ORIGINAL ARTICLE

Does Famotidine Reduce the Risk of Progression to Severe Disease, Death, and Intubation for COVID-19 Patients? A Systemic Review and Meta-Analysis

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Abstract

Background Famotidine was reported to potentially provide benefits to Coronavirus Disease 2019 (COVID-19) patients. However, it remains controversial whether it is effective in treating COVID-19.

Aims This study aimed to explore whether famotidine use is associated with reduced risk of the severity, death, and intubation for COVID-19 patients.

Methods This study was registered on International Prospective Register of Systematic Reviews (PROSPERO) (ID: CRD42020213536). A comprehensive search was performed to identify relevant studies up to October 2020. I-squared statistic and Q-test were utilized to assess the heterogeneity. Pooled risk ratios (RR) and 95% confidence intervals (CI) were calculated through the random effects or fixed effects model according to the heterogeneity. Subgroup analyses, sensitivity analysis, and publication bias assessment were also conducted.

Results Five studies including 36,635 subjects were included. We found that famotidine use was associated with a statistically non-significant reduced risk of progression to severe disease, death, and intubation for Coronavirus Disease 2019 (COVID-19) patients (pooled RR was 0.82, 95% CI = 0.52–1.30, $P = 0.40$).

Conclusion Famotidine has no significant protective effect in reducing the risk of developing serious illness, death, and intubation for COVID-19 patients. More original studies are needed to further clarify whether it is associated with reduced risk of the severity, death, and intubation for COVID-19 patients.

Keywords Famotidine · COVID-19 · Meta-analysis

Introduction

A new type of β-coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causing Coronavirus Disease 2019 (COVID-19) was first discovered in December 2019. The virus can be easily transmitted from person to person. Due to its strong pathogenicity [1–3], the virus can easily result in the spread of COVID-19 among population if limited or ineffective precautions are taken. Those infected with SARS-CoV-2 may present with fever, headache, and other mild symptoms, but in more severe cases, pneumonia, severe acute respiratory syndrome, and even death are also seen [4]. More than 34.8 million people were diagnosed with COVID-19 and 1,030,738 deaths were attributed to it as of October 4, 2020, making it a pandemic worldwide [5].

As a newly emerged infectious disease, evidence for treatment has been growing rapidly. Previous research has shown the potential role of famotidine [6], hydroxychloroquine [7], and remdesivir [8], in the treatment of COVID-19. Among them, famotidine was proposed to provide potential benefits, as a study identified famotidine could potentially inhibit the 3-chymotrypsin-like protease (3CLpro), which processes proteins that are essential for viral replication [9, 10]. Considering pathological histamine release and activation of dysregulated mast cells may be the factors leading to SARS-CoV2 infection, famotidine may act by antagonizing or anti-exciting histamine receptor 2 [11, 12]. However, new

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emerging studies have now refuted the hypotheses and argue against the activity of famotidine as a direct-acting antiviral inhibitor of either the main or papain-like protease (PLpro) of SARS-CoV-2 [11, 13, 14].

It remains controversial whether famotidine is effective in treating COVID-19. On one hand, Freedberg et al. [6] found that famotidine could significantly reduce the risks of death or intubation. A lower level of certain serum markers was also observed. Mather et al. [15] agreed with their findings and shared similar opinions. On the other hand, Cheung et al. [16] found no association between famotidine use and COVID-19 severity. Hence, it is necessary to assess effects of famotidine on improving the outcome of those suffered COVID-19 by a meta-analysis.

Methods

This meta-analysis was reported in conformity to the Preferred Reporting Project declared by the Systematic Review and Meta-Analysis (PRISMA) [17]. And it was registered on International Prospective Register of Systematic Reviews (PROSPERO) (ID: CRD42020213536).

