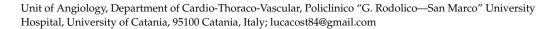




Editoria

Special Issue "COVID-19 and Venous Thromboembolism"

Luca Costanzo



In the last two years, the new coronavirus has afflicted the whole world causing a pandemic burdened by high morbidity and mortality [1]. Over recent months, increasing evidence has been brought to light that venous thromboembolism (VTE) was a frequent complication that adversely affected the clinical course of the coronavirus disease 2019 (COVID-19), especially in the most severe cases [2]. Consequently, numerous researchers around the world have focused efforts on identifying the underlying etiopathogenetic mechanisms of vascular involvement in COVID-19 and on potential therapies that can improve the outcome on these patients. The present Special Issue in the *Journal of Clinical Medicine* (JCM) is dedicated to COVID-19 and VTE, and high-quality scientific papers have been selected with the aim of implementing the scientific evidence on this topic.

In the first paper, Trimaille et al. [3] investigated the determinants and prognosis of acute pulmonary embolism (APE) during COVID-19. Among a total of 140 patients, authors noticed a decline in the non-COVID-19 incidence of APE. Additionally, although the characteristics of thrombus load and location did not differ among COVID-19 and non-COVID-19 patients, an increase of markers of coagulation and inflammation together with a worse outcome were observed in COVID-19 patients with APE. These results are in line with previous reports that emphasized the concept of immune-thrombosis in such subset of patients [4,5] and highlight the importance of VTE preventions in COVID-19 patients in view of the worst prognosis.

In the last year, thromboembolic complications in patients receiving the SARS-CoV-2 vaccine were reported [6,7]. It has been hypothesized that the SARS-CoV-2-vaccine might induce immune thrombotic thrombocytopenia (VITT) [8–11] and cerebral sinus vein thrombosis (CVT) complicated with intracerebral hemorrhage (ICH) [12]. Although rare, this complication implies potentially relevant consequences. In this Special Issue, Gessler et al. [13] proposed a treatment algorithm in case of VITT-related CVT. Particularly, authors provided neurosurgical and haematological considerations for the management of such complex patients to optimize neurosurgical care.

In a systematic review with meta-analysis, Tufano et al. [14] evaluated the risk difference (RD) of the occurrence of VTE, Pulmonary Embolism (PE) and Deep Vein Thrombosis (DVT) between COVID-19 cohorts and other pulmonary infection cohorts, particularly with influenza A (H1N1), and in an Intensive Care Unit (ICU) setting. Notably, they observed a 6% increased risk for VTE in COVID-19 patients as compared with non-COVID-19 patients, especially in patients admitted to the ICU. These results remarked the growing burden of evidence that reported a high prevalence of VTE events in COVID-19 patients, with an increased risk in the most critical ones [15,16].

In common clinical practice, D-dimer is routinely used in the diagnostic scoring systems to rule out PE [17]. However, D-dimer specificity decreases as the age of the patient increases, and the plasma levels of D-dimer increase during inflammation and infection; therefore, the use of this parameter is cumbersome in such clinical settings. Quezada-Feijoo and co-workers [18] evaluated the diagnostic accuracy and reproducibility of the Wells and Geneva clinical probability scales and their association with D-dimer in the diagnosis of PE in elderly patients with COVID-19. The group identified a D-dimer cut-off point



Citation: Costanzo, L. Special Issue "COVID-19 and Venous Thromboembolism". *J. Clin. Med.* **2022**, *11*, 3822. https://doi.org/10.3390/jcm11133822

Received: 24 June 2022 Accepted: 30 June 2022 Published: 1 July 2022

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Copyright: © 2022 by the author. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

J. Clin. Med. **2022**, 11, 3822

of >4.33 mg/L that could discriminate false positives with a specificity of 93.9%; therefore, an increased D-dimer value and clinical scales can help improve the diagnosis of PE in the elderly population.

Lastly, Mangiafico and co-workers [19] reviewed the pathophysiology of vascular damage and the hypercoagulative state related to SARS-CoV-2 infection and the role of heparin in various COVID-19 clinical settings according to the most recent evidence [20–24]. Authors concluded that the prophylactic dose of heparin is recommended in all hospitalized patients unless contraindicated, while the therapeutic dose could be considered in non-pregnant patients requiring low-flow supplemental oxygen, with increased D-dimer levels and low bleeding risk [25–27]. Prophylactic heparin could also have a role in the prevention of postdischarge COVID-19 sequelae, in the presence of high-risk clinical features that raise the risk of thrombotic complications [28,29].

Although COVID-19 continues to be a global emergency, great efforts have been made over the past two years to improve the prognosis of patients. Certainly, the papers published in this Special Issue contribute to the growing scientific evidence concerning the pathogenesis and treatment of thromboembolic complications in COVID-19. Therefore, my gratitude goes to the authors, the reviewers and the editorial office for the excellent work done.

Conflicts of Interest: The author declares no conflict of interest.

