

Occurrence of Coagulation disorders in hospitalized COVID-19 patients and its relationship with disease outcome: A Cross-sectional study

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Abstract

Background: Evidence suggests that patients afflicted with COVID-19 are subject to significant risks of thromboembolic complications. We aimed to evaluate the occurrence of coagulation disorders in patients suffering from COVID-19 and determine its relationship with the disease outcome. **Methods:** This cross-sectional study was conducted on 106 COVID-19 patients who were hospitalized in Imam Khomeini Hospital, Ardabil, Iran. After the preliminary completion of the information forms, 3 cc of intravenous blood sample was taken from each of the patients to check the patients' INR, PT, CBC, and D-dimer. The patients were monitored. Finally, the results obtained from these clinical assessments and tests were all recorded in checklists and statistically analyzed using SPSS Software, Version 19. **Results:** Of the total 106 COVID-19 patients who entered the study, 69 cases were discharged from the hospital alive while the other 37 cases died. The mean age of the patients was 58.99 ± 15.94 years and 56.6% of them were male. There were significant differences between the survived and the deceased patients in terms of D-dimer, LDH, PT, and INR levels ($p < 0.05$). Based on the results of logistic regression analysis, only D-dimer was found to have a significant effect on predicting mortality. More specifically, with the increase of each 1 unit in D-dimer level, the mortality risk increased by 0.99%. **Conclusion:** D-dimer has a higher sensitivity in comparison with other markers of coagulation and is of relatively greater value in terms of intensity. Compared to the high prevalence of thrombotic events, bleeding is not that common; therefore, standard anticoagulant therapy is highly recommended.

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Abstract

Background : Evidence suggests that patients afflicted with COVID-19 are subject to significant risks of thromboembolic complications. We aimed to evaluate the occurrence of coagulation disorders in patients suffering from COVID-19 and determine its relationship with the disease outcome.

Methods : This cross-sectional study was conducted on 106 COVID-19 patients who were hospitalized in Imam Khomeini Hospital, Ardabil, Iran. After the preliminary completion of the information forms, 3 cc of intravenous blood sample was taken from each of the patients to check the patients' INR, PT, CBC, and D-dimer. The patients were monitored. Finally, the results obtained from these clinical assessments and tests were all recorded in checklists and statistically analyzed using SPSS Software, Version 19.

Results : Of the total 106 COVID-19 patients who entered the study, 69 cases were discharged from the hospital alive while the other 37 cases died. The mean age of the patients was 58.99 ± 15.94 years and 56.6% of them were male. There were significant differences between the survived and the deceased patients in terms of D-dimer, LDH, PT, and INR levels ($p < 0.05$). Based on the results of logistic regression analysis, only D-dimer was found to have a significant effect on predicting mortality. More specifically, with the increase of each 1 unit in D-dimer level, the mortality risk increased by 0.99%.

Conclusion : D-dimer has a higher sensitivity in comparison with other markers of coagulation and is of relatively greater value in terms of intensity. Compared to the high prevalence of thrombotic events, bleeding is not that common; therefore, standard anticoagulant therapy is highly recommended.

Keywords : COVID-19, coagulation disorders, outcome, thrombocytopenia

What's known

- The novel coronavirus, SARS-CoV-2, has caused a global pandemic of a life-threatening, multi-organic disease i.e., COVID-19.
- The results of the studies on COVID-19 patients have shown that the affected patients are subject to higher risks of Diffuse Intravascular Coagulation (DIC).
- The present study aimed to investigate the occurrence of coagulation disorders in COVID-19 patients and determine its relationship with the disease outcome.

What's new

- The results showed a significant difference between the two groups (survivors and non-survivors) in terms of D-dimer, LDH, PT, and INR levels.
- Serum D-dimer level, LDH, PT, and INR in the deceased patients were significantly higher than those of the surviving patients
- the results of binary logistic regression indicated that serum D-dimer level had a significant effect on predicting mortality in a way that for each unit of increase in D-dimer level, mortality risk increased by 0.99% (OR=0.994; 95%CI: 0.992-0.997).
- Τηε αρεα υνδερ τηε POⁿ ζυρε ωας οβταινεδ το βε 85% φορ Δ-διμερ. Τηεν, βασειδ ον τηε φιγυρε, ιτς ζυτοφφ ποιντ ωας δετερμινεδ το βε 450 μγ/δλ ωιτη τηε σενσιτιβ οφ 98% ανδ σπεσιφικιτιφ οφ 97%.

