2020

Utility of D-dimer in predicting venous thromboembolism in non-mechanically ventilated COVID-19 survivors.

P. C. Nauka
Zucker School of Medicine at Hofstra/Northwell

S. W. Baron

A. Assa

L. Mohrmann

S. Jindal

See next page for additional authors

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Thrombosis Research 199 (2021) 82–84

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Letter to the Editors-in-Chief

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ARTICLE INFO

Keywords
Venous thromboembolism
COVID-19
D-dimer
Pulmonary embolism
Deep venous thrombosis

1. Introduction

Novel coronavirus disease 2019 (COVID-19) is increasingly recognized as a prothrombotic state with a high incidence of thrombotic complications, particularly in patients with a severe clinical course [1,2]. However, 70–81% of COVID-19 cases are associated with a non-severe clinical course and recover with supportive care [3,4]. The few studies that exist estimate the venous thromboembolism (VTE) risk among COVID-19 patients in the general medical wards to be between 5 and 10%, which is strikingly lower than the 30% seen in ICU patients with COVID-19 [1,5–7]. Historically, D-dimer has been utilized to exclude VTE, however, in COVID-19 patients, D-dimer level has been correlated with mortality and may also have a role in identifying patients who should be studied to rule out VTE [8]. In patients with COVID-19 admitted to the ICU, admission D-dimer may predict risk of VTE, but it is unclear if this is true for non-severe cases [5–7,9]. In this study, we examine the risk of and utility of D-dimer as a predictor of VTE among COVID-19 survivors who were not mechanically ventilated and were successfully discharged from the hospital.

2. Methods

This is a retrospective cohort analysis of all adult patients discharged from a large, urban, tertiary teaching health system between March 11, 2020 and May 2, 2020. This study was approved by the Institutional Review Board (IRB) at Albert Einstein College of Medicine.

The study included adult patients hospitalized with COVID-19 who were discharged from the hospitalization. COVID-19 status was confirmed by Real-Time polymerase chain reaction. Hospital admission date was the cohort entry date. Patients were excluded if they were mechanically ventilated or expired regardless of VTE status. The final cohort included patients who underwent imaging during hospitalization or within 14 days of discharge that could identify a new pulmonary embolism (PE) or deep vein thrombosis (DVT).

Clinical and demographic characteristics of identified patients were extracted from our electronic medical record. The first available laboratory value within 48 h of admission was reported. Thromboprophylaxis and full dose anticoagulation prior to diagnosis as well as imaging data were extracted via manual chart review.

The primary outcome was a VTE event which was a composite of DVT, PE, or both as identified by lower or upper extremity duplex studies for DVT or chest computerized tomography (CT) with contrast for PE. Studies completed up to 14 days after discharge date were included. Imaging was performed at the providers' discretion.

Patients with and without confirmed VTE were compared using Chi-squared for categorical variables and unpaired Student's *t*-test for continuous variables or nonparametric alternatives. Two measures of VTE prevalence were calculated. The Test Positivity Rate represents the proportion of tested patients in whom VTE was found. To provide a floor estimate of the prevalence of VTE in the population, the Estimated Population Prevalence (positive tests divided by number of eligible non-severe patients) was calculated.

D-dimer value on admission was stratified into four categories using integers for simplicity in clinical practice. The reference D-dimer category was <1 μg/mL, mild elevation was ≥1–2 μg/mL, moderate elevation was ≥2–5 μg/mL, and D-dimer ≥5 μg/mL was a severe elevation.

Logistic regression models were used to examine the association between D-dimer level and VTE events. Adjusted models included variables determined a priori to be potential confounders (gender, age, body mass index (BMI), CRP, ferritin, and LDH), and a separate model included variables significant on bivariate analysis. Goodness of fit was checked by Hosmer-Lemeshow test. All statistical analysis was performed using Stata version 16.1 (StataCorp LLC, College Station, Texas). All $p < 0.05$ in a two-tailed test were statistically significant.

