

## EDITORIAL

# Narrowing in on the True Rate of Venous Thromboembolism in Hospitalized Patients With COVID-19 Disease

Deborah M. Siegal, Peter L. Gross

**T**hrombosis first emerged as a potentially frequent and important complication of coronavirus disease 2019 (COVID-19) with the publication of a cohort study suggesting improved outcomes among affected patients treated with heparins in China—the initial epicenter of the pandemic.<sup>1</sup> Subsequent cohort studies reported high rates of venous thromboembolism (VTE) among patients with COVID-19 admitted to hospital wards (3%) or intensive care units (11%–69%) often despite the use of standard thromboprophylaxis measures.<sup>2–8</sup> For example, the incidence of deep vein thrombosis was 25% in a cohort of hospitalized COVID-19 patients in China.<sup>2</sup> The rate of pulmonary embolism was not reported in that study, and none of the 81 critically ill patients were treated with pharmacological thromboprophylaxis. In a Dutch cohort study of 138 critically ill patients with COVID-19, VTE events occurred in 27% despite the use of low-molecular-weight heparin at prophylactic or intermediate doses. One-quarter of the VTE events were subsegmental pulmonary embolism, which may be prognostically distinct from pulmonary embolism involving segmental or larger pulmonary arteries.<sup>3</sup> An autopsy series of 4 victims of COVID-19 from New Orleans, Louisiana, showed small firm thrombi in peripheral lung parenchyma.<sup>9</sup>

baseline risk, severity of disease, use of prophylactic anticoagulants, type of VTE, and methods of VTE ascertainment. Despite significant methodological limitations, these reports prompted consensus guidance and institutional protocols recommending administration of anticoagulant prophylaxis for all hospitalized patients with COVID-19 and consideration of higher-than-usual doses for select patients,<sup>10–14</sup> although the latter is controversial.<sup>15</sup> On July 9, 2020, <https://www.clinicaltrials.gov> lists 28 trials evaluating anticoagulation in patients with COVID-19. In addition, numerous laboratory investigations have begun to explore the possible mechanisms driving this thrombosis.<sup>16</sup>

Taken together, these studies suggest that the rate of VTE appears far higher in patients with COVID-19 than other hospitalized patients (1%) and intensive care unit patients (10%) receiving thromboprophylaxis.<sup>17,18</sup> However, the lack of comparator groups in these cohort studies precludes firm conclusions. Thus, uncertainty about the true incidence of VTE despite evidence-based thromboprophylaxis represents a major gap in our understanding about this complication of COVID-19.

In this issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, Mei et al<sup>19</sup> contribute important data to this literature by comparing the incidence of VTE in patients who were hospitalized with COVID-19 versus those who were hospitalized with community-acquired pneumonia (CAP) at a tertiary hospital in Yichang, China (Hubei Province), between January 1 and March 23, 2020. All patients presenting with fever and respiratory symptoms underwent COVID-19 testing by approved criteria, initially by clinical criteria and then by laboratory criteria once testing became available. The medical records of 616

---

See accompanying article on page 2332

---

The precise incidence of VTE among hospitalized COVID-19 patients remains uncertain with a wide range of estimates reflecting heterogeneity between studies with respect to population-based differences in

**Key Words:** Editorials ■ anticoagulants ■ cohort studies ■ critical illness ■ deep vein thrombosis ■ pulmonary embolism

---

Correspondence to: Peter L. Gross, MD, Thrombosis and Atherosclerosis Research Institute, 237 Barton St E, Hamilton, Ontario L8L 2X2, Canada. Email [peter.gross@taari.ca](mailto:peter.gross@taari.ca)  
For Disclosures, see page 1959.

© 2020 American Heart Association, Inc.

*Arterioscler Thromb Vasc Biol* is available at [www.ahajournals.org/journal/atvb](http://www.ahajournals.org/journal/atvb)

consecutive patients were retrospectively evaluated, thus including 256 patients with COVID-19 and 360 patients with CAP. Patients with COVID-19 were younger with fewer comorbidities such as coronary artery disease, cardiovascular risk factors, and malignancy and had longer average duration of admission to hospital (28 versus 9 days) and higher average Padua scores ( $2.4 \pm 1.5$  versus  $1.9 \pm 1.4$ ;  $P < 0.001$ ) compared with CAP patients. A higher severity of illness among patients with COVID-19 was suggested by a higher use of supplemental oxygen (19.9% versus 4.7%;  $P < 0.001$ ), continuous renal replacement therapy (5.9% versus 1.4%;  $P = 0.002$ ), and death (6.3% versus 3.9%;  $P = \text{nonsignificant}$ ) compared with patients with CAP. The overall rate of VTE (including symptomatic and asymptomatic events) during hospitalization was 2.0% in the patients with COVID-19 and 3.6% in the patients with CAP—a difference that was not statistically significant. The authors concluded that although hospitalized patients with COVID-19 disease have an increased VTE risk despite thromboprophylaxis, this is not different from those with CAP.

