Strength of Anticoagulation in Moderate to Severe COVID-19 Illness: In Medio Stat Virtus?

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One aspect of COVID-19 (coronavirus disease 2019) that has now been clarified, is that patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection manifest an extremely heterogeneous and variegated array of coagulopathies, ranging from asymptomatic and apparently innocent elevation of thrombosis biomarkers (namely fibrin/fibrinogen degradation products and/or D-dimer), up to a catastrophic syndrome characterized by disseminated intravascular coagulation, affecting several tissues and organs,[1] which may even persist for extended periods after hospital discharge.[2]

Among the various thrombotic events characterizing SARS-CoV-2 infection, especially appearing in patients with severe and/or critical disease who need prolonged and intensive care, venous thromboembolism (VTE) seems to play the lion's share. Several critical literature reviews and meta-analyses have in fact concluded that the burden of VTE is considerably high in such patients, approximating 13% (nearly 8% in non-critical disease, but increasing to around 25% in patients in the intensive care unit [ICU]), and with a frequency of pulmonary embolism (PE) and proximal deep vein thrombosis as high as 8 to 9% in patients hospitalized for COVID-19.[3,4] In a Swedish nationwide study, reporting the overall frequency of episodes of venous thrombosis and bleeding in patients with COVID-19, most thrombotic events were recorded between a few days from diagnosis up to 2 months thereafter.[5] It is also noteworthy that the development of any type of thrombosis seems to be associated with considerably high risk of unfavorable outcome, as emphasized by the meta-analysis of Xiao et al,[6] who concluded that COVID-19-related critical illness and mortality were up to threefold higher in COVID-19 patients diagnosed with thrombotic events.

In this alarming scenario, the use of anticoagulants (and/or antiplatelet agents) is now advocated for clinical management of patients with severe or critical COVID-19 illness, especially those with prolonged hospitalization or in the ICU, and largely favoring heparin, for its pleiotropic antiviral potential beyond the anticoagulant and anti-inflammatory properties,[7] an activity that has recently been demonstrated also for other anti-activated factor X oral anticoagulants, namely apixaban.[8] Irrespective of this solid position, there remains open discussion on the intensity of anticoagulation in patients presenting with COVID-19-related severe illness and without VTE, wherein some guidelines and/or expert opinions recommend therapeutic intensity over prophylactic-intensity anticoagulation and vice versa. With the awareness that a unique "truth" does not exist in medicine, and with COVID-19 representing perhaps the most paradigmatic example of a kaleidoscope of symptomology, we offer in this issue of the journal some space for commentaries representing some viewpoints on the use of therapeutic-intensity anticoagulation in patients with moderate or severe SARS-CoV-2 infection.[9–11]

Several definitions have been provided for the concept of "precision medicine," also often referred to as "personalized medicine." One of the most popular is indeed that endorsed by the U.S. Food and Drug Administration (FDA), according to which "precision medicine is an innovative approach to tailoring disease prevention and treatment that takes into account differences in people's genes, environments, and lifestyles."[12] This definition perfectly suits the many and variegated aspects of COVID-19, from pathogenesis to

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therapeutic management, as each single patient seems to be affected by his/her own personal disease.[13] As far as the onset of thrombotic episodes during SARS-CoV-2 infection is concerned, either localized or systemic, several lines of evidence now attest that such risk is considerably spotted and multifaceted.[14] A recent meta-analysis of 21 studies, totaling 5,296 patients, reported a significantly increased risk of VTE in patients with elevation of some well-known laboratory biomarkers such as D-dimer, troponin, and C-reactive protein (CRP), as well as with overall length of hospitalization, intubation, and inotropic drugs requirement, while no substantial associations were found with other conventional risk factors such as personal history of thrombosis, cancer, and overweight.[15] These results could be confirmed in another study, which concluded that the risk of PE was nearly 60% higher in males, nearly fourfold higher in patients needing mechanical ventilation, and threefold higher in those admitted to the ICU.[16] The superior role of D-dimer in predicting the risk of developing venous thrombosis in patients with SARS-CoV-2 infection has been confirmed in many other published studies,[17,18] and is now also endorsed by the European Society of Cardiology.[19]

