Original Research Article

Role of D dimer, Prothrombin Time, Activated partial thromboplastin time in predicting the severity and prognosis in patients with COVID-19: A Tertiary Care Centre Study In Gwalior

Reena Jain[1], Reema Bhushan[2],Prakriti Gupta[3],KS Mangal[4]

[1]Associate Professor, Gajra Raja Medical College, Gwalior , Madhya Pradesh, India
[2]Assistant Professor, Gajra Raja Medical College, Gwalior , Madhya Pradesh, India
[3]Demonstrator, Gajra Raja Medical College, Gwalior , Madhya Pradesh, India
[4]Professor and Head, Gajra Raja Medical College, Gwalior , Madhya Pradesh, India

Received: 12-03-2021 / Revised: 13-04-2021 / Accepted: 27-05-2021

Abstract

Introduction:COVID-19 has emerged as a pandemic. There is an overactivated immune response causing cytokine storm. Deranged haemostasis has been observed in patients with COVID-19 pointing more towards prothrombotic state. Clinical laboratory coagulation indexes, like D-dimer (DD), prothrombin time (PT), activated partial thromboplastin time (aPTT) can reflect the clotting state of the patient. Significant correlation between coagulating factors and disease outcome have been quoted by many studies. **Aim:**The aim of the study is to investigate role of the dynamic changes of coagulation parameters in predicting prognosis among the COVID-19 patients.**Material and Methods:**In this study, a total of 630 patients with confirmed COVID-19 were included. D-dimer, PT and aPTT values were obtained at the time of admission. Follow up second and third D-dimer values were also obtained wherever feasible. Comparison was made using each parameter between the mortality and non-mortality group.**Results:**There was a significant difference of D-Dimer (Baseline) between mortality and non-mortality group (W = 23581.000, p = <0.001), with the median D-Dimer (Baseline) being highest in the mortality present group. Similar result was seen with D-Dimer (1st Repeat) (W = 275.500, p = 0.049). Moreover, participants with baseline D-dimer > 2µg/ml had the larger largest proportion of mortality.
Conclusion: It was concluded that raised D – dimer among the covid-19 patients is associated with high risk of morbidity and mortality.

Keywords: D dimer, Covid -19, Coagulation

Introduction

COVID-19 is an acute infectious disease caused by a new strain of coronavirus family (SARS-CoV-2). COVID-19 presents mainly as mild to moderate fever [1,2,3]. However, some may gradually develop dyspnoea. In severe cases, the disease can progress rapidly, leading ultimately to severe septic shock and death [4-7]. COVID-19 severity is characterised by the diversity of symptoms, radiological manifestations, and disease progression. Interestingly, some severe, critical, and deceased patients have shown to suffer from significant coagulation dysfunction [8,9]. SARS-CoV-2 gain entrance in the body through the angiotensin-converting enzyme 2 (ACE2) receptor which is adsorbed on the surface of mucosal epithelial cells [4,5]. The pathogen associated molecular pattern (PAMP) linked to it can be quickly recognized by the immune system. As a result, the immune response undergo activation to clear the virus. However, this overactivated immune response sometime causes cytokine storm.This cytokine storm causes vascular endothelial damage, cytokine-induced overexpression of tissue factor, endothelial dysfunction with loss of antithrombotic properties of the endothelium, stasis, and hypoxia [10]. Excessive thromboses takes place in the microvascular system. This leads to disseminated intravascular coagulation (DIC). Additionally, there is microcirculatory disorder and serious multiple organ dysfunction [11].Clinical laboratory coagulation indexes, like D-Dimer(DD),prothrombin time (PT), activated partial thromboplastin time (aPTT), thrombin time (TT), and fibrinogen (Fg) can very well reflect the clotting state of the body. PT and aPTTare representative of exogenous and endogenous coagulating systems respectively. They can aid in early diagnosis of DIC [12].Studies have shown that the COVID- 19 coagulopathy mainly characterized by mild thrombocytopenia, prolongation of the prothrombin time, activated partial thromboplastin time, high levels of D-dimer, and elevated levels of fibrinogen, factor VIII, and von Willebrand factor [10]. Increased D dimer indicate towards hyper coagulating state and secondary fibrinolysis. This is caused by increased fibrinolytic activity within the body. The levels of D-dimer correlate with disease severity have been described in previous studies. It can help predict the risk of thrombosis, ventilatory support need and mortality among the admitted patients[10]. Considerable evidence in previous studies indicated that COVID-19 is a hypercoagulable state. Autopsy studies in COVID -19 revealed unsuspected deep vein thrombosis and multiple thrombi in the vessels of the lungs, kidneys, and other organs [13]. These findings have directed many clinicians to start the use of heparin or low molecular- weight heparin in critically ill COVID- 19 patients. Studies also showed a significant correlation between coagulating factors and disease outcome. Thus, suggesting that D dimer, PT, and aPTT could prove as indicators for disease progression and severity [12]. Therefore, early detection and correction of coagulation dysfunction among the COVID- 19 patients could effectively reduce mortality.The aim of the study is to investigate role of the dynamic changes of DD, PT and aPTT in predicting the severity and prognosis in patients with COVID-19.

