CLINICAL AND POPULATION STUDIES

Prevalence and Outcomes of D-Dimer Elevation in Hospitalized Patients With COVID-19

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OBJECTIVE: To determine the prevalence of D-dimer elevation in coronavirus disease 2019 (COVID-19) hospitalization, trajectory of D-dimer levels during hospitalization, and its association with clinical outcomes.

APPROACH AND RESULTS: Consecutive adults admitted to a large New York City hospital system with a positive polymerase chain reaction test for SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) between March 1, 2020 and April 8, 2020 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. Among 2377 adults hospitalized with COVID-19 and ≥1 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. The optimal management of patients with elevated D-dimer in COVID-19 requires further study.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: acute kidney injury ■ critical illness ■ epidemiology ■ mortality ■ thrombosis

The SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) coronavirus (coronavirus disease 2019 [COVID-19]) infection is a global pandemic, with >6 200 000 cases and 375 000 deaths confirmed as of June 1, 2020, and at least 376 000 confirmed cases in New York State alone. 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.[2–8] A recent report by our group 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 ($P<0.001$).[8] The most common pattern of abnormal coagulation observed in patients hospitalized with COVID-19 is characterized by elevations in fibrinogen and D-dimer levels.[9]

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.[11] Healthy

Nonstandard Abbreviations and Acronyms

ACE-I	angiotensin-converting enzyme-inhibitor
COVID-19	coronavirus disease 2019
IQR	interquartile range
PROTECT	Prophylactic versus Therapeutic Antico-agulation Trial
VTE	venous thromboembolism

Highlights

- In this cohort study of 2377 consecutive patients with confirmed coronavirus disease 2019 (COVID-19), D-dimer was elevated in 76% of patients at hospital presentation.
- D-dimer was independently associated with incidence of critical illness, thrombosis, acute kidney injury, and all-cause mortality.
- In patients hospitalized with COVID-19, level of D-dimer may be used to identify gradient of risk.

individuals have low levels of circulating D-dimer, whereas elevated levels are found in conditions associated with thrombosis.[11] D-dimer has been extensively investigated for the diagnosis, monitoring, and treatment of venous thromboembolism (VTE) for which it is used routinely.[12] D-dimer levels are also elevated in conditions of chronic inflammation, such as active malignancy, rheumatoid arthritis, sickle cell disease, and asthma.[13,14] In the setting of COVID-19, D-dimer has been reported to be higher in subjects who are critically ill or those who expire.[15–19] 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 trajectory of D-dimer in subjects with COVID-19 remains unexplored. Given that widespread microthrombi have been observed in COVID-19 in multiple organ systems,[20,21] 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.

We analyzed data from a large health system in New York City to examine the prevalence of D-dimer elevation at presentation and over time, and the association of the biomarker with incident thrombosis as well as acute kidney injury, critical illness, all-cause mortality, and likelihood of being discharged.

METHODS

Identifiable patient level data from this project are not available to the public.

Study Setting

The study was approved by the New York University (NYU) Grossman School of Medicine Institutional Review Board and performed with a waiver of informed consent. We identified consecutive adults aged ≥18 years with a positive real-time polymerase chain reaction COVID-19 test between March 1, 2020 and April 08, 2020 who were admitted to NYU Langone Health, a multihospital health system in New York City. Follow-up was complete through May 13, 2020.

Data Collection

Data were obtained from the electronic health record (Epic Systems, Verona, WI), which is an integrated electronic health record including all inpatient and outpatient visits in the health system.

Patients hospitalized with a positive polymerase chain reaction test for COVID-19 were eligible for this retrospective, observational study if ≥1 D-dimer was measured during hospital admission. At all 4 NYU Langone Health inpatient facilities, routine D-dimer surveillance for individuals with suspected or confirmed diagnoses of COVID-19 was included in COVID-19-specific admission order sets in the electronic heath record at the time of hospital admission starting March 25. At all NYU Langone Health sites, 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. We conducted sensitivity analyses using different D-Dimer categories: <230 ng/mL (normal), 230 to 500 ng/mL, 500 to 2000 ng/mL, and >2000 ng/mL.

Study Variables

Demographic variables included age, sex, race/ethnicity (defined as non-Hispanic White, non-Hispanic Black, Hispanic, Asian, multiracial/other, and unknown), smoking status, and body mass index. Preexisting comorbidities included hypertension, 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 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 χ^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 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.

