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## REFERENCES

1. Funk CD, Funk LB, Kennedy ME, Pong AS, Fitzgerald GA. Human platelet/erythroleukemia cell prostaglandin G/H synthase: cDNA cloning, expression, and gene chromosomal assignment. *FASEB J*. 1991;5:2304-2312.
2. Catella-Lawson F, Crofford LJ. Cyclooxygenase inhibition and thrombogenicity. *Am J Med*. 2001;110(Suppl 3A):28S-32S.
3. McAdam BF, Catella-Lawson F, Mardini IA, Kapoor S, Lawson JA, FitzGerald GA. Systemic biosynthesis of prostacyclin by cyclooxygenase (COX)-2: the human pharmacology of a selective inhibitor of COX-2. *Proc Natl Acad Sci USA*. 1999;96:272-277.
4. Bergendal A, Adami J, Bahmanyar S, et al. Non-steroidal anti-inflammatory drugs and venous thromboembolism in women. *Pharmacoepidemiol Drug Saf*. 2013;22:658-666.
5. Rabausch K, Bretschneider E, Sarbia M, et al. Regulation of thrombomodulin expression in human vascular smooth muscle cells by COX-2-derived prostaglandins. *Circ Res*. 2005;96:1-6.
6. Bancos S, Bernard MP, Topham DJ, Phipps RP. Ibuprofen and other widely used non-steroidal anti-inflammatory drugs inhibit antibody production in human cells. *Cell Immunol*. 2009;258:18-28.
7. Capuano A, Scavone C, Racagni G, Scaglione F. Italian Society of Pharmacology. NSAIDs in patients with viral infections, including Covid-19: victims or perpetrators? *Pharmacol Res*. 2020;157:104849.

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# Specific coagulation markers may provide more therapeutic targets in COVID-19 patients receiving prophylactic anticoagulant

Dear Editor,

I read with interest the recent published article from Professor Robert L. Medcalf, entitled "Fibrinolysis and COVID-19: a plasmin paradox."[1] As an indirect marker of thrombin and plasmin activation, D-dimer has been suggested to guide anticoagulant treatment in COVID-19 patients.[2,3] However, D-dimer may not be able to reflect accurate fibrinolysis status of COVID-19 patients, and therefore can't guide the possible antifibrinolysis or thrombolytic therapy in different stages of COVID-19, as Professor Medcalf discussed. Hence, we speculated that measuring direct markers of thrombin, plasmin, and so on may provide more therapeutic targets in COVID-19 patients with coagulopathy.

To describe the intuitive coagulation and fibrinolysis features of COVID-19 patients, we randomly enrolled 20 patients with critical COVID-19 entering the intensive care unit (ICU) of Tongji Hospital in Wuhan, China, from February 1 to February 20, 2020; all of these patients stayed in ICU for 15 to 20 days and received a prophylactic dose of low molecular weight heparin (LMWH) for at least 7 days. Their residual plasma samples for routine coagulation tests during ICU stay were reserved at −70 degrees. Recently, we detected the levels of thrombin-antithrombin complex (TAT), plasmin-antiplasmin complex (PAP), and tissue plasminogen activator-plasminogen activator inhibitor 1 complex (tPAI-C) of these samples using a HISCL 5000 analyzer and original chemiluminescence reagents (SYSMEX). Levels of these three markers reflect activities of thrombin, plasmin, and plasminogen activator inhibitor-1 (PAI-1), respectively.

Eventually, 8 patients (40%) died and 12 patients were discharged. The results of D-dimer, prothrombin time (PT), platelet count, TAT, and PAP on days 1, 4, 7, 10, and 14 between survivors and non-survivors were compared (Figure 1). In addition, the results of tPAI-C on days 1 and 14 between survivors and non-survivors were also compared.

Perhaps due to the fact that LMWH was routinely used in all of the enrolled patients, no significant difference on results of D-dimer, PT, and platelet count during the early and middle stage were found between survivors and non-survivors. Three (37.5%) of the non-survivors met the International Society on Thrombosis and Haemostasis (ISTH) diagnostic criteria for

