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Letter to the Editors-in-Chief

Asymptomatic deep vein thrombosis in critically ill COVID-19 patients despite therapeutic levels of anti-Xa activity

To the Editors-in-Chief:

Patients with severe COVID-19 pneumonia might experience a high cumulative incidence of thrombotic complications [1], due to coagulopathy, excessive inflammation, and vascular endothelial dysfunction [2]. Data regarding the incidence of deep vein thrombosis (DVT) in this patient subset, without clinical signs of venous thromboembolism (VTE), has not been deeply analyzed even though these patients are at higher risk of death [3]. Furthermore, thrombotic complications have been found in up to 31% of patients in the intensive care unit (ICU) despite systematic thromboprophylaxis [4,5]. A recent report has also addressed the incidence of asymptomatic DVT in hospitalized patients with COVID-19 [6], where screening ultrasound examination was performed > 72 h after admission, describing a DVT prevalence as high as 46.1%. Interestingly, 37.1% of patients were only given DVT prophylaxis, and 41.3% of patients received full-dose low-molecular-weight heparin (LMWH) therapy only after DVT ultrasound findings.

Thromboprophylaxis and high prophylactic doses have been the mainstay of treatment for VTE in COVID-19 hospitalized patients. Recommendations are based on the typical non-COVID-19 high VTE risk factors, and additional hypercoagulable state in severe COVID-19 [4,7]. Those rely on clinical suspicion, abrupt laboratory, or hemodynamic changes that are usually late VTE signs or have an emergency onset, not ideal for patients’ prognosis. Nevertheless, in this highly inflammatory novel viral illness, little has been explored of the role of screening ultrasound in patients admitted to the intensive care units (ICU) and the anticoagulation monitoring status by the time DVT is diagnosed.

We decided to (i) describe the clinical and ultrasonographic characteristics of patients critically ill COVID-19 who developed DVT during the stay at the ICU, and (ii) compare the characteristics of those with DVT against those who remained without DVT during the ICU stay. We performed a single-institution clinical and imaging screening to 30 critically ill COVID-19 patients admitted to the ICU, not suspected to have any VTE neither clinically nor calculated by a modified Well’s scale. The Institutional Ethics Committee approved the study, and all patients had informed written consent on admission.

Calf diameter was measured 10 cm below the tibial tuberosity, and patency of the superficial and deep venous system was evaluated with bedside compression ultrasound (C-US) and high-resolution mode B imaging (Sonoscape X5 Digital Color Doppler Ultrasound System equipped with an L741 Frequency Linear probe: 4.0–16.9 MHz). More than 3 cm of difference between calf sizing was considered significant along with the presence of unilateral swelling or pitting edema. The ultrasonographic examination included saphenous veins and its junctions, calf, popliteal, femoral, and iliac veins (assessed by phasicity and augmentation responses). DVT was defined as a non-compressible venous segment with or without echogenic thrombus within the lumen, increased venous diameter, or absence of spectral color Doppler signal. The echocardiographic assessment was performed in all patients found to have DVT with the same ultrasound system but equipped with a 3P-A probe (Frequency 1.0–6.0 Sweep sector: 90°).

All patients had COVID-19 diagnosis since admission and were considered as having high thrombotic risk (Padua score > 4) and received anticoagulation since day 1. Those with lower Padua scores received high-prophylactic doses; otherwise, they received full-dose anticoagulation. The anticoagulation scheme was instaurated either with LMWH (Enoxaparin) or unfractionated heparin according to the glomerular filtration rate. A multidisciplinary consensus was created for careful decision-making in prescribing anticoagulation in high IMPROVE bleeding score patients. Anti-factor-Xa Assay (Stago®) was systematically performed for anticoagulation monitoring and adjustment in obese patients (n = 12) and those with acute renal failure (n = 20) [8]. Platelet activity was also monitored in those found to have DVT despite therapeutic anti-factor-Xa activity, with Multiplate® due to its possible role when interacting with endothelial cells in the development of thrombosis and micro thrombosis in organs and tissues other than lungs [9].

Among the 30 evaluated patients, 30% developed asymptomatic DVT (Table 1). Patients in both groups had a high prevalence of the risk factors associated with severe SARS-CoV-2 pneumonia (age above 50 years old, male sex, hypertension, diabetes, obesity). None of them had previous chronic obstructive pulmonary disease or asthma. Few patients had previous cardiovascular disease: chronic heart failure (n = 2), acute myocardial infarction (n = 1), and cardiac surgery (n = 2). None of the patients had myocarditis, and only one had a previous VTE (non-DVT group). There were no differences in smoking between groups (33% vs. 48%, p = 0.691). All patients had mechanical ventilatory support.

