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EDITORIAL

COVID-19 and venous thromboembolism: current insights and prophylactic strategies

In December 2019, the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) appeared in Wuhan, China [1]. Despite the attempts to minimise exportation, SARS-CoV-2 showed an international spread, thus becoming a public health emergency [2]. As a consequence, in March 2020, the World Health Organisation (WHO) declared the novel coronavirus outbreak pandemic [3].

The rapidly increasing number of studies on SARS-CoV-2 infection indicate that this viral agent can cause the coronavirus disease 2019 (COVID-19) [4,5], a syndrome with a wide spectrum of clinical presentations, ranging from a mild disease with flu-like symptoms to a life-threatening condition that requires specialised management at Intensive Care Units (ICU) [6–8].

Among COVID-19 patients, it is reasonable to assume that those with a very severe disease could exhibit a high risk of venous thromboembolism (VTE) [9]. Critical patients with COVID-19 are bedridden in ICU because of an acute infective disease determining respiratory failure, thus resulting in a Padua prediction score [10] not inferior to 5. In keeping with this, it should be considered that obesity and an older age, which may further increase the VTE risk and the final Padua score, are potential risk factors for severe COVID-19 [5]. The Padua score was specifically designed to assess the indication to antithrombotic prophylaxis and, according to the American College of Chest Physicians (ACCP) guidelines, a score $\geq$4 represents a sufficient indication for thromboprophylaxis in adult non-pregnant patients without major contraindications [11].

Until now, only a few number of studies explored the role of thromboprophylaxis among patients with SARS-CoV-2 infection. Similarly, limited data are currently available about the prevalence of VTE in this clinical setting.

Among 81 Chinese patients with severe COVID-19 and no anti-thrombotic prophylaxis, a 25% prevalence of lower extremity venous thrombosis and $a \approx 10\%$ VTE-related death were reported [12]. In 2 studies [13,14] reporting on the same population of 449 severe COVID-19 patients admitted to Tongji Hospital in Wuhan, the use of heparin at prophylactic doses was reported by only 22% of patients, with similar mortality rates when comparing heparin users and non-users (30.3% *vs.* 29.7%). Of interest, when specifically considering patients with high D-dimer levels and those with a Sepsis-Induced Coagulopathy (SIC) score $\geq$4, significantly lower mortality in heparin users than in non-users was documented (32.8% *vs.* 52.4%, and 40.0% *vs.* 64.2%, respectively). In another study [15], among 107 COVID-19 patients, a high frequency (20.6%) of pulmonary embolism despite thromboprophylaxis was reported during ICU stay. The authors hypothesised that the high prevalence of obesity in their study population could significantly contribute to the hypercoagulable state of their patients. Similarly, the cumulative incidence of VTE among 184 ICU patients with proven COVID-19 pneumonia was 27% in 3 Dutch hospitals, despite all subjects had received thromboprophylaxis with nadroparin during hospital stay [16]. Therefore, the authors concluded that high prophylactic doses should be used in severe COVID-19, even in the absence of randomised evidence. Caution is recommended by Wang et al. [17], retrospectively analysing the data of 1,099 patients with laboratory confirmed COVID-19 from 31 Chinese regions. The authors reported a consistent mismatch between the percentage of patients at high risk of VTE (Padua score $\geq$4) and the prescription rate of antithrombotic prophylaxis. Although recognising that thromboprophylaxis was underprescribed in their study population, they also highlighted that 11% of the 407 patients at increased thrombotic risk had a concomitant high bleeding risk, thus suggesting the need of alternative VTE prevention strategies for these patients, such as elastic compression stockings or intermittent pneumatic compression.

