ORIGINAL ARTICLE

Gastrointestinal prophylaxis for COVID-19: an illustration of severe bias arising from inappropriate comparators in observational studies

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Abstract

Objectives: We aimed to use setting-appropriate comparisons to estimate the effects of different gastrointestinal (GI) prophylaxis pharmacotherapies for patients hospitalized with COVID-19 and setting-inappropriate comparisons to illustrate how improper design choices could result in biased results.

Study Design and Setting: We identified 3,804 hospitalized patients aged $\geq$ 18 years with COVID-19 from March to November 2020. We compared the effects of different gastroprotective agents on clinical improvement of COVID-19, as measured by a published severity scale. We used propensity score−based fine-stratification for confounding adjustment. Based on guidelines, we prespecified comparisons between agents with clinical equipoise and inappropriate comparisons of users vs. nonusers of GI prophylaxis in the intensive care unit (ICU).

Results: No benefit was detected when comparing oral famotidine to omeprazole in patients treated in the general ward or ICUs. We also found no associations when comparing intravenous famotidine to intravenous pantoprazole. For inappropriate comparisons of users vs. nonusers in the ICU, the probability of improvement was reduced by 32%−45% in famotidine users and 21%−48% in omeprazole or pantoprazole users.

Conclusion: We found no evidence that GI prophylaxis improved outcomes for patients hospitalized with COVID-19 in setting-appropriate comparisons. An improper comparator choice can lead to spurious associations in critically ill patients. © 2022 Elsevier Inc. All rights reserved.

Keywords: COVID-19; Epidemiology; Outcomes research; H2RA; PPI; GI prophylaxis

1. Introduction

The COVID-19 pandemic has raised questions about whether real-world data can be leveraged in better ways to guide treatment decisions and support more efficient investment in larger randomized controlled trials (RCTs). Optimizing the use of real-world data requires a valid study design and proper analytic strategies to minimize bias. Methodologically flawed observational studies may promote treatments that do not improve and may even negatively affect patient outcomes, redirecting finite resources away from trials that test more promising therapies.

Gastrointestinal (GI) prophylaxis with gastroprotective agents, including H2 receptor antagonists (H2RAs) and proton pump inhibitors (PPIs), is a common practice for hospitalized patients, particularly for critically ill patients [1−3]. Famotidine, an H2RA used to treat gastroesophageal reflux, was initially promoted for COVID-19 based on a molecular docking study showing that it inhibited 3 chymotrypsin-like

What is new?

Key findings
- The optimal gastrointestinal prophylaxis strategy for patients hospitalized with COVID-19 remains unknown, and the prior analyses failed to stratify patients by the general ward vs. intensive care unit (ICU).

- We found no clinical benefit when comparing famotidine to proton pump inhibitors stratified by general ward vs. ICU, but spurious associations were detected in the inappropriate nonuser comparison in the ICU.

What this adds to what was known?
- We found no evidence that gastrointestinal prophylaxis improved clinical outcomes for patients hospitalized with COVID-19.

What is the implication and what should change now?
- Improper choice of a referent group in observational studies can cause intractable confounding in critically ill patients.

proteases (or Nsp5) of SARS-CoV-2 [4]. Two observational studies in the United States subsequently demonstrated famotidine may decrease rates of intubation and in-hospital mortality in patients treated for COVID-19 [5,6], although later observational studies [7−9] and two recent systematic reviews [10,11] found no benefit. The prior observational studies on the treatment effect of H2RA and PPIs in patients with COVID-19 have produced conflicting results due to several unaddressed methodological issues. First, GI prophylaxis is preferentially recommended for patients in the intensive care unit (ICU), not for patients admitted to a general medical ward [12,13]. Therefore, a comparison between users vs. nonusers that does not account for treatment location is subject to substantial confounding by disease severity [5−11]. None of the prior studies consider care settings when choosing the comparators of the gastroprotective agents. Second, to choose the appropriate comparator group, investigators need to consider the route of administration because it correlates with disease severity. However, prior studies did not differentiate between oral and intravenous (IV) formulations, which may have led to intractable confounding bias [13,14].

