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Letter to the Editors-in-Chief

D-dimer cut-off points and risk of venous thromboembolism in adult hospitalized patients with COVID-19

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1. Introduction

The novel coronavirus disease 2019 (COVID-19) pandemic has led to more than 24 million confirmed cases and over 820,000 deaths worldwide as of late August 2020. Early observational studies reported high rates of venous thromboembolism (VTE) in critically ill patients with COVID-19 [1]. A recent meta-analysis reported an incidence of 26% for VTE among 3487 patients from 30 studies based on very low-quality evidence due to heterogeneity and risk of bias [2]. Furthermore, studies have reported that elevated D-dimer values in COVID-19 are associated with a higher risk of VTE, mechanical ventilation, and mortality [3–5]. However, the clinical implications of D-dimer values are unclear. We report VTE rates and analyze the diagnostic performance and relationship of D-dimer with VTE in a large observational cohort study of hospitalized adults with COVID-19.

2. Methods

We conducted a retrospective observational cohort study at New York-Presbyterian/Weill Cornell Medical Center, a quaternary referral center located in the Upper East Side of Manhattan, and New York-Presbyterian/Lower Manhattan Hospital, an affiliated community hospital. We included all consecutive adult (age ≥ 18 years) cases of COVID-19 confirmed by a positive SARS-CoV-2 reverse transcriptase-polymerase chain reaction test admitted between 3 March 2020, the date of the first positive case, and 15 May 2020. For patients who remained hospitalized at the end of the study period, data collection and analysis were complete through 5 June 2020.

Until 5 April 2020, institutional guidelines recommended standard thromboprophylaxis for all hospitalized patients [subcutaneous enoxaparin (30 mg or 40 mg once daily) or subcutaneous unfractionated heparin (5000 units or 7500 units every 8 to 12 h)]. After 5 April 2020, our hospitals implemented an intermediate-dose thromboprophylaxis guideline (Supplementary material).

The primary outcome was VTE, comprising lower or upper extremity deep vein thrombosis (DVT), and acute pulmonary embolism (PE). All VTE were objectively diagnosed by either compression ultrasound (CUS) or computed tomography pulmonary angiogram (CTPA). Patients were not screened for VTE—imaging studies were performed at the physician's discretion.

Univariate analysis and multivariable logistic regression analysis were performed to evaluate the association between the initial D-dimer value during hospitalization, clinical characteristics, and the odds of VTE. Complete case analysis was used for the multivariable logistic regression. Clinical characteristics with P values less than 0.05 in the univariate analysis were included in the multivariable logistic regression analysis.

Receiver operating characteristics (ROC) curve analysis was used in a subgroup of patients who had a lower or upper extremity CUS or CTPA performed and the closest D-dimer value within 48 h prior to the imaging study. In a post-hoc analysis, we determined optimal cut-off points by visually inspecting the ROC curve and identifying points on the curve at which the slope of the curve, which represents the likelihood ratio, significantly changed. We calculated 95% confidence intervals (CIs) for the likelihood ratios at each level (mutually exclusive, all-inclusive ranges for D-dimer values) to demonstrate non-overlapping CIs.

3. Results

A total of 1739 hospitalized patients with COVID-19 were included in the study. The median age was 66.5 years (IQR 53.7–77.3), 59% were men, and common comorbidities included hypertension (56%), diabetes mellitus (31%) and obesity (30%). Baseline characteristics of the study population are shown in Supplementary Table 1.

In our overall cohort, 123 of 1739 (7%) patients had objectively documented VTE during their hospitalization. There were 136 VTE events overall—79 lower extremity DVT, 16 upper extremity DVT, and 41 PE's. A significantly higher proportion of patients who required mechanical ventilation had VTE compared to patients who did not require mechanical ventilation (15% vs. 4%, $P < 0.001$). The median time from hospital presentation to diagnosis of first VTE event was 5 days (IQR 1–15) (Fig. 1). Among patients who had VTE, 77 (63%) had the event > 48 h from hospital presentation. For patients who had VTE while mechanically ventilated ($N = 68$), the median time from start of mechanical ventilation to VTE event was 10 days (IQR 6–23). Thirteen

