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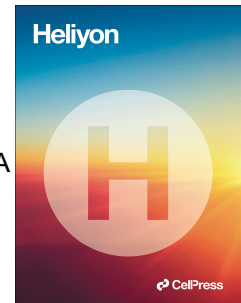
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# **Effectiveness of famotidine on the risk of poor prognosis in patients with COVID-19: A nationwide cohort study in Korea**

Running title: Famotidine and outcome of COVID-19

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**Abstract**

**Objective:** Famotidine has been proposed as a promising candidate for the treatment of coronavirus disease 2019 (COVID-19). However, there is limited research on the association of famotidine with the poor prognosis of COVID-19.

**Methods:** The Korean nationwide cohort included 6,556 patients who tested positive on RT-PCR for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The poor COVID-19-related outcomes were defined on the basis of having encountered the composite outcome of high oxygen therapy, intensive care unit admission, administration of mechanical ventilation, or death. In addition, we performed exposure-driven propensity score matching for no H<sub>2</sub>-blocker use versus current famotidine use, and other H<sub>2</sub>-blocker use versus current famotidine use.

**Results:** 4,785 (73.0%) patients did not use a H<sub>2</sub>-blocker, 393 (6.0%) patients were currently used famotidine, and 1,292 (19.7%) patients currently used H<sub>2</sub>-blocker other than famotidine. In multivariable analysis after matching (no H<sub>2</sub>-blocker use versus current famotidine use), there was no significant association between current famotidine use and composite outcomes (adjusted odd ratios [aOR]: 1.30, 95% confidence interval [CI]: 0.55-3.06). On the other hand, another matched cohort (other H<sub>2</sub>-blocker use versus current famotidine use), demonstrated a positive association between current famotidine use and composite outcomes (aOR: 3.56, 95% CI: 1.03-12.28)

**Conclusions:** Our study results did not support the potential of famotidine as a therapeutic agent for COVID-19. A rather unexpected result could be observed in the comparisons between current famotidine use and other H<sub>2</sub>-blocker use; it was observed that current famotidine use increased the risk of poor COVID-19 related outcomes. Further studies are needed to clearly prove the causal relationship with several H<sub>2</sub>-blockers, including famotidine.

**Keywords:** COVID-19; Famotidine; Intensive care unit; Mechanical ventilation; Mortality

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## 1. Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, is the greatest global health threat in the 21st century.<sup>1</sup> Even though most patients with COVID-19 have a good prognosis, a significant proportion of patients have a poor prognosis.<sup>2,3</sup> These patients may require mechanical ventilation, admission to an intensive care unit, or extended hospitalization, and some patients may have fatal outcomes.<sup>2,4</sup> Recent studies have identified elderly patients, and those with underlying medical conditions such as hypertension, diabetes mellitus, heart failure, atrial fibrillation, fatty liver diseases, dementia, epilepsy, insulin resistance, cancer, lung disease, chronic kidney disease, and cardiovascular disease are at higher risk of developing severe medical complications of COVID-19.<sup>5</sup> Furthermore, a patient's prognosis may depend on underlying health conditions and medications the patient has taken.

Many drugs have been proposed as a potential drug against COVID-19 and SARS-CoV-2, including ACE inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), hydroxychloroquine, metformin, and famotidine. Among them, famotidine has been identified as a potential repurposed drug candidate for COVID-19. It has been shown to bind to the SARS-CoV-2 papain-like protease with high affinity and inhibit its enzymatic activity, which is critical for viral replication and immune evasion.<sup>6</sup>

Famotidine is a histamine H<sub>2</sub>-receptor antagonist (H<sub>2</sub>-blocker) that inhibits gastric acid secretion and treats gastroesophageal reflux disease (GERD) and gastritis (Figure S1).<sup>7</sup> In addition to its use in treating GERD and gastritis, Famotidine has also been found to have immunomodulatory effects by reducing the levels of pro-inflammatory cytokines such as interleukin-6 and tumor necrosis factor-alpha.<sup>8</sup> Elevated levels of these cytokines have been

associated with severe COVID-19 and poor clinical outcomes. Due to reducing the inflammatory response<sup>9</sup>, it has been proposed as a potential inhibitor of 3-chymotrypsin-like protease in computational analysis and has been investigated as a potential treatment for COVID-19.<sup>10</sup>

The propensity score-matched retrospective, single-center cohort studies found that famotidine use significantly reduces the risks of mortality and intubation in patients with COVID-19.<sup>11,12</sup> However, a retrospective multi-center study and meta-analysis showed no correlation between famotidine use and poor COVID-19 related outcomes.<sup>13-17</sup>

Several retrospective analyses of famotidine use in COVID-19 have reported conflicting results due to several factors.<sup>13,16,18-20</sup> One probable reason for the lack of consistency in these studies is that famotidine's mechanism of action in COVID-19 is not fully postulated. While some studies have suggested that famotidine may benefit COVID-19 outcomes by modulating the interferon response and reducing inflammation, others have not found significant differences in outcomes between patients who received famotidine and those who did not. Another probable reason for the inconsistency in results is the differences in study design and patient populations (**Table S1**). Retrospective studies rely on data that has already been collected, which can limit the ability to control for confounding factors and can lead to selection bias. Additionally, the patient populations in these studies may vary in terms of age, country, comorbidities, and disease severity, which can also influence the effectiveness of famotidine.

Here, we hypothesized that the risk of poor outcomes from COVID-19 would decrease in current famotidine users. The purpose of this study was to investigate the association between famotidine use and poor prognosis of COVID-19 in a nationwide population-based cohort.