If there is no doubt that severe COVID-19 patients are at increased VTE risk (Padua score always $\geq$4), it should be considered that a non-negligible bleeding risk is also present in these patients. A number of clinical and physiological conditions may increase the risk of major bleedings [11]. Among them, old age is a risk factor for both thrombosis and bleeding [18], besides being an independent predictor of severity and mortality in SARS-CoV-2 infected subjects [5]. Similarly, literature evidence suggests that COVID-19 patients may develop different degrees of liver dysfunction [19], and the presence of liver disease with deranged liver markers is able to consistently increase the haemorrhagic risk [11]. Another major concern among COVID-19 patients in ICU is the impaired renal function [20], which may reduce heparin excretion and, in turn, increase the bleeding risk [11]. Accordingly, a dose adjustment of heparin may be required when the glomerular filtration rate falls below 30 mL/min per m^2 [21].

Overall, the limited evidence currently available seems to suggest that SARS-CoV-2 infection can rapidly develop

into a severe condition with renal, pulmonary and hepatic complications, potentially increasing both thrombotic and haemorrhagic risk. However, the exact mechanisms behind such haemostatic imbalance among severe COVID-19 patients are still unclear.

A number of previous studies analysed the association of COVID-19 severity with changes in primary and secondary haemostatic parameters, reporting that severe patients exhibit higher prothrombin time (PT) [22,23] and D-dimer values [24,25], with a lower platelet count [5] than subjects with mild disease. Similar results have been reported in non-survivors to COVID-19 as compared to survivors [26,27]. Among 183 in-hospital patients with SARS-CoV-2 infection, Tang et al. documented that 71.4% of non-survivors had an overt disseminated intravascular coagulation (DIC) as compared to only 0.6% of survivors [28]. The development of a consumption coagulopathy among critically ill patients with COVID-19 may justify the observed changes in primary and secondary haemostatic parameters. The pathogenesis of DIC is complex and multifactorial, and the "cytokine storm" described in ICU patients with SARS-CoV-2 infection may play a role in its development [29]. However, the management of DIC is currently based on the treatment of the primary underlying pathology [30]. Anticoagulants have appeared and disappeared in the different guidelines overtime and, at present, their use in patients with DIC remains controversial.

Further large cohort studies are needed to better address the issue of the haemostatic changes associated to SARS-CoV-2 infection. This could allow for a better understanding of the mechanisms behind the hypercoagulable state observed in this clinical setting. Moreover, considering the unknown long-term outcomes among survivors of severe SARS-CoV-2 infection and the risk of functional disability following ARDS [31–36], it is compelling to identify new biomarkers of disease severity in order to timely predict the clinical progression of this condition.

In the meantime, it seems clear that severe SARS-CoV-2 infection results in an increased thrombotic risk, with a non-negligible bleeding risk. As a consequence, regular assessment of the validated scores and of haemostatic parameters might be crucial to increase survival of severe patients. According to current guidelines, the indication for thromboprophylaxis should never be ignored in this (as in other) clinical setting(s). As suggested by the World Health Organisation (WHO) [37] and by the International Society of Thrombosis and Haemostasis (ISTH) [38], prophylactic low molecular weight heparin (LMWH) or subcutaneous unfractionated heparin (UFH) should be used in all hospitalised patients with COVID-19, especially in case of markedly elevated D-dimer or high SIC score. The evidence that heparin has both anti-inflammatory and anti-viral properties, together with the "feeling" that prophylactic doses of heparin may be insufficient to counteract the hypercoagulable state of COVID-19 patients, has spread the belief in the medical community that an "intensive" prophylactic approach should be used. However, there is no enough evidence supporting the use of intermediate or therapeutic doses regimens, which may conversely increase the bleeding risk, particularly in patients with liver and renal impairment.

To date, besides the anecdotic experience of some physicians, the most extensive case series documenting $a \approx 30\%$ rate of thrombosis despite prophylactic anticoagulation reported on the use of nadroparin among severe COVID-19 patients from 3 Dutch ICUs [16]. Nadroparin has a 8–10 h half-life, whereas the plasma half-life of enoxaparin is of approximately 7 h [39]. Of notice, fondaparinux may have a more favourable pharmacokinetics in the presence of such a strong thrombotic stimulus, considering that its elimination half-life is of about 17 h in healthy young subjects and 21 h in elderly individuals [40]. Because of its longer half-life, fondaparinux at a fixed dose of 2.5 mg (1.5 mg in case of severe renal impairment) could be preferred for an adequate anticoagulation coverage.