Importantly, unlike assessing the risk of VTE in the general population, the use of conventional predictive scores (e.g., Geneva, Wells, CHADS2/CHA2DS2VASc/M-CHA2DS2VASc and CHOD among others) does not yield satisfactory predictive performance in patients with COVID-19, as clearly highlighted in the systematic literature review published by Rindi et al,[20] thus underpinning the need to develop specific risk assessment models in COVID-19. Additional factors that may also enhance the risk of developing venous thrombosis in patients with SARS-CoV-2 infection are pre-existing pulmonary disorders,[21] obesity,[22] and, last but not least, prothrombotic mutations.[23] Obesity, D-dimer, blood lactate, CRP, and neutrophil count were also found to be independent predictors of venous thrombosis in an analysis of the COVID-19 Brazilian Registry.[24] The evidence that genetic predisposition may influence the clinical outcome of COVID-19 goes hand in hand with the results of a large genome-wide association study, which identified as many as 27 genes potentially associated with SARS-CoV-2-related hospitalization, many of which were related to coagulation pathways or inflammation and, most notably, associated with coagulation factor VIII and clinical phenotypes of VTE.[25] Interestingly, another preprint cross-trait analysis published by Huang et al found that VTE shared as many as eight and eleven genetic loci with severe SARS-CoV-2 infection and hospitalization for COVID-19, including genes participating to blood coagulation (e.g., *ADAMTS-13* [a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13] and *FV*).[26]

The evidence emerged so far would hence persuade us that, perhaps, the most reasonable approach is not a matter of whether therapeutic-intensity anticoagulation may be "good" or "bad," "safe," or "dangerous," in patients with severe COVID-19 illness, but rather whether the correct answer to the original question could be… "depends." Straightforwardly applying here the concept of precision medicine, one would need to estimate the individual risk of developing venous thrombosis (i.e., as from elements summarized in ►**Table 1**),[27,28] that would then be balanced against the risk of bleeding.

Table 1 Major factors influencing the decision on anticoagulation intensity in patients with coronavirus disease 2019 (COVID-19)

● Genetic predisposition (especially referring to pro-thrombotic mutations)
● Acquired pro-thrombotic risk factors
● Pre-existing pulmonary disease
● Demographical characteristics, especially:
◦ Older age
◦ Male sex
◦ Overweight/Obesity
● COVID-19 severity, including:
◦ Prolonged hospital stay
◦ Prolonged immobilization
◦ Mechanical ventilation
◦ ICU admission
● Enhanced values of (pro)thrombotic and (pro)inflammatory biomarkers, especially:
◦ D-dimer
◦ Ferritin/C reactive protein
◦ Neutrophils
◦ Lactate dehydrogenase
◦ Procalcitonin/Presepsin

This approach found reliable basis on the evidence that not only the incidence of venous thrombosis is higher in patients with SARS-CoV-2-related acute respiratory distress syndrome (ARDS) compared with those with ARDS caused by bacterial pneumonia, but the risk factor for thrombosis is also substantially different between these two populations.[29] It is also noteworthy that a recent study found that a predictive score called "TiC" (Thrombo inCode) encompassing several phenotypic ($n = 5$: sex, age, obesity, smoking, and diabetes) and genetic ($n = 16$) variables displayed accuracy (area under the curve [AUC]), sensitivity, and specificity as high as 0.78, 0.69, and 0.77 for predicting the risk of VTE in patients receiving thromboprophylaxis.[30] Similarly, Lee et al also evidenced that a multivariable model including both clinical and laboratory parameters (i.e., blood pressure, creatinine, electrolytes, hepatic enzymes and inflammatory biomarkers) predicted in-hospital VTE in COVID-19 patients with 0.83 AUC, 0.68 sensitivity, and 0.82 specificity, respectively.[31] Even the use of protocols including anticoagulant escalation based on D-dimer values enables to reduce the risk of death compared with standard thromboprophylaxis,[32] thus reinforcing the concept that a "personalized" treatment may be perhaps better than recommending a "standard" anticoagulant strategy.

Indeed, few doubts remain that the benefits of therapeutic anticoagulation will offset the risks in a male overweight patient with SARS-CoV-2 infection, inherited thrombophilia, and pre-chronic obstructive pulmonary disease, who has been hospitalized for a protracted period and whose values of laboratory biomarkers of thrombosis and inflammation are considerably enhanced. Nonetheless, this same conclusion would not probably apply to a relatively young patient hospitalized "with" COVID-19 and "for" gastric ulcer, who only displays one or two risk factors (as per those listed in ►**Table 1**, e.g., male sex and overweight). Although a precise estimation of his personal risk is obviously non-feasible, one could empirically conclude (according to the so-called "Gestalt," intuition-based medical reasoning, which is frequently better than any scores or diagnostic tests),[33] that prophylactic-intensity anticoagulation may be safer in this case. There is no discussion, instead, that routine primary thromboprophylaxis in symptomatic COVID-19 outpatients would not be clinically effective, and should hence be currently discouraged.[34,35]

