Original Research Article

Covid-19 associated coagulopathy with comparison of platelet parameters, PT, aPTT and D-Dimer in ICU and Ward patients

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Abstract

Background: SARS-COV2 is the third known corona virus responsible for fatal respiratory illness in humans. Emerging evidence suggested that severe COVID-19 may be complicated with coagulopathy. These coagulation parameters help in assisting the prognosis of the disease and in optimization of its clinical monitoring. **Aims**: To assess and compare the coagulation parameters (platelet parameters, PT, aPTT, D-dimer) amongst ward and ICU patients of COVID-19 disease. **Settings and Design**: The present study was Analytical Cross-Sectional Study. **Materials and Methods**: This study included 220 COVID-19 positive cases (110 ICU and 110 Ward) at a tertiary care hospital. Tests were done for platelet parameters, PT, aPTT and D-Dimer in ICU and Ward patients. **Statistical analysis used**: The presentation of the Categorical variables was done in the form of number and percentage (%). The quantitative data were presented as means ± SD and as median with 25th and 75th percentiles (interquartile range). **Results**: In this study, we compared coagulation parameters (Platelet count, PT, aPTT, D dimer) of 110 ICU and 110 Ward covid-19 patients. We found that PT, aPTT, platelets, PDW cv and PCT between Covid ICU and ward patients had no significant difference (p value>0.05). Patients admitted to ICU had higher D-dimer level and decreased platelet count. There was clear significant difference in levels of D- dimer, platelet count and MPV between two groups (ICU and ward, p value<0.05). **Conclusion**: It is clear that alterations in the coagulation parameters in COVID-19 patients are strongly disturbed and signify the disease progression, severity and mortality.

Keywords: Aptt, Coagulation profile, COVID 19 disease, D-Dimer, platelet parameters, PT

Introduction

The severe acute respiratory syndrome coronavirus2(SARS-CoV-2) that is responsible for coronavirus disease resulted in systemic inflammatory response and imbalance between haemostasis mechanisms of procoagulant and anticoagulant.[1]

Thrombotic complications seem to emerge as an important issue in patients with COVID-19. Preliminary reports on COVID-19 pandemic outcomes have shown that infected patients commonly develop thrombocytopenia (36.2%) and may have elevated D-dimer (46.4%), while these rates are even higher in patients with severe COVID-19 disease (57.7% and 59.6%, respectively).[2] Emerging data support that patients infected by this novel coronavirus are at risk of developing disseminated intravascular coagulation.[2,3,4] Increased D-dimer and fibrin degradation products levels, and prolonged prothrombin time have been associated with poor prognosis in patients affected by the novel coronavirus.[5]

Material and Methods

The present study was carried on COVID-19 patients admitted in wards and ICU of a tertiary care centre. Coagulation profile was done along with D-dimer levels. For coagulation profile, samples were received in citrate vacuette. PT and aPTT were performed by manual method.

The presentation of the Categorical variables was done in the form of number and percentage (%). On the other hand, the quantitative data were presented as the means ± SD and as median with 25th and 75th percentiles (interquartile range). The comparison of the variables which were quantitative in nature were analysed using Independent t test and the variables which were qualitative in nature were analysed using Chi-Square test.

The data entry was done in the Microsoft EXCEL spreadsheet and the final analysis was done with the use of Statistical Package for Social Sciences (SPSS) software, IBM manufacturer, Chicago, USA, ver 21.0. For statistical significance, p value of less than 0.05 was considered statistically significant.

Results

This study included 220 Covid-19 positive cases (110 ICU and 110 Ward patients)

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Table 1: Comparison of coagulation parameters between ICU and ward patients

