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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
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. 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. Further studies are necessary to look at the association between hepatitis 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.

The current interim guidelines 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 fundamentals 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.

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

REFERENCES
1. Thachil J, Tang N, Gando S, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemost. 2020;18(5):1023-1026.
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;18:1-4.
3. Wada H, Thachil J, Di Nisio M, et al. Guidance for diagnosis and treatment of disseminated intravascular coagulation from harmonization of the recommendations from three guidelines. J Thromb Haemost. 2013;11:761-767.
4. Schlipp CJ, Voelckel W, Inaba K, Maegle M, Ponschab M, Schöchl H. Estimation of plasma fibrinogen levels based on hemoglobin, base excess and Injury Severity Score upon emergency room admission. Crit Care. 2013;17(4):R137.
5. Spahn DR, Bouillon B, Cerny V, et al. Management of major bleeding and coagulopathy following trauma: fifth edition. Crit Care. 2019;23(1):98.
6. Alikhan R, Forster R, Cohen AT, Alikhan R. Heparin to prevent deep vein thrombosis or pulmonary embolism in acutely ill medical patients (excluding those with stroke or myocardial infarction). Cochrane Database of Systematic Reviews 2014, Issue 5. Art. No.: CD003747. DOI: 10.1002/14651858.CD003747.pub4.
7. Hunt BJ. Bleeding and coagulopathies in critical care. N Engl J Med. 2014;370:847-859.
8. Zhang C, Shi L, Wang F. Liver injury in COVID-19: management and challenges.
9. Faisal A, Andres K, Rind JAK, et al. Reducing the number of unnecessary routine laboratory tests through education of internal medicine residents. Postgrad Med J. 2018;94(1118):716-719.

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
LETTERS TO THE EDITOR

prophylactic low molecular weight heparin and noted some clinical patients with high platelet counts along with escalating the dose of leagues have tried adding antiplatelet agent in critically ill COVID-19

2 venous TE was 25%, some of whom died from this complication. 

Journal of Thrombosis and Haemostasis, the incidence of

7 of low molecular weight heparin or other types of heparin, the possi-

ars. If the platelet count does drop by 30% to 50% since the start

pathways are involved are certainly interesting areas of research.

percoagulability but the extent to which it does and which signalling

features but thrombocytosis has been reported. 

5 Ranucci and col-

COVID-19 literature is not replete with thrombocytopenia as a clini-

-Extremely high fibrinogen levels are noted in the COVID-19 pa-

tients. 

- Fibrinogen is another marker of hypercoagulability. 

- 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 to-

mography 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 clini-

cal feature but thrombocytosis has been reported. 

6 They also suggested D-dimers may be used to monitor the effectiveness of anticoagu-

lants, although this practice is not universally accepted. A recent case report also noted the “decrease” in D-dimers in a patient escala-
ted to treatment dose anticoagulation (D-dimers decreased from

6.26 to 1.94 mg/L) reflecting in clinical improvement. 

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 thrombo-

plastin 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 pa-

tients. 

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 to-

dagnosty 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 clini-
cal feature but thrombocytosis has been reported. 

5 Ranucci and col-

leagues have tried adding antiblet 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 hyper-

coagulability 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 hepar-

ins. If the platelet count does drop by 30% to 50% since the start of low molecular weight heparin or other types of heparin, the possi-

bility of heparin-induced thrombocytopenia (HIT) 

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 thresh-

holds for transfusion, which is gratefully accepted and acknowledged in the final document. We also stress the importance of taking ad-

cise from the transfusion experts in this regard. The need for trans-

fusion 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. 

It may be that less frequent tests are ordered once the clinical situa-
tion 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-in-
duced 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. 

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. 

In addition, the level of antithrombin, which is also a predictor of liver reserve, is maintained within normal range in most of COVID pa-
tients during most of the hospitalization, according to the study by Tang et al. 

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 radiogra-

phy 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, Daichi-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 com-

ments. All authors approved the final submission.

Jecko Thachil

Ning Tang

Satoshi Gando

Anna Falanga

Marcel Levi

Cary Clark

Toshiaki Iba

1Department of Haematology, Manchester University Hospitals, Manchester, UK

2Tongji Hospital, Huazhong University of Science and Technology, Wuhan, China
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 thrombembolic 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 non-survivors), 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