Introduction:

The novel coronavirus, SARS-CoV-2, has caused a global pandemic of a life-threatening, multi-organic disease i.e., COVID-19 (1). Its outbreak began in late 2019 and early 2020 in Wuhan, China by affecting a large number of people and then spread rapidly all around the world (2). Evidence suggests that patients afflicted

with COVID-19 are subject to significant risks of thromboembolic complications which affect mainly their intravenous system and sometimes, their arterial vascular system (3). Although the pathogenic mechanism of COVID-19 is not completely clear (4), it seems that coagulopathy is one of the serious problems that patients afflicted with COVID-19 grapple with (5). Based on the results of the preliminary investigations on COVID-19 pandemic, thrombocytopenia (36.2%) and elevated D-dimer level (46.4%) are usually observed in the affected patients (6). Yet, in patients affected by severe forms of the disease, the prevalence of these two conditions is even higher (57.7% and 59.6%, respectively) (6). The results of the studies on COVID-19 patients have shown that the affected patients are subject to higher risks of Diffuse Intravascular Coagulation (DIC) (6-8). Elevated D-dimer level, prolonged prothrombin, and increased level of fibrin degradation products have been reported to be associated with poor prognosis in COVID-19 patients (8). Therefore, the present study aimed to investigate the occurrence of coagulation disorders in COVID-19 patients and determine its relationship with the disease outcome.

Methods:

This cross-sectional study was conducted on 106 COVID-19 patients who were hospitalized in Imam Khomeini Hospital, Ardabil, Iran. The patients' affliction with COVID-19 was diagnosed and confirmed based on the results of RT-PCR, throat swab, and lung CT scan tests. In the first day of hospitalization, a written consent was obtained from each of the patients and then their demographic information including their age, gender, clinical symptoms, comorbidities, and history of smoking was recorded on an information form. After the preliminary completion of the information forms, 3 cc of intravenous blood sample was taken from each of the patients. Then serum was separated from the blood samples in order to check the patients' INR, PT, CBC, and D-dimer levels. After that, the patients were investigated and monitored in terms of their clinical course, response to treatment, the need to be transferred to ICU, percentage of arterial blood oxygen saturation, mortality, and the related complications. Then the obtained clinical information and test results were all recorded in checklists. Patients with history of malignancies, those suffering from chronic liver diseases, kidney diseases, hemoglobinopathy, and blood disorders, as well as those who used anticoagulant drugs were all excluded from the study.

Ethical approval

The current study was propounded and approved by the Research Ethics Committee of Ardabil University of Medical Sciences (IR.ARUMS.REC.1399.087).

Statistical analysis

All statistical analyses were fulfilled using IBM SPSS Statistics software (Version 24) (IBM SPSS Statistics, Armonk, USA). The normality of variables was established using the Kolmogorov-Smirnov test. To compare variables with non-normal distribution, Mann-Whitney U test was employed. The predictive value of serum D-dimer level was determined via measuring the Area Under Receiver Operating Characteristic (AUROC) curve. Finally, the optimal threshold value was obtained via the calculation of Youden index. A p-value of less than 0.05 was regarded to be statistically significant.

Results:

Of the total 106 COVID-19 patients who entered the study, 69 cases were discharged from the hospital alive while the other 37 cases died. The mean age of the patients was 58.99 ± 15.94 years and 56.6% of them were male. Moreover, the patients' average length of stay in hospital was 11.79 ± 8.22 days. Based on the disease outcome, the patients were divided into two groups: the survived and the deceased (Table 1). The demographic information and comorbidities of each group of the patients are represented in Table 1.

The results showed a significant difference between the two groups in terms of D-dimer, LDH, PT, and INR levels. However, in terms of hemoglobin level and platelet count, the differences between the two groups were not found to be statistically significant. More specifically, serum D-dimer level, LDH, PT, and INR in the deceased patients were significantly higher than those of the surviving patients (Table 2).

