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Associations between COVID-19 therapies and inpatient gastrointestinal bleeding: A multisite retrospective study

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Abstract

Little data is available regarding the incidence of gastrointestinal bleeding in adults hospitalized with COVID-19 infection and the influence of patient comorbidities and demographics, COVID-19 therapies, and typical medications used. In this retrospective study, we utilized the National COVID Cohort Collaborative to investigate the primary outcome of the development of gastrointestinal bleeding in 512 467 hospitalized US adults (age >18 years) within 14 days of a COVID-19 infection and the influence of demographics, comorbidities, and selected medications. Gastrointestinal bleeding developed in 0.44% of patients hospitalized with COVID-19. Comorbidities associated with gastrointestinal bleeding include peptic ulcer disease (adjusted odds ratio [aOR] 10.2), obesity (aOR 1.27), chronic kidney disease (aOR 1.20), and tobacco use disorder (aOR 1.28). Lower risk of gastrointestinal bleeding was seen among women (aOR 0.76), Latinx (aOR 0.85), and vaccinated patients (aOR 0.74). Dexamethasone alone or with remdesivir was associated with lower risk of gastrointestinal bleeding (aOR 0.69 and aOR 0.83, respectively). Remdesivir monotherapy was associated with upper gastrointestinal bleeding (aOR 1.25). Proton pump inhibitors were more often prescribed in patients with gastrointestinal

Abbreviations: ACTT-1, Adaptive COVID-19 Treatment Trial-1; AFIB, atrial fibrillation; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disorder; COVID-19, Novel Coronavirus Disease of 2019; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; ECMO, extracorporeal membrane oxygenation; EQUATOR, enhancing the quality and transparency of health research; GIB, gastrointestinal bleeding; IMV, invasive mechanical ventilation; LOINC, logical observation identifiers names and codes; N3C, national COVID cohort collaborative; NSAID, nonsteroidal anti-inflammatory drug; PE, pulmonary embolism; PPI, proton pump inhibitors; PUD, peptic ulcer disease; RECORD, Reporting of Studies Conducted Using Observational Routinely Collected Health Data.

Consortial contributors are in the process of being documented.

bleeding, likely representing treatment for gastrointestinal bleeding rather than a risk factor for its development. In adult patients hospitalized with COVID-19, the use of dexamethasone alone or in combination with remdesivir is negatively associated with gastrointestinal bleeding. Remdesivir monotherapy is associated with increased risk of upper gastrointestinal bleeding.

KEYWORDS
COVID-19, dexamethasone, GI bleeding, remdesivir

1 | INTRODUCTION

COVID-19 contributed to more than 1 million deaths in the United States as of June 28, 2022.[1] While the respiratory system is the most prominently affected system, other organ systems, including the gastrointestinal (GI) system, are affected. In one review, GI symptoms, including anorexia, diarrhea, nausea, hematemesis, and dysphagia, were present in 20% of patients.[2] Another observational study suggested the incidence of gastrointestinal bleeding (GIB) in hospitalized patients with COVID-19 was about 0.5%,[3] higher than the previously reported incidence of GIB in all hospitalized patients at 0.29%.[4] GIB remains a significant cause for morbidity and mortality in hospitalized patients with proton pump inhibitors (PPIs) and endoscopic hemostasis being the mainstay of treatment.[5]

Studies have identified factors that influence propensity to GIB in the hospitalized patient, including advancing age,[6] critical illness such as acute coronary syndrome or stroke,[7] past medical history of GIB,[8] liver or renal disease,[9] and tobacco or alcohol use.[8,10,11] Medications associated with GIB include antiplatelet medications, anticoagulants, nonsteroidal anti-inflammatory drugs (NSAIDs),[8,9] and corticosteroids, of which dexamethasone has emerged as a commonly used treatment for severe COVID-19.[10,12,13] Little is known about the risk of GIB with the use of novel COVID-19 therapeutics, such as remdesivir or baricitinib.

