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.

Use of Famotidine and Risk of Severe Course of Illness in Patients With COVID-19: A Meta-analysis

To The Editor: The article by Ghosh et al,[1] in which they discuss the potential of famotidine to regulate innate and adaptive immune responses, provides a rationale to repurpose famotidine for the treatment of coronavirus disease 2019 (COVID-19). There have been few studies evaluating the use of famotidine in patients with COVID-19, and thus we performed a meta-analysis to summarize the overall effect of famotidine on the clinical outcomes in this patient population.

We searched PubMed, Google Scholar, and medRxiv (preprint repository) databases, up to March 31, 2021, for studies evaluating the risk of a severe course of illness among famotidine users with COVID-19 compared with nonusers, with the following keywords and their MeSH terms: *COVID-19*, *famotidine*, and *histamine-2 recepto antagonist*, without language restrictions. Studies were included if they were original, observational (prospective or retrospective) studies, included patients with COVID-19 with documented use of famotidine, and reported adjusted estimates for mortality and other severe clinical outcomes with the use of famotidine relative to nonuse of famotidine. Each included article was independently evaluated by 2 authors (C.S.K. and S.S.H.), who extracted the study characteristics and measures of effect. The quality of observational studies was evaluated using the Newcastle-Ottawa Scale.[2] The outcome of interest was the development of a severe course of illness, characterized by death or other severe clinical outcomes.

Adjusted measures of association and the corresponding 95% confidence intervals (CIs) from each study were pooled using a random-effects model. Cochran's Q heterogeneity test (Q test) and its related metric, the I2 statistics, were used to evaluate heterogeneity across studies. The meta-analysis was performed with Meta XL, version 5.3 (EpiGear International, Queensland, Australia).

Our literature search yielded 46 unique abstracts. After deduplication and application of the eligibility criteria, 6 relevant articles were shortlisted for inclusion through full-text examination. Of these, 2 studies were excluded, as they reported no mortality or other severe clinical outcomes in COVID-19. Study characteristics are depicted in the Table.[3-7] All studies were retrospective and are deemed good quality with a Newcastle-Ottawa Scale ranging from 7 to 8 (Table). The meta-analysis of 3 studies[4,5,7] (n=31,563), which provided adjusted hazard ratio (aHR), revealed a nonsignificant association between the use of famotidine and the hazard for a severe course of illness in patients with COVID-19, relative to nonuse of famotidine (Figure; pooled HR=0.83; 95% CI, 0.49 to 1.41). Similarly, a separate meta-analysis of 2 studies[3,5] (n=1928), which provided adjusted odds ratio (aOR), revealed a nonsignificant association between the use of famotidine and the odds for a severe course of illness in patients with COVID-19, relative to nonuse of famotidine (Supplemental Figure, available online at http://www.mayoclinicproceedings.org); pooled OR=0.85; 95% CI, 0.27 to 2.63).

The finding of our meta-analysis suggests no significant benefits with the use of famotidine in terms of reducing the risk of a severe course of illness in patients with COVID-19.

Since the suppression of gastric acid by famotidine may lead to impaired clearance of the novel coronavirus, the possibility that impaired viral clearance negates the potential benefits conferred by the use of famotidine in COVID-19 requires further evaluation. However, the studies included in our meta-analysis are of retrospective design, and thus generalizability of the findings may be limited. Prospective studies are required to substantiate our findings.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