To address these knowledge gaps and illustrate the importance of choosing a context and setting-appropriate comparator group, we performed a longitudinal study comparing various GI prophylaxis approaches in patients hospitalized with COVID-19, stratified by treatment location and route of delivery. We used prespecified comparators, stratified by general ward or ICU, to estimate causal treatment effects of different GI prophylaxis strategies. In addition, we deliberately used inappropriate comparators to illustrate how such design choices could result in biased conclusions.

2. Methods

2.1. Source data

Data were drawn from Research Patient Data Registry [15], which contains electronic health records (EHRs) from Mass General Brigham (MGB), a large care delivery network in Massachusetts that includes facilities across the full continuum of care [16]. MGB consists of two tertiary hospitals, 11 secondary hospitals, and >30 ambulatory care centers. Research Patient Data Registry contains information on patient demographics, medical diagnoses and procedures, prescription dispensing and administrative data, vital signs, smoking status, body mass index (BMI), immunizations, laboratory data, and clinical reports. The MGB Human Research Committee approved the study protocol.

2.2. Study population by treatment status

We included all hospitalized patients aged 18 years or more infected with SARS-CoV-2 indicated by a positive result on a real-time reverse-transcriptase polymerase chain reaction assay of nasal or pharyngeal swab specimens at an MGB facility from March 1, 2020 to November 1, 2020. The date of testing was required to be either during the index hospitalization or within 14 days before the admission. Pregnant women and those receiving hospice or comfort care were excluded. Among patients meeting our inclusion criteria, we identified those receiving either PPIs or H2RAs during the hospitalization as per the inpatient medication administration records. We established a nonuser cohort by risk-set sampling; for each H2RA/PPI new user, we sampled 10 nonusers who met eligibility criteria and had not yet initiated an H2RA/PPI, matched on a hospital day. The cohort entry (index) date was the medication use date for users and the sampling date for nonusers. Although we did not limit to specific types of PPIs or H2RAs, due to facility formulary limitations, our database contained sufficient users for only omeprazole (oral), pantoprazole (IV), and famotidine (IV and oral).

2.3. Prespecifying context and setting-appropriate versus setting-inappropriate comparator groups

Because use of GI prophylaxis agents and administration routes is informed by clinical settings and disease severity [13,14], we deemed it important to stratify for these variables. For patients admitted to a general medical ward,

Table 1. Crude baseline characteristics

| Comparisons[a] | % Aged more than 75 years | % Male | % Black | % Overweight/Obese | % With eGFR <30 | Underlying GI indications | | | |
						% GERD	% GI bleeding	% Other GI events	% Gastritis
General ward									
1									
Oral-famotidine	25.3	44	21.3	63.9	9.3	38.7	2.7	48	22.7
Nonuse	24.9	56.7	15.6	73.3	4.8	14.8	3.9	19.5	18.3
2									
Oral-omeprazole	30.6	49.1	13.1	62.6	8.1	47.7	6.3	53.2	29.7
Nonuse	26.6	54.6	16.6	59.2	7.1	12.5	3.1	19.4	17.5
3									
IV-pantoprazole	34.9	49.2	17.5	71.4	15.9	19	42.9	31.7	39.7
Nonuse	23.4	55.6	16.6	73.1	7.1	13.2	3.6	18	18.9
4									
Oral-famotidine	25.3	44	21.3	63.9	9.3	38.7	2.7	48	22.7
Oral-omeprazole	30.6	49.1	13.1	62.6	8.1	47.7	6.3	53.2	29.7
ICU									
5									
Oral-famotidine	11.6	74.7	17.9	80	10.6	14.7	8.4	18.9	16.8
Nonuse	22.6	69.1	20.8	72.9	14.2	10.9	6.4	19.3	14.6
6									
Oral-omeprazole	25.3	69.9	18.1	83.1	6	18.1	3.6	24.1	9.6
Nonuse	22.9	70.3	21	71	9.6	9.6	7.5	16.8	13.1
7									
IV-famotidine	22.1	80.4	21.6	71.7	18.6	10.6	7.1	15	10.6
Nonuse	24	77.3	19.9	71	12.8	11.8	9.1	20.1	15.9
8									
IV-pantoprazole	23	63.5	18.3	73	17.4	16.7	18.3	21.4	17.5
Nonuse	20.3	68.3	21.1	69.2	12.2	11.9	6.3	18.1	13.5
9									
Oral-famotidine	11.5	74	17.7	80.2	10.4	15.6	8.3	19.8	17.7
Oral-omeprazole	25.3	69.9	18.1	83.1	6	18.1	3.6	24.1	9.6
10									
IV-famotidine	22.1	78.8	21.2	72.6	18.6	10.6	7.1	15	10.6
IV-pantoprazole	23	63.5	18.3	73	17.4	16.7	18.3	21.4	17.5

