Editorial

Understanding the COVID-19 coagulopathy spectrum

J Thachil [1] ***and S. Agarwal*** [2]

1 Consultant, Department of Haematology, 2 Consultant, Department of Anaesthesia, Manchester University Hospitals, Manchester, UK

Corresponding author: J. Thachil

Email: jecko.thachil@mft.nhs.uk

Keywords: COVID-19; thrombosis; coagulation

This article has been accepted for publication and undergone full peer review but has not been, through the copyediting, typesetting, pagination and proofreading process, which may lead to, differences between this version and the Version of Record. Please cite this article as doi: 10.1111/anae.15141

The SARS-Cov-2 (COVID-19) pandemic has already claimed over 200,000 lives. Quite early on in this pandemic, it was recognised that the virus triggers the immune system leading to a cytokine storm in some severely ill patients [1]. This hyper-responsiveness has been suggested to be the predominant aetiology for clinical deterioration and mortality in patients with this infection [2]. More recently, there have been several reports of increased thrombotic events in these patients [3-6]. From a laboratory perspective, this hypercoagulability is reflected in the marked elevation of the fibrinolytic marker, D-dimer, in almost all hospitalised COVID-19 patients [7]. We must, therefore, ask ourselves what is the link between the extremes of the immune system, presenting as cytokine storm, and the extremes of coagulation, presenting as arterial and venous thromboembolism?

Immunothrombosis and differences in COVID-19 clinical presentation

In embryological organisms such as the horse-shoe crab, the haemostatic system and the immune system were one and the same (haemolymph) [8]. The haemostatic system, by forming a blood clot, prevented the loss of important nutrients but also formed a barrier to pathogen invasion. This immune function has been explored by several researchers as an immunothrombosis concept [9]. The various components of the haemostatic system, including the platelets, coagulation factors and thrombin, are all immune workers. They function as chemotactic to the immune cells, stimulating the various immune components as well as being activated by the immune system themselves [10-12]. This bidirectional relationship could explain some common observations with COVID-19.

In the pandemic so far, we have seen that children rarely get a severe illness despite having proven infection, although there have been recent reports of a hyperinflammatory response in very small numbers of children [13]. This rarity of severe disease may be explained by the rarity of thrombotic complications in the paediatric age group in the absence of an underlying cancer or a central venous access device [14]. Similarly pregnant women, despite being at risk of clotting problems, tend to have milder illness. This may be because their immune system is suppressed during the gestational period to avoid foetal rejection and hence the double hit of immunothrombosis does not come into play [15]. On the other hand, older individuals, who are more prone to getting thrombotic complications in the pre-COVID-19 era, are more likely to get severe disease. The differences in mortality between the South East Asian and Western cohorts affected by COVID-19 could also be explained by the lack of prothrombotic tendencies in the South East Asian population [16]. We must wonder, however, why some Western patients affected by the virus get severe respiratory compromise requiring critical care support whilst others have a relatively mild illness?

Localised pulmonary to systemic coagulopathy

SARS-Cov-2 gains entry predominantly through the lungs. In the lungs, a localised coagulation system or broncho-alveolar haemostasis is present which tries to fight the infection along with the immune cells [17]. The proof for this lung-specific clot formation comes from two things. Firstly, the marked acute phase response includes platelets and fibrinogen in addition to other well-known markers such as C-reactive protein and ferritin. Platelet counts are increased in these patients in the initial stages (uncommonly reported in patients with infectious diseases) and are almost never severely low, even in critically ill COVID-19 patients [18]. Similarly, fibrinogen is markedly raised in these patients and has been historically recognised as a marker of hypercoagulability [19]. Secondly, post-mortem examinations have found evidence of pulmonary microthrombi in patients with COVID-19 [20]. There are also suggestions that the different ventilatory patterns in COVID-19 may suggest microthrombi to be a key component of clinical deterioration [21]. In non-severe COVID-19, these microthrombi are broken down by the highly active fibrinolytic function in the lungs to allow gas exchange which is noted as an elevation in D-dimers. In severely ill patients, the pulmonary coagulation system becomes markedly activated. This would be clinically manifest as increased oxygen requirements and possibly as an increased incidence of renal impairment (latest ICNARC data shows 23% of patients require renal support, https://www.icnarc.org/Our-Audit/Audits/Cmp/Reports, accessed 03/05/2020) and, in the worst cases, arterial and venous thrombosis including limb, intestinal and cerebral ischaemia and multi-organ failure. What is the clinical relevance of this spectrum of localised pulmonary coagulopathy to the more widespread systemic coagulopathy?