To close off this discussion, we should also point out the possibility for confusion in regards to the characterization of COVID-19 severity. In particular, the term "COVID-19-associated acute illness," which may alternatively be called "hospitalized non-critically ill," or as used in one Commentary in this issue as "COVID-19-associated moderate illness,"[11] has the potential to be confused with "COVID-19-associated severe illness" or "COVID-19-associated critical illness."[10] The former grouping (acute illness, non-critical illness, and moderate illness) comprises individuals "with clinical features that would typically result in admission to a medicine inpatient ward without requirement for intensive clinical support. Examples include patients with dyspnea or mild to moderate hypoxia."[36] Another definition of acutely ill COVID-19 patients is provided in an earlier guideline, as "Patients with COVID-19 who require hospital admission without advanced clinical support (i.e., not to the ICU/CCU), but could include treatment in other settings if the hospital was over capacity," with hospital capacity and admission criteria potentially varying according to the specific setting.[37] In contrast, the latter group (severe illness and critical illness) comprises "Patients with COVID-19 who develop respiratory or cardiovascular failure normally requiring advanced clinical support in the ICU or CCU, but could include admission to another department if the ICU/CCU was over capacity,"[37] with ICU/CCU capacity and admission criteria potentially varying according to the specific setting.

Conflict of Interest
None declared.

References

1 Lippi G, Sanchis-Gomar F, Favaloro EJ, Lavie CJ, Henry BM. Coronavirus disease 2019-associated coagulopathy. Mayo Clin Proc 2021;96(01):203–217
2 Fazio S, Tufano A, de Simone G. Sustained high D-dimer in outpatients who have recovered from mild to moderate coronavirus disease 2019 (COVID-19). Semin Thromb Hemost 2022;48(01):115–117
3 Di Minno A, Ambrosino P, Calcaterra I, Di Minno MND. COVID-19 and venous thromboembolism: a meta-analysis of literature studies. Semin Thromb Hemost 2020;46(07):763–771
4 Mansory EM, Srigunapalan S, Lazo-Langner A. Venous thromboembolism in hospitalized critical and noncritical COVID-19 patients: a systematic review and meta-analysis. TH Open 2021;5(03):e286–e294
5 Katsoularis I, Fonseca-Rodríguez O, Farrington P, et al. Risks of deep vein thrombosis, pulmonary embolism, and bleeding after COVID-19: nationwide self-controlled cases series and matched cohort study. BMJ 2022;377:e069590
6 Xiao D, Tang F, Chen L, Gao H, Li X. Cumulative evidence for the association of thrombosis and the prognosis of COVID-19: systematic review and meta-analysis. Front Cardiovasc Med 2022;8:819318
7 Lippi G, Henry BM, Favaloro EJ. The benefits of heparin use in COVID-19: pleiotropic antiviral activity beyond anticoagulant and anti-inflammatory properties. Semin Thromb Hemost 2023;49(01):73–75
8 Chaves OA, Sacramento CQ, Fintelman-Rodrigues N, et al. Apixaban, an orally available anticoagulant, inhibits SARS-CoV-2 replication and its major protease in a non-competitive way. J Mol Cell Biol 2022;14(06):mjac039
9 Rizk JG, Gupta A, Lazo JG Jr, et al. To anticoagulate or not to anticoagulate in COVID-19: lessons after 2 years. Semin Thromb Hemost 2023;49(01):62–72
10 Rizk JG, Lavie CJ, Henry BM. Against therapeutic anticoagulation in critically ill COVID-19 patients. Semin Thromb Hemost 2023;49(01):79–80
11 Cuker A. The case for therapeutic-intensity anticoagulation in patients with covid-19-associated moderate illness. Semin Thromb Hemost 2023;49(01):76–78
12 Food and Drug Administration. Precision Medicine. Accessed, July 4, 2022 at: https://www.fda.gov/medical-devices/in-vitro-diagnostics/precision-medicine
13 Lippi G, Sanchis-Gomar F, Henry BM. COVID-19: unravelling the clinical progression of nature's virtually perfect biological weapon. Ann Transl Med 2020;8(11):693
14 Lippi G, Favaloro EJ. What we know (and do not know) regarding the pathogenesis of pulmonary thrombosis in COVID-19. Semin Thromb Hemost 2023;49(01):27–33
15 Lobbes H, Mainbourg S, Mai V, Douplat M, Provencher S, Lega JC. Risk factors for venous thromboembolism in severe COVID-19: a study-level meta-analysis of 21 studies. Int J Environ Res Public Health 2021;18(24):12944
16 Gómez CA, Sun CK, Tsai IT, et al. Mortality and risk factors associated with pulmonary embolism in coronavirus disease 2019 patients: a systematic review and meta-analysis. Sci Rep 2021;11(01):16025
17 Riyahi S, Hectors SJ, Prince MR, et al. Predictors of acute deep venous thrombosis in patients hospitalized for COVID-19. Medicine (Baltimore) 2021;100(38):e27216
18 García de Guadiana-Romualdo L, Morell-García D, Favaloro EJ, et al. Harmonized D-dimer levels upon admission for prognosis of COVID-19 severity: results from a Spanish multicenter registry (BIOCOVID-Spain study). J Thromb Thrombolysis 2022;53(01):103–112
19 Baigent C, Windecker S, Andreini D, et al; Task Force for the management of COVID-19 of the European Society of Cardiology. European Society of Cardiology guidance for the diagnosis and management of cardiovascular disease during the COVID-19 pandemic: part 1-epidemiology, pathophysiology, and diagnosis. Cardiovasc Res 2022;118(06):1385–1412
20 Rindi LV, Al Moghazi S, Donno DR, Cataldo MA, Petrosillo N. Predictive scores for the diagnosis of pulmonary embolism in COVID-19: a systematic review. Int J Infect Dis 2022;115:93–100
21 Elmokadem AH, Bayoumi D, El-Morsy A, Ehab A, Abo-Hedibah SA. Relationship of the pulmonary disease severity scoring with thromboembolic complications in COVID-19. Emerg Radiol 2022;29(01):9–21

