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Efficacy of d-dimer level as a prognostic indicator in COVID-19 infection

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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2, was first reported in China in 2019 and later declared a pandemic. Coagulation abnormalities play the pivotal role in causing most of the symptoms related to COVId-19 infection. As the pathophysiology of COVID-19 is now being understood, it is found that these coagulation abnormalities, especially thrombosis are very well related to the severity of the disease. D-dimer is a potential biomarker for various thrombotic diseases. This study aims to determine the efficacy of D-dimer, Fibrinogen, Prothrombin time (PT), and activated partial thromboplastin time (aPTT) to determine the severity of COVID-19 infection. **Aims and Objectives:** The objectives of the study are as follows: (1). To determine the efficacy of D-dimer in assessing the severity of the disease in COVID-19 infection. (2). To determine the role of PT, aPTT, and Fibrinogen levels in assessing the severity of COVID-19 Infection. **Materials and Methods:** The study was conducted among 160 reverse transcription polymerase chain reaction confirmed COVID-19 patients admitted in Government Medical College, Kottayam. The sociodemographic profile and presenting complaints were obtained using a structured format. Blood samples were collected on the day of admission, the 5th day, and 10th day. Samples are tested for levels of D-dimer, Fibrinogen, PT, and aPTT. Based on the clinical outcome, patients were categorized into two groups: Mild group and severe group. **Results:** The difference between the median D-dimer at admission in the severe group (1339 ng/mL) and the mild group (390 ng/mL) was statistically significant. Area under the receiver operating characteristic (ROC) for D-dimer was 0.774 and cut-off value was found to be 569 µg/mL with a sensitivity of 83.3% and a specificity of 61.2%. The ROC curve analysis, area under the curve of PT also can be used for diagnosis with 76.3% with 76.3% sensitivity and 61.2% of specificity. **Conclusion:** Coagulopathy is an important complication of COVID-19 patients and is related to severity as well as prognosis of disease. D-dimer and PT can be used as reliable and convenient parameter for assessing coagulopathy and severity in COVID-19 infected patients.

Key words: Coronavirus disease 2019; Coagulopathy; D-Dimer

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INTRODUCTION

In early December 2019, an outbreak of coronavirus disease 2019 (COVID-19), caused by a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), occurred in Wuhan City, Hubei Province, China. By the end of 2020 January, the World Health Organization declared the SARS-CoV-2 outbreak as a Public Health Emergency of International Concern.[1]

Since the outbreak of the pandemic, till December 2022, there have been more than 640 million confirmed cases of COVID-19, including 6,681,433 deaths worldwide.[2] The COVID-19 pandemic has severely strained healthcare systems worldwide. There is a need of a reliable and easily detectable marker to assess the severity and predict the prognosis of the disease.

In severe cases, the disease can progress to acute respiratory distress syndrome (ARDS) and hypoxic respiratory failure, which is the leading cause of mortality in COVID-19 patients. Although the pulmonary manifestations are most common, extrapulmonary manifestations such as gastrointestinal,

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cardiovascular, and renal dysfunctions are reported.[3] Multiple studies have found that microvascular thrombotic and inflammatory processes may play a role in exacerbating ARDS and extrapulmonary events in COVID-19 patients.[4] Abnormal coagulation and inflammation parameters provide evidence for endothelium dysregulation in severe COVID-19 patients. The vascular changes occurring in the COVID-19 infection are distinctive. Diffuse intravascular coagulation and large-vessel thrombosis have been linked to multisystem organ failure.

D-dimer is a fibrin degradation product, which originates from the formation and lysis of cross-linked fibrin and reflects activation of coagulation and fibrinolysis. Change in the D-dimer levels and other hematological indices in infected patients have been documented and the pathophysiology behind is being studied. However, many studies have reported High D-Dimer levels on admission, and increasing D-dimer over the course of hospitalization is associated with increased mortality of COVID-19 patients and can be used as an indicator of prognosis.

This study is intended to know the efficiency of D-dimer in assessing the severity of the disease in COVID-19 infection and understand the role of Prothrombin Time (PT), Activated Partial Thromboplastin Time (aPTT), and Fibrinogen levels in assessing the severity of COVID 19 Infection. This will help in setting criteria to access the severity of the disease and predict prognosis in COVID-19 patients and help in their clinical management.

