D-Dimer Elevation and Venous Thromboembolism ≥90 Days following COVID-19: A Retrospective Study within a Learning Health System

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Abstract

Background: In acute COVID-19, plasma D-Dimer is a useful biomarker and venous thromboembolism (VTE) is common. However, it is less clear whether this is the case during long-term recovery.

Objectives: To report D-Dimer values and incidence of new VTE ≥90 days following COVID-19.

Methods: In British Columbia (BC), patients supported at the Post-COVID-19 Recovery Clinics underwent routine investigations including D-Dimer as part of a learning health system. Among patients with a positive D-Dimer (≥500ng/mL) test 90–180 days following COVID-19 symptom onset, we performed a retrospective chart review to determine whether imaging for VTE was done.

Results: There were 806 patients reviewed. Of these, 252 (30.3%) had a positive D-Dimer. Imaging was pursued in 56 (6.9%) and 9 (1.1%) were diagnosed with new VTE.

Interpretation: At ≥90 days post COVID-19, D-Dimer is often positive, but it is relatively rare to diagnose new VTE.

Résumé

Contexte: Dans les cas de COVID-19 aiguë, le D-dimère est un biomarqueur plasmatique utile et la thromboembolie veineuse (TEV) est fréquente. Toutefois, on ignore si c'est le cas au cours du rétablissement à long terme.

Objectifs: Connaître les taux plasmatiques de D-dimères et la fréquence d'une nouvelle TEV à 90 jours ou plus après avoir contracté la COVID-19.

Méthodologie: En Colombie-Britannique, les patients suivis par les cliniques de rétablissement de la COVID-19 ont subi des examens systématiques, dont le dosage des D-dimères, dans le cadre d'un système de santé apprenant. Chez les patients ayant obtenu un résultat positif au dosage des D-dimères (≥ 500 ng/ml) de 90 à 180 jours après l'apparition des symptômes de la COVID19, nous avons effectué un examen rétrospectif de leur dossier pour savoir si un examen d'imagerie pour la détection d'une TEV a été réalisé.

Résultats: Nous avons évalué 806 patients. De ce nombre, 252 (30,3 %) ont obtenu un résultat positif au dosage des D-dimères. Un examen d'imagerie a été réalisé chez 56 patients (6,9 %) et un diagnostic de nouvelle TEV a été posé chez 9 d'entre eux (1,1 %).
Interprétation: Quatre-vingt-dix jours ou plus après avoir contracté la COVID-19, le dosage des D-dimères est souvent positif, mais le diagnostic d'une nouvelle TEV est relativement rare.

Keywords: COVID-19; SARS-CoV-2; long COVID; venous thromboembolism; D-Dimer; learning health system

Introduction

Infection with the SARS-CoV-2 virus can lead to widespread coagulopathy and patients are at an increased risk for venous thromboembolism (VTE) during the early stages of their COVID-19 illness.[1–8] During the acute infection, several laboratory markers of coagulation and fibrinolysis may be abnormal.[1] For example, plasma D-Dimer is a fibrin degradation product that is commonly elevated.[1] D-Dimer is known as a sensitive marker for VTE, and although early evidence was mixed, several large studies have now suggested that higher values may predict other poor outcomes in COVID-19, including mortality and the need for critical care.[9–12] Furthermore, the risks of VTE in COVID-19 have prompted further investigations on whether anticoagulation may be beneficial in the early post-discharge period.[13–16] For example, prophylaxis with rivaroxaban has been shown to decrease the incidence of VTE after hospitalization for acute COVID-19 in patients with a high risk of thrombosis and/or elevated D-Dimer levels.[16]

However, we still require a greater understanding of whether coagulopathy plays a significant role during long-term COVID-19 recovery. It is unclear whether symptoms of post-COVID-19 conditions (also known as long COVID) can be partly attributed to microthrombosis.[17–18] The period ≥90 days following COVID-19 is typically when these conditions are diagnosed, further investigation is needed to determine whether VTE remains a significant risk and whether there is utility in measuring D-Dimer on a routine basis.[19]

In British Columbia (BC), Canada, patients recovering from COVID-19 are supported at Post-COVID-19 Recovery Clinics (PCRCs) as part of the Post-COVID-19 Interdisciplinary Clinical Care Network (PC-ICCN).[20–22] The PC-ICCN was designed as a learning health system in which research is integrated with care.[20–22] All PCRC patients were investigated with a standardized panel of investigations thought to have potential importance, including D-Dimer. In this retrospective study, we evaluated the prevalence of D-Dimer elevation and incidence of new VTE diagnosis in the period ≥90 days following COVID-19 symptom onset.

