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Estimation of D-Dimer level in Hospitalized Patients of COVID-19 in Tertiary Care Hospital Of Madhyapradesh And Its Prognostic Implications

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Abstract

Introduction: To determine the D-dimer levels in coronavirus disease 2019 patients, course of D-dimer levels during hospitalization, and its association with clinical outcomes.

Material & Methods: Consecutive adults admitted to Gandhi medical college Bhopal and Hamidia hospital with a positive RTPCR test for SARS-CoV-2 were identified. Elevated D-dimer was defined by the laboratory specific upper limit of normal (>230 ng/mL). Outcomes included critical illness (intensive care, mechanical ventilation, discharge to hospice, or death), thrombotic events, acute kidney injury, and death during admission.

Results: Among 2377 adults hospitalized with COVID-19 and D-dimer measurement, 1823 (76%) had elevated D-dimer at presentation. Patients with elevated presenting baseline D-dimer were more likely than those with normal D-dimer to have critical illness (43.9% versus 18.5%; adjusted odds ratio, 2.4 [95% CI, 1.9–3.1]; P<0.001), any thrombotic event (19.4% versus 10.2%; adjusted odds ratio, 1.9 [95% CI, 1.4–2.6]; P<0.001), acute kidney injury (42.4%)versus 19.0%; adjusted odds ratio, 2.4 [95% CI, 1.9–3.1]; P<0.001), and death (29.9% versus 10.8%; adjusted odds ratio,2.1 [95% CI, 1.6–2.9]; P<0.001). Rates of adverse events increased with the magnitude of D-dimer elevation; individuals with presenting D-dimer >2000 ng/mL had the highest risk of critical illness (66%), thrombotic event (37.8%), acute kidney injury (58.3%), and death (47%).

Conclusions: Abnormal D-dimer was frequently observed at admission with COVID-19 and was associated with higher incidence of critical illness, thrombotic events, acute kidney injury, and death.

Keywords: acute kidney injury , critical illness , epidemiology. mortality , thrombosisRTPCR,ARDS,AKI

Introduction

The SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) coronavirus (coronavirus disease 2019 [COVID-19]) infection is a global pandemic, with >3.48 crore cases and 4.8 lakh deaths in india. The clinical spectrum of COVID-19 infection is broad, encompassing asymptomatic infection, mild upper respiratory tract illness, respiratory failure, and death[1]. Recent reports highlight an alarming incidence of acute kidney injury and both arterial and venous thrombotic events[2].A recent report by group of scientist found the overall incidence of thrombosis in hospitalized patients with COVID-19 to be 16%, which after multivariable adjustment was associated with a 82% increased hazard of all-cause mortality (P<0.001)[3]. The most common pattern of abnormal coagulation observed in patients hospitalized with COVID-19 is characterized by elevations in fibrinogen and D-dimer levels[4].

D-dimer is the principal breakdown fragment of fibrin and is used as a biomarker of fibrin formation

and degradation[10]. Numerous studies have shown that D-dimer is a valuable marker of activation of coagulation and fibrinolysis[5]. Healthy individuals have low levels of circulating D-dimer, whereas elevated levels are found in conditions associated with thrombosis[6]. D-dimer has been extensively investigated for the diagnosis, monitoring, and treatment of venous thromboembolism (VTE) or which it is used routinely[7]. D-dimer levels are also elevated in conditions of chronic inflammation, such as active malignancy, rheumatoid arthritis, sickle cell disease, and asthma[8]. In the setting of COVID-19, D-dimer has been reported to be higher in subjects who are critically ill or those who expire[9]. However, the incidence of outcomes across different D-dimer levels both at clinical presentation and during the course of hospitalization are not well characterized. In addition, the course of D-dimer in subjects with COVID-19 remains unexplored. Given that widespread microthrombi have been observed in COVID- 19 in multiple organ systems, we hypothesized that elevated D-dimer levels would be associated with increased risk of clinically diagnosed thrombotic events, acute kidney injury, critical illness, and death among patients hospitalized with COVID-19[10].all inpatient hospitalised.

Patients hospitalized with a positive RTPCR test for COVID-19 were eligible for this retro- spective, observational study if D-dimer was measured during hospital admission. D-dimer assay was measured using the Hemosil D-dimer HS 500 on an automated coagulation analyzer (ACL TOP, Instrumentation Laboratory). The initial D-dimer and all D-dimers measured during hospital admission were recorded for all eligible patients. The upper limit of normal for the D-dimer assay is 230 ng/mL. Subjects were categorized into normal (D-dimer <230 ng/mL) and elevated (D-dimer >230 ng/mL) categories.

