# Real-world Evidence for Improved Outcomes with Histamine Antagonists and Aspirin in 22,560 COVID-19 Patients

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**Letter**

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# Real-world Evidence for Improved Outcomes with Histamine Antagonists and Aspirin in 22,560 COVID-19 Patients

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## Author contributions

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The COVID-19 pandemic has driven great interest in the therapeutic potential of repurposed drugs with well-established benefits and safety profiles (toxicity, bioavailability, etc.), many of which act via signal transduction pathways. One category of such drugs are those which reduce acid production in gastroenterological contexts. Acid-suppressing drugs belong to two main classes, based on their mechanisms of action: (i) Proton-pump inhibitors (PPIs) sterically block $H^+/K^+$-ATPase pumps, impeding the final step of acid release in the gastric mucosa. (ii) Histamine $H_2$ receptor antagonists (H2RA) competitively bind the H2R, a type of G-protein coupled receptor (GPCR),[1] and block the natural stimulation of its downstream signal transduction cascade by histamine; famotidine (e.g., Pepcid®) and ranitidine (e.g., Zantac®) are exemplary H2RAs.

A dense web of functional linkages exists between histamine and H2RAs, on the one hand, and disparate physiological pathways on the other hand. These downstream signaling pathways include gastrointestinal contexts (acid reduction) as well as the dysregulated inflammatory cascades (cytokine storm) that likely underlie much of the pathophysiology of COVID-19.[1] The mechanistic basis of a putative role of famotidine in COVID-19 likely involves its roles as an H2RA versus, for instance, direct binding to the viral protease $3CL^{pro}$ (and resultant inhibition), as was originally suspected from molecular docking studies.

Given its many possible mechanistic and regulatory linkages to signal transduction pathways, is famotidine beneficial in treating COVID-19, as gauged by outcomes involving either (i) *infection transmissibility*, (ii) *disease severity indicators* (e.g., likelihood of cases reaching the point of ventilation, WHO severity index), or (iii) *mortality rates*? This question remains unresolved, though not for lack of effort: since a pioneering report[2] of positive clinical outcomes with famotidine use in COVID-19, over 10 studies have considered the potential therapeutic benefits of famotidine. As we recently reviewed,[3] many of these reports concluded in favor of famotidine use, others found little to no association between famotidine (or PPIs) and 30-day mortality, and a recent study found a negative association for both PPIs and famotidine. These independent studies have been retrospective and observational; most were cohort-based, with some as case-series (e.g., symptom tracking across longitudinal data); most evaluated inpatient cases; and most attempted to account for confounders and other biases (e.g., via propensity-score matching). Given the conflicting reports thus far, particularly the evidence suggesting a beneficial impact of famotidine on mortality and overall disease progression (e.g., mechanical ventilation), we have undertaken the new analysis reported herein.

We note that all three parallel tracks of findings—those indicating for and against famotidine, as well as neutral (i.e., no association)—rest upon substantially smaller datasets than were drawn upon in our present work. Are any beneficial effects of famotidine detectable on population-wide, international scales? Is it synergistic to treat with famotidine in conjunction with aspirin, a general-purpose anti-inflammatory? Does famotidine use correlate with any measurable parameters that may serve as biomarkers, perhaps offering mechanistic clues (e.g., serum C-reactive protein [CRP] levels as a proxy for inflammation and the cytokine storm)? This work seeks to address these questions.

METHODS: We retrieved data from the COVID-19 Research Network supplied by TriNetX, comprising ≈400M patients from 130 health care organizations in 30 countries. TriNetX provides a global

federated health research network providing access to electronic medical records (diagnoses, procedures, medications, laboratory values, genomic information), and the TriNetX platform uses only aggregated counts and statistical summaries of de-identified information; no protected health information or personal data are made available on the platform. This work was reviewed by our IRB board (UVA IRB tracking ID #23100), who determined that this project did not meet the criteria for Human Subject Research; the IRB deemed no further submission/review necessary to proceed with this project. We analyzed a cohort of 22,560 COVID-19 patients taking $H_1$/$H_2$ receptor antagonists, with a special focus on 1,379 severe cases requiring respiratory support (see CONSORT flow diagram, Supp Figure 1). We defined death as the primary outcome, and, in order to try to mitigate confounder bias, we performed propensity score matching to achieve stratified and balanced subcohorts across age and gender; specifically, we balanced cohorts using a nearest-neighbor greedy matching algorithm with a caliper of 0.25 times the standard deviation. Measures of association, risk ratios (RRs) and odds ratios (ORs), along with their respective 95% CIs, were calculated. Kaplan-Meier survival curves were also computed for each analysis.

