We agree with the authors that it is impossible to distinguish between the laboratory changes seen in patients with coagulopathy due to sepsis-induced hepatic dysfunction rather than DIC.[7] This distinction becomes particularly relevant given the data which suggest that hepatitis is present in many patients with COVID-19, being most severe in those who are critically unwell, thus mirroring the coagulopathy.[8] Further studies are necessary to look at the association between the coagulopathy and liver disease. The possibility cannot be excluded that the coagulopathy seen in COVID-19 might largely or even solely represent COVID-19 sepsis-induced hepatopathy.

Finally, we must consider the very real risk of an iatrogenic anemia due to multiple blood sampling in seriously ill patients. We have an opportunity to recommend judicious testing to prevent patients with COVID-19 facing the same problem.[9]

The current interim guidelines [this letter refers to an earlier draft version of the Guidelines which have since been updated removing the recommendation to transfuse fibrinogen in non-bleeding patients] seem too quick to replace thorough clinical assessment with experimental biomarkers as the driver of crucial management decisions about the care of patients with COVID-19 associated coagulopathy. We feel that in times of crisis, when faced with a new and often lethal disease, clinicians must be steadfast in continuing to stress the fundamentals of thorough clinical assessment over reliance on unproven laboratory biomarkers. This challenge is a zeitgeist moment for the principles of clinical medicine—an opportunity for the reiteration of the fundamental importance of integrative clinical skills to help us in our task of providing the best clinical outcomes for people with COVID-19.

CONFLICTS OF INTEREST

No conflicts of interest to declare.

Satoshi Akima[1,2]
Claire McLintock[3]
Beverley J. Hunt[4,5]

[1]*Department of General Medicine, Campbelltown Hospital, Campbelltown, NSW, Australia*
[2]*The University of Western Sydney, Campbelltown, NSW, Australia*
[3]*Haematologist and Obstetric Physician, National Women's Health, Auckland City Hospital, New Zealand*
[4]*Thrombosis & Haemostasis, King's College, London, UK*
[5]*Depts of Haematology, Pathology & Rheumatology, Guy's & St Thomas' Trust, London, UK*

Correspondence
Satoshi Akima, Department of General Medicine, Campbelltown Hospital, Campbelltown, NSW, Australia.
Email: satoshi@fastmail.fm

ORCID

Claire McLintock https://orcid.org/0000-0002-4771-8760

TWITTER

Satoshi Akima @ToshiAkima

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Laboratory haemostasis monitoring in COVID-19

We thank the authors for their very useful and constructive criticisms about laboratory monitoring of haemostatic variables detailed in the International Society on Thrombosis and Haemostasis guidance document for coagulopathy in COVID-19. We still believe that the use of simple and easily available laboratory markers both at admission and while in the hospital is necessary in the management of COVID-19 patients. Since the writing of this guidance and the

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letter from the experts being sent to us, there have been several reports of very high incidence of both arterial and venous thromboembolism (TE) in patients with COVID-19.[1-3] In one report published in the *Journal of Thrombosis and Haemostasis*, the incidence of venous TE was 25%, some of whom died from this complication.[2] Laboratory markers including D-dimer were relevant in these patients. The authors used D-dimer cutoff of 1.5 μg/mL for predicting venous TE and demonstrated sensitivity of 85.0% and specificity of 88.5% and negative predictive value of 94.7%.[2] They also suggested D-dimers may be used to monitor the effectiveness of anticoagulants, although this practice is not universally accepted. A recent case report also noted the "decrease" in D-dimers in a patient escalated to treatment dose anticoagulation (D-dimers decreased from 6.26 to 1.94 mg/L) reflecting in clinical improvement.[4] In relation to other haemostatic tests, Klok et al studied 184 patients with proven COVID-19 pneumonia admitted to the critical care unit and identified age and coagulopathy, defined as spontaneous prolongation of the prothrombin time > 3 seconds or activated partial thromboplastin time > 5 seconds as independent predictors of thrombotic complications.[3] Fibrinogen is another marker of hypercoagulability. Extremely high fibrinogen levels are noted in the COVID-19 patients.[5] But we do understand measuring plasma fibrinogen is not routine in many laboratories and may not be "necessary" in all cases if there is overburden on the biomedical scientists' workload. On the other hand, monitoring of coagulation status by laboratory tests is useful especially when the manpower and access to computed tomography are limited.

In addition to measuring D-dimers and prothrombin time, platelet count measurements may also have clinical relevance in this scenario. COVID-19 literature is not replete with thrombocytopenia as a clinical feature but thrombocytosis has been reported.[5] Ranucci and colleagues have tried adding antiplatelet agent in critically ill COVID-19 patients with high platelet counts along with escalating the dose of prophylactic low molecular weight heparin and noted some clinical benefits.[6] Platelet activation is likely to be contributing to the hypercoagulability but the extent to which it does and which signalling pathways are involved are certainly interesting areas of research.

Certainly, we admit the risk of anticoagulant therapy using heparins. If the platelet count does drop by 30% to 50% since the start of low molecular weight heparin or other types of heparin, the possibility of heparin-induced thrombocytopenia (HIT)[7] as a complication should be considered. This adverse drug effect may be a cause for "failure of anticoagulation" and also the reason for the development of limb ischemia noted in some of these patients. We would consider HIT even if the platelet count is in the normal range but has decreased more than 50% in the 4 to 14 days of commencing heparin treatment.