Coagulation parameters	ICU (n=110)	Ward (n=110)	Total	P value
PT (seconds)				
Increase {>14 seconds}	62 (56.36%)	71 (64.55%)	133 (60.45%)	0.215‡
Normal {11-14 seconds}	48 (43.64%)	39 (35.45%)	87 (39.55%)	
APTT (seconds)				
Increase {>36 seconds}	70 (63.64%)	63 (57.27%)	133 (60.45%)	0.334‡
Normal {28-36 seconds}	40 (36.36%)	47 (42.73%)	87 (39.55%)	
D dimer (ng/mL)				
Increase {>=500 ng/mL}	99 (90%)	72 (65.45%)	171 (77.73%)	0.0001‡
Normal {<500 ng/mL}	11 (10%)	38 (34.55%)	49 (22.27%)	
Platelet count (cells/cubic mm)				
Increase {>4 lacs/cubic mm}	5 (4.55%)	12 (10.91%)	17 (7.73%)	0.037‡
Normal {1.5-4 lacs/cubic mm}	63 (57.27%)	71 (64.55%)	134 (60.91%)	
Decrease {<1.5lacs/cubic mm}	42 (38.18%)	27 (24.55%)	69 (31.36%)	
Platelet distribution width (%)				
Increase {>45%}	2 (1.82%)	4 (3.64%)	6 (2.73%)	0.068†
Normal {25-45%}	103 (93.64%)	106 (96.36%)	209 (95%)	
Decrease {<25%}	5 (4.55%)	0 (0%)	5 (2.27%)	
Platelet crit (%)				
Increase {>0.24 %}	21 (19.09%)	22 (20%)	43 (19.55%)	0.877‡
Normal {.22-.24%}	10 (9.09%)	12 (10.91%)	22 (10%)	
Decrease {<0.22%}	79 (71.82%)	76 (69.09%)	155 (70.45%)	
Mean platelet volume (fL)				
Increase {>12 fL}	1 (0.91%)	2 (1.82%)	3 (1.36%)	0.035†
Normal {8-12 fL}	67 (60.91%)	49 (44.55%)	116 (52.73%)	
Decrease {<8 fL}	42 (38.18%)	59 (53.64%)	101 (45.91%)	
International normalised ratio				
Mean ± SD	1.31 ± 0.67	1.13 ± 0.24	1.22 ± 0.51	0.011*
Median (25th-75th percentile)	1.11 (1.03-1.302)	1.08 (0.992-1.248)	1.1 (1.01-1.26)	
Range	0.77-4.4	0.76-2.49	0.76-4.4	
Mean platelet volume/platelet count ratio				
Mean ± SD	6.23 ± 5.67	4.7 ± 3.36	5.46 ± 4.71	0.016*
Median (25th-75th percentile)	4.4 (3.092-7.275)	3.97 (2.709-5.497)	4.1 (2.933-6.563)	
Range	1.32-44	0.92-23.66	0.92-44	

* Independent t test, † Fisher's exact test, ‡ Chi square test

We found that PT, aPTT, platelets on smear, PDWcv and PCT between Covid ICU and ward patients had no significant difference (p value>0.05). Patients admitted in ICU had higher D-dimer levels (p value=0.0001) and decreased platelet count (p value=0.037). There was a clear significant difference in level of D- dimer, platelet count, INR and MPV between two groups (ICU and ward, p value<0.05).

