Paolo Ruggero Errante http://orcid.org/0000-0002-6997-7587
Murched Omar Taha http://orcid.org/0000-0001-7323-1393
Djalma José Fagundes https://orcid.org/0000-0003-4813-2654
Afonso Caricati-Neto http://orcid.org/0000-0001-8615-4315

REFERENCES

1. Basu-Ray I, Soos MP. Cardiac manifestations of coronavirus (COVID-19). StatPearls. 2020.
2. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost*. 2020;18 (5):1094–1099.
3. Negri EM, Piloto BM, Morinaga LK, et al. Heparin therapy improving hypoxia in COVID-19 patients - a case series. São Paulo; 2020. https://doi.org/10.1101/2020.04.15.20067017.
4. Kochi AN, Tagliari AP, Forleo GB, Fassini GM, Tondo C. Cardiac and arrhythmic complications in patients with COVID-19. *J Cardiovasc Electrophysiol*. 2020;31(5):1003–1008.
5. Burzynski LC, Humphry M, Pyrillou K, et al. The coagulation and immune systems are directly linked through the activation of interleukin-1α by Thrombin. *Immunity*. 2019;50 (4):1033–1042.e6.
6. Godoy CMGd, Vasques ÊR, Caricati-Neto A, et al. Heparin oligosaccharides have antiarrhythmic effect by accelerating the sodium-calcium exchanger. *Front Cardiovasc Med*. 2018;5 67.
7. Fender AC, Wakili R, Dobrev D. Straight to the heart: Pleiotropic antiarrhythmic actions of oral anticoagulants. *Pharmacol Res* 2019;145 104257.
8. Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ*. 2020;m1091.
9. Konstantopoulou A. Mechanisms of drug-induced proarrhythmia in clinical practice. *World J Cardiol*. 2013;5(6):175.
10. Stolbach A, Paziana K, Heverling H, Pham P. A review of the toxicity of HIV medications II: interactions with drugs and complementary and alternative medicine products. *J Med Toxicol*. 2015;11 (3):326–341.

Received: 18 May 2020 | Accepted: 19 May 2020
DOI: 10.1111/jth.14939

All those D-dimers in COVID-19

One of the most consistent abnormal hemostatic laboratory markers in COVID-19 is raised D-dimers. Increased D-dimers have also been observed in several studies published in the *Journal of Thrombosis and Haemostasis* to have prognostic implications.[1,2] But, some of the perplexing questions in this regard are what may be the reasons for such marked elevation in D-dimers and may it have any "useful" purpose apart from prognostication?

SARS-CoV-2 is primarily a respiratory pathogen. An overlooked host defence mechanism to counter this virus is the activation of lung-specific coagulation system, otherwise termed broncho-alveolar hemostasis.[3] In healthy individuals, the coagulation-fibrinolysis balance of the broncho-alveolar hemostasis is shifted toward fibrinolysis.[4] This high fibrinolytic activity (predominantly urokinase plasminogen activator) diligently clears fibrin deposited in alveolar compartments and allows uninterrupted gas exchange.[4] However, in patients who develop acute lung injury secondary to COVID-19 (and other infectious states), this balance shifts toward the procoagulant side, with the purpose of creating pulmonary thrombi possibly to limit viral invasion.[3-5] Of course, the breakdown of these thrombi would cause an increase in D-dimers. But may there be other causes of these elevated D-dimers?

Coagulation and fibrinolysis do not always occur in the intravascular space, especially in the lungs. Wagers and colleagues have shown that one of the prominent features of airway inflammation is the leakage of plasma proteins including fibrinogen and thrombin into the airway lumen.[6] This elegant study demonstrated extravascular thrombin to convert fibrinogen into fibrin, which contributed to airway hyper-responsiveness.[6] The physiological purpose of this extravascular fibrin is possibly to serve as a matrix on which inflammatory cells can attach and function.[7] This extravascular fibrin breakdown could also explain the marked increase in D-dimers noted in patients with malignancies even in the absence of clots in the circulation.[8]

How is the extravascular fibrinolysis relevant to COVID-19? The intense lung inflammation caused by SARS-CoV-2 is associated with elevated fibrinogen levels. Cross-linked fibrin generated from the markedly increased fibrinogen that leaks into the extravascular space would be broken down by plasmin or proteolytic enzymes released from activated neutrophils.[9] D-dimers formed in this manner may not signify thrombus formation but could predict the need for mechanical ventilation, because they arise from lung exudates.