Aims and objectives

The objectives of the study are as follows:

(1) To determine the efficacy of D-dimer in assessing the severity of the disease in COVID-19 infection.
(2) To determine the role of PT, aPTT, and Fibrinogen levels in assessing the severity of COVID-19 Infection.

MATERIALS AND METHODS

Clinical details of patients included in the study wereobtained in case pro forma. Blood samples were collected from the patients satisfying inclusion criteria on the date of admission, on the 5th day, and on 10th day or composite endpoint (discharge from hospital). D-dimer, Fibrinogen, PT, aPTT were measured using Destiny plus coagulation analyzer. The values are entered in a Microsoft Excel sheet. Data analysis is done using SPSS software version 20.

Inclusion criteria

Patients of age more than or equal to 18 years admitted with reverse transcription polymerase chain reaction or Rapid antigen test confirmed COVID-19 disease were included in the study.

Exclusion criteria

The following criteria were excluded from the study:

- Pregnant and breastfeeding women
- Patients with previous history of coagulation disorders.

Study tools

Detailed pro forma to record serial number, name, age, sex, presenting complaints, vitals, and coagulation indices of each patient

- Blood sample
- Equipments- Destiny plus coagulation analyzer
- Reagents for coagulation tests
- TriniCLOT PT Excel S for PT
- TriniCLOT aPTT HS for aPTT
- TriniCLOT Fibrinogen reagent for Fibrinogen
- TriniLIA D-dimer for D-dimer analysis.

RESULTS

Sociodemographic features of study subjects	
Mild group (n=80)	**Severe group (n=80)**
Mean age=62.39±18.38 years Minimum age-19 years Maximum age-90 years	Mean age=67.60±13.81 years Minimum age-35 years Maximum age-92 years

Summary table – values of d-dimer, prothrombin time, activated partial thromboplastin time, and fibrinogen level in mild-and-severe group		
Coagulation indices	**Mild group**	**Severe group**
D-dimer (ng/mL)		
Day 0	Median-390.00 Minimum-46 Maximum-4020	Median-1339.00 Minimum-47 Maximum-5000
Day 5	Median-417.50 Minimum-80 Maximum-4050	Median-1726.00 Minimum-79 Maximum-4335
Day 10	Median-487.00 Minimum-85 Maximum-5021	Median-1719.00 Minimum-134 Maximum-4656
Fibrinogen (g/L)		
Day 0	Mean-382.64±178.66 Minimum-85 Maximum-803	Mean-480.05±140.44 Minimum-145 Maximum-756
Day 5	Mean-394.79±164.09 Minimum-145 Maximum-802	Mean-490.61±142.36 Minimum-150 Maximum-789
Day 10	Mean-394.89±178.9 Minimum-140 Maximum-810	Mean-504.29±138.55 Minimum-174 Maximum-860
Prothrombin time (seconds)		
Day 0	Mean-15.11±2.8 Minimum-10.4 Maximum-21.3	Mean-17.47±2.5 Minimum-11.5 Maximum-21.7
Day 5	Mean-15.59±2.8 Minimum-11.2 Maximum-21.9	Mean-18.05±2.9 Minimum-10.4 Maximum-22.3

Day 10	Mean-16.39±3.04 Minimum-11.1 Maximum-22.3	Mean-18.48±2.8 Minimum-11.5 Maximum-21.9
Activated partial thromboplastin time (seconds)		
Day 0	Mean-41.54±14.45 Minimum-18 Maximum-82	Mean-52.41±16.57 Minimum-25 Maximum-130
Day 5	Mean-42.94±12.75 Minimum-23.9 Maximum-74.9	Mean-53.2±15.07 Minimum-20.1 Maximum-103.6
Day 10	Mean-44.5±14.7 Minimum-20.5 Maximum-72.2	Mean-58.4±17.05 Minimum-20.7 Maximum-92

D-dimer

The efficacy of d-dimer in assessing the severity of the disease in COVID-19 infection	
	Mann–Whitney U
Mild group Median D-dimer on admission- 390 ng/mL	P=0.001
Severe group Median D-dimer on admission 1339 ng/mL	

There is a significant difference in the D-dimer value (measure on admission) of mild-and-severe cases, with a median D-dimer value 1339 for severe cases and 390 for mild cases.

