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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Letters

More Analysis Needed to Minimize Confounding

We read with great interest the pilot study by Clemente-Moragón et al (1) investigating the effect of the β-blocker metoprolol on the clinical outcomes of critically ill patients with COVID-19. Although Clemente-Moragón et al (1) demonstrated that intravenous metoprolol provides additional benefits in reducing lung inflammation, improving oxygenation, and shortening invasive mechanical ventilation time for these patients with COVID-19-associated acute respiratory distress syndrome (ARDS), we have several serious concerns about some residual confounding factors.

First, although the study and control group had similar baseline characteristics (age, sex, body mass index, comorbidities, previous treatment with a renin-angiotensin system inhibitor, anticoagulant, corticosteroid, melatonin, and acetylcysteine), the use of other anti-inflammatory agents was unclear, such as anti-interleukin (IL)-6 or the Janus kinase inhibitor. These agents could significantly influence both the outcome and the lung inflammation of patients with COVID-19 (2,3). In addition, the effect of statin on lung inflammation has been demonstrated in the animal sepsis model (4). Therefore, the use of these medications, including anti-IL-6, Janus kinase inhibitor, and statin, should be clarified in this study.

Second, significant associations between the release of neutrophil extracellular traps and bacterial and viral infections have been observed. For patients who are critically ill with COVID-19, coinfection is not uncommon (5). Therefore, the confounding effect of coinfection among COVID-19 patients with ARDS cannot be neglected in this study.

Finally, the no-double-blind study design may be associated with the bias in the care of the study participants, such as intensive care unit stay or extubation.

In conclusion, before these issues are clarified, this study's findings should be interpreted cautiously.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

REFERENCES

1. Clemente-Moragón A, Martínez-Milla J, Oliver E, et al. Metoprolol in critically ill patients with COVID-19. *J Am Coll Cardiol*. 2021;78:1001–1011.

2. Shankar-Hari M, Vale CL, Godolphin PJ, et al. Association between administration of IL-6 antagonists and mortality among patients hospitalized for COVID-19: a meta-analysis. *JAMA*. 2021;326:499–518.

3. Chen CY, Chen WC, Hsu CK, Chao CM, Lai CC. Clinical efficacy and safety of Janus kinase inhibitors for COVID-19: a systematic review and meta-analysis of randomized controlled trials. *Int Immunopharmacol*. 2021;99:108027.

4. Wang Y, Yang W, Zhao X, Zhang R. Experimental study of the protective effect of simvastatin on lung injury in rats with sepsis. *Inflammation*. 2018;41:104–113.

5. Lai CC, Wang CY, Hsueh PR. Co-infections among patients with COVID-19: the need for combination therapy with non-anti-SARS-CoV-2 agents? *J Microbiol Immunol Infect*. 2020;53:505–512.