



Elevated D-Dimer Is Associated with Multiple Clinical Outcomes in Hospitalized Covid-19 Patients: a Retrospective Cohort Study

Jason Wagner¹ · Victor Garcia-Rodriguez¹ · Abraham Yu¹ · Barbara Dutra¹ · Andrew DuPont² · Brooks Cash² · Ahmad Farooq^{2,3}

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Abstract

D-dimer is a prognostic marker for Covid-19 disease mortality and severity in hospitalized patients; however, little is known about the association between D-dimer and other clinical outcomes. The aim of this paper was to define a threshold of D-dimer to use in hospitalized patients with Covid-19 and to assess its utility in prognosticating in-hospital mortality, development of an acute kidney injury (AKI), and need for hemodialysis, vasopressors, or intubation. This is a single-center, retrospective, cohort review study of 100 predominantly minority patients (94%) hospitalized with Covid-19. The electronic medical record system was used to collect data. Receiver operating characteristics (ROC) and area under the curve (AUC) analysis were used to determine optimal thresholds of peak D-dimer, defined as the highest D-dimer obtained during admission that was clinically meaningful. Odds ratios were then used to assess the relationship between peak D-dimer thresholds and clinical outcomes. D-dimer > 2.1 µg/mL and > 2.48 µg/mL had > 90% sensitivity and > 50% specificity for predicting need for vasopressors (AUC 0.80) or intubation (AUC 0.83) and in-hospital mortality (AUC 0.89), respectively. Additionally, D-dimer > 4.86 µg/mL had a 100% sensitivity and 81% specificity for predicting the need for hemodialysis (AUC 0.92). Furthermore, peak D-dimer > 2.48 µg/mL was associated with in-hospital mortality ($p < 0.001$), development of an AKI ($p = 0.002$), and need for intubation ($p < 0.001$), hemodialysis ($p < 0.001$), and vasopressors ($p < 0.001$). Peak D-dimer > 2.48 µg/mL may be a useful threshold that is prognostic of multiple clinical outcomes in hospitalized patients with Covid-19.

Keywords Covid-19 · D-dimer · Prognostic factors · Acute kidney injury · Hemodialysis

Introduction

Covid-19 is a predominantly respiratory illness that is caused by the SARS-CoV-2 virus. The pathophysiology has been related in part to an exaggerated immune response, endothelial damage, and microvascular thrombosis that can lead to end-organ damage [1–5]. This damage is manifested as cardiac

injury, with resultant elevated troponin, signs of heart failure and cardiac ischemia [6–8], respiratory failure and the acute respiratory distress syndrome (ARDS) requiring intubation and mechanical ventilation [2], kidney injury [9], necessitating renal replacement therapy like hemodialysis, as well as septic shock, requiring vasopressors for hemodynamic support.

Biomarkers of inflammation, such as D-dimer and interleukin-6, have been used to assess Covid-19 severity [1]. In particular, elevated D-dimer levels are associated with in-hospital mortality [10] and illness severity [5, 11, 12]. Since thrombosis appears to be partially related to the disease progression, anticoagulation has become an important component of management in Covid-19 [1]. However, determining when to use anticoagulation has proven difficult. One retrospective work demonstrated that the use of anticoagulation with heparin in patients with D-dimer over 3.0 µg/mL was associated with improved 28-day mortality [13]. Thus, D-dimer may be helpful to assess the need for anticoagulation, for which there are ongoing clinical trials [14].

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✉ Ahmad Farooq
Ahmad.Farooq@uth.tmc.edu

- ¹ Department of Internal Medicine, University of Texas Health Science Center at Houston, 6431 Fannin, MSB 1.150, Houston, TX, USA
- ² Department of Medicine, Division of Gastroenterology, Hepatology and Nutrition, University of Texas Health Science Center at Houston, 6431 Fannin, MSB 1.150, Houston, TX, USA
- ³ Department of Medicine, Division of Gastroenterology and Hepatology, Duke University, Durham, NC, USA

However, aside from mortality, few studies have examined the association of D-dimer thresholds with other clinical outcomes of end-organ damage in Covid-19, such as development of an acute kidney injury (AKI) or need for hemodialysis (HD), vasopressors, or intubation. These are important clinical outcomes that should be included in assessing D-dimer thresholds; for example, AKI is associated with increased mortality in Covid-19 [7, 15, 16].