In the Adaptive COVID-19 Treatment Trial-1, remdesivir conferred shorter recovery time and reduced incidence of lower respiratory infection compared with placebo.[7] Baricitinib has traditionally been used to treat rheumatoid arthritis[14]; however, it was tested[15,16] and approved for the treatment of COVID-19 among hospitalized adults requiring supplemental oxygen, invasive mechanical ventilation (IMV), or extracorporeal membrane oxygenation (ECMO). Despite encouraging results, thrombotic events and serious infections have led to a Food and Drug Administration boxed warning for treatment with baricitinib.[15] The RECOVERY trial found that treatment with dexamethasone was found to reduce 28-day mortality among patients receiving respiratory support.[17]

Evidence suggests SARS-CoV-2 increases risk of thrombotic complications, including venous thromboembolism (VTE).[18] To reduce risk of these complications, anticoagulation of varying intensity is often used for patients hospitalized with COVID-19.[19,20] In one study, 78% of patients with COVID-19 and GIB were taking an anticoagulant.[3] Trials have studied the efficacy and safety of therapeutic dose anticoagulation compared to prophylactic dose in the treatment of COVID-19 and found that despite reducing the risk of VTE, therapeutic dosing was associated with increased bleeding events without mortality reduction.[21,22] When comparing mortality between hospitalized COVID-19 patients with and without GIB, conflicting impacts on mortality have been reported.[23]

To date, few studies have evaluated the relationship between COVID-19, GIB, and how approved (antiviral, immune modulators, and corticosteroids) and off-label (antithrombotic and NSAIDs) COVID-19 treatments influence the development of GIB. In this retrospective study, we evaluate the effect of medication exposure in hospitalized patients with COVID-19 on the development of GIB to better understand what may influence GIB in patients with COVID-19.

2 | METHODS

The National COVID Cohort Collaborative (N3C) Data Enclave is managed under the authority of the National Institutes of Health (NIH). The Data Enclave Data Access Committee approved this retrospective cohort study (DUR-8A44714). Additionally, this study received Institutional Review Board (IRB) approval from the University of Nebraska Medical Center (0506-21-EP). N3C data transfer to the National Center for Advancing Translational Sciences (NCATS) operates under the authority of the NIH IRB with Johns Hopkins University Reliance Protocol # IRB00249128 or individual site agreements with NIH. As the study used a deidentified limited data set, no informed consent was required or obtained. This study followed the Enhancing the Quality and Transparency of Health Research reporting guidelines: Reporting of Studies Conducted Using Observational Routinely Collected Health Data.[24] Data extraction and analyses were performed using Python, SQL, and R version 4.1.3 within the N3C Enclave in accordance with N3C privacy and download review policies.[25]

2.1 | N3C data enclave

The N3C Enclave has broad inclusion criteria and harmonizes data from 77 sites across the United States (See Supplemental Materials

eMethods S–2).[26] N3C collects longitudinal Electronic Health Record or Health Information Exchange data (with a lookback period to January 2018) on all persons with a positive SARS-CoV-2 polymerase chain reaction (PCR), antigen, or antibody test or a COVID-19 diagnostic code without a confirmed positive diagnostic test (with the last category accounting for approximately 20% of patients). While N3C sites are primarily tertiary care centers, they have patients from across the United States, including medically underserved populations and a proportionally representative sample of rural dwellers.[27] N3C also includes a demographically matched comparison group of SARS-CoV-2 uninfected patients. Source system SARS-CoV-2 testing protocols are mapped to standard terminologies for labs (logical observation identifiers names and codes [LOINC]) and COVID-19 conditions (ICD-10 CM and SNOMED CT) by the N3C Data Ingestion and Harmonization Workstream, which maintains a computable phenotype for defining presence of COVID-19.[28]

An overview of the ingestion and harmonization process, sampling approaches, and overall structure of the N3C Enclave, concept set definitions, and computable phenotypes utilized are provided in Supporting Information.

2.2 | Analytic cohort selection and data extraction

We included adult patients (>18 years old) with a confirmed SARS-CoV-2 lab test (PCR or antigen) or provider diagnosis hospitalized from 3 days before or up to 14 days after their first documented COVID-19 diagnosis between April 1, 2020, and June 30, 2022. Patient follow-up time was 14 days posthospital admission, censored at discharge or death. Patients with missing gender or age were excluded from the study. All patients meeting inclusion criteria were included, regardless of the severity of COVID-19 infection. A Selection Flow Diagram reflecting included and excluded patients is available in Supporting Information: Figure 1. Data from N3C's limited data set (including dates associated with clinical data) were extracted on December 15, 2022 (N3C release 104), in the Observational Medical Outcomes Partnership (OMOP) Common Data Model version 5.3.1.[29] This facilitates a minimum of 120 days for data reporting from initial COVID-19 hospitalization (cutoff June 30, 2022) through the end of the follow-up period (14 days post-COVID-19 hospitalization). All clinical concept sets were created collaboratively within the N3C Enclave, with at least one informatician and one clinical subject-matter expert reviewing each relevant concept set. Concept sets contain standardized terminology corresponding to clinical domains (e.g., LOINC, SNOMED CT, ICD-10-CM, RxNorm).