Search Strategy

A comprehensive search strategy was performed in Embase, PubMed, Cochrane Library, Web of Science, CNKI (China National Knowledge Infrastructure) China Biology Medicine (CBM), VIP (Chinese) database and Wanfang Data up to October 2020 to select relevant studies. The following terms were used: (histamine receptor antagonists OR histamine receptor blockers OR H2 antagonist OR H2 receptor antagonist OR H2RA OR H2 blockers OR ranitidine OR cimetidine OR nizatidine) AND (COVID-19 OR Novel coronavirus OR coronavirus disease OR SARS-CoV-2 OR Severe acute respiratory syndrome coronavirus 2). These words were replaced by Chinese phrases with the same meaning in Chinese databases.

Inclusion Criteria and Exclusion Criteria

Publications will be selected if they met the following inclusion criteria: (1) The research type was original studies; (2) the exposure was famotidine use without any other histamine receptor antagonists; (3) the subjects of the study were patients suffered from COVID-19; (4) the main outcome index is severe disease, death, and/or intubation rate; (5) hazard ratios (HRs) or relative risks (RRs) or odd ratios (ORs) were provided with its 95% confidence intervals (*CIs*) or enough data can be extracted to calculate the effect size; (6) second outcomes are the serum maker levels.

The following criteria were used to exclude studies:(1) The research was not human studies (such as reviews, meta-analyses, animal studies, or in vitro studies); (2) Cannot accurately determine the type of articles; (3) Unable to extract valid ending data and cannot calculate it; (4) Duplicate or studies reported the same data.

Data Extraction and Quality Assessment

Two reviewers (C. Sun and Y. Chen) looked through articles and extracted data independently. In case of discrepancies, consensus was reached by discussions and consulting with a third reviewer (Y. Wu). Information extracted contents include first author, geographic locations, sample size, exposure, dosage, outcomes, OR/HR/RR with its 95% CI, scores, adjustments. Newcastle–Ottawa Scale (NOS) was used to evaluate the quality of each study by two reviewers separately. A third person would be consulted to resolve the disparity when coming across disagreement. Any study that score of more than 7 stars was considered as a high-quality study, and those with a score between four and six stars were considered as moderate-quality studies [18].

Statistical Analysis

The association between famotidine use and progression to severe disease, death, or intubation was analyzed through pooling the RRs and corresponding 95% CIs. Considering the relative low incidence of severe cases, intubation, and death of COVID-19, HRs were viewed as RRs [19], and ORs are statistically transformed into RRs [20, 21]. Then, the results were combined. Heterogeneity between the results of the included studies was analyzed by Q-test and evaluated in conjunction with the I^2 statistic [22]. Fixed effects model was applied if the heterogeneity test showed non-significant results ($I^2 < 50\%$), otherwise a random effects model was applied ($I^2 > 50\%$) [23]. Pooled mean difference (MD) of ferritin level was analyzed by converting median to mean [24–28]. Sensitivity analysis was used to test the stability of results by excluding one study at a time to compare differences between the results after exclusion and the original results without exclusion [29]. Publication bias was visually assessed by a funnel plot and quantitatively assessed by Egger's test and Begg's test. [30, 31] All of the statistical analyses were performed through RevMan 5.3 and STATA 14.0. P values of less than 0.05 were taken to be statistically significant.

Results

Study Selection and Study Characteristics

Through systematic search and retrieving records from other sources, 87 documents were initially obtained. After removing duplicate documents, 57 articles remained. By screening the title and the abstract, we filtered out 35 potentially relevant articles. After reading the full text carefully, five articles were included. Figure 1 shows the detailed process.

Five published articles [6, 15, 16, 32, 33] with 36,635 participants were included. The NOS scores of the four studies were ≥ 6 scores, which suggested moderate or high quality for the included studies. The basic characteristics of the included literature are shown in Table 1. The doses of famotidine of each study were also reported in Table 1 except for Chueng's study that did not specify the dose.