**Correspondence*
Dr. Reema Bhushan
Assistant Professor, Gajra Raja Medical College, Gwalior , Madhya Pradesh, India
E-mail: drreems25@gmail.com

Material and Methods

A total of 630 patients with confirmed COVID-19 who were admitted between August 2020 till December 2020 were included in the study. Confirmation was done by positive result of the nucleic acid test of SARS-CoV-2 by real-time fluorescence RT-PCR. The laboratory data were collected at the point of admission. D dimer, PT and aPTT values were obtained. Two more d dimer levels among the patients were obtained wherever possible. Second d dimer was obtained three to four days after first value and third d dimer value was taken three to four days after second testing. These were labelled as baseline, D dimer 1st repeat and D dimer 2nd repeat respectively. Statistical analysis was conducted using the SPSS 25.0 software. Descriptive statistics included means with standard deviations, median and range among each variable. Shapiro–Wilk test was applied to predict the normality that is the data came from a normally distributed population. The Receiver Operating Characteristic curve (ROC curve) was used to calculate the area under the curve among PT, aPTT and D dimer in order to evaluate the sensitivity and specificity of these factors in predicting mortality and non-mortality. Odds ratio and relative risk were also obtained for each of these variables. A P value < 0.05 was considered statistically significant.

Results and Discussion

630 patients were included in the study. Baseline PT, aPTT and D dimer were obtained.Out of 630 patients, 443(70.3%) were male while 187(29.7%) of the participants were female. (fig 1).

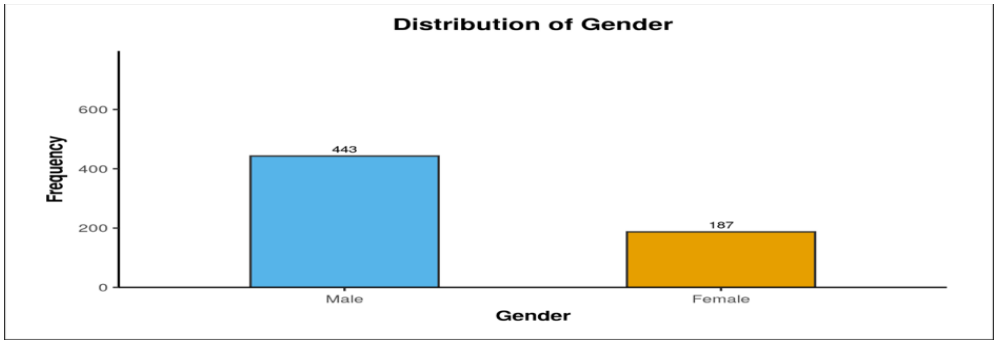

Fig 1: Male to female ratio among Covid-19 patients

Prothrombin time (PT) data was available for 590 patients. The PT ranged from 10.9 – 90 seconds. The mean (SD) of PT was 17.25 seconds (12.11 seconds). The median (IQR) of PT was 14.60 seconds (13.3-16.4 seconds). 424 (71.9%) participants had PT within normal range while 166 (28.1%) of the participants had raised PT. The variable PT was not normally distributed (Shapiro-Wilk Test: p = <0.001). aPTT data was available for 588 patients. The mean (SD) of aPTT was 32.73 (24.16) seconds. The median (IQR) of aPTT was 28.25 seconds (24.7-32.8 seconds). The aPTT ranged from 13.2 - 180seconds. 451 (76.7%) of the participants had aPTT within normal range. 137(23.3%) of the participants had raised aPTT. The variable aPTT was not normally distributed (Shapiro-Wilk Test: p = <0.001).

D Dimer baseline value was available in 552 participants. The D-Dimer (Baseline) ranged from 0.05 - 31.08 µg FEU/ml. The mean (SD) of D-Dimer (Baseline) was 3.03 µg FEU/ml (4.65 µg FEU/ml). The median (IQR) of D-Dimer (Baseline) was 1.00 µg FEU/ml (0.5-3.49 µg FEU/ml). 139 (25.2%) participants had D-Dimer <0.5 µg FEU/ml (Baseline) while 413 (74.8%) of the participants had D-Dimer >0.5 µg FEU/ml (Baseline). The variable D-Dimer (Baseline) was not normally distributed (Shapiro-Wilk Test: p = <0.001). D-Dimer (1st Repeat) was obtained in 52 participants. The D-Dimer (1st Repeat) ranged from 0.18 – 20 µg FEU/ml. The mean (SD) of D-Dimer (1st Repeat) was 3.54 µg FEU/ml (5.22 µg FEU/ml). The median (IQR) of D-Dimer (1st Repeat) was 1.67 µg FEU/ml (0.81-3.6 µg FEU/ml). Eight (15.4%) participants had D-Dimer <0.5 µg FEU/ml (1st Repeat) while 44 (84.6%) participants had D-Dimer >0.5 µg FEU/ml (1st Repeat). The variable D-Dimer (1st Repeat) was not normally distributed (Shapiro-Wilk Test: p = <0.001). Second repeat D dimer was obtained in 15 participants. The mean (SD) of D-Dimer (2nd Repeat) was 2.83 µg FEU/ml (3.73 µg FEU/ml). The median (IQR) of D-Dimer (2nd Repeat) was 1.07 µg FEU/ml (0.48-3.35 µg FEU/ml). The D-Dimer (2nd Repeat) ranged from 0.04 - 11.65 µg FEU/ml. 4 (26.7%) participants had D-Dimer <0.5 µg FEU/ml (2nd Repeat) while 11(73.3%) participants had D-Dimer >0.5 µg FEU/ml (2nd Repeat). The variable D-Dimer (2nd Repeat) was not normally distributed (Shapiro-Wilk Test: p = <0.001). Out of 630 participants, 87 were deceased. Chi-squared test was used to explore the association between 'mortality' and 'gender'. Out of 630 patients, 443(70.3%) were male while 187(29.7%) of the participants were female. Among the 443 male participants, 62 (14.0%) succumbed to covid-19. Among 187 female participants, 25 (13.4%) died due to covid-19 infection. There was no significant difference between the various groups in terms of distribution of mortality ($\chi2 = 0.048$, p = 0.827). (table 1)