Additionally, data assessing minority populations with Covid-19 is essential as these groups with Covid-19 have higher mortality [12, 17]. In this study, we analyzed the relationship between peak D-dimer and clinical outcomes such as the development of an acute kidney injury or need for hemodialysis, vasopressors, or intubation in hospitalized patients with Covid-19. Our principal aim was to determine the most appropriate D-dimer threshold to define disease severity, as assessed by the above clinical outcomes.

Methods

This is a retrospective, single-institution, cohort study conducted in patients admitted to one academic county hospital with Covid-19 in Houston, TX, USA. An institutional review board approval was granted by the University of Texas Health Science Center at Houston, Houston, TX, USA. Patient information was obtained from an electronic medical record system: International Classification of Disease (ICD) 10 codes for Covid-19 (U07.1) were used to pull patient records through a hospital technology department, and then each record was assessed for inclusion or exclusion. Patients were included if they were admitted to the hospital and discharged prior to August 20, 2020, tested positive for SARS-CoV-2 by polymerase chain reaction (PCR)-based testing at least once during admission or if they had a positive diagnosis as an outpatient, and were ≥ 18 years old. Patients were excluded if they were pregnant, not admitted for longer than 24 h, or if D-dimer was not measured during the hospital stay. Missing data for endpoints were removed from the analysis.

The primary outcome was to determine an optimal threshold of peak D-dimer to use based on in-hospital mortality. Peak D-dimer is defined as the highest or peak laboratory value of D-dimer during hospitalization. In-hospital mortality is defined as mortality at any time during hospitalization. Secondary outcomes included the odds of in-hospital mortality, acute kidney injury (AKI), and need for hemodialysis, vasopressors, supplemental oxygen, or intubation during admission based on D-dimer threshold above 2.48 $\mu\text{g/mL}$. Acute kidney injury (AKI) is defined as a rise in serum creatinine from baseline by > 0.3 mg/dL within 48 h or relative to another creatinine level obtained during admission. Additionally, a post hoc subgroup analysis was performed using sex as a category to determine if peak D-dimer was still

associated with mortality controlling for sex. Finally, data about venous thromboembolism was collected by analyzing imaging reports from computed tomography (CT) scans with contrast to identify pulmonary emboli (PE) or Doppler compression ultrasound studies conducted to identify deep venous thrombosis (DVT). In this study, a venous thromboembolism event was defined as any imaging finding that was concerning for a DVT or PE. Imaging was ordered by the admitting physician at their discretion. There was no formal VTE surveillance program at the time of this study.

Data was recorded and analyzed using the computer program Microsoft Excel (Redmond, WA, USA). The computer program R [18] and accompanying R-studio [19] (version 1.2.5033, Orange Blossom) were used for statistical computations. For continuous and categorical data, Welch's two-sided *t* test and a Fisher exact test were used to make comparisons, respectively, unless otherwise stated. Unless otherwise stated, continuous variables are expressed as mean \pm standard deviation, and categorical variables are expressed as raw count (% of total sample size *N*). For all analyses, a *p* value < 0.05 was considered statistically significant. Odds ratios were used to assess the directionality of an association. The package *epiR* [20] was used in the R-studio software to determine odds ratios, sensitivity, specificity, and their respective 95% confidence intervals. Code is available upon request. Receiver operating characteristics (ROC) and area under the curve (AUC) analysis were performed using the GraphPad (La Jolla, CA, USA, www.graphpad.com) Prism version 8 software program for Mac OS Catalina.

Results

Of 209 patients analyzed, 100 patients fit the inclusion criteria (Fig. 1). The average age of the sample was 53.82 ± 12.46 years, 64% of patients were male, and the average BMI ($N = 94$) was 32.71 ± 8.72 kg/m² (Table 1). Patients were admitted for an average of 16.17 ± 14.09 days. The most common comorbidities were hypertension (55%) and diabetes mellitus (44%). Mortality was 20% ($N = 20$). Patients were more likely to survive if they were female: 27% of males and 8% of females died ($p = 0.03$); the odds of death in females was 0.25 (95% CI: 0.07, 0.93; $p < 0.05$) that of males. The patient population was predominantly of minority background (94%). There was no difference in length of stay comparing those who died (18.11 ± 8.66 days) compared to those who did not (15.69 ± 15.15 days; $p = 0.35$).