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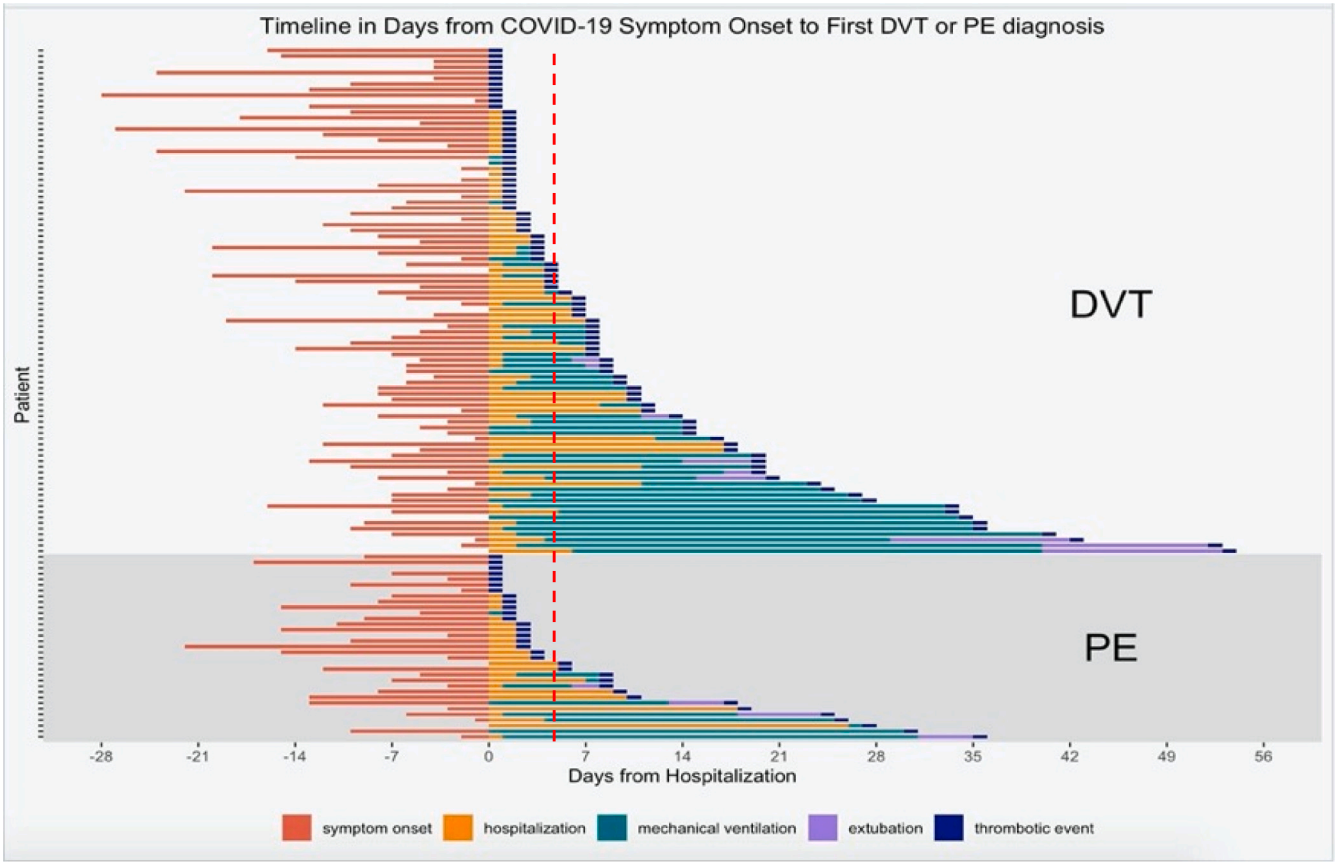

Fig. 1. Timeline of events in hospitalized patients with COVID-19 who had deep vein thrombosis (top panel) or pulmonary embolism (bottom panel). Abbreviations: COVID-19, coronavirus disease 2019; DVT, deep vein thrombosis; PE, pulmonary embolism. The dashed red line shows the median 5 days.

of 68 (19%) patients had VTE before the initiation of mechanical ventilation.

The multivariable regression model following univariate analysis of the clinical characteristics on presentation included the following covariates: gender, race, need for supplemental oxygen at presentation, first available platelet count, prothrombin time, and D-dimer (Supplementary Table 2). Multivariable regression analysis revealed that Black race (OR 2.66; 95% CI 1.48–4.77; $P = 0.001$), need for supplemental oxygen at presentation (OR 2.25; 95% CI 1.39–3.65; $P = 0.001$), prothrombin time (OR 1.02 per every 1 s; 95% 1.00–1.04; $P = 0.044$), and D-dimer (OR 1.09 for every 1000 ng/mL; 95% CI 1.06–1.11; $P < 0.001$) were associated with increased odds of VTE, when controlling for all other factors.

In the D-dimer analysis, we identified 485 patients who had a lower or upper extremity CUS or CTPA study performed and a D-dimer value within 48 h prior to the imaging study. A total of 666 imaging studies performed for these patients were analyzed and their demographic and clinical characteristics are shown in Supplementary Table 3. The ROC curve for D-dimer and VTE showed an area under the curve of 0.788 (95% CI, 0.746, 0.831) (Supplementary Fig. 1). Multilevel likelihood ratios significantly changed at the following D-dimer levels: < 1000 ng/mL: 0.14 (95% CI, 0.07–0.30); 1000–7500 ng/mL: 1.19 (0.97–1.47); and > 7500 ng/mL: 4.10 (2.94–5.71) (Table 1). With an overall prevalence of VTE of 16%, the posttest probabilities of VTE at each level were: 0.03 (95% CI, 0.01–0.05), 0.18 (0.14–0.23), and 0.43 (0.33–0.53), respectively.