Study Variables

Demographic variables included age, sex, smoking status, and body mass index. Preexisting comorbidities included hyper-tension, hyperlipidemia, coronary artery disease, heart failure, diabetes mellitus, chronic kidney disease, and atrial fibrillation. Prior medication information included statins, β-blockers, ACE (angiotensin-converting enzyme) inhibitor (ACE-I) or angiotensin receptor blocker, and oral anticoagulants.

Clinical Outcomes

All cause, in hospital mortality was recorded for all patients. Critical illness was defined by a composite of treatment in an intensive care unit, need for mechanical ventilation, discharge to hospice, or death. Thrombotic events, as determined by the treating physician, were defined as a composite of deep venous thrombosis, pulmonary embolism, myocardial

Methods

Study Setting

The study was approved by the Gandhi medical college and Hamidia hospital Bhopal Review Board . We identified consecutive adults aged 18 years with a positive RTPCR COVID-19 test .

Data Collection: Data were obtained from infarction, ischemic stroke, or systemic embolism[8]. Acute kidney injury was defined according to the acute kidney injury network guidelines as an absolute increase of 0.3 mg/dL or more or a relative increase of 50% or more from baseline to peak creatinine.[22] The most recent outpatient creatinine in the past 6 months was used as baseline. When no creatinine was available, admission creatinine was used.

Statistical Analyses

Continuous variables are shown using mean (SD) and median (interquartile range [IQR]) and compared using the nonparametric Mann-Whitney U test for all non-normally distributed data. Categorical variables are reported as frequency rates and percentages and compared by $\chi 2$ tests. The longitudinal trajectory of the mean D-dimer per day of hospitalization for patients in each outcome category was visualized using the fitted values from the loess regression for each end point separately. Logistic regression models were generated to estimate the odds of the study end points, adjusted for demographics, clinical comorbidities, vital signs at presentation, and baseline medications. Covariates in the multivariable models included age, sex, race, body mass index, tobacco use, hypertension, hyperlipidemia, chronic kidney disease, prior heart failure, atrial fibrillation, coronary artery disease, cancer, prior prescriptions for ACE or angiotensin receptor blockers, anticoagulants, statins, and β-blockers, and initial laboratory results for lymphocyte count, ferritin, and

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C-reactive protein. The c-index was reported as a measure of the model fitness. Statistical analyses were performed using statistical software R (R Foundation for Statistical Computing, Vienna, Austria), with packages forestplot, ggplot2, and base R. Statistical tests are 2-sided, and P values <0.05 were considered to be statistically significant. versus 0.9 [0.8–1.1], P<0.001), white blood cell count (4.0 [2.0–10] versus 3.0 [1.0–11], P<0.001), C-reactive protein (125 [71–187] versus 75.1 [37–124], P<0.001), platelet count (203 [157–265] versus 190 [155–242], P<0.001), ferritin (833 [402–1621] versus 543 [293– 983], P<0.001), and lower levels of lymphoctyes (0.8 [0.6–1.2] versus 0.9 [0.7–1.3], P<0.001; Table 1).

Clinical Outcomes

During the course of hospitalization, 899 (37.8%) had critical illness, 620 (26.1%) required mechanical ventilation, 410 (17.2%) had a thrombotic event, and 871 (36.8%) had acute kidney injury. Compared with those with normal baseline D-dimer, individuals with elevated D-dimer were more likely to become critically ill (43.9% versus 18.5%; P<0.001) and more often required invasive mechanical ventilation (29.9% versus 13.9%, P<0.001). Thrombotic events (19.4% versus 10.2%, P<0.001) and acute kidney injury (42.4% versus 19.0%, P<0.001) were more common in the elevated D-dimer group . After adjustment for demographics, comorbidities, prior medications, and baseline laboratory values, elevated D-dimer was associated with higher odds of critical illness (OR, 2.4 [95% CI, 1.9–3.1], P<0.001), thrombotic events (OR, 1.9 [95% CI, 1.4–2.6];

P<0.001), and acute kidney injury (OR, 2.4 [95% CI, 1.9–75th percentile, 237–713), and 1823 (76%) presented with an elevated D-dimer (>230 ng/mL). The median peak D-dimer was 767 (25th–75th percentile, 328–3372), and 2049 (86%) had an elevated D-dimer >230 ng/mL at some point during the course of hospitalization.