The peak D-dimer was found to be higher in patients who died (12.30 ± 6.73 $\mu\text{g/mL}$, $N = 20$), compared to those who survived to discharge (3.13 ± 3.69 $\mu\text{g/mL}$, $N = 80$; $p < 0.001$). Since there appeared to be a survival advantage comparing females to males, we performed a subgroup analysis, analyzing peak D-dimer's relationship to mortality in

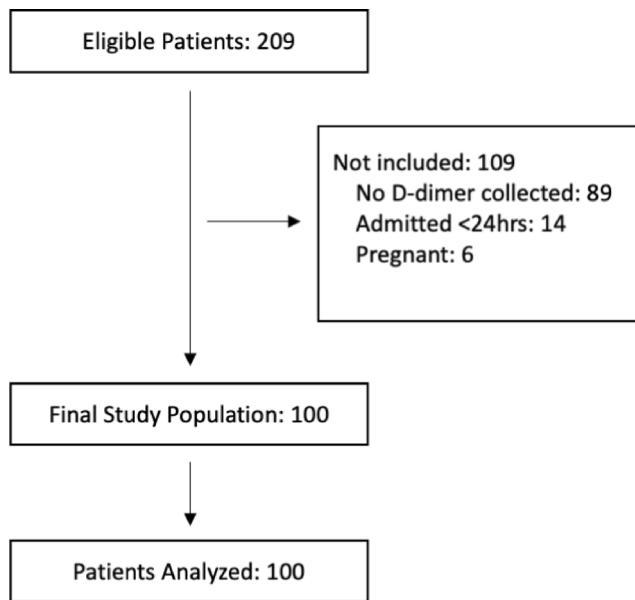


Fig. 1 STROBE flow diagram. The figure shows patients who were excluded from the study

both sexes. When analyzing the male subgroup, those who died (12.75 ± 7.00 $\mu\text{g/mL}$, $N = 17$) had a higher peak D-dimer compared to those who survived (3.10 ± 3.40 $\mu\text{g/mL}$, $N = 47$; $p < 0.001$). In the female group, there was no statistically significant difference found: peak D-dimer was 9.72 ± 5.07 $\mu\text{g/mL}$ ($N = 3$) in those who died compared to 3.17 ± 4.12 $\mu\text{g/mL}$ ($N = 33$) in those who survived ($p = 0.14$).

Using ROC analysis (Fig. 2, Table 2), we found that a peak D-dimer threshold of greater than 2.48 $\mu\text{g/mL}$ was 95% (95% CI: 76.63%, 99.74%) sensitive and 58.75% (95% CI: 47.8%, 68.89%) specific for assessing in-hospital mortality amongst Covid-19 patients. The optimal peak D-dimer cut-off for patients who were intubated or needed vasopressors was 2.1 $\mu\text{g/mL}$, with sensitivities $> 90\%$ and specificities $> 50\%$ (Table 2). A higher threshold was found to detect the need for hemodialysis at 4.86 $\mu\text{g/mL}$, albeit with a high sensitivity at 100% and specificity at approximately 80%. The use of peak D-dimer to predict the development of an AKI or need for supplemental oxygen was deemed to be poor, with high sensitivities ($> 90\%$) but very low specificities ($< 20\%$).

Table 1 Basic demographic data for the population studied

	Total	Alive at time of discharge	Deceased at time of discharge	Statistical difference
Sample size	100	80 (80)	20 (20)	–
Age, mean \pm SD, years	53.82 \pm 12.46	52.8 \pm 12.37	57.9 \pm 12.42	0.107, ns
BMI, mean \pm SD, kg/m^2	32.71 \pm 8.72	32.62 \pm 8.87, $N = 75$	33.06 \pm 8.29, $N = 19$	0.83, ns
Length of stay, mean \pm SD, days	16.17 \pm 14.09	15.69 \pm 15.15	18.11 \pm 8.66	0.35, ns
Charlson comorbidity index, median (IQR)	2 (1–4)	2 (1–4)	3 (2–4)	0.10 [§] , ns
Sex, count (% of total group size)				
Male	64	47 (73)	17 (27)	0.03*
Female	36	33 (92)	3 (8)	
Demographics, count (% of total group size)				
Black/AA	22	16 (72)	6 (27)	0.52 [‡] , ns
Hispanic	72	58 (80)	14 (19)	
Did not identify	4	4 (100)	0	
White/Caucasian	2	2 (100)	0	
Comorbidities, count (% of total group sample size)				
Hypertension	55	44 (55)	11 (55)	1, ns
Type II diabetes	44	35 (44)	9 (45)	1, ns
Congestive heart failure	12	10 (13)	2 (10)	1, ns
Myocardial infarction	7	6 (8)	1 (5)	1, ns
Chronic kidney disease	13	10 (13)	3 (15)	0.72, ns
ESRD	4	3 (4)	1 (5)	1, ns
Liver disease	5	4 (5)	1 (5)	1, ns
COPD	4	3 (4)	1 (5)	1, ns