Manuscript handled by: David Lillicrap
Final decision: David Lillicrap, 19 May 2020

D-dimers have always been considered a diagnostic rule-out test with well-established roles in the exclusion of venous thromboembolism. Serial D-dimer monitoring was not a common practice in the pre COVID-19 era except in critically ill patient for whom a possible diagnosis of DIC would be considered. But, based on intravascular and extravascular D-dimer generation in COVID-19, it would be worthwhile examining the following in future studies.

- Is it appropriate and safe to increase the dose of anticoagulation if the D-dimer increase was not caused by pulmonary or systemic thrombi?
- Could serial D-dimer monitoring predict who may require mechanical ventilation even in the absence of thrombus formation?
- In a similar manner, could serial D-dimer monitoring be helpful in de-escalating critical care support?
- Could D-dimers be used to guide the duration of post-discharge thromboprophylaxis in the COVID-19 setting (persistent raised levels suggest continued lung inflammation)?
- In patients with underlying malignancies, could D-dimer monitoring be helpful as a prognostic indicator?

CONFLICT OF INTEREST

None.

Jecko Thachil
Department of Haematology, Manchester University Hospitals, Manchester, UK

Correspondence
Jecko Thachil, Department of Haematology, Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL, UK.
Email: jecko.thachil@mft.nhs.uk

REFERENCES

1. Zhang L, Yan X, Fan Q, et al. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. *J Thromb Haemost*. 2020;18(6):1324-1329.
2. 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(4):844-847.
3. Hofstra JJ, Haitsma JJ, Juffermans NP, Levi M, Schultz MJ. The role of bronchoalveolar hemostasis in the pathogenesis of acute lung injury. *Semin Thromb Hemost*. 2008;34(5):475-484.
4. Shetty S, Padijnayayveetil J, Tucker T, Stankowska D, Idell S. The fibrinolytic system and the regulation of lung epithelial cell proteolysis, signaling, and cellular viability. *Am J Physiol Lung Cell Mol Physiol*. 2008;295(6):L967-L975.
5. Idell S, James KK, Levin EG, et al. Local abnormalities in coagulation and fibrinolytic pathways predispose to alveolar fibrin deposition in the adult respiratory distress syndrome. *J Clin Invest*. 1989;84(2):695-705.
6. Wagers SS, Norton RJ, Rinaldi LM, et al. Extravascular fibrin, plasminogen activator, plasminogen activator inhibitors, and airway hyperresponsiveness. *J Clin Invest*. 2004;114:104-111.
7. Weinberg JB, Pippen AM, Greenberg CS. Extravascular fibrin formation and dissolution in synovial tissue of patients with osteoarthritis and rheumatoid arthritis. *Arthritis Rheum*. 1991;34(8):996-1005.
8. Dvorak HF. Tumors: wounds that do not heal. Similarities between tumor stroma generation and wound healing. *N Engl J Med*. 1986;315(26):1650-1659.
9. Francis CW, Marder VJ. Degradation of cross-linked fibrin by human leukocyte proteases. *J Lab Clin Med*. 1986;107(4):342-352.

Received: 2 June 2020 | Accepted: 5 June 2020
DOI: 10.1111/jth.14953

Response to "All these D-dimers in COVID-19"

We appreciate the opportunity to respond to the letter from Dr Thachil,[1] who provided an interesting physiological explanation for coagulation-fibrinolysis balance shifts of the broncho-alveolar hemostasis during COVID-19 infection, and speculated that the extravascular fibrinolysis would be a source of elevated D-dimers.

Importantly, when we evaluate and use D-dimer in COVID-19, we should always be aware that D-dimer should not be a "stand-alone test" or a "one-size-fits-all test" in managing COVID-19.

The COVID-19 associated coagulopathy would be not only caused by lung-specific coagulation disorder, but also mainly caused by systemic inflammatory response syndrome. First, even though SARS-CoV-2 is primarily a respiratory pathogen, local inflammatory response would release proinflammatory factors into the whole blood circulation to stimulate serial reactions, resulting in coagulation activation, organ damage, etc.[2] Second, hypoxia, which is one of the common symptoms in severe COVID-19 also can stimulate thrombosis through increasing blood viscosity and a hypoxia-inducible transcription factor-dependent signaling pathway.[3] Third, underlying diseases, such as cancer and sepsis et al., are well known as risk factors of venous thromboembolism (VTE). These factors might exacerbate the inflammatory-thrombotic response.

The extravascular fibrinolysis relevant to COVID-19 seems to be reasonable. However, in our opinion, among contributions to the elevated D-dimer, the proportion of extravascular fibrinolysis should be relatively small. The primary source of D-dimer should still be

Manuscript handled by: David Lillicrap
Final decision: David Lillicrap, 05 June 2020