Original Research Article

D-Dimer and Coagulation profile are significant prognostic indicators in COVID-19 patients – A retrospective study in a tertiary healthcare hospital

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ABSTRACT

Background: To determine the value of coagulation indicators: D-dimer (DD), prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), in predicting the severity and prognosis of COVID-19.

Materials and Methods: Around 150 patients with confirmed COVID-19 disease, who were admitted at Rajarajeswari Medical College and Hospital, Bangalore between April 15th 2021 and July 15th, 2021, were included in the study. The changes of D-Dimer, PT, APTT were tested, and the correlation with, clinical classifications, demographics, CT imaging, vaccination status against COVID-19 and prognosis were observed.

Results: Coagulation disorder occurred at the early stage of COVID-19 infection, in a total of 150 patients observed, 109 (72.66%, St. deviation of 4.26) patients having DD increased at time of admission and 148 patients (98.66%) having increased coagulation profile. The levels of DD and coagulation profile were correlated with clinical classification and also the CT severity and vaccination status. Among 41(27.33%) patients who died, 31(20.66%) patients had DD increased at the first lab test, 40 (26.66%) patients had DD increased on the fifth day of lab tests. The results shows that D-dimer is raised in severe category of COVID-19 infection. Also the CT severity is high (severe, with CT score>15) 71(47.33%) patients with increased D-dimer on admission. It was observed that 41(27.33%) patients who were vaccinated had increased D-dimer 70(46.66%) compared to unvaccinated patients. In addition, with the progression of the disease, the change of CT imaging was closely related to the increase of the DD value (P <0.01).

Conclusions: Coagulation dysfunction is more likely to occur in severe and critically ill patients. DD and PT could be used as the significant indicators in predicting the mortality of COVID-19 and measuring the level of D-dimer and coagulation parameters from the early stage of the disease can also be useful in controlling and managing of COVID-19 disease, also vaccinated patients had better outcome among the unvaccinated patients.

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1. Introduction

COVID-19 disease has spread worldwide from December 2019 to the present day, the early stage of this disease can be associated with elevated levels of D-dimer, prolonged PT, indicating activation of coagulation pathways and thrombosis. The degree of D-dimer elevation positively correlates with mortality in COVID-19 patients. The lungs of patients with COVID-19 show extensive alveolar and interstitial inflammation.[1] COVID-19 causes a spectrum of disease, with frequent involvement of the hemostatic system.[2,3] Severe pulmonary inflammation causes activation and damage of the pulmonary vasculature

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and may trigger pulmonary thrombosis early in the disease.[4]

The SARS-CoV-2 virus does not appear to have intrinsic procoagulant effects itself; rather, the coagulopathy is most likely the result of the profound COVID-19 inflammatory response and endothelial activation/damage.[5] Recent COVID-19 autopsy reports demonstrate pulmonary endothelial viral inclusions and apoptosis, increased angiogenesis, and increased capillary microthrombi.[6,7]

Three stages of COVID-19-associated coagulopathy have been proposed:
Stage 1 showing elevated D-dimer,
Stage 2 showing elevated D-dimer together with mildly prolonged PT/INR and aPTT and mild thrombocytopeniad.
Stage 3 with critical illness and laboratory studies progressing towards classic DIC.[8]

Elevated D-dimers have been shown to be an independent biomarker for poor prognosis even in COVID-19 patients being treated with LMWH[9] D-dimers are significantly increased in COVID-19, likely reflecting pulmonary vascular bed thrombosis and fibrinolysis.[10] D-dimers reflect fibrin clot formation, clot crosslinking by FXIIIa, and fibrinolysis. The marked elevation of D-dimers in COVID-19 appears to reflect coagulation activation from viremia and cytokine storm, but super infection and organ dysfunction are other possible causes.

A D-dimer cut-off of >0.5 μg/mL may stratify COVID-19 patients at a higher risk of poor outcomes.[11] Increasing D-dimer levels indicate the progressive severity of COVID-19 infection and can be used as a predictor that more aggressive critical care will be needed.

Of nearly 1,500 COVID-19 hospital admissions, Li et al.[12] found two admission covariates that correlated with an increased risk of death: age (OR 1.18; 95% CI 1.02–1.36) and baseline

D-dimer level (OR 3.18; 95% CI 1.48–6.82). In a study by Zhou et al.,[13] factors associated with mortality included an elevated D-dimer >1.0 μg/mL (FEU or DDU units not specified) on admission and increased PT.

