Impact of Famotidine Use on Clinical Outcomes of Hospitalized COVID-19 Patients

Jeffrey F. Mather, MS; Richard L. Seip, PhD; Raymond G. McKay, MD

Divisions of Research Administration and Interventional Cardiology, Hartford Hospital, Hartford CT

Richard L. Seip, PhD

Richard.Seip@hhchealth.org

Raymond G. McKay, MD

Raymond.McKay@hhchealth.org

Address for correspondence:

Jeffrey F. Mather, MS

Division of Research Administration

Hartford Hospital

80 Seymour Street

Hartford CT 06115, USA

E-mail: jeffrey.mather@hhchealth.org

Telephone: 860-972-3560

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JM performed data acquisition. All authors had a role in interpretation and drafting the manuscript. JM and RS performed statistical analysis. RM and JM wrote the manuscript and all authors gave critical revision of the manuscript for important intellectual content

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Study Highlights:

What is known?

- Despite multiple trials that are currently underway to investigate the safety and efficacy of a large number of possible therapeutic agents, no drug to-date has been shown to reduce COVID-19 mortality.
- It has been postulated that famotidine's effect is achieved via its antagonism or inverse-agonism of the histamine-2 receptor, inferring that the SARS-CoV-2 infection that results in COVID-19 is at least partially mediated by pathological histamine release.
- As a histamine-2 receptor antagonist, famotidine is a therapeutic option in COVID-10 positive patient therapy.

What is new here?

- We describe a propensity-matched comparison of COVID-19 patients treated with and without famotidine.
- Famotidine use was significantly associated with a reduction in death and either death or intubation.
- Famotidine users demonstrated lower levels of serum markers for severe disease in hospitalized COVID-19 patients.

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Abstract

Objectives: To compare outcomes in patients hospitalized with COVID-19 receiving famotidine therapy to those not receiving famotidine.

Methods: Retrospective, propensity-matched observational study of consecutive COVID-19 positive patients between February 24, 2020 to May 13, 2020.

Results: Of 878 patients in the analysis, 83 (9.5%) received famotidine. In comparison to patients not treated with famotidine, patients treated with famotidine were younger (63.5 ± 15.0 vs 67.5 ± 15.8 years, p=0.021), but did not differ with respect to baseline demographics or pre-existing comorbidities. Use of famotidine was associated with a decreased risk of in-hospital mortality (OR 0.37, 95% CI 0.16-0.86, p=0.021), as well as combined death or intubation (OR 0.47, 95% CI 0.23-0.96, p=0.040). Propensity score matching to adjust for age difference between groups did not alter the effect on either outcome. In addition, patients receiving famotidine displayed lower levels of serum markers for severe disease including lower median peak C-reactive protein (CRP) levels (9.4 vs 12.7 mg/dl, p=0.002), lower median procalcitonin levels (0.16 vs 0.30 ng/ml, p=0.004) and a non-significant trend to lower median mean ferritin levels (797.5 vs 964.0 ng/ml, p=0.076). Logistic regression analysis demonstrated that famotidine was an independent predictor of both lower mortality and combined death/intubation, while older age, BMI > 30 kg/m^2, chronic kidney disease, the national early warning score (NEWS) and higher neutrophil-lymphocyte ratio were all predictors of both adverse outcomes.

Conclusions: Famotidine use in hospitalized COVID-19 patients 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 COVID-19 patients.

INTRODUCTION

Among the many therapeutic alternatives that are currently being tested for treating COVID-19 patients is the use of the histamine-2 receptor antagonist, famotidine. Following an early anecdotal report from Wuhan, China that suggested that famotidine use was commonly observed in COVID-19 survivors[1], a retrospective cohort study of 1,620 hospitalized COVID-19 patients demonstrated that patients receiving famotidine had statistically significant reductions in both in-hospital death as well as a combined death and intubation [2]. More recently, a small case series of non-hospitalized COVID-19 patients treated with high-dose oral famotidine documented a marked improvement in symptoms in all cases shortly after starting the drug[3]. In light of a potential beneficial therapeutic effect, the purpose of the present study was to examine the impact of famotidine on adverse clinical outcomes in a COVID-19 hospitalized cohort.

