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We consider that the variables included in the study are not well described in the paper since the only reference in the article by Tang et al is to the original SOFA score. Furthermore, it is possible that the weight of thrombopenia in the SIC score has been magnified, since thrombopenia is a criterion included in both scores (SOFA and SIC) as individual items. As thrombopenia has been described as a frequent finding in COVID-19,<sup>4</sup> it could be a consequent bias that limits the interpretation of the study.


#### CONFLICT OF INTEREST

Authors declare that there are no financial, labor or other relationships that may constitute a conflict of interest with respect to this work. That is to say, we have not received "benefits in money, goods, hospitality or subsidies" from any source that has a particular interest.

#### AUTHOR CONTRIBUTIONS

Rubén Coto-Hernández and María Teresa Fábregas Ruano contributed substantially to the discussion, research and writing of this letter to the editor. All authors discussed the results and contributed to the final manuscript.

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Received: 7 April 2020 | Accepted: 10 April 2020

DOI: 10.1111/jth.14851

## Response to 'Reply to Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy'

We appreciate the opportunity to respond to the comment about the Sequential Organ Failure Assessment (SOFA) score by Dr Ruben Coto. We admit that we misquoted the original SOFA score including six items<sup>1</sup> in our paper. But we did not double-count the thrombopenia for sepsis-induced coagulopathy (SIC) score<sup>2</sup> in practice, it's an obvious repetitive item.

The enrolled patients in our study met the definition of severe COVID-19 suggested by the National Health Commission of

China,<sup>3</sup> which reflected respiratory insufficiency based on three parameters. As PaO<sub>2</sub>/FiO<sub>2</sub> ≤ 300 mm Hg is one item of the severe COVID-19 definition, and respiratory support was given to almost all of the enrolled patients, in fact, most of our patients could get ≥2 points of respiratory SOFA score, meanwhile, some patients also got points on cardiovascular, hepatic, or renal SOFA score. Hence, the results of prothrombin time (international normalized ratio) and platelet count were commonly the determinants of SIC scoring in these patients.

We would like to modify the text about the SOFA score used in the SIC criteria before formal publication of this paper.

Manuscript handled by: David Lillcrap

Final decision: David Lillcrap, 10 April 2020

## CONFLICTS OF INTEREST

None declared.

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Received: 7 April 2020 | Accepted: 11 April 2020

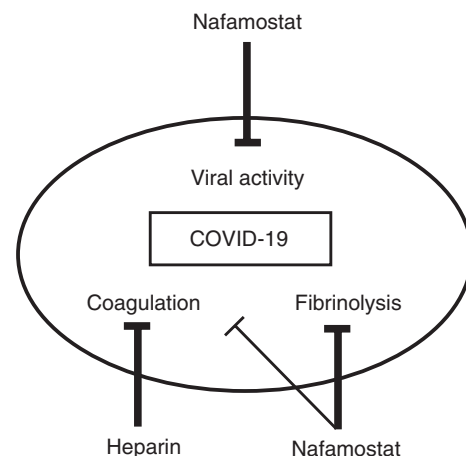
DOI: 10.1111/jth.14858

## Potential of heparin and nafamostat combination therapy for COVID-19

Tang et al recently reported that, in COVID-19 infections caused by the novel coronavirus (SARS-CoV-2), heparin anticoagulant therapy lowers the mortality rate in patients who present with markedly elevated concentrations of D-dimer.<sup>1</sup> In other words, abnormal coagulation may influence the prognosis of COVID-19. This is extremely interesting. The article did not describe to what extent heparin improves the abnormal coagulation and further studies by this group are anticipated. The authors reported in that article<sup>1</sup> and a previous article<sup>2</sup> that the abnormal coagulation seen in non-survivors of COVID-19 clearly differs from the abnormal coagulation typically seen in other severe infectious diseases. Specifically, markedly decreased fibrinogen levels and markedly elevated fibrin degradation product (FDP) levels have been observed in COVID-19 non-survivors. These observations carry the characteristics of disseminated intravascular coagulation (DIC) with enhanced fibrinolysis rather than the DIC with suppressed fibrinolysis that is caused by infectious diseases (where FDP and D-dimer levels are mildly elevated and fibrinogen is not decreased).<sup>3</sup> Regarding this point, we state that a rapid and progressive decrease in fibrinogen levels should be noted with caution in COVID-19. Most reports concerning COVID-19 non-survivors have shown that D-dimer levels are significantly increased in these patients, and that prognosis can be predicted based on D-dimer elevations.<sup>4-6</sup> Tang et al analyzed abnormal coagulation using fibrinogen and FDP in addition to prothrombin time (PT), activated partial thromboplastin time (APTT), and D-dimer<sup>2</sup> and found that heparin treatment may be effective.<sup>1</sup> Their reports

have been attracting attention to those perspectives. Because FDP increases more sensitively than D-dimer in DIC with enhanced fibrinolysis, evaluation of FDP rather than D-dimer may be an option to assess the prognosis of COVID-19.

Tang et al reported that heparin (particularly low molecular weight heparin) improves the prognosis of patients with high D-dimer level.<sup>1</sup> In Japan, anticoagulants used for DIC include heparin as well as antithrombin concentrates, recombinant human soluble thrombomodulin, and



**FIGURE 1** Anti-COVID-19 action by nafamostat (author's hypothesis). Nafamostat is anticipated to show anti-viral and anti-enhanced-fibrinolysis disseminated intravascular coagulation effects. Nafamostat has weak anticoagulant effects, and combination with heparin may therefore be effective