## 2. Methods

### 2.1. Study design and participants

Our study is a retrospective and observational study using a nationwide South Korea COVID-19 dataset. The National Health Insurance Service (NHIS), a single-payer national health insurance system in South Korea, has established a population-based cohort named National Health Information Database (NHID). This dataset includes health care information on demographics, hospital visits, diagnoses (via International Statistical Classification of Diseases and Related Health Problems [ICD]-10 codes), medical procedures, prescriptions, and mortality of the entire Korean population. In addition, the Korea Disease Control and Prevention Agency (KCDA) and NHIS released a nationwide COVID-19 dataset that encompasses from July 1, 2020 to December 31, 2020.<sup>2,4</sup> The Korea national COVID-19 dataset contained confirmed patients diagnosed based on of RT-PCR analysis taken from nasal and pharyngeal swabs. The RT-PCR assay kit has been certified by the KCDC according to the World Health Organization guideline.<sup>21</sup> We combined the NHIS claims-based data from January 1, 2017 to June 30, 2020, and extracted information on the age, sex, and region of residence from the eligible nationwide dataset. A total of 6556 patients among 212,768 were undergone SARS-COV-2 testing during the above period and were included in this study (**Fig. 1**).

The date when the patient tested positive for COVID-19 was defined as the index date. We divided patients into four groups based on the prescription of H<sub>2</sub>-blocker in an outpatient clinic or during hospitalization at the time of confirmation of COVID-19. Patient who were prescribed famotidine before and after July 1, 2020, were classified as the past famotidine use group and the current famotidine use group, respectively. Patients who received H<sub>2</sub>-blocker other than famotidine or did not receive any H<sub>2</sub>-blocker between January 1, 2020 and



December 31, 2020 were categorized as the other H<sub>2</sub>-blocker use group and the no H<sub>2</sub>-blocker group.

This study was approved by the Institutional Review Board of Seoul Hospital, Ewha Womans University College of Medicine (2020-10-021); since this was a retrospective analysis based on a fully anonymized dataset, the requirement for informed consent was waived.

## 2.2. Study outcomes

The poor prognosis of COVID-19 were composite outcomes of administration of high oxygen therapy, admission to intensive care unit, or administration of mechanical ventilation or death.<sup>21</sup> Administration of high oxygen therapy was established with claim codes, including intubation and/or mechanical ventilation (M5850, M5857, M5858, and M5860).

## 2.3. Covariates

We acquired information regarding sex, age at COVID-19 diagnosis, and region of residence. Comorbidities were defined using medical claims according to ICD-10 codes and medication prescription in the NHIS data before a RT-PCR test for SARS-CoV-2. Hypertension (I10-15), diabetes mellitus (E11–E14), cardiovascular disease (I21) and cerebrovascular disease (I60-63, and I69) were ascertained using ICD-10 codes.<sup>21-23</sup> Hypertension and diabetes mellitus were defined as having a diagnostic code for each disease and a claim code for antihypertensive or antidiabetic drugs at the same time.<sup>24</sup> Patients were classified as having cardiovascular disease or cerebrovascular disease if they had at least two outpatient visits or at least one admission with the relevant diagnostic codes with performed brain computed tomography/magnetic resonance image in case of cerebrovascular disease.<sup>25</sup> Patients were classified as having chronic obstructive pulmonary disease (COPD) or asthma

if they had a diagnostic code (COPD, J45; asthma, J46) as the primary diagnosis two or more times.<sup>26</sup> Chronic kidney disease was defined by the presence of the relevant diagnostic codes (N03, N05, N165, N18-9, N250, I12-3, Z490, Z491-2, Z940, Z992, E102, E112, E132, E142, or T861).<sup>27</sup> A study of diagnostic accuracy using ICD-10 codes for comorbidities was conducted and the results were 85.0%-94.1%.<sup>28,29</sup>

#### 2.4. Statistical analysis

Our study performed a comparative analysis of poor COVID-19 related outcomes using propensity score matching (PSM) with calipers less than 0.001.<sup>30</sup> PSM stabilization is a statistical technique that helps to balance the distribution of confounding factors between the treatment and control groups, which can reduce the potential for bias and improve the accuracy of the estimated treatment effect. Without PSM stabilization, it may be difficult to draw accurate conclusions about the effectiveness of a treatment, as the estimated treatment effect may be confounded by differences in baseline characteristics between the treatment and control groups. In doing so, PSM was performed using a greedy nearest-neighbour algorithm to compare the current famotidine use group with the no H<sub>2</sub>-blocker group and other H<sub>2</sub>-blocker use group using a 1:1 ratio. A standardized mean difference (SMD) of less than 0.1 indicated suitability.<sup>31</sup>

Logistic regression analysis was performed to investigate poor COVID-19 related outcomes depending on the use of famotidine. This is adjusted for sex, age, region of residence, hypertension, diabetes mellitus, cardiovascular disease, cerebrovascular disease, asthma, COPD, chronic kidney disease, and Charlson comorbidity index, and previous use of systemic steroid, proton pump inhibitor (PPI), aspirin, and metformin in cohorts balanced after PSM. For the sensitivity analysis, further analysis was performed by separating the high

oxygen therapy, composite outcomes of admission to intensive care unit, administration of mechanical ventilation, or death. The results were demonstrated with odds ratio (OR) and 95% confidence interval (CI). An analysis of covariance (ANCOVA) model with factors for sex, age, region of residence, hypertension, diabetes mellitus, cardiovascular disease, cerebrovascular disease, asthma, COPD, chronic kidney disease, and Charlson comorbidity index, and previous use of systemic steroid, PPI, aspirin, and metformin was adjusted to assess the heterogeneity of famotidine use on the length of hospitalization across groups. Statistical analyses were executed using SAS version 9.4 (SAS Inc., Cary, NC, USA).<sup>32-34</sup> Two-sided P-values less than 0.05 were considered significant.

### 3. Results

There were 6,556 participants who successfully met the inclusion criteria. This included those aged older than 18 years from the Korean nationwide COVID-19 cohort who tested positive for SARS-CoV-2 between July 1 and December 31, 2020. In the entire cohort, 4,785 (73.0%) patients were not used with H<sub>2</sub>-blocker, 393 (6.0%) patients were currently used with famotidine, 86 (1.3%) were previously used with famotidine, and 1,292 (19.7%) patients were currently used with H<sub>2</sub>-blocker other than famotidine. The baseline characteristics of the entire cohort are displayed in **Table 1** and **Fig. 2**. After applying PSM, we included 286 patients that do not have previous experience with the H<sub>2</sub>-blocker and 286 patients that are currently treated with famotidine; 204 patients used with other H<sub>2</sub>-blocker and 204 patients that are currently using with famotidine were also appropriately matched (**Table 2** and **Fig. 3**). No major imbalances in the demographics and clinical characteristics were observed for all variables when evaluated using the SMD within groups in the PSM cohorts (**Table 2**).