METHODS

Setting and Design

This retrospective, observational study was carried out at Hartford Hospital, an 890-bed tertiary care medical center in Hartford, Connecticut. The Hartford Hospital Institutional Review Board (Assurance number: FWA000000601) approved the study and certified that it met the criteria for a waiver of the requirement to obtain informed consent. Extracted data was reviewed by JM(author) and ST, MS (acknowledged) while blinded to famotidine use.

Study Population

The study group for this report was derived from an electronic database collected at Hartford Hospital encompassing consecutive patients screened for COVID-19 between February 24, 2020 and May 13, 2020. All patients who tested positive for SARS-CoV-2 by nasopharyngeal polymerase chain reaction and who required inpatient admission were included in this study.

Famotidine Use

Patients were classified as receiving famotidine if they were treated with either oral or intravenous 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 (EMR).

Primary and Secondary Outcomes

The primary outcomes of the study included in-hospital death as recorded in the discharge status of the patient, requirement for mechanical ventilation, and the composite of death or requirement for ventilation. Secondary outcomes included serum markers of disease severity including white blood cell count, lymphocyte count, eosinophil count, neutrophil-lymphocyte ratio, platelet count, serum ferritin, C-reactive protein, high sensitivity D-Dimer, NEWS score, and procalcitonin. All of these data were extracted from the EMR.

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 baseline demographics, pre-existing comorbidities, and treatment with antiviral, antimalarial and corticosteroid medications. Demographic variables included age, gender, race, smoking status, and body mass index (BMI). Comorbidities included history of pre-existing hypertension, diabetes mellitus, obesity (BMI > 30), coronary artery disease (CAD), heart failure, atrial fibrillation, chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), or prior history of malignancy. In-hospital treatment medications included use of hydroxychloroquine, azithromycin, remdesivir and corticosteroids.

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 chi-square test or Fisher exact test, as appropriate. Univariate analyses were performed using mortality or combined mortality/ventilation as the dependent variables, and multivariate logistic regression was performed by entering all predictors using a p value of less than 0.15 cutoff. Propensity score matching was performed to balance the groups. Patients treated with famotidine were matched 1:9 with patient not treated with famotidine using nearest neighbor matching with a caliper of 0.2. Additional analysis included logistic regression and Cox proportional hazard regression using the propensity-matched sample. Proportional hazard assumptions were checked by using log-log survival plots. All effects were considered significant at a p value of less than 0.05. The statistical analyses were performed with SPSS v26.0 (IBM, Armonk, NY). Propensity score matching was performed using Propensity Score Matching for SPSS, version 3.0.4 (SPSS, Chicago, IL) (27).

Sensitivity Analysis

To determine if there was any relationship between the level of patient acuity and the impact of famotidine on mortality, we performed an additional sensitivity analysis on two subsets of patients comparing results in patients with a mean NEWS Score ≤ 3 and a mean NEWS Score > 3.

RESULTS

Of 878 patients in the analysis, 83 (9.5%) received famotidine. The mean age of the entire study group was 67±16 years, and 480 were males (54.7%). A total of 191 (21.8%) patients died during the hospitalization, 239 (27.2%) required mechanical ventilation, and 101 (11.5%) met the criteria for combined death and intubation. **Table 1** lists baseline demographics, comorbidities, and severity of illness of the famotidine and non-famotidine study cohorts both pre and post matching. As shown, there were no significant differences in the propensity-matched cohorts.

Famotidine Use

Of the 83 patients that received famotidine, 55 (66.3%) patients received the drug only as an inpatient, 24 (28.9%) were taking the drug prior to hospital admission and received famotidine as an inpatient, and the remaining 4 (4.8%) were taking the drug prior to hospital admission and did not receive famotidine as an inpatient.

Famotidine was administered orally in 83% of cases and intravenously in the remaining 17%. Dosing for oral administered famotidine was 20 mg/day in 95.2% of cases and 40 mg/day in the remaining 4.8% of cases. Intravenous famotidine was administered as a 20 mg/2 ml solution in all cases,

For in-patient famotidine use, the median total dose was 80 mg (range 40-160 mg) and was received over a median of 4 days (range 2-8 days).

Hydroxychlorine, Azithromycin, Remdesivir and Corticosteroid Use

For the matched study group of 772 COVID-19 patients, a total of 394 (51.0%) received hydroxychloroquine, 391 (50.6%) received azithromycin, 27 (3.5%) received remdesivir, and 377 (48.8%) received corticosteroids. As depicted in **Table 2**, there was no significant difference between the famotidine and non-famotidine cohorts with respect to treatment for all four of these agents.