Abbreviations: COVID-19, coronavirus disease 2019; VTE, venous thromboembolism; DVT, deep venous thrombosis; PE, pulmonary embolism.

☆ All authors contributed to the preparation of this manuscript.

https://doi.org/10.1016/j.thromres.2020.12.023
Received 16 September 2020; Received in revised form 12 December 2020; Accepted 18 December 2020
Available online 26 December 2020

3. Results

A total of 3855 eligible adult patients with COVID-19 were identified and 1225 were excluded for mortality or mechanical ventilation during admission. Of the remaining 2630 patients, 306 underwent diagnostic imaging for VTE. Sixty-seven of these 306 patients had confirmed VTE leading to a Test Positivity Rate of 21.9% (67/306). The Estimated Population Prevalence was 2.5% (67/2630).

Of the 306 imaged patients, 92 underwent VTE imaging within 24 h of presentation and thus did not receive thromboprophylaxis. Of the remaining 214 patients, 21 (9.8%) received no thromboprophylaxis or anticoagulation, 116 (54.2%) received thromboprophylaxis and 77 (36.0%) received full dose anticoagulation.

Patients with and without confirmed VTE were of similar age (60.6 versus 61.7 years, p = 0.60), BMI (31.1 versus 30.3, p = 0.44) and race/ethnicity (p = 0.964) (Table 1). Patients with confirmed VTE were more likely to be male (67.2% versus 51.9%, p = 0.03). Patients with VTE also had higher white blood cell count (9.6 versus 7.5 k/μL, p = 0.008), LDH (464 versus 370 mg/dL, p = 0.005), neutrophil/lymphocyte ratio (0.8 versus 0.4, p = 0.009) and lower fibrinogen (594 versus 645 mg/dL, p = 0.07) than those without confirmed VTE.

Admission D-dimer levels were higher in patients with confirmed VTE (5.2 versus 1.7 μg/mL, p <0.001) among the 250 patients with admission D-dimer level. Among patients with a D-dimer who did not undergo any VTE imaging (n = 1586), median D-dimer level was 1.23 μg/mL (IQR 0.71 to 2.45 μg/mL) (not shown in Table 1).

There was an incremental and dose-dependent effect of admission D-dimer in predicting confirmed VTE (Table 2). Among imaged patients with reference D-dimer (<1 μg/mL) levels, the Test Positivity Rate was 7.6% and Estimated Population Prevalence was 0.7%. Test Positivity Rate and Estimated Population Prevalence were incrementally higher in the mildly (≥1–2 μg/mL) and moderately (≥2–5 μg/mL) elevated D-dimer levels compared to those with reference D-dimer level. Likewise, the odds of confirmed VTE were increased among mildly and moderately elevated D-dimer categories but non-significant compared to the reference D-dimer. Finally, for the severely elevated D-dimer category (≥5 μg/mL), the Test Positivity rate was 46.7% while Estimated Population Prevalence was 11.6%. The odds of confirmed VTE in the severely elevated D-dimer category demonstrated a tenfold increase in odds (OR 10.7, 95% CI: 3.7–30.3, p<0.001) as compared to the lowest category. Models with variables chosen a priori for adjustment (age, gender, BMI, CRP, ferritin, and LDH) and variables significant in bivariate analysis for adjustment (gender, WBC, neutrophil count, lymphocyte count, LDH) yielded similar odds ratios (Supplementary Table 1).

4. Discussion

In this large retrospective cohort study of non-severe COVID-19 patients who were not mechanically ventilated and survived to discharge, admission D-dimer level conferred an incremental, dose-dependent and predictable association with the odds of having a confirmed VTE during admission or within fourteen days following discharge. Our work suggests that not only do non-severe hospitalized COVID-19 patients have an elevated risk of VTE, but admission D-dimer level may help identify those at highest risk, creating opportunities for risk mitigation or potential treatment options to ameliorate the complications of VTE. D-dimer elevation has been previously associated with VTE in patients with COVID-19, however, these studies utilized small populations and severely ill patients which limits generalizability to most COVID-19 patients [5–7,9]. Admission D-dimer level conferred a predictable, dose-dependent, and incremental odds of confirmed VTE between 2.3-fold and 10.7-fold for categories of D-dimer above 1 μg/mL among non-severe COVID-19 patients. While D-dimer has been historically used for its high negative predictive value for VTE, given the degree of elevation in COVID-19 patients, it may have utility in stratifying VTE risk.