In the matched cohort with 572 patients with COVID-19 (no H<sub>2</sub>-blocker versus current famotidine use), there was no significant correlation between current famotidine use and composite outcomes of administration of high oxygen therapy, admission to intensive care unit, administration of mechanical ventilation, or death (crude OR: 1.20, 95% CI: 0.61-2.39), administration of high oxygen therapy (crude OR: 1.15, 95% CI: 0.72-1.82), or composite outcomes of admission to intensive care unit, administration of mechanical ventilation or death (crude OR: 1.17, 95% CI: 0.75-1.84). In the other matched cohort with 408 patients with COVID-19 (other H<sub>2</sub>-blocker use versus current famotidine use), there was also no significant correlation between current famotidine use and composite outcomes of administration of high oxygen therapy, admission to intensive care unit, administration of mechanical ventilation or death (crude OR: 2.43, 95% CI: 0.92-6.46), administration of high

oxygen therapy (crude OR: 1.57, 95% CI: 0.81-3.05), or composite outcomes of admission of intensive care unit, administration of mechanical ventilation or death (crude OR: 1.49, 95% CI: 0.80-2.77) (**Fig. 4**).

Adjustments for age and sex (minimally adjusted) in both PSM cohorts did not change the result. Adjustments for age, sex, region of residence, history of diabetes mellitus, cardiovascular disease, cerebrovascular disease, COPD, hypertension, chronic kidney disease, Charlson comorbidity index, and previous administration of steroids, aspirin, metformin, and PPI in both PSM cohort did not affect the associations between the current famotidine use and composite outcomes of admission of intensive care unit, administration of mechanical ventilation, or death (fully adjusted OR: 1.29, 95% CI: 0.74-2.24) and administration of oxygen therapy (fully adjusted OR: 1.30, 95% CI: 0.74-2.28) as compared to no H<sub>2</sub>-blocker group. However, we did identify a significant positive association between current famotidine use and composite outcomes of administration of high oxygen therapy, admission to the intensive care unit, administration of mechanical ventilation, or death (fully adjusted OR: 3.56, 95% CI: 1.03-12.28) as compared to other H<sub>2</sub>-blocker use group. Although not significant, similar trends were observed between current famotidine use and high oxygen therapy (fully adjusted OR: 2.09, 95% CI: 0.94-4.61), and between the current famotidine use and composite outcomes of admission to the intensive care unit, administration of mechanical ventilation, or death (fully adjusted OR: 2.07, 95% CI: 0.96-4.47). There was no significant difference in the length of hospitalization before and after adjustment in either PSM cohort (no H<sub>2</sub>-blocker versus current famotidine use, mean difference: -1.15 days, 95% CI: -3.81 to 0.96, other H<sub>2</sub>-blocker use versus current famotidine use, mean difference: -1.07 days, 95% CI: -3.66 to 1.52) (**Table 3**).

#### 4. Discussion

The key findings of this study are that famotidine use does not decrease the risk of poor COVID-19 related outcomes. A rather unexpected result could be observed in the comparisons between current famotidine use and other H<sub>2</sub>-blocker use; it was observed that current famotidine use increased the risk of poor COVID-19 related outcomes. This might be because there are differences between H<sub>2</sub> blockers in terms of potency, duration of action, and pharmacokinetics, which can influence their effectiveness in treating different conditions. Famotidine has a longer half-life and is more potent than other H<sub>2</sub> blockers, such as cimetidine or ranitidine. This may make famotidine more effective in reducing gastric acid production and treating GERD and gastritis. However, these differences in pharmacokinetics may not necessarily translate to differences in their effectiveness against COVID-19. Mechanistically, it is possible that the differences between H<sub>2</sub> blockers are due to their ability to modulate the immune response.

After famotidine emerged as an option for the treatment of COVID-19,<sup>7</sup> research on the correlation between famotidine use and clinical outcomes was conducted in various centers. Although some retrospective, single-center, PSM studies showed famotidine treatment significantly reduced the risk of poor COVID-19 related outcomes in patients with COVID-19, retrospective multicenter studies and a meta-analysis showed no correlation between famotidine use and poor COVID-19 related outcomes.<sup>11-17</sup> In the most recent randomized clinical trial of patients with COVID-19 with mild to moderate symptoms, patients in the high-dose famotidine use group had to earlier resolution of symptoms and inflammation than other patients. This result suggested that famotidine could be used to prevent the progression of COVID-19.<sup>18</sup> However, most of the previous studies conducted in the western countries, and although there were some multi-center studies, no studies have examined a nationwide

population in East Asia. Therefore, our research is significant because our results are consistent with previous studies. It also gives additional information regarding the no association of famotidine use with the decrease of poor prognosis of COVID-19 in the general population of East Asia.

There was no difference in poor COVID-19 related outcomes between COVID-19 patients who did and did not receive famotidine. However, logistic regression analysis between the current famotidine use and other H<sub>2</sub>-blocker use group showed a significant association between current famotidine use and increased poor COVID-19 related outcomes. COVID-19 is associated with a spectrum of severities, from asymptomatic disease to death. Various potential candidate for COVID-19 treatments have been proposed, and pharmaceutical companies in various countries have been competitively developing therapeutic agents. Some proven effective therapeutic agents in practice have been developed,<sup>35</sup> and some that have been proven safe are undergoing phase III clinical trials to determine their effectiveness. Representative examples include hydroxychloroquine, an antimalarial drug; metformin, an antidiabetic drug; and famotidine, an antiulcer drug. Famotidine has relatively few side effects, so it can be purchased over-the-counter in South Korea, and this H<sub>2</sub>-blocker is already being used by many patients. Since famotidine has been proposed as a treatment for COVID-19, in patients with severe initial symptoms or worsening of pneumonia, it is highly likely that doctors newly prescribed famotidine to patients who needed H<sub>2</sub>-blocker for the first time or changed the currently prescribed H<sub>2</sub>-blocker to famotidine. Thus, by administering famotidine over other H<sub>2</sub>-blocker to patients with severe or worsening symptoms, we observed no difference in poor COVID-19 related outcomes in the current famotidine use and no H<sub>2</sub>-blocker group. However, current famotidine use is associated with poor COVID-19 related outcomes when compared with other H<sub>2</sub>-blocker use.

