CONFLICTS OF INTEREST
The authors declare that they have no conflicts of interest.

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Dear Editor

We thank Tang et al for their perspective on the possible limitation of D-dimer levels guiding anticoagulant treatment in patients with COVID-19.\(^3\) Although there is a clear association with elevated D-dimer and severity of COVID-19 disease, it is important to highlight the fact that D-dimer has always been used in conjunction with clinical pretest probability as a predictive tool to help exclude a possible diagnosis of venous thromboembolism. It has never been validated to guide clinical treatment or anticoagulation. It has recently been noted that a significant proportion of the recent literature concerning D-dimer in COVID-19 is fraught with variable, poor, or incomplete reporting that further muddies its role in the management of COVID-19–related coagulopathy.\(^2\)

Tang et al suggest that other markers of coagulation and fibrinolysis may provide a more reflective picture of hemostatic abnormalities in patients with COVID-19. Tang et al report higher thrombin-antithrombin (TAT) complex levels in nonsurvivors compared with survivors during the first 7 days of admission, indicating greater thrombin generation had occurred in the nonsurviving cohort. At the same time point, no differences were seen in D-dimer levels, tissue-type plasminogen activator-plasminogen activator inhibitor-1 (tPA-PAI-1) complex, nor in plasmin-antiplasmin (PAP) complex levels, although it is possible that these results may be tempered because of the prophylactic anticoagulation administered to these patients. Nonetheless, they therefore suggest that TAT levels may be a more appropriate marker to guide decision-making for anticoagulation during early stages of COVID-19. In contrast, at day 14, TAT levels were similar in both survivors and in nonsurvivors, in fact at near baseline levels, perhaps due in part to thrombin consumption (because the same authors previously reported elevated levels of antithrombin in COVID-19 survivors\(^3\)), but there were significant increases in D-dimer and the levels of the tPA-PAI-1 complex. PAP levels, on the other hand, were significantly reduced in the nonsurvivors. The reduction in PAP levels seems at odds with the increase in D-dimer levels at the same time point because plasmin formation is required for both D-dimer generation and PAP complex formation. Could this be explained by differences in the plasma half-life of D-dimer and PAP complexes? However, this is not straightforward because the plasma half-life of D-dimer is reported to be ~8 hours,\(^4\) yet the plasma half-life of the PAP complex is less clear. A 1978 study reported a plasma half-life of 12 hours,\(^5\) whereas a study in 2000 reported a plasma half-life of PAP complexes to be ~4.5 hours.\(^6\)

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Fibrinolysis and COVID-19: A tale of two sites?

We thank Tang et al for their perspective on the possible limitation of D-dimer levels guiding anticoagulant treatment in patients with COVID-19.\(^3\) Although there is a clear association with elevated D-dimer and severity of COVID-19 disease, it is important to highlight the fact that D-dimer has always been used in conjunction with clinical pretest probability as a predictive tool to help exclude a possible diagnosis of venous thromboembolism. It has never been validated to guide clinical treatment or anticoagulation. It has recently been noted that a significant proportion of the recent literature concerning D-dimer in COVID-19 is fraught with variable, poor, or incomplete reporting that further muddies its role in the management of COVID-19–related coagulopathy.\(^2\)

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Another point about PAP levels is the degree to which changes in PAP levels reflect changes in fibrinolysis. Fibrin formation was aptly described by Gaffney et al to “orchestrate its own destruction” by initiating plasminogen activation. Although this will also result in an increase in PAP levels, it is important to highlight that increases or decreases in PAP levels may not necessarily reflect changes in fibrinolysis because misfolded and aggregated proteins can also promote plasminogen activation and generate PAP complexes. Hence, the reduction in PAP levels shown in the nonsurviving group, while consistent with a reduction in fibrinolysis, actually indicates that plasminogen activation has been reduced overall.

Taken together, these data are consistent with our view that the fibrinolytic system is initially activated and then suppressed in patients developing the more severe grades of COVID-19. We proposed that this could be a consequence of consumption from the overwhelming production of fibrin; however, active suppression or shutdown may also be occurring because of an elevation of PAI-1, although this has yet to be confirmed.

The use of plasma as a source for monitoring changes in fibrinolysis is perfectly reasonable when evaluating systemic fibrinolysis. But in the case of COVID-19, the integrity and responsiveness of the fibrinolytic system within the lung parenchyma is also critical and this may indeed be different to the circulation. So are there actually two fibrinolytic systems that we need to consider in patients with COVID-19? It is well-known that the main plasminogen activator that initiates plasmin formation in the lung is in fact urokinase (u-PA), rather than t-PA, and it would therefore seem important to also evaluate u-PA, together with other parameters of the fibrinolytic system (including D-dimer, PAP levels (tPA-PAI-1, and u-PA-PAI-1 complexes and indeed TAFI), in bronchoalveolar lavage fluid and to compare this in plasma taken at the same time point in patients with COVID-19. Preliminary studies from Wu et al reported seemingly beneficial effects of administration of nebulized plasminogen to patients with severe COVID-19. This implies that sufficient levels of endogenous plasminogen activators were indeed present in the lung parenchyma (presumably u-PA in this case) to activate the exogenous plasminogen into active plasin, despite the interesting findings from Tang et al indicating suppression of fibrinolysis in the circulation (as revealed by increased level of tPA-PAI-1 complexes and reduced PAP formation).

The alterations in both the coagulation and fibrinolytic systems in the progression of COVID-19 is clearly complex. The results of Tang et al agree with our view, and as proposed by others that there is certainly activation of fibrinolysis in the circulation during COVID-19 progression, but which is then subsequently overwhelmed and/or shutdown. What we need to understand now is how this important process is altered in the lung parenchyma and if we need to appreciate whether two fibrinolytic processes are existing simultaneously in COVID-19: one in the blood, and the other within the lung tissue itself.

CONFLICT OF INTEREST
The authors declare there are no conflict of interest with this manuscript.

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