Overall Meta-Analysis

Heterogeneity was observed in the result ($I^2 = 76\%$, $P_{heterogeneity} = 0.003$), and random effect model was applied. The pooled RR was 0.82 (95% CI = 0.52–1.30, $P = 0.40$), suggesting a non-significant effect of famotidine on reducing the risk of progression to severe disease, death, and intubation. (Fig. 2).

Subgroup Analyses

Association Between Famotidine Use and Death and Intubation for COVID-19 Patients

Further analysis of three studies regarding its effect on mortality and intubation [6, 15, 32] did not find a statistically significant protective effect (RR:0.63, 95% CI = 0.35–1.16, $P = 0.140$, $I^2 = 84\%$, $P_{heterogeneity} = 0.002$). Similarly, three studies investigating mortality only [15, 32, 33] did not show a statistically significant protective effect (RR:0.90, 95% CI = 0.49–1.65, $P = 0.73$, $I^2 = 82\%$, $P_{heterogeneity} = 0.003$) (Table 2). We also analyzed studies with famotidine doses ≤ 40 mg, which happened to be the same three articles [6, 15, 32] on mortality and intubation, showing the same result of pooled RR and 95% CI.

Association Between Famotidine Use and Serum Markers for COVID-19 Patients

A lower median ferritin levels among famotidine users (708 ng/mL vs 846 ng/mL, $P = 0.030$ and 797.5 ng/mL vs. 964.0 ng/mL, $P = 0.076$) were observed in two studies [6, 15]. A lower median CRP level (9.4 mg/mL vs. 12.7 mg/dL, $P = 0.002$), median procalcitonin level (0.16 ng/mL vs. 0.30 ng/mL, $P = 0.004$), and median ESR level (57.5 mm/h vs. 68 mm/h, $P = 0.190$) were also reported [15].
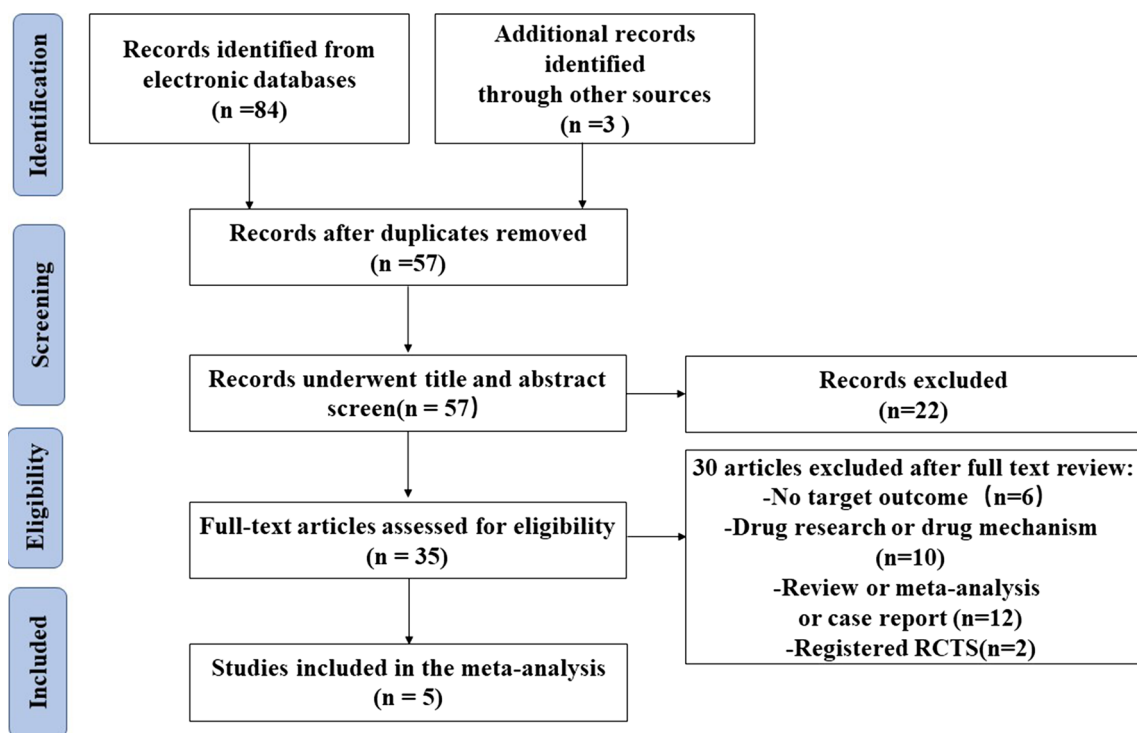