Thus, considering the high thrombotic risk of severe COVID-19 patients, it seems more reasonable to make a choice based on the different pharmacokinetic profiles of heparins rather than prescribing therapeutic doses regimens in the absence of specific indication. Another approach that could be adopted to optimise the antithrombotic prophylaxis in this clinical setting is the monitoring of anti-activated coagulation factor X (Xa) activity. Despite many limitations, anti-Xa assay remains the only available method to monitor LMWH efficacy [41]. Similarly, a very strict monitoring of activated partial thromboplastin time (aPTT) could be of help when UFH is chosen.

Overall, the current evidence suggests that a patient-tailored strategy with a case-by-case approach is needed when prescribing prophylactic anticoagulation to severe COVID-19 patients. To date, no evidence supports the use of high prophylactic doses of heparin in the absence of confirmed VTE, since the risk of bleedings is also relevant among severe COVID-19 patients. Great attention should be given to the early identification of changes in clinical and laboratory markers of DIC insurgence.

There is a urgent need of specifically designed studies, aiming at understanding the exact mechanisms leading to the haemostatic imbalance observed in this clinical setting. Failure of prevention and interventional strategies for the thrombotic risk of severe COVID-19 patients may dramatically impact their prognosis.

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References

[1] Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020; 382(8):727–733.
[2] World Health Organization Coronavirus disease 2019 (COVID-19). Situation Report – 1; [cited 2020 July 3]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports.
[3] World Health Organization Coronavirus disease 2019 (COVID-19). Situation Report – 51; [cited 2020 July 3]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports.
[4] Chan JF, Yuan S, Kok KH, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet. 2020;395(10223):514–523.
[5] Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020; 382(18):1708–1720.
[6] Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020; 395(10223):507–513.
[7] Wan S, Xiang Y, Fang W, et al. Clinical features and treatment of COVID-19 patients in northeast Chongqing. J Med Virol. 2020;92(7):797–806.
[8] Wu P, Hao X, Lau EHY, et al. Real-time tentative assessment of the epidemiological characteristics of novel coronavirus infections in Wuhan, China, as at 22 January 2020. Euro surveillance: bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin 2020. 25(3).
[9] Di Minno A, Ambrosino P, Calcaterra I, et al. COVID-19 and venous thromboembolism: a meta-analysis of literature studies. Semin Thromb Hemost. 2020. DOI:STH02813.
[10] Barbar S, Noventa F, Rossetto V, et al. A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: the Padua Prediction Score. J Thromb Haemost. 2010;8(11):2450–2457.
[11] Kahn SR, Lim W, Dunn AS, et al. Prevention of VTE in nonsurgical patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012;141(2 Suppl):e195S–e226S.
[12] Cui S, Chen S, Li X, et al. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. J Thromb Haemost. 2020;18(6):1421–1424.
[13] Tang N, Bai H, Chen X, et al. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost. 2020; 18(5):1094–1099.
[14] Yin S, Huang M, Li D, et al. Difference of coagulation features between severe pneumonia induced by SARS-CoV2 and non-SARS-CoV2. J Thromb Thrombolys. [cited 2020 Apr 3];[4p.]. DOI:10.1007/s11239-020-02105-8
[15] Poissy J, Goutay J, Caplan M, et al. Pulmonary embolism in COVID-19 patients: awareness of an increased prevalence. Circulation. 2020. DOI:10.1161/CIRCULATIONAHA.120.047430
[16] Klok FA, Kruip M, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res . 2020;191:148–150.
[17] Wang T, Chen R, Liu C, et al. Attention should be paid to venous thromboembolism prophylaxis in the management of COVID-19. Lancet Haematol . 2020;7(5):e362–e363.
[18] Brown JD, Goodin AJ, Lip GYH, et al. Risk stratification for bleeding complications in patients with venous thromboembolism: application of the HAS-BLED bleeding score during the first 6 months of anticoagulant treatment. J Am Heart Assoc. 2018;7(6):e007901.
[19] Bangash MN, Patel J, Parekh D. COVID-19 and the liver: little cause for concern. Lancet Gastroenterol Hepatol. 2020;5(6): 529–530.
[20] Zhu J, Ji P, Pang J, et al. C: clinical characteristics of 3,062 COVID-19 patients: a meta-analysis. J Med Virol. 2020 doi: 10.1002/jmv.25884.
[21] Smythe MA, Priziola J, Dobesh PP, et al. Guidance for the practical management of the heparin anticoagulants in the treatment of venous thromboembolism. J Thromb Thrombolysis. 2016;41(1):165–186.
[22] Chen G, Wu D, Guo W, et al. Clinical and immunologic features in severe and moderate Coronavirus Disease. J Clin Investigat. 2019;2020.doi: 10.1172/JCI137244
[23] Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497–506.
[24] Mo P, Xing Y, Xiao Y, et al. Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China. Clin Infec Dis. 2020;ciaa270 DOI:10.1093/cid/ciaa270
[25] Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Internal Medicine. 2020.DOI:10.1001/jamainternmed.2020.0994.
[26] Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020;8(5):475–481.
[27] Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan. China: a retrospective cohort study. Lancet. 2020;395(10229): 1054–1062.
[28] Tang N, Li D, Wang X, et al. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020; 18(4):844–847.
[29] Lillicrap D. Disseminated intravascular coagulation in patients with 2019-nCoV pneumonia. J Thromb Haemost. 2020;18(4): 786–787.
[30] Levi M, Scully M. How I treat disseminated intravascular coagulation. Blood. 2018;131(8):845–854.
[31] Herridge MS, Tansey CM, Matte A, et al. Functional disability 5 years after acute respiratory distress syndrome. N Engl J Med. 2011;364(14):1293–1304.
[32] Godeau E, Debeaumont D, Artaud-Macari E, et al. Sequelae of acute respiratory distress syndrome: interest of rehabilitation. Case Rep Crit Care. 2019;2019:7953141.
[33] Babu AS, Vasanthan LT. Critical care rehabilitation – is it the answer for reducing morbidity in ARDS survivors? Regarding