Inference

Receiver operating characteristic (ROC) curve is a plot of the sensitivity versus 1-specificity of a diagnostic test. The different points on the curve correspond to the different cut-points used to determine whether the COVID-19 infection is severe. Here, the ROC curve was used to depict the sensitivity and specificity of D-dimer value in diagnosing severity of COVID-19 infection.

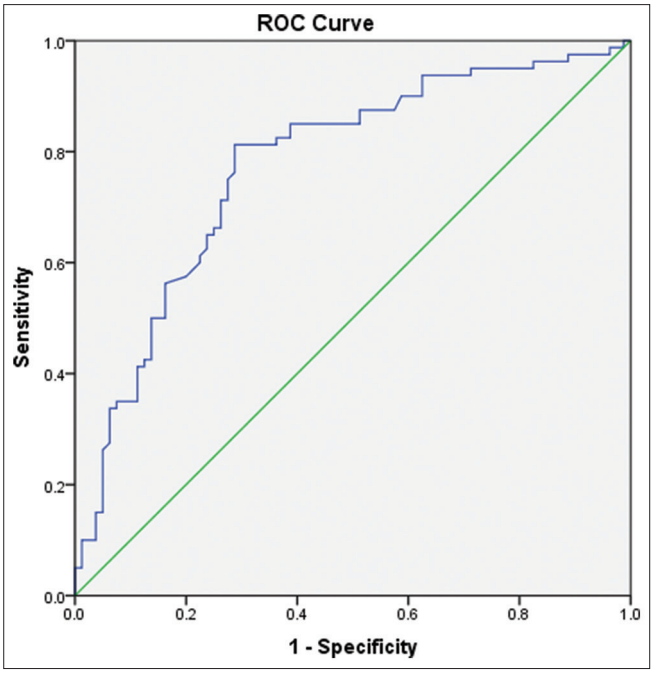

Figure 1: Receiver operator curve of D-dimer against the severity of coronavirus disease 2019 infection based on clinical outcome

In the analysis of ROC curves (Figure 1) the area under thr ROC curve of D-dimer value against the severity of COVID-19 infection was 0.774 (95% confidence interval [CI] 0.700, 0.848) with significant ability to diagnose severe COVID-19 infection (P=0.001) (Table 1). The ROC curve with area under the curve (AUC) of more than 0.7 is a fair test in diagnosis.

D-dimer value aids in identifying severity of COVID 19 infection and it can be accepted.

For diagnosing severe COVID-19 infection, a D-dimer value of 569 can be used. This cut-off point has got a sensitivity of 83.8% and a specificity 61.2%.

PT

The role of prothrombin time, activated partial thromboplastin time, and fibrinogen level in assessing the severity of the disease in COVID-19 infection	
	Mann–Whitney U
Mild group Mean prothrombin time on admission -15.11±2.8 s.	P=0.001
Severe group Mean prothrombin time- 17.47±2.5 s on admission.	

There is a significant difference in the PT (measured on admission) of mild and severe cases, with a mean PT 17.47±2.5 for severe cases and 15.11±2.8 for mild cases.

Inference

ROC curve is a plot of the sensitivity versus 1-specificity of a diagnostic test. The different points on the curve correspond to the different cut-points used to determine whether the COVID-19 infection is severe. Here, the ROC curve was used to depict the sensitivity and specificity of PT value in diagnosing the severity of COVID-19 infection.

In the analysis of the ROC curves (Figure 2), the areas under the ROC curve of PT value against the severity of COVID-19 infection was 0.736 (95% CI 0.659, 0.813) with significant ability to diagnose severe COVID-19 infection (P=0.001) (Table 1). The ROC curve with an AUC of more than 0.7 is a fair test in diagnosis.

PT value aids in identifying the severity of COVID-19 infection and it can be accepted.

For diagnosing severe COVID-19 infection, a PT value of 16.25 can be used. This cut-off point has got a sensitivity of 76.3% and a specificity of 61.2%.

