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Original Research Article

D-Dimer as a Predictive Biomarker of Severity and Mortality in COVID-19 Patients

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Abstract: ***Background:*** Since December 2019, Coronavirus has been spreading widely becoming a fatal global pandemic. We need to understand the pathophysiological mechanisms of the disease in order to determine early and effective predictive biomarkers for severity and mortality, therefore finding better treatment approaches. ***Object:*** We aim to investigate the predictive value of d-dimer in COVID-19 in order to determine the severity, mortality and the risk of developing thrombotic events. ***Methods:*** We enrolled patients with confirmed COVID-19 who referred to the COVID department at Tishreen University Hospital (Latakia, Syria) from May 2020 to March 2021. We retrospectively documented demographic characteristics, clinical data, laboratory parameters and chest computed tomography staging. We followed up the patients' clinical progress during hospitalization, as well as their need for supportive oxygen (invasive and non-invasive mechanical ventilation) and the occurrence of thrombotic complications during hospitalization. Finally, we listed the cases of recovery and death. ***Results:*** We included 284 patients (68.3% males and 31.7% females). The mean age was 65 years, ranging from 27 to 92. D-dimer was only obtained for 193 patients, which included 28 mild to moderate, 115 severe and 50 critically ill patients. D-dimer was elevated (≥ 500 ng/mL) in 110 patients. On admission, D-dimer level was associated with an increased clinical severity. It was higher in critically ill compared to moderate cases ([3397.5±3296.7]ng/mL vs [1066.1± 1963.2] ng/ml, P = 0.0001) as well as for radiographic severity ([626.5±1047.1] ng/mL vs [2262.6± 2751.2] ng/ml, P= 0.007), respectively. All of those who did not survive had increased D-dimer level upon admission. When compared between patients who survived and who died during hospitalization, a significantly higher D-dimer level was detected in non-survivors versus survivors ([3099.9±2808.2] ng/mL vs [1308.9± 2249.3] ng/ml, P= 0.0001). We found that high-risk COVID-19 patients who developed pulmonary embolism and arterial thrombosis had elevated D-dimer on admission, (P = 0.0001 for each), in contrary to patients who developed DVT (P = 0.3). Moreover, patients who demanded invasive mechanical ventilation also had higher D-dimer levels on admission (P = 0.003). ROC analysis identified D-dimer > 695.5 ng/mL upon admission as the optimal cutoff level to distinguish survivors from non-survivors with sensitivity of 78.8% and specificity of 61%. ***Conclusion:*** We concluded that higher D-dimer levels in COVID-19 patients were associated with a more severe disease, both clinically and on computed tomography, and a higher risk for developing PE and arterial thrombosis. We established a cutoff value for D-dimer on admission greater than 695.5 ng/mL which might early identify patients at higher risk for in-hospital mortality. We suggest conducting future studies on D-Dimer in order to find a more accurate cut-off value as a predictive indicator for mortality.

Keywords: COVID-19, D-dimer, severity, mortality.

INTRODUCTION

On the 9th of January 2020, a new disease caused by SARS-CoV-2, a novel β coronavirus of group 2B, emerged in Wuhan, Hubei Province, China, and then was declared a worldwide health emergency by the World Health Organization (WHO) [1-3]. The disease varies from asymptomatic to critical respiratory failure. Symptoms include fever, diarrhea, myalgia, coughing, dyspnea, severe lymphopenia, coagulation dysfunction, cardiac disease, and sudden death [1]. Therefore, predicting the early progression of the disease could help with risk stratification and early administration of appropriate treatment for COVID-19 patients [4]. Abnormal coagulation parameters, such as elevated D-dimer, predict the severity of COVID-19

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and are essential for detecting complications early [3]. D-dimer is the main breakdown fragment of fibrin and is used as an indicator of fibrin formation and degradation. Several studies have shown that D-dimer is a significant marker for the activation of coagulation and fibrinolysis, as well as other conditions e.g. chronic inflammation. In regard to COVID-19, D-dimer has been demonstrated to be more common in critical cases, and it elevates the probability of in-hospital death [5, 6]. D-dimer > 1000 ng/mL is associated with high mortality risk in COVID-19 indoor patients. However, the role of D-dimer in COVID-19 has yet to be uncovered [1]. In our cohort study, we demonstrated D-dimer concentrations at admission in patients with severe and non-severe infections, depending on clinical severity, chest CT staging and in-hospital death. We also investigated the occurrence of thrombotic complications with higher D-dimer concentrations.