In a study of 183 patients by Tang et al., 71.4% of non-survivors and 0.6% of recovered cases met the criteria for disseminated intravascular coagulation during hospitalization.[14] Recent autopsy data from Italy also observed fibrin thrombi in pulmonary small arterial vessels in 87% of fatal cases examined, suggesting the contribution of coagulation in diffuse alveolar and endothelial damage.[15] These data clearly suggest a state of hypercoagulability in severe COVID-19.

This paper aims to investigate the role of D- Dimer, PT, APTT and the co-relation of the CT severity and prognosis in patients with COVID-19.

In this study, was focused on if these indicators are related to the severity of COVID-19.

2. Materials and Methods

A total of 150 patients who are tested positive with RT-PCR COVID-19 who were admitted at Rajarajeswari medical college and hospital between April 15th to June 15th, 2021 was collected.

Cases were collected retrospectively from the medical records department (MRD).

The cases with incomplete laboratory data were excluded. Also patients who were already on anti-coagulation therapy for the respective diseases were excluded.

2.1. Clinical classifications

2.1.1. Case categorization

According to MoFW, management of any COVID-19 patient mandates the Health Care Personal (HCP) to be in full Personal Protection Equipment (PPE). Patients are categorized in to three groups:

1. Category A (mild): Asymptomatic / patients with mild symptoms- RR <24/m &SpO$_2$ >94% in room air.
2. Category B (moderate): symptomatic patient with mild to moderate pneumonia with no signs of severe disease. RR:24 -30 /m (or)SPO$_2$: 90%-94% at Room Air.
3. Category C (severe): Symptomatic patient with severe Pneumonia with RR> 30/min (or) SPO$_2$<90 % at room air (or) less than 94 % with oxygen, ARDS, Septic shock.
4. Critical cases met any of the following: respiratory failure occurs, and mechanical ventilation is required; shock occurs; or complicated with other organ failure that requires monitoring and treatment in ICU.

CT severity: the 25 point CT severity score correlates well with the COVID 19 clinical severity. The total CT score is the sum of the individual lobar scores and can range from 0 (no involvement) to 25 (maximum involvement), when all the five lobes show more than 75% involvement.

Table 1: Lobar CT severity scoring

Score	Category
0	Normal
1-8	Mild
9-15	Moderate
>15	Severe

2.1.2. Outcome of the patients

According to clinical progression, outcomes in endpoints were divided into four types:

1. ICU admission,
2. Hospital discharge
3. Death

2.1.3. Data collection

The laboratory data were collected retrospectively, from the medical records department, at three time points: admission, 3-5 days of hospitalization, and at the endpoint. DD, PT, APTT were obtained. The case identification and categorization were done, along with CT imaging identification, vaccination status and outcome of illness were defined.

2.1.4. Statistical methods

Statistical analysis was conducted using descriptive statistics included means and standard deviations. Inferential statistics like CHI square ROC curve. A P value < 0.05 was considered statistically significant. Using a statistical software MS Excel and SPSS V20 analysis was done.

2.1.5. Patients consent

This was a retrospective case series study, and no patients were involved in the study design, setting the research questions, or the outcome measures directly. No patients were asked to advice on the interpretations or writing up of results.

3. Results and Discussion

3.1. Demographic characteristics [Table 2]

Among 150 patients with COVID-19, the median ages were 48.5±13.43 (22-86) years old, male were 91 (60.66%) cases, female were 59 (39.33%) cases, and over 60 years old were 26 (17.33%) cases.

At the time of admission, moderate category patients were 85 patients (43±10.45) 56.66 % cases, 16 (10.66%) patients were smokers, and around 31(20.66%) patients were vaccinated and 65 (45±10.22) patients that is 43.3% were in severe category with 27 patients (18%).

In this study more patients were less than 60 years.

3.2. The Relationship between the Levels of DD1, PT1, APTT1 and Clinical Classification on admission

There are significant positive correlation between increase in D-dimer and severity of the disease, as the disease is increased DD1 increased. A positive correlation (<0.01) were found between DD1, PT1 and APTT1 with clinical classification of the disease.