Methods

Participants and setting

This study was approved by the University of British Columbia Research Ethics Board and the work was carried out in accordance with The Code of Ethics of the Declaration of Helsinki. Requirement for consent was waived, as all investigations were completed as part of clinical care.

The analyses included consecutive adult patients referred to and accepted by the PC-ICCN who had COVID-19 symptom onset between January 5, 2020 and August 16, 2021, and had D-Dimer testing 90–180 days thereafter. Referrals to the PC-ICCN were accepted for patients who were previously hospitalized for COVID-19 or were not hospitalized but tested positive and were experiencing persistent symptoms for ≥90 days. During the study period, there were PCRCs located at St. Paul's Hospital (Vancouver), Vancouver General Hospital (Vancouver), Jim Pattison Outpatient Care and Surgery Centre (Surrey) and Abbotsford Regional Hospital (Abbotsford). However, referrals were accepted from throughout the province and patients were commonly assessed through telehealth.

In addition to a questionnaire, patients completed a standardized set of blood work at their local laboratory before their first PCRC assessment. At the time of this study, plasma D-Dimer was routinely measured as part of this protocol. The lab results were reviewed by a PCRC Internist. There were no pre-specified criteria regarding when to order further investigations following an elevated D-Dimer, and this was left to the clinical judgment of the PCRC Internist. The rationale for ordering imaging varied by physician; factors considered may have included the magnitude of D-Dimer elevation, the patient's risk profile for VTE, prior investigations for VTE, symptoms reported by the patient (on the questionnaire and/or during

PCRC appointment) and physical examination. Further imaging could be ordered before or after the patient was formally assessed at their PCRC appointment.

Data collection and analyses

Demographic, COVID-19 and laboratory information was extracted from PCRC databases. D-Dimer was considered positive if it was ≥500 fibrinogen equivalent units (FEU). An age-adjusted D-Dimer cut-off was also calculated by the formula *age x 10 ng/ml* among patients ≥50 years old.[23]

For patients with a positive D-Dimer (≥500 ng/ml), we queried BC's province-wide health record system to determine whether imaging for VTE had been done following COVID-19 symptom onset. Diagnosis of VTE was confirmed if the radiology report indicated the presence of pulmonary embolism (segmental or subsegmental), lower or upper extremity (proximal, distal or superficial), or cerebral venous thromboses. Imaging reports were reviewed between July 8 and December 28, 2021, and at least 30 days following the D-Dimer test. Based on the dates of imaging investigations, we determined whether VTE was identified for the first time after the D-Dimer was done (i.e., a "new" VTE), or diagnosed after COVID-19 symptom onset, but before the D-Dimer.

The Wilcoxon rank-sum and chi-squared tests were used, and data were analyzed using SAS version 9.4 (SAS Institute, Cary, North Carolina). All statistical tests were two-sided, and significance was set at $p<0.05$.

Results

A total of 806 patients had D-Dimer tests performed at a median of 123 days (IQR 102–155) after acute COVID-19 symptom onset. There were 252 patients (31.3%) with a positive D-Dimer using a cut-off of ≥500 ng/mL, and 190 (23.6%) patients with a positive D-Dimer when using an age-adjusted cut-off. Patients with a positive D-Dimer (≥500 ng/ml) were older and more likely to have been hospitalized for acute COVID-19 than patients with negative D-Dimer (Table 1). Of these 252, VTE was identified in 15 (6.0%) following COVID-19 symptom onset but before the D-Dimer was tested. Among the remaining 237, 56 patients (22.2%) had imaging done and new VTE was identified in 9 (16.1%), or 3.6% of all patients with elevated D-Dimer results and 1.1% of all patients in the study (Figure 1). The incidence rate of VTE in the positive D-Dimer group was 52.7 per 1000 person-years. Of the 9 new VTE events, there were 4 segmental and 3 subsegmental pulmonary emboli, 1 superficial vein thrombosis and 1 deep vein thrombosis. Since their COVID-19 symptom onset, 2 of these patients had prior VTE imaging that was negative.

Among those with an elevated D-Dimer, patients with new VTE had a higher median value compared to those in whom no VTE was identified (1508 vs. 739 ng/ml, p = 0.0008) (Figure 2). Most VTE events were identified within 180 days of COVID-19 symptom onset (Figure 3), with the median time to diagnosis at 131 days (95%CI 107–174).

