bjh commentary

Thromboembolic risk and anticoagulant therapy in COVID-19 patients: emerging evidence and call for action

Anastasios Kollias, Konstantinos G. Kyriakoulis, Evangelos Dimakakos, Garyphallia Poulakou, George S. Stergiou and Konstantinos Syrigos

Third Department of Medicine, National and Kapodistrian University of Athens, School of Medicine, Sotiria Hospital, Athens, Greece

Summary

Emerging evidence shows that severe coronavirus disease 2019 (COVID-19) can be complicated with coagulopathy, namely disseminated intravascular coagulation, which has a rather prothrombotic character with high risk of venous thromboembolism. The incidence of venous thromboembolism among COVID-19 patients in intensive care units appears to be somewhat higher compared to that reported in other studies including such patients with other disease conditions. D-dimer might help in early recognition of these high-risk patients and also predict outcome. Preliminary data show that in patients with severe COVID-19, anticoagulant therapy appears to be associated with lower mortality in the subpopulation meeting sepsis-induced coagulopathy criteria or with markedly elevated d-dimer. Recent recommendations suggest that all hospitalized COVID-19 patients should receive thromboprophylaxis, or full therapeutic-intensity anticoagulation if such an indication is present.

Keywords: anticoagulant, prophylaxis, SARS-CoV-2, thromboembolism, thrombosis.

Emerging evidence shows that severe coronavirus disease 2019 (COVID-19) can be complicated with coagulopathy, namely disseminated intravascular coagulation, which has a rather prothrombotic character with high risk of venous thromboembolism (VTE).[1-3] Until recently, the association between COVID-19 and VTE including deep vein thrombosis and pulmonary embolism has been reported in case reports.[2] Recently, Cui *et al.* reported the prevalence of VTE in 81 severe COVID-19 patients with pneumonia admitted in the intensive care unit (ICU).[3] The incidence of VTE in these patients, who were not under thromboprophylaxis, was 25%, and eventually 40% of them died.[3] Increased levels of d-dimer > 1·5 μg/ml (normal range: 0·0–0·5 μg/ml) predicted VTE with sensitivity 85·0%, specificity 88·5% and negative predictive value 94·7%.[3] These important observations raise challenging questions: (i) does this emerging evidence point to an increased thromboembolic risk associated with COVID-19; (ii) what is the role and clinical relevance of d-dimer in COVID-19 patients; (iii) what is the current role of anticoagulant therapy in the prophylaxis and treatment of these patients?

The prevalence of VTE in the study population of Cui *et al.*[3] appeared to be in the higher range compared to that reported in other studies including patients admitted in ICUs for other disease conditions.[4,5] In a relevant review of four studies, the rate of VTE in ICU patients without thromboprophylaxis ranged from 13% to 31%.[4] In another meta-analysis of seven studies including 1 783 ICU patients, the mean rate of VTE diagnosis was 12·7% (95% CI 8·7–17·5%).[5] Interestingly, the rate of VTE was similar when studies that evaluated the presence of VTE in ICU populations not receiving pharmacological or mechanical antithrombotic prophylaxis were excluded (mean rate 12·0%; 95% CI: 7·8–16·9%).[5] Moreover, in this meta-analysis patients with VTE had a marginally increased risk of in-hospital mortality (relative risk 1·31; 95% CI: 0·99–1·74%).[5] Critically ill patients hospitalized in ICU are at high risk of VTE because of both individual patient-related risk factors (age, immobilization, obesity, past history of personal or familial VTE, cancer, sepsis, respiratory or heart failure, pregnancy, stroke, trauma, or recent surgery) and ICU-specific risk factors (sedation, immobilization, vasopressors or central venous catheters).[4]

Coagulopathy is known to occur in the majority of patients who die of COVID-19.[1] Interestingly, in a study of 449 patients with severe COVID-19, anticoagulant therapy mainly with low molecular weight heparin (LMWH) appeared to be associated with lower mortality in the subpopulation meeting sepsis-induced coagulopathy criteria or with markedly elevated d-dimer.[6]

Thus, it appears that severe COVID-19 patients are at high VTE and mortality risk and anticoagulant therapy might improve their prognosis. However, apart from the severe COVID-19 patients in ICUs, those hospitalized in hospital

Correspondence: Anastasios Kollias, Third Department of Medicine, National and Kapodistrian University of Athens, School of Medicine, Sotiria Hospital, 152 Mesogion Avenue, Athens 11527, Greece.
E-mail: taskollias@gmail.com

doi: 10.1111/bjh.16727

Table I. Current recommendations regarding thromboprophylaxis in COVID-19 patients.[9,10]

