

# Determining the Prognostic Value of Coagulation Parameters and D-dimer Plasma Level in Admitted COVID-19 Patients



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## ABSTRACT

**Background:** Severe acute respiratory syndrome coronavirus2 (SARS-CoV-2) has emerged as a global concern. Since its outbreak in December 2019, researchers and authorities have made numerous efforts to identify the disease's prognostic markers. Changes in the values of coagulation tests are common in these patients. This study aimed to study any possible association between coagulation parameters in COVID-19 patients with prognostic indicators and the disease severity.

**Materials and Methods:** This cross-sectional survey investigates the CBC, coagulation status, and plasma D-dimer level in confirmed cases of COVID-19 (RT-PCR and/or chest CT scan) admitted to Boo-Ali Sina and Imam Khomeini hospitals affiliated with Mazandaran University of Medical Sciences, in the north of Iran in the last three months of 2021. The tests were ordered at the beginning of hospitalization and discharge. The results included lung involvement percentage, intensive care unit (ICU) admission, and survival.

**Results:** Of 140 COVID-19 patients (Mean±SD age: 55.73±16.821 years) evaluated in this study, 51.4% were male. Among comorbidities, diabetes and hypertension were the most common ones. The Mean±SD hospitalization length was 8.47±7.8 days. Also, 56(40.0%), 40(28.6%), and the rest of the patients showed <25%, 25%-50%, and >50% of lung involvement, respectively. In addition, the CURB-65 score for pneumonia severity was low, medium, and high risk for 84, 34, and 22 patients, respectively. The most frequent abnormality among the results was prothrombin time (PT) (17.9%), thrombocytopenia (25.7%), partial thromboplastin time (PTT) (32.9%), and elevated D-dimer level (62.9%). The results showed a significant relationship between abnormal D-dimer levels and poor outcomes, including higher CURB-65 score, higher lung involvement in CT scans, more ICU admissions, and even death. Meanwhile, PT, PTT, and platelet count on admission did not help predict the study population's clinical course and general survival.

**Conclusion:** Disturbance of coagulation parameters in COVID-19 patients with no significant history can serve as an available and reliable prognostic marker in the patients' outcomes and clinical course.

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## Introduction

**C**oronaviruses are RNA viruses that can cause various infections, ranging from colds to pneumonia, bronchitis, and acute respiratory syndromes. In December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was announced as a new coronavirus causing COVID-19. The virus was first reported in Wuhan, China, and became a critical global health issue [1].

Transmission can occur through direct contact or aerosols. In this respect, evidence suggests angiotensin-converting enzyme 2 (ACE2) as a gateway for virus entry into the cells. Common symptoms, including fatigue, fever, cough, and sore throat, may occur after the incubation period, lasting up to 2 weeks [2].

The new coronavirus can be associated with laboratory abnormalities, including lymphopenia and changes in liver enzymes. In addition, it may lead to increased inflammatory markers, eg, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) [3]. Disruption of coagulation systems and platelet counts have also been reported [4].

About 20% of COVID-19 patients suffer from considerable coagulation disorders. Also, 25% are susceptible to thrombotic events and thus are hospitalized in the ICU for receiving anticoagulant prophylaxis [5]. Among the diseased COVID-19 patients, 71.4% showed diffuse intravascular coagulation symptoms, of which only 0.6% survived [6].

Coagulation factors such as D-dimer levels, fibrin degradation product (FDP) levels, prothrombin time (PT), and partial thromboplastin time (PTT) are laboratory diagnosis criteria serving as the most significant prognostic tools related to COVID-19. In addition, they are the best laboratory diagnosis markers for COVID-related homeostasis abnormalities and disease severity predictors [7]. D-dimer, a small product of fibrin degradation, is a fibrinolysis marker. In conditions of increased production and breakdown of thromboses, such as trauma, intravascular coagulation, infections, pulmonary embolism, and cardiac disorder, D-dimer levels considerably increase in the plasma [8]. The present research aims to evaluate D-dimer levels and coagulation parameters in patients with COVID-19. Also, it explores any possible association of these parameters with disease prognosis and severity.

## Materials and Methods

This cross-sectional study was conducted through simple random sampling to evaluate coagulation status and D-dimer level in COVID-19 confirmed cases (RT-PCR and or chest CT scan). The patients were chosen among those referring to [Boo-Ali Sina](#) and [Imam Khomeini](#) hospitals of [Mazandaran University of Medical Sciences](#) in the last three months of 2021. The exclusion criteria were patients under anticoagulant therapy, heparin-induced thrombocytopenia (HIT), pregnancy, current hematopoietic malignancy, disseminated intravascular coagulation (DIC), chronic kidney and liver, and coronary artery bypass surgery diseases.