Discussion

In a learning health system care model for patients following COVID-19, we performed routine D-Dimer testing 90–180 days after COVID-19 symptom onset. D-Dimer values were elevated in nearly one-third of patients and were more likely abnormal in older patients and those with more severe cases.

Table 1. Baseline Characteristics in Patients With Positive D Dimer versus Negative D Dimer

	All patients (N=806)	A) Negative D-Dimer (N=554)	B) Positive D-Dimer (N=252)	*P*
Male (%)	393 (48.4%)	271 (48.9%)	122 (48.4%)	0.894
Age (median [IQR])	53 [42–64]	50 [41–60]	61 [48–71]	<0.001
Days since COVID-19 symptom onset for D-Dimer test (median [IQR])	123 [102–155]	125 [103–158]	119 [101.0–146.5]	0.040
D-Dimer value (median [IQR]) (ng/mL)	N/A*	N/A*	747.5 [604.5–1069.5]	
Hospitalized (%)	485 (60.2%)	302 (54.5%)	183 (72.6%)	<0.001
Ward only (%)	332 (41.2%)	209 (37.7%)	123 (48.8%)	0.003
ICU (%)	153 (19.0%)	93 (16.8%)	60 (23.8%)	0.027

*Median among patients with negative (<500ng/mL) D-Dimer value was not calculated as some labs did not report actual values that were <220 ng/mL.

†p-values are calculated based on the Wilcoxon rank-sum test (continuous variables) or chi-squared test (categorical variables). IQR- interquartile range; ICU- intensive care unit.

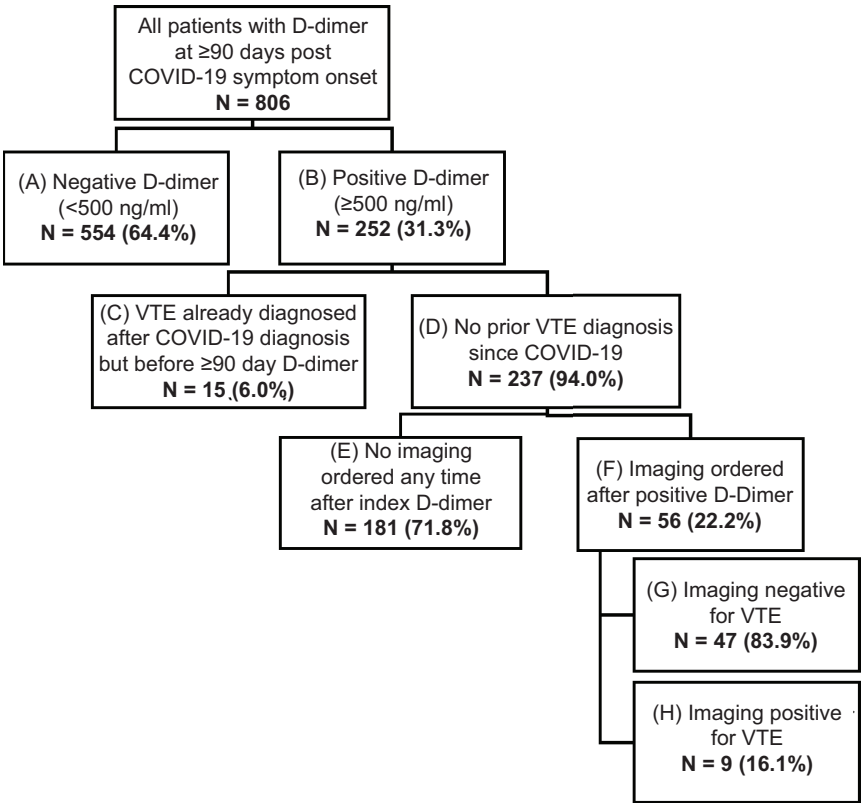

Figure 1. Breakdown of outcomes in patients with D-Dimer results. Of the 9 VTE events, there were 4 segmental and 3 subsegmental pulmonary emboli, 1 superficial vein thrombosis and 1 deep vein thrombosis. VTE- venous thromboembolism.