Table 1
Baseline characteristics of patients with confirmed VTE and without confirmed VTE.

	Total scans (N = 306)	Without confirmed VTE (N = 239)	Confirmed VTE (N = 67)	p-Value
Age, years (SD)	61.5 (15.7)	61.7 (15.8)	60.6 (15.7)	0.60
BMI, kg/m^2 (SD)[a]	30.4 (7.6)	30.3 (7.6)	31.1 (7.3)	0.44
Length of stay, days (SD)	9.9 (6.7)	9.4 (6.2)	11.6 (7.9)	0.06
Male sex, n (%)	169 (55.2)	124 (51.9)	45 (67.2)	0.03
Race/ethnicity, n (%)				0.96
Hispanic	114 (37.3)	89 (37.2)	25 (37.3)	
Black, not Hispanic	126 (41.2)	97 (40.6)	29 (43.3)	
White, not Hispanic	20 (6.5)	16 (6.7)	4 (6.0)	
Other/not specified	46 (15.0%)	37 (15.5)	9 (13.4)	
Comorbidity, n (%)				
Hypertension	190 (62.1)	148 (61.9)	42 (62.7)	0.91
Diabetes mellitus	112 (36.6)	91 (38.1)	21 (31.3)	0.31
Malignancy	67 (21.9)	60 (22.5)	7 (18.0)	0.52
Laboratory tests reported as median [IQR]				
WBC (4.8–10.8 k/μL)	8.0 [5.8–10.8]	7.5 [5.7–10.2]	9.6 [6.2–12.3]	0.01
Neutrophil count (1.8–7.7 k/μL)	5.8 [4.2–8.8]	5.7 [4.0–8.3]	7.9 [4.6–10.1]	0.008
Neutrophil/lymphocyte ratio	0.4 [0.2–1.0]	0.4 [0.2–0.9]	0.8 [0.3–1.3]	0.009
Hb (14.0–17.4 g/dL)	12.8 [11.1–14.3]	12.6 [11.0–14.1]	13.2 [11.5–14.5]	0.15
Platelet (150–400 k/μL)	235 [172–325]	219 [172–302]	276 [189–365]	0.06
Sodium (135–145 mEq/L)[a]	136 [133–140]	136 [133–140]	136 [133–141]	0.93
Creatinine (<1.50 mg/dL)	1.0 [0.8–1.6]	1.0 [0.8–1.5]	1.1 [0.8–1.9]	0.31
Carbon dioxide (20–30 mEq/L)[a]	23 [20–25]	23 [20–25]	23 [20–25]	0.55
D-dimer (0.00–0.50 μg/mL)[a]	1.9 [0.9–4.9]	1.7 [0.9–3.5]	5.2 [1.9–20.0]	<0.001
Procalcitonin (<0.1 ng/mL)[a]	0.2 [0.1–0.6]	0.2 [0.1–0.7]	0.2 [0.1–0.5]	0.33
CRP (<0.8 mg/dL)[a]	9.9 [3.7–20.6]	9.5 [3.4–20.4]	11.4 [4.7–21.2]	0.27
IL-6 (<5.00 pg/mL)[a]	34.3 [10.6–65.5]	28.0 [10.4–66.3]	45.2 [11.9–65.5]	0.38
Ferritin (25–270 ng/mL)[a]	749 [327–1617]	728 [320–1537]	908 [399–1957]	0.18
LDH (<240 mg/dL)[a]	392 [283–524]	370 [266–513]	464 [328–638]	0.005
Fibrinogen (187–502 mg/dL)[a]	634 [506–791]	645 [524–788]	594 [406–791]	0.07

For laboratory results, normal ranges are reported in parenthesis.
Laboratory reported values are the initial result within 48 h of admission.
Abbreviations: SD – standard deviation, VTE - venous thromboembolism, BMI - body mass index, WBC - white blood cell, Hb - hemoglobin, CRP - C-reactive protein, IL-6 - interleukin-6, LDH - lactate dehydrogenase.
[a] Observations available for analysis: BMI 297, sodium and carbon dioxide 305, D-dimer 250, procalcitonin 193, CRP 265, IL-6 165, ferritin 231, LDH 276, fibrinogen 197.