Antithrombotic management

Based on several reports of hypercoagulability, it is now recognised that all patients with COVID-19 requiring hospitalisation require prophylactic anticoagulation in the absence of absolute contra-indications [22, 23]. However, in patients where localised pulmonary coagulopathy may progress or have already become systemic, prophylactic anticoagulation might be inadequate. There are currently several trials looking at an increased dose of anticoagulation, even therapeutic anticoagulation in such patients. It is important to bear in mind that systemic coagulopathy may not be treated with full-dose anticoagulation in all cases. It is likely that extra-pulmonary coagulopathy requires more aggressive anti-thrombotic therapies (for example additional antiplatelet drugs or thrombolysis) and treatments which can impact on the immunothrombosis models (for example immunomodulatory agents and anti-complement drugs) [24-27]. It would be ideal in these situations

to depend on laboratory markers which can predict the transition from the beneficial pulmonary coagulation activation to harmful systemic spread.

Based on the currently available laboratory markers, of which D-dimers seem to be the most consistent, we provide a suggested approach but stress that this requires confirmation from ongoing trials (Fig. 1). When the patient presents to the hospital, if the D-dimers are increased, prophylactic anticoagulation with low molecular weight heparin should be given to all patients in the absence of contraindications as per current guidance documents [22,23]. If D-dimers continue to increase despite prophylactic anticoagulation and the patient deteriorates clinically, consideration should be made to intensifying anticoagulation; trials are examining double dose of prophylaxis or treatment dose anticoagulation. In these patients, it is important to consider imaging looking for pulmonary thrombi or thrombi in the systemic circulation, if clinical signs suggest. If thrombi are identified, therapeutic dose anticoagulation should be administered. It should, however, be borne in mind that patients with systemic anticoagulation may not respond to anticoagulation and additional strategies like antiplatelets and others (described above) should be considered in a trial setting. Thrombolysis using inhaled or systemic tissue plasminogen activator has been attempted in some patients who worsen despite therapeutic anticoagulation and maximal critical care support [27]. Regarding anticoagulation, the drug of choice is low molecular weight heparin due to better bioavailability and ease of use. However, in patients who may have severe renal impairment or extremely high risk of bleeding, unfractionated heparin may be considered.

Role of viscoelastic testing

Some early reports suggest that point of care viscoelastic tests such as thrombo-elastography (TEG) or rotational thrombo-elastometry (ROTEM) may be helpful in guiding treatment. Data from observational studies has shown evidence of hypercoagulability on TEG with decreased ‘r’ and ‘k’ times and increased maximum amplitudes (MA) in patients with known raised fibrinogen and D-dimer levels [29] This was also demonstrated with the ROTEM with a shorter clot formation time and high clot firmness [30]. A separate study using the Quantra (Hemosonics, Charlottesville, VA, USA) again demonstrated a procoagulant profile with increased clot strength, increased platelet and fibrinogen contributions in patients with known elevated D-dimer and fibrinogen levels [24]. It may be that those with greater hypercoagulability have a worse outcome. In addition, there may be a possibility of using one of these point of care viscoelastic tests as a screening tool. although this requires a great deal of further research. It may also be that these tests can be used optimise

anticoagulation therapy, particularly in the acute ICU setting, although this again needs further research.

Bleeding

Overt bleeding is rare in COVID-19 patients although there are patients who develop disseminated intravascular coagulation (DIC) in common with many patients who are critically unwell. However, heparinisation may be difficult to manage. Helms et al. recently reported that 96.6% of patients requiring renal replacement therapy experienced circuit clotting, and in twelve patients requiring extracorporeal membrane oxygenation (ECMO), there were three thrombotic occlusions of the centrifugal pump (in two patients) requiring prompt pump replacement [31]. This is turn may lead the clinician to increase heparin therapy leading to iatrogenic bleeding. The same authors found that 50 out of 57 patients tested had positive lupus anticoagulant. Lupus anticoagulant is known to prolong the actibated partial thromboplastin time (APTT); it may be that using the APTT to guide heparin therapy leads to underdosing, leading to an increase in thrombosis in artificial circuits.

