To the editor of Journal of Thrombosis and Haemostasis,

RE: ISTH interim guidance to recognition and management of coagulopathy in COVID-19

The unrelenting acceleration of COVID-19 infections due to SARS-CoV-2 is unquestionably the greatest medical challenge of our professional careers. The Scientific and Standardisation Committee (SSC) on disseminated intravascular coagulation (DIC) of the International Society on Thrombosis and Haemostasis (ISTH) is to be commended for the rapid publication of guidance for clinicians worldwide to assist in management of the coagulopathy widely reported to be associated with severe COVID-19 infection. However, we would like to offer constructive feedback as to how the SSC's interim guidance[1] might be improved.

Coagulopathy and DIC portend a poor prognosis in patients with COVID-19 although it is as yet unknown if this is due to a specific action of the SARS-CoV-2 or more likely due to the effects of hypoxia and sepsis[2]. However, it seems premature and potentially dangerous to recommend the use of coagulation biomarkers such as PT/INR, D-dimers, platelet count and plasma fibrinogen levels (not serum as stated in the interim guidance), to guide clinical decision-making to triage which patients can be discharged or need admission, or to identify high-risk cases that need treatment in intensive care. These decisions must be taken after complete clinical assessment of the patient. Whether a three to four-fold increase in D-dimers should warrant hospital admission for patients with COVID-19 who have no other symptoms of severity is uncertain. It is curious that this recommendation was not offered by the authors of the supportive citation to the article by Tang et al[2]. Nor can the assumption be made that the increase in D-dimers is solely the result of secondary fibrinolysis (triggered by thrombin generation), when it is unknown whether the increase is due to primary or secondary fibrinolysis in COVID-19 infected patients.

We are also concerned at the recommendation to administer blood products to patients who have deranged coagulation but are not bleeding. This runs counter to widely accepted current transfusion guidelines. Such a practice has not been shown to improve outcomes in the DIC settings and there is no evidence that patients with COVID-19 would require an approach so different as to necessitate disregarding previously published ISTH SSC guidance[3]. Transfusion of blood and plasma products carries potential for harm, while overtreatment has adverse economic and resource implications. In addition, transfusion of supplementary fibrinogen at a trigger of <2.0 g/l is recommended rather than the previously recommended trigger of <1.5 g/l in "actively bleeding" DIC patients as is suggested by the ISTH DIC guidance[3], published by the some of the very same authors as the present COVID-19 coagulopathy guidelines under discussion. While in trauma-associated bleeding, a fibrinogen of <1.5 g/l is considered low and <2 g/l is considered critical[4], the unexplained change to the more liberal transfusion threshold of <2.0 g/l in a medical DIC setting becomes all the more perplexing given that even the European trauma guidelines on management of bleeding and coagulopathy recommend that fibrinogen transfusion be triggered at <1.5 g/l[5]. Nor is the caveat found in the ISTH DIC guidance repeated that the grade of evidence to support this practice of transfusing fibrinogen at levels <1.5 g/l in the context of bleeding from DIC is "low level", let alone justification having been given as to why this practice ought now be widened to include nonbleeding patients.

The authors also suggest giving thromboprophylaxis to every patient who is admitted with COVID-19 in the absence of any contraindications. Again, it may be more advisable to

administer thromboprophylaxis to patients according to current thromboprophylaxis guidance based on clinical factors, and for which there is an enormous amount of evidence[6]. It also seems odd to recommend LMWH to reduce thrombotic risk while also recommending fibrinogen supplementation in the absence of bleeding, despite the risk of provoking thrombosis.

Of major concern with the current COVID-19 crisis is that it is overstretching the infrastructure capacity of even resource-rich nations. With a looming shortage of clinical and laboratory staff we must recognise that these precious resources are finite and require rational utilisation. While measurement of biomarkers may generate useful research data that can be reviewed in retrospect, it is imperative that our recommendations first provide guidance for laboratory analysis of biomarkers that is evidence-based and clinically useful so as to help clinicians manage patients with COVID-19. Reports from medical social media channels, which we have become more reliant on due to the necessary cancellations of medical and scientific congresses, suggest there is serial panic-ordering of many biomarkers ranging from d-dimers, fibrinogen, troponin, CRP, PT, to ferritin. If ordered daily or several times weekly by clinicians for all patients with COVID-19, there is a risk that this will prove an unproductive burden on finite phlebotomy and laboratory resources.

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 anaemia 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 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.

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