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Original Article

# Impact of Famotidine Use on Clinical Outcomes of Hospitalized Patients with COVID-19 in Taiwan: A Retrospective Study

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SUMMARY

*Objectives:* The aim of this study was to investigate the association between famotidine treatment and severity, as well as mortality, for patients with COVID-19. In addition, to investigate whether this association was changed in cases of concomitant treatment with corticosteroids, remdesivir, clarithromycin, low molecular weight heparin, or statin.

*Material and methods:* This is a retrospective cohort study conducted by analyzing electronic medical records of 171 hospitalized patients into the Infectious Disease Ward of a 2068-bed tertiary care medical center, with laboratory-confirmed COVID-19 between May 01, 2021 and August 31, 2021. Patients were classified as receiving famotidine if they were treated with oral drug, at any dose, within ± 7 days of COVID-19 screening and/or hospital admission. Famotidine use was extracted directly from the electronic medical record.

*Results:* Current study failed to identify famotidine as a protective factor associated with a significant reduction in the risk of in-hospital mortality (odds ratio 1.573, 95% confidence interval (CI) 0.464–5.325, $p = 0.467$) or a significant reduction in the risk of ICU admission (odds ratio 0.547, 95% confidence interval (CI) 0.286–1.045, $p = 0.068$). However, non-significant trend towards a lower rate of ICU admission in association with famotidine prescription was observed.

*Conclusions:* The results of this study reflect the real-world use of famotidine does not reduce the risk of in-hospital-mortality or ICU admission of hospitalized COVID-19 patients.



## 1. Background

The coronavirus disease 2019 (COVID-19) was first recognized in Wuhan, China, in December 2019. Since its recognition, COVID-19 has rapidly spread across mainland China and became a pandemic in less than 3 months.[1] The typical symptoms of a patient who has been infected with COVID-19 are fever, dry cough, dyspnea, myalgia, fatigue, normal or decreased leukocyte counts, and radiographic evidence of pneumonia. COVID-19 patients may also present with radiological ground-glass lung changes, lymphopenia, and thrombocytopenia.[2,3] Famotidine, a histamine-2 receptor antagonist that suppresses gastric acid production, has exhibited in vitro capability of inhibiting human immunodeficiency virus replication.[4] Recent computational prediction of protein structures encoded by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) genome identified famotidine as one of the drugs potentially capable of inhibiting 3-chymotrypsin-like protease ($3CL^{pro}$), a protein essential for viral replication.[5,6] Moreover, inhibition of pathologic histamine release as a result of antagonism or inverse-agonism of histamine signaling, and via arrestin biased activation after $H_2$ receptor binding, may further mediate potential clinical benefit in COVID-19 patients. Coincidentally, early clinical data indicate that famotidine treatment may reduce morbidity and mortality associated with COVID-19. A propensity score matched retrospective cohort study demonstrated that COVID-19 patients receiving famotidine during hospitalization (oral or IV, 20 mg or 40 mg daily) had a statistically significant reduction in the risk of death or intubation (adjusted hazard ratio 0.42, 95% CI 0.21–0.85) and also a reduction in the risk of death alone (aHR 0.30, 95% CI 0.11–0.80). In contrast, proton pump inhibitor prescription was not associated with reduced risk of death or intubation.[7] Furthermore, Mather et al., also in a retrospective observational study, showed famotidine use in hospitalized patients with COVID-19 is associated with a lower risk of mortality, lower risk of combined outcome of mortality and intubation, and lower levels of serum markers for severe disease in hospitalized patients with COVID-19.[8] In light of the potential beneficial therapeutic effects, the aim of this study was to investigate the association between famotidine treatment and severity, as well as mortality, for patients with COVID-19. In addition, to investigate whether this association was changed in cases of concomitant treatment with corticosteroids, remdesivir, clarithromycin, low molecular weight heparin, or statin.

