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.

2019 (COVID-19). Like our recent retrospective study on the same topic,[2] they classified the use of famotidine based on exposure within 24 hours after hospital admission and followed patients with COVID-19 for death for up to 30 days. Interestingly, although our study found a nearly 2-fold protective association between the use of famotidine and death or intubation (adjusted hazard ratio, 0.42; 95% confidence interval [CI], 0.21–0.85), Yeramaneni et al found no association between famotidine and death (adjusted odds ratio, 1.59; 95% CI, 0.94–2.71). Why might the 2 studies, so similar in design, have such different results?

First, it is possible that differences related to institutional patterns of use of famotidine underlie the discrepancy in study findings. For example, if famotidine was often used for stress ulcer prophylaxis in critically patients at Yeramaneni et al's institution, then patients who received famotidine may have been sicker at baseline than those who did not. Sixteen percent of patients used famotidine in Yeramaneni et al's study compared with 5% in ours, implying a fundamental difference related to institutional patterns of use. Before matching, patients who used famotidine at Yeramaneni et al's institution were sicker in almost every way (higher oxygen requirements, more comorbidities, etc), whereas this was not true in our cohort. After matching, differences within Yeramaneni et al's cohort are likely to persist in the unmatched categories. Given the significant baseline differences between those who used famotidine and those who did not, these residual confounders would likely bias results toward showing harm associated with famotidine.

Second, home use of famotidine may help to explain the differences between studies. An assumption of our study was that use of famotidine in the hospital represented a continuation of home use of famotidine. Intriguingly, home use of famotidine in Yeramaneni et al's study seemed to have the opposite relationship with death compared with use in the hospital (adjusted odds ratio, 0.49 [95% CI, 0.16–1.52] for home use of famotidine vs 1.59 [95% CI, 0.94–2.71] for use of famotidine in the hospital). This hint of an interaction between home and hospital use of famotidine is puzzling and suggests that hospital use of famotidine does not represent a continuation of home use in Yeramaneni et al's study. An analysis of home use of famotidine in Yeramaneni et al's prematched cohort, excluding those who used famotidine in the hospital, would be interesting. One possibility is that early, but not late, use of famotidine may be beneficial in COVID-19.[3]

Examining the totality of evidence, what do we have? Our study and other retrospective studies of famotidine suggest there may be an association between the use of famotidine and improved outcomes among hospitalized patients with COVID-19[4,5]; this was also suggested by a case series of famotidine with quantitative symptom tracking in nonhospitalized patients.[3] The data from Yeramaneni et al and other retrospective studies[6,7] show no association. We agree with Yeramaneni et al that famotidine should only be used as COVID-19 therapy in the context of a clinical trial. Such trials are ongoing, and the results of these trials will be the crucial next step in answering the question of whether there is a role for famotidine in the treatment of COVID-19.[8,9]

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Conflicts of interest
The authors disclose no conflicts.

Most current article

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Famotidine and Mortality in Coronavirus Disease 2019

Dear Editors:

We read with great interest the study by Yeramaneni et al[1] in which the authors have retrospectively analyzed the effect of famotidine on 30-day mortality in hospitalized patients with Coronavirus Disease 2019 (COVID-19). In a matched cohort of 410 patients who received famotidine and 746 who did not, 30-day mortality was higher with famotidine (15.1% vs 9.8%, $P = .007$). A few points merit consideration. First, the authors adjusted the 2 groups for World Health Organization severity within 48 hours of admission. World Health Organization severity level 5 includes patients on mechanical ventilation or extracorporeal membrane oxygenation. Of all patients, 6.3% and 0.5% in the famotidine and nonfamotidine groups, respectively, were classified as World Health Organization severity level 5, leading to a mismatch. Even the postmatch famotidine group had a higher proportion of patients with concomitant steroids, antiviral, and tocilizumab use because of severe disease. The mortality in the famotidine group among patients on mechanical ventilation was extremely high: 63 patients required mechanical ventilation and 62 (99%) patients died. In such patients, any drug is unlikely to be of much benefit. Second, the use of steroids and tocilizumab in the cohort was associated with higher mortality. In contrast, prior studies suggest reduced mortality in patients receiving steroids and tocilizumab.[2,3]