Table 1: Association Between Mortality and Gender (n = 630)

Gender	Mortality			Chi-Squared Test	
	Present	Absent	Total	χ2	P Value
Male	62 (14.0%)	381 (86.0%)	443 (100.0%)	0.048	0.827
Female	25 (13.4%)	162 (86.6%)	187 (100.0%)		
Total	87 (13.8%)	543 (86.2%)	630 (100.0%)		

Pt Performance:The variable PT was not normally distributed in the mortality present verses absent subgroups. Thus, non-parametric tests (Wilcoxon-Mann-Whitney U Test) were used to make group comparisons. The groups were divided into mortality present verses mortality absent. The mean (SD) of PT in the mortality present group was 17.08 (12.06) seconds. The mean (SD) of PT in the mortality absent group was 17.28 (12.14) seconds. The median (IQR) of PT in the mortality present group was 14.35 (13.2-15.95) seconds. The median (IQR) of PT in the Mortality Absent group was 14.6 (13.4-16.4) seconds. The PT in the mortality present group ranged from 11.3 – 90 seconds. The PT in the Mortality Absent ranged from 10.9 – 90 seconds. There was no significant difference between the groups in terms of PT (W = 20301.500, p = 0.529). (table 2)

Table 2: Comparison of the 2 Subgroups of the Variable Mortality in Terms of PT (n = 590)

PT	Mortality		Wilcoxon-Mann-Whitney U Test	
	Present	Absent	W	p value
Mean (SD) (seconds)	17.08 (12.06)	17.28 (12.14)	20301.500	0.529
Median (IQR) (seconds)	14.35 (13.2-15.95)	14.6 (13.4-16.4)		
Range(seconds)	11.3 - 90	10.9 - 90		

The area under the ROC curve (AUROC) for PT predicting mortality vs non mortality was 0.521 (95% CI: 0.454 - 0.589), thus demonstrating poor diagnostic performance. It was not statistically significant (p = 0.529). At a cut off of PT ≤14.5 seconds, it predicts mortality with a sensitivity of 55%, and a specificity of 52%. The odds ratio (95% CI) for mortality present when PT is ≤14.5 seconds was 1.29 (0.82-2.06). The relative risk (95% CI) for Mortality present when PT is ≤14.5 seconds was 1.25 (0.84-1.85). (table 3, figure 2). The cut-off and the diagnostic parameters reported above are not reliable as the test is not statistically significant.

Table 3: Diagnostic Performance of PT in Predicting Mortality: Present vs Mortality: Absent (n = 590)

Parameter	Value (95% CI)
Cut-off (p value)	≤ 14.5 seconds (0.529)
AUROC	0.521 (0.454 - 0.589)
Sensitivity	54.8% (44-66)
Specificity	51.9% (47-56)
Positive Predictive Value	15.9% (12-21)
Negative Predictive Value	87.3% (83-91)
Diagnostic Accuracy	52.3% (48-56)
Positive Likelihood Ratio	1.14 (0.92-1.41)
Negative Likelihood Ratio	0.87 (0.68-1.12)
Diagnostic Odds Ratio	1.31 (0.82-2.08)

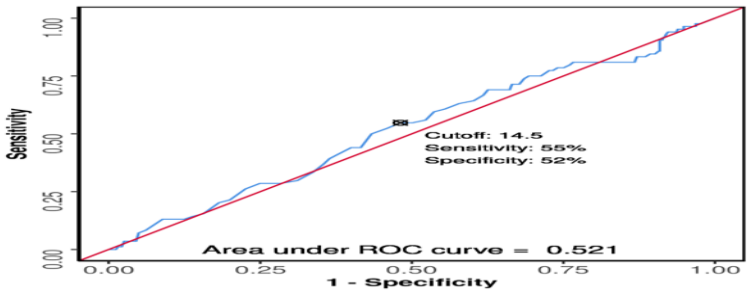

Fig 2:ROC Curve Analysis Showing Diagnostic Performance of PT in Predicting Mortality: Present vs Mortality: Absent (n = 590)

aPTT Performance: The variable aPTT was not normally distributed in the 2 subgroups i.e. mortality present verses mortality absent group. Thus, non-parametric tests (Wilcoxon-Mann-Whitney U Test) were used to make group comparisons. The mean (SD) of aPTT in the mortality present group was 32.15 seconds (24.48). The mean (SD) of aPTT in the mortality absent group was 32.84 (24.15) seconds. The median (IQR) of aPTT in the mortality present group was 27.05 (23.58-32.2) seconds. The median (IQR) of aPTT in the mortality absent group was 28.4 (25-32.9) seconds. The aPTT in the mortality present group ranged from 20 – 180 seconds. The aPTT in the mortality absent group ranged from 13.2 – 180 seconds. There was no significant difference between the groups in terms of aPTT (W = 19055.500, p = 0.150). (table 4)