RESULTS & DISCUSSION: We statistically analyzed outcomes for treatment with (i) the H1RAs loratadine (e.g., Claritin®) and cetirizine (e.g., Zyrtec®), (ii) the H2RA famotidine, (iii) aspirin, and (iv) a combination of famotidine & aspirin. For cases that reached the point of respiratory support, we found a significantly reduced fatality risk for famotidine treatment (OR 0.73, CI 0.57 to 0.94; Table 1, Supp Files 1-4). Dual-histamine receptor blockade, concurrently targeting the $H_1$ and $H_2$ receptors, has been thought to improve COVID-19 clinical outcomes[4]; however, significant improvements were not seen in our cohorts, versus famotidine alone (OR 0.75, CI 0.39 to 1.46; Supp Files 5-8). Notably, and perhaps unexpectedly, the combination of famotidine and aspirin (344 severe cases before matching) *did* exhibit a significant synergistic survival benefit (OR 0.55, CI 0.39 to 0.78; Supp Files 9-12). The RR for death decreased by 32.5%—an immense benefit, given the more than 2.6 million COVID-19–related deaths thus far.

Can our findings be reconciled with recent studies of famotidine in COVID-19? A case-series of 10 non-hospitalized patients found that self-administration of famotidine had uniformly beneficial impact on disease trajectories, based on quantitative symptom-tracking across longitudinal data.[3] Retrospective, single-center studies also found promising results, e.g. reduced risk of clinical deterioration (intubation and death) for famotidine usage in 83 and 84 hospitalized COVID-19 patients, corresponding to 9.5 and 5.1% of the analyzed cohorts, respectively. Notably, these past studies[3] found lower levels of serum markers for severe disease (e.g., ferritin, C-reactive protein, procalcitonin) in famotidine groups, consistent with our findings and with a potential role for this H2RA in attenuating cytokine release. Finally, a new systematic review and analysis (of published reports) suggests that famotidine may be beneficial, while two other recent meta-analyses are either neutral or (statistically) inconclusive.[3]

If indeed famotidine is beneficial in a significant share of COVID-19 cases, we suspect this could be because of the capacity of H2RAs to attenuate the pro-inflammatory pathways that become dysregulated upon infection (cytokine storms activate pro-fibrotic pathways; lung damage eventually results). Thus, a role for famotidine in COVID-19 may stem from cellular mechanisms and signaling pathways quite unrelated to its classic therapeutic role in gastroenterology—that, in

turn, is an important lesson as regards drug repurposing (from a systems pharmacology perspective), targeted therapeutics, and the general idea of a COVID-19 'disease map'.[5]

As SARS-CoV-2 infection rates continue surging worldwide, we desperately need more data on potential therapies. The large, international, multi-center retrospective study reported here, sampling over 250,000 COVID-19 cases, hopefully helps clarify the potential benefit of clinically-approved histamine antagonists such as famotidine. We anticipate that at least three prospective, randomized, controlled clinical trials that are currently underway—NCT04504240, NCT04370262 and NCT04545008—will illuminate famotidine's potential therapeutic profile. Given the findings reported here, alongside the cost-effectiveness and mild side-effects of OTC drugs like famotidine and aspirin, we suggest that further prospective clinical trials—perhaps utilizing the aspirin combination reported here—are advisable.

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PATIENT CONSENT FOR PUBLICATION: Not required; see METHODS section for IRB review.

## FIGURE CAPTIONS

**Figure 1**. **Kaplan-Meier survival curves** are shown for COVID-19 patients with (blue) or without (red) the dual combination treatment of famotidine and aspirin.

## TABLES

**Table 1**: **Statistical outcomes for patients requiring respiratory support**, considering use/disuse of (i) $H_1$- or $H_2$-receptor antagonists or aspirin, as well as (ii) a combination treatment with famotidine and aspirin.

| Drug compound [$H_1$ or $H_2$ antagonist] | Number of patients in cohort (after matching) | Outcome: Death | Odds ratio (OR) | Confidence interval (CI 95%) | Hazard ratio (HR) |
|---|---|---|---|---|---|
| Loratadine [$H_1$] | 88 | 29 | 1.00 | 0.55–1.87 | 0.84 |
| Cetirizine [$H_1$] | 95 | 25 | 0.85 | 0.45–1.61 | 0.80 |
| Famotidine [$H_2$] | 563 | 161 | 0.73 | 0.57–0.94 | 0.75 |
| Aspirin (Asp) | 527 | 165 | 0.79 | 0.61–1.02 | 0.71 |
| Famotidine + Asp | 305 | 83 | 0.55 | 0.39–0.78 | 0.53 |

## Supplementary Materials

The following supplementary figures, tables, and data files accompany this manuscript:

- Supplemental Figure 1: CONSORT Flow Diagram
- Supplemental Table 1:Lab Values and Standard Deviations for Serum Levels of C-reactive Protein
- Supplemental File 1: Measures of Association Data Graph for Famotidine
- Supplemental File 2: Measures of Association Data Table for Famotidine
- Supplemental File 3: Kaplan-Meier Raw Data Graph for Famotidine
- Supplemental File 4: Kaplan-Meier Raw Data Table for Famotidine
- Supplemental File 5: Measures of Association Data Graph for H1 and H2
- Supplemental File 6: Measures of Association Data Table for H1 and H2
- Supplemental File 7: Kaplan-Meier Raw Data Graph for H1 and H2
- Supplemental File 8: Kaplan-Meier Raw Data Table for H1 and H2
- Supplemental File 9: Measures of Association Data Graph for Famotidine and Asp
- Supplemental File 10: Measures of Association Data Table for Famotidine and Asp
- Supplemental File 11: Kaplan-Meier Raw Data Graph for Famotidine and Asp
- Supplemental File 12: Kaplan-Meier Raw Data Table for Famotidine and Asp