2.3 | Outcomes

The primary outcome in this study was incidence of upper or lower GIB during the first 14 days of COVID-19 hospitalization. Secondary outcomes included time to upper or lower GIB, IMV, or ECMO, and inpatient death. Lower and upper GI bleeding were identified with the OMOP standard vocabulary for conditions, SNOMED CT, parent code 87763006 and 37372002, respectively, and all of their descendants. 533 diagnoses or concepts encompassed Upper GI bleeding, and 367 encompassed lower GI bleeding. A full list of concept sets and all definitions used in this study are available in Supporting Information: eMethods S–1, and is intended to be comprehensive in diagnoses representing GI bleeding of all severities (including those that required no intervention).

2.4 | Definition of exposures

The primary study objective was to assess associations between COVID-19 therapies and incidence of GIB in hospitalized COVID-19 patients, adjusting for medications potentially modulating incidence based on a priori selection. Evaluated medications are listed in Supporting Information: eTable S–2, and include COVID-19 therapies (remdesivir, baricitinib, and dexamethasone), as well as potential modulating medications such as anticoagulants (warfarin, heparin, enoxaparin, and direct oral anticoagulants [DOACs] [apixaban, rivaroxaban, dabigatran, and edoxaban]), PPIs (omeprazole, pantoprazole, esomeprazole, or lansoprazole), H2 blockers (famotidine, ranitidine), NSAIDs (ibuprofen, naproxen, ketorolac), and antiplatelet agents (aspirin, prasugrel, clopidogrel). Patient exposure to medication events was assessed from hospital admission through the first of (1) GIB, (2) hospital discharge, (3) death, or (4) end of study period (14 days posthospitalization).

Additional control variables in our models included demographics (age, sex, and race/ethnicity), tobacco use history, COVID-19 vaccination status, and comorbid conditions of interest based on a priori assessment before hospitalization. Comorbid conditions included obesity (via body mass index (BMI) ≥ 30 or a diagnosis before hospitalization), history of peptic ulcer disease (PUD) or GIB, history of pulmonary embolism, or deep vein thrombosis (DVT), chronic kidney disease (CKD), atrial fibrillation, diabetes, congestive heart failure (CHF), chronic obstructive pulmonary disorder (COPD), and heart failure. To account for differences in treatment practices over time, we adjusted for era of hospitalization into four epochs based on vaccine availability and SARS-CoV-2 variant wave: prevaccine (before December 10, 2020, the date vaccinations became available in the United States), pre-Delta dominance (December 10, 2020 to June 14, 2021), Delta dominance (June 15, 2021 to December 21, 2021), and Omicron dominance (>December 21, 2021). Supporting Information: eMethods S–1 provides an overview of the N3C ingestion and harmonization process, study sampling approaches, concept sets, and logic used for all variables.

2.5 | Statistical analyses

Summary statistics for control variables (including demographics, smoking status, and comorbid conditions) and medication exposures

were calculated for all hospitalized COVID-19 patients and stratified by inpatient GIB occurrence. Medians and interquartile ranges (IQR) were reported for continuous measures, while frequencies and percentages within strata were reported for categorical measures. Differences in continuous measures were evaluated using Wilcoxon rank-sum tests, while comparisons of distributions of categorical measures were conducted with Pearson χ^2 tests. We assessed associations between medication exposures and GIB using univariable and multivariable logistic regression. Medication classes were evaluated individually and in combinations of COVID-19-specific therapies (dexamethasone alone, remdesivir alone, dexamethasone and remdesivir combined, and dexamethasone, remdesivir, and baricitinib combined).

Sensitivity analyses included restricting our primary analysis to only those patients with a PCR or Ag positive result during COVID-19 hospitalization, including patients with PPI usage in hospital, adjusting timing of PPI exposure to first 2 days of hospitalization, removing patients with a history of PPI usage, removing those with a history of GIB or PUD, removing vaccination history, and altering the follow-up time from 14 days to 7, 21, or 28 days (Supporting Information: eTable S–4)

All statistical analyses were conducted in R v4.1.3. The base "stats" package was used to perform Pearson's χ^2 and Wilcoxon rank sum tests. Data visualization was performed using "ggplot2."[1,30] and gGally packages.[31] $p < 0.05$ were considered statistically significant in hypothesis. All p values presented are for two-sided tests.