Few patients in both groups had clinical signs of chronic venous

Abbreviations: VTE, Venous thromboembolism; DVT, Deep vein thrombosis; LMWH, Low molecular weight heparin; UFH, Unfractionated heparin; ICU, Intensive care unit; DD, D-Dimer; HS-CRP, High sensitivity C-Reactive protein; LDH, Lactate Dehydrogenase; PT, prothrombin time; aPTT, activated partial thromboplastin time; ASA, Acetylsalicylic acid; ADP, adenine diphosphate
DVT patients had increased platelet function and were additionally function using a commercially available aggregometry test [10]. Two parin IV infusion (Table 2). All DVT patients were tested for platelet patient with chronic renal failure on a continuous unfractioned he-pagulation warrant further study.

CRP = C reactive protein; PT = prothrombin time; aPTT = activated partial Thrombosis Research 196 (2020) 268–271

Table 1

| Variable                        | Deep vein thrombosis | p               |
|---------------------------------|-----------------------|-----------------|
|                                 | Yes (N = 9)           | No (N = 21)     |
| Age (years)                     | 64 (39–79)            | 61 (33–74)      | 0.454 |
| Male sex                        | 8 (69%)               | 15 (71%)        | 0.297 |
| Diabetes mellitus               | 2 (22%)               | 11 (52%)        | 0.393 |
| Hypertension                    | 5 (56%)               | 6 (29%)         | 0.229 |
| Body mass index (Kg/m²)         | 30.0 (23.5–43.0)      | 27.0            | 0.141 |
| Obesity (class I or higher)     | 6 (66%)               | 6 (29%)         | 0.224 |
| Previous heart disease          | 1 (11%)               | 4 (20%)         | 0.634 |
| High sensitivity CRP (mg/L)     | 342 (264–463)         | 307 (73–521)    | 0.428 |
| D-Dimer on admission (μg/mL)    | 0.80 (0.24–15.2)      | 0.46            | 0.021 |
| D-Dimer max value (μg/mL)       | 6.30 (0.17–9.6)       | < 0.001         |
| D-Dimer duplication             | 6 (67%)               | 11 (52%)        | 0.691 |
| D-Dimer value > 1440 μg/mL      | 8 (89%)               | 6 (29%)         | 0.004 |
| Thrombocytopenia (< 150 × 10³/μL) | 3 (14%)             | 1 (11%)        | 1.000 |
| Lymphopenia (< 990 cell/μL)     | 9 (100%)              | 21(100%)        | –     |
| Elevated fibrinogen (> 5.13 g/L) | 9 (100%)            | 14(66%)        | 0.710 |
| PT (s)                          | 12.0 (10.0–14.7)      | 12.0            | 0.818 |
| aPTT (s)                        | 30.7 (26.0–40.0)      | 33.0            | 0.174 |
| Lactic dehydrogenase (mg/dL)    | 443 (269–685)         | 357 (251–900)   | 0.230 |
| Ferritin (ng/mL)                | 920 (377–1481)        | 1172            | 0.308 |
| LMWH (enoxaparin)               | 8 (89%)               | 18 (86%)        | 1.000 |
| Full dose anticoagulation       | 9 (100%)              | 8 (86%)         | 0.534 |
| Antiviral treatment             | 8 (89%)               | 19 (91%)        | 1.000 |

CRP = C reactive protein; PT = prothrombin time; aPTT = activated partial thromboplastin time; LMWH = Low molecular weight heparin.
Table 2
Relevant findings and treatment of patients with DVT.

| Patient | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---------|---|---|---|---|---|---|---|---|---|
| Affected limb | R | Bi | L | R | R | Bi | Bi | Bi | Bi |
| Laboratory | | | | | | | | | |
| DD (0.0–0.24 μg/mL) | 0.9 | 0.5 | 15.2 | 0.5 | 0.8 | 13.4 | 6.3 | 0.2 | 0.7 |
| DD abrupt increase (μg/mL) | 1.8 | 6.7 | b | 3.2 | 5.6 | 13.4 | 6.3 | 1.0 | 13.3 |
| PT (12.8–15.4 s) | 12.6 | 12.9 | b | 12.1 | 14.6 | 13.4 | 14.7 | 13.5 | 15.0 |
| aPTT (25.8–40.4 s) | 34.7 | 30.5 | b | 36.2 | 35.7 | 27.4 | 27.7 | 25.0 | 37.6 |
| Fibrinogen (1.9–5.3 g/L) | 6.5 | 6.5 | b | 7.8 | 6.3 | 6.1 | 6.6 | 7.3 | 10.4 |
| Fibrinolysis | 658 | 998 | 1125 | 377 | 1218 | 666 | 920 | 548 | 1481 |
| Lymphocytes (cel/μL) | 800 | 400 | 100 | 300 | 900 | 600 | 800 | 600 | 300 |
| Thrombocytes (x10³/μL) | 339 | 382 | 233 | 211 | 280 | 112 | 344 | 274 | 336 |