RESULTS

Of 2782 consecutive hospitalized subjects testing positive for SARS-CoV-2 between March 1, 2020 and April 8, 2020, a total of 405 (14.6%) subjects had no D-dimer drawn and were excluded (Figure I in the Data Supplement). 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–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.

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), coronary 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]

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 (Figure 1; Table I in the Data Supplement). 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, 1.9–3.1]; P<0.001). Rates of critical illness, thrombosis, and acute kidney injury increased with the level of D-dimer (Figure II in the Data Supplement), 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 into hospitalization.

D-Dimer and All-Cause Mortality

Among the 2377 hospitalized patients with COVID-19, 608 (25.6%) died or were discharged to hospice, 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,

**Table 1. Patient Characteristics According to Baseline D-Dimer**

	D-Dimer, ng/mL		
	Normal <230 ng/mL	Elevated ≥230 ng/mL	
	N=554	N=1823	P Value
Age, y; median (IQR)	58 (46–68)	65 (54–76)	<0.001
Age ≥75 y	76 (13.7%)	498 (27.3%)	<0.001
Female	211 (37.8%)	671 (36.7%)	0.672
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%)	128 (7.0%)	
Other/multiracial	56 (10.0%)	144 (7.9%)	
Unknown	27 (4.8%)	67 (3.7%)	
Tobacco use (%)			0.008
Current smoker	30 (5.4%)	90 (4.9%)	
Former smoker	86 (15.4%)	391 (21.4%)	
Body mass index, kg/m²; median (IQR)	29.9 (26.2–34.4)	28.8 (25.2–33.1)	<0.001
Clinical history on admissions (%)			
Hypertension	322 (57.71%)	1160 (63.46%)	0.016
Hyperlipidemia	212 (37.99%)	807 (44.15%)	0.012
Coronary artery disease	89 (15.95%)	427 (23.36%)	<0.001
Heart failure	50 (8.96%)	254 (13.89%)	0.003
Diabetes mellitus	220 (39.43%)	700 (38.29%)	0.666
Cancer	46 (8.24%)	195 (10.67%)	0.113
Chronic kidney disease	78 (13.98%)	421 (23.03%)	<0.001
Atrial fibrillation	46 (8.26%)	154 (8.46%)	0.949
Medications before admission			
Statin	85 (15.2%)	242 (13.2%)	0.259
β blocker	61 (11.0%)	233 (12.8%)	0.277
ACE-I or ARB	83 (14.9%)	303 (16.7%)	0.361
Oral anticoagulant	41 (7.4%)	160 (8.8%)	0.33
Presentation on admission			
Temperature at presentation median (IQR), °C	37.6 (37.1–38.3)	37.4 (36.9–38.2)	0.004
Oxygen saturation at presentation median (IQR; %)	94 (92–96)	93 (89–96)	<0.001
Initial laboratory markers (median [IQR])			
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)	0.038
Lymphoctye, ×10⁹/L	0.9 (0.7–1.3)	0.8 (0.6–1.2)	<0.001
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
Platelet count, ×10³/μL	190 (155–242)	203 (157–265)	0.004
Ferritin, ng/mL	543 (293–983)	833 (402–1621)	<0.001
D-dimer, ng/mL	195 (149–204)	490.5 (332–928)	<0.001

ACE-I indicates angiotensin-converting enzyme–inhibitor; ARB, angiotensin receptor blocker; IQR, interquartile range; and NH, Non-Hispanic.

hypertension, atrial fibrillation, and kidney disease (Figure III in the Data Supplement). 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.