Previous studies have shown that famotidine acts as an antagonist or inverse-agonist of histamine-mediated mast cell activation leading to acute bronchoconstriction and inflammation due to SARS-CoV-2 infection.<sup>36,37</sup> Another study showed that famotidine could inhibit histamine-induced expression of toll-like receptor 3 (TLR3) in SARS-CoV-2 infected cells and reduce TLR3-dependent signaling.<sup>38</sup> Famotidine has the above-mentioned anti-inflammatory effect and inhibits 3-chymotrypsin-like protease, an important protein for viral replication.<sup>7</sup> The steady-state concentration varies depending on the dose of famotidine, and the half maximal inhibitory concentration (IC<sub>50</sub>) must be reached for a gastric acid inhibitory through the inhibiting H<sub>2</sub>-receptor. Although the IC<sub>50</sub> of famotidine for GERD has been standardized (20mg BID or 20mg TID), the IC<sub>50</sub> to properly inhibit SARS-CoV-2 infection is unknown.<sup>36</sup> A preceding case series study and randomized clinical trial reported that high-dose of oral famotidine improved the prognosis in COVID-19 patients,<sup>18,39</sup> suggesting that the IC<sub>50</sub> level of famotidine for inhibiting SARS-CoV-2 infection is higher than that of treating GERD. Therefore, propensity score matching with large cohort studies using higher doses than those used for GERD are needed in patients with severe COVID-19 symptoms.

There are some limitations to this study. First, it is difficult to generalize our results across ethnicities because our dataset consisted of only Koreans. Second, detailed information on each patient's daily and total doses of famotidine could not be acquired because the dataset did not include detailed drug dose information. Therefore, the analysis could not be performed depending on the famotidine dose. Third, only patients who had a SARS-CoV-2 test were included in our study, and patients who took the test were not assigned randomly, which might have caused a selection bias, although Korea government performed nationwide and complementary SARS-CoV-2 test. Fourth, in this study we used prescription data from



the hospitals' claim based data and could not verify if the prescriptions were actually filled. Besides, famotidine can be sold at pharmacies but records of over-the-counter-famotidine sales did not include in our data. However, most of famotidine is sold when the prescription is written. Finally, although some drugs (steroids, aspirin, metformin, and PPIs) were considered as confounders in the logistic regression analysis, we did not include all drugs such as ACEIs/ARBs and histamines known to affect the prognosis of COVID-19 <sup>40,41</sup>.

**Conclusion**

Our study did not support the hypothesis that famotidine use reduces the risk of poor COVID-19 related outcomes in the general population in Asian countries. Further study including large sample size randomized clinical trials should be needed to confirm whether famotidine use can reduce poor COVID-19 related outcomes, particularly in COVID-19 positive patients with moderate to severe COVID-19 related complications.

**Author contribution Statement**

Rosie Kwon, Hyung Jun Kim, Seung Won Lee,: Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Lee Smith, Ai Koyanagi: Contributed reagents, materials, analysis tools or data.

Jae Il Shin, Tae-Jin Song, Dong Keon Yon: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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**Conflicts of interest**

The authors declare no conflicts of interest.

**Additional information**

No additional information is available for this paper.

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**Table1.** Demographic and clinical characteristics of patients with confirmed positive of SARS-CoV-2 in the Korean nationwide cohort.

Characteristic	Entire cohort	No H <sub>2</sub> -blocker	Current famotidine use	Past famotidine use	Other H <sub>2</sub> -blocker use
Total	6556	4785	393	86	1292
Age, years (SD)	46.98 ( $\pm$ 19.0)	45.44 ( $\pm$ 18.8)	52.32 ( $\pm$ 18.7)	47.83 ( $\pm$ 20.9)	50.99 ( $\pm$ 18.9)
Sex					
Female	3867 (59.0)	2682 (56.1)	270 (68.7)	52 (60.5)	863 (66.8)
Region of residence					
Rural	3147 (48.0)	2367 (49.5)	164 (41.7)	36 (41.9)	580 (45.0)
Urban	3409 (52.0)	2418 (50.5)	229 (58.3)	50 (58.1)	712 (55.1)
History of diabetes mellitus	846 (12.9)	524 (11.0)	74 (18.8)	14 (16.3)	234 (18.1)
History of cardiovascular disease	457 (7.0)	263 (5.5)	47 (12.0)	7 (8.1)	140 (10.8)
History of cerebrovascular disease	420 (6.4)	272 (5.7)	35 (8.9)	10 (11.6)	103 (8.0)
History of COPD	310 (4.7)	185 (3.9)	30 (7.6)	4 (4.7)	91 (7.0)
History of asthma	615 (9.4)	338 (7.1)	61 (15.5)	6 (7.0)	210 (16.3)
History of hypertension	1468 (22.4)	945 (19.8)	112 (28.5)	25 (29.1)	386 (29.9)
History of chronic kidney disease	236 (3.6)	150 (3.1)	23 (5.9)	3 (3.5)	60 (4.6)

## Charlson comorbidity index

0	4399 (67.1)	3431 (71.7)	211 (53.7)	46 (53.5)	711 (55.0)
1	704 (10.7)	439 (9.2)	58 (14.8)	15 (17.4)	192 (14.9)
$\geq 2$	1453 (22.2)	915 (19.1)	124 (31.6)	25 (29.1)	389 (30.1)
Previous use of systemic steroid	1801 (27.5)	1030 (21.5)	179 (45.6)	26 (30.2)	566 (43.8)
Previous use of PPI	845 (12.9)	489 (10.2)	85 (21.6)	16 (18.6)	255 (19.7)
Previous use of aspirin	279 (4.3)	166 (3.5)	28 (7.1)	6 (7.0)	79 (6.1)
Previous use of metformin	490 (7.5)	315 (6.6)	46 (11.7)	6 (7.0)	123 (9.5)

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Data were presented as number (%).