In order to determine the relationship between mortality and the variables under investigation, binary logistic regression was applied on the data, the result of which are presented in Table 3 below. As can be seen, the results indicated that serum D-dimer level had a significant effect on predicting mortality in a way that for each unit of increase in D-dimer level, mortality risk increased by 0.99% (OR=0.994; 95%CI: 0.992-0.997). In order to determine the cutoff point of serum D-dimer level for the prediction of mortality, Receiver Operating Characteristic (ROC) curve was used. Figure 1 shows the related ROC curve. The area under the ROC curve was obtained to be 85% for D-dimer. Then, based on the figure, its cutoff point was determined to be 450 $\mu\text{g/dL}$ with the sensitivity of 98% and specificity of 97%.

Discussion:

This study was conducted with the aim of investigating the occurrence of coagulation disorders in COVID-19 patients and determining its relationship with the disease outcome. The results indicated that the prevalence of coagulation disorders was significantly higher in the deceased patients as compared to the surviving ones. Moreover, a positive correlation was observed between serum D-dimer level and mortality risk. Therefore, the level of D-dimer can be used as a prognostic risk factor in patients with COVID-19.

In their study, Tang et al. (2020) attempted to determine the poor prognosis of COVID-19 patients based on the aberrant coagulation parameters in the first 28 days of hospitalization. Their findings revealed that during these 28 days, elevated D-dimer level, prolonged PT, and higher age were associated with the highest levels of mortality while higher platelet counts were associated with the lowest levels of mortality (8). The findings of their study regarding the relationship of elevated D-dimer, PT, and age with mortality are consistent with the findings of the present study.

The results of the meta-analytic study conducted by Lippi et al. demonstrated that the platelet count in patients afflicted with COVID-19 was significantly lower than normal. Moreover, they found that the risk of being afflicted with thrombocytopenia was 5 times more in patients suffering from severe forms of COVID-29 as compared to normal patients (9). However, this finding is not in line with our finding. This inconsistency might be related to the fact that we checked the patients' platelet counts only at the beginning of the study while it is possible for patients to develop thrombocytopenia during hospitalization, which was not investigated at all in the current study.

In Brazil, Dolhnikoff et al. conducted a pathological study on 10 deceased patients (5 male and 5 female cases with the mean age of 67.8 years). Pathological observations were indicative of higher incidence of coagulation disorders among patients in critical condition. They also showed that renal microthrombosis was more prevalent among these patients (10).

In a retrospective study, whose findings tuned out to be in line with ours, Yin et al. (2020) compared the coagulation status and clinical characteristics of patients with SARS-CoV-2-induced severe pneumonia (COVID group) and those of the patients with non-SARS-CoV-2-induced severe pneumonia (non-COVID group). They observed that severe forms of COVID-19 were usually accompanied by coagulation disorders. Therefore, they suggested that higher levels of D-dimer can be helpful in deciding whether to use anticoagulant therapy or not (11).

In the present study, 87% of the patients had elevated D-dimer levels. In line with our finding in this regard, Yao et al. (2020) also observed elevated D-dimer levels in 74.6% of the total patients under investigation. In their study too, D-dimer level significantly increased as the severity of COVID-19 symptoms increased. This finding was confirmed by the clinical observations and CT results. In their study, the hospital mortality rate was 6.9%. Furthermore, the mean D-dimer level in the deceased patients was significantly higher than that of the surviving patients. Moreover, hospital mortality rate was predicted based on the D-dimer level of higher than 2.14 mg/L with the sensitivity of 88.2% and specificity of 71.3% (12). This level for D-dimer in the current study was found to be 450 $\mu\text{g/dL}$. Thrombocytopenia and elevated D-dimer level can be explained by the over-activation of coagulation cascades and platelets. Viral infections induce systemic inflammatory response and cause imbalance in procoagulant and anticoagulant hemostatic mechanisms (13). Multiple pathogenic mechanisms are involved here which include endothelial dysfunction, increase in von

Willebrand factor, Toll-like receptor activation, and the activation of tissue factor pathway (13). After recognizing the antigen, platelets become activated and interact with it. White blood cells are also activated and clot formation is accelerated (14). Platelets are the main mediators of inflammation and detect infectious agents via perceiving the interaction of cell-surface receptors and pathogens as well as the activation of, and interaction among, macrophages, monocytes, endothelial cells, platelets, and lymphocytes. Therefore, they play an important role in the prognostic effect of viral infections (15).