Fig. 1 PRISMA flowchart

Table 1 Characteristics of studies included in this meta-analysis

First author	Country	Sample size		Exposure	Dosage	Outcome	OR/HR (95% CI)	Adjustment	Study design	NOS scores
		Famotidine use	Non-famotidine use							
Cheung [16]	China	23	929	On the day of admission	NA	Critical complication [respiratory failure, septic shock, and/or multiple organ dysfunction], ventilatory support, intensive care unit admission, and/or death	OR: 1.34(0.24–7.48)	Adjusted[a]	Cohort	9
Freedberg [6]	USA	84	1536	Within 24 h of hospital admission	10, 20, or 40 mg/d IV a median 5.8 days of drug for a total median dose of 136 mg (63–233 mg)	A composite of death or endotracheal intubation from hospital day 2 to day 30 (intubation-free survival)	HR: 0.43(0.21–0.88)	Propensity score matching[b]	Cohort	8
Mather [15]	USA	83	795	Within +/− 7 days of COVID-19 screening and/or hospital admission	20,40 mg/d IV 20 mg/2 ml oral median total dose was 80 mg (40–160 mg) median of 4 days (2–8 days)	(1) In-hospital death, requirement for mechanical ventilation, and the composite of death or requirement for ventilation (2) Mortality	(1) HR: 0.51(0.31–0.79) (2) HR: 0.39(0.20–0.74)	Propensity score matching[c]	Cohort	8
Shoaibi [32]	USA	1623	24,404	On the day of admission	20 or 40 mg oral and/or IV	(1) Death and 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 (2) Mortality	(1) HR: 1.00(0.86–1.16) (2) HR: 1.03(0.86–1.24)	Propensity score matching[d]	Cohort	9

Table 1 (continued)

First author	Country	Sample size Famotidine use	Non-famotidine use	Exposure	Dosage	Outcome	OR/HR (95% CI)	Adjustment	Study design	NOS scores
Yeramaneni [33]	USA	1127	6031	Within 24 h of admission	A median 6.0 days and median cumulative dose of 160 mg (IQR, 80–300 mg)	30-day mortality	OR: 1.59(0.94–2.71)	Adjusted[e]	Cohort	7

NA not applicable

[a]Adjusted for age, sex, comorbidities (diabetes mellitus, hypertension, ischemic heart disease, stroke, and atrial fibrillation), other medications (angiotensin converting enzyme inhibitors, angiotensin receptor blockers, aspirin, statins, and prednisolone), and laboratory parameters (leukocyte, platelet, C-reactive protein, urea, creatinine, sodium, potassium, bilirubin, alkaline phosphatase, alanine aminotransferase, albumin, globulin, and lactate dehydrogenase)

[b]The variables used for the propensity score calculation including age, sex, race, body mass index (BMI), comorbidities (diabetes, hypertension, coronary artery disease, heart failure, end-stage renal disease or chronic kidney disease, chronic pulmonary disorders), Initial oxygen requirement (room air, nasal cannula, non-rebreather, or similar)

[c]The variables used for the propensity score calculation including age, sex, smoking status, body mass index (BMI), comorbidities (atrial fibrillation, asthma, coronary artery disease, cancer, chronic obstructive pulmonary disease, diabetes, heart failure, hypertension, obesity, kidney disease)

