The association between famotidine and in-hospital mortality of patients with COVID-19

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Abstract
Famotidine has been considered to be a potential treatment for COVID-19 but the current data is conflicting. This retrospective study was conducted by utilizing data of 9565 COVID-19 hospitalized patients. Patients treated with and without famotidine were matched by propensity score using a 1:1 matching scheme. A total of 1593 patients (16.7%) received famotidine. In-hospital mortality was similar in patients treated with and without famotidine in the propensity-matched cohorts (28.3% vs. 28.2%, \( p = 0.97 \)), which remains similar irrespective of severity or concomitant treatment by steroids. Famotidine treatment was not associated with a lower risk of in-hospital mortality of COVID-19 patients.

KEYWORDS
COVID-19, famotidine

Famotidine has been considered to be a potential treatment for COVID-19 since the pandemic started in 2020. Since the hypothesis derives from the concept that severe acute respiratory syndrome coronavirus 2 infections can cause histamine release via mast cell activation, which leads to systemic inflammation and cytokine release, it has been expected that famotidine can reduce systemic inflammation and cytokine release. Nonetheless, it remains uncertain whether famotidine is effective for the treatment of COVID-19. While some observational studies showed potential benefit of famotidine by decreasing mortality due to COVID-19, another study demonstrated no benefit of famotidine. In addition, we hypothesized that steroids treatment which is the standard treatment of COVID-19 as of May 15, 2021, might mitigate the effect of famotidine since steroids also reduce inflammation and cytokine release through mast cells.

The aim of this study was to investigate the association between famotidine treatment and mortality for patients with COVID-19. In addition, we aimed to research if this association was changed in cases of steroids treatments.

This retrospective study was conducted by analyzing electronic medical records of 9565 patients hospitalized at the Mount Sinai Health System with laboratory-confirmed COVID-19 between March 1, 2020 and March 30, 2021. Patients were divided into two groups, those with and those without treatment with famotidine. The primary outcome was in-hospital mortality. Patients treated with famotidine and without famotidine were matched by propensity score using a 1:1 matching scheme without replacement. Good balance (standardized mean difference < 0.10) was achieved for patients’ baseline characteristics including age, sex, comorbidities, vital signs at admission, laboratory data, and in-hospital treatment including the use of steroids, interleukin-6 (IL-6) inhibitor, convalescent plasma, and remdesivir. As a sensitivity analysis, we performed inverse probability treatment weighted (IPTW) analysis. In addition, multiple imputations for missing data were conducted (R software MICE package).

We performed several analyses where we investigated the effect of famotidine on different subgroups of patients. We compared in-hospital mortality for patients with steroid treatment (\( N = 4751, 49.7\% \)), which is the current standard treatment, and those without steroid treatment (\( N = 4814, 50.3\% \)); for patients with oxygen saturation \( \leq 94\% \) (moderate or severe COVID-19 patients, \( N = 8295, 86.7\% \)) and those who required intensive care unit and/or endotracheal intubation (severe COVID-19 patients, \( N = 2130, 22.2\% \)), and for patients with age \( \geq 75 \) years old (\( N = 3102, 32.4\% \)).
All statistical calculations and analyses were performed in R, with \( p < 0.05 \) considered statistically significant.

Among 9565 patients with COVID-19, 1593 patients (16.7\%) received famotidine. Baseline characteristics, treatments, and in-hospital outcomes were shown in Table 1. Patients treated with famotidine were younger, less likely to be male, and had lower oxygen saturation levels at admission. Patients treated with famotidine were likely to receive steroids, remdesivir, IL-6 inhibitor, and convalescent plasma (Table 1).

After matching by propensity score (\( N = 1566 \) in each group) (Table 1), in-hospital mortality was similar in patients treated with and without famotidine in the propensity-matched cohorts (28.3\% vs. 28.2\%, odds ratio [OR] (95\% confidential interval [CI]): 1.00 [0.86–1.17], \( p = 0.97 \)) (Table 2). Multiple imputations of missing data analysis showed the similar result (OR for in-hospital mortality [95\% CI]: 1.15 [0.97–1.38], \( p = 0.11 \)). The results were confirmed using IPTW analysis (OR [95\% CI]: 1.06 [0.93–1.20], \( p = 0.37 \)) as well as IPTW with multiple imputations (OR [95\% CI]: 1.07 [0.94–1.22], \( p = 0.31 \)).

Table 2 shows in-hospital mortality by subgroups. In the propensity analysis limiting patients with steroids treatment (934 pairs) or those without (634 pairs), in-hospital mortality was not different between patients with and without famotidine among patients treated with steroids (34.7\% vs. 32.0\%, \( p = 0.22 \)) as well as among those treated without steroids (19.1\% vs. 18.5\%, \( p = 0.77 \)) (Table 2).

In addition, in-hospital mortality for moderate or severe patients with and without famotidine did not differ (1410 pairs; 31.1\% vs. 30.0\%, \( p = 0.51 \)) as well as severe patients (584 pairs; 55.1\% vs. 52.9\%, \( p = 0.44 \)) and elderly patients (age ≥ 75 years old, 448 pairs; 42.4\% vs. 38.2\%, \( p = 0.20 \)).