GERD, gastroesophageal reflux disease.
[a] Comparisons 5—8, comparing treatments with nonuse in the ICU setting, were deemed inappropriate.

GI prophylaxis is not routinely recommended [12,13], so we considered it appropriate to compare users of different gastroprotective agents, such as famotidine vs. omeprazole and famotidine vs. pantoprazole, and to compare users with nonusers. By contrast, in the ICU setting, because gastroprotective agents are routinely prescribed to prevent stress ulcers in patients with critical illness [2,3], we considered comparisons between gastroprotective agents as appropriate but comparisons of users to nonusers inappropriate. We aimed to use context and setting-appropriate comparisons to estimate causal treatment effects and inappropriate comparisons to illustrate how improper comparator choices can lead to biased results.

2.4. Outcome definition

The primary end point was an improvement by two levels on a modified COVID-19 disease severity scale. This severity scale included the following categories: level 1, discharged home; level 2, hospitalized but not requiring supplemental oxygen; level 3, hospitalized and requiring supplemental oxygen ≤2 L per minute (L/min); level 4, hospitalized and requiring oxygen therapy 3—4 L/min; level 5, hospitalized and requiring oxygen therapy ≥ 5 L/min or receiving high-flow nasal cannula, nonrebreather, or noninvasive mechanical ventilation; level 6, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation or admitted to an ICU; and level 7, death

Table 2. Gastroprotective agent effects in the general ward on clinical improvement on the severity scale[a]

Gastroprotective agents (exposed vs. referent group)	Exposed events		Referent group events/IR (per 100 person-day)		Crude HR (95% CI)	Weighted HR (95% CI)[b]	Fully adjusted HR (95% CI)[c]
	# Of events	IR (per 100 PD)	# Of events	IR (per 100 PD)			
Oral famotidine vs. nonuse	64	16.12	34	13.77	1.14 (0.88, 1.48)	1.24 (0.97, 1.58)	1.23 (0.96, 1.57)
Oral omeprazole vs. nonuse	185	14.90	1,876	14.28	0.89 (0.69, 1.15)	0.86 (0.67, 1.10)	0.86 (0.67, 1.10)
IV pantoprazole vs. nonuse	48	13.04	535	14.08	0.93 (0.69, 1.25)	0.90 (0.67, 1.20)	0.97 (0.70, 1.35)
IV famotidine vs. nonuse	15	12.00	151	12.09	1.14 (0.88, 1.48)	1.24 (0.97, 1.58)	1.23 (0.96, 1.57)
Oral famotidine vs. omeprazole	64	16.12	185	14.90	1.05 (0.79, 1.39)	1.22 (0.82, 1.82)	1.14 (0.79, 1.64)

[a] Two-level improvement on a modified COVID-19 disease severity scale during hospitalization [25].