Activated partial thromboplastin time

	Mann–Whitney U
Mild group	P=0.001
Mean Activated partial thromboplastin time on admission - 41.54±14.45 s.	
Severe group	
Mean Activated partial thromboplastin time on admission 52.41±16.57 s.	

There is a significant difference in the aPTT value (measured on admission) of mild-and-severe cases, with a mean aPTT value 52.41±16.57 s for severe cases and 41.54±14.45 s for mild cases.

Inference

ROC curve is a plot of the sensitivity versus 1-specificity of a diagnostic test. The different points on the curve correspond to the different cut-points used to determine whether the COVID-19 infection is severe. Here, the ROC curve was used to depict the sensitivity and specificity of aPTT in diagnosing the severity of COVID-19 infection.

In the analysis of the ROC curves, (Figure 3) the areas under the ROC curves aPTT against the severity of COVID-19 infection was 0.697 (95% CI 0.616, 0.778) with significant ability to diagnose severe COVID 19 infection (P=0.001) (Table 3). The ROC curve with an AUC of 0.6–0.7 is a poor test in diagnosis.

aPTT aids in identifying the severity of COVID-19 infection and it can be accepted.

For diagnosing severe COVID-19 infection, aPTT of 42.55 can be used. This cutoff point has got a sensitivity of 75% and a specificity of 57.5%.

Fibrinogen level

	Mann–Whitney U
Mild group	P=0.001
Mean Fibrinogen level on admission – 382.64 ± 178.66 g/l	
Severe group	
Mean Fibrinogen level on admission – 480.05 ± 140.44 g/l	

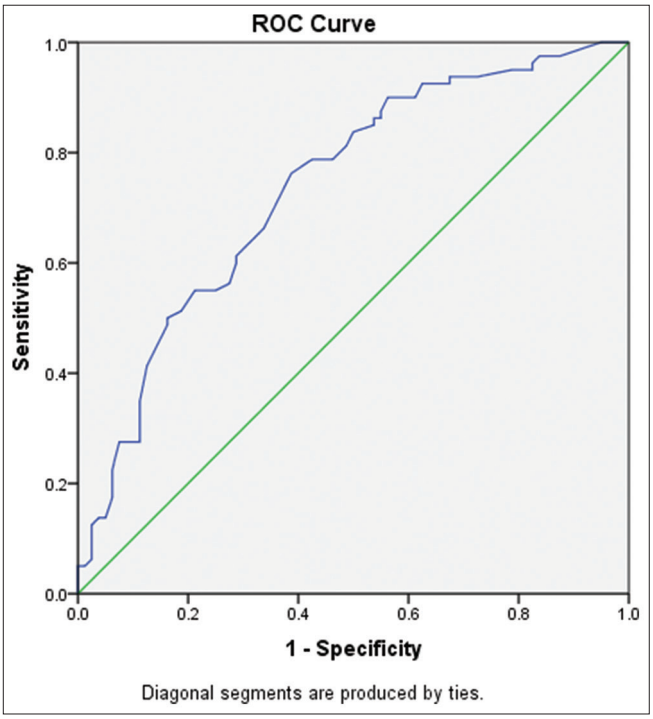

Figure 2: Receiver operator curve of Prothrombin time against the severity of coronavirus disease 2019 infection based on clinical outcome