3.3. Analysis of the clinical classification and the CT severity score

There was a significant difference with Ct severity scoring between different clinical classifications (P<0.05). The severity of the disease increased with the severe score ;52 (34.66%) patients in moderate category had CT severity of more than 15 and 47 (31.33%) patients in severe category
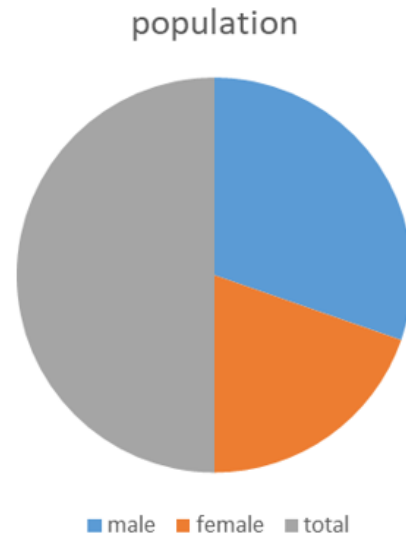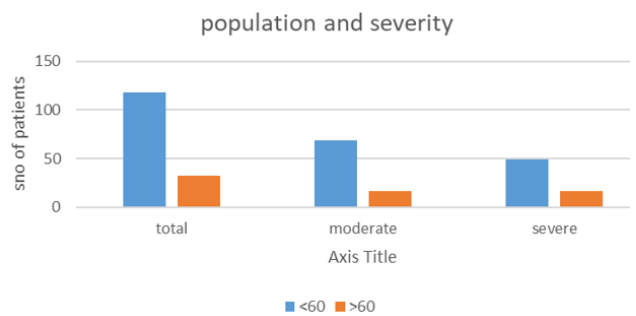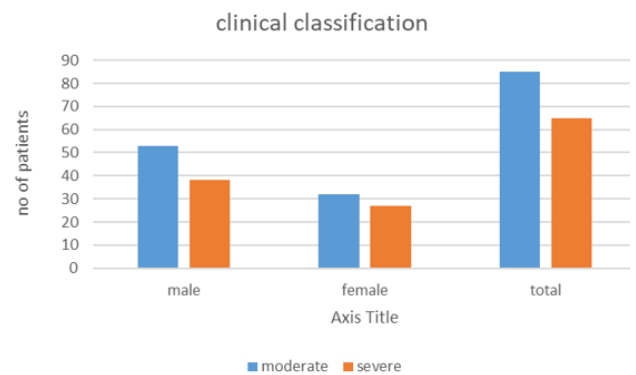

Fig. 1:

Fig. 2:

Fig. 3:

Table 2: Characteristicsof patients with COVID-19

Demographic		Clinical classification on admission		Vaccination status		Smoking		Outcome	
Age, years (x±s)		Moderate 43±10.45	Severe 45±10.22	Moderate 48.5±13.434	Severe	Moderate	Severe	Discharge	Death
Distribution, n (%)									
<60	118(78.66%)	69(46%)	49(32.66%)	26(17.33%)	19(12.66%)	12 (8%)	18(12%)	84(56%)	34(22.6%)
≥60	32(21.33%)	16(10.66%)	16(10.66%)	6(4%)	8(5.33%)	4(2.66%)	4(2.66%)	24(16%)	8(5.33%)
Total	85(56.66%)	65(43.3%)						108(72%)	42(28%)
Gender									
Male	91(60.66%)	53(35.5%)	38(25.33%)	18(12%)	16(10.66%)			66(44%)	24(16%)
Female	59(39.33%)	32(21.33%)	27(18%)	14(9.33%)	18(12%)			42(28%)	18(12%)
Total	150	85(56.66%)	65(43.3%)	32(21.33%)	34(22.6%)			108(72%)	42(28%)

vaccination and age
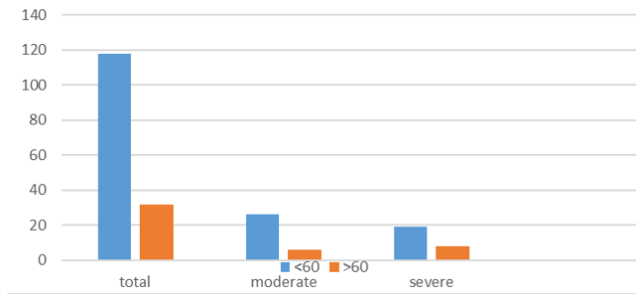
Fig. 4:

outcome
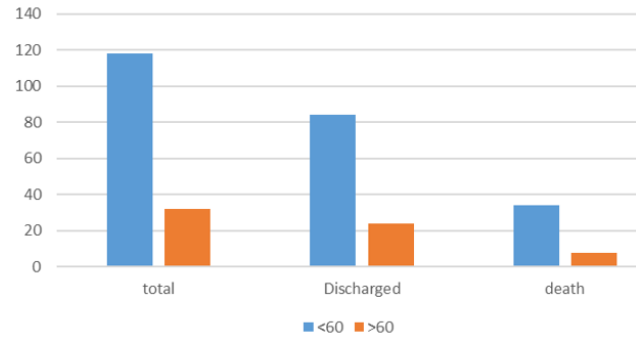
Fig. 5:

Table 3:

Parameters	Moderate	Severe	Total
DD1(M±SD)	4.115±3.65	3.68±4.26	
<0.5	22(14%)	19(12.66%)	41(27.33%)
0.5-1.0	4(2.66%)	7(4.66%)	11(7.33%)
>1.0	59(39.3%)	39(26%)	98(65.33%)
Total	85(56.66%)	65(43.3%)	150

X^2.P X^2=2.50 P > 0.05
r.P r = 0.756 P < 0.01

Table 4:

Parameters	Moderate	Severe	Total
PT 1 (M±SD)	13.55±0.771	13.62±0.91	
<9	0	0	0
9-15	72(48%)	53(35.33%)	125(83.33%)
>15	13(8.66%)	12(8%)	25(16.66%)
Total	85(56.66%)	65(43.33%)	150

X^2.P X^2= 0.266 P >0.05 (0.606)
r.P r = 0.6609 P<0.001

Table 5:

Parameters	Moderate	Severe	Total
APTT1 (M±SD)	30.8±3.95	29.2±1.69	
<21	0	2(1.33%)	2(1.33%)
21-37	67(44.66%)	51(34%)	118(78.6%)
>37	18(12%)	12(8%)	30(20%)
	85	65	150

X^2.P X^2= 2.75 P>0.05 (0.253)
r.P r = 0.8673 P < 0.001

had CT severity score more than 15. The significant difference (p<0.05) and positive correlation (p<0.05) were found between clinical classification and Ct score.

Table 6:

Ct score	Moderate	Severe	Total
0	0	0	0
1-8	2(1.33%)	5(3.33%)	7(4.66%)
9-15	31(20.66%)	13(8.66%)	44(29.33%)
>15	52(34.66%)	47 (31.33%)	99(66%)
	85	65	150

X^2.P X^2= 6.35 P<0.05 (0.02)
r.P r = 0.341 P < 0.05(0.042)

3.4. Analysis of the D-Dimer and the CT severity score

A positive correlation (p<0.01) was found between a higher DD and higher (>15) CT severity score

Table 7: D-dimer

Ct score	<0.5	0.5-1.0	>1.0
0	0	0	0
1-8	3(2%)	1(0.66%)	3(2%)
9-15	10(6.66%)	4(2.66%)	30(20%)
>15	28(18.66)	6(4%)	65(43.33)

X^2.P X^2= 2.45 P >0.05 (0.653)
r.P r = 0.756 P < 0.001

3.5. Analysis of D-Dimer and PT in Predicting Hospital Discharge and Mortality of COVID-19

Table 8:

Parameters	Outcomes at composite end point		
DD1 4.15 ±3.65	Hospital discharge	Death	Total
<0.5	31(20.66%)	10(6.66%)	41(27.33%)
0.5-1.0	7(4.66%)	4(2.66%)	11(7.33%)
>1.0	70(46.66%)	28(18.66%)	98(65.33%)
	108(72%)	42(28%)	150

X^2.P X^2= 3.53 P >0.05 (0.474)
r.P r = 0.03424

Table 9: DD 5

<0.5	11(7.33%)	1(0.66%)	12(8%)
0.5-1.0	14(9.33%)	1(0.66%)	15(10%)
>1.0	83(55.33%)	40(26.66%)	123(82%)
	108(72%)	42(28%)	150

X^2.P X^2= 7.45 P <0.05
r.P r = 1 p< 0.05

Table 10: DD discharge

<0.5	30(20%)	2(1.33%)	32(21.33%)
0.5-1.0	27(18%)	10(6.66%)	37(24.66%)
>1.0	51(34%)	30(20%)	81(54%)
	108(72%)	42(28%)	150

X^2.P X^2= 10.8 P <0.05
r.P r = 1 p< 0.05

Table 11: PT1

Parameters	Outcomes at composite end point		
PT1	Hospital discharge	Death	Total
<9	0	0	0
9-15	87(58%)	38(25.33%)	125(83.33%)
>15	21(14%)	4(2.66%)	25(16.66%)
	108(72%)	42(28%)	150