COPD chronic obstructive pulmonary disease, SD standard deviation, ESRD end-stage renal disease; [‡] Pearson's Chi-squared used to calculate significance; [§] Mann Whitney *U* test used to calculate significance

Welch's two-sided *t* test or a Fisher exact test was used to make comparisons for continuous and categorical data, respectively, unless otherwise indicated, with $p < 0.05$ indicating statistical significance. Statistical significance in the comorbidities group represent comparisons of the presence of the comorbidity and survival. An asterisk (*) implies a significant result. Sample sizes (N) are indicated next to data point if different from the main group heading

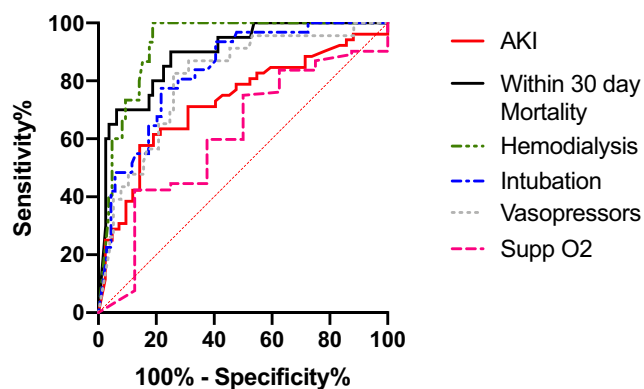


Fig. 2 Receiver operating characteristics (ROC) analysis of peak D-dimer assessing the diagnostic utility for multiple clinical outcomes in Covid-19. Clinical outcomes assessed are labeled in the key. *AKI* acute kidney injury, *Supp* supplemental

Using the area under the curve (AUC) analysis (Fig. 2; Table 2), the peak D-dimer was a highly accurate test in predicting the need for hemodialysis (AUC 0.92) and in-hospital mortality (AUC 0.89) in patients with Covid-19. Peak D-dimer was less accurate in predicting need for intubation (AUC 0.83), need for vasopressors (AUC 0.80), development of an AKI (AUC 0.72), and need for supplemental oxygen (AUC 0.61) during admission.

Since mortality is the most severe outcome in Covid-19, the peak D-dimer threshold of 2.48 $\mu\text{g/mL}$ was used to determine its prognostic significance for in-hospital mortality. The odds of in-hospital mortality (Table 3) based on a peak D-dimer greater than 2.48 $\mu\text{g/mL}$ was 27.06 (95% CI: 3.45, 212.22; $p < 0.001$). Peak D-dimer $> 2.48 \mu\text{g/mL}$ was found to be prognostic of other markers: patients with a peak D-dimer $> 2.48 \mu\text{g/mL}$ (Table 3) were more likely to have an AKI by an OR of 3.87 (95% CI: 1.63, 9.19; $p = 0.002$), require intubation by an OR of

8.60 (95% CI: 2.94, 25.17 $p < 0.001$), and need vasopressor support by an OR of 9.38 (95% CI: 2.57, 34.24; $p < 0.001$). Additionally, 29% ($N = 15$) of patients with a peak D-dimer $> 2.48 \mu\text{g/mL}$ required hemodialysis compared to none with a peak D-dimer below this threshold ($p < 0.001$).

Finally, we determined if D-dimer $> 2.48 \mu\text{g/mL}$ had any prognostic significance in diagnosing venous thromboembolism events (VTE) in this cohort of patients. In total, there were 28 patients (28%) who were assessed for VTE, defined as a pulmonary embolism or evidence of deep venous thrombosis on computed tomography scans with a PE protocol or with Doppler ultrasound studies to assess for DVT. Of these studies, only 5 (18%) patients were found to have a VTE: 4 DVTs and 1 PE were diagnosed. Using ROC/AUC analysis, the peak D-dimer was not found to be an accurate diagnostic tool for VTE events. The AUC was 0.66 (95% CI: 0.41, 0.90; $p = 0.26$). Based on this information, a D-dimer $\geq 2.48 \mu\text{g/mL}$ had 80% (95% CI: 28%, 99%) sensitivity and a 30% (95% CI: 13%, 53%) specificity for diagnosing a VTE event. This D-dimer threshold was not prognostic of VTE events: the odds ratio was 1.75 (95% CI: 0.16, 18.62), $p = 0.64$.