Conclusion:

The results of the present study indicated that coagulation disorders are more prevalent in patients with severe forms of COVID-19. It was also found that serum D-dimer level is positively associated with mortality. Although coagulation disorders in COVID-19 patients are still being investigated, the evidence thus far suggests that thrombotic coagulation disorder is quite prevalent in severe cases of COVID-19. The results also indicated that D-dimer has higher sensitivity in comparison with other coagulation markers and is of greater value in severity. Compared to the high prevalence of thrombotic events, bleeding is not that common; therefore, standard anticoagulant therapy is highly recommended.

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Authors' Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Conflict of interest

Authors confirm that they have no conflict of interest to declare.

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Table 1: Demographic characteristics, underlying disease and length of hospital stay of patients by groups

Variables	Variables	All patients (n = 106)	Non survivors (n = 37)	survivors (n = 69)
Age(year)	Age(year)	58.99 ± 15.94	60.09 ± 17.12	58.43 ± 15.41
Sex, n (%)	male	60 (56.6 %)	21 (56.8%)	39 (56.5 %)
	female	46 (43.4%)	16 (43.2%)	30 (43.5 %)
Saturation, n (%)	> 93%	23 (21.7)	18 (48.6 %)	5 (7.2 %)
	< 93%	83 (78.3)	19 (51.4 %)	64 (92.8 %)
Hospital Duration(day)	Hospital Duration(day)	11.79 ± 8.22	11.03 ± 10.7	12.06 ± 6.59

Table2. The Laboratory findings of patients by groups

Variables	All patients (n = 106)	survivors (n = 37)	Non survivors (n = 69)	P value*
White Blood Cell	7899.06 ± 4264.57	9589.19 ± 5362.35	6999.75 ± 3235.93	0.01
Hemoglobin	13.46 ± 1.99	13.66 ± 2.23	13.36 ± 1.86	0.45
Platelet	200.15 ± 82.85	198.41 ± 84.44	201.09 ± 82.59	0.87
D-dimer	941.43 ± 958.90	1340.59 ± 915.48	727.39 ± 918.10	<0.001
PT	13.36 ± 1.83	13.79 ± 1.91	13.13 ± 1.76	0.01
INR	1.18 ± 0.29	1.24 ± 0.28	1.14 ± 0.28	0.03

Variables	All patients (n = 106)	survivors (n = 37)	Non survivors (n = 69)	P value*
PTT	35.33 ± 7.34	35.65 ± 6.05	35.16 ± 7.99	0.625
LDH	813.19 ± 586.65	881.89 ± 414.06	719.19 ± 290.11	0.029

Notes: [?] Independent samples t-test between two groups. The data are presented as mean ± SD. P-values of statistical significance ($p < 0.05$) are presented in bold.

Abbreviation: PT; prothrombin time, INR; international normalized ratio, PTT; partial thromboplastin time, LDH; lactate dehydrogenase

Table 3: Results of logistic regression to determine the relationship between study variables and disease outcome

Variable	Sig.	Exp(B)	95% C.I. for EXP(B)	95% C.I. for EXP(B)
			Lower	Upper
PT	.772	1.081	.641	1.823
INR	.297	.190	.008	4.320
D-dimer	.000	.994	.992	.997
LDH	.986	1.000	.998	1.002

P-values of statistical significance ($p < 0.05$) are presented in bold. **Abbreviation:** PT; prothrombin time, INR; international normalized ratio, PTT; partial thromboplastin time, LDH; lactate dehydrogenase

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FIGURE1.docx available at <https://authorea.com/users/726330/articles/708899-occurrence-of-coagulation-disorders-in-hospitalized-covid-19-patients-and-its-relationship-with-disease-outcome-a-cross-sectional-study>