Society	Recommendation for venous thromboembolic prophylaxis
International Society on Thrombosis and Haemostasis	All patients (including non-critically ill) who require hospital admission for COVID-19 infection should receive prophylactic dose LMWH, unless they have contra-indications (active bleeding and platelet count $<25 \times 10^9$/l)
American Society of Hematology	All hospitalized patients with COVID-19 should receive pharmacologic thromboprophylaxis with LMWH or fondaparinux (suggested over unfractionated heparin to reduce contact), unless there is increased bleeding risk. With a history of heparin-induced thrombocytopenia, use fondaparinux. When anticoagulants are contraindicated or unavailable, use mechanical thromboprophylaxis (e.g. pneumatic compression devices). Seriously ill COVID-19 patients should not receive therapeutic-intensity anticoagulation empirically (i.e. in the absence of confirmed venous thromboembolism)

LMWH, low molecular weight heparin.

wards share common predisposing factors for VTE, namely strict and long isolation and subsequently immobilization. Any severe infection can predispose to VTE. However, it appears that in COVID-19 additional mechanisms might contribute to increased VTE risk, including endothelial damage, microvascular thrombosis and occlusion, or even autoimmune mechanisms.[7] Future research is needed to elaborate on the possible mechanisms underlying this association.

Another important issue is the clinical significance of increased d-dimer in predicting VTE in severe COVID-19 cases. D-dimer is a biomarker of fibrin formation and degradation. However, the accumulating evidence in COVID-19 implies that d-dimer can be used not only for the prediction of VTE, but as a prognostic tool for risk stratification. In a study of 199 COVID-19 patients a d-dimer value above 1 μg/ml was associated with an adjusted hazard ratio of 18·4 (95% CI: 2·6, 128·6) for in-hospital mortality.[8] According to the International Society on Thrombosis and Haemostasis (ISTH), in patients with markedly raised d-dimers (arbitrarily defined as 3–4-fold increase), hospital admission should be considered even in the absence of other symptoms suggesting disease severity, as this clearly signifies increased thrombin generation.[9]

Recent statements by the ISTH and the American Society of Hematology suggest that all hospitalized COVID-19 patients should receive thromboprophylaxis, or full therapeutic-intensity anticoagulation if such an indication is present (Table I).[9,10] However, crucial questions remain to be addressed, including the following:

1. Should all hospitalized patients with severe COVID-19 presenting respiratory deterioration and/or haemodynamic instability be treated with empirical intermediate or therapeutic-intensity anticoagulation until diagnostic assessment for VTE is available?
2. Should thromboprophylaxis be continued after hospital discharge and for how long?
3. Should selected COVID-19 patients not admitted in hospital receive thromboprophylaxis, particularly if considerably immobilized and with additional prothrombotic factors? The lack of serial d-dimer assessment may occasionally delay the recognition of an increased VTE risk.

Evidence is emerging calling for prompt actions. All hospitalized COVID-19 patients should receive prophylactic anticoagulation therapy, yet a more aggressive individualized strategy might be required in selected cases.

Author contributions

AK performed the research and drafted the manuscript. KGK, ED, GP performed the research and provided critical review. GSG, KS provided critical review.

Conflicts of interest

The authors declare to have no potential conflicts of interest regarding the present work.

References

1. 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**:844–7.
2. Danzi GB, Loffi M, Galeazzi G, Gherbesi E. Acute pulmonary embolism and COVID-19 pneumonia: a random association? *Eur Heart J*. 2020. https://doi.org/10.1093/eurheartj/ehaa254.
3. 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. https://doi.org/10.1111/jth.14830.
4. Minet C, Potton L, Bonadona A, Hamidfar-Roy R, Somohano CA, Lugosi M, et al. Venous thromboembolism in the ICU: main characteristics, diagnosis and thromboprophylaxis. *Crit Care*. 2015;**19**:287.
5. Malato A, Dentali F, Siragusa S, Fabbiano F, Kagoma Y, Boddi M, et al. The impact of deep vein thrombosis in critically ill patients: a meta-analysis of major clinical outcomes. *Blood Transfus*. 2015;**13**:559–68.
6. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z, et al. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost*. 2020. https://doi.org/10.1111/jth.14817.
7. Zhang Y, Xiao M, Zhang S, Xia P, Cao W, Jiang W, et al. Coagulopathy and antiphospholipid antibodies in patients with Covid-19. *N Engl J Med*. 2020. https://doi.org/10.1056/NEJMc2007575.

8. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, 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**:1054–62.
9. Thachil J, Tang N, Gando S, Falanga A, Cattaneo M, Levi M, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. published: 25 March 25, 2020. https://clotconnect.wpcomstaging.com/2020/03/26/covid-19-and-coagulopathy-two-management-guidance-documents-for-health-care-professionals/. https://doi.org/10.1111/jth.14810
10. COVID-19 and VTE/Anticoagulation: Frequently asked questions. https://www.hematology.org/covid-19/covid-19-and-vte-anticoagulation