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## 2. Methods

### 2.1. Study population and data collection

This retrospective study was conducted by analyzing electronic medical records of 171 patients hospitalized at the McKay Memorial Hospital, a 2068-bed tertiary care medical center in Taipei and New Taipei City, Taiwan, with laboratory-confirmed COVID-19 between May 01, 2021 and August 31, 2021. The MacKay Memorial Institutional Review Board (Judgment protocol number: 21MMHIS226e) approved the study and certified that it met the criteria for a waiver of the requirement to obtain informed consents. All patients who tested positive for severe acute respiratory syndrome (SARS-CoV-2) by nasopharyngeal polymerase chain reaction and who required inpatient admission were included in this study.

Patients were classified as receiving famotidine if they were treated with oral drug, at any dose, within ± 7 days of COVID-19 screening and/or hospital admission. Famotidine use was extracted directly from the electronic medical record.

### 2.2. Primary and secondary outcomes

The primary outcomes of the study included in-hospital death as recorded in the medical chart, requirement for intensive care unit (ICU) admission, and composite of death or requirement for intensive care unit admission. Secondary outcomes include serum markers of disease severity included white blood cell count, lymphocyte count, percent neutrophils count, percent band cells count, platelet count, serum ferritin, C-reactive protein (CRP), high sensitivity D-dimer, erythrocyte sedimentation rate (ESR), and procalcitonin. All data were extracted from the electronic medical record.

### 2.3. Additional variables

Potential predictive variables were chosen based on prior reports of risk factors for acute outcomes in patients positive for COVID-19. Covariates included pre-existing comorbidities, and treatment with antiviral, antibacterial, and corticosteroid medications. Demographic variables included age, sex, and body mass index (BMI). Comorbidities included history of pre-existing hypertension, diabetes mellitus, obesity (BMI > 30 kg/$m^2$), coronary artery disease, heart failure, atrial fibrillation, chronic obstructive pulmonary disease, chronic kidney disease (CKD), or prior history of malignancy. In-hospital treatment medications included use of statin, low molecular weight heparin, clarithromycin, remdesivir, and corticosteroids.

### 2.4. Statistical approach

Continuous variables that were normally distributed were compared with a Student t test. If not normally distributed, the Mann-Whitney U test was used. Categorical variables were analyzed using the $X^2$ test or Fisher exact test, as appropriate. Univariate analyses were performed using mortality or ICU admission as the dependent variables. All effects were considered significant at a $p$ value of less than 0.05. The statistical analyses were performed with IBM SPSS release 26.0 (IBM, Armonk, New York).

## 3. Results

Of 171 patients in the analysis, 103 (60.2%) received famotine. The mean age of the entire study group was 61.85 ± 15.794 years, and 91 were males (53.2%). A total of 13 (7.60%) patients died during hospitalization, 56 (32.7%) required mechanical ventilation, and 9 (5.26%) met the criteria for combined death and intubation. Table 1 exhibits baseline demographics, comorbidities, and severity of illness upon admission of the famotidine and non-famotidine study groups. As shown, there were not significant differences in the study cohorts.

Of the 103 patients who received famotidine, all patients received oral famotidine within 24 hours of hospital admission. One hundred percent of all famotidine doses were administered orally; 79 (76.7%) were 20 mg, and 24 (23.3%) were 40 mg. Famotidine users received prescription from admission till discharge. There were minimal differences comparing patients who used famotidine with those who did not.

For the matched study group of 171 patients with COVID-19, a total of 45 (26.3%) received remdesivir, 136 (79.5%) received corticosteroids, 21 (12.3%) received clarithromycin, 49 (28.7%) received low molecular weight heparin, and 16 (9.4%) received statin. As shown in Table 2, significant differences were found for clarithromycin and low molecular weight heparin between the famotidine and non-famotidine cohorts with respect to treatment for these agents.

