Comparative Effectiveness of Famotidine in Hospitalized COVID-19 Patients

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INTRODUCTION: **Famotidine has been posited as a potential treatment for coronavirus disease 2019 (COVID-19). We compared the incidence of COVID-19 outcomes (i.e., death and death or intensive services use) among hospitalized famotidine users vs proton pump inhibitors (PPIs) users, hydroxychloroquine users, or famotidine nonusers separately.**

METHODS: **We constructed a retrospective cohort study using data from COVID-19 Premier Hospital electronic health records. The study population was COVID-19 hospitalized patients aged 18 years or older. Famotidine, PPI, and hydroxychloroquine exposure groups were defined as patients dispensed any medication containing 1 of the 3 drugs on the day of admission. The famotidine nonuser group was derived from the same source population with no history of exposure to any drug with famotidine as an active ingredient before or on the day of admission. Time at risk was defined based on the intention-to-treat principle starting 1 day after admission to 30 days after admission. For each study comparison group, we fit a propensity score model through large-scale regularized logistic regression. The outcome was modeled using a survival model.**

RESULTS: **We identified 2,193 users of PPI, 5,950 users of the hydroxychloroquine, 1,816 users of famotidine, and 26,820 nonfamotidine users. After propensity score stratification, the hazard ratios (HRs) for death were as follows: famotidine vs no famotidine HR 1.03 (0.89–1.18), vs PPIs: HR 1.14 (0.94–1.39), and vs hydroxychloroquine: 1.03 (0.85–1.24). Similar results were observed for the risk of death or intensive services use.**

DISCUSSION: **We found no evidence of a reduced risk of COVID-19 outcomes among hospitalized COVID-19 patients who used famotidine compared with those who did not or compared with PPI or hydroxychloroquine users.**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/B846; http://links.lww.com/AJG/B847; http://links.lww.com/AJG/B848

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INTRODUCTION

Famotidine, a specific histamine type 2 receptor antagonist that suppresses gastric acid production, has been proposed as an attractive candidate for coronavirus disease 2019 (COVID-19) treatment based on the potential role that the histamine pathway may play in immune modulation (1) and its long history of safe use (2).

Severe acute respiratory syndrome coronavirus 2 virus infection can induce histamine release via aberrant mast cell activation. The pathological histamine release has a potential to provoke the excessive synthesis of proinflammatory cytokines that may lead to acute respiratory distress syndrome observed in patients with severe COVID-19 (1). The finding of lower levels of inflammatory markers (e.g., C-reactive protein, ferritin, etc.) in famotidine-treated patients with COVID-19 suggests that the drug can dampen an uncontrolled proinflammatory immune response. This has prompted recent studies to postulate that the above effect of famotidine can be mediated via the antagonism and/or inverse agonism of histamine type 2 receptors (3). In another bioinformatics study, Wu et al. (4) identified famotidine as one of the drugs most likely to inhibit the 3-chymotrypsin-like protease, which processes proteins essential for viral replication. Furthermore, famotidine has been shown *in vitro* to inhibit human immunodeficiency virus replication (5). Famotidine is currently being tested under an investigational new drug waiver for treating COVID-19 in a double-blind randomized clinical trial at high intravenous doses (360 mg/d) in combination with either hydroxychloroquine or remdesivir (ClinicalTrials.gov Identifier: NCT04370262).

Recently, several observational studies have investigated the effect of famotidine on COVID-19 outcomes but have been limited to single-institutional explorations of small samples with varying statistical methods and inconsistent results. Freedberg et al. (6) reported that 84 patients receiving famotidine during a

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hospital stay had a significantly reduced risk of death or intubation when compared with patients who did not. Another study using electronic health data from Hartford hospital included 83 patients receiving famotidine and produced similar estimates (7). In addition, a sequential case series suggested benefits of famotidine treatment in an outpatient setting (8). In contrast to these findings, a territory-wide study in Hong Kong found no significant association between severe COVID-19 disease and use of famotidine (9).

Real-world data can potentially provide critical and timely evidence on the effectiveness of famotidine on improving COVID-19 outcomes. However, the design and interpretation of an observational population-level effect estimation study might be challenging. The appropriateness in the selection of a comparator and adequacy of adjustment of baseline covariates can impact the risk of selection bias and confounding. Given the recency of this pandemic, assessments are further challenged by insufficient sample size, which introduces random error and also can limit the fidelity of any statistical adjustment performance.

