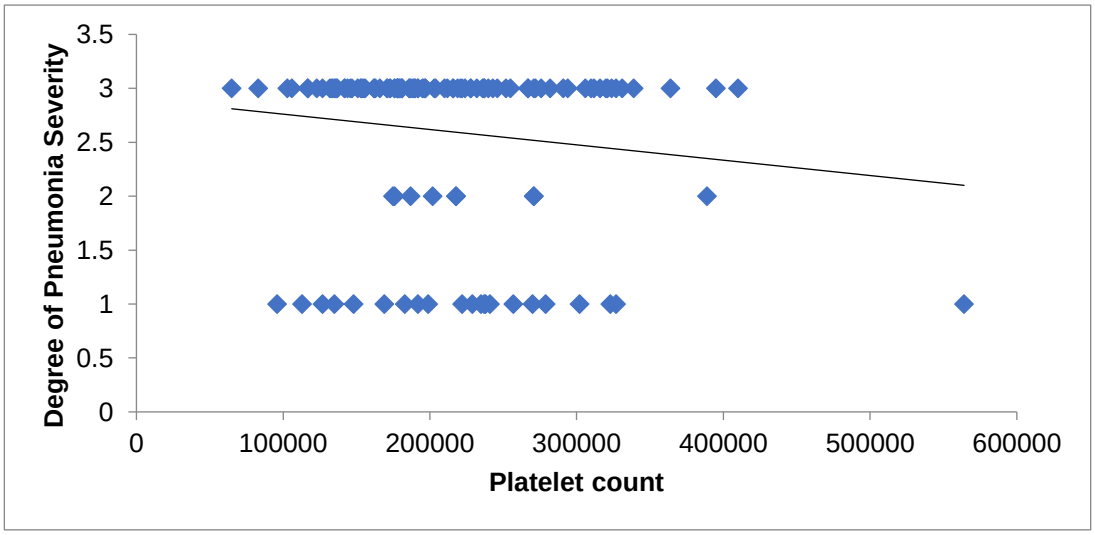

Figure 4. Correlation between of platelet count with the degree of pneumonia. The blue quadriangle dots showed the platelet counts. Straight line from upper down to lower right showed the negative correlation between degree of pneumonia and the platelet counts.

https://doi.org/10.33508/jwm.v8i2.4321

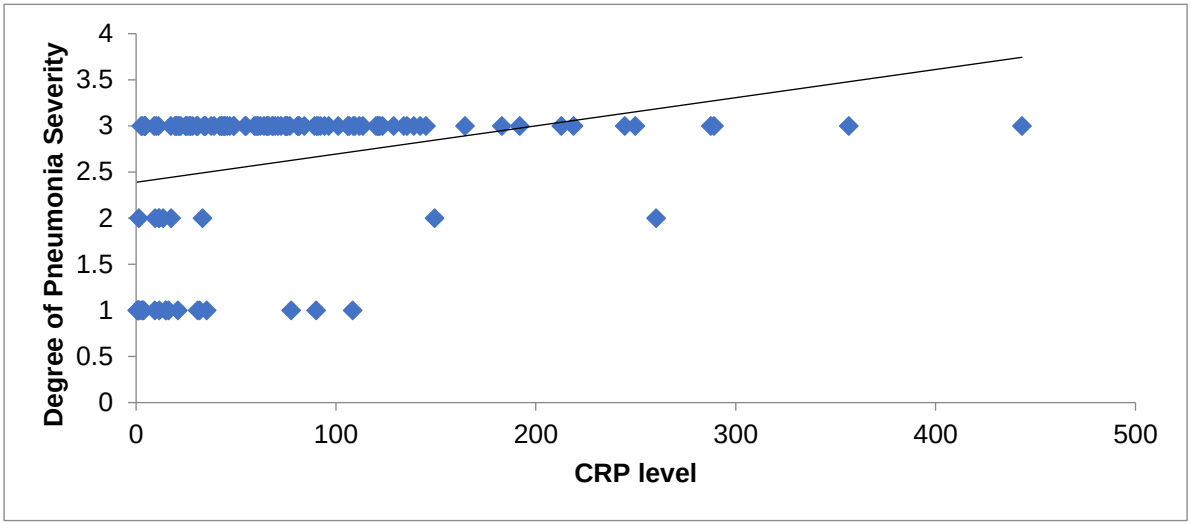

Figure 5. Correlation between of CRP level with the degree of pneumonia. The blue quadriangle dots showed the CRP level. Straight line from lower left to the upper right showed the positive correlation between degree of pneumonia and the level of CRP.

