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.

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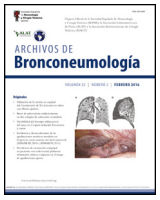

Letter to the Director

Aspirin Therapy in COVID-19: Prevention of NETosis

To the Director,

We read with immense interest the multicentre, retrospective cohort study performed and reported by Lal et al.,[1] which aimed to investigate the associations between prehospital use of aspirin and clinical outcomes in hospitalized patients with laboratory confirmed COVID-19. Consistent with the previously reported systematic reviews and meta-analyses,[2] the study[1] observed statistically significantly lower in-hospital mortality among patients who received aspirin compared to their counterparts who did not receive aspirin (adjusted hazard ratio = 0.89; 95% confidence interval 0.82–0.97; $P = 0.01$). Nevertheless, as pointed also by the authors, the large, randomized, open-label trial[3] performed by the RECOVERY Collaborative Group which aimed to evaluate the efficacy and safety of *de novo* introduction of aspirin therapy in patients hospitalized with COVID-19 observed no significant difference in the risk of mortality between aspirin users and non-users (rate ratio = 0.96; 95% confidence interval 0.89–1.04; $P = 0.35$). The RECOVERY trial[4] excluded patients who were receiving aspirin or another anti-platelet treatment during patient recruitment. The authors did not discuss adequately the discrepancy in the mortality outcomes between patients who were newly initiated on aspirin and patients who received aspirin therapy prior to hospitalization, which can suggest important clinical implications.

We believe one possible explanation of the discrepancy is that the ability of aspirin to reduce neutrophil extracellular trap (NET) formation upon the development of COVID-19, is the main driver of their mortality benefits, instead of the proposed antiviral and anti-inflammatory activities. A growing understanding of COVID-19 has discovered that the formation of neutrophil extracellular traps (NET) in the early stage of illness contribute to its pathophysiology.[4] The findings where the pre-hospitalization use of aspirin was associated with potential mortality benefits may be due to the early prevention of NET formation with the use of aspirin through the inhibition of nuclear factor (NF)-κB, an inflammatory transcriptional regulator that promotes NETosis. The *de novo* introduction of aspirin in patients with COVID-19, especially after hospital admission, may be too late for the protective effects of aspirin to be of help. This is owing to the fact that NETosis most probably has already developed before patients receive aspirin therapy.

Therefore, we believe future clinical trials investigating the efficacy of aspirin therapy in patients with COVID-19 should preferably administer these agents for pre-exposure prophylaxis and target especially high-risk patients prone to mortality. In addition, aspirin therapy should be recommended for indicated patients for primary/secondary prevention during the COVID-19 pandemic, to reduce their risk of COVID-19-related death should they acquire this deadly infection.[5]

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Conflict of interest

All authors declare that they have no potential conflicts of interest that might be relevant to the contents of this article.

References

1. Lal A, Garces JPD, Bansal V, Tekin A, Zec S, Khanna AK, et al. Pre-hospital aspirin use and patient outcomes in COVID-19: results from the International Viral Infection and Respiratory Illness Universal Study (VIRUS). Arch Bronconeumol. 2022. S0300-2896(22)00510-5 [published online ahead of print, 08.09.22].
2. Kow CS, Hasan SS. Use of antiplatelet drugs and the risk of mortality in patients with COVID-19: a meta-analysis. J Thromb Thrombolysis. 2021;52:124–9.
3. RECOVERY Collaborative Group. Aspirin in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2022;399:143–51.
4. Carmona-Rivera C, Zhang Y, Dobbs K, Markowitz TE, Dalgard CL, Oler AJ, et al. Multicenter analysis of neutrophil extracellular trap dysregulation in adult and pediatric COVID-19. JCI Insight. 2022:e160332 [published online ahead of print, 19.07.22].
5. Kow CS, Ramachandram DS, Hasan SS. Use of aspirin for primary prevention in patients with diabetes during the COVID-19 pandemic. Ir J Med Sci. 2022;191:1667–8.

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