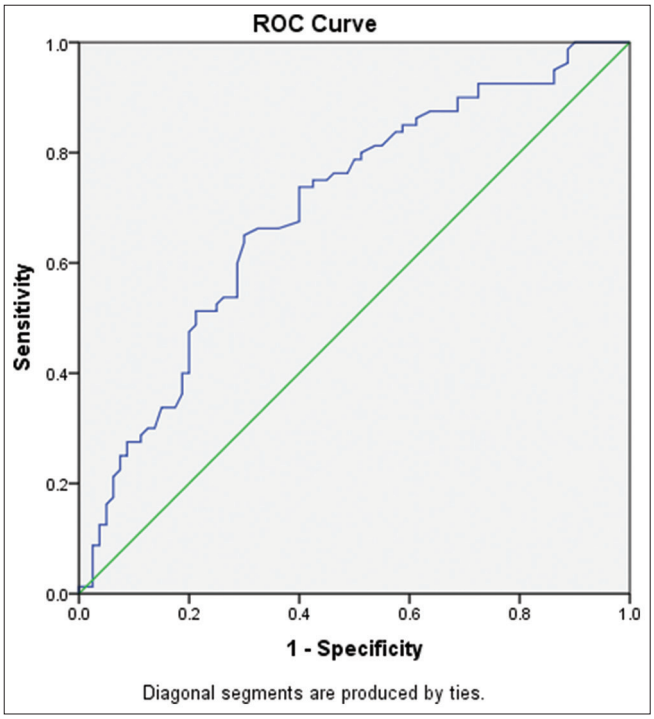

Figure 3: Receiver operator curve of Activated partial thromboplastin time against the severity of coronavirus disease 2019 infection based on clinical outcome

There is a significant difference in the Fibrinogen level (measured on admission) of mild and severe cases, with a mean Fibrinogen level 480.05±140.44 for severe cases and 382.64±178.66 for mild cases.

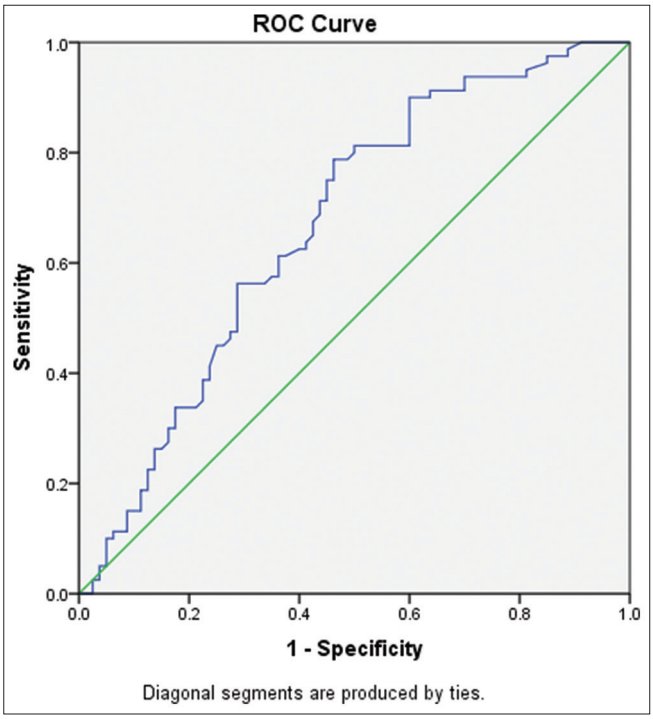

Figure 4: Receiver operator curve of Fibrinogen level against the severity of coronavirus disease 2019 infection based on clinical outcome

Table 1: Area under the curve and its 95% CI with P-value

Area under the curve	Standard error	P-value	95% CI	
			Lower bound	Upper bound
0.774	0.038	0.001	0.700	0.848

CI: Confidence interval

Table 2: Area under the curve and its 95% CI with P-value

Area under the curve	Standard error	P-value	95% CI	
			Lower bound	Upper bound
0.736	0.039	0.001	0.659	0.813

CI: Confidence interval

Table 3: Area under the curve and its 95% CI with P-value

Area under the curve	Standard error	P-value	95% CI	
			Lower bound	Upper bound
0.697	0.042	0.001	0.616	0.778

CI: Confidence interval

Inference

ROC curve is a plot of the sensitivity versus 1- specificity of a diagnostic test. The different points on the curve correspond to the different cutoff points used to determine whether the COVID-19 infection is severe. Here, the ROC curve was used to depict the sensitivity and specificity of the Fibrinogen level in diagnosing the severity of COVID-19 infection.

Table 4: Area under the curve and its 95% CI with P-value

Area under the curve	Standard error	P-value	95% confidence interval	
			Lower bound	Upper bound
0.669	0.043	0.001	0.585	0.753

CI: Confidence interval

In the analysis of the ROC curves, (Figure 4) the areas under the ROC curves Fibrinogen level against the severity of COVID-19 infection was 0.669 (95% CI 0.585, 0.753) with significant ability to diagnose severe COVID-19 infection (P=0.001) (Table 4). However, the ROC curve with an AUC of 0.6–0.7 is a poor test in diagnosis.