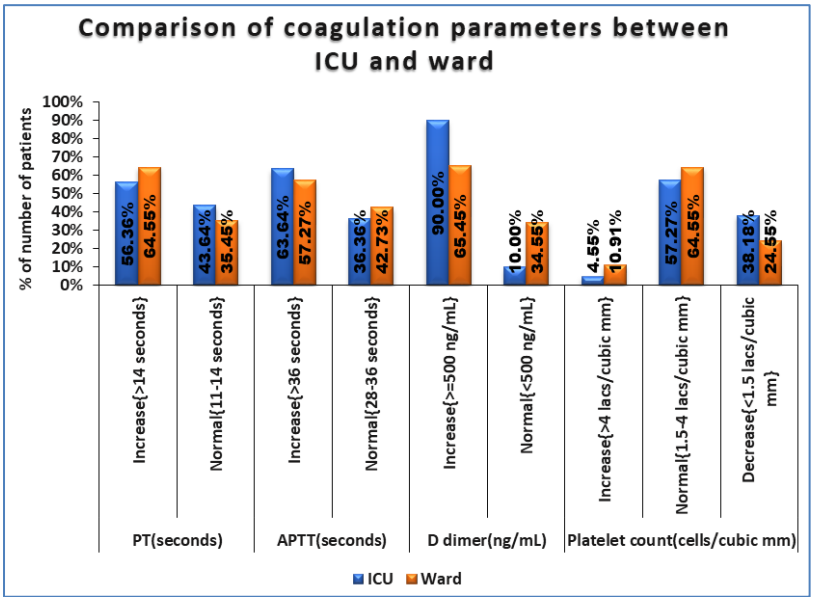

Chart 1: Comparison of coagulation parameters between ICU and ward

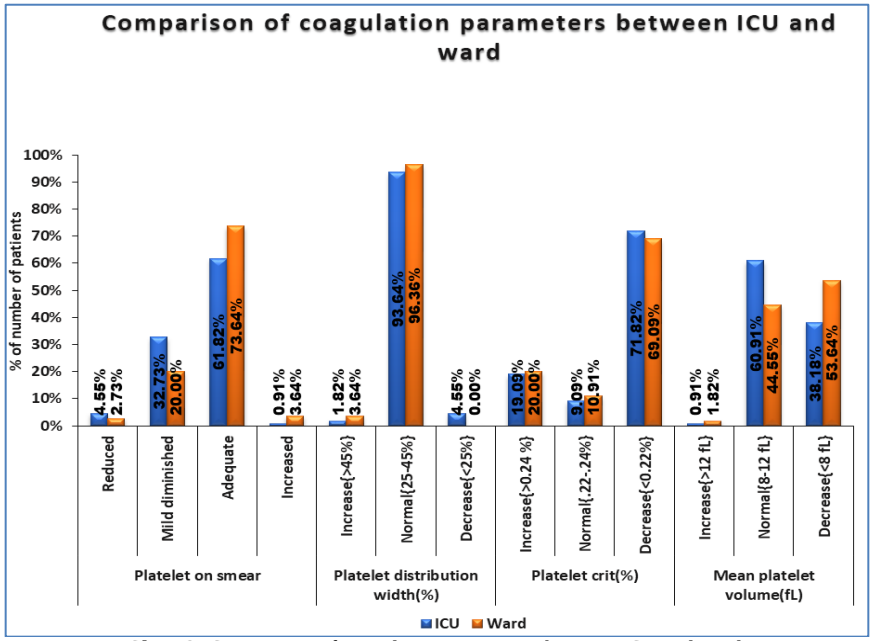

Chart 2: Comparison of coagulation parameters between ICU and ward

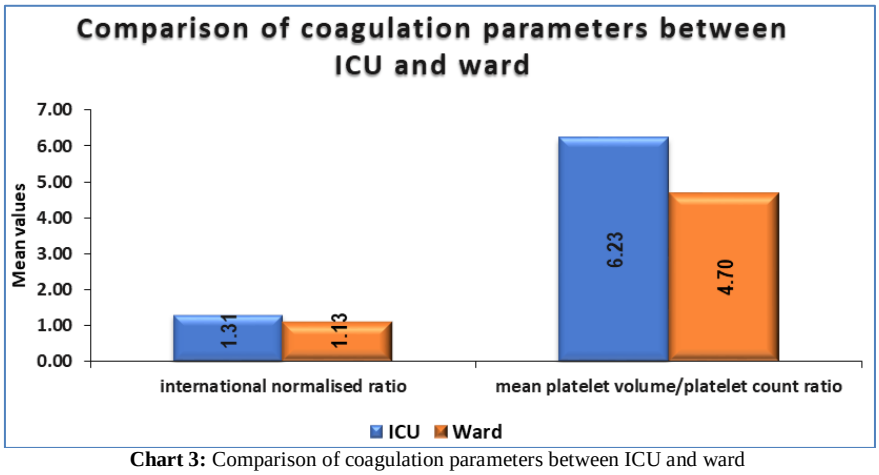

Chart 3: Comparison of coagulation parameters between ICU and ward

Table 2: Comparison of coagulation parameters between patients with and without co-morbidities