Discussion

D-dimer is a by-product generated when plasmin degrades fibrin clots; it is a useful marker of thrombotic activity [21]. Because of its prognostic significance, it has become a useful laboratory marker to assess disease severity in hospitalized Covid-19 patients [7, 10, 22]. Although frequently used to assess venous thromboembolism, D-dimer is under investigation to determine its utility in assessing the need for anticoagulation in Covid-19 patients. Clinical trials are

Table 2 Area under the curve (AUC) analysis, optimal D-dimer threshold found, and sensitivity and specificity data for peak D-dimer thresholds for multiple clinical outcomes in patients with Covid-19

	Area under the curve (95% CI), p value	Optimal D-dimer cut-off ($\mu\text{g/mL}$)	Sensitivity (%) of cut-off (95% CI)	Specificity (%) of cut-off (95% CI)
In-hospital mortality	<i>0.89 (0.82, 0.96)***</i>	2.48	95 (76.39, 99.74)	58.75 (47.8, 68.89)
Development of an AKI	<i>0.72 (0.62, 0.83)***</i>	0.73	90.38 (79.39, 95.82)	21.43 (11.71, 35.94)
Need for hemodialysis	<i>0.92 (0.87, 0.97)***</i>	4.86	100 (79.61, 100.0)	81.18 (71.59, 88.07)
Need for Intubation	<i>0.83 (0.75, 0.91)***</i>	2.1	90.32 (75.10, 96.65)	59.42 (47.64, 70.21)
Need for vasopressors	<i>0.80 (0.70, 0.90)***</i>	2.1	91.30 (73.20, 98.45)	54.55 (43.47, 65.19)
Need for supplemental oxygen	0.61 (0.40, 0.81), ns	0.71	90.22 (82.44, 94.77)	12.5 (0.64, 47.09)

Italicized values indicate statistically significant results, which is explained in the result section

AKI acute kidney injury, *CI* confidence interval

AUC scores of 1.0 and 0.5 indicate perfect and no ability, respectively, to distinguish the clinical outcome being measured. Significance indicated by the following: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table 3 Association of peak D-dimer > 2.48 µg/mL and clinical outcomes in Covid-19

	Peak D-dimer > 2.48 µg/mL, no (%)	Peak D-dimer < 2.48 µg/mL, no (%)	Odds ratio (95% CI)	Statistical significance
Sample size (<i>N</i>)	52	48	–	–
Mortality	19 (37)	1 (2)	27.06 (3.45, 212.22)	< 0.001
AKI	33 (72), <i>N</i> = 46	19 (40)	3.87 (1.63, 9.19)	0.002
Require hemodialysis	15 (29)	0 (0)	–	< 0.001
Require supplemental oxygen	49 (94)	43 (90)	1.90 (0.43, 8.42)	0.47, ns
Require intubation	26 (50)	5 (10)	8.60 (2.94, 25.17)	< 0.001
Require vasopressors	20 (38)	3 (6)	9.38 (2.57, 34.24)	< 0.001

AKI acute kidney injury, CI confidence interval, ns non-significant

Fisher exact test was used to make comparisons between groups, with $p < 0.05$ indicating statistical significance. Data presented as count (% of total sample size, *N*) or as odds ratio (95% CI). Sample sizes are indicated next to data point if different from main group heading

ongoing currently in the USA [14]. However, there is little data that has established an important threshold: a recent paper found that patients on heparin anticoagulation had improved mortality when the D-dimer was > 3.0 µg/mL [13]; other groups have found that D-dimer > 2.14 mg/L (equivalent to µg/mL) obtained on hospital admission was 88.2% sensitive and 71.3% specific in detecting in-hospital mortality [22]. Similar to these results, we find here that mortality is associated with higher peak D-dimer levels and that an optimal peak D-dimer level of > 2.48 µg/mL has a 95% sensitivity and 58% specificity for in-hospital mortality. This threshold was found to be a prognostic factor for the development of an AKI, need for intubation, hemodialysis, or vasopressors. We additionally show that peak D-dimer above this threshold may more accurately predict the need for hemodialysis or need for intubation relative to other clinical endpoints.

