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.

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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

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endovascular fibrinolysis, even just undetectable microthrombus or thrombus but not detected by imaging examination. Of course, this hypothesis needs further pathological studies to verify.

Up to now, D-dimer has served as one of the most important markers in management of COVID-19. The potential uses of D-dimer in COVID-19 has been revealed in recent studies.

1. D-dimer levels on admission might be used to distinguish patients who have potentially high in-hospital mortality.[4] For COVID-19 patients who have markedly raised D-dimers (four-fold increase), admission to hospital and close monitoring should be considered even in the absence of other severe symptoms.
2. Serial D-dimer monitoring might be used to indicate the occurrence of VTE. A rapid increase of D-dimer levels or a peak D-dimer might be associated with venous thromboembolism development.[5,6] D-dimer might serve as a screening tool when imaging examination was limited in management of COVID-19.
3. D-dimer might be used to guide whether anticoagulation therapy should be initiated in patients with COVID-19,[7] and also can be used to evaluate the anticoagulant effect. Whether D-dimer can be used to guide the dose of anticoagulation needs further studies to confirm. However, our team conducted a randomized clinical trial and found D-dimer can be used to guide the anticoagulation intensity in patients receiving warfarin therapy.[8]
4. D-dimer might be used to monitor disease progression of COVID-19. Previous studies have observed that continuous raised D-dimer has been observed to be common in non-survivors of COVID-19.[9,10] Thus, dynamic monitoring of D-dimer might be used to evaluate whether the situation is getting worse or better.

We agree with Dr Thachil that future studies are needed to evaluate whether D-dimer can be used to guide anticoagulation adjustment, initiating mechanical ventilation, de-escalating critical care support, and indicating prognosis of malignancies. Previous studies have suggested that D-dimer could be used to determine the duration of oral anticoagulation in patients with VTE;[11] however, whether this application could still work in post-discharge thromboprophylaxis in the COVID-19 setting remain unknown. Thus, we are carrying out an observational study involving approximately 200 post-discharge COVID-19 patients to evaluate the correlation between laboratory testing (including D-dimer) and prognosis.

Finally, there are many limitations and uncertainties for D-dimer in COVID-19 and other situations; however, we still believe that the use of D-dimer would not only be limited in the traditional applications, but also it would open a new page in the COVID-19 era.

CONFLICTS OF INTEREST

The author declares that he has no conflicts of interest regarding this article.

KEYWORDS

coagulopathy, COVID-19, D-dimer, SARS-CoV-2, thrombosis

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