Coagulation parameters	Patients with co-morbidities (n=99)	Patients without co-morbidities (n=121)	Total	P value
PT(seconds)				
Increase {>14 seconds}	60 (60.61%)	73 (60.33%)	133 (60.45%)	0.967‡
Normal {11-14 seconds}	39 (39.39%)	48 (39.67%)	87 (39.55%)	
APTT(seconds)				
Increase {>36 seconds}	58 (58.59%)	75 (61.98%)	133 (60.45%)	0.608‡
Normal {28-36 seconds}	41 (41.41%)	46 (38.02%)	87 (39.55%)	
D dimer(ng/mL)				
Increase {>=500 ng/mL}	80 (80.81%)	91 (75.21%)	171 (77.73%)	0.321‡
Normal {<500 ng/mL}	19 (19.19%)	30 (24.79%)	49 (22.27%)	
Platelet count(cells/cubic mm)				
Increase {>4 lacs/cubic mm}	8 (8.08%)	9 (7.44%)	17 (7.73%)	
Normal {1.5-4 lacs/cubic mm}	55 (55.56%)	79 (65.29%)	134 (60.91%)	0.315‡
Decrease {<1.5 lacs/cubic mm}	36 (36.36%)	33 (27.27%)	69 (31.36%)	

Platelet distribution width (%)				
Increase {>45%}	0 (0%)	6 (4.96%)	6 (2.73%)	0.004†
Normal {25-45%}	99 (100%)	110(90.91%)	209 (95%)	
Decrease {<25%}	0 (0%)	5 (4.13%)	5 (2.27%)	
Platelet crit (%)				
Increase {>0.24 %}	20 (20.20%)	23 (19.01%)	43 (19.55%)	0.018‡
Normal {.22-.24%}	16 (16.16%)	6 (4.96%)	22 (10%)	
Decrease {<0.22%}	63 (63.64%)	92 (76.03%)	155 (70.45%)	
Mean platelet volume (fL)				
Increase {>12 fL}	1 (1.01%)	2 (1.65%)	3 (1.36%)	0.793†
Normal {8-12 fL}	50 (50.51%)	66 (54.55%)	116 (52.73%)	
Decrease {<8 fL}	48 (48.48%)	53 (43.80%)	101 (45.91%)	
International normalised ratio				
Mean ± SD	1.24 ± 0.54	1.21 ± 0.49	1.22 ± 0.51	0.645*
Median (25th-75th percentile)	1.11 (1.01-1.27)	1.1 (1.01-1.26)	1.1 (1.01-1.26)	
Range	0.76-4.4	0.77-4.4	0.76-4.4	
Mean platelet volume/platelet count ratio				
Mean ± SD	5.7 ± 5.36	5.27 ± 4.11	5.46 ± 4.71	0.496*
Median (25th-75th percentile)	4.14 (2.81-7.055)	4.09 (3.091-5.827)	4.1 (2.933-6.563)	
Range	0.92-44	1.23-26.22	0.92-44	

* Independent t test, † Fisher's exact test, ‡ Chi square test

The abnormal pattern of PT (>14 sec) was observed in 60(60.61%) out of 99 patients with comorbidities. D-dimer level was increased in 80 (80.81%) out of 99 patients with comorbidities. Platelet count was decreased in 36 (36.36%) out of 99 patients with comorbidities. The abnormal pattern of aPTT was observed in 58 out of 99 patients with comorbidities. Mean level of INR was 1.24 ± 0.54 and mean level of Mean platelet volume/platelet count ratio was 5.7 ± 5.36 in all patients with co-morbidities. The level of PT, aPTT, D-dimer, INR, platelet count, platelet on smear and MPV had no statistical difference between patients with co-morbidities(n=99) and patients without co-morbidities (p>0.05).