The future

Currently, the only marker for coagulation activation is markedly elevated D-dimers, which is not specific to systemic coagulopathy. Since the vascular endothelium is at the interface of coagulation and immune system (recently termed as endothelilitis), markers of endothelial activation would be an interesting research area [30,32]. Ruan et al. showed that interleukin-6 concentrations differed significantly in survivors and non-survivors of COVID-19, with non-survivors having almost double the level as survivors [33]. Ranucci et al., discussing 16 patients with COVID-19 who required mechanical ventilation, found an increase in interleukin-6 (IL-6) levels, which correlated with increased fibrinogen levels, confirming the link between inflammation and a procoagulant state [24].

It is vital that healthcare workers who deal with patients suffering from COVID-19 are familiar with the spectrum of coagulopathy in this disease. However, there remain many questions which need to be answered. These include: should all patients hospitalised with severe COVID-19 be treated empirically with therapeutic anticoagulation until venous thromboembolism is discounted? How should we manage antiocoagulation for these patients on ICU for renal replacement therapy or ECMO? And as we restart semi-elective surgery should we give patients subsequently found to be COVID-19 positive additional thromboprophylaxis? If so, for how long, when do we think the additional risk has passed? At present we simply do not have adequate answers for these questions.

.

Acknowledgements

JT has received honoraria from Bayer, BMS-Pfizer, Daichii-Sankyo, Boehringer, Mitsubishi, Novo Nordisk, Octapharma, Amgen, Norgine, Alexion, Sobi, CSL- Behring and Roche- Chugai, none of which were involved in this editorial. SA is an editor of *Anaesthesia*. She has received research funding and honoraria from Haemonetics, Pharmacosmos, Octapharma, CSL Behring, and Nordic Pharma, none of which were involved in this editorial. No other competing interests declared.

References

1. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the 'Cytokine Storm' in COVID-19. *Journal of Infection* 2020. Epub 10 April. doi.org/10.1016/j.jinf.2020.03.037.
2. Zhang W, Zhao Y, Zhang F, et al. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): the perspectives of clinical immunologists from China. *Clinical Immunology* 2020; **214**: 108393.
3. Llitjos JF, Leclerc M, Chochois C, et al. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. *Journal of Thrombosis and Haemostasis* 2020. Epub 22 April. doi.org/10.1111/jth.14869.
4. 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. *Journal of Thrombosis and Haemostasis* 2020; **18**: 1094–9
5. Klok FA, Kruipb MJHA, van der Meerc NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thrombosis Research* 2020. Epub 10 April. doi.org/10.1016/j.thromres.2020.04.013.
6. Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. *Journal of Thrombosis and Haemostasis* 2020. Epub 9 April. doi.org/10.1111/jth.14830.
7. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia *Journal of Thrombosis and Haemostasis* 2020; **18**: 844-7.
8. Iwanaga S, Kawabata S, Muta T. New types of clotting factors and defence molecules found in horseshoe crab hemolymph: their structures and functions. *Journal of Biochemistry* 1998; **123**: 1-15.
9. Engelmann B, Massberg S. Thrombosis as an intravascular effector of innate immunity. *Nature Reviews Immunology* 2013; **13**: 34-45.
10. Conway EM. Reincarnation of ancient links between coagulation and complement. *Journal of Thrombosis and Haemostasis* 2015; **13** (Suppl 1): S121-32.
11. Maas C, Renné T. Coagulation factor XII in thrombosis and inflammation. *Blood* 2018; **131**: 1903-9.
12. Herter JM, Rossaint J, Zarbock A. Platelets in inflammation and immunity. *Journal of Thrombosis and Haemostasis* 2014; **12**: 1764-75.