Using real-world data from a large national database on hospitalized patients with COVID-19, we aimed to estimate and compare the incidence of COVID-19 outcomes (i.e., death and death or intensive services) among hospitalized famotidine users vs proton pump inhibitors (PPIs) users, hydroxychloroquine users, or famotidine nonusers separately.

METHODS

We conducted a prevalent-user comparative retrospective cohort study measuring the association between famotidine use and severity of COVID-19 outcomes among patients hospitalized with COVID-19 in the United States. This study was approved under protocol (CCSDIH002924; https://github.com/ohdsi-studies/Covid19EstimationFamotidine/blob/master/Protocol/Covid19EstimationFamotidineProtocol.pdf).

Data source

The study population comprised hospitalized patients with a diagnosis of COVID-19 available in the COVID-19 Premier Hospital Database (PHD). The PHD contains complete clinical coding, hospital cost, and patient billing data from approximately 700 hospitals throughout the United States. It captures from 20% to 25% of all inpatient admissions in the United States. Premier collects deidentified data from participating hospitals in its healthcare alliance. The hospitals included are nationally representative based on bed size, geographic region, location (urban/rural), and teaching hospital status. The database contains medications administered during the hospitalization; laboratory, diagnostic, and therapeutic services; and primary and secondary diagnoses for each patient's hospitalization. Identifier-linked enrollment files provide demographic and payor information. Detailed service-level information for each hospital day is recorded; this includes details on medication and devices received. All data were standardized to the Observational Health and Data Sciences and Informatics Observational Medical Outcomes Partnership Common Data Model version 5.3. The full description of the extract, transform, and load of the data can be found here: https://github.com/OHDSI/ETL-CDMBuilder/blob/master/man/PREMIER/Premier_ETL_CDM_V5_3.doc. PHD contains deidentified patient information, is Health Insurance Portability and Accountability Act compliant, and is considered exempt from institutional review board approval (10).

Study period and follow-up

The study period started February 1, 2020, and ended May 30, 2020, the latest available date for all data in 2020. Figure 1 illustrates the retrospective study design schematic. As illustrated in Figure 1, follow-up for each of the cohorts started at an index date defined by the first inpatient admission (day 0). Time at risk was defined based on the intention-to-treat principle starting 1 day after admission and continuing up until the first of outcome of interest, loss to follow up, or 30 days after admission.

Study population

We included patients aged 18 years or older with an inpatient visit occurring after February 1, 2020, with a condition, measurement, or observation indicative of COVID-19 during or within 21 days before admission. Patients with evidence of intensive services (i.e., mechanical ventilation, tracheostomy, or extracorporeal membrane oxygenation) at or within 30 days before admission were excluded.

Exposures, outcomes, and confounders

Using a "nonusers" (i.e., unexposed group) group as a comparator can potentially increase the risk of confounding since the persons who used Famotidine are likely different than those who did not on several factors (11). To mitigate that risk, we included 2 active comparator groups. PPI users are expected to be clinically similar to famotidine users, given that both drugs have similar indications. However, whether PPI happens to have its own effect on COVID-19 outcome, an artificial relative difference may be observed. We included hydroxychloroquine users as another comparative group, given the accumulating evidence on the null effect of hydroxychloroquine on COVID-19 outcome, making it a possible ideal negative control for the analysis (12).

Famotidine, PPI, and hydroxychloroquine exposure groups were defined as patients dispensed any medication containing 1 of the 3 drugs of interest—as an ingredient—on the day of admission. Patients who received both famotidine and any of the comparator drugs on day of admission were excluded. The famotidine nonuser group was derived from the same source population (participants) with no history of exposure to any drug with famotidine as an active ingredient before or on the day of admission.

Outcomes of interest were death and death or intensive services (combined). Death was identified based on patient discharge status within admission records and International Classification of Diseases, Ninth Revision diagnosis codes provided by the source data. Only deaths that occur during hospitalization were captured. No additional death adjudication was performed.

Intensive services were defined as any condition, procedure, or observation code indicative of mechanical ventilation, tracheostomy, or extracorporeal membrane oxygenation. The code list used to identify study participants, exposures, and outcomes can be found at: https://github.com/ohdsi-studies/Covid19EstimationFamotidine/blob/master/Protocol/Annex%20I%20-%20Concept%20Set%20Expressions.xlsx.