4. Discussion

In this study of a large cohort of hospitalized COVID-19 patients in New York City, the prevalence of objectively confirmed VTE was 7%. The rate of VTE in our study was lower than previously reported studies in Europe and Asia, but similar to a recent US study comprising 400 patients (144 critically ill) in which the overall rate VTE and the rate of VTE in critically COVID-19 patients was 5% and 8%, respectively [1,2,6].

Elevated D-dimer levels were associated with higher odds of VTE, consistent with reports by others [1]. Other significant predictors of VTE in our cohort included Black race, need for supplemental oxygen on presentation, higher platelet counts, and prolonged prothrombin time. Higher odds of VTE among Black patients has been reported previously [7]. A possible explanation for this is that Black patients have a greater prevalence of comorbidities such as obesity, hypertension and diabetes, and may have sickle cell trait [8].

In our analysis of the diagnostic performance of D-dimer, we identified three levels of D-dimer that stratified patients into low-probability (< 1000 ng/mL), intermediate-probability (1000–7500 ng/mL), and high-probability groups (> 7500 ng/mL). With a VTE prevalence of 16% in our D-dimer analysis, the posttest probabilities of VTE at each level were 3%, 18%, and 43%, respectively. A recent study of D-dimer levels in critically ill patients with COVID-19 on intermediate-dose thromboprophylaxis reported that D-dimers < 2000 ng/mL had a 100% negative predictive value for VTE and > 8000 ng/mL had a

Table 1
Multilevel likelihood ratios for D-dimer and venous thromboembolism risk.

D-dimer intervals (ng/mL)	VTE	No VTE	LR (95% CI)	Posttest probability (95% CI)
< 1000	7	264	0.14 (0.07–0.30)	0.03 (0.01–0.05)
1000–7500	53	240	1.19 (0.97–1.47)	0.18 (0.14–0.23)
> 7500	44	58	4.10 (2.94–5.71)	0.43 (0.33–0.53)
Total	104	562		

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; LR, likelihood ratio; VTE, venous thromboembolism.
Note: Includes patients who underwent compression ultrasound or computed tomography pulmonary angiogram imaging. D-dimer values evaluated were the closest to the time of imaging.

significantly increased likelihood ratio, concluding that cut-off points of 2000 ng/mL and 8000 ng/mL appear useful to identify patients with low and high probability of having developed VTE, respectively [9]. We identified similar cut-off points that appear to be useful for identifying patients at varying probabilities of having developed VTE. However, even our lowest D-dimer level of < 1000 ng/mL still identified 7 patients with VTE. Clinicians should use caution with using a low D-dimer alone to rule-out VTE in patients with COVID-19.

It is also worth mentioning that the use of diagnostic tests for the assessment of VTE is influenced by a number of factors that limit interpretation of any retrospective analysis of D-dimer cut-off points. Diagnostic testing is influenced by the pretest probability based on the patient's history, physical examination findings, other clinical data, and clinical judgment. D-dimer results, specifically, are likely to influence the rate of diagnostic imaging for VTE. For example, higher D-dimer values will be associated with a higher likelihood of diagnostic imaging compared to lower (or the absence of) D-dimer values. The cost or risk of testing, especially in the context of the COVID-19 pandemic, may also have influenced judicious use of diagnostic tests due to concerns of exposure to hospital staff and equipment. Use of diagnostic tests may also vary by clinical setting, for example increased testing in the intensive care unit compared to hospital ward units. Thus, our evaluation of D-dimer cut-off points and risk of VTE require independent, prospective investigation prior to making recommendations on diagnostic or treatment decisions based on D-dimer values at these cut-off points.

Our study has a few limitations. First, the cut-off points and likelihood ratios in our study are biased by the post-hoc selection of the cut-off points. Second, there is verification bias given the variability in testing strategies among clinicians. Diagnostic imaging rates may be different in other settings due to inherent patient differences, provider preferences, or temporal trends as health systems became better equipped to function during the pandemic and as clinicians gained greater understanding of thrombotic complications in COVID-19. However, our posttest probabilities of VTE at each D-dimer level are not affected by verification bias [10]. Finally, the patients received varying doses of prophylactic anticoagulation during the study period, including the crossover of patients from standard to intermediate dose thromboprophylaxis. Although these data were not available on an individual patient level, future studies should investigate the effect of varying doses of pharmacologic prophylaxis on VTE event rates, especially as the majority of VTE events occurred well into hospitalization.

In conclusion, marked elevations of D-dimer is a risk factor for VTE in patients with COVID-19 and different levels of D-dimer values can identify those at varying risk and probabilities of VTE. Prospective studies are needed to determine the utility of cut-off levels of D-dimers as a diagnostic and treatment strategy in COVID-19 patients.

Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2020.09.022.

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