Results

Of 2782 consecutive hospitalized subjects testing positive for SARS-CoV-2 , a total of 405 (14.6%) subjects had no D-dimer drawn and were excluded. Of the remaining 2377, the median age was 64 (IQR, 52–74), and 39% were female. Overall, the initial median D-dimer was 387 (25th–

Compared with patients with a normal baseline D-dimer, patients with an elevated baseline D-dimer were older (median age, 65 [IQR=54–77] versus 58 [46–68] years; P<0.001) and had a lower body mass index (median [IQR], 28.8 [25.2–33.1] versus 29.9.0 [26.2–34.4]; P<0.001; Table 1). Comorbidities were more frequent among patients with an elevated D-dimer, including hypertension (63.5% versus 57.7%, P=0.016), hyperlipidemia (44.2% versus 38.0%, P=0.012), coro- nary artery disease (23.4% versus 16.0%, P=0.001), and chronic kidney disease (23.0% versus 14.0%, P<0.001). Cardiovascular medications were also more common in the elevated baseline D-dimer group. In terms of laboratory findings, patients with elevated baseline D-dimer had higher levels of median creatinine (1.0 [IQR=0.8–1.5].1]; P<0.001). Rates of critical illness, thrombosis, and acute kidney injury increased with the level of D-dimer , which remained significant after multivariable adjustment (Table 2). Individuals with a presenting D-dimer >2000 ng/mL had the highest risk of critical illness (65.4%), thrombotic event (36.9%), and acute kidney injury (58.7%). All adjusted models had c-indices >0.75, indicating reasonable discriminatory ability of the models. D-dimer trajectory by critical illness, thrombosis, and acute kidney injury are presented in Figure 2A through 2C. D-dimer levels generally peaked 5 days after hospitalization.

D-Dimer And All-Cause Mortality

Among the 2377 hospitalized patients with COVID-19, 608 (25.6%) died or were discharged , 1652 patients (69.5%) were discharged, and the rest (117 [4.9%]) remained hospitalized. Unadjusted mortality was higher among patients with versus without elevated baseline D-dimer (548 [29.9%] versus 60 [10.8%]; OR, 3.5 [95% CI, 2.7–4.7]; P<0.001) as shown in Figure 3. The multivariable adjusted odds ratio showed a significantly higher odds of death in patients with elevated D-dimer than in those without (OR, 2.1 [95% CI, 1.6– 2.9]; P<0.001). Mortality increased in association with the level of D-dimer (Figure 3). The association between elevated D-dimer and mortality was consistent across multiple subgroups, including age, sex, body mass index.

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Table 1. Patient Characteristics According to Baseline D-Dimer

	D-Dimer, ng/mL		P value
	Normal < 230 ng/ml	Elevated ≥230 ng/ml	
	N=554	N=1823	
P Value			<0.001
	Normal <230 ng/mL	Elevated □230 ng/mL	<0.001
	N=554	N=1823	0.672
Age, y; median (IQR)			58 (46–68)
Age □75 y	76 (13.7%)	498 (27.3%)	
Female	211 (37.8%)	671 (36.7%)	
Race/ethnicity	0.001		
White NH	190 (34.1%)	733 (40.1%)	
Black NH	60 (10.8%)	278 (15.2%)	
Hispanic	183 (32.8%)	478 (26.2%)	
Asian			42 (7.5%)
Other/multiracial	56 (10.0%)	144 (7.9%)	
Unknown	27 (4.8%)	67 (3.7%)	
Tobacco use (%)	0.008		<0.001
Current smoker			
Former smoker	86 (15.4%)	391 (21.4%)	0.016
Body mass index, kg/m2; median (IQR)	29.9 (26.2–34.4)	28.8 (25.2–33.1)	0.012
Clinical history on admissions (%)			<0.001
Hypertension	322 (57.71%)	1160 (63.46%)	0.003
Hyperlipidemia	212 (37.99%)	807 (44.15%)	0.666
Coronary artery disease	89 (15.95%)	427 (23.36%)	0.113
Heart failure	50 (8.96%)	254 (13.89%)	<0.001
Diabetes mellitus	220 (39.43%)	700 (38.29%)	0.949
Cancer			
Chronic kidney disease	78 (13.98%)	421 (23.03%)	0.259
Atrial fibrillation	46 (8.26%)	154 (8.46%)	0.277
Medications before admission			0.361
Statin	85 (15.2%)	242 (13.2%)	0.33
β blocker			
ACE-I or ARB	83 (14.9%)	303 (16.7%)	0.004
Oral anticoagulant	41 (7.4%)	160 (8.8%)	<0.001
Presentation on admission			
Temperature at presentation median (IQR),	37.6 (37.1–38.3)	37.4 (36.9–38.2)	<0.001
Oxygen saturation at presentation median	94 (92–96)	93 (89–96)	0.038
Initial laboratory markers (median [IQR])			<0.001
Creatinine, mg/dL	0.9 (0. 8–1.1)	1.0 (0.8–1.5)	<0.001
White blood cell, ×109/L	3 (1–11)	4 (2–10)	<0.001
Lymphoctye, ×109/L	0.9 (0.7–1.3)	0.8 (0.6–1.2)	0.004
C-reactive protein, mg/L	75.1 (37–124)	125 (71–187)	<0.001
Hemoglobin, g/dL	13.5 (12.4–14.6)	13.1 (11.8–14.3)	<0.001