Table 4: Comparison of the 2 Subgroups of the Variable Mortality in Terms of aPTT (n = 588)

aPTT	Mortality		Wilcoxon-Mann-Whitney U Test	
	Present	Absent	W	p value
Mean (SD) (seconds)	32.15 (24.48)	32.84 (24.15)	19055.500	0.150
Median (IQR) (seconds)	27.05 (23.58-32.2)	28.4 (25-32.9)		
Range(seconds)	20 - 180	13.2 - 180		

The area under the ROC curve (AUROC) for aPTT predicting mortality present vs absent was 0.549 (95% CI: 0.48 - 0.618), thus demonstrating poor diagnostic performance. It was not statistically significant (p = 0.150). At a cut-off of aPTT ≤25.2 seconds, it predicts mortality with a sensitivity of 43% and specificity of 72%. The cut-off and the diagnostic parameters reported above are not reliable as the test is not statistically significant. (table 5, fig 3)

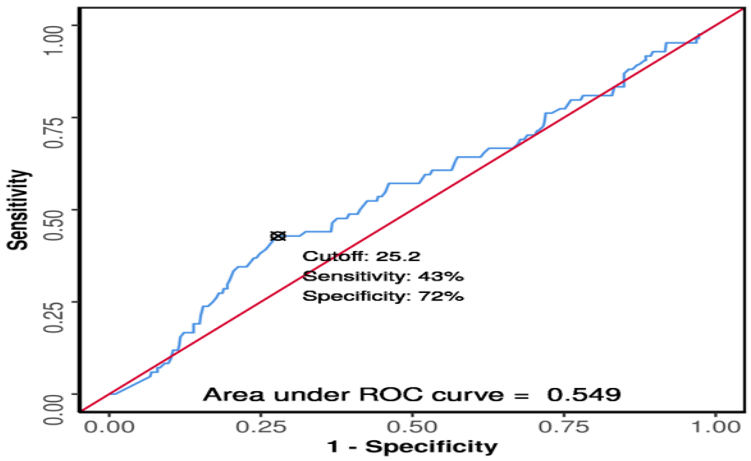

Fig 3: ROC Curve Analysis Showing Diagnostic Performance of aPTT in Predicting Mortality: Present vs Mortality: Absent (n = 588)

Table 5: ROC Curve Analysis Showing Diagnostic Performance of aPTT in Predicting Mortality: Present vs Mortality: Absent (n = 588)

Parameter	Value (95% CI)
Cut-off (p value)	≤ 25.2 seconds (0.150)
AUROC	0.549 (0.48 - 0.618)
Sensitivity	42.9% (32-54)
Specificity	72.2% (68-76)
Positive Predictive Value	20.5% (15-27)
Negative Predictive Value	88.3% (85-91)
Diagnostic Accuracy	68.0% (64-72)
Positive Likelihood Ratio	1.54 (1.16-2.05)
Negative Likelihood Ratio	0.79 (0.65-0.96)
Diagnostic Odds Ratio	1.94 (1.21-3.12)

D dimer (baseline) Performance: The variable D-Dimer (Baseline) was not normally distributed in the mortality present verses mortality absent subgroups. Thus, non-parametric tests (Wilcoxon-Mann-Whitney U Test) were used to make group comparisons. The mean (SD) of D-Dimer (Baseline) in the mortality present group was 4.98 µg FEU/ml (5.99 µg FEU/ml). The mean (SD) of D-Dimer (Baseline) in the mortality absent group was 2.71 µg FEU/ml (4.32 µg FEU/ml). The median (IQR) of D-Dimer (Baseline) in the mortality present group was 2.3 µg FEU/ml (0.67-6.46 µg FEU/ml). The median (IQR) of D-Dimer (Baseline) in the mortality absent group was 0.94 µg FEU/ml (0.49-2.94 µg FEU/ml). The D-Dimer (Baseline) in the mortality present group ranged from 0.18 - 20.29 µg FEU/ml. The D-Dimer (Baseline) in the mortality absent group ranged from 0.05 - 31.08 µg FEU/ml. There was a significant difference between the 2 groups in terms of D-Dimer (Baseline) (W = 23581.000, p = <0.001), with the median D-Dimer (Baseline) being highest in the mortality present group. (table 6)

Table 6: Comparison of the 2 Subgroups of the Variable Mortality in Terms of D-Dimer (Baseline) (n = 552)

D-Dimer (Baseline)	Mortality		Wilcoxon-Mann-Whitney U Test	
	Present	Absent	W	p value
Mean (SD)(µg/ml)	4.98 (5.99)	2.71 (4.32)	23581.000	<0.001
Median (IQR) (µg/ml)	2.3 (0.67-6.46)	0.94 (0.49-2.94)		
Range(µg/ml)	0.18 - 20.29	0.05 - 31.08		