In-hospital death, intubation, and combined death/intubation occurred in 9 (8.8%), 28 (27.2%), and 6 (5.83%) patients in the famotidine group, respectively, compared with 4 (5.88%), 28 (41.2%), and 3 (4.41%) in the non-famotidine group, respectively. The results of the logistic regression to assess the independent predictors of death in the matched cohort are shown in Table 3 and Figure 1. The analysis failed to identify famotidine as a protective factor associated with a significant reduction in the risk of in-hospital mortality (odds ratio 1.573, 95% confidence interval (CI) 0.464–5.325, $p$ = 0.467). Furthermore, current study revealed no risky association of ICU admission with the famotidine use. (odds ratio 0.547, CI 0.286–1.045, $p$ = 0.068) (Table 4). However, a non-significant trend towards a lower rate of ICU admission in association with famotidine prescription can be observed (Figure 2). The used of remdesivir, dexamethasone, clarithromycin, and statin also revealed no ICU admission association or risk of death. Low-molecular heparin was the only treatment identified in the current study to be associated with increasing risk of ICU admission (odds ratio 2.913, CI 1.447–5.866, $p$ = 0.003) (Table 4). The possible explanation may be due to higher O2 demand at baseline and increased chance to respiratory failure.

Table 5 shows laboratory test results for the famotidine and non-famotidine groups at follow-up after one week of oral famotidine prescription. Patients receiving famotidine failed to express lower levels of serum markers for severe disease including mean CRP levels (2.99 vs. 3.26 mg/dL, $p$ = 0.707), mean procalcitonin levels (0.32 vs. 0.13 ng/mL, $p$ = 0.205), and mean serum ferritin levels (627.95 vs. 566.24 ng/mL, $p$ = 0.640). However, current study does show patients receiving famotidine expressed a non-significant trend towards lower levels of median D-dimer levels (514 vs. 1217, $p$ = 0.090).

## 4. Discussion

Famotidine has rarely been studied in patients for anti-viral effects, however, since the retrospective cohort study published by Freedberg et al.[7] in 2020, shedding light on the possible association between famotidine and improved clinical outcomes in hospitalized COVID-19 patients, enthusiasm towards the elucidation of this association, and its potential underlying mechanisms have been high. Freedberg et al. examined the effect of famotidine use on clinical outcomes in 1,620 consecutive hospitalized patients with COVID-19 infection at a single medical center. An association of reduced risk of

**Table 1**
Demographics and comorbidities: all patients and subpopulations with and without famotidine.

| Variable: n (%), median (IQR), mean (±SD) | All patients | | |
|---|---|---|---|
| | Famotidine (n = 103) | No famotidine (n = 68) | *p* value |
| Age | | | |
| < 50 | 19 (18.5%) | 13 (19.1%) | 0.555 |
| 50–65 | 43 (41.7%) | 23 (33.8%) | 0.760 |
| > 65 | 41 (39.8%) | 32 (47.1%) | 0.280 |
| Sex | | | |
| Male | 50 (48.5%) | 41 (60.3%) | > 0.999 |
| Female | 53 (51.5%) | 27 (39.7%) | 0.133 |
| BMI | | | |
| < 18.0 | 13 (12.6%) | 4 (5.9%) | 0.662 |
| 25.0–29.9 (Overweight) | 9 (8.7%) | 1 (1.5%) | 0.616 |
| ≥ 30.0 (Obese) | 6 (5.8%) | 1 (1.5%) | 0.788 |
| Charlson Comorbidity Index | | | |
| 0 | 13 (12.6%) | 11 (16.2%) | 0.787 |
| 1–2 | 41 (39.8%) | 25 (36.8%) | 0.304 |
| 3–4 | 25 (24.3%) | 20 (29.4%) | 0.501 |
| 5–6 | 16 (15.5%) | 9 (13.2%) | 0.306 |
| 7+ | 8 (7.8%) | 3 (4.4%) | 0.610 |
| Quick COVID-19 Severity Index (qCSI) | | | |
| 0–2 (0) | 76 (73.8%) | 51 (75%) | 0.499 |
| 3–5 (1) | 16 (15.5%) | 11 (16.2%) | 0.223 |
| 6–7 (2) | 3 (2.9%) | 4 (5.9%) | 0.252 |
| ≥ 8 (3) | 8 (7.8%) | 2 (2.9%) | 0.128 |
| The Venilation In COVID-19 Estimation (VICE) Score | 0.184 (±0.223) | 0.217 (±0.254) | 0.383 |
| Ordinal Scale at admission | | | |
| 3 | 41 (39.8%) | 36 (52.9%) | 0.410 |
| 4 | 37 (35.9%) | 25 (36.8%) | 0.651 |
| 5 | 19 (18.5%) | 6 (8.8%) | 0.810 |
| 6 | 4 (3.9%) | 0 (0.0%) | 0.726 |
| 7 | 2 (1.9%) | 1 (1.5%) | > 0.999 |
| Comorbidities | | | |
| Diabetes | 23 (22.3%) | 22 (32.4%) | 0.159 |
| Hypertension | 40 (38.8%) | 25 (36.8%) | 0.872 |
| Kidney disease | 11 (10.7%) | 2 (2.9%) | 0.079 |
| Liver cirrhosis | 1 (1%) | 0 | > 0.999 |
| Heart failure | 1 (1%) | 1 (1.5%) | > 0.999 |
| COPD | 7 (6.8%) | 4 (5.9%) | > 0.999 |
| Cancer | 7 (6.8%) | 3 (4.4%) | 0.741 |
| Autoimmune disease | 2 (1.94%) | 1 (1.5%) | > 0.999 |
| Human immunodeficiency virus (HIV) | 4 (3.88%) | 0 | 0.298 |

