Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Arian Arjomandi Rad and Robert Vardanyan equally contributed to this work.

ORCID

Arian Arjomandi Rad https://orcid.org/0000-0002-4931-4049
Robert Vardanyan https://orcid.org/0000-0002-8111-2084

REFERENCES

1. Klok F, Kruip M, van der Meer N, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res*. 2020. https://doi.org/10.1016/j.thromres.2020.04.013
2. Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. *J Thromb Haemost*. 2020; https://doi.org/10.1111/jth.14830
3. Wang T, Chen R, Liu C, et al. Attention should be paid to venous thromboembolism prophylaxis in the management of COVID-19. *Lancet Haematol*. 2020;7(5):e362-e363.
4. Liu T, Zhang J, Yang Y, et al. The potential role of IL-6 in monitoring coronavirus disease 2019. *SSRN Electr J*. 2020. https://doi.org/10.2139/ssrn.3548761
5. Libby P, Simon D. Inflammation and thrombosis. *Circulation*. 2001;103(13):1718-1720.
6. Kearney P, Baigent C, Godwin J, Halls H, Emberson J, Patrono C. Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. *BMJ*. 2006;332(7553):1302-1308.
7. Biere-Rafi S, Di Nisio M, Gerdes V, et al. Nonsteroidal anti-inflammatory drugs and risk of pulmonary embolism. *Pharmacoepidemiol Drug Saf*. 2011;20(6):635-642.
8. Schmidt M, Christiansen CF, Horváth-puhó E, Glynn RJ, Rothman KJ, Sørensen HT. Non-steroidal anti-inflammatory drug use and risk of venous thromboembolism. *J Thromb Haemost*. 2011;9(7):1326-1333.
9. Ungprasert P, Srivali N, Wijarnpreecha K, Charoenpong P, Knight E. Non-steroidal anti-inflammatory drugs and risk of venous thromboembolism: a systematic review and meta-analysis. *Rheumatology*. 2014;54(4):736-742.
10. Lee T, Lu N, Felson D, et al. Use of non-steroidal anti-inflammatory drugs correlates with the risk of venous thromboembolism in knee osteoarthritis patients: a UK population-based case-control study. *Rheumatology*. 2016;55(6):1099-1105.

Received: 20 May 2020 | Accepted: 21 May 2020

DOI: 10.1111/jth.14934

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 (PGI_2), and thromboxane (Tx) A_2 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 PGI_2.[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 PGI_2 and TXA_2, resulting in a relative increase in TXA_2, 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.

Manuscript handled by: David Lillicrap.

Final decision: David Lillicrap, 21 May 2020.

Songping Cui
Shuo Chen
Lihui Ke

Department of Thoracic Surgery, Beijing Chaoyang Hospital, Capital Medical University, Beijing, China

Correspondence
Songping Cui, Department of Thoracic Surgery, Beijing Chaoyang Hospital, Capital Medical University, Beijing 100020, China.
Email: cuisp95322@163.com

Songping Cui, Shuo Chen, and Lihui Ke are contributed equally.

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.

Received: 20 June 2020 | Accepted: 25 June 2020
DOI: 10.1111/jth.14988

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

Manuscript handled by: David Lillicrap
Final decision: David Lillicrap, 25 June 2020