The area under the ROC curve (AUROC) for D-Dimer (Baseline) predicting mortality was 0.632 (95% CI: 0.563 - 0.702). It was statistically significant (p = <0.001). At a cut-off of D-Dimer (Baseline) ≥1.6 µg FEU/ml, it predicts mortality with a sensitivity of 62% and specificity of 66%. The odds ratio (95% CI) for mortality present when D-Dimer (Baseline) is ≥1.6 µg FEU/ml was 2.99 (1.83-4.88). The relative risk (95% CI) for mortality when D-Dimer (Baseline) is ≥1.6 µg FEU/ml was 2.53 (1.67-3.84). (fig4, table 7)

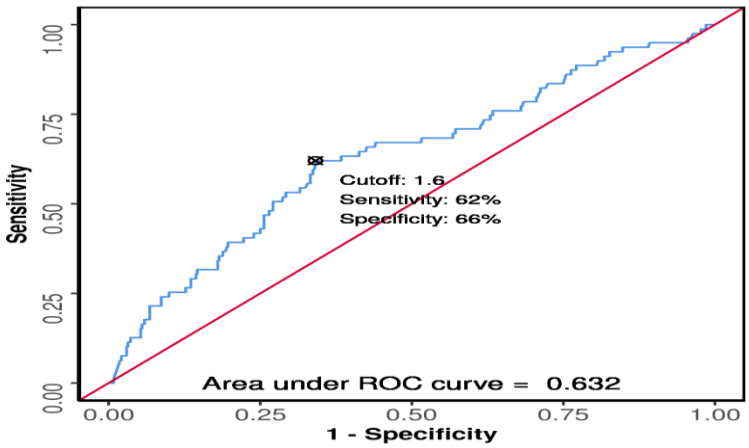

Fig 4: ROC Curve Analysis Showing Diagnostic Performance of D-Dimer (Baseline) in Predicting Mortality: Present vs Mortality: Absent (n = 552)

Table 7: ROC Curve Analysis Showing Diagnostic Performance of D-Dimer (Baseline) in Predicting Mortality: Present vs Mortality: Absent (n = 552)

Parameter	Value (95% CI)
Cut-off (p value)	≥ 1.6 µg/ml (<0.001)
AUROC	0.632 (0.563 - 0.702)
Sensitivity	62.0% (50-73)
Specificity	65.9% (61-70)
Positive Predictive Value	23.3% (18-30)
Negative Predictive Value	91.2% (88-94)
Diagnostic Accuracy	65.3% (61-69)
Positive Likelihood Ratio	1.82 (1.47-2.25)
Negative Likelihood Ratio	0.58 (0.43-0.77)
Diagnostic Odds Ratio	3.16 (1.93-5.16)

D Dimer (1st Repeat) Performance: The variable D-Dimer (1st Repeat) was not normally distributed in the mortality present verses absent groups. Thus, non-parametric tests (Wilcoxon-Mann-Whitney U Test) were used to make group comparisons. The mean (SD) of D-Dimer (1st Repeat) in the mortality present group was 5.73 µg FEU/ml (6.26 µg FEU/ml). The mean (SD) of D-Dimer (1st Repeat) in the mortality absent group was 3.08 µg FEU/ml (4.94 µg FEU/ml). The median (IQR) of D-Dimer (1st Repeat) in the mortality present group was 2.84 µg FEU/ml (1.88-6.96 µg FEU/ml). The median (IQR) of D-Dimer (1st Repeat) in the mortality absent group was 1.44 µg FEU/ml (0.64-3 µg FEU/ml). The D-Dimer (1st Repeat) in the mortality present group ranged from 0.72 - 20 µg FEU/ml.The D-Dimer (1st Repeat) in the mortality absent group ranged from 0.18 - 20 µg FEU/ml. There was a significant difference between the 2 groups in terms of D-Dimer (1st Repeat) (W = 275.500, p = 0.049), with the median D-Dimer (1st Repeat) being highest in the mortality present group. (table 8)

Table 8: Comparison of the 2 Subgroups of the Variable Mortality in Terms of D-Dimer (1st Repeat) (n = 52)

D-Dimer (1st Repeat)	Mortality		Wilcoxon-Mann-Whitney U Test	
	Present	Absent	W	p value
Mean (SD) (µg/ml)	5.73 (6.26)	3.08 (4.94)	275.500	0.049
Median (IQR) (µg/ml)	2.84 (1.88-6.96)	1.44 (0.64-3)		
Range (µg/ml)	0.72 - 20	0.18 - 20		

The area under the ROC curve (AUROC) for D-Dimer (1st Repeat) for predicting mortality was 0.712 (95% CI: 0.533 - 0.891), thus demonstrating fair diagnostic performance. It was statistically significant (p = 0.049). At a cut-off of D-Dimer (1st Repeat) ≥1.88 µg FEU/ml, it predicts mortality with a sensitivity of 78% and specificity of 60%. The odds ratio (95% CI) for mortality present when D-Dimer (1st Repeat) is ≥1.88 µg FEU/ml was 3.06 (0.67-13.91). The relative risk (95% CI) for mortality present when D-Dimer (1st Repeat) is ≥1.88 µg FEU/ml was 2.52 (0.77-8.5). (fig5, table 9)