13. Riphagen S, Gomez X, Gonzalez-Martinez C et al. Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet* 2020. Epub 6 May. doi.org/10.1016/S0140-6736(20)31094-1
14. Chan AK, Monagle P. Updates in thrombosis in pediatrics: where are we after 20 years? *Hematology* 2012; **2012**: 439-43.
15. Della Gatta AN, Rizzo R, Pilu G, Simonazzi G. COVID19 during pregnancy: a systematic review of reported cases. *American Journal of Obstetrics and Gynecology* 2020. Epub 7 April. doi.org/10.1016/j.ajog.2020.04.013.
16. Fogarty H, Townsend L, Cheallaigh CN, et al. COVID-19 coagulopathy in caucasian patients. *British Journal of Haematology* 2020. Epub 24 April. doi.org/10.1111/bjh.16749.
17. Glas GJ, Van Der Sluijs KF, Schultz MJ, Hofstra JJ, Van Der Poll T, Levi M. Bronchoalveolar hemostasis in lung injury and acute respiratory distress syndrome. *Journal of Thrombosis and Haemostasis* 2013; **11**: 17-25.
18. Yang X, Yang Q, Wang Y, et al. Thrombocytopenia and its association with mortality in patients with COVID-19. *Journal of Thrombosis and Haemostasis* 2020. Epub 17 April. doi.org/10.1111/JTH.14848
19. Machlus KR, Cardenas JC, Church FC, Wolberg AS. Causal relationship between hyperfibrinogenemia, thrombosis, and resistance to thrombolysis in mice. *Blood* 2011; **117**: 4953-63.
20. Dolhnikoff M, Duarte-Neto AN, de Almeida Monteiro RA, et al. Pathological evidence of pulmonary thrombotic phenomena in severe COVID-19. *Journal of Thrombosis and Haemostasis* 2020. Epub 15 April. doi.org/10.1111/jth.14844.
21. Gattinoni L, Chiumello D, Caironi P, et al: COVID-19 pneumonia: different respiratory treatments for different phenotypes? *Intensive Care Medicine* 2020; **14**: 1-4.
22. Thachil J, Wada H, Gando S, et al: ISTH interim guidance on recognition and management of coagulopathy in COVID-19. *Journal of Thrombosis and Haemostasis* 2020; **18**: 1023–6.
23. Bikdeli B, Madhavan MV, Jimenez D, et al. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up. *Journal of the American College of Cardiology* 2020. Epub 17 April. doi.org/10.1016/j.jacc.2020.04.031.
24. Ranucci M, Ballotta A, Di Dedda U et al. The procoagulant pattern if patients with COVID-19 acute respiratory distress syndrome. *Journal of Thrombosis and Hemostasis* 2020. Epub 17 April. doi.org/10.1111/jth.14854
25. Whyte CS, Morrow GB, Mitchell JL, Chowdary P, Mutch NJ. Fibrinolytic abnormalities in acute respiratory distress syndrome (ARDS) and versatility of thrombolytic drugs to treat

COVID-19. *Journal of Thrombosis and Haemostasis* 2020. Epub 23 April. doi.org/10.1111/jth.14872.

26. Licciardi F, Giani T, Baldini L, Favalli EG, Caporali R, Cimaz R. COVID-19 and what pediatric rheumatologists should know: a review from a highly affected country. *Pediatric Rheumatology Online Journal* 2020; **18**: 35.
27. Karasu E, Nilsson B, Köhl J, Lambris JD, Huber-Lang M. Targeting complement pathways in polytrauma- and sepsis-induced multiple-organ dysfunction. *Frontiers in Immunology* 2019; **10**: 543.
28. Wang J, Hajizadeh N, Moore EE, et al. Tissue plasminogen activator (tPA) treatment for COVID-19 associated acute respiratory distress syndrome (ARDS): a case series. *Journal of Thrombosis and Hemostasis* 2020. Epub 8 April. doi.org/10.1111/jth.14828.
29. Panigada M, Bottino N, Tagliabue P et al. Hypercoaguability of COVID-19 patients in Intensive Care Unit. A report of thromboelastography findings and other parameters of hemostasis. *Journal of Thrombosis and Hemostasis* 2020. Epub 17 April. doi.org/10.1111/jth.14850
30. Spiezia L, Boscolo A, Poletto F, et al. COVID-19-related severe hypercoagulability in patients admitted to intensive care unit for acute respiratory failure. *Thrombosis and Haemostasis* 2020. Epub 21 April. doi.org/10.1055/s-0040-1710018
31. Helms J, Tacquard C, Severac F, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicentre prospective cohort study. *Intensive Care Medicine* 2020. Epub 4 May. doi.org/10.1007/s00134-020-06062-x
32. Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet* 2020; 395: 1417–8.
33. Page AV, Liles WC. Biomarkers of endothelial activation/dysfunction in infectious diseases. *Virulence* 2013; **4**: 507-16.
34. Ruan Q, Yang K, Wang W et al. Clinical predictors of mortality due to COVID-19 based on analysis of data of 150 patients from Wuhan, China. *Intensive Care Medicine* 2020; Epub 3 March. doi.org/10.1007/s00134-020-05991-x

Figure 1

Antithrombotic management of COVID-19 coagulopathy based on D-dimers and platelet counts