Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

A Review of Venous Thromboembolism Phenomena in COVID-19 Patients

Mohammad Kermani-Alghoraishi, MD[a], and Rahil Ghahramani, MD[b]

From the [a] Interventional Cardiology Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran and [b] Cardiac Rehabilitation Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran.

Abstract: With the outbreak of the second peak of COVID-19 in many countries of the world, the symptoms and complications of this disease has received a great deal of attention. One of the most important known complications of severe acute respiratory syndrome coronavirus 2 is the occurrence of venous thromboembolic events, especially in critically ill patients who are hospitalized in the intensive care unit. The pathology of this event is complex and multifactorial, but the main problem now is the timely diagnosis of these phenomena, which can reduce the mortality and morbidity of patients. Deterioration of clinical condition in patients with severe acute respiratory syndrome coronavirus 2 infection along with increased coagulation markers can increase clinical suspicion of venous thromboembolic events. Imaging techniques, especially computed tomography pulmonary angiography, can well solve this puzzle and lead to timely treatment of these patients. (Curr Probl Cardiol 2021;46:100692.)

Introduction

In late 2019, a new coronavirus called COVID-19 broke out in Wuhan, Hubei province, China, rapidly becoming a catastrophic pandemic.[1] The spread, virulence and pathogenicity of this virus is

Curr Probl Cardiol 2021;46:100692
0146-2806/$ – see front matter
https://doi.org/10.1016/j.cpcardiol.2020.100692

so high that The World Health Organization (WHO) announced a total of 18,614,177 cases affected and 702,642 deaths in the 199th situational report on August 6, 2020.[2] The main complication of COVID-19 is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), with fever, dry cough, and shortness of breath being the common primary symptoms.[3] One of the important pathologies discovered in the course of this disease was an increase in coagulation status. In this regard, the occurrence of numerous venous thromboembolic (VTE) events attracted the attention of medical staff, recording various reports and papers. Therefore, in this review, the pathogens, epidemiology, diagnosis, and therapeutic management of COVID-19 patients with VTE disease are discussed.

VTE pathology in COVID-19 patients

As previously reported, severe viral infections such as influenza and SARS-CoV-1 either directly and indirectly cause hypercoagulability conditions and VTE events.[4-6] Although the mechanism of VTE with COVID-19 infection has not been fully understood yet, it might be related to the endothelial cell damage caused by the virus which induces a hypercoagulant state.[7] In this way and as the main pathology of COVID-19, SARS-CoV-2 invades host cells through the binding of spike glycoprotein, blocking angiotensin-converting enzyme 2 (ACE2) receptor and inhibition of transmembrane protease serine 2 (TMPRSS2) activity which causes endothelial dysfunction, followed by hypoxia and thrombosis due to increased viscosity and increased signals of coagulation cascade activation.[8] The above theory could explain pulmonary embolism in COVID-19 patients who are not in critical condition. On the other hand, severe infection and sepsis dysregulate hemostatic pathways and activate coagulation cascade by inducing inflammation status with exceeded cytokines releases along with elevated D-dimer, fibrinogen and fibrinogen degradation products (FDP).[3,9-11]

These possible hypotheses are in addition to the clinical condition of patients admitted to the ICU with multiple organ failure and loss of consciousness. Although the exact mechanism of coagulopathy in patients with COVID-19 is very complex and multifactorial, the triangle of abnormal hemostasis, severe inflammation and endothelial dysfunction is the most logical pathology in VTE events.[12-14]

Epidemiology

The incidence of pulmonary embolism has been reported differently in different studies and locations. In a retrospective observational

multicenter study in France, out of 1240 patients infected with COVID-19 who had a computed tomography pulmonary angiography (CTPA), only 103 (8.3%) had evidence of pulmonary embolism,[15] while most studies report an incidence of 20%-40%.[16-18] The difference in the report of these studies was related to the type of patients studied. In the French study, patients who had been admitted to the intensive care unit (ICU) from the beginning were excluded; in contrast, in other studies, the main target group was critically ill patients admitted to the ICU.[17-19]

The prevalence of deep vein thrombosis (DVT) has varied widely in studies, ranging from 0% to 69%.[20-22] This difference is also due to the severity of the disease and the clinical condition of the patients, such that Llitjos et al report 69% cumulative incidence of peripheral VTE in patients with severe novel coronavirus pneumonia.[20] In contrast, screening ultrasound in non-ICU ward 64 patients in Northern Italy showed no evidence of venous thrombosis.[22] The difference between the prevalence of venous thrombosis and pulmonary embolism indicates the independent pathology of thrombus formation in the lung mentioned above.