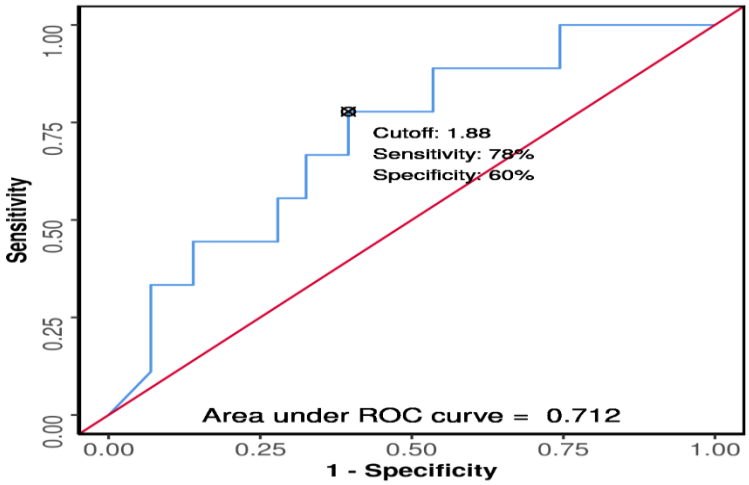

Fig 5:ROC Curve Analysis Showing Diagnostic Performance of D-Dimer (1st Repeat) in Predicting Mortality: Present vs Mortality: Absent (n = 52)

Table 9:ROC Curve Analysis Showing Diagnostic Performance of D-Dimer (1st Repeat) in Predicting Mortality: Present vs Mortality: Absent (n = 52)

Parameter	Value (95% CI)
Cut-off (p value)	≥ 1.88 µg/ml (0.049)
AUROC	0.712 (0.533 - 0.891)
Sensitivity	77.8% (40-97)
Specificity	60.5% (44-75)
Positive Predictive Value	29.2% (13-51)
Negative Predictive Value	92.9% (76-99)
Diagnostic Accuracy	63.5% (49-76)
Positive Likelihood Ratio	1.97 (1.18-3.27)
Negative Likelihood Ratio	0.37 (0.11-1.28)
Diagnostic Odds Ratio	5.35 (0.99-28.9)

D Dimer (2nd Repeat) Performance: The variable D-Dimer (2nd Repeat) was not normally distributed in the Mortality present verses absent group. Thus, non-parametric tests (Wilcoxon-Mann-Whitney U Test) were used to make group comparisons. The mean (SD) of D-Dimer (2nd Repeat) in the mortality present group was 4.67 µg FEU/ml (4.61 µg FEU/ml). The mean (SD) of D-Dimer (2nd Repeat) in the mortality absent group was 2.17 µg FEU/ml (3.36 µg F'EU/ml). The median (IQR) of D-Dimer (2nd Repeat) in the mortality present group was 3.35 µg FEU/ml (1.23-6.79 µg FEU/ml). The median (IQR) of D-Dimer (2nd Repeat) in the mortality absent group was 0.96 µg FEU/ml (0.38-2.32 µg FEU/ml). The D-Dimer (2nd Repeat) in the mortality present group ranged from 1.07 - 10.9 µg FEU/ml.The D-Dimer (2nd Repeat) in the mortality absent group ranged from 0.04 - 11.65 µg FEU/ml. There was no significant difference between the groups in terms of D-Dimer (2nd Repeat) (W = 34.000, p = 0.138). (table 10)

Table 10: Comparison of the 2 Subgroups of the Variable Mortality in Terms of D-Dimer (2nd Repeat) (n = 15)

D-Dimer (2nd Repeat)	Mortality		Wilcoxon-Mann-Whitney U Test	
	Present	Absent	W	p value
Mean (SD) (µg/ml)	4.67 (4.61)	2.17 (3.36)	34.000	0.138
Median (IQR) (µg/ml)	3.35 (1.23-6.79)	0.96 (0.38-2.32)		
Range (µg/ml)	1.07 - 10.9	0.04 - 11.65		

The area under the ROC curve (AUROC) for D-Dimer (2nd Repeat) predicting mortality was 0.773 (95% CI: 0.518 - 1). It was not statistically significant (p = 0.133). At a cut off of D-Dimer (2nd Repeat) ≥1.067 µg FEU/ml, it predicts mortality with a sensitivity of 100%, and a specificity of 64%. The odds ratio (95% CI) for mortality present when D-Dimer (2nd Repeat) is ≥1.067 µg FEU/ml was 5.25 (0.4-68.95). The relative risk (95% CI) for mortality present when D-Dimer (2nd Repeat) is ≥1.067 µg FEU/ml was 3.43 (0.62-21.42). (fig6, table 11)

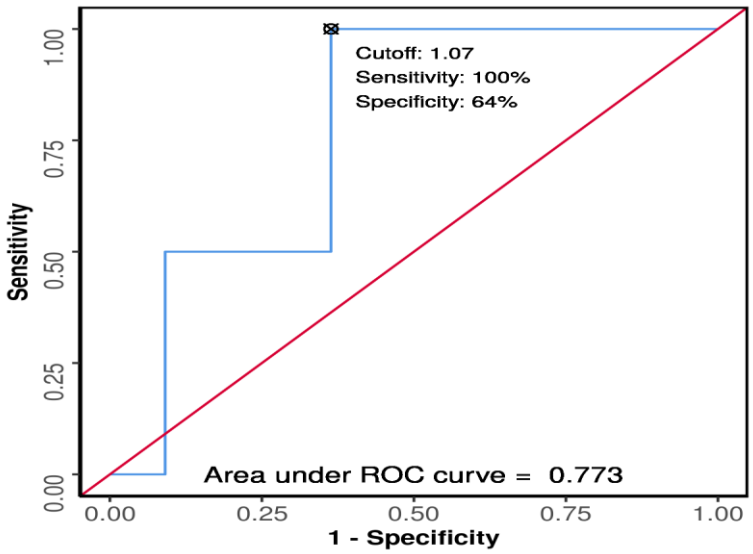

Fig 6:ROC Curve Analysis Showing Diagnostic Performance of D-Dimer (2nd Repeat) in Predicting Mortality: Present vs Mortality: Absent (n = 15)