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 (Figure IV
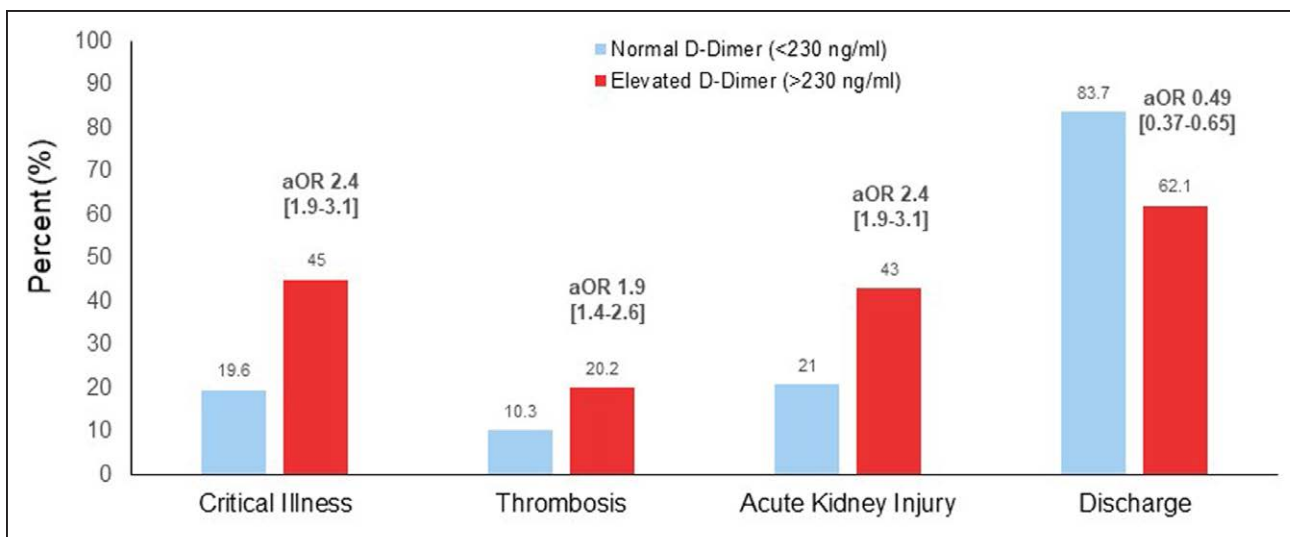
Figure 1. Baseline D-dimer measurements and adverse events.
aOR indicates adjusted odds ratio.

in the Data Supplement). 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 in the Data Supplement).

DISCUSSION

Among 2377 adults hospitalized with COVID-19 at 4 hospitals within a large health system in New York City, 1823 (76%) had evidence of elevated D-dimer above the laboratory-specific upper limit of normal at hospital
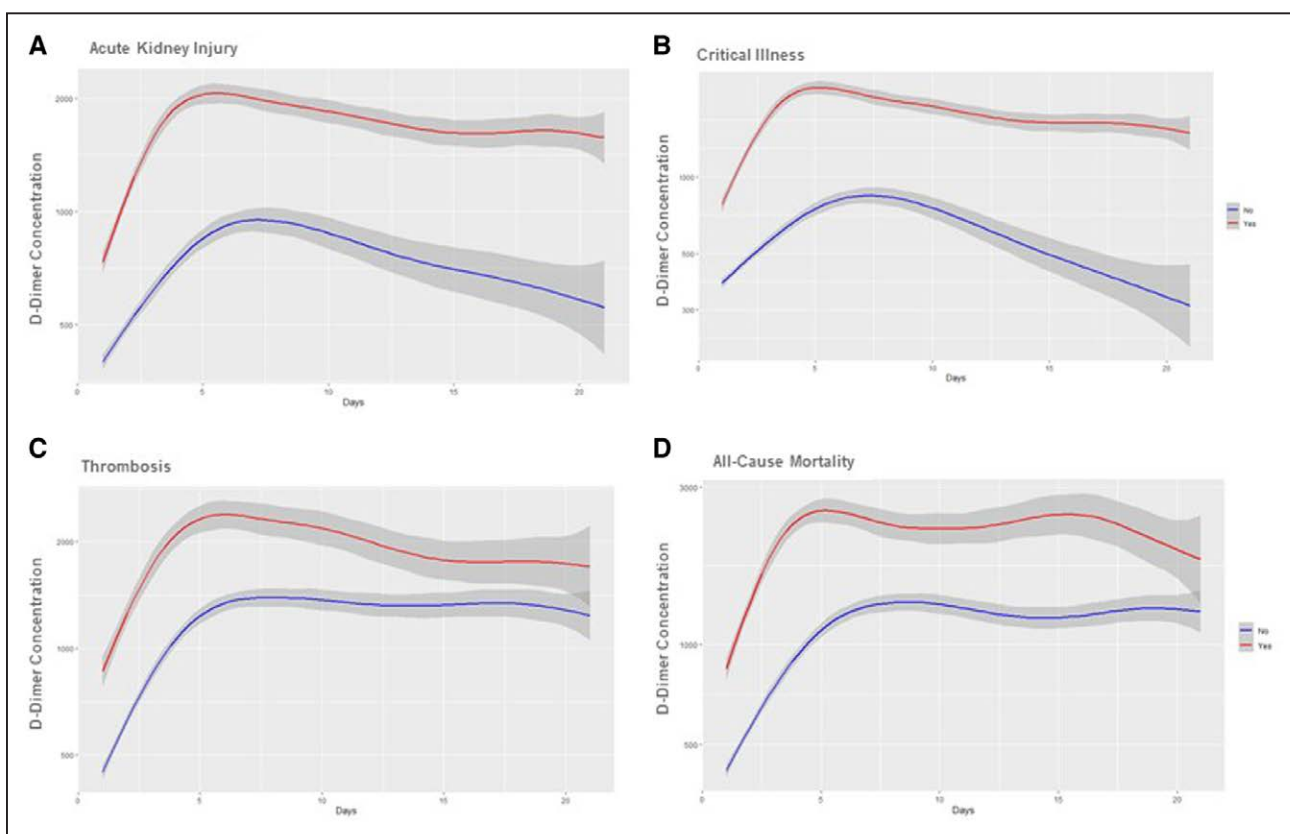
Figure 2. Trajectory of D-dimer during the first 21 d of hospitalization.
Patients are stratified by (**A**) acute kidney injury, (**B**) critical illness, (**C**) thrombosis, and (**D**) all-cause mortality. The breakdown of thrombosis is: all thrombosis, n=410; deep venous thrombosis, n=103; pulmonary 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 (95% CI)	P Value	Adjusted OR* (95% CI)	P Value
Acute kidney injury				
Normal D-dimer (<230 ng/mL)	1.0		1.0	
Elevated D-dimer (≥230 ng/mL)	3.08 (2.45–3.89)	<0.001	2.44 (1.89–3.14)	<0.001
D-dimer level, ng/mL				
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 ng/mL)	1.0		1.0	
Elevated D-dimer (≥230 ng/mL)	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 ng/mL)	1.0		1.0	
Elevated D-dimer (≥230 ng/mL)	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 ng/mL)	1.0		1.0	
Elevated D-dimer (≥230 ng/mL)	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 ng/mL)	1.0		1.0	
Elevated D-dimer (≥230 ng/mL)	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.

