

Association Between Famotidine Use and Clinical Outcomes in Patients With COVID-19: Assessment of Available Evidence

Tianyi Ma, MD¹ and Meng Wu, MD¹

Am J Gastroenterol 2020;00:1. <https://doi.org/10.14309/ajg.0000000000001008>

We read with great interest the article by Mather et al. (1), who reported that famotidine reduced mortality and the risk of death or intubation in hospitalized patients with coronavirus disease 2019 (COVID-19) by 63% and 53%, respectively, even after propensity score matching. Despite its innovation, the study had limitations.

First, data on the indications for famotidine use were missing. A recent study (2) noted that the use of proton pump inhibitors as gastric acid inhibitors, with indications similar to those for the use of famotidine, were considered to be associated with an increased risk of severe clinical outcomes of COVID-19. This study lacked information regarding the use of proton pump inhibitors as concomitant medication. Second, we noted that in 83% of the users, famotidine

was administered orally. However, the common over-the-counter famotidine chewable formulations commonly contain calcium carbonate. Based on this, a recent study (3) suggested that calcium supplementation in early stages improved the prognosis of patients with COVID-19. This potential protective effect must be considered. Finally, as the authors mentioned, the differences in clinical outcomes between treatment groups with different doses, treatment durations, and routes of administration were not elaborated.

This study suggested that add-on famotidine therapy was independently associated with low incidence of adverse clinical outcomes. However, another recent retrospective cohort study of 952 patients in Hong Kong suggested that famotidine use was not associated with the severity of COVID-19 (4). Because of contradictory evidence, we conducted a meta-analysis to investigate the beneficial effects of famotidine on COVID-19.

A systematic literature search was conducted using PubMed, EMBASE, and Web of Science for relevant studies published before September 12, 2020. The inclusion criteria were studies investigating the effect of famotidine on the clinical outcomes of COVID-19 and reporting risk estimates such as odds ratio (OR), relative risk, or hazard ratio. The quality of the included studies was evaluated according to the Newcastle-Ottawa scale. The analysis was performed using the pooled OR and 95% confidence interval. If the heterogeneity was low ($I^2 < 25\%$), we reported the results with fixed-effect model.

Finally, 3 observational studies (1,4,5) consisting of 3,450 participants were included. These included 2 high-quality studies and 1 medium-quality study. The pooled results showed that the use of famotidine was associated with lower incidence of adverse clinical outcomes in hospitalized patients with COVID-19 (pooled OR 0.50, 95% confidence interval: 0.31–0.80, $P < 0.05$; heterogeneity: $I^2 = 0\%$, $P = 0.442$). Because of the lack of

clinical data, we did not conduct further subgroup analysis.

Although this meta-analysis revealed positive results, the inherent bias of these retrospective, observational studies cannot be avoided. Another potential bias might be due to the heterogeneity of standard-of-care in each study. Hence, the results should be interpreted cautiously. In the absence of reliable evidence, the role of famotidine remains uncertain, and the outcome of ongoing clinical trials (NCT04370262) is eagerly anticipated.

CONFLICTS OF INTEREST

Guarantor of the article: Tianyi Ma, MD.

Specific author contributions: T.M. and M.W. drafted the manuscript.

Financial support: None to report.

Potential competing interests: None to report.

REFERENCES

- Mather JF, Seip RL, McKay RG. Impact of famotidine use on clinical outcomes of hospitalized patients with COVID-19. *Am J Gastroenterol* 2020;115(10):1617–23.
- Lee SW, Ha EK, Yeniova AO, et al. Severe clinical outcomes of COVID-19 associated with proton pump inhibitors: A nationwide cohort study with propensity score matching. *Gut* 2020. doi:10.1136/gutjnl-2020-322248.
- El-Kurdi B, Khatua B, Rood C, et al. Mortality from coronavirus disease 2019 increases with unsaturated fat and may be reduced by early calcium and albumin supplementation. *Gastroenterology* 2020; 159(3):1015–8.e4.
- Cheung KS, Hung IF, Leung WK. Association between famotidine use and COVID-19 severity in Hong Kong: A territory-wide study. *Gastroenterology* 2020. doi:10.1053/j.gastro.2020.05.098.
- Freedberg DE, Conigliaro J, Wang TC, et al. Famotidine use is associated with improved clinical outcomes in hospitalized COVID-19 patients: A propensity score matched retrospective cohort study. *Gastroenterology* 2020;159(3):1129–31.e3.

¹Department of Hepatopancreatobiliary Medicine, The Second Hospital of Jilin University, Jilin, China. **Correspondence:** Tianyi Ma, MD. E-mail: matianyi1994@163.com.