

# COVID-19 Induced Coagulopathy: A Common Challenge in Intensive Care Units

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## ABSTRACT:

The ongoing Coronavirus disease (COVID-19) pandemic has caused widespread global transmission. Hemostatic disorders are known complications of the disease, leading to blood clots and bleeding. These disorders are associated with high mortality rates. This study aimed to determine the prevalence of hemostatic disorders among COVID-19 patients admitted to intensive care units (ICUs). During a one-year period, an observational cross-sectional study was conducted on COVID-19 patients admitted to Imam Khomeini Hospital in Ardabil. This study assessed 911 patients with COVID-19 who were hospitalized in the ICU, aged of 62.26 years on average, of which 54.3% were males. The mortality rate was 52.3% mortality rate. 8.6% of patients had thromboembolic or bleeding disorders. Most cases involved bleeding (5.9%), followed by DVT (2.1%) and PTE (0.8%). In our study, we found that patients with a history of thromboembolism (P-Value = 0.000), cancer (P-Value = 0.000), cardiovascular disease (P-Value = 0.025), hypertension (P-Value = 0.030), and rheumatological diseases (P-Value = 0.035) had significantly higher rates of thromboembolism and hemorrhagic events. The prevalence of thromboembolic and bleeding disorders was also significantly higher in patients with elevated LDH (0.001), INR (0.014), D-dimer (0.015), CRP (0.039), and BUN (0.046) levels. Our study elucidates three critical aspects of COVID-19-associated coagulopathy in patients admitted to the intensive care unit. The prevalence of hemostatic disorders was notably 8.6%, with bleeding complications being the most common at 5.9%. Significant associations were observed between thromboembolic events and pre-existing conditions, particularly prior thromboembolism and cancer. Laboratory markers, such as elevated levels of LDH, D-dimer, and INR, possess prognostic significance for identifying patients at high risk.

**Keywords:** Hemorrhage; Hemostatic disorders; Intensive care unit; Pulmonary embolism; SARS-CoV-2 infection; Venous thrombosis.

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## 1. Introduction

The COVID-19 pandemic, caused by the SARS-CoV-2 virus, rapidly spread worldwide after its initial identification in Wuhan, China (1). It is characterized by

symptoms such as fever, cough, fatigue, respiratory issues, and shortness of breath in severe cases (2). In addition, non-respiratory organs, including the liver, heart, kidneys, and multiple organs, can fail simultaneously, with common symptoms (3).

Coagulopathy is a common disease complication (4-6). The inflammatory response to COVID-19 and activation of innate immunity may cause this coagulopathy. Prothrombotic effects are induced when serum inflammatory cytokines are increased (7-9). While the association between COVID-19 and coagulopathy has been established in various populations, critical gaps remain in our understanding of their clinical implications, particularly in specific demographic contexts. In our clinical observations at Imam Khomeini Hospital, Ardabil, we noted substantial variation in coagulopathic manifestations among COVID-19 patients, particularly those with pre-existing conditions. This variability prompted us to systematically investigate three key aspects: the prevalence of coagulopathy among hospitalized COVID-19 patients, the relationship between coagulopathy and specific underlying medical conditions, and the associations between coagulation abnormalities and clinical outcomes.

## 2. Materials & Methods

This descriptive cross-sectional study analyzed all patients with COVID-19 who were admitted to the intensive care units (ICUs) of Imam Khomeini Hospital, Ardabil, Iran, between March 2020 and March 2021. The study protocol was approved by the Ethics Committee of Ardabil University of Medical Sciences (IR.ARUMS.MEDICIN.REC.1400.013). Demographic and clinical data were extracted from hospitalization records, including patient characteristics (age, sex, and comorbidities), disease severity (classified as severe or critical based on the WHO criteria (1)), laboratory markers (D-dimer, INR, CRP, LDH, and other relevant tests), and outcomes (mortality and thromboembolic/bleeding events [DVT, PE, and major bleeding]). All patients received prophylactic enoxaparin (40 mg/day) or unfractionated heparin (5000 IU two or three times a day) unless contraindicated; therapeutic doses were administered for confirmed venous thromboembolism (VTE). Data were analyzed using SPSS v26. Continuous variables were compared using *t*-tests, and categorical variables were assessed using chi-square tests. A *p*-value <0.05 was considered statistically significant. Missing data due to unrequested tests were noted but excluded from analysis. Patient data were anonymized and stored securely, with strict adherence to confidentiality protocols.