"Acute respiratory distress syndrome: a clinical review". Pulm Circ. 2012;2(2):265.
[34] Brugliera L, Spina A, Castellazzi P, et al. Rehabilitation of COVID-19 patients. J Rehabil Med. 2020;52(4):jrm00046.
[35] Borg K, Stam H. Covid–19 and physical and rehabilitation medicine. J Rehabil Med. 2020;52(4):jrm00045.
[36] Ambrosino P, Papa A, Maniscalco M, Di Minno MND. COVID-19 and functional disability: current insights and rehabilitation strategies. Postgrad Med J. 2020. DOI:10.1136/postgradmedj-2020-138227
[37] World Health Organization. Clinical management of severe acute respiratory infection when novel coronavirus (2019-nCoV) infection is suspected. IInterim guidance 28 January 2020; [cited 2020 July 3]. Available from: https://www.who.int/docs/defaultsource/coronaviruse/clinical-management-of-novel-cov.pdf.
[38] Thachil J, Tang N, Gando S, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemost. 2020;18(5):1023–1026.
[39] Samama MM, Gerotziafas GT. Comparative pharmacokinetics of LMWHs. Semin Thromb Hemost. 2000;26(Suppl 1):31–38.
[40] Turpie AG, Lensing AW, Fuji T, et al. Pharmacokinetic and clinical data supporting the use of fondaparinux 1.5 mg once daily in the prevention of venous thromboembolism in renally impaired patients. Blood Coagul Fibrin. 2009;20(2):114–121.
[41] Hutt Centeno E, Militello M, Gomes MP. Anti-Xa assays: what is their role today in antithrombotic therapy? Cleve Clin J Med. 2019;86(6):417–425.

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