ACE-I indicates angiotensin-converting enzyme-inhibitor; ARB, angiotensin receptor blocker; IQR, interquartile range;hypertension, atrial fibrillation, and kidney disease (Figure III). Individuals with a presenting D-dimer >2000 ng/mL had the highest risk of all-cause mortality (48.3%). D-dimer trajectory by all-cause mortality is presented in Figure 2D.

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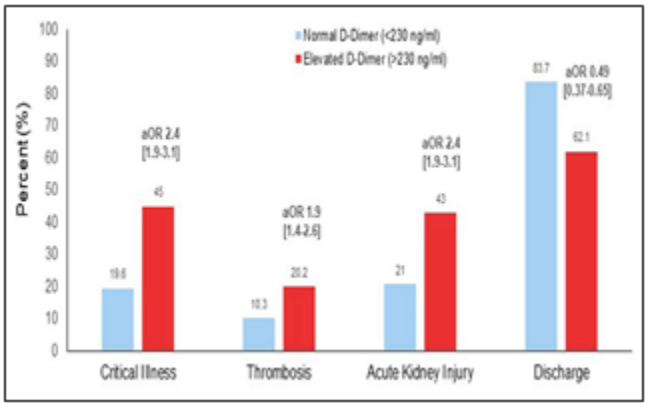
Peak D-Dimer and Clinical Outcomes

Individuals with the highest peak D-dimer concentrations had the highest risk of critical illness, thrombotic events, acute kidney injury, and mortality. Among 301 (12.7%) individuals with a peak D-dimer >10 000 ng/mL, critical illness was present in 86.1%, thrombotic events in 39.5%, and acute kidney injury in 80.8%, and in- hospital mortality was 60.5% (Table II).



Discussion

Among 2377 adults hospitalized with COVID-19 , 1823 (76%) had evidence of elevated D-dimer above the laboratory-specific upper limit of normal at hospital