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation; COPD, chronic obstructive pulmonary disease; PPI, proton pump inhibitor

**Table 2.** Baseline characteristics of propensity-score matching cohort among no H<sub>2</sub>-blocker versus current famotidine use group, or other H<sub>2</sub>-blocker versus current famotidine use group, current famotidine use group versus past famotidine use group in patients with positive of SARS-CoV2 infection test.

Characteristic	No H <sub>2</sub> -blocker vs. Current famotidine use			Other H <sub>2</sub> -blocker use vs. Current famotidine use			Current famotidine use vs. Past famotidine use		
	No H <sub>2</sub> -blocker	Current famotidine use	SMD	Other H <sub>2</sub> -blocker use	Current famotidine use	SMD	Current famotidine use	Past famotidine use	SMD
Total	286	286		204	204		15	15	
Age, years (SD)	49.3 (±19.4)	49.0 (±18.5)	-0.014	45.5 (±17.7)	46.0 (±18.0)	0.022	33.3 (±14.1)	32.7 (±16.4)	0.030
Sex			0.058			0.021			-0.140
Male	92 (32.2)	100 (35.0)		62 (30.4)	64 (31.4)		3 (20.3)	4 (26.7)	
Female	194 (67.8)	186 (65.0)		142 (69.6)	140 (68.6)		12 (80.0)	11 (73.3)	
Region of residence			-0.014			-0.040			-0.270
Rural	122 (42.7)	124 (43.4)		91 (44.6)	95 (46.6)		8 (53.3)	6 (40.0)	
Urban	164 (57.3)	162 (56.6)		113 (55.4)	109 (53.4)		7 (46.7)	9 (60.0)	
History of diabetes mellitus	32 (11.2)	31 (10.8)	0.010	23 (11.3)	19 (9.3)	0.051	0 (0.0)	0 (0.0)	<0.001
History of cardiovascular disease	19 (6.6)	21 (7.3)	-0.025	13 (6.4)	10 (4.9)	0.046	0 (0.0)	0 (0.0)	<0.001
History of	19 (6.6)	21 (7.3)	-0.027	7 (3.4)	9 (4.4)	-0.035	0 (0.0)	0 (0.0)	<0.001

cerebrovascular  
disease

History of COPD	18 (6.3)	14 (4.9)	0.060	5 (2.5)	9 (4.4)	-0.075	0 (0.0)	0 (0.0)	<0.001
History of asthma	23 (8.0)	28 (9.8)	-0.056	19 (9.3)	23 (11.3)	-0.054	0 (0.0)	0 (0.0)	<0.001
History of hypertension	68 (23.8)	61 (21.3)	0.058	35 (17.2)	37 (18.1)	-0.022	0 (0.0)	0 (0.0)	<0.001
History of chronic kidney disease	11 (3.9)	13 (4.6)	-0.034	4 (2.0)	4 (2.0)	0.000	0 (0.0)	0 (0.0)	<0.001
Charlson comorbidity index			-0.035			0.007			0.131
0	188 (65.7)	181 (63.3)		142 (69.6)	141 (69.1)		0 (0.0)	0 (0.0)	
1	32 (11.2)	41 (14.3)		20 (9.8)	28 (13.7)		0 (0.0)	0 (0.0)	
≥2	66 (23.1)	64 (22.4)		42 (20.6)	35 (17.2)		2 (13.3)	0 (0.0)	
Previous use of systemic steroid	95 (33.2)	96 (33.6)	-0.008	89 (43.6)	87 (42.7)	0.020	5 (33.3)	5 (33.3)	<0.001
Previous use of PPI	39 (13.6)	41 (14.3)	-0.019	24 (11.8)	32 (15.7)	-0.097	0 (0.0)	0 (0.0)	<0.001
Previous use of aspirin	9 (3.2)	12 (4.2)	-0.047	9 (4.4)	8 (3.9)	0.020	0 (0.0)	0 (0.0)	<0.001
Previous use of metformin	22 (7.7)	18 (6.3)	0.049	9 (4.4)	9 (4.4)	0.000	0 (0.0)	0 (0.0)	<0.001
Composite outcomes*									
Crude	1.00	1.20		1.00	2.43		1.00	NA	

	(reference)	[0.61:2.39]	(reference)	[0.92:6.46]	(reference)	
Minimally adjusted	1.00	1.31	1.00	2.70	1.00	NA
OR†	(reference)	[0.60:2.88]	(reference)	[0.92:7.93]	(reference)	
Fully adjusted OR‡	1.00	1.30	1.00	<b>3.56</b>	1.00	NA
	(reference)	[0.55:3.061]	(reference)	<b>[1.03:12.28]</b>	(reference)	
Oxygen therapy						
Crude	1.00	1.15	1.00	1.57	1.00	NA
	(reference)	[0.72:1.82]	(reference)	[0.81:3.05]	(reference)	
Minimally adjusted	1.00	1.27	1.00	1.61	1.00	NA
OR	(reference)	[0.75:2.15]	(reference)	[0.78:3.33]	(reference)	
Fully adjusted OR	1.00	1.30	1.00	2.09	1.00	NA
	(reference)	[0.74:2.28]	(reference)	[0.94:4.61]	(reference)	
Composite outcomes§						
Crude	1.00	1.17	1.00	1.49	1.00	NA
	(reference)	[0.75:1.84]	(reference)	[0.80:2.77]	(reference)	
Minimally adjusted	1.00	1.29	1.00	1.53	1.00	NA
OR	(reference)	[0.77:2.17]	(reference)	[0.77:3.06]	(reference)	
Fully adjusted OR	1.00	1.29	1.00	2.07	1.00	NA
	(reference)	[0.74:2.24]	(reference)	[0.96:4.47]	(reference)	

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Data were presented as number (%).