METHODS

Patients

We enrolled, in our retrospective cohort study, patients with confirmed COVID-19 who referred to the COVID department at Tishreen University Hospital (Latakia, Syria) from May 2020 to March 2021. Laboratory confirmation was obtained for SARS-COV-2 by real-time reverse-transcriptase-polymerase-chain-reaction (RT-PCR) through a nasal swab, according to the World Health Organization (WHO) last update in public health surveillance for COVID-19, published in 16 December 2020 (supplement table 1). Exclusion criteria included hematologic and solid malignancies, acute coronary syndrome, chronic liver disease, pregnancy and surgery or trauma within 30 days. We collected demographic characteristics, clinical data, laboratory parameters and chest CT scans. Furthermore, we followed patients' clinical progress during hospitalization, as well as their need for supportive oxygen (invasive and non-invasive mechanical ventilation) and the occurrence of thrombotic complications during hospitalization. Finally, we listed the cases of recovery and death.

Laboratory and imaging methods

D-dimer level is tested using fluorescence Immunoassay (FIA) with a reference rage of 0-500 ng/mL (I-Chroma analyzer), for all patients upon admission. Likewise, all inpatients had Chest CT scans on admission. Patients with high clinical suspicion of pulmonary embolism/deep vein thrombosis (PE/DVT) or arterial thrombosis were subjected to Doppler ultrasound and CT pulmonary angiography. No routine screening for asymptomatic DVT or PE was performed.

Severity assessment

The severity of cases was evaluated according to the Novel Coronavirus Pneumonia Diagnosis and Treatment Guideline (6thed.) [7], Figure 1.

Mild	Mild clinical manifestation None Imaging Performance
Moderate	Fever, respiratory symptoms, pneumonia performance on X-ray or CT
Severe	Meet any of the followings: 1. Respiratory distress, RR ≥ 30/min; 2. Oxygen saturation ≤ 93% at rest state; 3. Arterial partial pressure of oxygen (PaO_2)/Fraction of inspiration O_2 (FiO_2) ≤ 300 mnHg, 1 mmHg = 0.133 kPa
Critically severe	Meet any of the followings: 1. Respiratory failure needs mechanical ventilation; 2. Shock; 3. Combined with other organ failure, patients need ICU monitoring and treatment

Figure 1: The Novel Coronavirus Pneumonia Diagnosis and Treatment Guideline (6thed.) by the National Health Commission of China

Radiologically, each patient's chest CT after admission was first assessed for typical findings of COVID-19 pneumonia (bilateral, multilobe, posterior peripheral ground glass opacities) as defined by the *RSNA Consensus Statement* [8]. Severity then was assessed using the following scoring system which depends on the visual assessment of each lobe involved [9, 10], Figure 2.

Percentage of lobar involvement	Score
5% or less	1
5%-25%	2
26%-49%	3
50%-75%	4
> 75%.	5

Figure 2: The scoring system of radiographic severity according to percentage of lobar involvement

The sum of the lobar scores indicates the overall severity, Figure. 3.