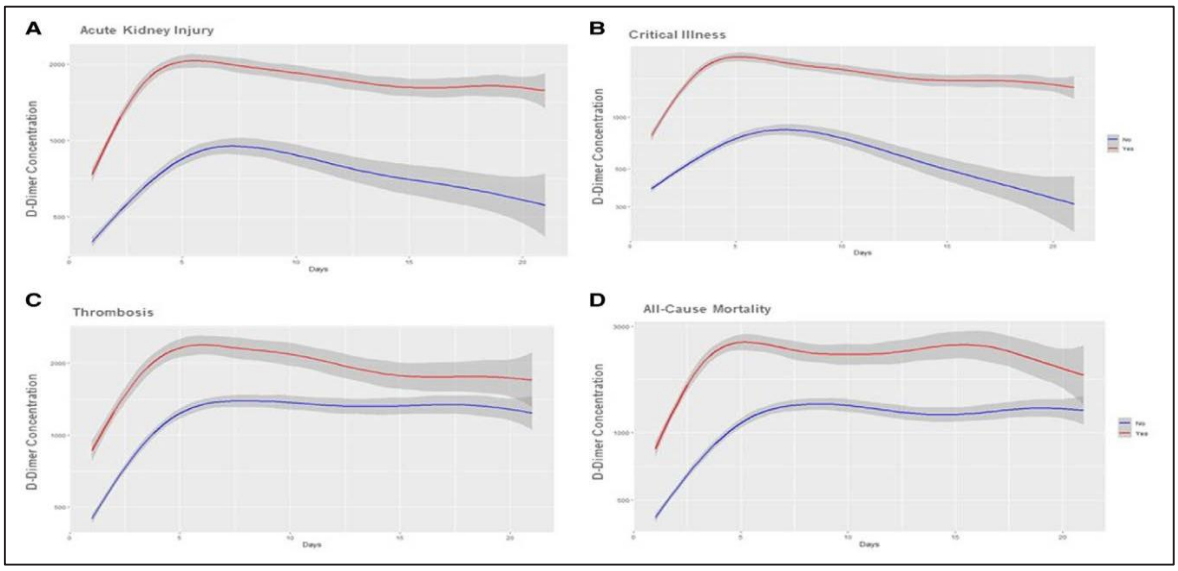


Figure 2. Trajectory of D-dimer during the first 21 d of hospitalization

Patients are stratified by (A) acute kidney injury, (B) critical illness, (C) thrombosis, and (D) all-cause mortality. The breakdown of thrombosis is: all thrombosis, n=410; deep venous thrombosis, n=103; pulmonary embolism, n=68; myocardial infarction, n=208; ischemic stroke, n=37; systemic embolism, n=22

Table 2. Unadjusted and Adjusted OR for Patient Outcomes

	Unadjusted OR	*P* Value	Adjusted OR*	*P* Value
Acute kidney injury				
Normal D-dimer (<230	1.0		1.0	
Elevated D-dimer (<230	3.08 (2.45–3.89)	<0.001	2.44 (1.89–3.14)	<0.001
D-dimer level, ng/mL				

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230–500	2.23 (1.73–2.87)	<0.001	1.95 (1.49–2.56)	<0.001
>500 and <2000	3.71 (2.85–4.83)	<0.001	2.82 (2.1–3.78)	<0.001
>2000	5.99 (4.33–8.3)	<0.001	4.5 (3.14–6.45)	<0.001
Critical illness				
Normal D-dimer (<230	1.0		1.0	
Elevated D-dimer (230	3.54 (2.8–4.48)	<0.001	2.44 (1.89–3.14)	<0.001
D-dimer level, ng/mL				
230–500	2.32 (1.8–2.99)	<0.001	1.75 (1.34–2.30)	<0.001
>500 and 2000	4.48 (3.43–5.86)	<0.001	3.07 (2.3–4.11)	<0.001
>2000	8.58 (6.15–11.98)	<0.001	5.6 (3.91–8.03)	<0.001
Thrombosis†				
Normal D-dimer (<230	1.0		1.0	
Elevated D-dimer (<230	2.09 (1.55–2.82)	<0.001	1.88 (1.37–2.58)	<0.001
D-dimer level, ng/mL				
230–500	1.38 (0.99–1.92)	0.06	1.33 (0.94–1.88)	0.115
>500 and 2000	2.25 (1.61–3.15)	<0.001	2.03 (1.41–2.91)	<0.001
>2000	5.1 (3.51–7.39)	<0.001	4.92 (3.29–7.36)	<0.001
All-cause mortality‡				
Normal D-dimer (<230	1.0		1.0	
Elevated D-dimer (□230	3.54 (2.66–4.71)	<0.001	2.14 (1.56–2.92)	<0.001
D-dimer level, ng/mL				
230–500	2.35 (1.73–3.2)	<0.001	1.66 (1.19–2.32)	<0.001
>500 and 2000	4.26 (3.11–5.83)	<0.001	2.34 (1.65–3.31)	<0.001
>2000	7.69 (5.36–11.03)	<0.001	4.15 (2.79–6.18)	<0.001
Discharged, no critical illness				
Normal D-dimer (<230	1.0		1.0	
Elevated D-dimer (230	0.31 (0.24–0.4)	<0.001	0.49 (0.37–0.65)	<0.001
D-dimer level, ng/mL				
230–500	0.45 (0.34–0.6)	<0.001	0.63 (0.47–0.85)	<0.001
>500 and □2000	0.26 (0.2–0.35)	<0.001	0.45 (0.33–0.61)	<0.001
>2000	0.14 (0.1–0.19)	<0.001	0.23 (0.16–0.34)	<0.001

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; and OR, odds ratio. presentation and 2049 (86%) had an elevated D-dimer at any point during the hospitalization before discharge[11]. Outcomes of patients with elevated D-dimer at the time of admission were particularly poor, with 45% critically ill, 20% with thrombosis, and 43% with acute kidney injury. D-dimer level was independently associated with these outcomes after multivariable adjustment for demographics,clinical characteristics, and other biomarkers that we have previously shown are associated with adverse outcomes[12]. In contrast, individuals without an elevated D-dimer at presentation were more likely to be discharged without developing a critical illness. This study demonstrate a robust associa- tion between elevated D-dimer, measured at admission and during hospitalization, and critical illness and mortality after covariate adjustment and provide associations between D-dimer and other important clinical outcomes, such as thrombosis and acute kidney injury and analyze the relationship between level of D-dimer and trajectory with the frequency of adverse clinical events[13].