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SMD, standardized mean difference; SD, standard deviation; COPD, chronic obstructive pulmonary disease; PPI, proton pump inhibitor; OD, odds ratio

An SMD <0.1 indicates no major imbalance.

\*Composite outcomes of administration of high oxygen therapy, admission of intensive care unit, mechanical ventilation or death.

† Minimally adjusted: adjustment for age and sex.

‡ Fully adjusted: adjustment for age, sex, region of residence, history of diabetes mellitus, cardiovascular disease, cerebrovascular disease, COPD, hypertension, and chronic kidney disease, and Charlson comorbidity index, previous use of steroid, aspirin, metformin, PPI.

§ Composite outcomes of admission of intensive care unit, mechanical ventilation or death.

Numbers in bold indicate significant differences ( $p < 0.05$ ).



**Table 3.** Propensity-score-matching subgroup analyses for difference in length of stay at hospitalization according to famotidine use using analysis-of-covariance model.

Length of stay at hospitalization, day	No H <sub>2</sub> -blocker vs. Current famotidine use	Other H <sub>2</sub> -blocker use vs. Current famotidine use	Current famotidine use vs. Past famotidine use
	Mean difference (95% CI)	Mean difference (95% CI)	Mean difference (95% CI)
Crude	-1.42 (-3.81:0.96)	-0.91 (-3.52:1.70)	-6.20 (-14.3:-1.87)
Minimally adjusted*	-1.31 (-3.61:0.99)	-0.97 (-3.56:1.62)	-6.02 (-13.8:1.76)
Fully adjusted†	-1.15 (-3.41:1.10)	-1.07 (-3.66:1.52)	-4.39 (-12.2:3.46)

CI, confidence interval;

\* Minimally adjusted: adjustment for age and sex.

† Fully adjusted: adjustment for age, sex, region of residence, history of diabetes mellitus, cardiovascular disease, cerebrovascular disease, COPD, hypertension, and chronic kidney disease, and Charlson comorbidity index, previous use of steroid, aspirin, metformin, PPI.

Numbers in bold indicate significant differences ( $p < 0.05$ ).

**Table S1.** Characteristics of relative studies

Study	Study Design	Country	Sample size	Age	Sex	Population	Outcome	Famotidine Dosage	Limitation
Brennan, 2022	Randomized controlled trial	USA	55	35.0±20.0	N/A	Symptomatic unvaccinated adult outpatients with confirmed COVID- 19 between January 2021 and April 2021 from two US centers.	Time for symptom resolution	80mg	- Small number of sample size - Phase 2 RCT
Siraj, 2022	Retrospective cohort	India	1000	56 (IQR 45-65)	Male: 646 (64.6) Female: 354 (35.4)	Confirmed COVID-19 cases treated at a tertiary care hospital in J&K UT between March 2020 and December 2020.	All-cause mortality and survival.	N/A	- Published treatment data derive exclusively from observational data or small clinical trials introducing higher bias risks

Kuno, 2022	Retrospective cohort	USA	3132	64.3	Male: 1655 (52.8) Female: 1477 (47.2)	Patients were hospitalized at the Mount Sinai Health System with laboratory-confirmed COVID-19 between March 1, 2020, and March 30, 2021.	In-hospital mortality	N/A	- Could not adjust for potential confounders such as vaccination status, prior history of COVID-19, prior use of famotidine or other types of H2 receptor blockers, and interactions of famotidine with other medications
Mura, 2021	Retrospective cohort	USA, Germany	563	59±19.9	Male: 304 (54) Female: 259 (46)	COVID-19 with a special focus on severe cases requiring respiratory support	Death	N/A	- Did not further group cases into sub-cohorts based on disease severity
Pahwani, 2022	Two-arm open-label randomized interventional study	Pakistan	178	51.5	Male: 122 n (68) Female: 56 (32)	Patients hospitalized with COVID-19	The days taken to be symptom-free, the number of days spent in the hospital, the need for intensive care units and/or mechanical ventilation, and death.	40mg	- Conducted in a single institute the sample size was less diverse

Samimagham, 2021	Randomized clinical trial	Iran	20	46±13	Male: 12 (60) Female: 8 (40)	Hospitalized patients with COVID-19.	Length of stay in the hospital and length of stay in the ICU	160mg (4times/day)	- Very small population - Did not follow up patients after discharge
Shoaibi, 2021	Retrospective Cohort	USA	26027	N/A	N/A	Hospitalized patients with a diagnosis of COVID-19.	Death, death or intensive services (combined). Intensive services were defined as any condition, procedure or observation code indicative of mechanical ventilation, tracheostomy or extracorporeal membrane oxygenation.	20mg (73.29%) 40mg (20.59%)	- Did not consider strength or dose or duration of exposure for any of the exposures

Stolow, 2021	Retrospective cohort	USA	489	N/A	N/A	COVID-19 positive patients admitted to a tertiary care center between June and August 2020	Mortality, ICU	N/A	- Result was 518.9% higher risk of death, which is an outlier results among other studies
Wagner, 2021	Retrospective cohort	USA	1457	N/A	N/A	Patients ages 18 years or older treated for COVID-19 from March 2020 through March 2021.	All-cause mortality and the secondary outcomes of mechanical ventilation, vasopressor use, acute kidney injury, and gastrointestinal bleed.	N/A	- Adjusted for many relevant covariates to potentially address this concern
Yeraman eni, 2021	Retrospective cohort	USA	1156	62.13	Male: 544 (47) Female: 612 (53)	Admitted adults to affiliated hospitals who tested positive for SARS-CoV-2 by reverse transcriptase polymerase chain reaction between February 11, 2020 and May 8, 2020	All-cause mortality in the hospital within 30 days of admission.	160mg (IQR 80-300)	- Over 95% of our cohort received low to medium doses, excluding the possibility of evaluating famotidine's effectiveness on mortality at high doses