Primary Outcomes

In-hospital death, intubation and combined death/intubation occurred in 12 (14.5%), 18 (21.7%) and 6 (7.2%) patients in the famotidine group, respectively, as compared to 179 (26.0%), 221 (32.1%) and 95 (13.8%) patients in the non-famotidine, respectively. The results of the logistic regression to assess the independent predictors of death in the matched cohort are shown in **Figures 1.** The analysis identified famotidine use to be associated with a significant reduction in the risk of in-hospital mortality (OR 0.366, 95% CI 0.155-0.862, p=0.021). This association was replicated using the combined death or intubation endpoint, (OR 0.469, 95%

CI 0.228-0.965, p=0.04). Age, BMI > 30 kg/m^2, chronic kidney disease, and NEWS Score were significantly associated with an increase risk in both models. A higher neutrophil-lymphocyte ratio was associated with an increased risk of death, while an increase white blood cell count was associated with death and/or intubation.

When performing a Cox proportional hazards model on the propensity-matched cohorts, the results were similar to the logistic regression model. Famotidine use was associated with a significant reduction in the risk of in-hospital mortality (HR 0.386, 95% CI 0.202-0.740, p=0.004), **Figure 2**. This association was again replicated using the combined death or intubation endpoint, (HR 0.495, 95% CI 0.310-0.789, p=0.003). Propensity score matching between famotidine and non-famotidine patients to correct for age difference did not alter the significance of differences in either mortality or combined mortality and intubation in the analysis.

Secondary Outcomes

Table 3 depicts laboratory test results for famotidine and non-famotidine groups. Patients receiving famotidine expressed lower levels of serum markers for severe disease including median peak CRP levels (9.4 vs 12.7 mg/dl, p=0.002), median procalcitonin levels (0.16 vs 0.30 ng/ml, p=0.004) and a non-significant trend to lower median mean ferritin levels (797.5 vs 964.0 ng/ml, p=0.076).

Additional Sensitivity Analysis

An additional sensitivity analysis demonstrated a relationship between the level of patient acuity and the impact of famotidine on mortality. In the cohort with a mean NEWS Score of ≤ 3, after adjusting for age, history of atrial fibrillation, heart failure, chronic kidney disease, obesity, neutrophil-lymphocyte ratio, white blood cell count and asthma, the famotidine association was not significant (HR 0.86, 95% CI 0.10-7.91). In the cohort with a mean NEWS score of >3 with similar adjustment, however, famotidine was significant (HR 0.43, 95% CI 0.19-0.99, p = .046).

DISCUSSION

As of early June 2020, there have been nearly 7 million cases of diagnosed COVID-19 and over 400,000 deaths reported worldwide. While approximately 80% of patient report mild or moderate symptoms, the remaining 20% develop severe or critical disease and require hospitalization. In-hospital mortality has been reported to range from 10-26%, but rises much higher in those that require admission to an intensive care unit and those that require mechanical ventilation. Despite multiple trials that are currently underway to investigate the safety and efficacy of a large number of possible therapeutic agents, no drug to-date has been shown to reduce COVID-19 mortality.

The main finding of our single-center, retrospective study of hospitalized COVID-19 patients is that use of famotidine is associated with improved clinical outcomes including lower in-hospital mortality and a lower composite endpoint of death and/or intubation. The impact of the drug on mortality appears to be most pronounced in patients with the highest level of acuity as measured by mean NEWS Score. In addition, famotidine patients were shown to have lower levels of markers for serious disease including serum ferritin levels, CRP and procalcitonin. The observed benefit of famotidine was unrelated to concurrent use of experimental treatments including hydroxychloroquine, azithromycin, remdesivir and corticosteroids. Apart from the impact of famotidine, our analyses demonstrating the increased risk of death in COVID-19 patients who are older, having co-morbidities of obesity and chronic kidney disease, or having higher NEWS Scores and higher neutrophil-lymphocyte ratios, are in agreement with the literature.