We showed 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. Our data supports the most recent observational study.4 In addition, our data might attract attention because the effect of famotidine was not observed among patients even treated without steroids which could mitigate the effect of famotidine for COVID-19.5 There is an ongoing clinical trial (Clinical Trials: NCT04370262) which will provide further insights into famotidine treatment for COVID-19.

According to an experimental study, famotidine leads to a release of proinflammatory cytokines and chemokines. Famotidine acts as an

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**TABLE 1** Baseline characteristics of patients admitted with COVID-19 and treated with and without famotidine

|                          | All hospitalizations | Propensity-matched hospitalizations |
|--------------------------|----------------------|------------------------------------|
|                          | Without famotidine   | With famotidine                    | Without famotidine | With famotidine |
|                          | \((n = 7972)\)       | \((n = 1593)\)                     | \((n = 1566)\)      | \((n = 1566)\)      |
| Age, mean (SD) (year)    | 65.2 (17.1)          | 64.0 (16.2)                        | 64.3 (16.4)        | 64.3 (16.0)        | 1.00 |
| Male, n (%)              | 4403 (55.2)          | 832 (52.2)                         | 831 (53.1)         | 824 (52.6)         | 0.83 |
| Asthma, n (%)            | 444 (5.6)            | 99 (6.2)                           | 97 (6.2)           | 95 (6.1)           | 0.94 |
| COPD, n (%)              | 345 (4.3)            | 81 (5.1)                           | 84 (5.4)           | 81 (5.2)           | 0.87 |
| Hypertension, n (%)      | 2863 (35.9)          | 612 (38.4)                         | 641 (40.9)         | 607 (38.8)         | 0.23 |
| Diabetes mellitus, n (%) | 1852 (23.2)          | 393 (24.7)                         | 403 (25.7)         | 389 (24.8)         | 0.59 |
| Cancer, n (%)            | 699 (8.8)            | 165 (10.4)                         | 161 (10.3)         | 163 (10.4)         | 0.95 |
| Heart failure, n (%)     | 712 (8.9)            | 148 (9.3)                          | 134 (8.6)          | 145 (9.3)          | 0.53 |
| Oxygen saturation, median [IQR] | 90.0 [84.0, 93.0] | 89.0 [77.0, 92.0]              | <0.001             | 89.0 [78.0, 92.0]  | 0.52 |
| Respiratory rate, median [IQR] | 20.0 [18.0, 21.0]   | 20.0 [18.0, 22.0]              | 0.13               | 20.0 [18.0, 22.0]  | 0.77 |
| D-Dimer, median [IQR] [μg/ml] | 1.35 [0.75, 2.55] | 1.38 [0.75, 2.63]              | 0.66               | 1.35 [0.76, 2.63]  | 1.00 |
| C-reactive protein, median [IQR] [mg/L] | 87.3 [37.5, 167.0] | 89.3 [41.2, 164.9]            | 0.68               | 95.5 [44.3, 176.9] | 0.075 |
| eGFR, median [IQR] [ml/min/1.73 m²] | 68.5 [41.8, 94.0] | 68.9 [44.5, 94.2]              | 0.46               | 68.6 [42.4, 94.2]  | 0.75 |
| Steroid during hospitalization, n (%) | 3809 (47.8)          | 942 (59.1)                        | <0.001             | 938 (59.9)         | 0.77 |
| Use of remdesivir        | 1289 (16.2)          | 307 (19.3)                         | 300 (19.2)         | 303 (19.3)         | 0.93 |
| Use of IL-6 inhibitor    | 237 (3.0)            | 87 (5.5)                           | <0.001             | 94 (6.0)           | 0.49 |
| Convalescent plasma      | 860 (10.8)           | 253 (15.9)                         | <0.001             | 241 (15.4)         | 0.77 |

Abbreviations: COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; ICU, intensive care unit; IL-6: interleukin-6; IQR, interquartile range; SD, standard deviation.
antagonist or inverse-agonist of histamine-mediated mast cell activation due to COVID-19 infection. Thus famotidine has an anti-inflammatory effect rather than the direct binding and action as an inhibitor of SARS-CoV-2 papain-like protease or direct-acting inhibitor of SARS-CoV-2 infection or replication as originally was expected based on the binding activity on computational analysis.\(^1\) Another experimental study showed that famotidine could inhibit histamine-induced expression of toll-like receptor 3 (TLR3) in SARS-CoV-2 infected cells and reduce the TLR3-dependent signaling process.\(^11\)

Our study has a limitation. Since this is a retrospective observational study, we could not adjust for potential confounders such as vaccination status, prior history of COVID-19, prior use of famotidine or other types of histamine-2 receptor blockers, and interactions of famotidine with other medications, because we have no access to the text of the clinical history, nor we able to link patient information to the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Toshiki Kuno. Data curation: Toshiki Kuno, Mai Takahashi, and Natalia N. Egorova. Acquisition, analysis, or interpretation of data: Toshiki Kuno, Mai Takahashi, and Natalia N. Egorova. Drafting of the manuscript: Toshiki Kuno. Critical revision of the manuscript for important intellectual content: Toshiki Kuno, Mai Takahashi, Natalia N. Egorova, and Matsuo So. Statistical analysis: Toshiki Kuno and Mai Takahashi. Administrative, technical, or material support: Natalia N. Egorova. Study supervision: Natalia N. Egorova.

**DATA AVAILABILITY STATEMENT**
Data are available from the corresponding author upon reasonable request.

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