Overall, in a recent full systematic review and meta-analysis, the occurrence of VTE was approximately 20%, while in cumulative incidences it could rise up to 49% during hospitalization; however, their post-hoc meta-analysis indicated high statistical heterogeneity and risk of publication bias. As an absolute finding, they acknowledged that there was more embolism in patients admitted to the ICU.[23]

VTE diagnosis in COVID-19 patients

Diagnosis of VTE disease, especially pulmonary embolism, in patients with SARS-CoV 2 infections are incredibly difficult and challenging. In most COVID-19 patients, no association was found between traditional major risk factors (age, history of VTE disease, malignancy history, smoking and cardiovascular comorbidities including diabetes, hypertension, chronic heart failure and coronary artery disease) and VTE diseases.[15,24-25] Male gender and obesity were risk factors directly associated with an increased incidence of pulmonary embolism.[15-16,26] As a noteworthy point in Poyiadji et al study, patients who were on satin therapy prior to admission proved to have fewer pulmonary embolisms occurrence.[16]

Therefore, using Wells and Geneva risk scores to predict the occurrence of pulmonary embolism is of low value and difficult.[25,27] As the first para-clinical approach in the diagnostic algorithm of pulmonary embolism, the use of D-dimer in the patients admitted with SARS-CoV 2 infection is controversial, because this marker has been increased as an

acute reaction factor in hospitalized patients in need of respiratory care and loses its predictive value due to its low specificity.[28] However, in most reports and studies, the increase in D-dimer level is considered as a contributing factor along with clinical evidence, especially the clinical worsening of the patient's condition.[16,18,29] Lung ventilation perfusion imaging (VQ Scans) is also limited in use due to lung tissue involvement and reduced test accuracy, as well as the possibility of contamination of the environment and medical staff. When CTPA is contraindicated and Doppler ultrasound of the limbs has no evidence of thrombosis VQ Scans can be useful. Finally, the most accurate modality in the diagnosis of pulmonary embolism, especially in critically ill COVID-19 patient's pulmonary infection, is CTPA.[30]

According to European Society of Radiology and the European Society of Thoracic imaging advices, CTPA is recommended to rule out pulmonary embolism if supplementary oxygen is needed in COVID-19 lung infected patients when disease extension was limited.[31] The European Society of Cardiology also recommends that CTPA may [or should] be considered for SARS-Cov2 patients before leaving the radiology department if unenhanced lung CT cannot explain the severity of respiratory failure.[32] Therefore, if we have clinical suspicion of pulmonary embolism, especially in the cases with clinical deterioration and disturbances in coagulation parameters and rising D-dimer, CTPA is recommended as a preferred step in the diagnosis.[27,33-34]

Treatment

The predominant pattern of pulmonary embolism in COVID-19 patients is both segmental and sub-segmental,[16-18,35] and treatment should be guided based on risk stratification and extent of lung involvement.[32] Patients in shock state and unstable hemodynamic should receive immediate reperfusion therapy.[24] In patients with stable hemodynamic or low/intermediate VTE risk treatment with unfractionated heparin (UFH), low molecular weight heparin (LMWH) or oral anticoagulant agent including Non-vitamin K antagonist oral anticoagulants (NOACs) and warfarin is recommended. UFH and LMWH are the most practical anticoagulants at time of admission, basically changing to oral medications at discharge time. NOACs use compared to that of warfarin was significant in most patients; however, it is necessary to pay attention to the interaction between these drugs and medication used in Covid-19 treatment, such as levofloxacin, azithromycin and anti-viral drugs including lopinavir/ritonavir or darunavir/ritonavir which increase the bleeding risk

by inhibiting Cytochrome P450 3A4 (CYP3A4) and/or P-glycoprotein (P-gp) pathways.[32,36] Due to the need for close monitoring and the possibility of disease spread, warfarin is recommended only in patients with mechanical prosthetic valve or antiphospholipid syndrome.[32]

The decision on the duration of anticoagulation depends on the existence of provocative factor. Therefore, it makes sense to perform anticoagulant therapy for at least 3 months in critically ill patients, especially those admitted to the ICU as provoked VTE. Moreover, it might be reasonable to extend the duration of anticoagulation and VTE prophylaxis in COVID-19 infected patients based on the patient's condition and risk factors.