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5 Loucera, C. *et al.* Drug Repurposing for COVID-19 Using Machine Learning and Mechanistic Models of Signal Transduction Circuits Related to SARS-CoV-2 Infection. *Signal Transduct Target Ther* **5**, 290, doi:10.1038/s41392-020-00417-y (2020).

# Figures

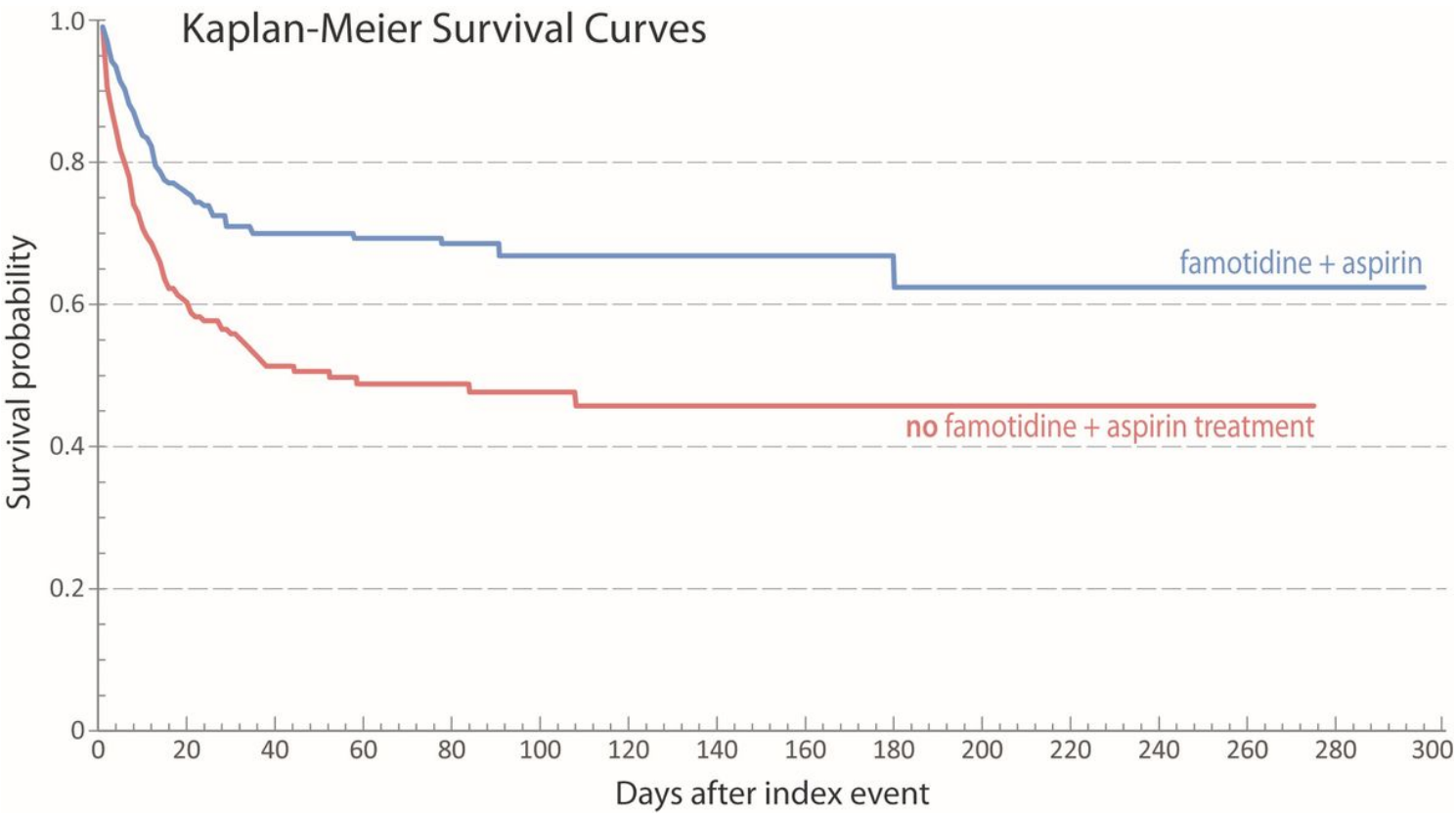


**Figure 1**

Kaplan-Meier survival curves are shown for COVID-19 patients with (blue) or without (red) the dual combination treatment of famotidine and aspirin.

# Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- MuraPreissneretalSupplementalFigure1mar2021v1.pdf
- MuraPreissneretalSupplementalTable1mar2021v3.pdf
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