The 2.5% Estimated Population Prevalence in the non-severe COVID-19 population is on par with the risk of developing a symptomatic VTE following a high-risk surgical procedure (neurosurgery, major vascular surgery, total hip replacement, or radical cystectomy) [10]. Admission D-dimer identified populations with lower and higher prevalence of VTE, from 0.7% in the reference D-dimer category to 11.6% in the

Table 2
Test Positivity Rate, Estimated Population Prevalence, and odds of developing imaging confirmed VTE during admission or within fourteen days of discharge based on D-dimer category.

D-dimer range[a]	Number of patients in range	Test positivity Rate n (%)	Estimated Population Prevalence n (%)[b]	Odds ratio (95% CI)[c]	p-Value
<1 μg/mL	66	5 (7.6%)	5 (0.7%)	Reference	Reference
≥1 to <2 μg/mL	62	10 (16.1%)	10 (2.0%)	2.3 (0.8–7.3)	0.1
≥2 to <5 μg/mL	62	12 (19.4%)	12 (3.1%)	2.9 (1.0–8.9)	0.06
≥5 μg/mL	60	28 (46.7%)	28 (11.6%)	10.7 (3.7–30.3)	p < 0.001

[a] Normal D-dimer range: 0.00–0.5 μg/mL. The 1–2 μg/mL range excludes 2 μg/mL. The 2–5 μg/mL range excludes 5 μg/mL. There were 56 patients with imaging but without admission D-dimer result who were not included in the analysis.

[b] Percentage of imaging that confirmed presence of VTE out of eligible non-severe patients.

[c] Unadjusted odds ratio shown here. Adjusted models did not yield meaningful differences in odds ratios (Supplementary Table 1).

severely elevated D-dimer category (D-dimer ≥5 μg/mL). While these categories were not intended to guide clinical decisions, they may begin to offer potential for clinical care. For example, it might seem reasonable to initiate diagnostic testing or pursue more aggressive thromboprophylaxis for those with an 11.6% risk of VTE.

This retrospective analysis has some limitations. First, this study was performed in one hospital system that serves a socioeconomically disadvantaged population and may not be generalizable. VTE risk is known to be higher in the African-American population which composes a large proportion of our patients [11]. Secondly, we could not evaluate our primary outcome in any patient without appropriate imaging, which was complicated during the pandemic when in-hospital movement of highly contagious patients was limited; this likely led to an underdiagnosis of VTE and underestimate of VTE risk. Thirdly, a D-dimer result was not available for all imaged patients. Given the standard practice to initiate therapeutic anticoagulation if pre-test probability for VTE was high without checking D-dimer, true population VTE prevalence is likely higher than our estimation.

In sum, these findings suggest that physicians should have a high index of suspicion for VTE in patients admitted with non-severe COVID-19. In addition, admission D-dimer levels may help stratify VTE risk among admitted non-severe COVID-19 patients, thereby aiding with diagnostic and potential treatment decisions to ameliorate the complications of VTE.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2020.12.023.

Declaration of competing interest

We have no conflicts of interest to disclose or any financial disclosures to report.

Acknowledgements

SC had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. PN and SC contributed to study conception. SC, PCN, AA, LM, SJ, EO, GG, SB, WS contributed substantially to study design, data acquisition, data analysis and interpretation and writing of the manuscript.