Finally, according to recent studies, it is recommended that most of the hospitalized COVID-19 patients, especially critically ill patients admitted to ICU or cases with high D-dimer level, use pharmacological VTE prophylaxis.[23,37]

Authors' contribution

M K-A: Conceptualization, Investigation, Writing - Review & Editing, Supervision.

R GH: Methodology, Investigation, Writing - Original Draft.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of Interest

The authors declare no conflict of interest.

REFERENCES

1. Wang C, Horby PW, Hayden FG, et al. A novel coronavirus outbreak of global health concern. *Lancet* 2020;395:470–3. https://doi.org/10.1016/S0140-6736(20)30185-9.
2. World Health Organization. Coronavirus disease (COVID-19) pandemic. Accessed August 6, 2020. Availble at: https://www.who.int/docs/default-source/coronaviruse/situation reports/20200806-covid-19-sitrep-199.pdf?sfvrsn=6b9d262d_2.
3. 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;18:1094–9. https://doi.org/10.1111/jth.14817.
4. Obi AT, Tignanelli CJ, Jacobs BN, et al. Empirical systemic anticoagulation is associated with decreased venous thromboembolism in critically ill influenza A H1N1 acute

respiratory distress syndrome patients. *J Vasc Surg Venous Lymphat Disord* 2019;7:317–24. https://doi.org/10.1016/j.jvsv.2018.08.010.
5. Dimakakos E, Grapsa D, Vathiotis I, et al. H1N1-induced venous thromboembolic events? Results of a single-institution case series. *Open Forum Infect Dis* 2016;3: ofw214. https://doi.org/10.1093/ofid/ofw214.
6. Shen K, Yang Y, Wang T, et al. Diagnosis, treatment, and prevention of 2019 novel coronavirus infection in children: experts' consensus statement [published online February 7, 2020]. World J Pediatr. doi:10.1007/s12519-020-00343-7.
7. Visseren FL, Bouwman JJ, Bouter KP, et al. Procoagulant activity of endothelial cells after infection with respiratory viruses. *Thromb Haemost* 2000;84:319–24.
8. Zheng YY, Ma YT, Zhang JY, et al. COVID-19 and the cardiovascular system. *Nat Rev Cardiol* 2020;17:259–60. https://doi.org/10.1038/s41569-020-0360-5.
9. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan. *China. Lancet* 2020;395:497–506. https://doi.org/10.1016/S0140-6736(20)30183-5.
10. Foley JH, Conway EM. Cross talk pathways between coagulation and inflammation. *Circ Res* 2016;118:1392–408. https://doi.org/10.1161/CIRCRESAHA.116.306853.
11. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020;382:1708–20. https://doi.org/10.1056/NEJMoa2002032.
12. 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;18:844–7. https://doi.org/10.1111/jth.14768.
13. Bikdeli B, Madhavan MV, Jimenez D, et al. COVID-19 therapy, and follow-up. *J Am Coll Cardiol* 2020. https://doi.org/10.1016/j.jacc.2020.04.031.
14. Driggin E, Madhavan MV, Bikdeli B, et al. Cardiovascular considerations for patients, health care workers, and health systems during the coronavirus disease 2019 (COVID-19) pandemic. *J Am Coll Cardiol* 2020;75:2352–71. https://doi.org/10.1016/j.jacc.2020.03.031.
15. Fauvel C, Weizman O, Trimaille A, et al. Pulmonary embolism in COVID-19 patients: a French multicentre cohort study. *Eur Heart J* 2020. https://doi.org/10.1093/eurheartj/ehaa500. Online ahead of print.
16. Poyiadji N, Cormier P, Patel PY, et al. Acute pulmonary embolism and COVID-19. *Radiology* 2020:201955. https://doi.org/10.1148/radiol.2020201955.
17. Grillet F, Behr J, Paul Calame P, et al. Acute pulmonary embolism associated with COVID-19 pneumonia detected by pulmonary CT angiography. *Radiology* 2020;296: E186–8. https://doi.org/10.1148/radiol.2020201544.
18. Leonard-Lorant I, Delabranche X, Severac F, et al. Acute pulmonary embolism in COVID-19 patients on CT angiography and relationship to D-Dimer levels. *Radiology* 2020;296:E189–91. https://doi.org/10.1148/radiol.2020201561.
19. Poissy J, Goutay J, Caplan M, et al. Pulmonary embolism in COVID-19 patients: awareness of an increased prevalence. *Circulation* 2020. https://doi.org/10.1161/circulationaha.120.047430.