3 | RESULTS

Our sample included 512 467 patients hospitalized for COVID-19 during the study period. Of these eligible patients, 2279 (0.44%) experienced a GIB within 14 days of COVID-19 diagnosis. In crude bivariate analyses (Table 1), patients who developed GIB were less likely to be given any of the three primary COVID-19 treatments studied here than patients who did not develop GIB: 12% versus 22% for remdesivir ($p < 0.001$), 18% versus 37% for dexamethasone ($p < 0.001$), and 1.4% versus 2.5% for baricitinib ($p = 0.001$). Conversely, PPI medications were more likely to be given to those who developed GIB (32% vs. 25%, $p < 0.001$).

As shown in Table 1, patients with GIB were older than those without, with a median (IQR) of 64 (50–75) versus 62 (47–74), respectively. Those with GIB were also more likely to be non-Hispanic White (60% vs. 57%), less likely to be Hispanic (10% vs. 14%), and more likely to be male (56% vs. 50%). Patients with tobacco use disorder experienced GIB more frequently (11% vs. 7%), were more likely to carry all comorbidities observed (with obesity showing a nonsignificant trend toward increased risk of GIB) and were more likely to have received a primary COVID-19 vaccination (8.9% vs. 7.5% during the study period). Observed differences were large for conditions related to GIB such as history of GIB or PUD (42% vs. 6%) but were sizeable for some other conditions as well, including CKD (31% vs. 21%), CHF (20% vs. 13%), COPD (32% vs. 25%), and diabetes (35% vs. 31%). Some variation in the proportion of patients being diagnosed with GIB was noted over time, with the incidence gradually increasing across all time periods: prevaccine 0.39%, pre-Delta dominance 0.43%, Delta dominance 0.44%, and Omicron dominance 0.55%.

Severe outcomes were more common in GIB patients with 23% experiencing IMV or ECMO and 13% dying compared to only 8% and 8% for those outcomes among patients without GIB, respectively. Time to upper and lower GIB was 4 (IQR 1–7) days. Among those with GIB, 39% had a lower GIB, 49% had an upper GIB, and 13% had both lower and upper GIB.

3.1 | Univariable logistic regression for GIB in COVID-19 hospitalized patients

Univariable logistic regression models (Table 2) showed lowered odds of GIB in females relative to males (odds ratio [OR] 0.79 [95% confidence interval 0.72–0.85]), Hispanic relative to non-Hispanic Whites (OR 0.72 [0.63–0.83]), and increased odds of GIB in the Omicron period relative to the pre-Delta period (OR 1.26 [1.12–1.42]). There were protective associations between the initiation of the three COVID-specific therapies and GIB: remdesivir (OR 0.50 [0.44–0.57]), dexamethasone (OR 0.37 [0.33–0.41]), and baricitinib (OR 0.56 [0.39–0.78]). No association was observed between administration of antivitamin K medications and GIB, but all other modulating medications initiated during COVID-19 hospitalization were associated with decreased odds of GIB except for PPI, which was associated with 40% increased odds of GIB (OR 1.40 [1.28–1.53]). All observed comorbid conditions were associated with an increased odds of GIB except obesity, which showed no association with GIB. Patients with a history of GIB or PUD had a significantly increased odds of GIB (OR 10.8 [9.9–11.8]) relative to those with no documented history of GIB or PUD.

3.2 | Multivariable logistic regression for GIB in COVID-19 hospitalized patients by individual drugs or drug classes

Largely similar findings of associations between each medication and whether a patient developed GIB were observed after adjusting for demographic measures, COVID-19 period, vaccination status, and comorbid conditions, but without adjustment for multiple therapies (Table 2, full model specifications are available in Supporting Information: eTable S–1). Strong protective associations were shown in adjusted models for all COVID-19-specific therapies: remdesivir (adjusted odds ratio [aOR] 0.48 [0.42–0.54]), dexamethasone (aOR 0.35 [0.31–0.39]), and baricitinib (aOR 0.57 [0.39–0.80]). After adjustment, all GIB-modulating medications were associated with lower odds of GIB except PPIs, which had no association.