X^2.P X^2= 2.14 P >0.05 (0.143)
r.P r = 0.890

Table 12: PT 5

<9	2(1.33%)	0	2(1.33%)
9-15	55(36.66%)	21(14%)	76(50.66%)
>15	51(34%)	21(14%)	72(48%)
	108(72%)	42(28%)	150

X^2.P X^2= 0.438 P >0.05
r.P r = 1 P<0.05

Table 13: PT discharge

<9	7(4.66%)	2(1.33%)	9(6%)
9-15	48(32%)	17(11.33%)	65(43.33%)
>15	53(35.33%)	23(15.33%)	76(50.66%)
	108(72%)	42(28%)	150

X^2.P X^2= 0.452 P >0.05
r.P r = 1.2 p< 0.05

Table 14: APTT1

Parameters	Outcomes at composite end point		
APTT1	Hospital discharge	Death	Total
<21	1(0.66%)	1(0.66%)	2(1.33%)
21-37	83(55.33%)	35(23.33%)	118(78.66%)
>37	24(16%)	6(4%)	30(20%)
	108(72%)	42(28%)	150

X^2.P X^2= 1.54 P >0.05 (0.4506)
r.P r = 0.99501 P<0.01

Table 15: PT 5

<21	6(4%)	3(2%)	9(6%)
21-37	93(62%)	29(19.33%)	122(81.33%)
>37	9(6%)	10(6.66%)	19(12.66%)
	108(72%)	42(28%)	150

X^2.P X^2= 6.9276 P < 0.05(0.0313)
r.P r = 0.99654 P<0.01

Table 16: PT discharge

<21	35(23.33%)	1(0.66%)	9(6%)
21-37	71(47.33)	38(25.33%)	65(43.33%)
>37	3(2%)	4(2.66%)	76(50.66%)
<21	108(72%)	42(28%)	150

X^2.P X^2= 17.20 P < 0.05
r.P r = 1 p< 0.05

3.6. Analysis of CT and vaccinated patients and their outcome

Table 17:

Ct score	Vaccinated	Discharge	Death
Mild (1-8)	4(2.66%)	6(4%)	1(0.66%)
Moderate (9-15)	20(13.33%)	36(24%)	7(4.66%)
Severe (>15)	35(23.33%)	65(43.33%)	34(22.66%)

Among 46 (30.66%) vaccinated patients who died had high CT severity score, also 65 (43.33%) vaccinated patients were discharged who had high CT severity score.
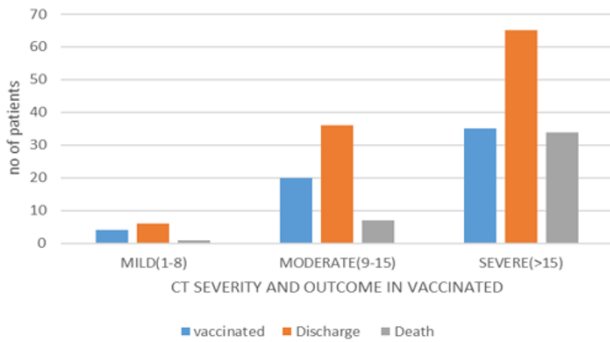

Fig. 6:

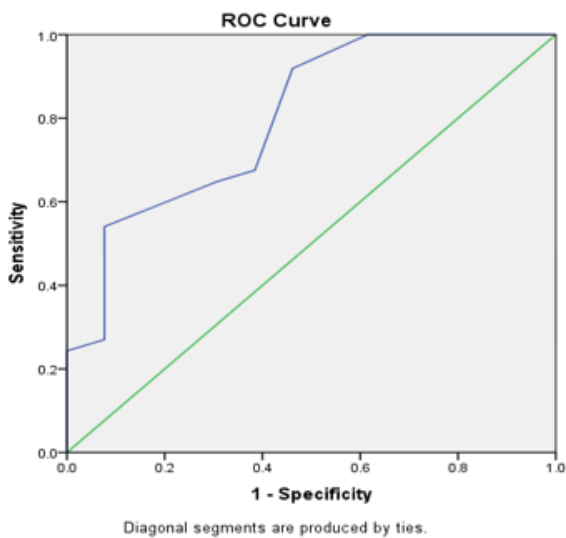### 3.7. Changes of Chest CT Imaging, DD and CTA in COVID-19 patients

Diagonal segments are produced by ties.