*Odds ratios adjusted for age, sex, race, body mass index, tobacco use, hypertension, hyperlipidemia, chronic kidney disease, prior heart failure, atrial fibrillation, coronary artery disease, cancer, outpatient prescriptions for ACE or ARBs, anticoagulants, statin, β-blocker use, initial laboratory results for lymphocyte count, ferritin, and C-reactive protein.

†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.

‡Defined as death or transfer to inpatient hospice.

presentation and 2049 (86%) had an elevated D-dimer at any point during the hospitalization before discharge. 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.[1] In contrast, individuals without an elevated D-dimer at presentation were more likely to be discharged without developing a critical illness. This is the first report to (1) demonstrate a robust association between elevated D-dimer, measured at admission and during hospitalization, and critical illness and mortality after covariate adjustment, (2) provide associations
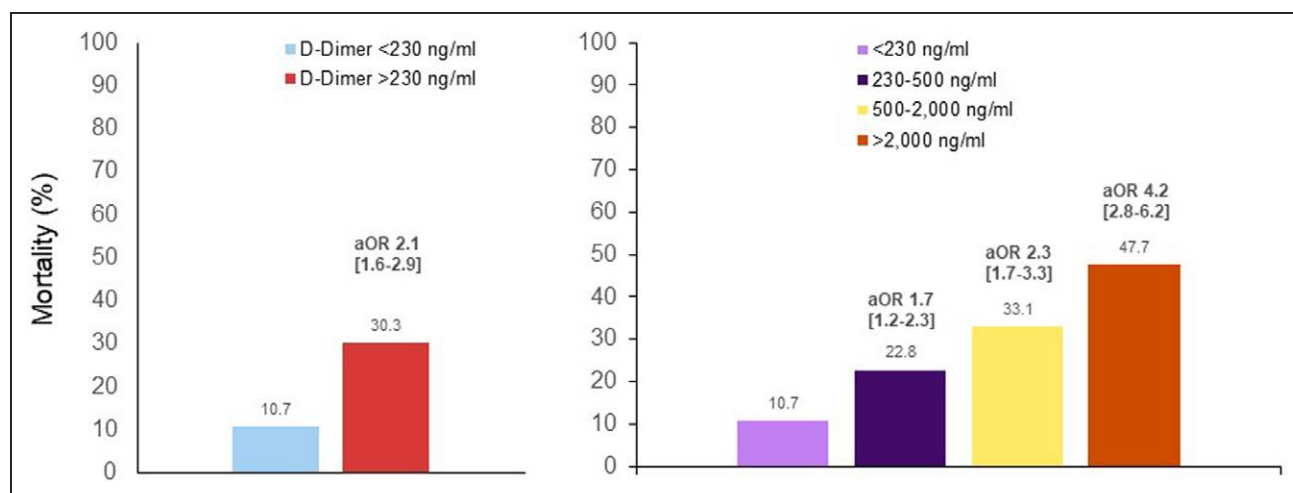
Figure 3. Baseline D-dimer measurements and all-cause mortality.
All-cause mortality is defined as death or transfer to inpatient hospice. aOR indicates adjusted odds ratio.