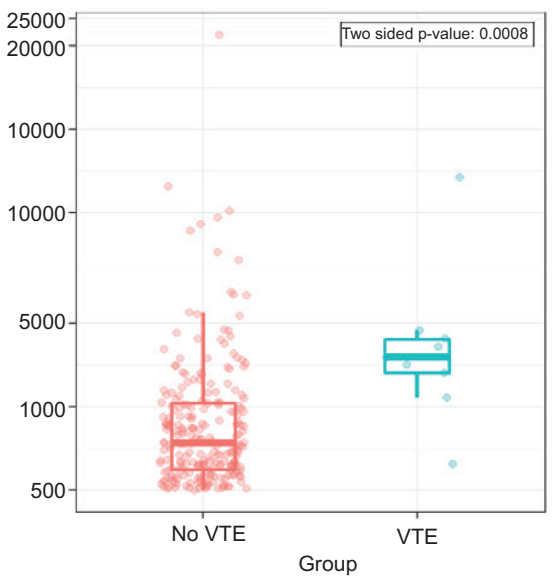

Figure 2. Box and whisker plot comparing D-Dimer in patients with VTE (Group "H" in Figure 1) vs those with positive D-Dimer but no VTE (Groups "E"+"G") (n=237); *p*=0.0008 by Wilcoxon rank-sum test. The total range and IQR of values were 621–6710 and 1321–1751 in the VTE group vs. 501–21883 and 591–1028 in the no VTE group. VTE- venous thromboembolism.

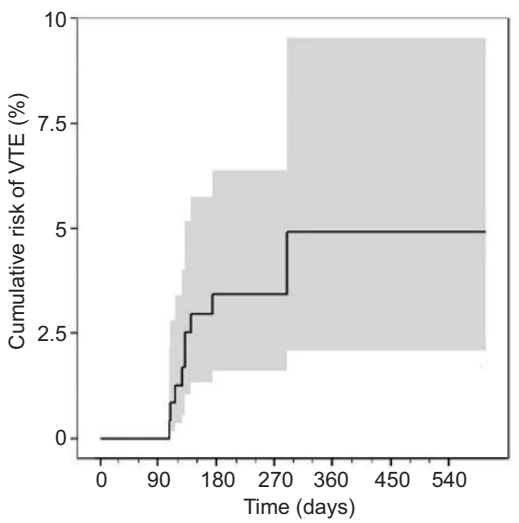

Figure 3. Cumulative risk of VTE events in all patients with elevated D-Dimer at ≥90 days after symptom onset and no prior VTE. Median time from COVID-19 symptom onset to VTE among patients with VTE (Group "H" in Figure 1) was 131 days (95%CI 107–174). VTE- venous thromboembolism.

New VTE was uncommon (3.6%) in patients with elevated D-Dimer.

The overall prevalence of new VTE in our cohort (1.1%) was lower than in acute COVID-19 patients during hospitalization, post-discharge, or those that presented to the emergency department but was similar to what has been reported for never-hospitalized patients.[2–7] Furthermore, the unadjusted incidence rate among patients with positive D-Dimer was higher than what was reported in a 2015 prospective study of non-COVID-19 patients.[24] Our work also extends findings from population-level data which suggest that the risk of VTE attributable to COVID-19 declines considerably with time since infection.[4–6]

Our study has limitations and must be interpreted in the context of the study design. First, there was bias in how our cohort was selected, as our PCRCs accepted only severe (hospitalized) or chronically symptomatic, non-hospitalized COVID-19 patients, and therefore our results may not be generalizable to all patients following COVID-19. Second, we were unable to evaluate the predictive value of D-Dimer testing because not all patients were routinely imaged for VTE.[7] Third, clinicians were not blinded to the D-Dimer results, which could have influenced the decision to pursue imaging, regardless of the presence or absence of VTE symptoms. Lastly, we did not capture detailed medical history on patients in this cohort. The lack of these details the small sample size and low VTE rate precluded us from generating multivariable models to identify risk factors for elevated D-Dimer and VTE.

Further research is required to fully elucidate the incidence of thrombosis in post-COVID-19 conditions and assess the utility of D-Dimer for predicting other long-term complications and symptomology. However, this study revealed that ≥90 days after COVID-19, many patients will have an elevated D-Dimer and there remains an association between D-Dimer and VTE. However, it is uncommon to radiologically detect VTE during this period. We have therefore removed routine D-Dimer testing in our post-COVID-19 learning health system.

Author Contributions

HN, RL, JG, ZS, PB, MM, AYYL and AL contributed to conception and design. HN, SS, MM, RL and KD contributed to procurement of data. HN and SS contributed to analysis of data. HN and RL contributed to drafting of the original manuscript, and all authors contributed to critical review of the manuscript.

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Conflicts of Interest

The authors have no conflicts of interest to declare related to this manuscript.

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