TABLE 1 Baseline characteristics of patients hospitalized with COVID-19 between April 1, 2020, and June 30, 2022.

Characteristics	Overall, *N* = 512 467	No GI bleed in hospital, *N* = 510 188	GI bleed in hospital, *N* = 2279	*p* Value[a]
Age at COVID-19 diagnosis, median (IQR)	62 (47, 74)	62 (47, 74)	64 (50, 75)	<0.001
Sex, count (%)				<0.001
Female	256 469 (50%)	255 464 (50%)	1005 (44%)	
Male	255 998 (50%)	254 724 (50%)	1274 (56%)	
Race/ethnicity, count (%)				<0.001
White non-Hispanic	292 517 (57%)	291 144 (57%)	1373 (60%)	
Black or African American non-Hispanic	96 578 (19%)	96 140 (19%)	438 (19%)	
Hispanic or Latino any race	69 738 (14%)	69 501 (14%)	237 (10%)	
Other/unknown	53 634 (10%)	53 403 (10%)	231 (10%)	
Acute COVID-19 epoch, count (%)				<0.001
Prevaccine (<December 10, 2020)	165 170 (32%)	164 530 (32%)	640 (28%)	
Pre-Delta (December 10, 2020 to June 14, 2021)	127 953 (25%)	127 398 (25%)	555 (24%)	
Delta (June 15, 2021 to December 21, 2021)	111 931 (22%)	111 434 (22%)	497 (22%)	
Omicron (>December 21, 2021)	107 413 (21%)	106 826 (21%)	587 (26%)	
Comorbidities, count (%)				
Documented history of smoking	34 713 (6.8%)	34 461 (6.8%)	252 (11%)	<0.001
Obesity	221 401 (43%)	220 398 (43%)	1003 (44%)	0.4
History of GI bleed or peptic ulcer	32 874 (6.4%)	31 919 (6.3%)	955 (42%)	<0.001
Pulmonary embolism or DVT	32 903 (6.4%)	32 664 (6.4%)	239 (10%)	<0.001
Atrial fibrillation	69 922 (14%)	69 495 (14%)	427 (19%)	<0.001
Heart failure	68 976 (13%)	68 530 (13%)	446 (20%)	<0.001
COPD	129 906 (25%)	129 186 (25%)	720 (32%)	<0.001
Chronic kidney disease	106 683 (21%)	105 983 (21%)	700 (31%)	<0.001
Diabetes (with and without complications)	156 969 (31%)	156 175 (31%)	794 (35%)	<0.001
Cancer (any malignancy except skin)	62 671 (12%)	62 276 (12%)	395 (17%)	<0.001
COVID-19 vaccination before infection, count (%)	38 477 (7.5%)	38 274 (7.5%)	203 (8.9%)	0.012
Medication exposure during COVID-19 hospitalization, count (%)				
Remdesivir	110 466 (22%)	110 190 (22%)	276 (12%)	<0.001
Dexamethasone	189 971 (37%)	189 564 (37%)	407 (18%)	<0.001
Baricitinib	12 616 (2.5%)	12 584 (2.5%)	32 (1.4%)	0.001
Antiplatelet medications	92 426 (18%)	92 206 (18%)	220 (9.7%)	<0.001
Antivitamin K medications	10 733 (2.1%)	10 693 (2.1%)	40 (1.8%)	0.3
Injectable anticoagulants	306 662 (60%)	306 024 (60%)	638 (28%)	<0.001
Direct-acting oral anticoagulants	48 160 (9.4%)	48 062 (9.4%)	98 (4.3%)	<0.001
NSAIDs	68 616 (13%)	68 523 (13%)	93 (4.1%)	<0.001
H2 blockers	73 668 (14%)	73 515 (14%)	153 (6.7%)	<0.001
PPIs	128 886 (25%)	128 158 (25%)	728 (32%)	<0.001

(Continues)

TABLE 1 (Continued)

Characteristics	Overall, *N* = 512 467	No GI bleed in hospital, *N* = 510 188	GI bleed in hospital, *N* = 2279	*p* Value[a]
Outcomes				
Time to GI bleed, median (IQR)	4 (1, 7)	N/A	4 (1, 7)	
Lower GI bleed, count (%)	1173 (51%)	N/A	1173 (51%)	
Time to lower GI bleed, median (IQR)	4 (1, 7)	N/A	4 (1, 7)	
Upper GI bleed, count (%)	1392 (61%)	N/A	1392 (61%)	
Time to lower GI bleed, median (IQR)	4 (1, 7)	N/A	4 (1, 7)	
IMV or ECMO, count (%)	44 860 (8.8%)	44 338 (8.7%)	522 (23%)	<0.001
Death in hospital, count (%)	42 579 (8.3%)	42 283 (8.3%)	296 (13%)	<0.001