Freedberg, 2020	Retrospective cohort	USA	1620 Famotidine (n=84)	<50: 333 50-65: 514 >65: 773	Male: 731 (45) Female: 889 (55)	Admitted adults from February 25, 2020, to April 13, 2020, and tested positive for SARS-CoV-2 within no more than 72 hours following admission.	Composite of death or endotracheal intubation within 30 days of hospital admission (intubation-free survival)	20 mg (47%), 40 mg (35%), 10 mg (17%)	- Taking proton pump inhibitors did not show a significant reduction
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IQR, interquartile range; N/A, not available

Figure 1. Flow chart of study population selection

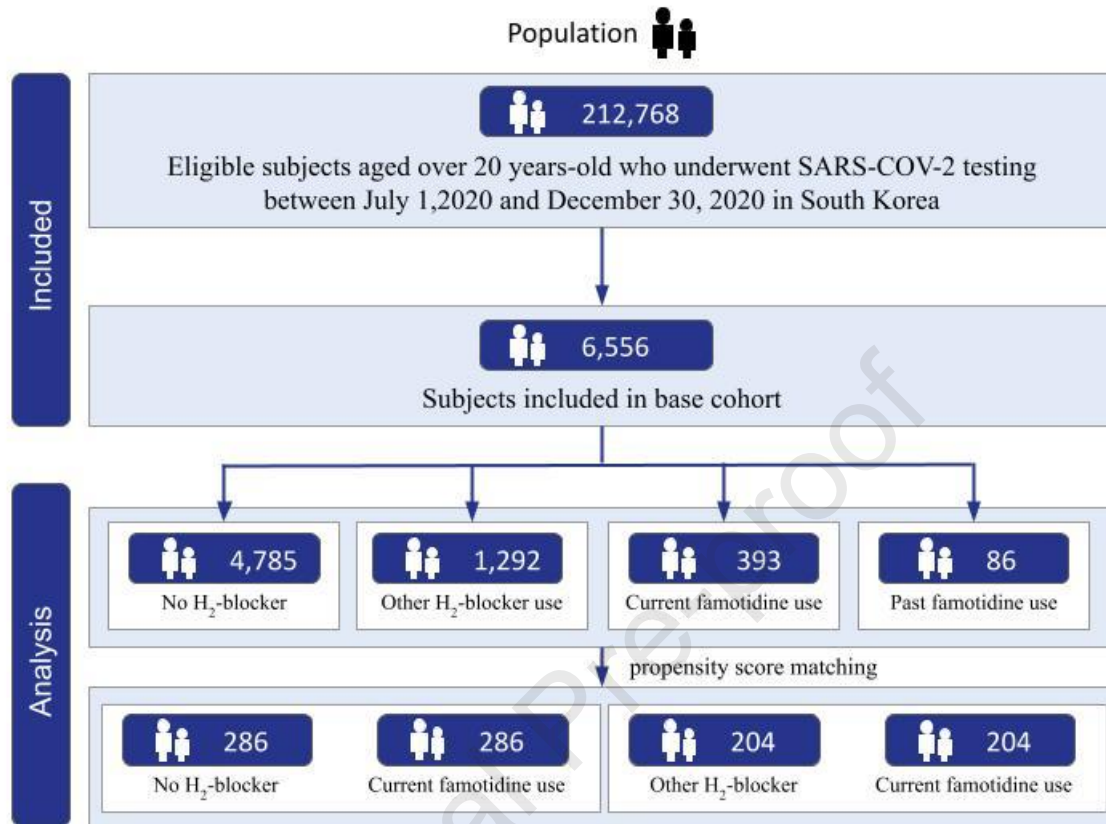


Figure 2. No H<sub>2</sub> blockers *versus* current famotidine users among all patients who were tested for SARS-CoV-2. After matching, the blue and red lines are nearly overlapping, as observed.

No H<sub>2</sub> blockers *versus* current famotidine users among all patients who were tested for SARS-CoV-2

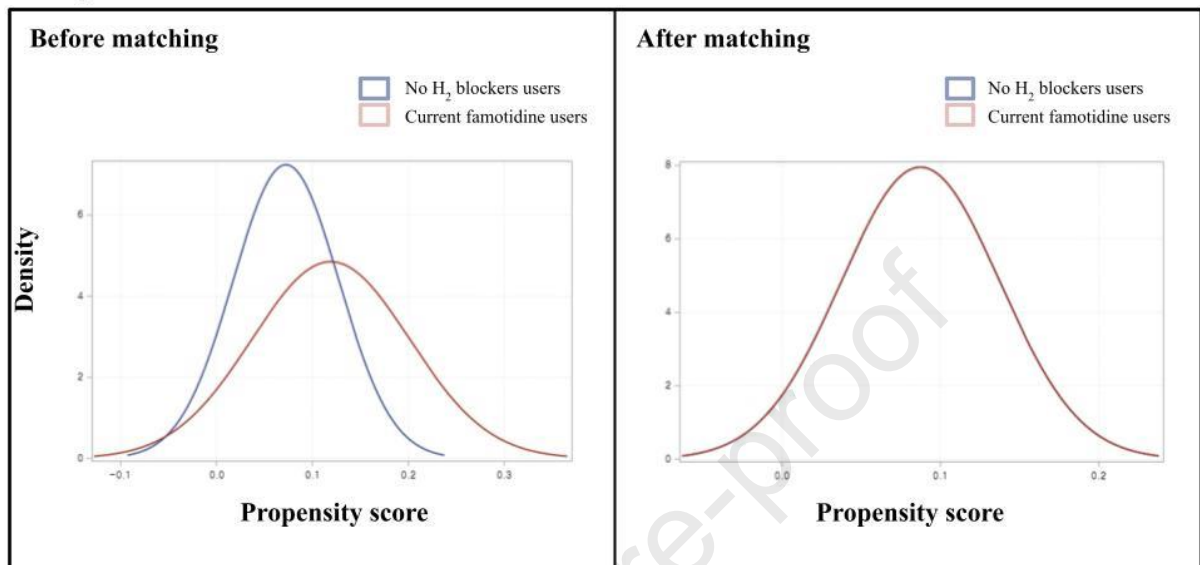




Figure 3. Other H<sub>2</sub> blockers *versus* current famotidine users among all patients who were tested for SARS-CoV-2. After matching, the blue and red lines are nearly overlapping, as observed.