Statistical methods

To adjust for potential measured confounding and improve the balance between comparison cohorts, we built large-scale propensity score (PS) models for each comparison using regularized regression (13). We used a Laplace previously (LASSO) with the optimal hyperparameter to fit the model, determined through 10-

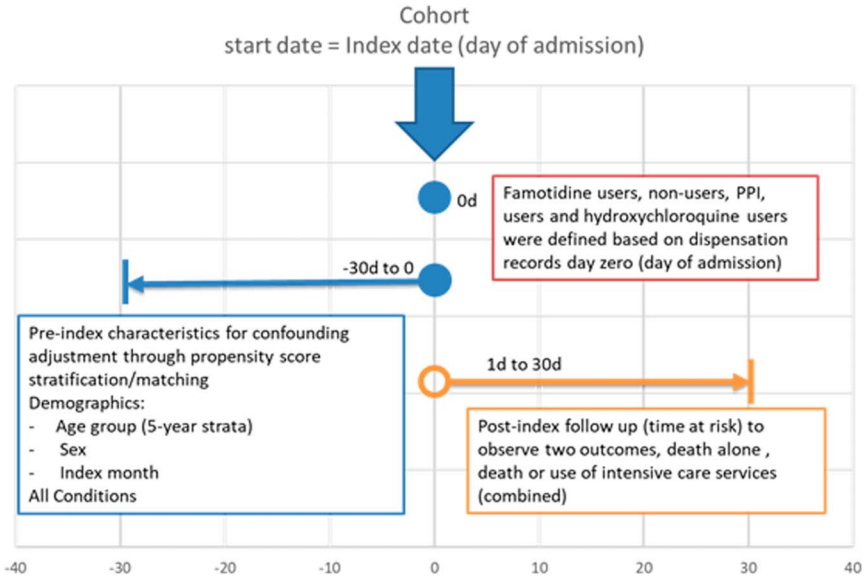

Figure 1. The study design schematic. We highlight index day specification, exposure definitions, adjustment strategies, outcome definitions, and time at risk. Exposure involves prescriptions to drugs with RxNorm ingredients that map to famotidine, proton pump inhibitors (PPIs), or hydroxychloroquine. The famotidine nonuser group was derived from the same source population (participants) with no history of exposure to any drug with famotidine as an active ingredient before or on the day of admission.

fold cross validation in which the outcome is a binary indicator for the potential comparator. This process used a large set of predefined baseline patient characteristics, including patient demographics (i.e., gender, age, and index month) and all observed conditions within 30 days before or on admission. For computational efficiency, we excluded all features that occurred in fewer than 0.1% of patients within the target and comparator cohorts before PS model fitting. For the main analysis, we stratified into 5 PS strata and used conditional Cox proportional hazards models to estimate hazard ratios (HRs) between target and alternative comparator treatments for the risk of each outcome. The regression for the outcome models conditioned on the PS strata with treatment as the sole explanatory variable.

As a sensitivity analysis, we used a 1:1 PS matching and used an unconditional Cox proportional hazards model to estimate HRs in the matched set. We declared a HR as significantly different from no effect when its $P < 0.05$ without correcting for multiple testing.

Blinded to the results, the study team evaluated study diagnostics for these treatment comparisons to assess whether they were likely to yield unbiased estimates. The suite of diagnostics included (i) minimum detectible risk ratio, (ii) preference score (a transformation of the PS that adjusts for prevalence differences between populations) distributions to evaluate empirical equipoise (14) and population generalizability, and (iii) extensive patient characteristics to evaluate cohort balance before and after PS-adjustment. We defined target and comparator cohorts to achieve sufficient balance if all after-adjustment baseline characteristics return absolute standardized mean differences (SMD) <0.1 (15).

We conducted this study using the open-source Observational Health and Data Sciences and Informatics CohortMethod R package (https://ohdsi.github.io/CohortMethod/) with large-scale analytics made possible through the Cyclops R package (https://ohdsi.github.io/Cyclops/) (16). The prespecified protocol and start-to-finish open and executable source code are available at: https://github.com/ohdsi-studies/Covid19EstimationFamotidine. To promote transparency and facilitate sharing and exploration of the complete result set, an interactive web application (https://data.ohdsi.org/Covid19EstimationFamotidine/) serves up study diagnostics and results for all study effects.