It is important to note that all patients received either pharmacological or mechanical thromboprophylaxis. Patients with a high risk of VTE (defined as Padua score  $> 4$ ) underwent screening imaging to exclude VTE. A higher proportion of patients with COVID-19 were classified as high risk compared with patients with CAP (15.6% versus 10.0%). In these high-risk patients, VTE was diagnosed in 12.5% of those with COVID-19 and 16.7% of those with CAP. The incidence of VTE appeared higher among patients who required ventilatory support than those who did not in both the COVID-19 (6.7% versus 0.9%;  $P = \text{nonsignificant}$ ) and CAP (13% versus 2%;  $P < 0.001$ ) groups.

The major limitation of this study is the retrospective data collection at a single center and associated risks of selection and ascertainment biases among patients who were treated during routine clinical practice. Given growing concerns about thrombosis in COVID-19 patients, the threshold for testing and the rate of testing for VTE might have been different between the groups. Further, some patients with VTE may not have been tested. Although there is potential for misclassification due to false-negative COVID-19 testing, the authors reported that none of the patients classified as CAP were subsequently diagnosed with COVID-19.

When interpreting these findings, it is important to note that patients in these groups were likely prognostically different at baseline based on differences in key patient characteristics. Moreover, ethnorracial variation in VTE risk is an important consideration when generalizing these findings to other populations. For example, VTE is lower among East Asians compared with white Caucasians and could explain some of these findings.<sup>20</sup>

This publication is important because the findings suggest a lower rate of VTE than previously reported among patients hospitalized with COVID-19, which was similar to the rate of VTE in hospitalized patients with CAP. Moreover, these findings support the need for randomized trial evidence before implementing unproven higher dose anticoagulation strategies to avoid exposure of acutely ill patients to an increased bleeding risk in the setting of uncertain benefit.

## ARTICLE INFORMATION

### Affiliations

From the Department of Medicine, McMaster University, Hamilton, Ontario, Canada; and Thrombosis and Atherosclerosis Research Institute, Hamilton, Ontario, Canada.

### Disclosures

None.

## REFERENCES

- Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost.* 2020;18:844–847. doi: 10.1111/jth.14768
- Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. *J Thromb Haemost.* 2020;18:1421–1424. doi: 10.1111/jth.14830
- Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers D, Kant KM, Kaptein FHJ, van Paassen J, Stals MAM, Huisman MV, et al. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: an updated analysis. *Thromb Res.* 2020;191:148–150. doi: 10.1016/j.thromres.2020.04.041
- Middeldorp S, Coppens M, van Haaps TF, Foppen M, Vlaar AP, Muller MCA, Bouman CCS, Beenen LFM, Kootte RS, Heijmans J, et al. Incidence of venous thromboembolism in hospitalized patients with covid-19 [published online May 5, 2020]. *J Thromb Haemost.* doi: 10.1111/jth.14888
- Poissy J, Goutay J, Caplan M, Parmentier E, Duburcq T, Lassalle F, Jeanpierre E, Rauch A, Labreuche J, Susen S; Lille ICU Haemostasis COVID-19 Group. Pulmonary embolism in patients with COVID-19: awareness of an increased prevalence. *Circulation.* 2020;142:184–186. doi: 10.1161/CIRCULATIONAHA.120.047430
- Litjens JF, Leclerc M, Chochois C, Monsallier JM, Ramakers M, Auvray M, Merouani K. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. *J Thromb Haemost.* 2020;18:1743–1746. doi: 10.1111/jth.14869
- Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet.* 2020;395:507–513. doi: 10.1016/S0140-6736(20)30211-7
- Nahum J, Morichau-Beauchant T, Daviaud F, Echegut P, Fichet J, Maillet JM, Thierry S. Venous thrombosis among critically ill patients with coronavirus disease 2019 (COVID-19). *JAMA Netw Open.* 2020;3:e2010478. doi: 10.1001/jamanetworkopen.2020.10478
- Fox SE, Akmatbekov A, Harbert JL, Li G, Quincy Brown J, Vander Heide RS. Pulmonary and cardiac pathology in African American patients with COVID-19: an autopsy series from New Orleans. *Lancet Respir Med.* 2020;8:681–686. doi: 10.1016/S2213-2600(20)30243-5
- Barnes GD, Burnett A, Allen A, Blumenstein M, Clark NP, Cuker A, Dager WE, Deitelzweig SB, Ellsworth S, Garcia D, et al. Thromboembolism and anticoagulant therapy during the COVID-19 pandemic: interim clinical guidance from the anticoagulation forum. *J Thromb Thrombolysis.* 2020;50:72–81. doi: 10.1007/s11239-020-02138-z
- Bikdeli B, Madhavan MV, Jimenez D, Chuich T, Dreyfus I, Driggin E, Nigoghossian C, Ageno W, Madjid M, Guo Y, et al; Global COVID-19 Thrombosis Collaborative Group, Endorsed by the ISTH, NATF, ESVM, and the IUA, Supported by the ESC Working Group on Pulmonary Circulation and Right Ventricular Function. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up:

- JACC state-of-the-art review. *J Am Coll Cardiol*. 2020;75:2950–2973. doi: 10.1016/j.jacc.2020.04.031
12. Marietta M, Ageno W, Artoni A, De Candia E, Gresele P, Marchetti M, Marcucci R, Tripodi A. COVID-19 and haemostasis: a position paper from Italian Society on Thrombosis and Haemostasis (SISET). *Blood Transfus*. 2020;18:167–169. doi: 10.2450/2020.0083-20
  13. Artifoni M, Danic G, Gautier G, Gicquel P, Boutoille D, Raffi F, Néel A, Lecomte R. Systematic assessment of venous thromboembolism in COVID-19 patients receiving thromboprophylaxis: incidence and role of D-dimer as predictive factors. *J Thromb Thrombolysis*. 2020;50:211–216. doi: 10.1007/s11239-020-02146-z
  14. Barrett CD, Moore HB, Yaffe MB, Moore EE. ISTH interim guidance on recognition and management of coagulopathy in covid-19: a comment [published online April 17, 2020]. *J Thromb Haemost*. doi: 10.1111/jth.14860
  15. Cattaneo M, Bertinato EM, Birocchi S, Brizio C, Malavolta D, Manzoni M, Muscarella G, Orlandi M. Pulmonary embolism or pulmonary thrombosis in covid-19? Is the recommendation to use high-dose heparin for thromboprophylaxis justified [published online April 29, 2020]? *Thromb Haemost*. doi: 10.1055/s-0040-1712097
  16. Mackman N, Antoniak S, Wolberg AS, Kasthuri R, Key NS. Coagulation abnormalities and thrombosis in patients infected with SARS-CoV-2 and other pandemic viruses. *Arterioscler Thromb Vasc Biol*. 2020;40:2033–2044. doi: 10.1161/ATVBAHA.120.314514
  17. Schünemann HJ, Cushman M, Burnett AE, Kahn SR, Beyer-Westendorf J, Spencer FA, Rezende SM, Zakai NA, Bauer KA, Dentali F, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and nonhospitalized medical patients. *Blood Adv*. 2018;2:3198–3225. doi: 10.1182/bloodadvances.2018022954
  18. New Zealand Intensive Care Society Clinical Trials Group; Cook D, Meade M, Guyatt G, Walter S, Heels-Ansdell D, Warkentin TE, Zytaruk N, Crowther M, Geerts W, Cooper DJ, et al. Dalteparin versus unfractionated heparin in critically ill patients. *N Engl J Med*. 2011;364:1305–1314. doi: 10.1056/NEJMoa1014475
  19. Mei F, Fan J, Yuan J, Liang Z, Wang K, Sun J, Guan W, Huang M, Li Y, Zhang WW. Comparison of venous thromboembolism risks between COVID-19 pneumonia and community-acquired pneumonia patients. *Arterioscler Thromb Vasc Biol*. 2020;40:2332–2337. doi: 10.1161/ATVBAHA.120.314779
  20. White RH, Keenan CR. Effects of race and ethnicity on the incidence of venous thromboembolism. *Thromb Res*. 2009;123(suppl 4):S11–S17. doi: 10.1016/S0049-3848(09)70136-7