Table 11:ROC Curve Analysis Showing Diagnostic Performance of D-Dimer (2nd Repeat) in Predicting Mortality: Present vs Mortality: Absent (n = 15)

Parameter	Value (95% CI)
Cut-off (p value)	≥ 1.067 µg/ml (0.133)
AUROC	0.773 (0.518 - 1)
Sensitivity	100.0% (40-100)
Specificity	63.6% (31-89)
Positive Predictive Value	50.0% (16-84)
Negative Predictive Value	100.0% (59-100)
Diagnostic Accuracy	73.3% (45-92)
Positive Likelihood Ratio	2.75 (1.26-6.01)
Negative Likelihood Ratio	0 (0-NaN)
Diagnostic Odds Ratio	Inf (NaN-Inf)

Relationship between the Dynamics Changes of D dimer and the Prognosis of COVID-19: Association was also studied among the D-Dimer >0.5 µg FEU/ml (Baseline), D-Dimer >0.5 µg FEU/ml (1st Repeat), D-Dimer >0.5 µg FEU/ml (2nd Repeat), D-Dimer > 2 µg FEU/ml (Baseline), D-Dimer > 2 µg FEU/ml (1st Repeat), D-Dimer > 2 µg FEU/ml (2nd Repeat) in both mortality verses non mortality groups.

There was a significant difference between the mortality verses non mortality group in terms of distribution of mortality ($\chi2$ = 17.254, p = <0.001) in 'D-dimer > 2 µg FEU/ml (Baseline). Chi-squared test was used to explore the association between 'mortality' and 'D-dimer > 2 µg FEU/ml (Baseline)'. Participants in the group D-dimer > 2 µg FEU/ml (Baseline) had the larger largest proportion of mortality (table 12)

Table 12: Association Between Mortality and D-Dimer > 2 (Baseline) (n = 552)

D-Dimer > 2 µg/ml (Baseline)	Mortality			Chi-Squared Test	
	Present	Absent	Total	$\chi2$	P Value
No	37 (10.0%)	334 (90.0%)	371 (100.0%)	17.254	<0.001
Yes	42 (23.2%)	139 (76.8%)	181 (100.0%)		
Total	79 (14.3%)	473 (85.7%)	552 (100.0%)		

Pairwise comparison of parameters for predicting mortality (parameters have been arranged in descending order of AUROC): There was no significant difference in the diagnostic performance of D-Dimer (2nd Repeat) and D-Dimer (1st Repeat) (DeLong's Test p = 0.557). There was no significant difference in the diagnostic performance of D-Dimer (2nd Repeat) and D-Dimer (Baseline) (DeLong's Test p = 0.417). The diagnostic performance of D-Dimer (2nd Repeat) (AUC = 0.773) was significantly better than that of aPTT (AUC = 0.563) (DeLong's Test p = 0.047). There was no significant difference in the diagnostic performance of D-Dimer (2nd Repeat) and PT (DeLong's Test p = 0.202). There was no significant difference in the diagnostic performance of D-Dimer (1st Repeat) and D-Dimer (Baseline) (DeLong's Test p = 0.967). There was no significant difference in the diagnostic performance of D-Dimer (1st Repeat) and aPTT (DeLong's Test p = 0.160). There was no significant difference in the diagnostic performance of D-Dimer (1st Repeat) and PT (DeLong's Test p = 0.100). There was no significant difference in the diagnostic performance of D-Dimer (Baseline) and aPTT (DeLong's Test p = 0.253). There was no significant difference in the diagnostic performance of D-Dimer (Baseline) and Change in D-Dimer (1st Repeat) (DeLong's Test p = 0.385). The diagnostic performance of D-Dimer (Baseline) (AUC = 0.632) was significantly better than that of PT (AUC = 0.521) (De

Long's Test p = 0.030). There was no significant difference in the diagnostic performance of aPTT and PT (DeLong's Test p = 0.278).