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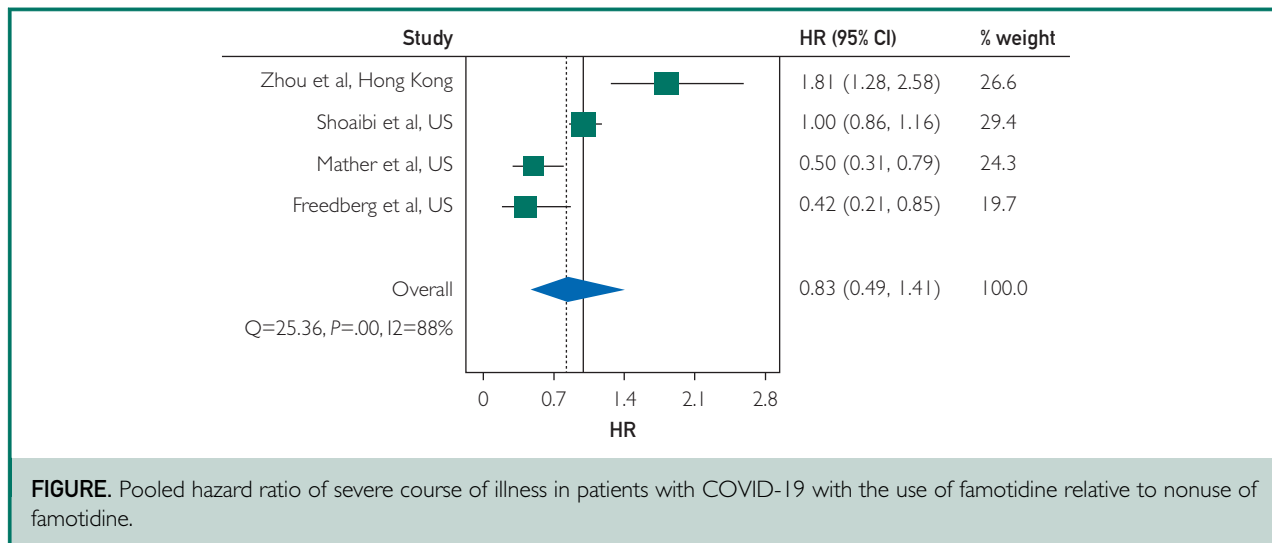University of Newcastle
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TABLE. Characteristics of Included Studies

Study	Country	Design	Total number of patients	Age (median/mean unless otherwise specified)	Severe course of illness[a]			Covariates adjustment	NOS
					Famoti-dine users (n/N; %)	Nonusers of famoti-dine (n/N; %)	Adjusted estimate		
Zhou et al[7]	Hong Kong	Retrospective database review	3144	All patients=44.8	Not reported	Not reported	OR=1.34 (0.24-6.06)	Age, comorbidities, use of co-medications, neutrophil count, lymphocyte count, serum platelet level, serum urea level, serum creatinine level, serum albumin level, serum glucose level	7
Yeramaneni et al[3]	United States	Retrospective, multienter	1156	Famotidine users=62.2 Nonusers of famotidine =62.1	62/410 (15.1)	73/746 (9.8)	OR=1.49 (0.80-2.79)	Age, sex, race, ethnicity, BMI, comorbidities	8
Shoaibi et al[4]	United States	Retrospective database review	26,027	Famotidine users with ≥60 years: 55.2%	326/1623 (20.0)	5534/24404 (22.7)	HR=1.00 (0.86-1.16)	Age, sex, index month, comorbidities	8
Mather et al[5]	United States	Retrospective, single center	772	Famotidine users=63.3 Nonusers of famotidine =66.4	36/83 (43.3)	495/689 (71.8)	OR=0.47 (0.23-0.97) HR=0.50 (0.31-0.79)	Age, sex, race, smoking status, BMI, comorbidities, National Early Warning Score	7
Freedberg et al[6]	United States	Retrospective, single center	1620	Famotidine users with >65 years: 47.6% Famotidine users with >65 years: 42.6%	8/84 (9.5)	332/1536 (21.6)	HR=0.42 (0.21-0.85)	Age, sex, race, BMI, comorbidities, initial oxygen requirements	8

[a]In the study by Cheung et al,[7] the severe course of illness was defined as requirement for intensive care unit admission, intubation, or death. In the study by Yeramaneni et al,[3] the severe course of illness was defined as death within 30 days of hospitalization. In the study by Shoaibi et al,[4] the severe course of illness was defined as combined death and/or the requirement for mechanical ventilation, tracheostomy, or extracorporeal membrane oxygenation. In the study by Mather et al,[5] the severe course of illness was defined as a composite of death or requirement for ventilation. In the study by Freedberg et al,[6] the severe course of illness was defined as a composite of death or endotracheal intubation from day 2 to day 30 of hospitalization.