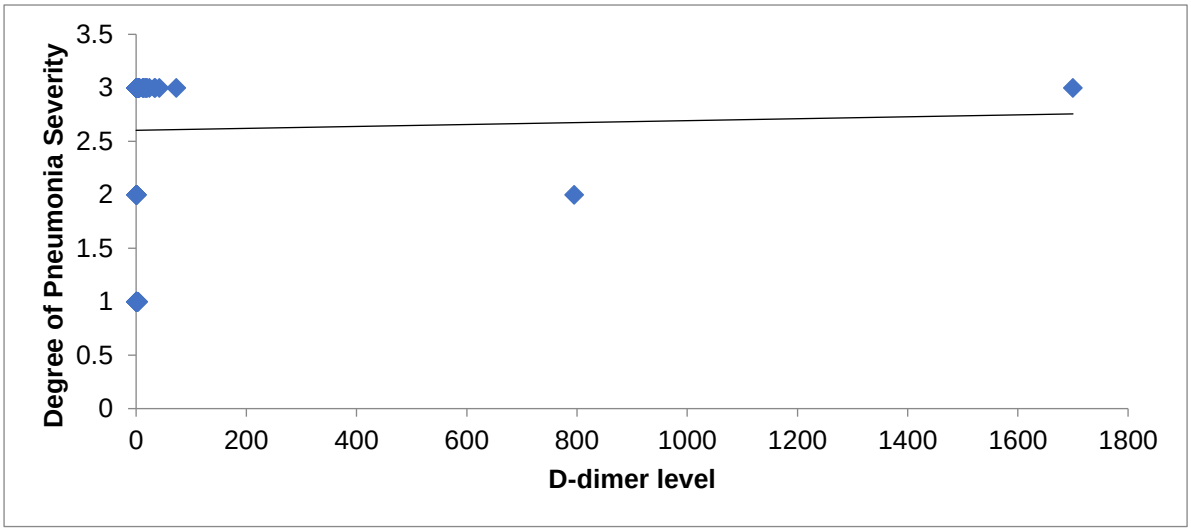

Figure 6. Correlation between D-dimer level with the degree of pneumonia. The blue quadriangle dots showed the D-dimer level. Straight line from lower left to the upper right showed the positive correlation between degree of pneumonia and the level of CRP. This almost horizontally line show that there is no significant correlation between them

DISCUSSION

This study shows the relationship between COVID-19 infection and diabetes mellitus by examining coagulation parameters (platelet, CRP, and D-dimer levels). The mean platelet level of COVID-19 patients in the DM group showed a difference compared to the non-DM group, 216075±8796 vs. 210333±6820, p=0.763 (Table 2), but was not significant. It shows that platelets are not a specific inflammatory parameter in comorbid COVID-19 patients. These results align with previous studies conducted on 178

COVID-19 patients, where 49 patients had severe COVID-19, and 129 patients were not severely affected. Patients with severe COVID-19 showed a higher reduction in platelet count than those without severity, but there was no significant difference between COVID-19 patients with and without comorbidities.20 A previous study conducted on 255 patients receiving anticoagulants and immunosuppressant drugs also showed decreasing platelets and increasing CRP in both comorbid and non-comorbid COVID-19 patients.21

Parameters of CRP level showed important results. The mean CRP level in the DM group was different from that in the non-DM group, 45.49 ± 268.41 vs. 11.97 ± 82.22 (Table 2), and this difference was significant (p = 0.076). A meta-analysis study of 15,282 COVID-19 patients (4,733 DM patients and 10,549 non-DM) published in 29 articles examining the CRP and D-dimer parameters showed a significant difference between subjects with DM and without DM, or 2,855 non-DM patients and 6,457 non-DM (OR 0.41).22 Previous studies carried out also obtained almost the same results that the CRP level of Covid-19 patients with DM was higher than non-DM, with a significance level of p = 0.028.23,24

Examination of D-dimer level showed almost the same results as CRP. The mean level of D-dimer in the DM group was significantly different from the non-DM group, 80.19±73.42 vs. 66.31±66 (p=0.593) (Table 3). These results are in accordance with the research conducted by Miri et al. (2021) on 201 COVID-19 patients with DM and non-DM.18 Almost the same results were obtained in the previous study with an average D-dimer level of 1,590 ng/mL in DM patients and 515 ng/mL in non-DM patients, and the results were very significant. It was also found in a study conducted by Pangaribuan (2021), which compared D-dimer level with the average HbA1c in COVID-19 patients.25 Likewise, the results of the meta-analysis conducted by Debi et al. on the CRP examination showed the same results.23 It is in accordance with the theory that D-dimer is a coagulation parameter produced in acute inflammatory conditions, and its levels are higher in conditions of metabolic disorders, in this case, diabetes mellitus.18,26

This study also presented the results that looked at the correlation between the degree of pneumonia with the parameters of platelet, CRP, and D-dimer levels. The results showed that the platelet level decreased with the severity of pneumonia (Figure 4), and the same with the CRP and D-dimer levels. This study showed that the more severe the degree of pneumonia, the higher the levels of CRP and D-dimer (Figures 5 and 6).

Many studies have not linked the degree of pneumonia with these coagulation parameters because the findings of infectious diseases due to COVID-19 are still relatively new. Studies conducted by Chen (2020) and Avci et al. (2021), which examined the relationship between the severity of pneumonia with inflammatory parameters, in this case, PT (Prothrombine Time),, a PTT (activated Plasma Thrombine Time), and INR (International Prothrombine Time) showed beingan increased along with the severity of COVID-19 pneumonia and specifically liver damage and the degree of pneumonia.27,28 Arslan et al. (2010) conducted a study to see the relationship between the degree of pneumonia (but not COVID-19 cases) and D-dimer level using the Pneumonia Severity Index and showed a correlation between D-dimer level and the severity of pneumonia.29

Many other inflammatory and coagulation parameters can be used as a differentiator between COVID-19 patients with and without comorbidities and as predictors of therapeutic success. These other parameters are Ferritin, Interleukin-6, Procalcitonin, and Fibrinogen levels.12,14,15,16,30 Considering that not all these parameters were available at Panti Nirmala Hospital, the coagulation markers examined were only platelets, CRP, and D-dimer levels.

CONCLUSIONS

This study describes the differences and correlations between several coagulation parameters in COVID-19 patients with comorbid and without comorbid type 2 DM. The results showed significant differences in the examination of platelet, CRP, and D-dimer levels between COVID-19 patients with and without type 2 diabetes. It proves that comorbidities significantly affect the disease course, the recovery rate, the treatment length, and the risk of death in COVID-19 sufferers. Therefore, medical personnel should be more careful in dealing with COVID-19 sufferers with certain comorbid diseases.

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