Our results on mortality and combined mortality/intubation corroborate the findings from the recent report by Freedberg et al. that examined the effect of famotidine use on clinical outcomes in 1,620 consecutive hospitalized patients with COVID-19 infection from February 25, 2020 to April 13, 2020 at a single medical center [2]. The authors reported that famotidine, received within 24 hours of hospital admission in 84 Covid-19 patients, was associated with reduced risk for death or intubation (adjusted hazard ratio (HR) 0.42, 95% CI 0.21-0.85) and also with reduced risk for death alone (HR 0.30, 95% CI 0.11-0.80). After baseline patient characteristics were balanced using propensity score matching, these relationships were unchanged (HR for famotidine and death or intubation: 0.43, 95% CI 0.21-0.88).

The mechanism by which famotidine might improve COVID-19 outcomes is currently unknown. One theory, based upon earlier reports on the efficacy of famotidine in inhibiting HIV replication[4], is that famotidine may directly inhibit the SARS-CoV-2 virus. Recent studies employing a Vero E6 cell-based assay, however, have failed to demonstrate any direct inhibitory effect of famotidine on SARS-CoV-2 infection[5]. A second theory, based upon computational methods that identified famotidine as a potential agent capable of binding and inhibiting key SARS-CoV-2 proteases critical to viral replication [6,7], has likewise been discounted [5].

A more recent mechanism that has been postulated is that famotidine's effect is achieved via its antagonism or inverse-agonism of the histamine-2 receptor, inferring that the SARS-CoV-2 infection that results in COVID-19 is at least partially mediated by pathological histamine release and perhaps dysfunctional mast cell activation [5,8]. Preventing the deleterious sequelae of this histamine release has been suggested as fundamental to preventing the cytokine storm that may cause acute respiratory distress syndrome, leading to hypoxia, sepsis, organ failure and ultimately death in the COVID-19 patient [8] . Lower levels of ferritin, CRP, and procalcitonin in famotidine-treated patients in this study are compatible with the hypothesis that the drug may limit the abnormal excessive cytokine release from an uncontrolled immune activation.

Additionally, it is notable that certain unusual clinical aspects of COVID-19 could be explained by excessive histamine release and stimulation of the histamine-2 receptor. First, along with early typical non-specific viral symptoms of fever, sore throat, cough, headache, diarrhea and myalgia, some COVID-19 patients may experience anosmia, ageusia, and skin rashes including pruritis and urticarial symptoms [9,10]. All of these symptoms could be explained by histamine signaling. Second, seriously ill COVID-19 patients with hypoxia and abnormal pulmonary CT findings who require intubation have been found to have near normal compliance (i.e. >50 mLcmH_2O) with little response to positive end-expiratory pressure (PEEP) ventilation [5]. In part, this observation could be related to a loss of pulmonary restriction mediated by the histamine-2 receptor on smooth muscle cells and/or pericytes. Third, it is notable that limited lung autopsy specimens have demonstrated a paucity of neutrophils and eosinophils in post-mortem photomicrographs [11]. The histamine-2 receptor has been documented to inhibit neutrophil effector functions including O_2-release [12], platelet activating factor-induced chemotaxis [13] and leukotriene biosynthesis [14], as well as inhibition of eosinophil peroxidase release [15] and eosinophil chemotaxis [16].

In humans, histamine is found in nearly all tissues of the body stored in the granules of tissue mast cells and serum basophils. Mast cells located in the submucosa of the respiratory tract and in the nasal cavity represent a barrier of protection against microorganisms [17]. Their functions include mastocytosis by secreting histamine, leukotrienes and proteases [18]. They also play a role in inflammation development via release of multiple pro-inflammatory cytokines and chemokines [19]. Mast cells are known to be triggered by viruses[20], and it has been documented that they have the angiotensin-converting enzyme 2 (ACE2) receptor used by SARS-CoV-2 to gain entry to cells and replicate [21].

The findings in this report should be interpreted with caution in light of the single-center, retrospective and observational nature of the study. Assessment of ~~sensitivity analysis that included an~~the possible effects of additional H2 receptor antagonists (such as cimetidine, nizatidine, or ranitidine) was not possible due to limited cases. Additional studies are needed to ascertain the potential efficacy of famotidine in the COVID-19 patient, including the impact of drug dose, route of administration and timing of therapy. In light of the need for additional trials, famotidine is currently being tested under an IND waiver for treating

COVID-19 in a double blind randomized clinical trial in combination with either hydroxychloroquine or remdesivir (ClinicalTrials.gov Identifer: NCT04370262).