[b] Adjusted for LASSO-selected variables among patient demographics, BMI, smoking, oxygen therapy, and vital signs upon admission, asthma, chronic obstructive pulmonary disease, tuberculosis, cystic fibrosis, GI illness and bleeding, hypertension, diabetes, hypercholesterolemia, adverse cardiovascular events, malignancy, and viral infections. Baseline medication exposure included nonsteroidal anti-inflammatory drugs, corticosteroids, cardiovascular medication classes, PPIs, H2RAs, antidiabetics, antiasthmatics, antidepressants, anticonvulsants, chemotherapy, and biologics.

[c] In addition to the variables adjusted in the weighted analysis, we further included covariates with a standardized difference >0.1 in the final Cox proportional hazards model.

or conversion of code status into comfort care/hospice. This scale was modified from an ordinal scale used in RCTs [17–19] with further subdivisions for those receiving oxygenation and/or ventilation support as per measures in the literature [20–22]. The outcome ascertainment started on the index date and continued until death, comfort care or hospice, hospital discharge, 28 days after the index date, or the end of the study (November 1, 2020).

2.5. Covariates

We considered a comprehensive list of potential confounders: patient demographics, BMI, smoking, oxygen therapy, and vital signs upon admission. We also assessed baseline comorbidities using diagnosis and procedure codes and prior drug exposure using electronic ordering system records, medication reconciliation, and dispensing data available in the EHR during the 365 days before and including the index date. Comorbidities assessed included, but were not limited to, asthma, chronic obstructive pulmonary disease, tuberculosis, cystic fibrosis, GI illness and bleeding, hypertension, diabetes, hypercholesterolemia, adverse cardiovascular events, malignancy, and non-COVID-19 viral infections. Baseline medication exposure included nonsteroidal anti-inflammatory drugs, corticosteroids, cardiovascular medication classes, PPIs, H2RAs, antidiabetics, inhalers, antidepressants, anticonvulsants, chemotherapy, and biologics. Detailed definitions for each comorbidity and generic names for each medication class are listed in Appendix Table S1.

2.6. Statistical analysis

We used a least absolute shrinkage and selection operator regression [23] to select influential confounders among the aforementioned factors. We built a propensity score (PS) by logistic regression with the least absolute shrinkage and selection operator—selected variables along with age, gender, calendar time, BMI, severity, coagulopathy, end-stage renal disease, systolic blood pressure, temperature, estimated glomerular filtration rate (eGFR) (categorical with missing indicator), gastroesophageal reflux disease, GI bleeding, and other GI illnesses to build a PS model predicting treatment status on the index date. To balance baseline covariate distribution, we used PS fine stratification with 20 strata using the distribution of PS in the exposed group to create weights for the exposed and unexposed in each stratum (based on the trimmed population) [24]. We then used the weighted Cox proportional hazards model to compute crude and PS-stratified hazard ratio (HR) estimates with 95% confidence intervals (CIs) (denoted as "weighted HR"). The balance between comparator groups at baseline was examined by computing standardized differences. Any covariates with a standardized difference >0.1 indicated imbalanced covariate distribution and were further adjusted in the final Cox model (denoted as "fully adjusted HR"). The proportional hazard assumption was checked by inspection of the Kaplan—Meier survival curve. All analyses were stratified by ICU status. Missing data were handled by the missing indicator method. All analyses were performed using SAS statistical software, version 9.4 (SAS Institute, Inc., Cary, North Carolina).