RESULTS

Population and incidence

A total of 2,193 users of PPI, 5,950 users of the hydroxychloroquine, 1,816 users of famotidine, and 26,820 non-famotidine users were identified in the data and were eligible for the study. Table 1 illustrates patient cohort size, follow-up duration, incidence of the 2 outcomes, and minimum detectible risk ratio for each famotidine/drug comparison for the PS-stratified analysis. Among the famotidine group, a total of 1,331 (73.29%) and 374 (20.59%) patients received a dose of 20 and 40 mg of famotidine on the day of admission, respectively. Furthermore, 1,155 (63.60%) and 709 (39.04%) patients received oral and IV formulations of famotidine on the day of admission, respectively, with 1.4% (n = 25) of patients receiving both oral and IV formulations.

Famotidine users vs PPI users

After PS stratification, a total of 1,527 COVID-19 patients exposed to famotidine were compared with 1,855 patients exposed to PPI. Among famotidine users, the incidence of death alone was 12.83% (196 patients) vs 15.20% (282 patients) among PPI users. The incidence of death or intensive services (combined) was 18.96% (298 patients) vs 22.10% (410 patients) among famotidine and PPI users, respectively.

Famotidine users vs hydroxychloroquine users

After PS stratification, a total of 1,186 COVID-19 patients exposed to famotidine were compared with 5,047 patients exposed to hydroxychloroquine. Among famotidine users, the incidence of death alone

Table 1. Populations and death events for PPI users, hydroxychloroquine users, and famotidine users and nonusers

	Patients		Time (person-years)		Outcome events		
	Target	Comparator	Target	Comparator	Target	Comparator	MDRR
Famotidine users vs PPI users							
Outcome = death	1,527	1,855	33	45	196	282	1.29
Outcome = death or intensive services	1,527	1,855	28	38	298	410	1.24
Famotidine users vs hydroxychloroquine users							
Outcome = death	1,186	5,047	27	109	159	686	1.28
Outcome = death or intensive services	1,186	5,047	23	89	238	1,077	1.22
Famotidine users vs nonusers							
Outcome = death	1,623	24,404	36	546	214	3,923	1.20
Outcome = death or intensive services	1,623	24,404	30	457	326	5,534	1.16

We report population size, total exposure time, outcome events, and MDRR for the propensity score–stratified analysis.
MDRR, minimal detectable risk ratio; PPI, proton pump inhibitor.

was 13.40% (159 patients) vs 13.59% (686 patients) among hydroxychloroquine users. The incidence of death or intensive services (combined) was 20.07% (238 patients) vs 22.10% (1,077 patients) among famotidine and hydroxychloroquine users, respectively.

Famotidine users vs nonusers

After PS stratification, a total of 1,623 COVID-19 patients exposed to famotidine were compared with 24,404 patients in the famotidine nonuser group. Among famotidine users, the incidence of death alone was 13.19% (214 patients) vs 16.09% (3,923 patients) among nonusers. The incidence of death or intensive services (combined) was 20.09% (326 patients) vs 22.68% (5,534 patients) among famotidine users and nonusers, respectively.

Characteristics of patients

Selected baseline characteristics of famotidine users compared with PPI users before and after PS stratification are shown in Table 2. Compared with PPI users, before PS adjustment, famotidine users were younger and had fewer comorbid conditions (based on [SMD] >0.1). Specifically, PPI users were more likely to have chronic liver diseases, chronic obstructive lung disease, gastroesophageal reflux disease (GERD), gastrointestinal hemorrhage, hyperlipidemia, lesion of liver, osteoarthritis, renal impairment, rheumatoid arthritis, viral hepatitis C, and cardiovascular disease.

Selected baseline characteristics of famotidine users compared hydroxychloroquine users and famotidine nonusers, before and after PS stratification, are shown in Supplementary Tables 1 and 2 (see Supplementary Digital Content 3, http://links.lww.com/AJG/B848), respectively. Compared with hydroxychloroquine users, before PS adjustment, famotidine users were more likely to be women, have GERD, some cardiovascular diseases, urinary tract infections, and depressive disorder but were less likely to have pneumonia. Compared with nonusers, famotidine users were less likely to be in the older age group (85–89 years) but were more likely to have GERD.

Selected drugs use of famotidine users compared with all other comparator groups at baseline and during follow-up is provided in Table 3. Compared with the nonusers, famotidine users had a general higher proportion of drug use. However, no substantial differences can be observed.