In summary, we found that famotidine is associated with improved clinical outcomes in COVID-19 hospitalized patients, including lower in-hospital mortality, a lower composite of death and/or intubation, and lower levels of serum markers for serious disease. Additional studies are warranted to fully evaluate the impact of famotidine in the COVID-19 population.

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Conflicts of Interest: None

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Figure 1 Adjusted Odds Ratio’s for the Risk of Death.

Figure 2 Adjusted Hazard Ratios and Number at Risk of Death for Famotidine vs Non-Famotidine Users.

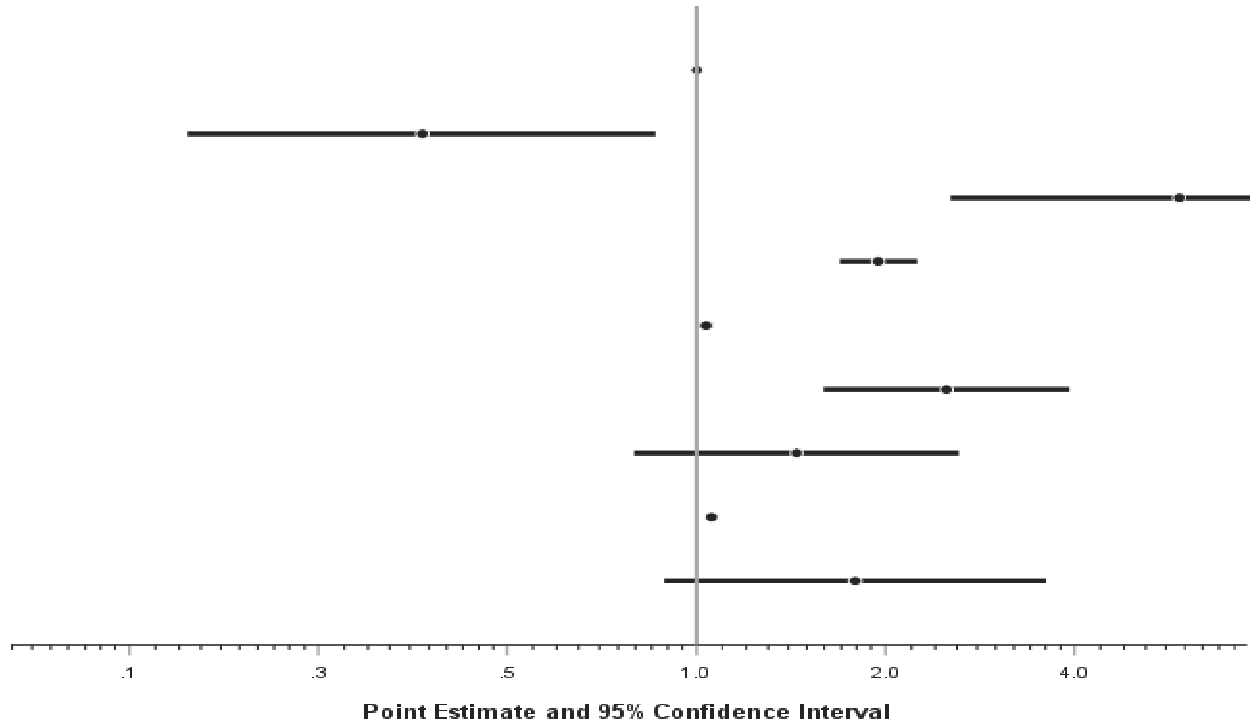
Table 1 Demographics and comorbidities: All Patients and Subpopulations With and Without Famotidine

Table 2. Treatment with Hydroxychloroquine, Remdesivir, Corticosteroids

Table 3 Laboratory Findings: All Patients and In Subpopulations with and Without Famotidine