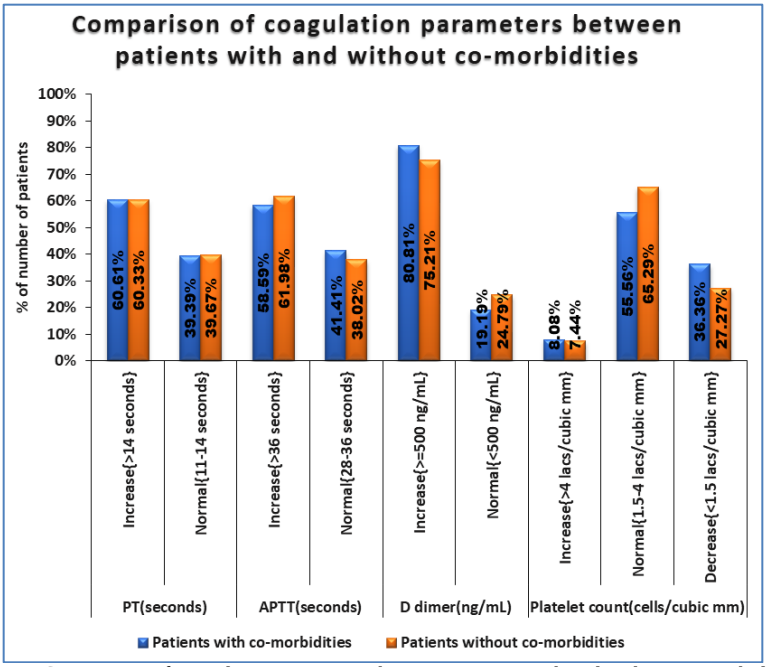

Chart 4: Comparison of coagulation parameters between patients with and without co-morbidities

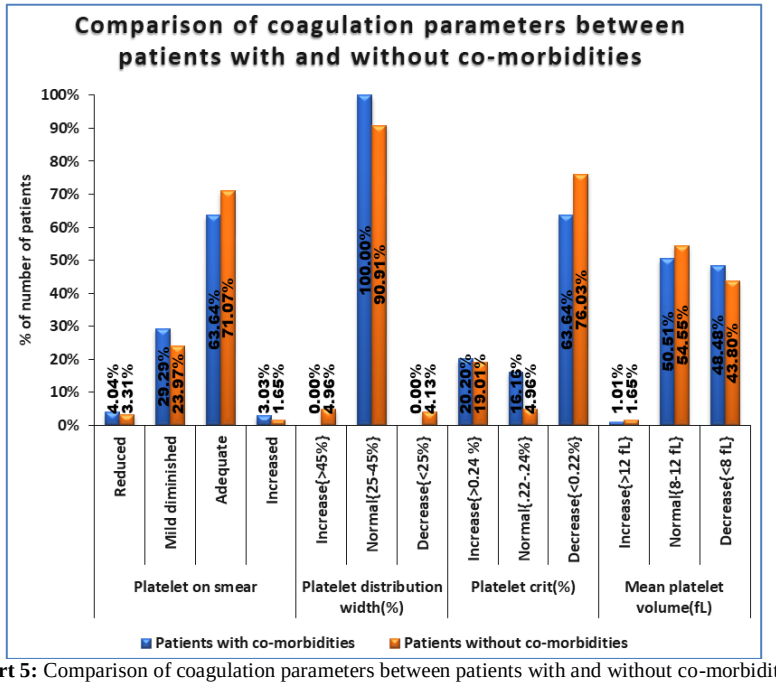

Chart 5: Comparison of coagulation parameters between patients with and without co-morbidities

Discussion

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that is responsible for coronavirus disease 2019 (COVID-19) resulted in systemic inflammatory response and imbalance between homeostatic mechanisms of procoagulant and anticoagulant. Therefore, early detection and correction of coagulation dysfunction among COVID-19 patients could effectively reduce mortality. Clinical laboratory coagulation index like D- dimer, prothrombin time (PT), activated partial thromboplastin time(aPTT) and platelet counts can very well reflect the clotting state of body.

Here we studied derangements in coagulation parameters of COVID-19 positive patients and compare and relate all these blood coagulation parameters (PT, aPTT, D-dimer and platelet count) among ward and ICU patients of COVID-19 disease. Out of 220 patients, 146 were males (66.36%) and 74 were females (33.63%). Study of coagulation parameters done by Long H et al [6] included 57.4% males and 42.6% females. The mean age at disease onset was 54.2 years (range,16-92 years) which was similar to study done by Tang N et al [7] (mean age 54.1 years).

Upon evaluation of common complaints, fever (72.27%), cough (72.73%) and breathlessness (78.18%) were the most observed, followed less often by weakness, headache and diarrhoea. The results of present study were found to be noticeably compatible with previous research. The research conducted by Yang et al.[8] also revealed fever and cough to be the most common complaints. In a study by Guan et al[9], fever and cough and less frequently nausea, vomiting and diarrhoea, were observed. The study by Huang et al[10] showed that fever (40/41 patients [98%]), cough (31/41patients [76%]) and myalgia or fatigue (18/41 patients [44%]) were the most commonly seen symptoms at onset of the disease.