**Table 2**
Treatment with remdesivir, corticosteroids, clarithromycin, low molecular weight heparin, and statin.

| Agent | Famotidine (n = 103) | No famotidine (n = 68) | *p* value |
|---|---|---|---|
| Remdesivir | 31 (30.1%) | 14 (20.6%) | 0.357 |
| Corticosteroids[a] | 84 (81.6%) | 52 (76.5%) | 0.552 |
| Clarithromycin | 21 (20.4%) | 0 (0.0%) | **< 0.001** |
| Low molecular weight heparin (Enoxaparin) | 39 (37.9%) | 10 (14.7%) | **0.002** |
| Statin[b] | 13 (12.6%) | 3 (4.4%) | 0.058 |

[a] Corticosteroid medications include prednisolone, methylprednisolone, hydrocortisone, and dexamethasone.
[b] Statin medications include atorvastatin, rosuvastatin, pitavastatin.

**Table 3**
Treatment with famotidine, remdesivir, corticosteroids, clarithromycin, low molecular weight heparin, and statin.

| Agent | Mortality (n = 13) | Survive (n = 158) | OR (95% CI) | *p* value |
|---|---|---|---|---|
| Famotidine | 9 (69.2%) | 93 (58.9%) | 1.573 (0.464–5.325) | 0.467 |
| Remdesivir | 6 (46.2%) | 39 (24.7%) | 2.088 (0.660–6.610) | 0.211 |
| Corticosteroids[a] | 12 (92.3%) | 124 (78.5%) | 3.00 (0.376–23.956) | 0.300 |
| Clarithromycin | 3 (23.1%) | 18 (11.4%) | 2.333 (0.587–9.278) | 0.229 |
| Low molecular weight heparin (Enoxaparin) | 5 (38.5%) | 44 (27.8%) | 1.534 (0.476–4.948) | 0.474 |
| Statin[b] | 2 (15.4%) | 14 (8.9%) | 1.857 (0.374–9.231) | 0.449 |

[a] Corticosteroid medications include prednisolone, methylprednisolone, hydrocortisone, and dexamethasone.
[b] Statin medications include atorvastatin, rosuvastatin, pitavastatin.