[d]The variables used for the propensity score calculation including age, gender, general medical history (acute respiratory disease, attention deficit hyperactivity disorder, chronic liver disease, chronic obstructive lung disease, Crohn's disease, dementia, depressive disorder, diabetes mellitus, gastroesophageal reflux disease, gastrointestinal hemorrhage, human immunodeficiency virus infection, hyperlipidemia, hypertensive disorder, lesion of liver, obesity, osteoarthritis, pneumonia, psoriasis, renal impairment, rheumatoid arthritis, schizophrenia, ulcerative colitis, urinary tract infectious disease, viral hepatitis C, visual system disorder), cardiovascular medical history (atrial fibrillation, cerebrovascular disease, coronary arteriosclerosis, heart disease, heart failure, ischemic heart disease, peripheral vascular disease, pulmonary embolism, venous thrombosis), neoplasms history (hematologic neoplasm, malignant lymphoma, malignant neoplasm of anorectum, malignant neoplastic disease, malignant tumor of breast, malignant tumor of colon, malignant tumor of urinary bladder, primary malignant neoplasm of prostate)

[e]Adjusted for baseline World Health Organization severity, smoking and use of other medications

Pooled MD of ferritin level was analyzed by converting median to mean [24–28], and a reduced MD of -226.38 (95% CI: -333.95, -118.80, $P < 0.001$; $I^2 = 0\%$, $P_{heterogeneity} = 0.380$) was found.

Sensitivity Analyses

Sensitivity analysis was conducted by excluding each article and calculating the heterogeneity and effect size. The fluctuation of the pooled RRs was found to be between 0.68 and 0.97 with lower limit of 95% CI constantly remained less than 1 and upper limit of 95% CI constantly remained more

than 1, and P value constantly remained more than 0.05, suggesting the stability of this meta-analysis. By changing the random effect model to fixed effect model, the overall result was not altered significantly (RR = 0.94, 95% CI: 0.83–1.08), further confirmed the stability.

Publication Bias

Funnel plot was shown to be symmetrical (Fig. 3). In addition, no publication bias was detected by Begg's test ($z = -0.24$, $P = 1.000$) and Egger's test ($t = -0.55$, $P = 0.621$).
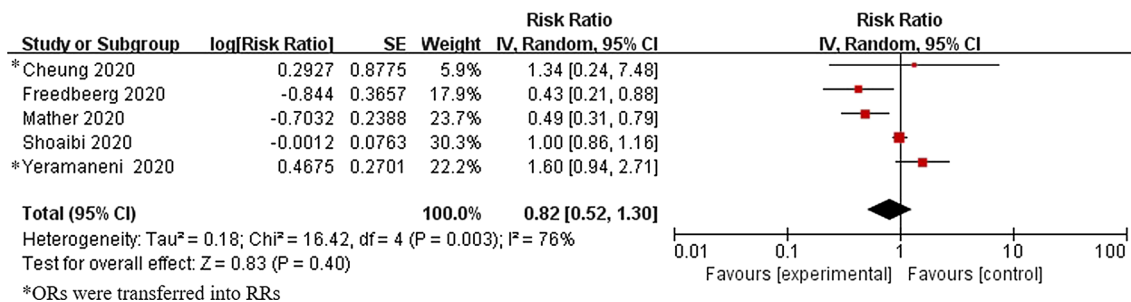
Fig. 2 Forrest plot: Association between famotidine and the risk of progression to severe disease, death, and intubation for COVID-19 patients

Table 2 Association between famotidine use and COVID-19 outcomes

Analysis	Number of studies	OR (95% CI)	P	Heterogeneity	
				$P_{Heterogeneity}$	I^2 (%)
Severity, mortality and intubation	5	0.82(0. 52–1.30)	0.400	0.003	76
Mortality and intubation	3	0.63(0.35–1.16)	0.140	0.002	84
Mortality only	3	0.90(0.49–1.65)	0.730	0.003	82

