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Reply to “Ibuprofen and thromboembolism in SARS-COV2”

We appreciate the opportunity to respond to the comments by Drs. Rad et al. Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used in many countries for the relief of symptoms of pain, inflammation, and fever, which reduce the conversion of arachidonic acid to prostaglandins, prostacyclin (PGI₂), and thromboxane (Tx) A₂ by inhibiting cyclooxygenase (COX). At present, it is recognized that there are two related but different types of COX activity, COX-1 and COX-2. COX-1 is continuously expressed in most tissues, and platelets containing COX-1 are the main source of TXA₂,¹ which affects vascular smooth muscle contraction and platelet aggregation.² COX-2 is mainly expressed in the inflammatory response and is the main source of PGI₂.³ According to the different selectivity for COX inhibition, NSAIDs are divided into nonselective and COX-2 selective. Ibuprofen is a type of nonselective NSAIDs.

As the authors said, several studies have confirmed that NSAIDs (including ibuprofen) are significantly associated with the occurrence of venous thromboembolism, especially in selective COX-2 inhibitors, and are related to the dose and duration of administration, but the mechanism is not clear. The primary hypothesis is that NSAIDs may create an imbalance between PGI₂ and TXA₂, resulting in a relative increase in TXA₂, leaving the body in a hypercoagulable state.⁴

Moreover, the reduction of prostaglandin leads to the decrease of thrombomodulin, which increases the incidence of thrombosis.⁵

During COVID-19 treatment, the use of NSAIDs was very common. In addition to increasing the risk of thrombosis, NSAIDs (including ibuprofen) may also reduce host defense capability during infection.⁶ On the one hand, NSAIDs may mask the early symptoms of the disease, leading to delays in diagnosis and treatment; on the other hand, NSAIDs can inhibit the immune response of the body through a variety of ways, leading to disease progression.⁷ Even though some studies have shown that NSAIDs may be beneficial to patients with viral infection, it is still necessary to use them with great caution.

In the clinical diagnosis and treatment of novel coronavirus patients, more attention should be paid to the use and management of NSAIDs. Clinicians need to determine whether patients have a history of gastrointestinal ulcers and cardiovascular events, and avoid overdose or long-term medication. Now, more research is really needed to determine the effects of NSAIDs on the incidence of venous thromboembolism and viral infection in novel coronavirus patients.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

All the authors participated in the coordination and drafting of the text. All the authors read and approved the final manuscript.

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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