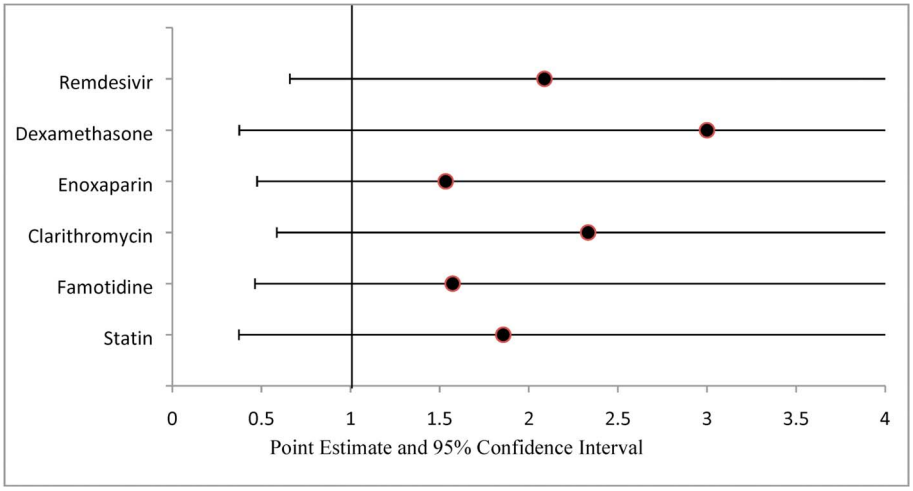


**Figure 1.** Unadjusted odds ratio for the risk of death.

**Table 4**
Treatment with famotidine, remdesivir, corticosteroids, clarithromycin, low molecular weight heparin, and statin.

| Agent | Admission into ICU (n = 56) | No admission into ICU (n = 116) | OR (95% CI) | *p* value |
|---|---|---|---|---|
| Famotidine | 28 (50%) | 75 (64.7%) | **0.547 (0.286–1.045)** | **0.068** |
| Remdesivir | 19 (33.9%) | 26 (22.4%) | **1.865 (0.898–3.873)** | **0.095** |
| Corticosteroids[a] | 48 (85.7%) | 88 (75.9%) | **2.455 (0.947–6.359)** | **0.064** |
| Clarithromycin | 7 (12.5%) | 14 (12.1%) | 1.031 (0.391–2.717) | 0.951 |
| Low molecular weight heparin (Enoxaparin) | 24 (42.9%) | 25 (21.6%) | **2.913 (1.447–5.866)** | **0.003** |
| Statin[b] | 6 (10.7%) | 10 (8.6%) | 1.298 (0.446–3.774) | 0.632 |

[a] Corticosteroid medications include prednisolone, methylprednisolone, hydrocortisone, and dexamethasone.
[b] Statin medications include atorvastatin, rosuvastatin, pitavastatin.