Total score (numerical)	Severity (category)
7 or less	Mild
8-17	Moderate
18 or more	Severe

Figure 3: The sum of the lobar scores of radiographic severity

Statistics

Statistical analysis methods include descriptive statistics which consist of qualitative variables expressed as frequencies and percentages, and quantitative variables expressed by measures of central tendency and measures of dispersion. We relied upon the IBM SPSS Statistics (Statistical Package for the Social Sciences for Windows; Version 20) program to calculate the statistical parameters and analyze the results. Correlations of D-dimer with clinical staging, chest CT staging, and in-hospital mortality were evaluated by Kendall's tau-b coefficient analysis. To assess the predictive value of D-dimer for mortality, receiver operating characteristic (ROC) analysis was conducted with calculations of the area under the ROC curve (AUC), sensitivity and specificity. *P* value less than 0.05 was considered statistically significant.

RESULTS

After applying the exclusion criteria, 284 patients (68.3% males and 31.7% females) were included in the final analysis. The mean age of patients was 65 years, ranging from 27 to 92 years. Clinical severity was classified into mild to moderate (18%), severe (60.5%), and critically ill (21.5%). Radiologically, the majority of patients (52.5%) developed severe lung disease. 50 patients received mechanical ventilation, including non-invasive C-PAP (6.3%) and invasive (11.3%). The most common complication was PE (5.6%). 71 patients died during hospitalization. D-dimer was only obtained for 193 patients which included 28 mild to moderate, 115 severe and 50 critically ill patients. D-dimer was elevated (≥ 500 ng/mL) in 110 patients Table 1.

Table 1: Clinical and imaging characteristics of 284 COVID-19 patients

Variable	n	Percentage
Clinical severity		
Mild/moderate	51	18%
Severe	172	60.5%
Critically ill	61	21.5%
Radiographic severity		
Mild	31	10.9%
Moderate	104	36.6%
Severe	149	52.5%
Mechanical ventilation		
Non-invasive	18	6.3%
Invasive	32	11.3%
D-Dimer		
Normal	83	29.2%
Elevated (>500 µg/ml)	110	38.7%

Variable	n	Percentage
Complications		
Arterial thrombosis	3	1.1%
PE	16	5.6%
DVT	3	1.1%
Death	71	25%

On admission, D-dimer level was associated with an increased clinical severity. It was higher in critically ill compared to moderate cases ([3397.5±3296.7] ng/mL vs [1066.1± 1963.2] ng/mL, P = 0.0001) as well as radiographic severity ([626.5±1047.1] ng/mL vs [2262.6± 2751.2] ng/ml, P= 0.007) Table 2.

Table 2: Correlations of D-dimer levels with clinical and imaging severity

Clinical severity	N	Mean ± SD	P-value
Mild/moderate	28	1066.1 ±1963.2	0.0001
Severe	115	1269.8 ±1921.1	
Critically ill	50	3397.5 ±3296.7	
Radiographic severity			
Mild	19	626.5 ±1047.1	0.007
Moderate	66	1356.01 ±2288.8	
Severe	108	2262.6 ±2751.2	

All of those who did not survive had increased D-dimer levels upon admission. When comparing patients who survived and who died during hospitalization, significantly higher D-dimer levels were detected in non-survivors versus survivors ([3099.9±2808.2] ng/mL vs [1308.9± 2249.3] ng/ml, P= 0.0001). Documented thrombotic complications of the final population were PE (16 patients), DVT (3 patients) and arterial thrombosis (3 patients). We found that high-risk COVID-19 patients who developed pulmonary embolism and arterial thrombosis had elevated D-dimer on admission, (P = 0.0001 for each), in contrary to patients who developed DVT (P = 0.3). Moreover, patients who demanded invasive mechanical ventilation also had higher D-dimer levels on admission (P = 0.003) Table 3.