## 3. Results & Discussion

### 3.1 Demographic Data

The demographic findings revealed that of the 911 patients studied, 495 (54.3%) were men, and the average

age was 62.26 years. A total of 395 patients (39.4%) were in severe condition, while 552 patients (60.6%) were in critical condition. Hypertension was common underlying medical conditions (33.3%). A total of 435 patients (47.7%) were cured and discharged from the hospital, whereas 476 patients (52.3%) died (Table 1).

**Table 1:** Demographic characteristics of patients.

Gender (N, %)	Male (495, 54.3%)
	Female (416, 45.7%)
Age (Mean ± SEM)	62.26 ± 16.54
Disease Severity (N, %)	Severe (359, 39.4 %)
	Critical (552, 60.6 %)
Underlying medical condition (N, %)	Hypertension (303, 33.3 %)
	Diabetes (267, 29.3 %)
	Cardiovascular disease (153, 16.8 %)
	Lung disease (105, 11.5 %)
	Kidney disease (87, 9.5 %)
	Cerebrovascular disease (74, 8.1 %)
	Cancer (29, 3.2 %)
	Liver disease (15, 1.6 %)
	History of Thromboembolism (14, 1.5 %)
	Rheumatological diseases (9, 1 %)
Outcome (N, %)	Remission (435, 47.7 %)
	Death (476, 52.3 %)

SEM: Standard Error of the Mean.

### 3.2 The frequency of thromboembolic and bleeding disorders in patients

A total of 80 cases were diagnosed with thromboembolic and bleeding disorders, with bleeding being more prevalent (N= 54 [67.5%] vs. N= 26 [32.5%]). Blood loss from the gastrointestinal tract was more common (N=38 [70.36 %]).

### 3.3 The incidence of thromboembolic events and bleeding among patients, categorized by sex, age, and treatment outcomes

Analysis of thromboembolism and bleeding incidence rates showed that there were no statistically significant differences observed between men and women in both the under-65 and over-65 age groups. Thromboembolic and hemorrhagic disorders were not statistically significantly different between the two groups of recovered and deceased patients (Table 2).

**Table 2:** The incidence of thromboembolic events and bleeding among patients, categorized by sex, age, and treatment outcomes.

	Gender			Age			Patient outcome		
	Male [N (%)]	Female [N (%)]	P value	<65 [N (%)]	>65 [N (%)]	P value	Remission [N (%)]	Death [N (%)]	P value
Bleeding	28 (51.9)	26 (48.1)	0.4	24 (44.4)	30 (55.6)	0.1	23 (42.6)	31 (57.4)	0.2
DVT	12 (63.2)	7 (36.8)	0.2	12 (63.2)	7 (36.8)	0.2	10 (52.6)	9 (47.4)	0.4
PE	2 (28.6)	5 (71.4)	0.1	4 (57.1)	3 (42.9)	0.5	4 (57.1)	3 (42.9)	0.4

DVT: Deep vein thrombosis, PE: Pulmonary embolism.

### 3.4 The Frequency of thromboembolic and bleeding disorders in patients based on underlying disease

Based on Fisher's test (P-Value < 0.05), it was found that thromboembolic and bleeding disorders were statistically significantly higher in patients with previous thromboembolic history (P-Value = 0.000), Cancer (P-Value = 0.000), cardiovascular diseases (P-Value=0.25), Hypertension (P-Value=0.030) and rheumatological diseases (P-Value=0.035).

### 3.5 Laboratory Data of Patients Categorized on VTE/Bleeding Incidence and Patient Outcome

LDH (P-Value = 0.001), INR (P-Value = 0.014), D-dimer (P-Value = 0.015), CRP (P-Value = 0.039), and BUN (P-Value = 0.046) levels were significantly higher in patients with thromboembolic and bleeding disorders. Upon examining the laboratory findings of patients with thromboembolic and hemorrhagic disorders, data collected from the study showed that there was no statistically significant difference between the groups of patients: those who recuperated and those who succumbed to the illness (Table 3).

In this study, the incidence of thromboembolic and bleeding disorders was 8.6%. Bleeding was the most common disorder, occurring at a rate of 5.9%, followed by DVT at 2.1% and PTE at 0.8%. Al-Samkari and his colleagues studied 3239 covid-19 patients hospitalized in the ICU and found the incidence of VTE and Major Bleeding to be 6.3% and 2.8%, respectively (12). In a 2021 systematic review, Jenner and colleagues analyzed 28 valid scientific studies with 2928 patients. They reported similar rates of thrombotic events, DVT, and PTE at 34%, 16.1%, and 12.6% (13). In previous studies, thromboembolic disorders were more common than bleeding disorders. However, our study found that bleeding was the most common. On the other hand, the lower incidence of thromboembolic disorders in our study compared to other studies suggests that different anticoagulant mechanisms may play a role in these disorders. Additionally, it appears that various viral variants may have different effects on thromboembolic

and bleeding disorders, highlighting the need for further investigation.

The study of hemostatic disorders based on gender revealed that thromboembolic and bleeding disorders were more common in male patients. In spite of this, there was no noticeable divergence between the male and female groups. The findings of Tamayo-Velasco, Mohamud, and Xiong et al. suggest that thromboembolic disorders are more prevalent in men than women; however, there was no statistically significant difference observed between the two genders (14-16). One notable point is that the difference in thromboembolic and hemorrhagic disorders between genders was less in our study than other studies. This difference decreases in more severe patients hospitalized in the ICU, and coagulopathy mechanisms aren't related to gender in severe cases.

In this study, it was found that thromboembolic and bleeding disorders were the same in two age groups above and below 65 years. No significant difference was observed in age. In a study of 2,894 Covid-19 patients, Tamayo-Velasco and colleagues found that thromboembolic disorders occurred significantly more frequently in patients over 65 years of age. A meta-analysis by Xiong et al. Reported that thrombotic events in patients increased with age but did not show a significant correlation (14, 16).

In analyzing the correlation between prevalent medical conditions and the occurrence of blood clotting and bleeding issues in patients, it was determined that individuals with a prior diagnosis of thromboembolism, cancer, cardiovascular illness, hypertension, or rheumatology displayed a significantly greater incidence of thromboembolic and bleeding disorders. According to a 2022 study by Tamayo-Velasco and colleagues involving 2894 Covid-19 patients, thromboembolic disorders were considerably more prevalent in patients with a cancer history (14). Additionally, Mohamud and colleagues found that patients with a history of ischemic heart disease, diabetes, and chronic liver disease experienced significantly increased thromboembolic disorders (15).

In this study, a history of previous thromboembolism and cancer was included in the first category of underlying diseases affecting thromboembolic and bleeding disorders.

**Table 3:** Laboratory Data of Patients Categorized on VTE/Bleeding Incidence and Patient Outcome.

Laboratory findings (Mean $\pm$ SEM)	VTE/Bleeding incidence			Patient outcome		
	Yes	No	P-value	Remission	Death	P-value
WBC	10301 $\pm$ 5797.04	9485 $\pm$ 5307.19	0.2	10346 $\pm$ 6081	10262 $\pm$ 5615	0.9
Neutrophil %	81.05 $\pm$ 9.60	81.07 $\pm$ 10.53	0.1	79.27 $\pm$ 11.20	82.60 $\pm$ 7.75	0.2
Lymphocyte %	14.51 $\pm$ 8.75	14.90 $\pm$ 10.53	0.1	15.97 $\pm$ 10.70	13.24 $\pm$ 6.45	0.06
Monocyte %	3.06 $\pm$ 2.14	3.01 $\pm$ 2.55	0.6	3.33 $\pm$ 2.19	2.82 $\pm$ 2.10	0.9
Eosinophil %	1.35 $\pm$ 1.25	1.37 $\pm$ 1.20	0.6	1.33 $\pm$ 1.33	1.36 $\pm$ 1.19	0.4
Hemoglobin	12.40 $\pm$ 2.66	13.25 $\pm$ 2.35	0.4	12.39 $\pm$ 3.04	12.41 $\pm$ 2.32	0.4
Hematocrit	38.08 $\pm$ 7.23	40.63 $\pm$ 16.06	0.9	37.85 $\pm$ 8.58	38.27 $\pm$ 5.95	0.3
Platelet	203589.74 $\pm$ 103365.12	200910.95 $\pm$ 90851.52	0.3	219060.14 $\pm$ 115099.91	190330.51 $\pm$ 91469.21	0.2
PTT	37.30 $\pm$ 14.03	36.58 $\pm$ 11.08	0.3	37.55 $\pm$ 16.10	37.09 $\pm$ 12.45	0.5
INR	1.34 $\pm$ 0.81	1.20 $\pm$ 0.58	<b>0.01</b>	1.24 $\pm$ 0.60	1.42 $\pm$ 0.94	0.1
Blood sugar	164.51 $\pm$ 106.90	183.56 $\pm$ 113.08	0.1	171.19 $\pm$ 134.81	158.75 $\pm$ 76.80	0.1
Creatinine	1.34 $\pm$ 0.95	1.30 $\pm$ 0.92	0.9	1.23 $\pm$ 0.61	1.44 $\pm$ 1.17	0.07
BUN	66.14 $\pm$ 58.21	55.26 $\pm$ 46.94	<b>0.04</b>	70.25 $\pm$ 66.40	62.61 $\pm$ 50.72	0.1
Sodium	139.04 $\pm$ 5.83	139.47 $\pm$ 4.86	0.3	138.78 $\pm$ 6.40	139.26 $\pm$ 5.37	0.5
Potassium	4.21 $\pm$ 0.53	4.14 $\pm$ 0.62	0.4	4.16 $\pm$ 0.49	4.25 $\pm$ 0.57	0.4
ALT	80.72 $\pm$ 202.43	78.32 $\pm$ 244.30	0.8	88.05 $\pm$ 199.60	74.63 $\pm$ 207.02	0.6
AST	98.46 $\pm$ 205.95	109.98 $\pm$ 400.77	0.6	85.20 $\pm$ 74.39	110.08 $\pm$ 274.52	0.2
ALKP	252.29 $\pm$ 201.29	234.12 $\pm$ 161.39	0.07	249.06 $\pm$ 162.17	255.03 $\pm$ 231.39	0.6
ESR	44.23 $\pm$ 26.71	45.21 $\pm$ 24.84	0.7	51.27 $\pm$ 27.41	39.06 $\pm$ 25.40	0.5
CRP	10.31 $\pm$ 37.06	7.45 $\pm$ 21.24	<b>0.03</b>	14.62 $\pm$ 48.91	6.95 $\pm$ 24.48	0.1
LDH	1245.70 $\pm$ 2571.48	962.45 $\pm$ 917.16	<b>0.001</b>	878.60 $\pm$ 447.03	1567.0 $\pm$ 3485.08	0.06
D-dimer	1161.60 $\pm$ 1196.98	735.18 $\pm$ 1011.45	<b>0.015</b>	1565.40 $\pm$ 1241.53	870.00 $\pm$ 1107.10	0.4
Ferritin	962.53 $\pm$ 685.88	882.07 $\pm$ 678.52	0.7	907.97 $\pm$ 695.85	1013.80 $\pm$ 683.10	0.8
Albumin	2.99 $\pm$ 0.50	3.20 $\pm$ 0.57	0.2	3.08 $\pm$ 0.39	2.94 $\pm$ 0.56	0.3

ALT: Alanine aminotransferase, ALKP: Alkaline phosphatase, AST: Aspartate aminotransferase, BUN: Blood urea nitrogen, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, INR: International normalized ratio, LDH: Lactate dehydrogenase, PTT: Partial thromboplastin time, SEM: Standard error of the mean, VTE: Venous thromboembolism, WBC: Wight blood cell.

According to the Padua criteria, these two disease histories can directly impact VTE occurrence. Additionally, they may be linked to VTE through other mechanisms related to Covid-19 so further investigation is needed to determine their role in increasing VTE (17). Thromboembolic and bleeding disorders were more common in deceased patients. In contrast, no significant differences were observed between the groups of recovered patients and those who died. In a similar systematic review, Jenner and his colleagues found that thrombotic events were associated with high mortality rates. Chen and his colleagues found that the mortality rate was relatively higher in DVT patients, but there was no significant difference (18). The above findings show that thromboembolic and bleeding disorders were more common in deceased patients, but there was no definite relationship between them. But it seems that thromboembolic and hemorrhagic disorders are weaker

in patients admitted to the ICU. This issue can be related to the high severity of the disease in these patients.

Laboratory findings of patients with thromboembolic and bleeding disorders were examined. It was found that WBC, BUN, ALKP, CRP, LDH, D-Dimer and Ferritin were significantly higher in patients with thromboembolic and bleeding disorders. In contrast, Hb, HCT, BS, and AST were lower in these patients. Additionally, LDH, INR, D-Dimer, CRP, and BUN levels were significantly elevated in patients with thromboembolic and bleeding disorders.

Studies indicate a correlation between LDH levels and Major Bleeding. Additionally, patients with thrombotic disorders show an increase in D-Dimer and aPTT levels. On the other hand, patients with hemostatic disorders exhibit an increase in platelet and CRP levels. Finally, an increase in D-Dimer levels is associated with increased DVT (18-22). This study indicates that LDH, INR, D-

Dimer, CRP, and BUN levels were significantly elevated in patients with thromboembolic and bleeding disorders. COVID-19's coagulopathy mechanism helps explain elevated biomarker levels. Therefore, analyzing these biomarkers could benefit patients suspected of experiencing thromboembolic and bleeding events

In this study, it was found that PLT, BS, ALT, ESR, CRP, and D-Dimer were higher in patients with improved thromboembolic and bleeding disorders. However, AST, LDH, and ferritin were lower in these patients. Furthermore, the laboratory results for patients with thromboembolic and hemorrhagic disorders did not show any significant differences between the cohort of recovered individuals and the group of deceased patients. It seems that in these patients, the severity of the disease and coagulopathic events caused an increase in laboratory biomarkers. The outcome of this study showed no disparity between the group of recuperated patients and the group of patients who had passed away. In contrast, Zinellu and his team's study found that the International Normalized Ratio (INR) was significantly elevated in the deceased patients (23).

The study has several limitations, including the size of the population, the time frame, and the different supportive-therapeutic interventions in the patients. It is suggested that further studies with a larger sample size in two groups of patients hospitalized in the normal ward and the ICU, taking into account different time periods to determine the frequency of hemostatic disorders for various viral variants and in diverse centers, should be done comparative. Additionally, future studies should investigate the quantitative level of fibrinogen and determine the predictive power of laboratory findings related to hemostatic disorders. Finally, a reliable cut off point based on laboratory findings should be established to provide effective prophylaxis with COVID-19 anticoagulants.

#### 4. Conclusion

Thromboembolic and hemorrhagic disorders are common in COVID-19 patients in the ICU. The poor prognosis of hemostatic disorders in COVID-19 emphasizes the importance of monitoring underlying diseases and laboratory results. Based on research, individuals with a background of thromboembolism, cancer, cardiovascular disease, hypertension, and rheumatological illnesses are at an elevated risk for thromboembolic and bleeding disorders. The presence of elevated levels of biomarkers such as LDH, INR, D-Dimer, CRP, and BUN in these patients can aid in the timely diagnosis of these conditions.

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