Fibrinogen level aids in identifying the severity of COVID-19 infection and it can be accepted.

For diagnosing severe COVID-19 infection, a Fibrinogen level of 462 can be used. This cut-off point has got a sensitivity of 56.3% and a specificity of 66.2%.

DISCUSSION

In this study, the age of patients ranged between 19 years and 92 years. The mild group included patients between the age group 19–90 years with a mean value of 62.39±18.3 years whereas the severe group had patients aged between 35 and 92 years with a mean age of 67.6±13.8 years. The severe group had the majority adults in middle age and elderly age. A statically significant relation was found between the age and severity of disease in this study. The study by Huang et al., in China among ICU patients reported lesser median age (49 years IQR 41–58 years)[5] compared to this study. The study by Ahirwar et al., in India, was comparable with this study.[6] The systematic review of studies on D-dimer as an indicator of prognosis also showed the range of mean age of COVID-19 patients was between 47 and 73 years and included both middle age and elderly age groups. The patient's age was related significantly to D-dimer values in various studies done so far.[7]

This study showed that severe groups had more females (51.2%). The mild group had 41.1%, female patients. Whereas the study done by Zhou et al. showed, 73% of patients with severe symptoms were men.[8]

Comorbidities in COVID-19 patients and their relation with D-dimer

Various studies have reported that COVID-19 patients, those with underlying health conditions or comorbidities, have an increasingly rapid and severe progression, often leading to death.

In the present study, 63.7% of patients in the mild group and 52.5% in the severe group were diabetic. 55% in the mild and 76.3% in the severe group were hypertensive. 32.5% in the mild and 43.75% in the severe group were both diabetic and hypertensive. Hence, there is a statistically significant relation between diabetes and hypertension and the severity of the disease.

The study by Pérez-García et al., said diabetes mellitus was the most common comorbidity in patients.[9] Whereas the study by Fazio et al., found 48% of non-survivors were hypertensive and 31% were diabetic.[10] Hypertension was the second most common comorbidity. About 76% of patients in the severe group were hypertensive whereas only 55% in the mild group were hypertensive. Yao et al., also reported that 31.5% of ICU patients had hypertension.[11]

Values of D-dimer and COVID-19 infection

D-dimer is an investigation of choice for diseases with thrombus formation like pulmonary embolism PVT and cardiovascular disease. D-dimer had been used as a biomarker for various thrombotic diseases.

In our study, the median D-dimer at admission in the severe group was raised (1339) compared to that of the mild group (390) and is statistically significant (P=0.001).

The study by Guan et al., also showed that the D-dimer was elevated and there was difference in elevation of D-dimer between survivors and non-survivors.[12] Similarly Huang et al., also reported the mean D-dimer values were elevated in ICU patients when compared to non-ICU patients but the values were not statistically significant. ICU admission is considered as severe disease.[5]

D-dimer values for assessment of the severity of COVID-19 infection

The study found the cutoff of 569 μg/mL of D-dimer at a sensitivity of 83.8% and specificity of 61.2% as ideal value for determining the severity of COVID infection in patients. The study of Vivan et al., found a concentration of 0.5 μg/mL or above associated with severe infection with a sensitivity of 98.2% but a specificity of 5.7%.[13]

The observation that patients with COVID-19 frequently have elevated D-dimer was a significant finding of the pathophysiology of the syndrome involving the coagulation cascade. However, the D-dimer test can be a fair test to the severity of the disease with limitations. The use of this test in isolation needs to be further studied. Early and effective predictors of clinical outcomes are urgently needed to improve the management of COVID-19 patients. Among routine tests, D-dimer might be used as the best early marker to assess severity of COVID-19 patients.

The role of PT, aPTT, and fibrinogen levels in assessing the severity of COVID-19 infection

Fibrinogen, also known as Factor I, is a glycopeptide composed of three pairs of polypeptides covalently linked by disulfide bonds. Fibrinogen plays a major role in platelet aggregation through enzymatic conversion to fibrin and is also the main determinant of plasma viscosity and erythrocyte aggregation. The present study found a statistical difference between mean fibrinogen levels at admission in the mild group (382.64 mg/dL) and severe group (480.05 mg/dL).