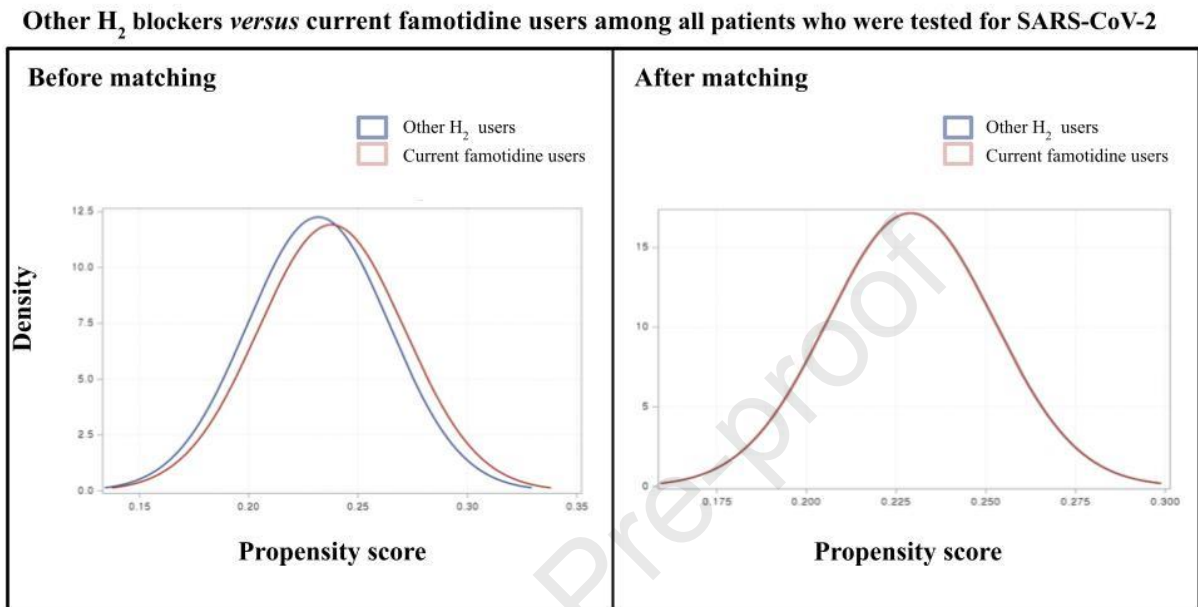


Figure 4. Current famotidine *versus* past famotidine users among all patients who were tested for SARS-CoV-2. After matching, the blue and red lines are nearly overlapping, as observed.

**Current famotidine *versus* past famotidine users among all patients who were tested for SARS-CoV-2**

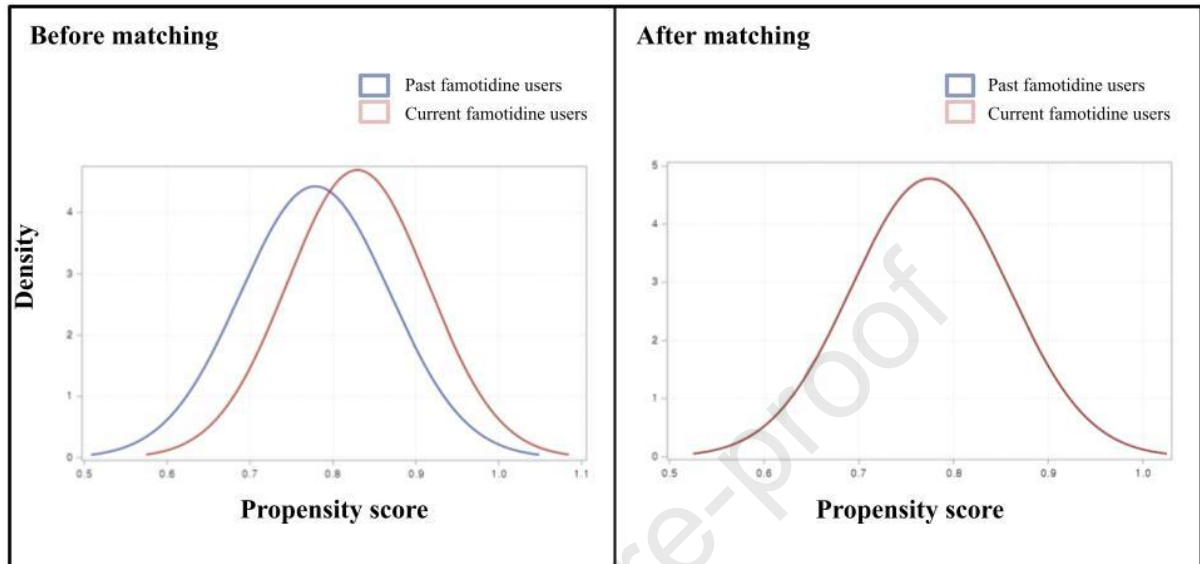
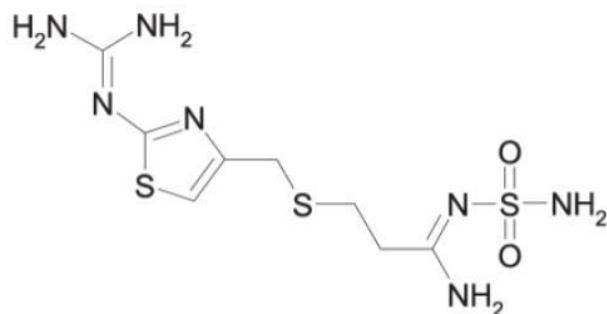


Figure S1. Chemical structure of famotidine



**Declaration of interests**

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: