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## The clinical significance of ultra-high D-dimer levels

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### ABSTRACT

**Objective:** Plasma D-dimer levels >5000 ng/mL are encountered in a number of conditions other than venous thromboembolism (VTE). Recent studies have used plasma D-dimer levels as a prognostic indicator for coronavirus disease 2019 (COVID-19) infection. The implications of abnormal levels are less clear for patients diagnosed with COVID-19 with a baseline elevation in plasma D-dimer levels. In the present study, we reviewed the occurrence of plasma D-dimer levels >5000 ng/mL and investigated the clinical significance of this finding before the onset of the COVID-19 pandemic.

**Methods:** Inpatient records for a 4-year period were screened for laboratory results of plasma D-dimer levels >5000 ng/mL. The patient data were reviewed for the clinical identifiers commonly associated with elevated plasma D-dimer levels, including VTE, cancer, sepsis, pneumonia, other infection, bleeding, and trauma. The patients were then categorized into groups stratified by the plasma D-dimer level to allow for comparisons between the various clinical diagnoses.

**Results:** A total of 671 patients were included in the present study. VTE was the most common diagnosis for patients with a plasma D-dimer level >5000 ng/mL, followed by cancer and pneumonia. Multiple clinical diagnoses were present in 61% of the patients. No clear cause for the ultra-high plasma D-dimer level could be identified in 11.3% of the patients. Among the patients lacking a clinical diagnosis at discharge, mortality was 24% in the 5000- to 10,000-ng/mL group, 28.6% in the 10,000- to 15,000-ng/mL group, and 75% in the >15,000-ng/mL group.

**Conclusions:** VTE, cancer, and pneumonia were frequently present when ultra-high plasma D-dimer levels were encountered, and mortality was high when the levels were >15,000 ng/mL. The results from our study from a pre-COVID-19 patient population suggest that ultra-high plasma D-dimer levels indicate the presence of severe underlying disease. This should be considered when using the plasma D-dimer level as a screening tool or prognostic indicator for COVID-19 infection. (*J Vasc Surg Venous Lymphat Disord* 2022;10:8-13.)

**Keywords:** Cancer; Coronavirus; D-dimer; Screening; Thrombosis

D-dimer is a protein fragment found in the plasma when a blood clot undergoes degradation by fibrinolysis. Although D-dimer can exist at low levels in the plasma of healthy individuals from the physiologic breakdown of fibrin, elevated levels develop in a number of pathologic conditions.<sup>1</sup> Plasma D-dimer measurements are routinely obtained in clinical practice to diagnose venous thromboembolism (VTE) owing to the test's high degree of sensitivity, and levels >500 ng/mL are frequently used to denote a "positive" test result.<sup>2,3</sup> In situations in which the clinical probability of VTE is low, a normal plasma D-dimer level can reliably rule out clinically significant VTE.<sup>4</sup> In contrast, elevated plasma D-dimer levels increase

the likelihood of VTE when the pretest probability is low, and higher values represent a greater likelihood. VTE is the most common source of elevated plasma D-dimer levels; however, incitement of fibrin cleavage is not specific to VTE, and elevated plasma D-dimer levels also occur in conditions such as cancer, sepsis, infection, trauma, and massive bleeding.<sup>1,5,6</sup>

Measuring plasma D-dimer levels has become routine practice during the coronavirus disease 2019 (COVID-19) pandemic, with the levels used to assist with diagnosis and gauge the prognosis.<sup>7-11</sup> Because acute viral infection incites the production of proinflammatory cytokines and the generation of a prothrombotic state, plasma D-dimer levels increase and can serve as a marker of disease progression and severity.<sup>12,13</sup> Most COVID-19-positive patients have not had previous plasma D-dimer tests, and their baseline D-dimer levels are, therefore, unknown. Thus, interpreting abnormal results in these patients can be problematic if an underlying disease exists that is known to increase the plasma D-dimer levels. Before the current pandemic, we observed a substantial number of patients with "ultra-high" plasma D-dimer levels of >5000 ng/mL. To date, limited data exist on the significance of this finding in patients without underlying VTE or other disorders that lack overt thrombosis. The aim of the

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present study was to describe a group of patients with plasma D-dimer levels >5000 ng/mL before the current pandemic. We hypothesized that ultra-high plasma D-dimer levels reflect the presence of significant underlying disease that will be undiagnosed in some patients. This information could be helpful when studying the association between the plasma D-dimer levels and the presence and/or severity of COVID-19 infection and making clinical decisions based in part on the plasma D-dimer level.

## METHODS

**Study design.** The present study was designed as a cross-sectional observational study. The inpatient medical records from three metropolitan hospitals in our health system during a 4-year period were screened for plasma D-dimer laboratory results >5000 ng/mL. The results from January 2013 to January 2017 were included. All inpatients aged >18 years with at least one plasma D-dimer assay result >5000 ng/mL were eligible for inclusion in the present study. Plasma D-dimer assays were ordered as a part of a routine inpatient workup according to the admitting chief complaint, and the initial results were routinely obtained within 24 hours of admission. It is standard practice at our institution's clinical laboratory to repeat a plasma D-dimer assay when the result is >1000 ng/mL. Therefore, repeat assays were performed for all study patients within 24 hours of the first measurement. The plasma D-dimer levels were measured by latex agglutination (HemosIL D-Dimer HS with ACL TOP 50 reagent; Instrumentation Laboratory, Bedford, Mass). Laboratory testing was standardized across all three hospitals. Following these initial assays, repeat D-dimer levels were not routinely obtained throughout the hospitalization or on discharge, with ongoing laboratory evaluations left to the discretion of the treating physician. All study patients had had two or more plasma D-dimer assays obtained with most having two results. The highest measured value was used to categorize patients into the D-dimer groups. Patients aged <18 years were excluded, as were patients whose plasma D-dimer results were from an outpatient setting. For the purposes of the present study, ultra-high D-dimer levels were defined as plasma D-dimer levels >5000 ng/mL; a level previously described in the literature.<sup>14</sup> The institutional review board of our hospital system approved the study protocol, and the requirement for written informed consent was waived owing to the retrospective nature of the present study.

**Data collection and analysis.** All inpatient clinical, laboratory, and imaging information was retrospectively reviewed for predefined clinical identifiers commonly associated with elevated plasma D-dimer levels. The identifiers used included VTE (deep vein thrombosis/pulmonary embolism), cancer, sepsis, pneumonia, infection, bleeding, hyper-fibrinolysis, and traumatic injury. "Infection"

## ARTICLE HIGHLIGHTS

- **Type of Research:** A multicenter, retrospective cross-sectional study of inpatients from three metropolitan hospitals
- **Key Findings:** Venous thromboembolism, cancer, and pneumonia were the most common diagnoses in 671 patients with plasma D-dimer levels >5000 ng/mL. No clear cause of the ultra-high D-dimer level was identified in 11.3% of patients, and mortality approached 75% in the subset with plasma D-dimer levels >15,000 ng/mL.
- **Take Home Message:** Ultra-high plasma D-dimer levels can be present in patients with no identified pathology during hospitalization and after discharge. The high mortality rate observed in these patients suggests the presence of significant undiagnosed disease. These patients should receive ongoing evaluations to identify the source of the ultra-high D-dimer level.

included common clinical entities: bacteremia, diverticulitis, osteomyelitis, wound infection, abscess, urinary tract infection, cholecystitis, pyelonephritis, meningitis, and so forth. For the purposes of data collection, pneumonia was treated as a separate clinical identifier. If multiple diagnoses were found in a single patient, each was included separately for analysis.

The patients were categorized into three groups according to the plasma D-dimer level and the clinical diagnoses compared. The plasma D-dimer cutoffs used for each group were as follows: 5000 to 10,000 ng/mL, 10,000 to 15,000 ng/mL, and >15,000 ng/mL. The medical records of all study patients were also reviewed at a mean of 60 days (range, 40-80 days) after discharge for the development of any new clinical diagnoses associated with elevated plasma D-dimer levels and patient mortality. A new clinical diagnosis was defined as that made during the follow-up after hospitalization that was not present at discharge. Repeat plasma D-dimer levels were not obtained as a part of routine follow-up. All study patients completed the postdischarge follow-up through in-person clinic follow-up or telephone. The medical record review was performed by two qualified independent reviewers (F.L., D.O.).

The total number of diagnoses were calculated across the different plasma D-dimer groups. Analysis of variance was performed to compare the diagnoses between the groups. A *P* value of  $\leq .05$  was used to determine the statistical significance. Statistical analysis was performed using SPSS Statistics, version 25 (IBM Corp, Armonk, NY).

## RESULTS

A total of 45,490 adult inpatients had been admitted at all three hospitals during the study period. Of these

**Table I.** Patient characteristics

Characteristic	No. (%) or mean $\pm$ SD
Sex	
Male	314 (46.8)
Female	357 (53.2)
Race	
White	508 (75.7)
Black/African American	97 (14.5)
Hispanic or Latino	16 (2.4)
Asian or Pacific Islander	1 (0.1)
Other/unknown	49 (7.3)
Age, years	66.9 $\pm$ 18.0
SD, Standard deviation.	

patients, 18,421 had had D-dimer assays obtained as a part of their inpatient workup. A total of 671 patients (3.64%) had had a D-dimer level  $>5000$  ng/mL and were included in the present study. Patient demographic information is included in Table I. The plasma D-dimer levels ranged from 5000 to 67,000 ng/mL, with most patients (65.3%) having a plasma D-dimer level between 5000 and 10,000 ng/mL. VTE was the most common diagnosis present across all study patients, followed by cancer and pneumonia. No statistically significant differences were found between the D-dimer groups in the prevalence of each diagnosis (Table II). Multiple diagnoses were identified in 61% of the patients.

No clear source of the ultra-high plasma D-dimer level was identified in 11.3% of the study patients. The frequency of no clear source identified was consistent among the D-dimer groups. In the patients with plasma D-dimer levels of 5000 to 10,000 ng/mL and no clear source identified, 20% had developed a new clinical diagnosis and 24% had died during the follow-up period. The most common new clinical diagnosis in these patients was VTE. No new clinical diagnoses were found among the patients with plasma D-dimer levels  $>10,000$  ng/mL. Mortality during the follow-up period for the patients in the 10,000- to 15,000-ng/mL and  $>15,000$ -ng/mL D-dimer groups was 28.6% and 75%, respectively. Overall, 283 patients (42%) had died at the end of the follow-up period (Table II).

## DISCUSSION

The results of the present study from a pre-COVID-19 patient population revealed that ultra-high plasma D-dimer levels are not uncommon and, when present, indicate the presence of severe underlying disease. We identified 671 patients with plasma D-dimer levels  $>5000$  ng/mL during the 4-year study period, and plasma D-dimer levels as high as 67,000 ng/mL were encountered. In nearly 90% of patients, a clinical diagnosis was apparent during

hospitalization that could reasonably explain the ultra-high plasma D-dimer level, and 61% of the patients had had multiple diagnoses. The most common diagnosis observed was VTE (71.5%); however, infectious processes (64.2%) and cancer (35.3%) were also found in a large number of patients. This trend was consistent across the three D-dimer groups. Our findings suggest that consideration should be given to diagnoses, in addition to VTE, during the initial workup in view of the regularity with which these diagnoses were found either alone or in multiples.

To the best of our knowledge, only one previous study has investigated ultra-high plasma D-dimer levels in patients before the onset of the COVID-19 pandemic. In a retrospective study, Schutte et al<sup>14</sup> found that plasma D-dimer levels  $>5000$   $\mu$ g/L carried a very high predictive value for serious disease. Of their 581 study patients, 93% were diagnosed with VTE, cancer, or infection. VTE (40%) was the most common diagnosis, followed by cancer (29%) and infection or sepsis (24%). Furthermore, the investigators reported on the frequencies of other rare disease entities that can be challenging to diagnose such as aortic aneurysm/dissection (6.0%), thrombotic microangiopathy (2.6%), autoimmune disorders (2.4%), and arterial thrombus (1.4%), which further supports the necessity for heightened suspicion and completing a thorough workup for these patients.<sup>14</sup> We observed a similar frequency of cancer (35%) and sepsis (21%) in our patient population; however, the incidence of VTE (71.5%) and the presence of multiple diagnoses (61% vs 43%) were notably higher. The reasons behind this finding are unclear given the differences in clinical sites and patient populations.

One prominent difference between our investigation and previous work is the inclusion of mortality data. In the present study, overall mortality was notably high, with 42% of patients (283 of 671) having died by the end of the follow-up period. Most of the deaths occurred after discharge (256 deaths). No clear cause of ultra-high D-dimer levels was identified in 11.3% of the study population, and significant mortality was also observed in these patients (range, 24%-75%). It seems unlikely that processes such as significant infections (sepsis or pneumonia) and VTE in the setting of an ultra-high D-dimer level would be missed during hospitalization. Thus, death in the patients without a clear diagnosis had likely resulted from disease processes that did not cause the patients to appear seriously ill or other occult events such as a large proximal deep vein thrombosis or in-transit thrombus that led to a significant pulmonary embolism after discharge. The effect of these findings lies in increasing clinicians' awareness to the presence of significant diagnoses other than VTE in patients with ultra-high plasma D-dimer levels. Thus, suspicion should remain high in cases in which no diagnosis is clinically evident.

**Table II.** Diagnoses of patients with elevated plasma D-dimer levels stratified by group

Diagnosis	D-dimer level, ng/mL			Total (n = 671)	P value
	5000-10,000 (n = 438)	10,000-15,000 (n = 120)	>15,000 (n = 113)		
VTE					
DVT	179 (40.9)	46 (38.3)	42 (37.2)	267 (39.8)	.72
PE	152 (34.7)	30 (25.0)	31 (27.4)	213 (31.7)	.07
Cancer	142 (32.4)	53 (44.2)	42 (37.2)	237 (35.3)	.06
Pneumonia	92 (21.0)	36 (30.0)	24 (21.2)	152 (22.7)	.11
Sepsis	91 (20.8)	24 (20.0)	26 (23.0)	141 (21.0)	.80
Infection <sup>a</sup>	81 (18.5)	27 (22.5)	30 (26.5)	138 (20.6)	.14
Trauma	46 (10.5)	14 (11.7)	17 (15)	77 (11.5)	.40
No diagnosis	50 (11.4)	14 (11.7)	12 (10.6)	76 (11.3)	NA
Total deaths	0 (0)	0 (0)	0 (0)	283 (42.2)	NA
Death without a diagnosis	12 (24.0)	4 (28.6)	9 (75.0)	25 (3.8)	NA

DVT, Deep vein thrombosis; NA, not applicable; PE, pulmonary embolism; VTE, venous thromboembolism.  
Data presented as number (%).  
<sup>a</sup>All infectious processes other than sepsis, including urinary tract infection, cellulitis, abscesses, osteomyelitis, and so forth.

The relationship between the plasma D-dimer levels and mortality is not fully understood but likely reflects the presence of serious underlying disease processes that do not create the outward appearance of illness or have not manifested clinical symptoms. Some evidence has suggested that elevated plasma D-dimer levels might be a predictor of all-cause mortality. In a study of 17,359 individuals free of cardiovascular disease and cancer, the incidence of death increased from 1.1% to 2.8% across quartiles of plasma D-dimer concentrations.<sup>15</sup> This relationship is logical because many serious diseases are known to influence coagulation.

Likewise, patients diagnosed with VTE in the setting of an ultra-high plasma D-dimer level should have their response to treatment closely monitored in the chance that multiple diagnoses could coexist. In both studies, the presence of multiple diagnoses was high. Schutte et al<sup>14</sup> found that 29.6% of patients with plasma D-dimer levels >5000 µg/L and a diagnosis of VTE had a concurrent cancer diagnosis and 50% of these patients had plasma D-dimer levels >20,000 µg/L. Our study demonstrated a similar correlation between the plasma D-dimer levels and the presence of cancer, with 37.2% of patients with levels >15,000 ng/mL having an active cancer diagnosis.

The association between elevated plasma D-dimer levels and cancer has been previously reported. The angiogenesis required for rapid tumor growth and dissemination is thought to activate the coagulation cascade, with tumor cells displaying clot-promoting properties.<sup>16</sup> Metastatic progression further contributes to fibrin generation and subsequent lysis, leading to a stepwise increase in plasma D-dimer levels that correlates with the tumor burden and the number of metastatic sites.<sup>17-19</sup> This has been further demonstrated

in clinical research, with the risk of malignancy increasing in patients with plasma D-dimer levels >8000 ng/mL.<sup>20</sup> Our results suggest that an elevated plasma D-dimer level should reinforce strict adherence to age-appropriate cancer screening.

The current COVID-19 pandemic has resulted in the increased measurement of inflammatory markers in an attempt to predict for disease severity and prognosis.<sup>21,22</sup> Acute viral infection results in a profound inflammatory response that leads to a subsequent coagulopathic state characterized by elevated plasma D-dimer levels.<sup>23</sup> In patients with severe infection as defined by clinical examination and imaging findings, the plasma D-dimer levels have been nearly 2.5 to 5.0 times greater than those found in patients with mild disease, with a level >1 to 2 µg/mL representing the greatest risk of mortality.<sup>7,24-27</sup> A retrospective study from Wuhan, China found that the plasma D-dimer levels were nine times greater, on average, in patients who had died of their infection compared with those who had survived.<sup>27</sup>

Despite the known utility of obtaining plasma D-dimer levels in patients with suspected or diagnosed COVID-19 infection, a number of issues arise from the test's low specificity and a lack of information on each patient's baseline levels. As we have shown in a pre-COVID-19 patient population, a number of common disease processes can drive plasma D-dimer levels above the normal threshold, and the absence of an apparent clinical diagnosis in this setting should not be considered lightly, because the mortality in these cases is high. Furthermore, little is known about the contribution of patients' baseline comorbid conditions to plasma D-dimer elevation. Zhou et al<sup>27</sup> observed that nearly one half of the patients hospitalized for COVID-19 infection with elevated plasma D-dimer levels had had at least one

comorbid diagnosis on admission, which might suggest a degree of comorbid contribution. To what extent comorbid conditions contributed to increases above the baseline plasma D-dimer levels vs the contribution by acute viral infection is not known. However, additional outpatient studies investigating the effect of common comorbidities on plasma D-dimer levels could help clarify this issue. Clinicians must be aware of these factors when relying on plasma D-dimer levels as a screening tool and prognostic indicator during the current COVID-19 pandemic.

The present study had many limitations that should be considered. We retrospectively gathered data from patient medical records across a number of years and hospital sites to find cases of ultra-high D-dimer levels. No specific information was gathered outlining what constituted the standard workup at a given site for a specific complaint. It is possible that the evaluations for a given complaint varied through time and across sites, which could have affected the diagnosis numbers. No information was gathered on the total number of D-dimer assays obtained during the study period or the number of abnormal results. This information could be useful to determine the incidence of ultra-high D-dimer levels and the breakdown of abnormal results stratified by clinical site. Another significant limitation was the lack of data on the cause of death. Inpatient mortality was relatively low (27 of 283 patients), and most patients had died after discharge. The cause of death data were, therefore, not available for most patients through our electronic medical record system. It would be valuable to compare this information with the overall diagnosis numbers to determine which diagnosis carried the greatest risk of mortality. Plasma D-dimer levels could also have been compared between the patients who had survived and those who had died before follow-up. Finally, no additional laboratory results were collected other than the plasma D-dimer levels. Additional tests, including hemostatic parameters and inflammatory and tumor markers, could help point toward certain diagnoses, which would have been particularly useful for the patients who lacked a diagnosis. Future studies would benefit from the prospective enrollment of patients across multiple hospitals, implementing standardized medical workups, and prospectively monitoring plasma D-dimer levels.

## CONCLUSIONS

The results from our study have shown that VTE, cancer, pneumonia, and other proinflammatory conditions are commonly present when ultra-high plasma D-dimer levels are found, although a clear diagnosis might not be evident. Mortality in these patients was high and approached 75% in patients with plasma D-dimer levels >15,000 ng/mL. In the patients with plasma D-dimer levels >5000 ng/mL and no clear clinical diagnosis,

further workup should be pursued owing to the high mortality rate in this population. The results of our study from a pre-COVID-19 patient population suggest that ultra-high plasma D-dimer levels might reflect the presence of severe underlying disease that clinicians must be aware of when using the plasma D-dimer level as a screening tool and prognostic indicator during the current COVID-19 pandemic.

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