Table 3: Correlations between D-dimer levels and the incidence of thrombotic events, invasive and non-invasive ventilation and mortality

Complication	Mean ± SD (D-Dimer)	P-value
PE		
Present	5027.9 ±3337.5	0.0001
Absent	1498.9 ±2239.3	
DVT		
Present	3185.6 ±4950.2	0.3
Absent	1769.4 ±2496.1	
Arterial thrombosis		
Present	6806.7 ±383.6	0.0001
Absent	1712.3 ±2441.2	
Invasive mechanical ventilation		
Required	3177.7±2755.2	0.003
Not required	1585.2±2440.9	
Death		
Survivors	3099.9±2808.2	0.0001
Non-survivors	1308.9±2249.3	

ROC analysis identified D-dimer > 695.5 ng/mL upon admission as the optimal cutoff level to distinguish survivors from non-survivors (AUC 0.76, 95% confidence interval [CI] 0.9-1, P = 0.000); Figure 4. For predicting in-hospital mortality, a D-dimer level above 695.5 ng/mL had a sensitivity of 78.8% and a specificity of 61%.

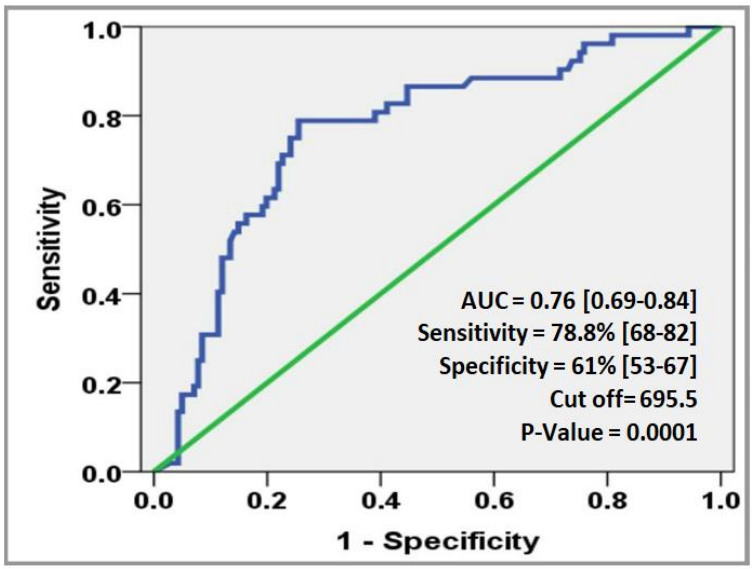

Figure 4: Correlation between D-dimer levels and mortality through ROC curve

DISCUSSION

In our study, we demonstrated that high levels of D-dimer at the time of admission in patients with COVID-19 were correlated with increased disease severity and in-hospital mortality. D-dimer is produced when fibrin is formed and degraded into clots by plasmin, providing a reflective marker for activation of coagulation and fibrinolysis. However, any process that increases fibrin generation or breakdown also elevates plasma D-dimer levels [11]. For example, events like pulmonary embolism, deep vein thrombosis, arterial thrombosis, disseminated intravascular coagulation, inflammation, cancer, pregnancy, chronic liver diseases, post trauma and surgery [12]. It was found that Infusion of purified human fragment D into rabbits causes pulmonary capillary leakage and hypoxemia. Fragment D also motivates platelet aggregation and prostaglandin synthesis, activates complement, and stimulates chemotaxis of neutropenia [6]. Patients with COVID-19 are more likely to be in a hypercoagulable state, which could be explained by different reasons such as the insufficient control of an anti-inflammatory response that usually accompany virus infections, which might cause a dysfunction in endothelial cells, resulting in excess thrombin production. Other than that, in-hospital patients with COVID-19 are more susceptible to having underlying comorbidities, older ages, long-term bed rest, and invasive treatment, which are all risk factors of thrombosis or hypercoagulation.