References

[1] S. Bilaloglu, Y. Aphinyanaphongs, S. Jones, E. Iturrate, J. Hochman, J.S. Berger, Thrombosis in hospitalized patients with COVID-19 in a New York City health system, JAMA 324 (2020) 799–801.
[2] D. Wichmann, J.P. Sperhake, M. Lütgehetmann, S. Steurer, C. Edler, A. Heinemann, F. Heinrich, H. Mushumba, I. Kniep, A.S. Schröder, C. Burdelski, G. de Heer, A. Nierhaus, D. Frings, S. Pfefferle, H. Becker, H. Bredereke-Wiedling, A. de Weerth, H.R. Paschen, S. Sheikhzadeh-Eggers, A. Stang, S. Schmiedel, C. Bokemeyer, M.M. Addo, M. Aepfelbacher, K. Püschel, S. Kluge, Autopsy findings and venous thromboembolism in patients with COVID-19, Ann Intern Med 173 (2020) 268–277.
[3] S. Richardson, J.S. Hirsch, M. Narasimhan, J.M. Crawford, T. McGinn, K.W. Davidson, a.t.N.C.-R. Consortium, Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area, JAMA (2020).
[4] Z. Wu, J.M. McGoogan, Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention, JAMA 323 (13) (2020) 1239–1242.
[5] F.A. Klok, M. Kruip, N.J.M. van der Meer, M.S. Arbous, D. Gommers, K.M. Kant, F. H.J. Kaptein, J. van Paassen, M.A.M. Stals, M.V. Huisman, H. Endeman, Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: an updated analysis, Thromb Res 191 (2020) 148–150.
[6] C. Lodigiani, G. Iapichino, L. Carenzo, M. Cecconi, P. Ferrazzi, T. Sebastian, N. Kucher, J.-D. Studt, C. Sacco, B. Alexia, M.T. Sandri, S. Barco, Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy, Thrombosis Research 191 (2020) 9–14.
[7] S. Middeldorp, M. Coppens, T.F. van Haaps, M. Foppen, A.P. Vlaar, M.C.A. Müller, C.C.S. Bouman, L.F.M. Beenen, R.S. Kootte, J. Heijmans, L.P. Smits, P.I. Bonta, N. van Es, Incidence of venous thromboembolism in hospitalized patients with COVID-19, Journal of Thrombosis and Haemostasis n/a(n/a).
[8] D. Wang, B. Hu, C. Hu, F. Zhu, X. Liu, J. Zhang, B. Wang, H. Xiang, Z. Cheng, Y. Xiong, Y. Zhao, Y. Li, X. Wang, Z. Peng, Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China, JAMA 323 (11) (2020) 1061–1069.
[9] J.-F. Llitjos, M. Leclerc, C. Chochois, J.-M. Monsallier, M. Ramakers, M. Auvray, K. Merouani, High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients, Journal of Thrombosis and Haemostasis n/a(n/a).
[10] R.H. White, H. Zhou, P.S. Romano, Incidence of symptomatic venous thromboembolism after different elective or urgent surgical procedures, Thromb Haemost 90 (3) (2003) 446–455.
[11] R.H. White, The epidemiology of venous thromboembolism, Circulation 107 (23 Suppl 1) (2003) I4–I8.

Peter C. Nauka[a,1], Sarah W. Baron[b,1], Andrei Assa[b], Laurel Mohrmann[b], Shawn Jindal[a], Erick Oran[b], Galina Glazman-Kuczaj[a], William N. Southern[b], Sweta Chekuri[b,*]

[a] *Albert Einstein College of Medicine and Montefiore Medical Center, Department of Medicine, Internal Medicine Residency Program, Bronx, NY, USA*

[b] *Albert Einstein College of Medicine and Montefiore Medical Center, Department of Medicine, Division of Hospital Medicine, Bronx, NY, USA*

[*] Corresponding author at: Montefiore Medical Center, Moses Division, Department of Medicine, 111 East 210th Street, Bronx, NY 10467-2401, USA.
E-mail address: schekuri@montefiore.org (S. Chekuri).

[1] Both authors contributed equally.