The AUC of ROC was 0.669. Hence, it is a poor test to be used for accessing severity.

The mean PT value in this study is 15.11±2.8 s in the mild and 17.47±2.5 s in the severe group. The difference in the mean was statistically significant at admission and after 5 days. This study found 16.25 s as the cut-off value of PT with 76.3% sensitivity and 61.2% specificity.

Similarly, APTT also showed a statisticaly significant difference from admission to 10 days. A cutoff of 42.55 s was found. Since, the AUC determined was 0.69 (<0.7), aPTT is a poor test for accessing the severity of the diseases.

Limitations of the study

This study has a few limitations like the sample size being less and the study is done in a single center. Further studies needs to done to determine the role of various coagulation factors to be used in the multiparameter approach.

CONCLUSION

D-dimer can be effectively used as an indicator of the severity in COVID-19 disease. A cut-off of 569 μg/mL of D-dimer is found out to determine the severity of COVID-19 infection in patients.

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REFERENCES

1. Weiss SR and Navas-Martin S. Coronavirus pathogenesis and the emerging pathogen severe acute respiratory syndrome coronavirus. Microbiol Mol Biol Rev. 2005;69(4):635-664.
   https://doi.org/10.1128/MMBR.69.4.635-664.2005
2. WHO Coronavirus (COVID-19) Dashboard. World Health Organization.
3. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. Lancet. 2020;395(10223):507-513.
   https://doi.org/10.1016/S0140-6736(20)30211-7
4. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382(18):1708-1720.
   https://doi.org/10.1056/NEJMoa2002032
5. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506.
   https://doi.org/10.1016/S0140-6736(20)30183-5 Erratum in: Lancet. 2020.
6. Ahirwar A, Takhelmayum R, Sakarde A, Rathod B, Jha P, Kumawat R, et al. The study of serum hsCRP, ferritin, IL-6 and plasma D-dimer in COVID-19: A retrospective study. Horm Mol Biol Clin Investig. 2022;43(3):337-344.
   https://doi.org/10.1515/hmbci-2021-0088
7. Poudel A, Poudel Y, Adhikari A, Aryal BB, Dangol D, Bajracharya T, et al. D-dimer as a biomarker for assessment of COVID-19 prognosis: D-dimer levels on admission and its role in predicting disease outcome in hospitalized patients with COVID-19. PLoS One. 2021;16(8):e0256744.
   https://doi.org/10.1371/journal.pone.0256744
8. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with covid-19 in Wuhan, China: A retrospective cohort study. Lancet. 2020;395(10229):1054-1062.
   https://doi.org/10.1016/S0140-6736(20)30566-3
9. Pérez-García N, García-González J, Requena-Mullor M, Rodríguez-Maresca MÁ and Alarcón-Rodríguez R. Comparison of analytical values D-dimer, glucose, ferritin and C-reactive protein of symptomatic and asymptomatic COVID-19 patients. Int J Environ Res Public Health. 2022;19(9):5354.
   https://doi.org/10.3390/ijerph19095354
10. Fazio S and Tufano A, De Simone G. Sustained high D-dimer in outpatients who have recovered from mild to moderate coronavirus disease 2019 (COVID-19). Semin Thromb Hemost. 2021;48(1):115-117.
    https://doi.org/10.1055/s-0041-1729857
11. Yao Y, Cao J, Wang Q, Shi Q, Liu K, Luo Z, et al. D-dimer as a biomarker for disease severity and mortality in COVID-19 patients: A case control study. J Intensive Care. 2020;8(1):49.
    https://doi.org/10.1186/s40560-020-00466-z
12. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382(18):1708-1720.
    https://doi.org/10.1056/NEJMoa2002032

Authors Contributions:
RS- Concept, design, protocol, sample collection, analysis, manuscript preparation, data analysis, result analysis, interpretation, and literature survey; **LV-** Guiding the process of the study. Review of result analysis and interpretation, guidance, and support, review of manuscript; **DS-** Guiding the process of the study. Review of result analysis and interpretation, guidance, and support, review of the manuscript; **SS-** Concept of the study, guidance, and support

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