Anticoagulation

| Patient | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---------|---|---|---|---|---|---|---|---|---|
| Heparin | | | | | | | | | |
| Dose | 80 mg BID | 80 mg BID | 80 mg BID | 80 mg BID | 80 mg BID | 80 mg BID | 80 mg BID | 80 mg BID | 1800 U/h/2000 U/h |
| Anti-Xa assay (U/mL) | 0.61 | 0.4/0.8 b | 0.51 | 0.42 | 0.98 | 0.83 | 0.54 | 0.26/0.4 f | |
| Platelet function | | | | | | | | | |
| ADP test (127–224 U) | 165 | 237 | b | 83³ | 120 | 107 | 89 | 196 | 28 |
| ASPI test (129–224 U) | 222 | 232 | b | 48³ | 154 | 64 | 75 | 171 | 21 |
| Additional ASA | No | Yes | No | Yes | No | No | No | No | No |

R = right; L = left; Bi = bilateral; En = Enoxaparin; ASA = Acetylsalicylic acid; DVT/PE = Deep-vein thrombosis/Pulmonary Embolism; RV = Right ventricle; DD = D-Dimer; HSCRP = High-sensitivity C reactive protein; LDH = Lactate dehydrogenase; PT = Prothrombin time; aPTT = activated partial thromboplastin time; UFH = Unfractionated heparin; ADP = Adenosine diphosphate.

References

[1] S. Lax, K. Skok, P. Zechnor, H. Kessler, N. Kaufmann, C. Koelblinger, et al., Pulmonary arterial thrombosis in COVID-19 with fatal outcome: results from a prospective, single-center, clinicopathologic case series, Ann. Intern. Med. (2020), https://doi.org/10.7326/M20-2566.

[2] F. Zhou, T. Yu, R. Du, G. Fan, Y. Liu, Z. Liu, et al., Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study, Lancet 395 (2020) 1054–1062, https://doi.org/10.1016/S0140-6736(20)30566-3.

[3] C. Zhang, Z. Zhang, J. Mi, X. Wang, Y. Zou, X. Chen, et al., The cumulative venous thromboembolism incidence and risk factors in intensive care patients receiving the guideline-recommended thromboprophylaxis, Medicine 98 (23) (2019) e15833, https://doi.org/10.1097/MD.0000000000015833.

[4] P. Ekel, M. Krupi, N. van der Meer, M. Arbous, D. Gommers, K. Kant, et al., Incidence of thrombotic complications in critically ill ICU patients with COVID-19, Thromb. Res. (2020), https://doi.org/10.1016/j.thromres.2020.04.013.

[5] F. Ekel, M. Krupi, N. van der Meer, M. Arbous, D. Gommers, K. Kant, 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), https://doi.org/10.1016/j.thromres.2020.04.013.

[6] L. Zhang, X. Feng, D. Zhang, C. Jiang, C. Mei, J. Wang, et al., Deep vein thrombosis in hospitalized patients with coronavirus disease 2019 (COVID-19) in Wuhan, China: prevalence, risk factors, and outcome, Circulation (2020), https://doi.org/10.1161/CIRCULATIONAHA.120.046702.

[7] F. Violi, D. Pastori, R. Cangemi, P. Pignatelli, L. Loffredo, Hypercoagulability and antithrombotic treatment in coronavirus 2019: a new challenge, Thromb. Haemost. 120 (06) (2020) 949–956, https://doi.org/10.1055/s-0040-1710317.

[8] C. Penazzi, A. Prataz, M. Scherfer, Utility of anti-factor Xa monitoring in surgical patients receiving prophylactic doses of enoxaparin for venous thromboembolism prophylaxis, Am. J. Surg. 213 (6) (2017) 1143–1152, https://doi.org/10.1016/j.amjsurg.2016.08.010.

[9] F. Salamanna, M. Maglio, M. Landini, M. Fini, Platelet functions and activities as potential hematologic parameters related to coronavirus disease 2019 (COVID-19), Platelets 31 (5) (2020) 627–632, https://doi.org/10.1080/09537104.2020.1762852.

[10] S. Pedersen, E. Grove, H. Nielsen, J. Mortensen, S. Kristensen, A. Hvas, Evaluation of aspirin response by Multiplate® whole blood aggregometry and light transmission aggregometry, Platelets 20 (6) (2009) 415–420, https://doi.org/10.1080/0953710090310642.

[11] D. Wichmann, J. Sperhake, M. Lütghehmann, S. Steurer, C. Edler, A. Heinemann, et al., Autopsy findings and venous thromboembolism in patients with COVID-19, Ann. Intern. Med. (2020), https://doi.org/10.7326/M20-2003.

[12] M. Gheblawi, K. Wang, A. Viverio, Q. Nguyen, J. Zhong, A. Turner, et al., Angiotensin-converting enzyme 2: SARS-CoV-2 receptor and regulator of the renin-angiotensin system, Circ. Res. 126 (10) (2020) 1456–1474, https://doi.org/10.1161/CIRCRESAHA.120.317015.

[13] S. Ahmed, P. Anirvan, Targeting the immunology of coronavirus disease-19: synchronisation creates symphony, Rheumatol. Int. 40 (8) (2020) 1343–1345, https://doi.org/10.1007/s00296-020-04624-2.

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