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 Editor

No evidence of clinical efficacy of famotidine for the treatment of COVID-19: a systematic review and meta-analysis

Dear Editor,

We read with great interest the recent article by Qian et al. that reported paxlovid as an efficacious treatment for COVID-19 patients.[1] However, the relatively high cost of paxlovid and the other currently available oral antiviral, molnupiravir, will likely curtail their access in lower-income countries.[2,3] Therefore, as the quest to find efficacious and cost-effective therapies for COVID-19 patients is still ongoing, repurposing drugs, that are approved for other indications, to treat COVID-19 is an attractive option. A recent trial by Brennen Christina et al.[4] showed that the use of famotidine for treating mild to moderate COVID-19 patients was associated with improved recovery without any significant adverse events. However, another study by Jiandong et al.[5] reported that famotidine use is associated with a higher risk of severe COVID-19 disease. Considering the newly published studies evaluating the effectiveness of famotidine and their conflicting results, we conducted a meta-analysis to determine its potential role in treating COVID-19 patients.

A systematic search was conducted on MEDLINE (via PubMed), Embase, and the Cochrane Library for relevant studies published before 15 September 2022. The inclusion criteria were comparative studies investigating famotidine for treating COVID-19 patients. Studies that used famotidine as a prophylactic agent were excluded from our analysis. The quality of the included studies was assessed using the National Institutes of Health (NIH) Quality Assessment Tool for observational cohort studies (Supplementary Table 1) and the revised Cochrane Risk of Bias Tool (RoB 2.0) for randomized controlled trials (RCTs) (Supplementary Fig. 1). The primary outcomes were all-cause mortality and the rate of no recovery. The secondary outcomes included intensive care unit (ICU) admission, time to symptom resolution, and length of hospital stay. We used RevMan 5.4 to conduct random-effects meta-analyses with odds ratios (ORs) and mean differences (MDs) as effect measures.

A total of 10 studies were included in our meta-analysis (Supplementary Table 2), of which 3 were RCTs,[4,6,7] and 7 were retrospective cohort studies.[8–14] Our analysis showed that famotidine has no effect on mortality (OR 0.96; 95% CI: 0.34, 2.70; I^2 = 100%; Fig. 1); the results remained non-significant in a sensitivity analysis conducted by excluding low-quality studies (OR 0.90; 95% CI: 0.74, 1.10; I^2 = 66%).[9–11] In terms of time to symptom resolution, a non-significant reduction was observed in the famotidine group (MD -1.86; 95% CI: -4.08, 0.36; I^2 = 81%; Fig. 2). Famotidine use reduced the length of hospital stay (MD -1.74; 95% CI: -2.30, -1.19; I^2 = 0%; Supplementary Fig. 2) but had no effect on the number of patients with no recovery (OR 0.55; 95% CI: 0.20, 1.52; I^2 = 0%; Supplementary Fig. 3) and the number of patients requiring admission to ICU (OR 1.04; 95% CI: 0.86, 1.25; I^2 = 0%; Supplementary Fig. 4).

The idea of suppressing the immunological dysregulation caused by SARS-CoV-2 as a suggested treatment is evident in the literature.[15] By producing histamine, prostaglandin D2 (PGD2), and leukotriene C4 (LTC4), it is believed that mast cells, stimulated by coronaviruses, were able to cause lung inflammation.[16] Hence, famotidine, by virtue of its histamine H2-receptor (H2R) antagonism, may be involved in modifying the pulmonary pathogenic process.

There is a paucity of data regarding the impact of famotidine on COVID-19 patients. Only studies examining famotidine as a treatment modality were included in our review. However, it is worth noting that several studies have also reported a beneficial prophylactic effect of this drug.[17,18] Freedberg et al. found that the initial use of famotidine in hospitalized COVID-19 patients was significantly associated with a decreased rate of intubation and death.[17] These results were further corroborated by a retrospective study by Mather Jeffrey et al.[18] Among the included studies in our meta-analysis, only six reported a beneficial effect of famotidine as a potential treatment.[4,6,7,9,11,13] It is worth noting that two studies have reported increased COVID-19 severity in the group receiving famotidine[5,10]; it is likely that the highest benefit of famotidine might be seen with use early in the course of the disease.