22 Wang SY, Singh A, Eder MD, et al. Association of obesity with venous thromboembolism and myocardial injury in COVID-19. Obes Res Clin Pract 2021;15(05):512–514
23 Stevens H, Canovas R, Tran H, Peter K, McFadyen JD. Inherited thrombophilias are associated with a higher risk of COVID-19-associated venous thromboembolism: a prospective population-based cohort study. Circulation 2022;145(12):940–942
24 da Silveira WC, Ramos LEF, Silva RT, et al. Predictors of venous thromboembolism in COVID-19 patients: results of the COVID-19 Brazilian Registry. Intern Emerg Med 2022;17(07):1863–1867
25 Pathak GA, Singh K, Miller-Fleming TW, et al. Integrative genomic analyses identify susceptibility genes underlying COVID-19 hospitalization. Nat Commun 2021;12(01):4569
26 Huang X, Yao M, Tian P, et al. Shared genetic etiology and causality between COVID-19 and venous thromboembolism: evidence from genome-wide cross trait analysis and bi-directional Mendelian randomization study. medRxiv 2022 Jun 1: 2022.05.21.22275413. Doi: 10.1101/2022.05.21.22275413
27 Henry BM, de Oliveira MHS, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. Clin Chem Lab Med 2020;58 (07):1021–1028
28 Agarwal G, Hajra A, Chakraborty S, et al. Predictors and mortality risk of venous thromboembolism in patients with COVID-19: systematic review and meta-analysis of observational studies. Ther Adv Cardiovasc Dis 2022;16:17539447221105013
29 Cui N, Jiang C, Yang C, Zhang L, Feng X. Comparison of deep vein thrombosis risks in acute respiratory distress syndrome caused by COVID-19 and bacterial pneumonia: a retrospective cohort study. Thromb J 2022;20(01):27
30 Soria JM, Mojal S, Martinez-Perez A, et al. A validated clinical-genetic score for assessing the risk of thrombosis in patients with COVID-19 receiving thromboprophylaxis. Haematologica 2022;107(09):2244–2248
31 Lee Y, Jehangir Q, Li P, et al. Venous thromboembolism in COVID-19 patients and prediction model: a multicenter cohort study. BMC Infect Dis 2022;22(01):462
32 Tassiopoulos AK, Mofakham S, Rubano JA, et al. D-dimer-driven anticoagulation reduces mortality in intubated COVID-19 patients: a cohort study with a propensity-matched analysis. Front Med (Lausanne) 2021;8:631335
33 Cervellin G, Borghi L, Lippi G. Do clinicians decide relying primarily on Bayesians principles or on Gestalt perception? Some pearls and pitfalls of Gestalt perception in medicine. Intern Emerg Med 2014;9(05):513–519
34 Barco S, Voci D, Held U, et al; OVID investigators. Enoxaparin for primary thromboprophylaxis in symptomatic outpatients with COVID-19 (OVID): a randomised, open-label, parallel-group, multicentre, phase 3 trial. Lancet Haematol 2022 (e-pub ahead of print). Doi: 10.1016/S2352-3026(22)00175-2
35 Cools F, Virdone S, Sawhney J, et al; ETHIC investigators. Thromboprophylactic low-molecular-weight heparin versus standard of care in unvaccinated, at-risk outpatients with COVID-19 (ETHIC): an open-label, multicentre, randomised, controlled, phase 3b trial. Lancet Haematol 2022 (e-pub ahead of print). Doi: 10.1016/S2352-3026(22)00173-9
36 Cuker A, Tseng EK, Nieuwlaat R, et al. American Society of Hematology living guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19: January 2022 update on the use of therapeutic-intensity anticoagulation in acutely ill patients. Blood Adv 2022;6(17):4915–4923
37 Cuker A, Tseng EK, Nieuwlaat R, et al. American Society of Hematology 2021 guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19. Blood Adv 2021; 5(03):872–888