PS model adjustment and cohort balance

More than 2,400 baseline patients' characteristics were available for PS adjustment. After large-scale PS stratification or matching, SMDs for most baseline characteristics were <0.1. In the PPI comparison, SMD exceeded 0.1 for 21 covariates after PS stratification, including gastrointestinal hemorrhage, anemia due to blood loss, melena, pregnancy and pregnancy complications, venous varices, diaphragmatic hernia, and chronic pulmonary edema. In the hydroxychloroquine comparison, the SMD exceeded 0.1 for the following covariates: age group 30–34, venous varices, distention of vein, ectactic vein, pneumonia, and influenza. In the famotidine nonusers comparison, all SMDs for baseline characteristics were less than 0.1 after PS stratification. All baseline characteristics before and after PS adjustment for famotidine users compared with PPI users are plotted in Figure 2. All baseline characteristics before and after PS adjustment for famotidine users compared with hydroxychloroquine users and famotidine nonusers before and after PS stratification are plotted in Supplementary Figures 1 and 2 (see Supplementary Digital Contents 1 and 2, http://links.lww.com/AJG/B846 and http://links.lww.com/AJG/B847), respectively. The complete list of baseline characteristics before and after matching is available in the study link above, under the tab Covariate balance.

Risk of death and death or intensive services

HRs for the relative risk of incidence of death and death or intensive services are presented in Table 4 for the PS-stratified and PS-matched analyses. The risk of death was not significantly different among famotidine users compared with PPI users with PS stratification (HR 1.14, 95% confidence interval [CI] 0.94–1.39). Similarly, the risk of death or intensive services (combined) was similar among the 2 groups (HR 1.13, 95% CI 0.96–1.32) after PS stratification. When comparing famotidine users with hydroxychloroquine users, both the risk of death (HR 1.03, 95% CI 0.85–1.24) and the risk of death or intensive services (combined) (HR 1.05, 95% CI 0.90–1.22) were similar between groups after PS stratification. Finally, when comparing famotidine users with nonusers, no significant difference in the risk of death (HR 1.03, 95% CI 0.89–1.18) or the risk of death or

Table 2. Cohorts characteristics of famotidine and proton pump inhibitor users

Characteristic	Before PS adjustment			After PS adjustment		
	Target (%)	Comparator (%)	SMD	Target (%)	Comparator (%)	SMD
Age group						
15–19	<0.3	<0.2	0.02	<0.3	<0.2	0.04
20–24	1.3	0.6	0.07	1	0.8	0.01
25–29	2.7	1	0.13	1.9	1.2	0.06
30–34	4.3	1.8	0.15	3	2.1	0.06
35–39	3.8	2.6	0.07	3	3.3	−0.01
40–44	5.9	3.2	0.13	4.8	3.8	0.05
45–49	7.4	4.8	0.11	6.2	5.5	0.03
50–54	7.9	7.4	0.02	6.9	7.7	−0.03
55–59	11.2	9.7	0.05	10.2	9.6	0.02
60–64	11.5	10.9	0.02	12.2	11.1	0.03
65–69	11	12.1	−0.03	12	12.1	0
70–74	9.5	11.8	−0.08	10.5	11.9	−0.04
75–79	8.3	11	−0.09	9.2	10	−0.03
80–84	6.3	9.5	−0.12	7.9	8.6	−0.03
85–89	6.1	10	−0.14	8	8.9	−0.03
90–94	2.5	3.3	−0.05	2.8	3.2	−0.02
Gender: female	50	51.7	−0.03	51.9	51.6	0.01
Medical history: general						
Acute respiratory disease	54.9	60.1	−0.1	61	58.3	0.05
Attention deficit hyperactivity disorder	<0.3	0.6	−0.07	<0.3	0.5	−0.06
Chronic liver disease	1.6	4.1	−0.15	2.4	3.1	−0.04
Chronic obstructive lung disease	12.3	19.6	−0.2	17.4	16.8	0.01
Crohn's disease	0.4	0.5	−0.02	0.5	0.4	0.01
Dementia	12.1	13.7	−0.05	15.5	12.9	0.07
Depressive disorder	13.1	16.6	−0.1	16.5	15.2	0.04
Diabetes mellitus	38.8	40.9	−0.04	41.3	40.1	0.02
Gastroesophageal reflux disease	23.5	42.3	−0.41	36.7	33.2	0.07
Gastrointestinal hemorrhage	1.3	8.9	−0.35	3	6.3	−0.16
Human immunodeficiency virus infection	1.3	1.4	−0.01	1.3	1.4	−0.01
Hyperlipidemia	42.6	50.4	−0.16	50.1	47.3	0.06
Hypertensive disorder	43.1	43.3	0	42.8	43.8	−0.02
Lesion of liver	1.6	4.6	−0.17	2.2	3.7	−0.09
Obesity	24.1	22.6	0.03	24.5	23.2	0.03
Osteoarthritis	10.4	13.7	−0.1	13.4	12	0.04
Pneumonia	80.5	76.2	0.1	80.4	79.7	0.02
Psoriasis	0.3	0.9	−0.08	0.4	0.8	−0.06
Renal impairment	33.6	44.6	−0.23	41.2	40.7	0.01
Rheumatoid arthritis	1.3	3.4	−0.14	1.8	2.9	−0.07
Schizophrenia	0.8	1.5	−0.06	1.1	1.6	−0.04
Ulcerative colitis	0.5	0.4	0.01	0.4	0.4	0.01
Urinary tract infectious disease	8.5	9.2	−0.03	9.8	8.8	0.04
Viral hepatitis C	0.9	2.8	−0.14	1.5	2.4	−0.07

Table 2. (*continued*)

Characteristic	Before PS adjustment			After PS adjustment		
	Target (%)	Comparator (%)	SMD	Target (%)	Comparator (%)	SMD
Visual system disorder	6.1	6.7	−0.02	7.6	6	0.06
Medical history: cardiovascular disease						
Atrial fibrillation	12.8	19.9	−0.19	16.9	17.4	−0.01
Cerebrovascular disease	1.3	1	0.03	2	0.9	0.09
Coronary arteriosclerosis	16.9	26.1	−0.23	23.8	21.5	0.06
Heart disease	38.6	52.2	−0.28	47.9	46.2	0.03
Heart failure	13.1	24	−0.28	19.8	19.6	0
Ischemic heart disease	9.3	15	−0.17	12.2	12.7	−0.02
Peripheral vascular disease	4.9	8.2	−0.14	7.5	6.6	0.04
Pulmonary embolism	1.9	2.3	−0.02	2.3	2.2	0
Venous thrombosis	1.8	1.6	0.01	2.5	1.4	0.08
Medical history: neoplasms						
Hematologic neoplasm	1.5	1.3	0.01	1.9	1.3	0.05
Malignant lymphoma	0.8	1	−0.03	1	1.2	−0.02
Malignant neoplasm of anorectum	<0.3	<0.2	−0.03	<0.3	<0.2	−0.01
Malignant neoplastic disease	5.9	7	−0.04	7.3	6.7	0.02
Malignant tumor of breast	0.4	0.3	0.01	0.5	0.3	0.03
Malignant tumor of colon	<0.3	0.3	−0.06	<0.3	<0.2	−0.04
Malignant tumor of urinary bladder	<0.3	<0.2	−0.02	<0.3	<0.2	−0.02
Primary malignant neoplasm of prostate	0.4	0.7	−0.04	0.5	0.7	−0.02

We report the proportion of based-line characteristics and the SMD before and after stratification. Less extreme SMD through stratification suggest improved balance between patient cohorts through PS adjustment.
PS, propensity score; SMD, standardized mean difference.

intensive services (combined) (HR 1.03, 95% CI 0.95–1.15) was observed after PS stratification. PS matching HRs followed the same trend.

DISCUSSION

Using real-world data from a large multi-institutional hospital database, we found no evidence of a reduced risk of death among

Table 3. Selected drugs use of famotidine users compared with all other comparator groups at baseline and during follow-up

Drug	At baseline (on admission)				During follow-up			
	Famotidine users (%)	PPI users (%)	HCQ users (%)	Famotidine nonuser (%)	Famotidine users (%)	PPI users (%)	HCQ users (%)	Famotidine nonuser (%)
Dexamethasone	1.71	1.14	0.55	0.67	1.98	1.96	1.39	2.02
Prednisone	4.07	6.25	3.04	1.80	10.84	13.04	13.36	8.63
Hydrocortison	0.55	0.68	0.34	0.34	2.15	2.78	2.39	2.29
HCQ	27.90	24.76	100.00	19.77	50.52	46.37	92.47	50.39
Atrovastatine	45.84	42.41	54.10	40.19	45.90	39.72	46.57	44.41
Heparin	2.81	3.83	1.68	1.91	6.16	8.12	3.78	5.83
Enoxaparin	31.10	33.56	33.27	21.49	51.51	46.47	57.95	49.69
Apixaban	7.37	7.52	7.59	4.22	12.60	12.59	19.22	12.77
Atorvastatin	21.24	30.10	18.06	11.97	28.84	35.52	28.01	25.86
Remdesivir	0.00	0.00	0.00	0.00	0.11	0.14	0.03	0.06

We report the proportion at baseline and during follow-up.
HCQ, hydroxychloroquine; PPI, proton pump inhibitor.

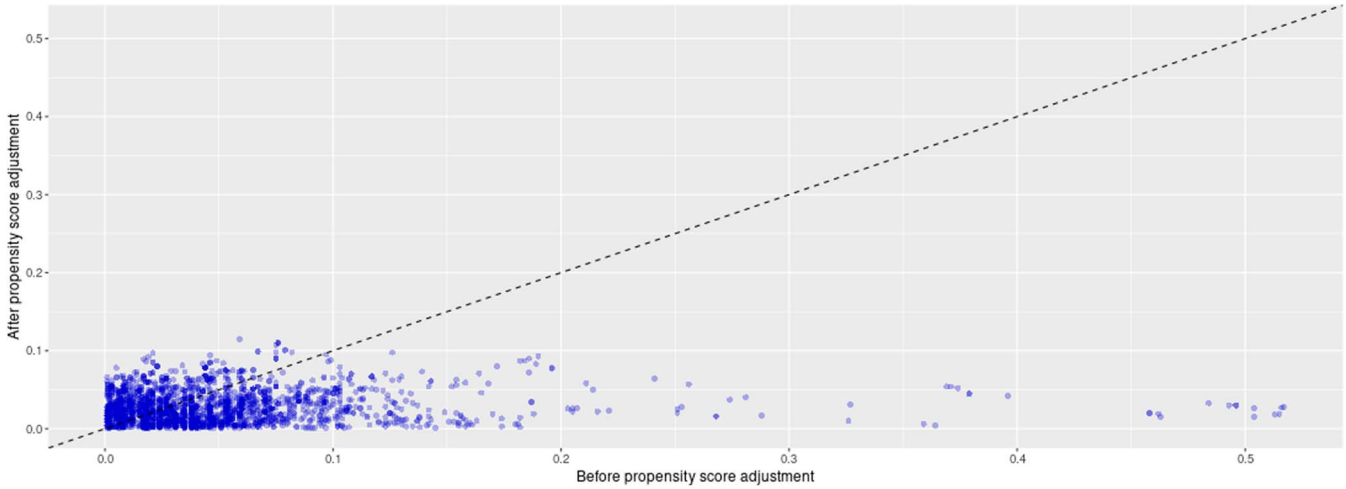

Figure 2. Covariate balance before and after propensity score adjustment for famotidine users vs proton pump inhibitor users. We plotted the absolute standardized difference of population proportions of all available patient characteristics on demographics and conditions before and after propensity score stratification.

hospitalized COVID-19 patients who used famotidine compared with those who did not or compared with PPI or hydroxychloroquine users. Similarly, there was no observed effect on the composite outcome of death or intensive services when comparing famotidine users with patients in the 3 comparator groups.

Previous literature on safety and mortality outcomes among COVID-19 patients treated with famotidine is limited to a series of mostly single-institution studies, and the results from these studies are conflicting. Freedberg et al. (6) found that after PS matching, patients who used famotidine (84 users) were at reduced risk of death or intubation (combined outcome) with a HR of 0.43 (95% CI 0.21–0.88). Another retrospective observational study found that when comparing hospitalized COVID-19 patients who received famotidine (83 patients) with those who did not, famotidine users were at reduced risk of in-hospital mortality (odds ratio [OR] 0.37, 95% CI 0.16–0.86, $P = 0.021$) and combined death or intubation (OR 0.47, 95% CI 0.23–0.96, $P = 0.040$) (7). However, the results from a retrospective cohort study conducted on 51 patients in Hong Kong found no significant association between severe COVID-19 disease and use of famotidine compared with nonusers (OR 1.34, 95% CI 0.24–6.06; $P = 0.72$) (9). Recently, Yeramaneni et al. (17) reported on another multicenter retrospective study among 7,158 (1,127 patients exposed to famotidine and 6,031 unexposed) hospitalized COVID-19 patients. The authors found that famotidine use within 24 hours of admission did not confer additional risk or benefit to 30-day mortality. The inconsistency of the findings across multiple retrospective studies could be potentially attributed to confounding and selection bias in comparator selection, 2 sources of systematic error that our study sought to address. In addition, the high variability of famotidine dosage may explain some of the observed inconsistency. Although most of the famotidine-exposed

Table 4. Relative risk of death and death or intensive care services for PPI users, hydroxychloroquine users, and famotidine users and nonusers

	PS stratified		PS matched	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Famotidine users vs PPI users				
Outcome = death	1.14 (0.94–1.39)	0.18	1.02 (0.82–1.27)	0.85
Outcome = death or intensive services	1.13 (0.96–1.32)	0.14	1.09 (0.91–1.31)	0.33
Famotidine users vs hydroxychloroquine users				
Outcome = death	1.03 (0.85–1.24)	0.79	0.98 (0.77–1.23)	0.85
Outcome = death or intensive services	1.05 (0.90–1.22)	0.55	1.12 (0.93–1.37)	0.24
Famotidine users vs nonuser				
Outcome = death	1.03 (0.89–1.18)	0.67	1.03 (0.86–1.24)	0.74
Outcome = death or intensive services	1.03 (0.92–1.15)	0.62	1.00 (0.86–1.16)	0.99

We report HR and their 95% CI and *P* value, with PS stratification or matching.
CI, confidence intervals; HR, hazard ratios; PPI, proton pump inhibitor; PS, propensity score.

population in this study were on the same low dose, dosage variability was evident from other existing studies.

We implemented large scale PS adjustment to account for possible measured confounding (13). We also implemented a set of study diagnostics and included 3 different comparators to increase our confidence in the study findings by evaluating consistency against different possible biases related to the choice of the comparator group. However, measurement error and residual confounding due to unobserved factors, such as preadmission drug use, may still exist, as evidenced by having some SMDs >0.10 even after PS adjustment. In specific, the concomitant use of remdesivir or steroids (18,19), both considered potentially effective for severe COVID-19, may in theory be an issue. However, the use of remdesivir was extremely rare in all study populations. In addition, no significant difference in steroid use among the famotidine users and any of the comparator groups was observed. Although PHD contains hospital data from multiple institutions, this study still represents results from 1 data source and further replication across other sources would increase confidence in the findings. Our study did not consider strength or dose or duration of exposure for any of the exposures and may not generalize to the high-dose exposure under investigation in the ongoing clinical trial or in other clinical contexts outside of hospital admission. In addition, the analysis is limited to famotidine use on day of admission, and different results may be observed when considering famotine use at any time during hospitalization (e.g., day 1 or 2 after admission).

Our study findings reflect the real-world use of famotidine at the day of admission for hospitalized COVID-19 patients. However, given the conflicting findings and the inherent bias of existing observational studies, further evidence is needed to demonstrate its effectiveness. Until such evident is available through the ongoing randomized clinical trial, the results from observational studies should be interpreted with caution.

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Study Highlights

WHAT IS KNOWN

- ✓ Famotidine was been posited as a potential treatment for COVID-19.
- ✓ Insufficient evidence exists about its effects.

WHAT IS NEW HERE

- ✓ There was no evidence of a reduced risk of death among COVID-19 patients who used famotidine compared with those who did not.
- ✓ We found no evidence of a reduced risk of death among hospitalized COVID-19 patients who used famotidine compared with proton pump inhibitors or hydroxychloroquine users.
- ✓ Study findings reflect the real-world use of famotidine in hospitalized COVID-19 patients.

CONFLICTS OF INTEREST

Guarantor of the article: Azza Shoaibi, PhD.

Specific author contributions: All authors contributed to the conceptualization and design of the study. S.F.: authored the protocol of the study design. A.S.: implemented the statistical analysis. R.W., P.R., and J.A.B.: reviewed and approved the study diagnostics and results. A.S.: drafted the manuscript and all coauthors reviewed and contributed to the manuscript writing.

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Potential competing interests: A. Shoaibi, S. Fortin, R. Weinstein, and P. Ryan are employees of Janssen Research and Development and shareholder of Johnson & Johnson, the product manufacturer of famotidine. J.A. Berlin is an employee and shareholder of Johnson & Johnson.

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