Discussion

Out of 630 patients, 443 (70.3%) were males while 187 (29.7%) of the participants were female. Study of coagulation parameters done by Long H et al[12]included 57.4% males and 42.6% females. In his study, significant difference ($P < 0:05$) and positive correlation were found between D-dimer, PT, and endpoint outcomes. Correlation in third detection was stronger than that in first and second detection of these variables. However, in the present study, baseline PT, baseline aPTT and baseline D dimer were tested with first repeat and second repeat of D dimer. Association was also studied among the D-dimer >0.5 µg FEU/ml (Baseline), D-dimer >0.5 µg FEU/ml (1st Repeat), D-dimer >0.5 µg FEU/ml (2nd Repeat), D-dimer > 2 µg FEU/ml (Baseline), D-dimer > 2 µg FEU/ml (1st Repeat), D-dimer > 2 µg FEU/ml (2nd Repeat) in both mortality verses non mortality groups. Significant difference ($P < 0:05$) and positive correlation were found between D-dimer (1st Repeat), D-dimer (Baseline), D-dimer>2 µg FEU/ml (Baseline) and outcomes i.e., mortality vs non mortal. The AUCs of D dimer baseline, D- dimer 1st repeat, and D dimer 2nd repeat in the study done by Long H et al to predict hospital discharge and mortality were 0.742, 0.818, and 0.851, respectively. In present study, The AUCs of D-dimer baseline, D-dimer 1st repeat, and D-dimer 2nd repeat were 0.632, 0.712, 0.773. The pathogenesis in COVID 19 differs from disseminated intravascular coagulation with associated primary pulmonary localization. There is pulmonary coagulopathy which is intravascular with associated component of thrombo-inflammation. This is reflected in the lab tests with an increase in D-dimer. Raised D-dimer have been found to be associated with severity and outcomes of the disease[14]. Other coagulation parameters such as prothrombin time, activated partial thromboplastin time are only mildly prolonged. Coagulopathy among the covid-19 patients is associated with poor prognosis. Most consistent data reported was for D-dimer[15-20]. Elevated D-dimer value at admission is a predictor for both severity[16-19] and mortality of COVID-19 patients[17,20]. A study done by Zhou F et al suggested that D-dimer greater than 1 µg/mL is associated with fatal outcome of COVID-19 [20]. Zhang et al concluded that D-dimer > 2.0 µg/mL at admission had a sensitivity of 92.3% and specificity of 83.3% to predict mortality; hazard ratio: 51.5, 95% CI 12.9–206.7. In the present study, D-dimer > 2.0 µg/mL(baseline) showed sensitivity of 53.2%, specificity of 70.6%, diagnostic accuracy of 68.1%, odds ratio of 2.72 and p value <0.001 to predict mortality. Helms et al. did study on 150 covid-19 ICU admitted patients. Among them >95% showed elevated d dimer elevated D-dimer on admission. In present study, 74.8% showed elevated d dimer at the time of admission.

Conclusion

Elevated baseline D-dimer levels are associated with inflammation and coagulopathy in COVID-19 patients. The change in the d dimer parameter should be observed dynamically in COVID-19 patients as COVID-19 associated coagulopathy is associated with high risk of morbidity and mortality

References

1. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. Journal of Thrombosis and Haemostasis. 2020; 18(4):844–847.
2. Huang C, Wang Y, Li X. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet. 2020; 395(10223):497–506.
3. Wang D, Hu B, Hu C. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020;323(11):1061.
4. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus. Journal of Virology, 2020;94(7):1
5. Kowalczyk S, Borer A, Tietze N, Vanslambrouck JM, Rasko JEJ, Broer S. A protein complex in the brush-border membrane explains a Hartnup disorder allele. The FASEB Journal. 2008; 22(8):2880–2887.
6. Gates B. Responding to COVID-19 - a once-in-a-century pandemic?. New England Journal of Medicine. 2020; 382(18):1677–1679.
7. Zhou T, Liu Q, Yang Z. Preliminary prediction of the basic reproduction number of the Wuhan novel coronavirus 2019-nCoV. Journal of Evidence-Based Medicine. 2020; 13(1):3-7.
8. Guan WJ, Ni ZY, Hu Y. Clinical characteristics of coronavirus disease 2019 in China. The New England Journal of Medicine. 2020; 382(18):1708-1720.
9. Zhu N, Zhang D, Wang W. A novel coronavirus from patients with pneumonia in China, 2019. The New England Journal of Medicine. 2020;382(8):727–733.
10. Chan NC, Weitz JI. COVID-19 coagulopathy, thrombosis, and bleeding blood. 2020; 136(4):381-383.
11. Cohen J. The immunopathogenesis of sepsis. Nature. 2002;420(6917):885–891.
12. Long H, Nie L, Xiang X, Li H, Zhang X, Fu X. D- Dimer and Prothrombin Time Are the Significant Indicators of Severe COVID-19 and Poor Prognosis. HindawiBioMedResearch International. 2020; Article ID 6159720:1-10
13. Deshpande C. Thromboembolic findings in COVID-19 autopsies: pulmonary thrombosis or embolism? Ann Intern 2020:M20-3255
14. Aggarwal M, Dass J, Mahapatra M. Hemostatic Abnormalities in COVID-19: An Update. Indian J Hematol Blood Transfus. 2020;36(4):616–626.
15. Simmons J, Pittet JF. The coagulopathy of acute sepsis. CurrOpinAnaesthesiol. 2015; 28:227-236.
16. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y. Clinical features of patientsinfected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497–506.
17. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associatedwith poor prognosis in patients with novel coronavirus pneumonia. J ThrombHaemost.2020;18:844–847.
18. Guan W, Ni Z, Hu Y, Liang WH, Ou CQ, He JX. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382:1708–1720.
19. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020;323:1061–1069.
20. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395: 1054–1062.
21. Helms J, Tacquard C, Severac F, Leonard-Lorant I, Ohana M, Delabranche X.High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med. 2020;4:1-10.

Conflict of Interest: Nil Source of support:Nil