The present study showed that 59.54% had comorbidities including Hypertension (25%), Diabetes mellitus (20.45%), ischemic heart disease (2.27%), cerebrovascular stroke, COPD, Alcoholic liver disease, asthma, chronic kidney disease, Tuberculosis and others. The study by Sayad B et al.[11]showed that 69% had comorbidities (hypertension, diabetes mellitus, coronary artery disease, cancer, renal transplantation, chronic obstructive pulmonary disease, and osteomyelitis). The study by Tang N et al[7]showed that 41% had chronic diseases including cardiovascular and cerebrovascular diseases, respiratory system disease, malignant tumor, chronic liver and kidney disease and others.

Thrombocytopenia is a common complication in severe ill patients with the accompanying risk of developing intravascular coagulopathies resulting in multiple organ damage. Studies done by Lippi G et al [12], Yang X at el.[13] Henry BM et al.[14], Terpos E at el.[15] on COVID-19 infected patients showed the presence of thrombocytopenia. In present study, out of 220 patients,69(31.36%) showed decrease platelet count,134(60.91%) showed normal platelet count and 17 (7.73%) showed increase platelet count (Table 2). Study done by Zhang A et al[16] showed Platelet count between ICU and non-ICU patients had no statistical difference. [MD = 0.19, 95%CI = (-20.22, 19.85), P > 0.05). In contrast to that our study showed clear significant difference in level of platelet count and MPV between the two groups (covid-ICU and ward, p value<0.05) (Table 4).

Table 3: Studies and main findings for platelet count in Covid-19 patients

First author (year)	Sample size	Categorization of hematological parameters	Main findings
Guan (2020) [9]	1099	Thrombocytopenia was defined as a platelet count of less than 150 000/mm^3	Thrombocytopenia was present in 36.2% of patients on admission. Also, 46.6% (27/58) of patients with the composite primary endpoint (admission to an intensive care unit, use of mechanical ventilation, or death) presented with thrombocytopenia vs 35.5% (288/811) of patients without the primary endpoint (P = .091[a]). Severe cases presented thrombocytopenia more frequently (57.7%, 90/156) vs non-severe cases (31.6%, 225/713); P < .001[a]
Huang (2020) [17]	41	Low platelet count of <100 x10^9 platelets per	8% (1/13) of patients needing ICU care presented low platelet count vs 4% (1/27) of patients that did not need ICU care (P = .45).

First author (year)	Sample size	Categorization of hematological parameters	Main findings
		Litre	
Wang (2020) [18]	138	Platelets treated as a continuous variable, $x10^9$ per L	No significant difference (P = .78) was noted in platelet count between ICU cases (median:142, IQR: 119-202) vs non-ICU cases (median: 165, IQR: 125-188); P = .78.
Wu (2020) [19]	201	Platelets treated as a continuous variable, $x10^9$ /mL	Platelet counts did not differ between patients with ARDS vs those without ARDS (difference: −4.00, 95%CI: −27.00 to +20.00, P = .73). Accordingly, no significant difference was noted in dead vs alive ARDS patients (P = .10).
Young (2020) [20]	18	Platelets treated as a continuous variable, $x10^9$ per L	Median platelet count was 156 (IQR: 116-217) in patients that required supplemental O_2 and 159 (IQR: 128-213) in those that did not; no statistical comparison was undertaken.
Fan (2020) [21]	69	Low platelet count: platelet of $<100 \times 10^9$/L.	Low platelets were not associated with ICU care either at admission (P = .67) or as a nadir during hospital stay (P = .69)
Yang (2020) [22]	52 critically ill patients	Platelets treated as a continuous variable ($\times 10^9$/L)	Platelet count noted in non-survivors was 191 (63) and 164 (74) in survivors; no statistical tests were presented.
Arentz (2020) [23]	21 ICU patients	Platelets presented as a continuous variable ($\times 10^9$/L)	Mean baseline platelet count was 235 (ranging between 52 and 395), whereas the reference range was 182-369 $\times 10^9$/L
Bhatraju (2020) [24]	24 ICU patients	Platelet counts presented as a continuous variable (cells per mm^3)	Median of lowest platelet count was 180 000 (IQR: 109000-257 000)
Zhou (2020) [25]	191	Platelets treated as a continuous variable ($\times 10^9$/L)	Median platelet count was lower in non-survivors (165.5, IQR: 107.0-229.0) vs survivors (220.0, IQR: 168.0-271.0), P < .001
Lippi (2020) [12]	9 published studies	Platelets treated as a continuous variable	Platelet count was significantly lower in patients with more severe COVID-19 (WMD -31×10^9/L, 95% CI, −35 to -29×10^9/L), with very high heterogeneity (I^2 = 92%). A more substantial drop in platelets was observed in non-survivors.
Present study	110 ICU patients and 110 ward patients	Platelet counts presented as a continuous variable (cells per mm^3)	There was clear significant difference in level of platelet count between two groups (ICU and ward, p value=0.037).