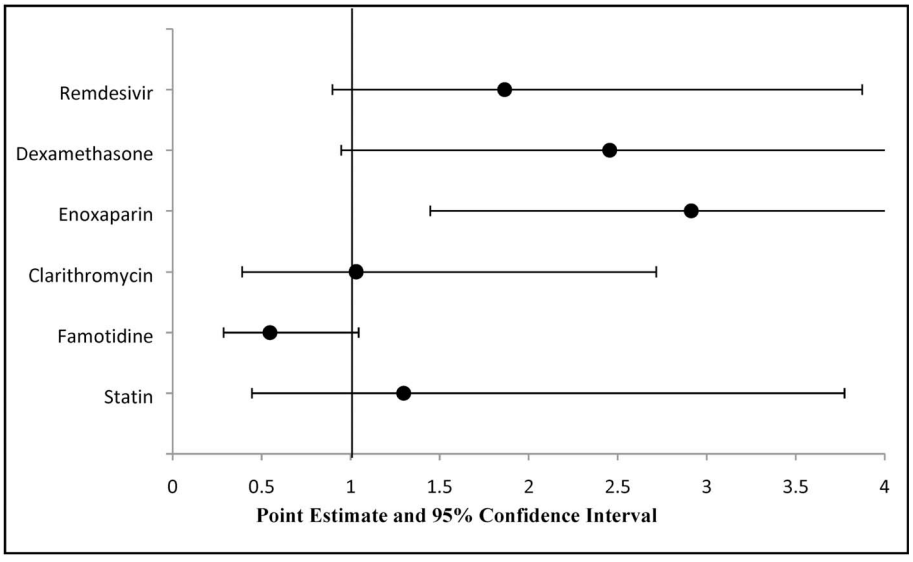


**Figure 2.** Unadjusted odds ratio for the risk of ICU admission. ICU, intensive care unit.

death or intubation (adjusted HR 0.42, 95% CI 021–0.85) and for death alone (HR 0.30, 95% CI 0.11–0.80) was observed in patients receiving famotidine treatment within 24 hours of hospital admission with COVID-19. The association was retained even after baseline patient characteristics were balanced using propensity score matching. After analyzing 878 patients, Mather et al.[8] in a retrospective, propensity-matched observational study of consecutive COVID-19-positive patients, also reported that the use of famotidine was associated with a decreased risk of in-hospital mortality (odds ratio 0.37, 95% CI 0.16–0.86, $p = 0.021$) and combined death or intubation (odds ratio 0.47, 95% CI 0.23–0.96, $p = 0.040$). Mather et al. further presented laboratory findings of lower levels of serum markers for severe disease in famotidine patients, including median C-reative protein (CRP) levels (9.4 vs. 12.7 mg/dL, $p = 0.02$), lower median procalcitonin levels (0.16 vs. 0.30 ng/mL, $p = 0.004$), and nonsignificant lower median ferritin levels (797.5 vs. 964.0 ng/mL, $p = 0.076$).

According to prior studies, famotidine may improve COVID-19 outcomes by several mechanisms. First, famotidine could potentially inhibit the 3-chymotrypsin-like protease (3CLpro), which processes proteins essential for viral replication.[5,6,8] Moreover, famotidine was postulated to activate G-protein-coupled receptors (GPCRs) which may act to activate immune cell mobilization, and results in vascular inflammation.[9,10] Alternatively, recent studies have reported that

**Table 5**
Laboratory findings: all patients and in subpopulations with and without famotidine.

| Laboratory values Mean (± SD) or Median (IQR) | Reference range | All patients (n = 171) | Famotidine (n = 103) | No famotidine (n = 68) | *p* value |
|---|---|---|---|---|---|
| Hematologic | | | | | |
| WBC × $10^9$/L[a] | 4.0–10.0 | 8.21 (± 4.036) | 7.00 (4) | 8.00 (5) | 0.476 |
| Lymphocytes × $10^9$/L[a] | 20–40 | 15.61 (± 10.135) | 13.70 (13) | 14.00 (13) | 0.918 |
| Percent neutrophils count (%)[a] | 55–75 | 74.65 (± 12.349) | 76.10 (18) | 77.20 (15) | 0.803 |
| Percent band cells count (%)[a] | 0–6 | 0.40 (± 1.202) | 0.00 (0) | 0.00 (0) | 0.586 |
| Platelets × $10^9$/L | 140–450 | 240.99 (± 105.184) | 241.50 (± 112.643) | 240.26 (± 94.511) | 0.948 |
| Biochemical | | | | | |
| AST (U/L) | 15–41 | 44.01 (± 62.276) | 48.48 (± 72.938) | 37.32 (± 40.768) | 0.346 |
| ALT (U/L)[a] | 14–40 | 53.84 (± 73.998) | 38.00 (19) | 27.00 (35) | 0.203 |
| BUN (mg/dL) | 8–20 | 20.92 (± 17.638) | 21.83 (± 20.029) | 19.60 (± 13.533) | 0.477 |
| Creatinine (mg/dL) | 0.4–1.2 | 1.06 (± 0.736) | 0.90 (± 0.265) | 0.92 (± 0.277) | 0.732 |
| PT | 8.0–12.0 | 11.07 (± 1.112) | 11.04 (± 1.161) | 11.10 (± 1.055) | 0.846 |
| aPTT | 23.9–35.5 | 27.32 (± 5.070) | 27.03 (± 5.295) | 27.79 (± 4.755) | 0.563 |
| D-dimer[a] | < 0.55 | 1124.69 (± 1075.084) | 514 (296) | 1217.00 (3195) | 0.090 |
| Infection-related indexes | | | | | |
| CRP (mg/dL) | 0–0.79 | 3.09 (± 3.737) | 2.99 (± 3.875) | 3.26 (± 3.574) | 0.707 |
| Serum ferritin (ng/mL) | 11–336 | 605.77 (± 500.640) | 627.95 (± 498.743) | 566.24 (± 512.766) | 0.640 |
| Procalcitonin (ng/mL) | < 0.09 | 0.25 (± 0.301) | 0.32 (± 0.360) | 0.13 (± 0.020) | 0.205 |
| ESR (mm/hr) | 0–15 | 48.42 (± 45.234) | 44.63 (± 31.334) | 68.65 (± 101.599) | 0.414 |