Fig. 3 Funnel plot
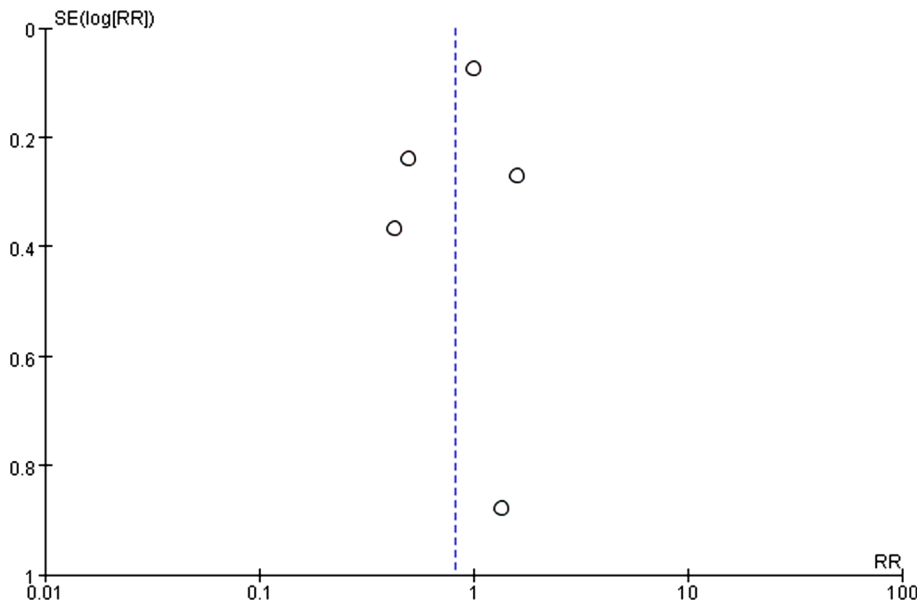
Discussion

In the overall pooled analysis, one study [16] reported severity (including critical complication, ventilatory support, ICU admission, and/or death), and three [6, 15, 32] reported death and intubation and one [33] reported death of COVID-19. Moreover, two randomized controlled trials (RCTs) were registered (ClinicalTrials.gov Identifier: NCT04370262 and NCT04545008), but no results have been reported yet. Consequently, famotidine was not associated with a reduced risk of progression to severe disease, intubation, and death of COVID-19. At the same time, subgroup analysis further confirmed the irrelevance between intubation and death and famotidine use. Moreover, three studies [15, 32] investigating mortality only did not find a protective effect, and one study [16] investigating severity only showed no association either. When sensitivity analysis was performed, the results of this meta-analysis did not change dramatically after excluding any of the included studies, suggesting the stability of this meta-analysis.

The combined results of the three studies [6, 15, 32] on relatively low-dose famotidine were not statistically significant, suggesting that the standard over-the-counter (OTC) doses for treatment of gastroesophageal reflux disease (GERD) (20 mg PO per day to 40 mg PO per day in split dose) of famotidine might be insufficient to yield significant clinical benefit in COVID-19 disease. However, this result should be interpreted with caution as only three studies were included in this subgroup. Freedberg's study concluded that famotidine reduced the risk of death and intubation, whereas the Shoaibi's article concluded that the assessment of both intubation and death, as well as death alone, was not statistically insignificant. In addition, only Freedberg's study and Yeramanei' study reported a cumulative dose, so it is difficult to assess the cumulative effect. It should also be noted that therapeutic efficacy of a pharmacological antagonist requires a steady-state concentration that substantially exceeds the half maximal inhibitory concentration (IC50) for its target. Famotidine has predicted steady-state concentration at different doses [11]. This might explain why higher than standard OTC doses of famotidine were reported to have potential benefits [34]. Nevertheless, published information indicating the effectiveness of higher doses of famotidine alone at treating COVID-19 in either inpatients or outpatients was very limited, especially no large cohort studies investigating the effectiveness of famotidine at COVID-19 treatment with doses higher than those used in gastroesophageal reflux disease (GERD) have been published yet. Therefore, how effective the higher dose of famotidine at treating COVID-19 remains speculative.