Abbreviations: ARDS, acute respiratory distress syndrome; IQR, interquartile range.

aP-values calculated by Terpos et al, on the basis of contingency tables (Pearson's chi-square test) in articles that did not present formal statistical comparison.

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 levels. Raised D-dimer levels have been found to be associated with severity and outcomes of the disease.

Helms et al. [26] did study on 150 covid-19 ICU admitted patients. Among them >95% showed elevated D-dimer on admission. In present study, 77.73% showed elevated D – dimer levels at the time of admission which ranged from 96 to 30930 ng/ml. Out of 110 ICU patients, 90% show elevated D-dimer level which was more compared to ward patients (increased D- dimer level was 65.45%). There was clear significant difference in level of D- dimer between two groups (ICU and ward, p value<0.05). In contrast to present study, Study done by Zhang A at el[16] showed no statistical difference between D-dimer levels of ICU and non-ICU patients. [MD = 3.51, 95%CI = (-7.40, 14.41), P > 0.05).

Table 4: Studies and main findings for D-dimer in Covid-19 patients

First author (year)	Sample size	Categorization of hematological parameters	Main findings
Guan (2020) [9]	1099	Elevated D-dimer: ≥0.5 mg/L	Patients with the composite primary endpoint (admission to an intensive care unit, use of mechanical ventilation, or death) presented with elevated D-dimer more frequently: 69.4% (34/49) vs 44.2% (226/511; P = .001[a]). Accordingly, severe cases presented elevated D-dimer more frequently (59.6%, 65/109) vs non-severe cases (43.2%, 195/451); P = .002
Huang (2020) [17]	41	D-dimer treated as a continuous variable, in mg/L	Patients necessitating ICU care presented with higher D-dimer levels (median: 2.4; IQR: 0.6-14.4) vs non-ICU patients (median: 0.5, IQR: 0.3-0.8), P = .0042.
Wang (2020) [18]	138	D-dimer treated as a continuous variable, in mg/L	ICU cases presented with higher D-dimer level (median:414, IQR: 191-1324) vs non-ICU cases (median: 166, IQR: 101-285); P < .001. Longitudinal increase was noted in non-survivors.
Wu (2020)	201	D-dimer treated as a continuous variable (μg/mL) in a bivariate	Higher D-dimer level was associated with ARDS development (HR = 1.03, 95%CI: 1.01-1.04, P < .001) and poor survival (HR = 1.02, 95%CI:

First author (year)	Sample size	Categorization of hematological parameters	Main findings
[19]		Cox regression model	1.01-1.04, *P* = .002) in the incremental models.
Zhou (2020) [25]	191	D-dimer greater than 1 µg/mL in a multivariate logistic regression model	Higher D-dimer was associated with higher odds of death (OR = 18.42, 95%CI: 2.64-128.55; *P* = .003)
Lippi (2020) [12]	553 (4 published studies)	D-dimer treated as a continuous variable; the definition of COVID-19 disease Severity was not provided during the synthesis of studies	D-dimer values were considerably higher in COVID-19 patients with severe disease than in those without (WMD = 2.97 mg/L; 95% CI: 2.47-3.46 mg/L). However, heterogeneity across synthesized studies was very high (I^2 = 94%).
Present study	110 ICU patients and 110 ward patients	D-dimer treated as a continuous variable, in ng/mL	ICU cases presented with higher D-dimer level (99 cases,90%) vs ward cases (72 cases,65.45%); Mean ± SD =5122.74 ± 7403.67 ng/ml; Range:96-30930 ng/ml; P < 0.0001.