The elevation in D-dimer levels has been reported as one of the most noted laboratory findings in COVID-19 in-hospital patients [13]. A study by Zhang et al. Showed that D-dimer was noticeably higher in severe cases compared to non-severe ones [14]. Huang et al. reported similar results where they categorized patients based on their need to critical care support. Patients without an elevated D-dimer at the time of admission were more likely to be discharged without exacerbations [15]. In addition, Hai-Han et al. found that the level of D-dimer was markedly elevated in patients with severe COVID-19, and the meta-analysis further asserted that odds of severe COVID-19 was linked with D-dimer higher than 500 ng/mL [5]. Similarly in our study, we found that there is a significant association between elevated D-dimer concentrations and disease severity, stratified by clinical severity as well as the percentage of lung involvement on chest CT. Moreover, we demonstrated that D-dimer levels on admission were higher in patients who developed thrombotic events and in those who needed invasive mechanical ventilation later. Some of the most critical factors that contribute to mortality in severe COVID patients are prothrombotic coagulation abnormalities and thromboembolism [16]. Pulmonary embolism (PE) accounts for the majority of these complications [17]. A French research demonstrated the association between the rise in D-dimer levels and the risk of PE. D-dimer levels higher than 2660 ng/mL showed a sensitivity of 100% and a specificity of 67% for PE. Yet the specificity value for VTE was low because other other conditions like pregnancy, sepsis and malignancy could be responsible for these levels [18]. Another retrospective analysis of 156 non-ICU COVID-19 patients by Demelo-Rodríguez et al found that D-dimer levels were 4527 ng/mL vs 2050 ng/mL in patients with and without DVT, respectively [19]. However, our results showed no significant relation between D-dimer levels and the risk of DVT in COVID-19 patients.

This could be justified by the inability to perform Doppler ultrasound on all admitted patients. Instead, it was only performed on symptomatic patients. Resembling our results, Zhao et al found that patients who required invasive mechanical ventilation had higher concentrations of D-dimer [20]. We also found that there is a significant association between D-dimer concentration on admission and the risk of developing

arterial thrombosis later. A multi-centered Saudi study showed unexpectedly that the risk of developing arterial thrombosis and hemorrhagic events was higher than venous thrombosis in severe COVID patients. The forementioned study found that D-dimer levels on admission could predict those events [21]. Fournier et al showed that D-dimer levels > 1250 ng/mL on admission could determine patients at risk for developing arterial thrombosis later [22]. Elevated concentrations of D-dimer were also found to be associated with increased in-hospital mortality rate. This suggests that it could be used as a single useful biomarker for clinical outcome in patients with COVID-19 [1]. A multi-centered study from China by Guan and colleagues included 1099 patients with COVID-19. They found that non-survivors had a significantly higher D-dimer (median, 2.12 µg/mL) than that of survivors (median, 0.61 µg/mL) [23]. In their retrospective study, Zhou et al. concluded that D-dimer > 1000 ng/mL is a risk for mortality [24], and according to Wang et al. those concentrations continue to rise until death [25]. However, none of the studies provided a well evaluated cutoff value for D-dimer. Recently a study by Zhang et al. has established a cutoff value (2.0 µg/mL, fourfold increase) for D-dimer [13], while Yao et al. suggested another cutoff value for D-dimer level on admission (> 2.14 mg/L) to identify in-hospital mortality risk [1]. In our cohort study, we established a cutoff value of 695.5 ng/mL on admission to determine high-risk patients and predict mortality. Appropriate therapeutic anticoagulants should be started early for these patients. We can justify the difference between our results and the previous studies by the small size of our sample, as well as the lack of human and material resources. We suggest conducting future studies on D-Dimer in order to find a more accurate predictive cut-off value for mortality.

CONCLUSION

In conclusion, we demonstrated that higher D-dimer levels in COVID-19 patients were associated with a more severe disease, both clinically and on computed tomography. Patients with higher D-dimer levels also had higher risk of developing PE and arterial thrombosis than those with normal levels. Regular radiographic scanning (Chest CT with contrast – Doppler ultrasonography) should be performed to detect these complications early and treat them appropriately.

Abbreviations:

COVID-19: coronavirus disease-19
SARS-COV: Severe acute respiratory syndrome coronavirus
PE: Pulmonary embolism
DVT: Deep vein thrombosis
VTE: Venous thromboembolism
CT: Computed tomography
RT-PCR: Reverse transcription polymerase chain reaction
AUC: area under the curve
ROC: receiver operating characteristic

Declaration of competing interest

No conflict of interest needs to be disclosed.

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