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; WBC, white blood cells.
[a] Mann-Whitney *U* test.

famotidine does not inhibit PLpro and Mpro nor does it inhibit SARS-CoV-2 infection.[9] The contradictory findings and hypothesis stimulated the enthusiasm for more well-designed investigations into the effects of famotidine on SARS-CoV-2 infection. Second, prior studies have shown mast cells activated by coronavirus produce histamine, prostaglandin D2 (PGD2), and leukotriene C4 (LTC4), resulting in acute bronchoconstriction and severe lung inflammation.[11] Since pneumocytes present H1 and H2 receptors, it has been postulated that local mast cell degranulation resulting in histamine release could play a major role in the aforementioned disease mechanisms;[12] therefore, famotidine and other H2RA may modulate the pulmonary pathological process through inhibition of histamine receptors. As demonstrated by a recent cohort study of 110 hospitalized COVID-19 patients, a combined treatment of famotidine and cetirizine resulted in decreased incidences of death and progression of disease.[13]

Disappointingly, several recent studies have generated evidence contradictory to prior results supporting the association between famotidine use and better COVID-19 outcomes. A recent systematic review and meta-analysis based on existing observational studies, showed that famotidine use is not associated with a reduced risk of mortality or combined outcome of mortality, intubation, and/or intensive care services in hospitalized individuals with COVID-19.[14] However, high heterogeneity existed in the prior mentioned study. Furthermore, a recent retrospective study conducted via analyzing electronic medical records hospitalized at the Mount Sinai Health System with laboratory-confirmed COVID-19 also derived the conclusion that treatment with famotidine was not associated with a decreased risk of in-hospital mortality of COVID-19 irrespective of the severity of COVID infection or concomitant treatment by steroids.[15] The findings of which echoed the analysis made by Shoaibi et al. from their retrospective cohort study, which concluded that there was no evidence of a reduced risk of COVID-19 outcomes among hospitalized COVID-19 patients who used famotidine compared with those who did not.[16] Moreover, a territory-wide retrospective cohort study conducted in Hong Kong also failed to find support for any association between famotidine and COVID-19 severity.[17]

Our results on mortality and disease severity corroborate with the findings from two recent studies,[18,19] presenting evidences that suggest there is no association between famotidine use in hospitalized COVID-19 patients and a reduction in the risk of mortality. However, a non-significant trend towards a lower rate of ICU admission suggests famotidine treatment may exert a protective effect towards progression to severe disease. Furthermore, contrary to the findings reported by Mather et al.,[8] famotidine patients failed to show lower levels of biomarkers for serious disease after one week of treatment, including serum ferritin levels, CRP, procalcitonin, and ESR. However, interestingly, famotidine patients did present lower levels of serum D-dimers upon follow-up. The clinical significance of this finding still awaits further elucidation.

The results in study are from a single-center, retrospective and observational in nature, thus the findings should be interpreted with caution. Our study did not consider strength or dose or duration of exposure for any of the treatments and may not generalize to the high-dose exposures under investigation. Additional studies are needed to ascertain factors that may potentially impact the efficacy of famotidine in patients with COVID-19, including various dosing regimens, routes of administration, and timing of treatment initiation. In addition, confounding due of unobserved factors, such as pre-admission drug use, may exist. Our study findings reflect the real-world use of famotidine during admission for hospitalized COVID-19 patients. Given the conflicting findings and inherent bias of existing observational studies, further evidence is needed to demonstrate its effectiveness.

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