We also thank the authors for pointing out the different thresholds for transfusion, which is gratefully accepted and acknowledged in the final document. We also stress the importance of taking advice from the transfusion experts in this regard. The need for transfusion in COVID-19 patients is not high, however, because in our clinical experience bleeding is extremely uncommon because the hemostatic balance is shifted markedly toward thrombosis. We also acknowledge the important issue of iatrogenic anemia, something that has been highlighted by one of the authors for many years.[8] It may be that less frequent tests are ordered once the clinical situation improves is a possible solution.

The authors considered the possibility that the coagulopathy seen in COVID-19 might largely or even solely represent COVID-19 sepsis-induced hepatopathy. However, a recent retrospective study has described that although abnormalities of liver function indexes are common in COVID-19 patients, the impairment of liver function is not a prominent feature of COVID-19.[9] Another review also summarized that liver injury has often manifested as transient elevation of serum aminotransferases, and acute liver failure has been seldom reported in the available studies.[10] In addition, the level of antithrombin, which is also a predictor of liver reserve, is maintained within normal range in most of COVID patients during most of the hospitalization, according to the study by Tang et al.[5] It seems that changes of coagulation markers in COVID-19 cannot be attributed to liver failure based on current evidence.

Clinical assessment should clearly trump in all situations including COVID-19. But, laboratory markers may be relevant in raising suspicion of an underlying thrombotic problem in these patients in addition to a good clinical assessment. The diagnosis of TE is often overlooked for several reasons: respiratory symptoms attributed to pneumonia or acute respiratory distress syndrome, chest radiography being unreliable for identifying thrombosis, inability to perform computed tomography scans because of practical issues, and the belief that prophylactic anticoagulation would prevent thrombosis in all cases. Laboratory markers may be helpful in these cases and also in early recognition of complications like HIT and even possibly noticing an improvement in patient status.

CONFLICT OF INTEREST

Dr. Thachil has received honoraria from Bayer, BMS-Pfizer, Daichii-Sankyo, Boehringer, Mitsubishi, Novo Nordisk, Octapharma, Novartis, Amgen, Norgine, Alexion, Sobi, and CSL-Behring. Others declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Jecko Thachil wrote the response. Ning Tang, Satoshi Gando, Anna Falanga, Marcel Lewis, Cary Clark, and Toshiaki Iba gave crucial comments. All authors approved the final submission.

Jecko Thachil[1]
Ning Tang[2]
Satoshi Gando[3]
Anna Falanga[4]
Marcel Levi[5]
Cary Clark[6]
Toshiaki Iba[7]

[1]*Department of Haematology, Manchester University Hospitals, Manchester, UK*
[2]*Tongji Hospital, Huazhong University of Science and Technology, Wuhan, China*

[3]Department of Acute and Critical Care Medicine, Sapporo Higashi Tokushukai Hospital, Sapporo, Japan
[4]Department of Medicine and Surgery, University of Milan Bicocca, Hospital Papa Giovanni, XXIII, Bergamo, Italy
[5]Department of Medicine and Cardio-metabolic Programme-NIHR UCLH/UCL BRC, University College London Hospitals NHS Foundation Trust, London, UK
[6]Director of Programs and Education, International Society on Thrombosis and Haemostasis, Carrboro, UK
[7]Department of Emergency and Disaster Medicine, Juntendo University Graduate School of Medicine, Tokyo, Japan

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

ORCID
Satoshi Gando https://orcid.org/0000-0002-3525-0750

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ISTH interim guidance on recognition and management of coagulopathy in COVID-19: A comment

We read with interest the International Society on Thrombosis and Haemostasis (ISTH) interim guidance on recognition and management of coagulopathy in COVID-19.[1] We applaud this group's efforts in releasing a timely article on the pandemic affecting all regions of the globe. Although we agree that this interim guidance addresses important considerations for monitoring the disease process, we believe that the proposed treatment strategy of prophylactic low molecular weight heparin (LMWH) to treat severe COVID-19 coagulopathy is an unconvincing strategy. Patients that are critically ill with COVID-19 have hallmark signs of disseminated intravascular coagulation (DIC),[2] and as noted in the ISTH interim guidance and our own clinical practice, thrombosis is the overwhelming phenotype with rare bleeding complications. We address this concern with the existing data on the severe hypercoagulable state of COVID-19 victims and advocate for consideration of systemic anticoagulation with unfractionated heparin to prevent life-threatening micro- and macrovascular thrombosis to mitigate their associated consequences, up to and including progression of respiratory and organ failure.

First, as noted, it has become clear that critically ill COVID-19 patients are hypercoagulable. Although no reliable published epidemiologic data exist yet on thromboembolic complications, the clinical experience has been one of patients frequently clotting off their central venous catheters (eg, dialysis catheters), clogging their dialysis filters, and having unusually frequent thrombotic complications including ischemic limbs, strokes, and venous thromboembolism. These clinical observations are supported by several findings in hospitalized patients with COVID-19, including high D-dimer levels, high fibrinogen levels (especially in nonsurvivors), low antithrombin levels, a high incidence of venous thromboembolism (~20%), and nearly three-quarters of nonsurvivors meeting ISTH criteria for DIC, whereas in contrast just 0.6% of survivors meet them.[3-8] It is not infrequent at our institutions to see patients with fibrinogen levels >700 mg/dL (and

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