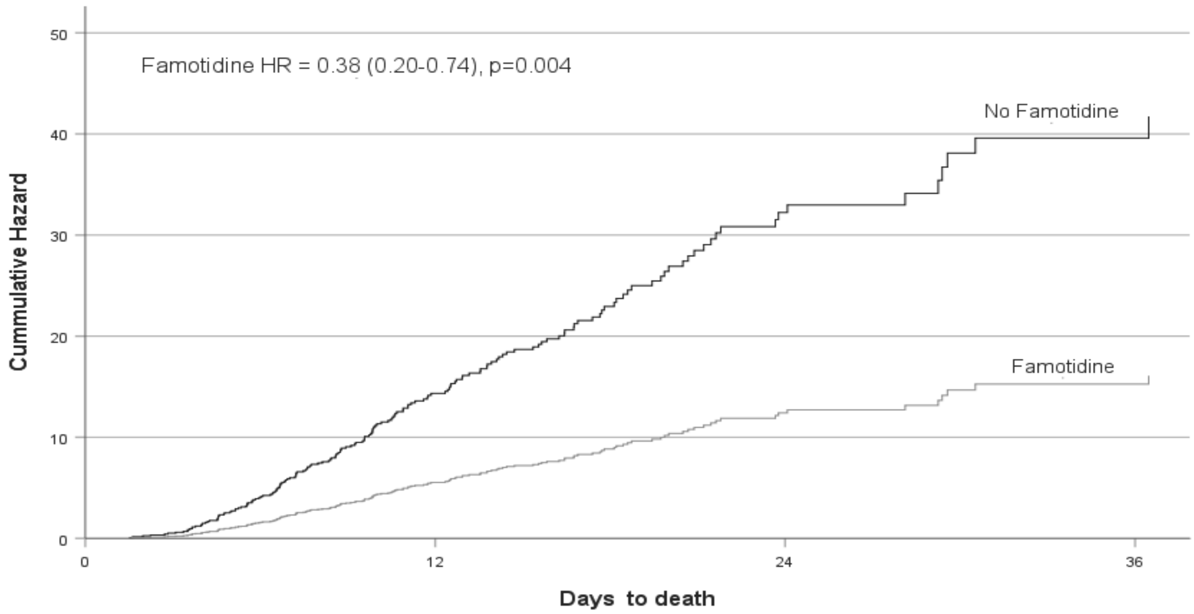
Figure 1

Variable	OR(95% CI)
WBC	1.00 (0.98-1.02)
Famotidine	0.37 (0.16-0.86)
Obesity	5.87 (2.54-13.6)
NEWS Score	1.95 (1.69-2.24)
NLR	1.04 (1.01-1.06)
Kidney Disease	2.50 (1.60-3.93)
Heart Failure	1.44 (0.80-2.62)
Age	1.06 (1.04-1.08)
Afibrillation	1.79 (0.89-3.61)



Abbrevations: WBC = White blood cells; NLR = Neutrophile-to-lymphocyte ratio.

Figure 2



No. at risk				
No Famotidine	689	293	80	23
Famotidine	83	46	9	4

Table 1. Demographics and comorbidities: All Patients and Subpopulations With and Without Famotidine

	All Patients			Matched		
Variable: n(%), median(IQR), mean(±SD)	Famotidine (n=83)	No Famotidine (n=795)	p value	Famotidine (n=83)	No Famotidine (n=689)	p value
Age	63.3(±15.0)	67.5(±15.8)	0.021	63.3(±15.0)	66.4(±14.3)	0.064
Gender (Male)	44(53.0%)	436(54.8%)	0.75	44(53.0%)	384(55.7%)	0.638
Caucasian	41(49.4%)	427(53.7%)	0.319	41(49.4%	361(52.4%)	0.209
Smoking Status			0.274			0.249
Never	37(78.7%)	411 (74.3%)		37(78.7%)	350(73.2%)	
Current	2(4.3%)	65(11.8%)		2(4.3%)	59(12.3%)	
Ex	8(17.0%)	77(13.9%)		8(17.0%)	69(14.4%)	
BMI	30.6(26.8-35.1)	29.6(24.8-35.7)	0.463	30.6(26.8-35.1)	30.2(25.2-36.3)	0.957
Comorbidities						
Atrial fibrillation	5(6.2%)	76(9.6)	0.29	5(6.2%)	54(8.3%)	0.52
Asthma	5(6.0%)	38(4.8%)	0.617	5(6.0%)	33(5.1%)	0.658
CAD	6(7.2%)	43(5.4%)	0.492	6(7.2%)	40(6.2%)	0.643
Cancer	8(9.6%)	41(5.2%)	0.124	8(9.6%)	40(5.2%)	0.192
COPD	8(9.6%)	49(6.2%)	0.221	8(9.6%)	37(5.7%)	0.132
Diabetes	18(21.7%)	174(21.9%)	0.967	18(21.7%)	157(24.2%)	0.738
Heart Failure	8(9.6%)	105(13.2%)	0.356	8(9.6%)	79(12.2%)	0.371
Hypertension	27(32.5%)	279(35.1%)	0.641	27(32.5%)	226(34.8%)	0.849
Obesity	4 (4.8%)	48(6.0%)	0.81	4 (4.8%)	42(6.5%)	0.34
Kidney Disease	22(26.5%)	237(29.8%)	0.53	22(26.5%)	196(30.2%)	0.619
News Score	3.6(±1.9)	3.9(±1.8)	0.148	3.6(±1.9)	3.9(±1.8)	0.100
Abbreviations: BMI: body mass index, CAD: coronary artery disease, COPD, chronic obstructive pulmonary disease.						