The results of our meta-analysis for the outcome of all-cause mortality are in line with those reported by Chiu *et al.* and Sun *et al.* in their meta-analyses.[19,20] However, these reviews only included 5 and 4 studies, respectively. Our study pooled the results from 10 studies, thereby extending the results of the previous meta-analyses with a significantly increased statistical power. Furthermore, we found that using famotidine reduced the length of hospital stay; there was also a trend towards benefit in the famotidine group for the outcomes of time to symptom resolution and the rate of no recovery. However, these estimates are based on the results of two studies each, precluding any strong conclusions, and requiring further confirmation by well-designed, large-scale RCTs which have not been conducted so far for famotidine. Another limitation of our meta-analysis is that the pooled estimates are based mostly on observational studies due to the scarcity of available RCTs; hence, they are susceptible to confounding bias.

In conclusion, famotidine is not effective in reducing mortality or increasing the rate of recovery in COVID-19 patients; hence it should not be used for this indication until large-scale RCTs have established its efficacy.

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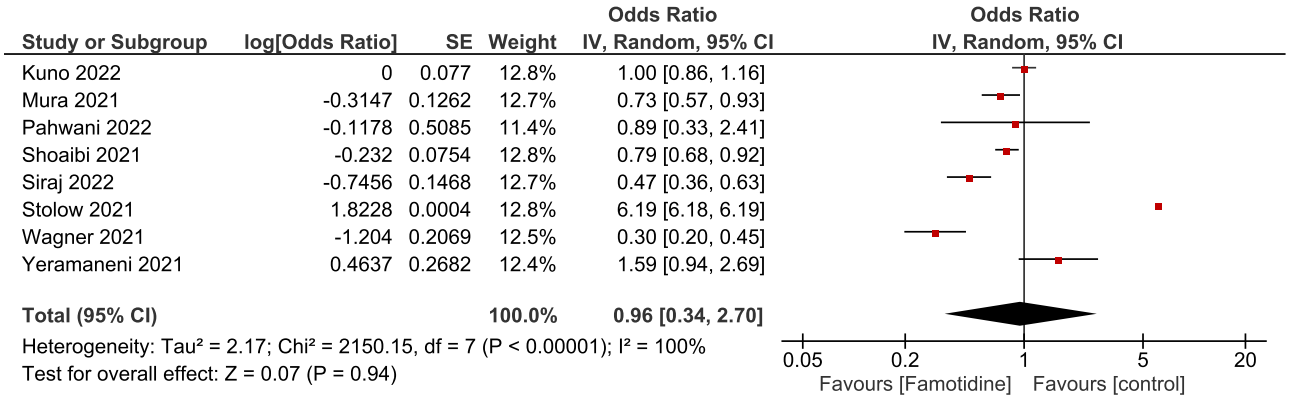

Fig. 1. Effect of famotidine use on all-cause mortality in COVID-19 patients.

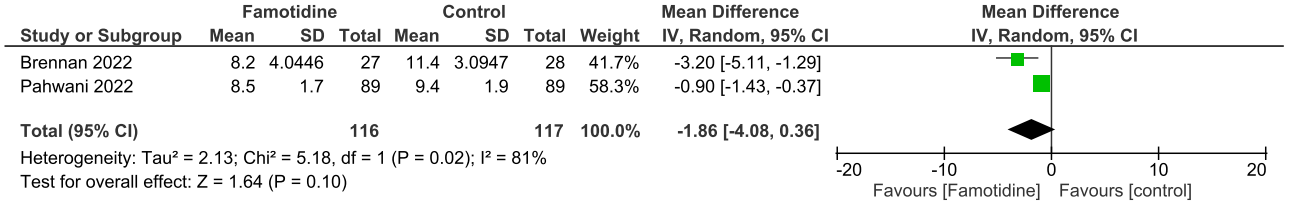

Fig. 2. Effect of famotidine use on time to symptom resolution.

Human and animal participants

Research involving human participants and/or animals: No animals or human subjects were used in the current study.

Informed consents

No informed consents were required for the purpose of the current study.

Availability of data

The data that support the findings of this study are available from the corresponding author, HAC, upon reasonable request.

Declaration of Competing Interest

The authors report no relationships that could be construed as a conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2022.11.022.

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