References

- 1. COVID Live Update: 542,599,590 Cases and 6,336,895 Deaths from the Coronavirus—Worldometer. Available online: Worldometers.info (accessed on 16 June 2022).
- 2. Schulman, S.; Hu, Y.; Konstantinides, S. Venous thromboembolism in COVID-19. *Thromb. Haemost.* **2020**, 120, 1642–1653. [CrossRef] [PubMed]
- 3. Trimaille, A.; Curtiaud, A.; Matsushita, K.; Marchandot, B.; Von Hunolstein, J.J.; Sato, C.; Leonard-Lorant, I.; Sattler, L.; Grunebaum, L.; Ohana, M.; et al. Acute pulmonary embolism in patients with and without COVID-19. *J. Clin. Med.* **2021**, *10*, 2045. [CrossRef] [PubMed]
- 4. Costanzo, L.; Failla, G.; Antignani, P.L.; Fareed, J.; Gu, Y.; Pitha, J.; Aluigi, L.; Karplus, T.; Mansilha, A. The vascular side of COVID-19 disease. Position paper of the international union of angiology. *Int. Angiol.* **2020**, *39*, 445–451. [CrossRef] [PubMed]
- 5. Bonaventura, A.; Vecchié, A.; Dagna, L.; Martinod, K.; Dixon, D.L.; Van Tassell, B.W.; Dentali, F.; Montecucco, F.; Massberg, S.; Levi, M.; et al. Endothelial dysfunction and immunothrombosis as key pathogenic mechanisms in COVID-19. *Nat. Rev. Immunol.* **2021**, *21*, 319–329. [CrossRef]
- 6. Carli, G.; Nichele, I.; Ruggeri, M.; Barra, S.; Tosetto, A. Deep vein thrombosis (DVT) occurring shortly after the second dose of mRNA SARS-CoV-2 vaccine. *Intern. Emerg. Med.* **2021**, *16*, 803–804. [CrossRef]
- 7. Bikdeli, B.; Jiménez, D.; Demelo-Rodriguez, P.; Galeano-Valle, F.; Porras, J.A.; Barba, R.; Ay, C.; Malý, R.; Braester, A.; Imbalzano, E.; et al. Venous thrombosis within 30 days after vaccination against SARS-CoV-2 in a multinational venous thromboembolism registry. *Viruses* 2022, 14, 178. [CrossRef]
- 8. Lee, E.J.; Cines, D.B.; Gernsheimer, T.; Kessler, C.; Michel, M.; Tarantino, M.D.; Semple, J.W.; Arnold, D.M.; Godeau, B.; Lambert, M.P.; et al. Thrombocytopenia following Pfizer and Moderna SARS-CoV-2 vaccination. *Am. J. Hematol.* **2021**, *96*, 534–537. [CrossRef]
- 9. Tarawneh, O.; Tarawneh, H. Immune thrombocytopenia in a 22-year-old post COVID-19 vaccine. *Am. J. Hematol.* **2021**, *96*, E133–E134. [CrossRef]
- 10. Greinacher, A.; Thiele, T.; Warkentin, T.E.; Weisser, K.; Kyrle, P.A.; Eichinger, S. Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination. *N. Engl. J. Med.* **2021**, *384*, 2092–2101. [CrossRef]
- 11. Makris, M.; Pavord, S.; Lester, W.; Scully, M.; Hunt, B. Vaccine-induced immune thrombocytopenia and thrombosis (VITT). *Res. Pract. Thromb. Haemost.* **2021**, *5*, e12529. [CrossRef]
- 12. Sánchez van Kammen, M.; Aguiar de Sousa, D.; Poli, S.; Cordonnier, C.; Heldner, M.R.; Van De Munckhof, A.; Krzywicka, K.; Van Haaps, T.; Ciccone, A.; Middeldorp, S.; et al. Characteristics and outcomes of patients with cerebral venous sinus thrombosis in SARS-CoV-2 vaccine-induced immune thrombotic thrombocytopenia. *JAMA Neurol.* 2021, 78, 1314–1323. [CrossRef] [PubMed]
- Gessler, F.; Schmitz, A.K.; Dubinski, D.; Bernstock, J.D.; Lehmann, F.; Won, S.-Y.; Wittstock, M.; Güresir, E.; Hadjiathanasiou, A.; Zimmermann, J.; et al. Neurosurgical considerations regarding decompressive craniectomy for intracerebral hemorrhage after SARS-CoV-2-vaccination in vaccine induced thrombotic thrombocytopenia—VITT. J. Clin. Med. 2021, 10, 2777. [CrossRef] [PubMed]

J. Clin. Med. **2022**, 11, 3822

14. Tufano, A.; Rendina, D.; Abate, V.; Casoria, A.; Marra, A.; Buonanno, P.; Galletti, F.; Di Minno, G.; Servillo, G.; Vargas, M. Venous thromboembolism in COVID-19 compared to non-COVID-19 cohorts: A systematic review with meta-analysis. *J. Clin. Med.* **2021**, 10, 4925. [CrossRef] [PubMed]