To date, few studies have analyzed the prognostic utility of D-dimer to assess other clinical outcomes. Here, we present ROC/AUC data showing that peak D-dimer may be a useful rule-out test, but not a rule-in test to evaluate in-hospital mortality and need for HD or intubation. The thresholds used resulted in high sensitivity and relatively low specificity, particularly when assessing AKI and need for supplemental oxygen. Thus, D-dimer testing may not be as useful when assessing these outcomes. It is important to realize that this is a relatively small, retrospective, single-center study, thus limiting the generalizability of the findings. Nevertheless, this data will be useful for clinicians who use D-dimer to gauge the severity of Covid-19 and predict clinical outcomes in hospitalized patients.

We believe that the association between elevated peak D-dimer, AKI, and need for hemodialysis presented here is of particular importance. AKI is associated with increased

mortality in Covid-19 [7, 15, 16] and may be preventable if certain practices, such as avoidance of nephrotoxic agents, are implemented early on during treatment. Of note, D-dimer in the setting of renal impairment has been shown to be less useful in diagnosing other illnesses like pulmonary embolism [23]. Nevertheless, given the findings in this paper, we recommend that patients with elevated D-dimer be watched closely for AKI development.

Interestingly, D-dimer > 2.48 µg/mL was not found to be prognostic of VTE in this study. The reported incidence of VTE events was found to be 18%, which is below that of 26% reported by a recent meta-analysis [24]. However, the number of events was low ($N = 5$), and only 26% of the population was assessed for VTE events, which likely makes this a falsely low measurement. Nevertheless, the event rate is higher than that reported in hospitalized patients in the USA, estimated to be as high as 14.9% [25], which is in agreement with recently published studies on VTE events in Covid-19 [24] patients.

Interestingly, similar to what others have found [26], we present evidence that the mortality may be lower in females compared to males in patients hospitalized with Covid-19: we find that the odds of death in females is approximately 25% that of males. We additionally find that peak D-dimer was not found to be different in relation to mortality in females. It is important to note that the sample sizes for the female group were smaller compared to males, which may have skewed the results. Future studies should explore the clinical utility of D-dimer in assessing clinical outcomes controlling for sex.

A particular strength of this analysis involves the patient population that was studied: 94% of patients represent the minority groups that are most impacted by Covid-19 [11, 17]. Similar to other studies [7, 27], we found that the

population was obese and that risk factors such as male sex, hypertension, and diabetes were highly prevalent. Importantly, D-dimer was found to be associated with multiple clinical outcomes in this population. Thus, we provide evidence that D-dimer is a useful prognostic tool when applied to minority populations hospitalized with Covid-19.

Finally, it should be emphasized that this paper assessed peak D-dimer values, which are the highest obtained during hospitalization, not those obtained at admission. Prognostic markers are likely to have much more practical and clinical utility when assessed at admission. However, by assessing peak D-dimer data, we believe that this may give a more accurate representation of thresholds to use. This is especially true given that D-dimer will change over time from those values obtained at admission. Using peak D-dimer data thus may give a more accurate reflection of the patient's clinical course and outcome severity. For example, it is possible that a patient with a low D-dimer at admission may go on to develop severe disease, with the development of an AKI and need for hemodialysis, which would be missed by assessing admission D-dimer. Given the data presented here, we recommend that patients with D-dimers exceeding the aforementioned thresholds be watched closely for clinical decline. Future prospective clinical trials are needed to assess these thresholds in dictating the need for treatment, such as with anticoagulation, to determine if there is a mortality benefit.

Limitations of this study include its retrospective, single-center study design and smaller relative sample size. Additionally, data was not collected regarding the incidence of disseminated intravascular coagulation or venous thromboembolism, all of which can increase the D-dimer value. Finally, we collected no data on treatment or decision-making, and thus, this study's results should not be used to dictate management without further prospective trials. In summary, we find that D-dimer levels $> 2.48 \mu\text{g/mL}$ may be a clinically useful threshold in a predominantly minority patient population hospitalized with Covid-19. Furthermore, we find that this threshold is prognostic of multiple clinical outcomes, including in-hospital mortality, development of an AKI, and the need for hemodialysis, vasopressors, or intubation.

Authors' Contributions JW, VR, AY, BD, and AF were involved in planning the study. JW, VR, AY, and BD collected data. JW, VR, AY, BD, BC, AD, and AF performed data analysis and wrote the manuscript.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent As this was a retrospective analysis, informed consent was not deemed necessary per the University of Texas Health Science Center Institutional Review Board, Houston, TX, USA.

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