Table 3. Gastroprotective agent effects in the intensive care unit on clinical improvement on the severity scale[a]

Prophylaxis regimen (exposed vs. referent group)	Exposed events		Referent group events/IR (per 100 person-day)		Crude HR (95% CI)	Weighted HR (95% CI)[b]	Fully adjusted HR (95% CI)[c]
	# Of events	IR (per 100 PD)	# Of events	IR (per 100 PD)			
Oral famotidine vs. omeprazole	59	4.04	47	4.14	0.96 (0.66, 1.41)	1.27 (0.73, 2.23)	1.23 (0.75, 2.04)
IV famotidine vs. pantoprazole	63	3.66	71	3.76	0.96 (0.69, 1.35)	0.84 (0.53, 1.32)	0.77 (0.45, 1.31)

[a] Two-level improvement on a modified COVID-19 disease severity scale during hospitalization [25].

[b] Adjusted for LASSO-selected variables among patient demographics, BMI, smoking, oxygen therapy, and vital signs upon admission, asthma, chronic obstructive pulmonary disease, tuberculosis, cystic fibrosis, GI illness and bleeding, hypertension, diabetes, hypercholesterolemia, adverse cardiovascular events, malignancy, and viral infections. Baseline medication exposure included nonsteroidal anti-inflammatory drugs, corticosteroids, cardiovascular medication classes, PPIs, H2RAs, antidiabetics, antiasthmatics, antidepressants, anticonvulsants, chemotherapy, and biologics.

[c] In addition to the variables adjusted in the weighted analysis, we further included covariates with a standardized difference >0.1 in the final Cox proportional hazards model.

3. Results

3.1. Patient characteristics

We identified 3,804 patients with laboratory-confirmed COVID-19, including a total of 305 oral omeprazole users (matched with 3,032 nonusers), 189 IV pantoprazole users (matched with 1,744 nonusers), 170 oral famotidine users (matched with 1,683 nonusers), and 129 IV famotidine users (matched with 1,274 nonusers; Table 1 and Appendix Table S2).

3.2. General medical ward

Comparing oral famotidine users (N = 75) with nonusers (N = 750), PS weighting yielded a satisfactory covariate balance (Appendix Table S3) and the adjusted HR (aHR) of clinical improvement was 1.23 (0.96, 1.57). Comparing patients receiving oral omeprazole (N = 222) with matched nonusers (N = 2,217), after PS weighting, the patient characteristics had satisfactory balance (Appendix Table S3) and the aHR was 0.86 (0.67, 1.10). The corresponding aHR was 1.23 (0.96, 1.57) comparing use vs. nonuse of IV famotidine and 0.97 (0.7, 1.35) comparing use vs. nonuse of IV pantoprazole (Table 2). When comparing users of oral famotidine (N = 75) vs. omeprazole (N = 222), age, oxygen requirement, and BMI were imbalanced after PS weighting and further adjusting for these factors in the outcome model yielded an aHR of 1.14 (0.79, 1.64). The comparison between IV famotidine and IV pantoprazole was not performed as there were only 16 new users of IV famotidine in the general ward.

3.3. Intensive care unit

Comparing users of oral famotidine (N = 95) vs. omeprazole (N = 83), age, BMI, and eGFR were imbalanced after PS weighting (Appendix Table S3), and after further adjusting for these factors in the outcome model, the aHR of clinical improvement was 1.23 (0.75, 2.04; Table 3). When

comparing users of IV famotidine (N = 113) vs. IV pantoprazole (N = 126), age, code status, diabetes mellitus, end-stage renal disease, GI illness, BMI, and eGFR were imbalanced after PS weighting (Appendix Table S3), and further adjusting for these factors in the outcome model, the aHR of clinical improvement was 0.77 (0.45, 1.31; Table 3).