Although no decreased risk of severe illness, intubation, and mortality of COVID-19 was found among famotidine users, famotidine might still be potentially beneficial as lower serum markers were observed. A statically significantly lower median ferritin level [6], median CRP level, and median procalcitonin level [15] among famotidine users were also reported. For ferritin level, the pooled analysis of two studies [6, 15] also found a statistically significant lower level among famotidine users. Ferritin, CRP, procalcitonin, and other serum markers were thought to be potential prognosis predicators [35–37]. However, more investigation on these serum markers among COVID-19 patients on famotidine are needed to further elaborate this potential benefits.

According to the previous studies, famotidine may improve COVID-19 outcomes by several mechanisms. First, famotidine could potentially inhibit the 3-chymotrypsin-like protease (3CLpro), which processes proteins essential for viral replication [9, 10, 15]. Famotidine may also activate G-protein-coupled receptors (GPCRs) which was presumed to active immune cell mobilization, and result in vascular inflammation [11, 38]. In contrast, Singh et al. found weak, nonspecific binding of famotidine to both PLpro and 3 chymotrypsin-like protease (3CLpro), which is the reverse of previous molecular docking studies [13]. And it was also recently reported that famotidine does not inhibit PLpro and Mpro nor does it inhibit SARS-CoV-2 infection [11, 14]. These controversial findings prompt the necessity of more investigation regarding the effect of famotidine on SARS-CoV-2 infection. Second, mast cells activated by coronavirus were shown to produce histamine, prostaglandin D2 (PGD2), and leukotriene C4 (LTC4), inducing acute bronchoconstriction and lung inflammation [12]. Pneumocytes that are positive for H1 and H2 receptors could respond to local histamine release following mast cell degranulation [39]; therefore, famotidine and other H2RA may play a role in modulating the pulmonary pathological process. A recent cohort of 110 COVID-19 patients treated with famotidine and cetirizine by RB Hogan et al. exhibited that the combination of these two drugs can be very beneficial in terms of the incidence of death and progression of disease in hospitalized patients [40]. However, considering that our inclusion criteria require exposure to famotidine but not with other histamine receptor blockers, it was not included in the meta-analysis. Third, lung autopsy specimens have demonstrated a paucity of neutrophils and eosinophils in postmortem photomicrographs [41]. It is known that histamine 2 receptors could inhibit neutrophil effector functions such as oxygen release, chemotaxis induced by platelet-activating factor, and leukotriene biosynthesis [42–44], as well as inhibition of peroxidase release and chemotaxis by eosinophil [45, 46].

Several inherent limitations in this study should be mentioned. First, this meta-analysis included studies with relatively small sample size thus the results might be biased. Second, heterogeneity was noticed in overall analysis. The

outcomes in the included studies are different, which may contribute to the heterogeneity. Third, in-hospital treatment and concomitant use of other medications use may also affect the COVID-19 outcome. But it is not adjusted for other in-hospital medications in the included studies. Fourth, pooled RR estimates had a bias because of the use of different RR indicators (HR or OR or RR) as the same effect measures. Fifth, two articles by Freedberg et al. and Mather et al. did not adjust for sufficient confounders. Last but not least, medians of ferritin levels were converted to mean for the pooled analysis, which might not be accurate for skewed distribution.

Despite the limitations, the advantages are as follows: First, our meta-analysis incorporated more articles and performed a more detailed analysis than the previous one [47]. Second, there was no publication bias. The sensitivity analysis found a robust result for the effects of famotidine, prompting our results to be credible.

In short, non-significant effect of famotidine on reducing the risk of progression to severe disease, death, and intubation. However, only limited number of original studies are available, more original studies are urgently needed to further clarify whether famotidine is associated with reduced risk of the severity, death, and intubation for COVID-19 patients.

Compliance with Ethical Standards

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