After the initial assessment, we took venous blood samples from the patients before hospitalization and discharge. In addition, demographic factors (age and gender) and comorbidity disease were recorded. Also, hemostasis parameters such as D-dimer, prothrombin time (PT), platelets count (PLT), and partial thromboplastin time (PTT) were determined for all subjects. The immunofluorescence sandwich immune-detection method by [ichroma™](#) reader was applied to measure D-dimer levels of patients' plasma samples. Finally, a coagulation analyzer was used to measure patients' PTT and PT.

## Statistical analysis

The analyses were performed using SPSS software, version 22, with a  $P < 0.05$  considered the statistically significant level. Qualitative and quantitative data were expressed as number (percentage) and Mean $\pm$ SD, respectively. Furthermore, the relationship between patient prognosis and D-dimer was determined using the chi-square test.

## Results

Of 140 evaluated COVID-19 patients (Mean $\pm$ SD age: 55.73 $\pm$ 16.821; range 17-88 years), 51.4% were male. [Table 1](#) presents comorbidities, of which diabetes and hypertension were the most common health problems. Their Mean $\pm$ SD hospitalization stay was 8.47 $\pm$ 7.808 days. All patients were ordered for laboratory tests and chest CT scans upon admission. Also, 56(40.0%), 40(28.6%), and the rest of the patients showed <25%, 25%-50%, and >50% of lung involvement, respectively. The CURB-65 score calculated for pneumonia severity was categorized as follows: 84 patients (level 1; low risk), 34 patients (level 2; medium risk), and 22 patients (level 3; high risk). Laboratory findings are categorized in [Table 2](#). The most frequent abnormalities included elevated D-dimer level, PTI, PT, and thrombocytopenia in 62.9%, 32.9%, 17.9%, and 25.7% of the patients, respectively.

**Table 1.** Prevalence of co-morbidity disease in COVID-19 patients (n=140)

Parameter	No. (%)	
	Yes	No
Diabetes	37(26.4)	103(73.6)
Hypertension	33(23.6)	107(76.4)
Hyperlipidemia	3(2.1)	137(97.9)
Non-hematopoietic malignancy	6(4.3)	134(95.7)
Chronic obstructive pulmonary disease	2 (1.4)	138(98.6)
Asthma	2(1.4)	138(98.6)
Ischemic heart disease	10(7.1)	130(92.9)
Cerebrovascular accident	3(2.1)	137(97.9)
Rheumatic disorders	1(0.7)	139(99.3)

**Table 2.** Patients' coagulation test results (n=140)

Lab Test	Normal Value (Unit)	No. (%)	
		Normal	Abnormal
D-dimer level	≤500 ng/mL	52(37.1)	88(62.9)
PT	11-13 s	115(82.1)	25(17.9)
PTT	24-35 s	94(67.1)	46(32.9)
PLT	140–450 x 10 <sup>9</sup> /L	103(73.6)	37(26.4)

Abbreviations: PT: Prothrombin time; PTT: Partial thromboplastin time; PLT: Platelet count.

**Table 3.** Association between coagulation parameters level and prognostic factors (n=140)

Outcome		No. (%)									
		Outcome		ICU Admission		Lung Involvement in CT			CURB-65 Score		
		Death	Health	Positive	Negative	<25	25-50	≥50	1	2	3
D-dimer	Normal	2(3.8)	50(96.2)	6(11.6)	46(88.5)	32(61.5)	11(21.2)	9(17.3)	37(71.2)	13(25)	2(3.8)
	Abnormal	30(34.1)	58(65.9)	38(43.2)	50(56.8)	24(27.3)	29(33)	35(39.8)	47(53.4)	21(23.9)	20(22.7)
PT	Normal	21(18.3)	94(81.7)	32(27.8)	83(72.2)	47(40.9)	32(27.8)	36(31.3)	68(59.1)	31(27)	16(13.9)
	Abnormal	11(44)	14(56)	12(48)	13(52)	9(36)	8(32)	8(32)	16(64)	3(12)	6(24)
PTT	Normal	18(19.1)	76(80.9)	27(28.7)	67(71.3)	45(47.9)	20(21.3)	29(30.9)	54(57.4)	24(25.5)	16(17)
	Abnormal	14(30.4)	32(69.6)	17(37)	29(63)	11(23.9)	20(43.5)	15(32.6)	30(65.2)	10(21.7)	6(13)
PLT	Normal	19(18.4)	84(81.6)	32(31.1)	71(68.9)	42(40.8)	28(27.2)	33(32)	65(63.1)	21(20.4)	17(16.5)
	Abnormal	13(35.1)	24(64.9)	12(32.4)	25(67.6)	14(37.8)	12(32.4)	11(29.7)	19(51.4)	13(35.1)	5(13.5)

Abbreviations: PT: Prothrombin time; PTT: Partial thromboplastin time; PLT: Platelet count.



As shown in Table 3, abnormal levels of coagulation parameters were associated with poor outcomes, such as CURB-65 score, higher lung involvement in CT-scan, more frequent ICU admission, and even death.

## Discussion

The new coronavirus disease causes a wide range of symptoms. The Centers for Disease Control and Prevention (CDC) reported that only about 20% of patients develop acute and critical conditions, and the rest experience mild to moderate symptoms [9].

Disease and its severity predictions in patients can be used to improve clinical outcomes of COVID-19 patients. In this respect, laboratory tests (eg. abnormal PLT, PTT, and PT and elevated D-dimer level) are considered coagulating factors for the early detection of DIC through abnormalities in laboratory coagulation [10].

This study investigated coagulation patterns in 140 COVID-19 cases admitted to a University Hospital in Mazandaran Province, north of Iran. Of this population, 51.4% were males, and 48.6% were females. This demographic pattern is similar to that of previous studies, which reported male predominance and increased disease susceptibility among older people. An explanation for the lower susceptibility of the females to COVID-19 infection might be their stronger immune response [11]. The Mean±SD age of patients infected with COVID-19 was 55.73±16.821 years, consistent with previous studies [10, 12].

In our study, about 71.4% of the COVID-19 patients attended the hospital with severe (22 cases) and moderate (34 cases) symptoms. Consistent with the previous studies, these high statistics might be due to their older age and poor immune response [10, 12, 13].

Impaired coagulation (coagulopathy) has been reported in some COVID-19 cases. A high rate of thrombotic events is observed in both clinical and postmortem studies [14].

Studying the coagulation patterns reveals that abnormal D-dimer levels are related to poor prognosis, including increased lung involvement in CT scans, the need for ICU admission, and death. The D-dimer values for the moderate, severe, and critical COVID-19 patients show significant differences from those with mild and asymptomatic symptoms. This result is consistent with previous research on disease severity [5, 10]. Elevated D-dimer has been confirmed among the important labo-

ratory indicators for hospitalized COVID-19 patients. These markers correlate with the greater risk of thrombotic ICU-associated problems and even death among COVID-19 patients.

Tang et al. are among the first researchers who reported disrupted coagulation tests in COVID-19 subjects and their association with poor prognosis. In their study on 183 patients, PT, D-dimer level, and fibrin degradation products (FDPs) showed significantly different values between survivors and non-survivors. Also, DIC was associated with mortality [15]. In a study in Iran, Sayad et al. found that about 30% and 42% of patients had thrombocytopenia and abnormal PT, respectively, which are higher than our results. D-dimer was accessible in 16 patients, which was higher in deceased patients but not statistically significant [16]. Zhou et al. assessed 17 COVID-19 patients (5 severe and 12 non-severe) and reported significant differences in lymphocyte and CD4+ T cell counts between the two groups. However, the results did not apply to D-dimer levels [17].

Several etiologies have been proposed for coronavirus-induced coagulopathy. In this respect, vascular endothelium is among the most important components of maintaining homeostasis. Endothelial cells and their components prevent clot formation and thrombosis. These dynamic properties can be replaced with clot-promoting properties under certain conditions [18].

## Conclusion

The present study had some limitations that should be addressed. D-dimer measurement was performed once, and any possible changes were not monitored. Related laboratory markers that could affect D-dimer levels (e.g. pro-inflammatory cytokine levels) were not measured. Therefore, inflammation might affect D-dimer levels. However, excluding patients with possible conditions affecting coagulation tests and applying the severity of disease and lung involvement are among the strengths of the present study. Finally, although abnormal D-dimer levels are reliable in predicting a patient's prognosis, future investigations are needed to elucidate the trend of changes in coagulation parameters and the effectiveness of anticoagulant treatment in COVID-19 subjects.

## Ethical Considerations

### Compliance with ethical guidelines

The Ethics Committee of [Mazandaran University of Medical Sciences](#) approved the research (IR.MAZUMS.REC.1399.157).

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### Authors contribution's

Study design, supervision: Maryam Ghasemi, Somayeh Sheidaei, and Parvaneh Afshar; Statistical analysis: Mohammad Khademloo; Writing the article and data acquisition: Elahe Kavooosi and Fatemeh Abedian; Manuscript revision, review, and final approval: All authors

### Conflict of interest

The authors declared no conflict of interest.

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