3.4. Inappropriate comparisons of gastrointestinal prophylaxis in the intensive care unit

Comparing patients receiving oral famotidine (N = 95) vs. matched nonusers (N = 933) in the ICU, after PS weighting, age, eGFR, BMI, respiratory rates, and multiple comorbidity and medication use variables were not balanced (Appendix Table S3) and the aHR of clinical improvement was 0.68 (0.50, 0.94; Table 4). Comparing patients receiving oral omeprazole (N = 83) vs. matched nonusers (N = 815) in the ICU, after PS weighting, coagulation profiles, BMI, and comorbidities were not balanced (Appendix Table S3) and the aHR of clinical improvement was 0.79 (0.58, 1.08; Table 4). The corresponding aHR was 0.55 (0.37, 0.82) when comparing use vs. nonuse of IV famotidine and 0.52 (0.41, 0.66) when comparing use vs. nonuse of IV pantoprazole (Table 4).

4. Discussion

In a cohort of hospitalized COVID-19 patients, we found that famotidine was not associated with improvement compared to PPIs among those treated in the general medical wards and the ICU. No benefit was detected when comparing oral famotidine vs. omeprazole or when comparing IV famotidine vs. pantoprazole. Neither famotidine nor PPIs were associated with improved outcomes when compared to nonuse of these agents in patients treated in the general wards. However, in the prespecified inappropriate comparison of users vs. nonusers of gastroprotective agents in the ICU, we observed the likely spurious associations showing that the probability of improvement was

Table 4. Inappropriate comparisons of gastroprotective regimens in the intensive care unit on the severity scale[a]

Prophylaxis regimen (exposed vs. referent group)	Exposed events		Referent group events/IR (per 100 person-day)		Crude HR (95% CI)	Weighted HR (95% CI)[b]	Fully adjusted HR (95% CI)[c]
	# Of events	IR (per 100 PD)	# Of events	IR (per 100 PD)			
Oral famotidine vs. nonuse	58	4.00	642	6.52	0.66 (0.50, 0.86)	0.66 (0.50, 0.88)	0.68 (0.50, 0.94)
Oral omeprazole vs. nonuse	47	4.14	585	6.94	0.63 (0.47, 0.85)	0.82 (0.62, 1.08)	0.79 (0.58, 1.07)
IV famotidine vs. nonuse	63	3.65	749	6.00	0.63 (0.49, 0.82)	0.57 (0.43, 0.74)	0.55 (0.37, 0.82)
IV pantoprazole vs. nonuse	71	3.76	893	7.28	0.55 (0.43, 0.7)	0.53 (0.42, 0.67)	0.52 (0.41, 0.66)

[a] Two-level improvement on a modified COVID-19 disease severity scale during hospitalization [25].

[b] Adjusted for LASSO-selected variables among patient demographics, BMI, smoking, oxygen therapy, and vital signs upon admission, asthma, chronic obstructive pulmonary disease, tuberculosis, cystic fibrosis, GI illness and bleeding, hypertension, diabetes, hypercholesterolemia, adverse cardiovascular events, malignancy, and viral infections. Baseline medication exposure included nonsteroidal anti-inflammatory drugs, corticosteroids, cardiovascular medication classes, PPIs, H2RAs, antidiabetics, antiasthmatics, antidepressants, anticonvulsants, chemotherapy, and biologics.

[c] In addition to the variables adjusted in the weighted analysis, we further included covariates with a standardized difference >0.1 in the final Cox proportional hazards model.

reduced by 32%–45% in famotidine users and 21%–48% in omeprazole or pantoprazole users.

Many prior studies examining H2RAs and PPIs lacked an active control group. We considered nonuser comparisons inappropriate in the ICU setting because GI prophylaxis is indicated routinely in critically ill patients. Comparing GI-protective agent users to nonusers may be subject to refractory confounding. Indeed, we found a harmful effect of H2RAs and PPIs when comparing patients on these therapies to nonusers in the ICU. Indications for stress ulcer prophylaxis in the ICU, although debated, include bleeding diatheses, mechanical ventilation >48 hours, prior GI ulceration or bleeding, traumatic brain injury, sepsis with GI bleeding risk factors, and nonsteroidal anti-inflammatory drugs or antiplatelet use [26,27]. These high-risk patients may have been at a greater risk for clinical deterioration, including respiratory deterioration, than nonusers lacking high-risk characteristics. Conversely, we did not find such associations in the general medical ward. This is consistent with the fact that GI prophylaxis is not routinely recommended for general medical ward patients [12,13]. Therefore, substantial confounding by disease severity is not expected. Nevertheless, there are several conditions for which a general medical ward patient might receive GI prophylaxis, including GI bleeding and prednisone use, which both may be associated with the outcome of interest. However, these factors were measured and adjusted in our propensity score models, so we did not observe similarly confounded results shown in the ICU settings. Our findings highlight the importance of study design and reference group choice when comparing therapeutic efficacies using observational data.