BMI, body mass index; HR, hazard ratio; NOS, Newcastle-Ottawa Scale; OR, odds ratio.

Study		HR (95% CI)	% weight
Zhou et al, Hong Kong		1.81 (1.28, 2.58)	26.6
Shoaibi et al, US		1.00 (0.86, 1.16)	29.4
Mather et al, US		0.50 (0.31, 0.79)	24.3
Freedberg et al, US		0.42 (0.21, 0.85)	19.7
Overall		0.83 (0.49, 1.41)	100.0
Q=25.36, P=.00, I2=88%			

FIGURE. Pooled hazard ratio of severe course of illness in patients with COVID-19 with the use of famotidine relative to nonuse of famotidine.

1. Ghosh R, Chatterjee S, Dubey S, Lavie CJ. Famotidine against SARS-CoV2: a hope or hype? *Mayo Clin Proc.* 2020;95(8):1797-1799.

2. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2013. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed November 7, 2020.

3. Yeramaneni S, Doshi P, Sands K, Cooper M, Kurbegov D, Fromell G. Famotidine use is not associated with 30-day mortality: a coarsened exact match study in 7158 hospitalized COVID-19 patients from a large healthcare system. *Gastroenterology.* 2021;160(3):919-921.e3.

4. Shoaibi A, Fortin S, Weinstein R, Berlin J, Ryan P. Comparative effectiveness of famotidine in hospitalized COVID-19 patients. *Preprint. medRxiv.* 2020.

5. Mather JF, Seip RL, McKay RG. Impact of famotidine use on clinical outcomes of hospitalized patients with COVID-19. *Am J Gastroenterol.* 2020. https://doi.org/10.14309/ajg.0000000000000832.

6. 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):1129-1131.e3.

7. Zhou J, Wang X, Lee S, et al. Proton pump inhibitor or famotidine use and severe COVID-19 disease: a propensity score-matched territory-wide study [published online ahead of print December 4, 2020]. Gut. http://doi.org/10.1136/gutjnl-2020-323668.

In Reply—Use of Famotidine and Risk of Severe Course of Illness in Patients With COVID-19: A Meta-analysis

To The Editor: Kow and colleagues' interest in our recent letter to the editor[1] regarding the potential for famotidine in COVID-19 infection was much appreciated. Obviously, their meta-analysis is small and probably not adequately powered but still suggested 37% and 7% reductions in severe disease in the general and adjusted analyses, respectively: obviously, with wide confidence intervals that were not close to statistical significance. A large-scale randomized study that was adequately powered, preferably with famotidine, started early in COVID-19, would be required to fully determine the full potential of the benefits of famotidine in COVID-19; this type of study is likely not coming in this pandemic. However, their meta-analysis does not provide much reason for concern regarding significant harms or risks with famotidine in COVID-19.

At present, many clinicians are recommending not only famotidine but several other nonprescription fairly harmless therapies including vitamins C and D, zinc, melatonin, and H1 antihistamine agents for outpatient therapy in COVID-19, all with various degrees of evidence.[2] At present, an old generic prescription medication, colchicine, typically used for gout,[3] but also for pericarditis, is now used with considerable evidence for coronary artery disease.[3] Colchicine is now being considered in COVID-19, originally based on the Greek Study in the Effects of Colchicine in Covid-19 Complications Prevention (GREECO-19) study[4,5] and now with considerably more evidence in the recently released Colchicine Coronavirus SARS-CoV2