20. Llitjos JF, Leclerc M, Chochois C, et al. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. *J Thromb Haemost* 2020 https://doi.org/10.1111/jth.14869.
21. Cui S, Chen S, Li X, et al. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. *J Thromb Haemost* 2020 https://doi.org/10.1111/jth.14830.
22. Cattaneo M, Bertinato EM, Birocchi S, et al. Pulmonary embolism or pulmonary thrombosis in COVID-19? Is the recommendation to use high-dose heparin for thromboprophylaxis justified? *Thromb Haemost* 2020 https://doi.org/10.1055/s-0040-1712097.
23. Al-Ani F, Chehade S, Lazo-Langner A. Thrombosis risk associated with COVID-19 infection. A scoping review. *Thromb Res* 2020;192:152–60. https://doi.org/10.1016/j.thromres.2020.05.039.
24. Akel T, Qaqa F, Abuarqoub A, et al. Pulmonary embolism: a complication of COVID 19 infection. *Thromb Res* 2020;193:79–82. https://doi.org/10.1016/j.thromres.2020.05.033.
25. Vannini L, Gómez JML, Quijada-Fumero A, et al. COVID-19 quarantine and acute pulmonary embolism. *Rev Esp Cardiol (Engl Ed)* 2020;73:680–2. https://doi.org/10.1016/j.rec.2020.05.010.
26. Abernethy K, Sivakumar P, Patrick T, et al. Coexistent COVID-19 pneumonia and pulmonary embolism: challenges in identifying dual pathology. *Thorax* 2020;75:812–4. https://doi.org/10.1136/thoraxjnl-2020-215011.
27. Lorenzo C, Francesca B, Francesco P, et al. Acute pulmonary embolism in COVID-19 related hypercoagulability. *Thromb Thrombolysis* 2020;50:223–6. https://doi.org/10.1007/s11239-020-02160-1.
28. Oudkerk M, Buller HR, Kuijpers D, et al. Diagnosis, prevention, and treatment of thromboembolic complications in COVID-19: report of the National Institute for Public Health of the Netherlands. *Radiology* 2020:201629. https://doi.org/10.1148/radiol.2020201629. Online ahead of print.
29. Chen J, Wang X, Zhang S, et al. Findings of acute pulmonary embolism in COVID-19 patients. *Société Française d'Anesthésie et de Réanimation* 2020. Available at SSRN: https://ssrn.com/abstract=3548771 or 102139/ssm3548771Google Scholar.
30. Zuckier LS, Moadel RM, Haramati LB, et al. Diagnostic evaluation of pulmonary embolism during the COVID-19 pandemic. *J Nucl Med Off Publ Soc Nucl Med* 2020;61:630–1. https://doi.org/10.2967/jnumed.120.245571.
31. Revel M-P, Parkar AP, Prosch H, et al. European Society of Radiology (ESR) and the European Society of Thoracic Imaging (ESTI). COVID-19 patients and the radiology department - advice from the European Society of Radiology (ESR) and the European Society of Thoracic Imaging (ESTI). *Eur Radiol* 2020:1–7. https://doi.org/10.1007/s00330-020-06865-y.
32. The European Society for Cardiology. ESC Guidance for the Diagnosis and Management of CV Disease during the COVID-19 Pandemic. https://www.escardio.org/Education/COVID-19-and-Cardiology/ESC-COVID-19-Guidance. (Last update: 10 June 2020)

33. Safari S, Mehrani M, Yousefifard M. Pulmonary thromboembolism as a potential cause of clinical deterioration in COVID-19 patients; a commentary. *Arch Acad Emerg Med* 2020;8:e52.
34. Bompard F, Monnier H, Saab I, et al. Pulmonary embolism in patients with COVID-19 pneumonia. *Eur Respir J* 2020;56:2001365. https://doi.org/10.1183/13993003.01365-2020.
35. Rech TH, Girardi AM, Gazzana MB. Incidence of pulmonary embolism in patients with COVID-19. *Intensive Care Med* 2020:1–2. https://doi.org/10.1007/s00134-020-06081-8.
36. Testa S, Prandoni P, Paoletti O, et al. Direct oral anticoagulant plasma levels' striking increase in severe COVID-19 respiratory syndrome patients treated with antiviral agents: the Cremona experience. *J Thromb Haemost* 2020;18:1320–3. https://doi.org/10.1111/jth.14871.
37. Ahmed SI, Khan Sh. Coagulopathy and plausible benefits of anticoagulation among COVID-19 patients. *Curr Probl Cardiol* 2020;45:100648. https://doi.org/10.1016/j.cpcardiol.2020.100648.