between D-dimer and other important clinical outcomes, such as thrombosis and acute kidney injury, and (3) analyze the relationship between level of D-dimer and trajectory with the frequency of adverse clinical events.

Coagulation abnormalities are increasingly recognized in hospitalized patients with COVID-19, including increased D-dimer, elevated fibrinogen, and increasing prothrombin time. While the most typical finding in patients with COVID-19 and a prothrombotic state is an increased D-dimer concentration,[15] the level of D-dimer at presentation and its trajectory during the course of hospitalization is largely unknown. 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.[23] 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. This is the first report to examine the D-dimer trajectory during hospitalization.

Abnormalities in D-dimer in patients with COVID-19 is associated with an increased risk of critical illness and death.[4,5,18] A meta-analysis of 18 studies with 3682 patients noted a higher D-dimer in patients with severe versus nonsevere infection.[16] 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.[16] In one study of 191 patients from Wuhan, China with 54 deaths, Zhou et al[18] found that D-dimer >1000 ng/mL at baseline was associated with an 18-fold increased risk of mortality after multivariable adjustment. However, because of the limited sample size and wide CIs, much uncertainty remains around this association.

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.[11] In fact, several pathological reports demonstrate massive amounts of micro and macro thrombi in multiple vascular beds in COVID-19.[24,25] There is also evidence to suggest that D-dimer may not only be a marker of hypercoagulability and a prothrombotic state but may 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.[26] Fragment D also increases platelet aggregation and prostaglandin synthesis, activates complement, and induces chemotaxis of neutropenia.[27]

Our results boost the scientific rationale for clinical trials to reduce thrombotic risk and adverse outcomes. Patients with COVID-19 are at heightened risk for both arterial and venous thrombotic events.[4,5] Cohort studies suggest that the incidence of thromboembolic complications in patients with COVID-19 ranges from 11% to 35%.[15] 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.[28] 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.[29] A retrospective study of 109 patients hospitalized with severe COVID-19 infection found a high incidence of thromboembolic events despite VTE prophylaxis.[30] 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.[31] Of note, patients infected with COVID-19 treated with anticoagulation are experiencing significant bleeding complications as well.[32] The optimal strategy to prevent adverse clinical events is being studied in the ACTIV-4 (Accelerating COVID-19 Therapeutic Interventions and Vaccines-4) Antithrombotic Trial (URL: http://www.clinicaltrials.gov). Unique identifier: NCT04359277) among hospitalized patients with COVID-19 with elevated D-dimer.

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 may have had D-dimers checked more frequently. Nonetheless, 85% of all subjects hospitalized had at least one D-dimer level measured, and associations between baseline D-dimer and outcomes were robust even after adjustment for demographics, clinical characteristics, baseline medications, and initial laboratory results. Moreover, a standardized admission laboratory protocol was only established about 2 weeks into the epidemic, resulting in missing D-dimer data for earlier patients, especially those who were less acutely ill. However, missing D-dimer was not associated with clinical events.[1] Second, although critical illness, acute kidney injury, and mortality were objective end points, thrombotic events were based on diagnoses assigned by treating physicians and were not independently adjudicated. The impact of ascertainment bias or diagnostic suspicion bias is unknown. Third, it is possible that the observed associations between D-dimer and outcomes are confounded by yet-to-be-determined factors; however, we adjusted our analysis for established and novel risk factors. Furthermore, we found comparable and robust odds ratios in and across risk groups, including low and high cardiovascular risk groups. Finally, only in-hospital events were captured in this analysis. We did not assess the association between D-dimer and subsequent cardiovascular events after hospital discharge.

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 factors. The present study provides additional support that COVID-19 is a coagulopathic condition with D-dimer representing a direct link between COVID-19 infection and adverse outcomes.

ARTICLE INFORMATION

Affiliations

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Disclosures

None.

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