Both H2RAs and PPIs are approved, effective therapies for gastroesophageal reflux disease and peptic ulcer disease.. However, only H2RAs inhibit the three chymotrypsin-like proteases (or Nsp5) of SARS-CoV-2 in

in-vitro studies [4]. PPIs are not thought to provide protection against SARS-CoV-2 via this mechanism. In fact, some studies have reported PPIs may increase rates of COVID-19 [28] and lead to worse outcomes among patients with COVID-19 [25,29–31], potentially from impairment of host viral defenses associated with hypochlorhydria. Because PPIs lack the mechanism thought to provide protection against SARS-CoV-2 that H2RAs possess, we would expect famotidine to be associated with better clinical outcomes than PPIs if this mechanism was protective. Yet, after granular confounding adjustment for important clinical and lifestyle factors and proper stratification by treatment location and delivery method, famotidine was not associated with better outcomes compared to PPIs.

Our study has several limitations. First, residual unmeasured confounding remains possible despite controlling for numerous covariates in our primary analysis. Second, the populations for our analyses were small and confidence intervals wide. Therefore, we may have been unable to detect small treatment effects. Third, our results may not be generalizable to all H2RAs, PPIs, or to all hospital systems due to formulary limitations and study site restrictions in a Massachusetts metropolitan healthcare system. Finally, our study cohort may not receive care exclusively within our EHR system. In-system EHR discontinuity may lead to chronic comorbidity misclassification before hospitalization. We supplemented the records in the baseline covariate assessment period with conditions recorded during the index admission, assuming chronic conditions, such as diabetes or chronic obstructive pulmonary disease, were pre-existing before admission. Reassuringly, the key chronic condition prevalence was similar in our study when compared to RCTs of patients hospitalized for COVID-19. For example, the prevalence of diabetes was 34.9% and hypertension 57.2% in our study, compared to 29.1% and 49.6% in an RCT [32]. Nonetheless, other conditions may be under-recorded and misclassification is still possible.

5. Conclusion

We did not find evidence for the association between famotidine and improved clinical outcomes in hospitalized patients with COVID-19 compared to PPIs. We used prespecified inappropriate comparisons between users and nonusers of gastroprotective agents in the ICU setting to demonstrate how an improper choice of comparators in nonrandomized studies can lead to spurious associations. Thoughtful consideration of care settings and route of administration while choosing treatment regimens being compared could minimize confounding that is otherwise a major threat to observational studies of medication outcomes.

CRediT authorship contribution statement

Kueiyu Joshua Lin: Conceptualization, Funding acquisition, Investigation, Methodology, Writing − original draft, Writing − review & editing. **William B. Feldman:** Conceptualization, Investigation, Methodology, Writing − original draft. **Shirley Wang:** Conceptualization, Writing − original draft. **Siddhi Pramod Pramod Umarje:** Formal analysis, Investigation. **Elvira D'Andrea:** Conceptualization, Methodology. **Helen Tesfaye:** Conceptualization, Methodology. **Luke E. Zabotka:** Writing − original draft. **Jun Liu:** Formal analysis, Investigation. **Rishi J. Desai:** Conceptualization, Investigation, Writing − original draft.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclinepi.2022.07.009.

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