Table 2. Treatment With Hydroxychloroquine, Remdesivir, Corticosteroids

Agent	Group		p-value
	Famotidine (n = 83)	No Famotidine (n = 689)	
Hydroxychloroquine	36(43.4%)	358(52.0%)	0.139
Azithomycin	36(43.4%)	355(51.5%)	0.161
Remdesivir	3 (3.6%)	24 (3.5%)	0.951
Cortocosteroids*	48(57.8%)	329(47.8%)	0.083

* Corticosteroid medications include: Betamethasone, Budesonide, Dexamethasone, Fludrocortisone Acetate, Hydrocortisone, Methylprednisolone, Prednisolone, Prednisone, Triamcinolone Acetonide

table 3

Table 3. Laboratory Findings: All Patients and In Subpopulations with and Without Famotidine

Laboratory Values, median (IQR)	**Reference Range**	**All Patients (n=772)**	**No Famotidine (n=689)**	**Famotidine (n=83)**	**p value[a]**
Hematologic					
WBC, x 109/L[b]	3.5 - 9.5	11.30(7.60-17.20)	11.30(7.60-17.40)	10.80(6.80-16.00)	0.424
Lymphocytes, x 109/L[c]	1.50 - 4.50	0.60(0.40-0.94)	0.60(0.40-0.93)	0.66(0.37-1.09)	0.666
NLR, x 109/L[b]	0.78 - 3.53	9.30(5.07-16.96)	9.43(5.05-17.25)	8.11(5.48-14.86)	0.403
Monocytes, x 109/L[c]	0.2 - 1.50	0.28(0.17-0.46)	0.29(0.18-0.46)	0.27(0.15-0.43)	0.401
Platelets, x 109/L[c]	150 - 400	164.00(119.00-212.00)	167.00(119.00-212.00)	148.00(107.00-201.00)	0.093
Eosinophils, x 109/L[b]	0 - 0.7	0.07(0.01-0.19)	0.08(0.01-0.19)	0.07(0.01-0.20)	0.273
Biochemical					
AST, U/L[b]	10 - 40	55.00(36.00-8100)	56.00(36.00-81.00)	48.00(35.00-77.00)	0.203
ALT, U/L[b]	10 - 40	38.00(21.00-71.00)	39.00(21.00-71.00)	36.00(22.00-71.00)	0.732
BUN, mg/dL[c]	20-Aug	15.00(11.00-26.00)	15.00(11.00-27.00)	14.00(11.00-19.00)	0.073
Albumin, g/dL[c]	3.5 - 5.5	2.80(2.30-3.20)	2.80(2.30-3.20)	3.00(2.50-3.40)	0.028
Infection related indices					
hsCRP, mg/L[b]	0.0 - 3.0	12.31(6.48-20.74)	12.83(6.77-21.22)	9.41(4.82-14.08)	0.002
ESR, mm/h[b]	0 -15	65.00(41.00-88.00)	67.00(41.50-88.00)	57.50(35.00-84.00)	0.19
Serum ferritin, ng/mL[b]	11 - 336	940.00(426.00-1,929.00)	964.00(452.00-1,947.00)	797.50(343.00-1,345.50)	0.076
Procalcitonin, ng/ml[b]	0.10 - 0.49	0.29(0.12-1.00)	0.30(0.13-1.06)	0.16(0.08-0.45)	0.004

Abbreviations: WBC, white blood cell count; NLR, neutrophil-to-lymphocyte ratio; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BUN, blood urea nitrogen; hsCRP, high-sensitivity C-reactive protein; ESR, erythrocyte sedimentation rate

[a] Mann-Whitney U test.
[b] Maximum value used.
[C] Minimum value used.