Fig. 7:

Table 18:

Area Under the Curve
Test Result Variable(s): CT

Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.801	.073	.001	.659	.944

4. Conclusions

COVID-19 (Coronavirus disease 2019) causes a spectrum of disease; some patients develop a severe pro -inflammatory state which can be associated with coagulopathy and procoagulant endothelial phenotype. Initially, COVID-19 infection produces a prominent elevation of fibrinogen and D-dimer/ fibrinogen degradation products. This is associated with systemic hypercoagulability and frequent venous thromboembolic events. The degree of D-dimer elevation positively correlates with mortality in COVID-19 patients. Elevated D-dimer at admission and markedly increasing D-dimer levels (3- to 4-fold) over time are associated with high mortality, likely reflecting coagulation activation from infection/sepsis, cytokine storm and impending organ failure.COVID-19 also leads to arterial thrombotic events (including strokes and ischemic limbs) as well as microvascular thrombotic disorders (as frequently documented at autopsy in the pulmonary vascular beds). Disseminated intravascular coagulopathy (DIC) and severe bleeding events are uncommon in COVID-19 patients.

The severity and prognosis of COVID-19 are complicated by the diversity of symptoms, radiological manifestations, and disease progression.

The SARS-Cov2 virus uses angiotensin converting enzyme-2 (ACE-2) as its main receptor, this membrane protein is expressed in the blood vessels, lungs, heart, kidneys, and numerous other tissues. The SARS-CoV-2 binding to ACE-2 leads to local and systemic inflammatory response, endothelial injury, and an imbalance in pro- and anticoagulant signals, with resultant macro- and micro vascular thrombosis. Therefore, early detection and correction of coagulation dysfunction could effectively reduce mortality.

Commonly used laboratory coagulation indicators include D-Dimer, PT, and APTT. D-Dimer is the product of fibrinolytic solubilization of fibrin, and the elevated level of D-Dimer indicates that there is a hyper coagulating state and secondary fibrinolysis in the body, which can be seen in increased fibrinolytic activity of the body system.[16–18] PT and APTT are exogenous and endogenous coagulating system factors, which can be used for early diagnosis of DIC. DD, PT, and APTT can be used as sensitive indicators to reflect different degrees of coagulating dysfunction

The results of this study showed that D-Dimer, PT and APTT could be used as new indicators for the clinical classification of COVID-19. In the first test of D-Dimer, 109 out of 150 patients (72.66%) had abnormal levels of DD (>0.55 mg/L).

Of the 65 severe ill patient, 46 (30.66%) were >0.55 mg/L, accounting for 50% more than the normal reference value. The results of the study indicate that the levels of D-Dimer significantly increased in moderate and severe ill patients, and some patients deteriorated during treatment, suggesting that COVID-19 patients,

especially severe patients, have a high risk of thrombosis. In addition, the results of this study also show a significant correlation between coagulating factors and disease outcome, suggesting DD, PT, and APTT could serve as diagnostic indicators for disease progression.

Among the 42 (28%) patients who deceased, 32 (21.3%) had abnormal DD in the first test, among which 41 (27.3%) patients had DD level two times more than the normal reference value by day 5,when the viral phase is maximum and 40 patients d-dimer was high measured last value before death.

The PT tests, there were 150 (100%) patients was elevated on admission and 144 patients (96%) was elevated on day 5, respectively, and in 34 (22.6%) patients among in deceased patients. The gradually increasing DD and PT levels suggest the significant correlation with disease progression.

In this study, D-dimer PT and APTT prolonged in 34 (22.6%) deceased patients, and 46(30.66%) patients who have been discharged and the prolongation was more significant in the second, indicating the patients were in the transition from the high coagulating state into fibrinolytic state due to the excessive consumption of coagulating factors.

CT imaging has been regarded as a valuable tool in diagnosis and prognosis of COVID-19. The study results showed that D-Dimer was correlated with CT imaging in predicting the progression of disease. Specifically, the increased level of DD suggests hyper coagulating state and the possible pulmonary embolism, which could be further confirmed by CT angiography (CTA)

The coagulation indicators such as D-Dimer and PT should be monitored as early as possible in order to detect thrombotic complications. It is imperative to take preventive treatment to reduce the risk of thromboembolism and DIC secondary to coagulation disorder, thereby decreasing the morbidity and mortality of COVID-19-infected patients.

5. Acknowledgment

6. Conflict of Interest

The authors declare that there are no conflicts of interest in this paper

7. Source of Funding

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