The imbalance in steroid use across groups may indicate that the severity of patients may not have been matched despite the multivariable model with Coarsened Exact Matching, because sicker patients are more likely to be administered steroids. In this case, it cannot be ruled out that the increase in mortality due to famotidine use observed in this study is a spurious association because of confounding. It has been reported earlier that failing to adjust for time-dependent variables may lead to a spurious increase in mortality. Therefore, a conventional analysis adjusted for baseline characteristics will not account for confounders, and an analysis that considers time-dependent variables would do better. However, even such a sophisticated analysis is no substitute for randomization. Even the best observational studies can be affected by residual confounding, and randomized controlled trials often reveal contrasting effects. Their Supplementary Table 1 mentions the number of patients intubated, receiving mechanical ventilation, and 30-day mortality as 21.4, 27.7, and 72.9, respectively, which needs to be rechecked.

Their results are in contrast to other published studies. However, it is difficult to directly compare their results with those of other studies because of heterogeneity at multiple levels. We conducted a systematic review and meta-analysis of the previously published studies.[4] We searched the databases Medline, Embase, Cochrane CENTRAL, and Medrxiv for title, abstract, and full-text screening. We calculated pooled hazard ratios and 95% confidence intervals (CIs) for the composite outcome of death and intubation using the Generic Inverse Variance approach. The random-effects model was used to conduct the meta-analysis. We carried out the statistical analysis using Review Manager 5.3. Heterogeneity was assessed using visual inspection of forest plots and the I^2 statistic. The risk of bias was assessed using the revised version of the Newcastle-Ottawa scale for cohort studies, and the Grading of Recommendations, Assessment, Development and Evaluations methodology was used to rate the certainty of evidence. Of the 13 studies identified, 5 studies were eligible for inclusion.[4] These studies included 2643 patients with COVID-19, of whom 312 patients received famotidine. All except 10 patients were hospitalized with a moderate to severe illness. The dose of famotidine varied from 40–233 mg/day given for 5–21 days. Two cohort studies[5,6] with matched control subjects that included 84 and 83 patients on famotidine and 1536 and 795 control subjects without famotidine, respectively, showed a significant reduction in mortality: 58% (hazard ratio, 0.42; 95% CI, 0.21–0.85; $P = .02$) and 63% (odds ratio, 0.37; 95% CI, 0.16–0.86; $P = .02$). A meta-analysis of 2 cohort studies showed a statistically significant decrease in the composite outcome of death and intubation with famotidine (hazard ratio, 0.44; 95% CI, 0.27–0.73).[4] Heterogeneity regarding disease severity, inconsistency in severity classification, variation in the dose, timing and route of famotidine, confounding due to co-medications, and comorbidities are likely to explain the differences in the results by Yeramaneni et al and our meta-analysis.

We believe this study's results reporting no benefit of famotidine need to be interpreted cautiously. Famotidine is an over-the-counter drug with an excellent safety profile and can be a useful adjunct in patients with mild to moderate disease. The discrepancy in the results of Yeramaneni et al and our meta-analysis calls for a randomized trial during the ongoing pandemic.

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Conflicts of interest
The authors disclose no conflicts.

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AGA Clinical Practice Guidelines on the Gastrointestinal Evaluation of Iron Deficiency Anemia

Dear Editors:

This letter is in response to the recently published AGA Clinical Practice Guidelines regarding the gastrointestinal evaluation of iron deficiency anemia (IDA).[1]

We thank the editors of *Gastroenterology* for compiling such complete and well researched guidelines regarding the diagnosis, treatment, and testing for IDA. In particular, the recommendations regarding the management of patients