Coagulation abnormalities are increasingly recognized in hospitalized patients with COVID-19, including increased D-dimer, elevated fibrinogen, and increasing prothrombin time[14]. While the most typical finding in patients with COVID-19 and a prothrombotic state is an increased D-dimer concentration, the level of D-dimer at presentation

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and its trajectory during the course of hospitalization is largely unknown[15]. In a series of patients with COVID-19 across mainland China, elevated D-dimer (>500 ng/mL) on admission was present in 260 (46%) of 560 patients[16]. A report of 172 patients from Wuhan, China noted that 32%, 26%, and 42% had a baseline D-dimer 500, >500 to 1000, and >1000 ng/mL, respectively[18]. Most studies reporting on D-dimer do not report the proportion of individuals with abnormal D-dimer (>upper limit of normal) nor do they characterize different D-dimer cutoffs.

Abnormalities in D-dimer in patients with COVID-19 is associated with an increased risk of critical illness and death[17,18]. A meta-analysis of 18 studies with 3682 patients noted a higher patients with severe versus nonsevere infection[19]. In a subgroup of 4 studies that reported critical illness (n=1218) and death (n=795), there was a 2-fold and 4-fold higher risk with of critical illness and death, respectively, among patients with D-dimer >500 versus <500 ng/mL. In one study of 191 patients from Wuhan, China with 54 deaths, Zhou et al found that D-dimer >1000 ng/mL at baseline was associated with an 18-fold increased risk of mortal-ity after multivariable adjustment[20].

D-dimer can only be generated when there is formation and degradation of cross-linked fibrin, provides a global marker of activation of the coagulation and fibrinolysis, and is therefore reflective of enhanced thrombotic activity[21]. In fact, several pathological reports demon- strate massive amounts of micro and macro thrombi in multiple vascular beds in COVID-19[22]. There is also evidence to suggest that D-dimer will not only be a marker of hypercoagulability and a prothrombotic state but will participate in pathogenesis. Fibrin degradation products induce acute pulmonary dysfunction and have a direct procoagulant effect. Infusion of purified human fragment D into rabbits induces pulmonary capillary leakage and hypoxemia[23]. Fragment D also increases platelet aggregation and prostaglandin synthesis, activates complement, and induces chemotaxis of neutropenia[24].

Patients with COVID-19 are at heightened risk for both arterial and venous thrombotic events[25]. Cohort studies suggest that the incidence of thromboembolic complications in patients with COVID-19 ranges from 11% to 35%. A retrospective study done in China that included 449 hospitalized critically ill COVID-19 patients showed a lower mortality in patients who received prophylactic heparin >7 days than in patients not receiving anticoagulant treatment[26]. Based on the limited data available, the International Society of Thrombosis and Hemostasis recommends a universal strategy of routine prophylactic dosed anticoagulation with unfractionated heparin or low-molecular weight heparin, after careful assessment of bleeding risk[27]. A retrospective study of 109 patients hospitalized with severe COVID-19 infection found a high incidence of thromboembolic events despite VTE prophylaxis. A retrospective analysis of 2773 hospitalized patients with COVID-19 found no benefit of high-dose anticoagulation; however, a subgroup analysis in subjects treated with mechanical ventilation suggested a potential benefit with high-dose anticoagulation. Patients infected with COVID-19 treated with anticoagulation are experiencing significant bleeding complications as well.

Limitations

D-dimer levels were not routinely collected in all individuals; patients without any D-dimer level collected were excluded, and patients with worsening disease will have had D-dimers checked more frequently. Nonetheless, 85% of all subjects hospitalized had at least one D-dimer level measured, and associations betweenbaseline D-dimer and outcomes were robust even adjustment for demographics, clinical characteristics, baseline medications, and initial laboratory results.

Conclusions

D-dimer levels were independently associated with a higher risk of critical illness, thrombosis, acute kidney injury, and all-cause mortality among patients with COVID-19, independent of previously identified risk fac- tors. The present study provides support that COVID-19 is a coagulopathic condition with D-dimer representing a direct link between COVID-19 infection and adverse outcomes.

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