- 15. Klok, F.A.; Kruip, M.J.H.A.; van der Meer, N.J.M.; Arbous, M.S.; Gommers, D.A.M.P.J.; Kant, K.M.; Kaptein, F.H.J.; van Paassen, J.; Stals, M.A.M.; Huisman, M.V.; et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb. Res.* **2020**, *191*, 145–147. [CrossRef]
- 16. Mohamed, M.F.H.; Al-Shokri, S.D.; Shunnar, K.M.; Mohamed, S.F.; Najim, M.S.; Ibrahim, S.I.; Elewa, H.; Abdalla, L.O.; El-Bardissy, A.; Elshafei, M.N.; et al. Prevalence of venous thromboembolism in critically ill COVID-19 Patients: Systematic review and meta-analysis. *Front. Cardiovasc. Med.* **2021**, *7*, 598846. [CrossRef]
- 17. Crawford, F.; Andras, A.; Welch, K.; Sheares, K.; Keeling, D.; Chappell, F.M. D-dimer test for excluding the diagnosis of pulmonary embolism. *Cochrane Database Syst. Rev.* **2016**, 2016, CD010864. [CrossRef]
- 18. Quezada-Feijoo, M.; Ramos, M.; Lozano-Montoya, I.; Sarró, M.; Cabo Muiños, V.; Ayala, R.; Gómez-Pavón, F.J.; Toro, R. Elderly population with COVID-19 and the accuracy of clinical scales and D-Dimer for pulmonary embolism: The OCTA-COVID Study. *J. Clin. Med.* **2021**, *10*, 5433. [CrossRef]
- 19. Mangiafico, M.; Caff, A.; Costanzo, L. The role of heparin in COVID-19: An update after two years of pandemics. *J. Clin. Med.* **2022**, *11*, 3099. [CrossRef]
- 20. Kow, C.S.; Ramachandram, D.S.; Hasan, S.S. The effect of higher-intensity dosing of anticoagulation on the clinical outcomes in hospitalized patients with COVID-19: A meta-analysis of randomized controlled trials. *J. Infect. Chemother.* **2022**, *28*, 257–265. [CrossRef]
- 21. Hasan, S.S.; Radford, S.; Kow, C.S.; Zaidi, S.T.R. Venous thromboembolism in critically ill COVID-19 patients receiving prophylactic or therapeutic anticoagulation: A systematic review and meta-analysis. *J. Thromb. Thrombolysis* **2020**, *50*, 814–821. [CrossRef]
- 22. Abdel-Maboud, M.; Menshawy, A.; Elgebaly, A.; Bahbah, E.I.; El Ashal, G.; Negida, A. Should we consider heparin prophylaxis in COVID-19 patients? A systematic review and meta-analysis. *J. Thromb. Thrombolysis* **2021**, *51*, 830–832. [CrossRef] [PubMed]
- 23. Parisi, R.; Costanzo, S.; Di Castelnuovo, A.; de Gaetano, G.; Donati, M.B.; Iacoviello, L. Different anticoagulant regimens, mortality, and bleeding in hospitalized patients with COVID-19: A systematic review and an updated meta-analysis. *Semin. Thromb. Hemost.* **2021**, 47, 372–391. [CrossRef] [PubMed]
- 24. Giossi, R.; Menichelli, D.; Pani, A.; Tratta, E.; Romandini, A.; Roncato, R.; Nani, A.; Schenardi, P.; Diani, E.; Fittipaldo, V.A.; et al. A systematic review and a meta-analysis comparing prophylactic and therapeutic low molecular weight heparins for mortality reduction in 32,688 COVID-19 patients. *Front. Pharmacol.* 2021, 12, 698008. [CrossRef] [PubMed]
- 25. Cuker, A.; Tseng, E.K.; Nieuwlaat, R.; Angchaisuksiri, P.; Blair, C.; Dane, K.; Davila, J.; DeSancho, M.T.; Diuguid, D.; Griffin, D.O.; et al. American society of hematology 2021 guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19. *Blood Adv.* 2021, 5, 872–888. [CrossRef] [PubMed]
- 26. Cuker, A.; Tseng, E.K.; Nieuwlaat, R.; Angchaisuksiri, P.; Blair, C.; Dane, K.; Davila, J.; DeSancho, M.T.; Diuguid, D.; Griffin, D.O.; et al. American society of hematology living guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19: May 2021 update on the use of intermediate-intensity anticoagulation in critically ill patients. *Blood Adv.* 2021, 5, 3951–3959. [CrossRef]
- 27. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available online: https://www.covid19treatmentguidelines.nih.gov/ (accessed on 19 March 2022).
- 28. Giannis, D.; Allen, S.L.; Tsang, J.; Flint, S.; Pinhasov, T.; Williams, S.; Tan, G.; Thakur, R.; Leung, C.; Snyder, M.; et al. Post discharge thromboembolic outcomes and mortality of hospitalized patients with COVID-19: The CORE-19 registry. *Blood* **2021**, 137, 2838–2847. [CrossRef]
- 29. Courtney, L.A.; Trujillo, T.C.; Saseen, J.J.; Wright, G.; Palkimas, S. Evaluation of the clinical impact of thromboprophylaxis in patients with COVID-19 following hospital discharge. *Ann. Pharmacother.* 2022; *Epub ahead of print.* [CrossRef]