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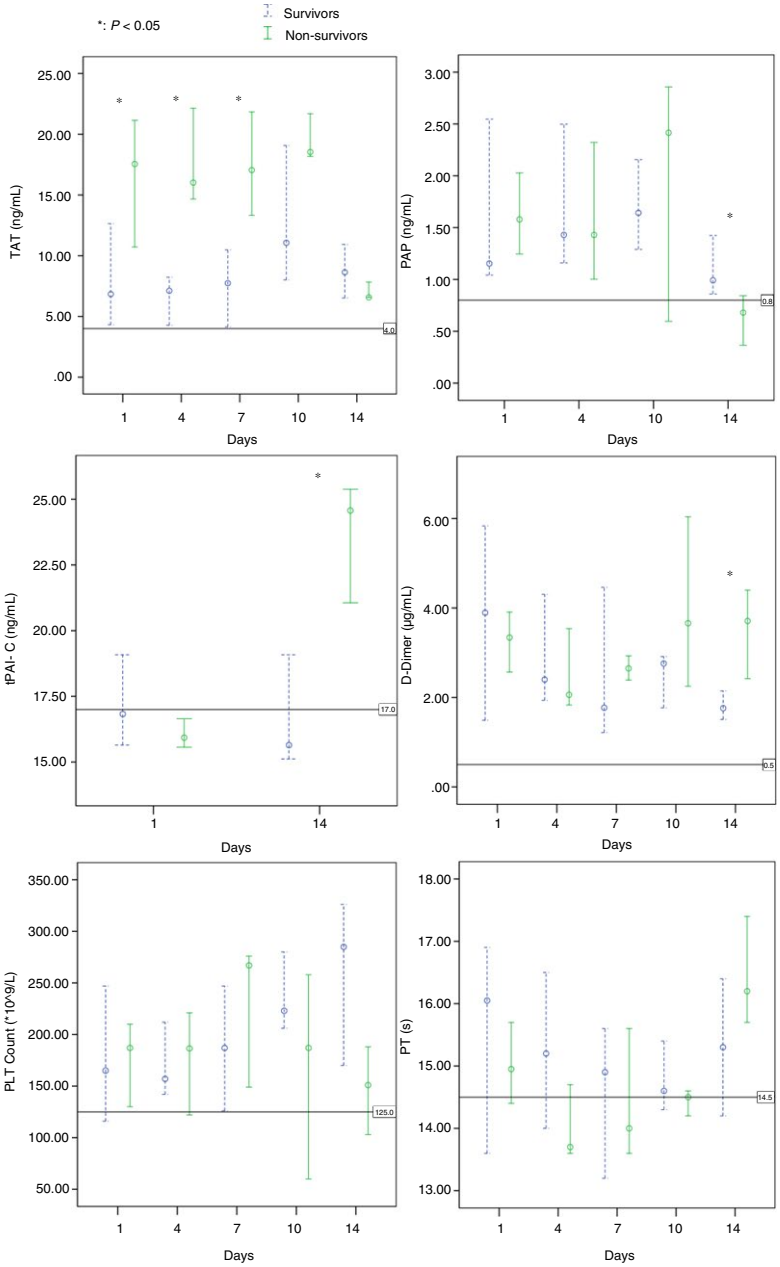


**FIGURE 1** Dynamic profile of coagulation parameters in critical COVID-19 patients. Timeline charts illustrate the changes of coagulation parameters in 20 critical patients with COVID-19 (8 non-survivors and 12 survivors) during intensive care unit stay. The error bars show medians and 25% and 75% percentiles. The horizontal lines show the upper normal limits of thrombin-antithrombin complex (TAT; 4.0 ng/mL), plasmin-antiplasmin complex (PAP; 0.8 µg/mL), tissue plasminogen activator-plasminogen activator inhibitor 1 complex (TPAI-C; 17.0 ng/mL), D-dimer (0.5 µg/mL), and prothrombin time (PT; 14.5 s), and the lower normal limits of platelet count (125 × $10^9$/L), respectively. *, $P < .05$ for survivors versus non-survivors with Mann-Whitney *U* test

disseminated intravascular coagulation (DIC) during ICU stay; this incidence rate was also lower than that in our previous study (71.4%, $P < .05$).[4]

Interestingly, the other specific coagulation markers we detected might provide more therapeutic targets: the higher TAT levels in non-survivors than in survivors during the early and middle stage reflected more excess generation of thrombin,[5] and might indicate higher dose of anticoagulant; the higher tPAI-C levels in non-survivors than in survivors during the late stage reflected fibrinolysis shutdown due to endothelial dysfunction,[6] and might indicate further thrombolytic therapy with tissue plasminogen activator.

Although D-dimer levels in non-survivors increased significantly at the late stage, the PAP levels in them were decreased and significantly lower than survivors; this perhaps implies a hypofibrinolysis status due to increased PAI-1 (reflected by tPAI-C level) as well as excess consumption of plasminogen.[7] Hence, PAP levels could reflect more accurate fibrinolytic status than D-dimer at the late stage, and avoid unnecessary (even harmful) anti-fibrinolytic therapy in critical COVID-19 patients. In addition, as Professor Medcalf mentioned in his article, if an antifibrinolytic agent such as tranexamic acid was to be given early to COVID-19 patients for inhibiting infectivity of coronavirus, at what point would this need to be stopped? We consider that PAP level may be used to guide the antifibrinolysis therapy with appropriate thresholds.

Our study was retrospective and with small sample size, the results should be confirmed in an adequately powered intervention study. As the mortality seems still high in critical COVID-19 patients receiving prophylactic anticoagulant, whether treatment strategies based on these specific coagulation markers could further improve outcome of critical COVID-19 patients was the issue worthy of investigation.

## CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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## REFERENCES

1. Medcalf RL, Keragala CB, Myles PS. Fibrinolysis and COVID- 19: a plasmin paradox. *J Thromb Haemost*. 2020. [Epub ahead of print] https://doi.org/10.1111/jth.14960
2. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost*. 2020;18(5):1094-1099.
3. 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.
4. Tang N, Li D, Wang X, et al. Abnormal Coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost*. 2020;18(4):844-847.
5. Gando S, Nanzaki S, Sasaki S, Kemmotsu O. Significant correlations between tissue factor and thrombin markers in trauma and septic patients with disseminated intravascular coagulation. *Thromb Haemost*. 1998;79(6):1111-1115.
6. Schmitt FCF, Manolov V, Morgenstern J, et al. Acute fibrinolysis shutdown occurs early in septic shock and is associated with increased morbidity and mortality: results of an observational pilot study. *Ann Intensive Care*. 2019;9(1):19.
7. Semeraro N, Ammollo CT, Semeraro F, Colucci M. Sepsis, thrombosis and organ dysfunction. *Thromb Res*. 2012;129(3):290-295.

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

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.[1] 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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