Abbreviations: ARDS, acute respiratory distress syndrome; IQR, interquartile range.

aP-values calculated by Terpos et al., on the basis of contingency tables (Pearson's chi-square test) in articles that did not present formal statistical comparison.

PT and aPTT are representative of exogenous and endogenous coagulating systems respectively. Present study showed increased in PT in 133 patients (60.45%) and increased in aPTT level 133 patients (60.45%) in studied patients. The Mean SD of PT was 16.11 ± 6.8 seconds and ranged from 11 to 60 seconds. The Mean SD of aPTT was 35.48 ± 10.9 seconds and ranged from 20.2 to 78.1 seconds. PT and APTT between Covid ICU and ward patients had no significant difference (p value>0.05). Study done by Zhang A at el[16] showed that APTT between ICU and non-ICU patients had no statistical difference [MD = 0.59, 95%CI = (-1.84, 0.67), P > 0.05] and The PT of ICU patients was higher than that of non-ICU patients [MD = 0.54, 95%CI = (0.13, 0.95), P < 0.05].

Table 5: Comparison of PT(in seconds) between ICU and non-ICU in different studies

Study	ICU		Non-ICU	
	Mean	SD	Mean	SD
Huang C et al [17]	12.273	1.8272	10.8785	1.7967
Lei S et al [27]	11.5815	1.7176	11.464	1.3616
Peng Y et al [28]	13.7189	1.7069	13.2112	1.2043
Wang D et al [18]	13.3422	1.6986	12.8648	0.8272
Present study	16.98	9.15	15.24	2.88

Table 6: Comparison of aPTT (in seconds) between ICU and non-ICU in different studies

Study	ICU		Non-ICU	
	Mean	SD	Mean	SD
Huang C et al [17]	27.66	9.4683	28.9494	7.2648
Lei S et al [27]	28.3267	3.5169	28.4926	5.4466
Peng Y et al [28]	37.9893	8.9004	35.7852	6.3224
Wang D et al [18]	30.6488	4.2464	31.5944	2.9328
Present study	41.50	10.89	36.32	6.12

In our study, Plateletcrit was decreased in 155 patients (70.45%) out of 220 patients. MPV was decreased in 101 patients (45.91%) while at normal level in 52.73% patients. PDW was normal in 95% patients. Study done by Ertugrul Guclu et al[29] showed Platelet indices, MPV, and PDW, were found to be higher in non-survivors on both admission day and third follow-up days. The mechanism of change in platelet indices in COVID-19 patients is probably multifactorial. Three hypotheses related to platelet count and structure are proposed in COVID19. Firstly, as with other coronaviruses, thrombocytopenia is possibly due to infection of the bone marrow. Secondly, platelet destruction by the immune system. Thirdly, platelet consumption due to aggregation in the lungs. Generally, platelet production increases as platelet count decreases. An increased number of young platelets is also functionally more active than older platelets. These changes may explain the increase in platelet indices, MPV, and PDW.

Conclusion

It is clear that alterations in the haemostatic balance in COVID-19 patients are strongly disturbed and contribute to a high prothrombotic status, justifying the use of anticoagulant therapy. This study demonstrated the benefits of screening abnormal coagulation parameters such as decreased Platelet levels, prolonged PT, and elevated D -dimer levels for predicting the severity and prognosis of COVID-19. We suggest clinicians to pay attention to changes in blood coagulation parameters of COVID-19 patients and explore their potential guidance for therapy. Severe COVID-19 patients had low levels of PLT and high PT that were associated with poor prognosis. Coagulation tests such as PLT, PT, aPTT and D-dimer should be performed at hospital admission stage in patients suspected or confirmed to have COVID-19 infection in order to provide useful prognostic information.

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