Abbreviations: COPD, chronic obstructive pulmonary disorder; DVT, deep vein thrombosis; ECMO, extracorporeal membrane oxygenation; GI, gastrointestinal; IMV, invasive mechanical ventilation; IQR, interquartile range; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor.
[a]Wilcoxon rank sum test; Pearson's χ^2 test.

3.3 | Multivariable logistic regression for GIB in COVID-19 hospitalized patients by combined drugs and drug classes

The results of a multivariable logistic regression which includes all drug and drug classes as well as demographic and comorbidity measures in a single model are shown in Table 3. Among COVID-19 therapies, remdesivir and baricitinib showed no association with GIB, while dexamethasone was protective (aOR 0.67 [0.58–0.76]). Among GIB-modulating medications, use of antivitamin K medications showed no association with GIB, while antiplatelet (aOR 0.74 [0.64–0.86]), injectable anticoagulants (aOR 0.30 [0.26–0.33]), DOACs (aOR 0.77 [0.62–0.96]), NSAIDs (aOR 0.44 [0.26–0.33]), and H2 blockers (aOR 0.82 [0.69–0.97]) demonstrated decreased risk of developing GIB. When independently analyzed, similar results were observed in both upper and lower GIB (Table 3 & Figure 1), apart from remdesivir, which showed minor increased odds of upper GIB (aOR 1.25 [1.04–1.51]) but no association with lower GIB. History of smoking (aOR 1.43 [1.20–1.69]) and CKD (aOR 1.32 [1.15–1.51]) were associated with higher odds of upper GIB, while no association was observed for lower GIB.

To assess interactions between COVID-19 therapies, we performed multilevel multivariable logistic regression using dexamethasone or remdesivir alone, in combination, or in a triple treatment with baricitinib, compared against a reference of no COVID-19 specific medication (Supporting Information: eTable S–3). In this model, dexamethasone alone (aOR 0.69 [0.53–0.88]), remdesivir alone (0.55 [0.47–0.64]), and combined dexamethasone and remdesivir (aOR 0.83 [0.70–0.98]) were protective against GIB while dexamethasone, remdesivir, and baricitinib combined showed no significant associations with GIB.

3.4 | Sensitivity analyses

To assess model robustness, we performed several sensitivity analyses (Supporting Information: eTable S–4). Because of concern over the inability to disentangle prophylactic versus therapeutic PPI use, we excluded PPI from the main models. In models including all drug classes, including PPI, adjusted for background differences, PPI usage was associated with increased odds of GIB when administered before the date GIB was first documented (aOR 2.26 [2.02–2.52]; Supporting Information: eTable S–4, SA–1) or when PPI was administered only in the first 2 days of hospitalization (aOR 1.92 [1.72–2.15]; Supporting Information: eTable S–4, SA–2). Other drug point estimates were similar when adjusting for PPI utilization, although the protective effect of remdesivir and baricitinib was no longer present in either model.

We also evaluated the role of exposures by removing patients with a history of GIB or PUD (Supporting Information: eTable S–4, SA–3), with a history of PPI usage (Supporting Information: eTable S–4, SA–4), or with both a history of PPI usage and GIB or PUD (Supporting Information: eTable S–4, SA–5). The main findings were consistent, although SA3-5 removed the protective effect documented for remdesivir, baricitinib, and H2 blockers. Because COVID-19 vaccinations were not present throughout the entire study period and many vaccination events were inconsistently documented when not administered in N3C participating sites, we removed vaccination history (Supporting Information: eTable S–4, SA–6) and found similar findings. We also modified the follow-up period from 14 days to 7 days (Supporting Information: eTable S–4 SA–7), 21 days (Supporting Information: eTable S–4, SA–8), and 28 days (Supporting Information: eTable S–4, SA–9) to assess differences in GIB development for those with shorter or longer lengths of stay. The protective effect of dexamethasone attenuated as the duration of follow-up period lengthened from 14 days (aOR 0.67 [0.58–0.76]) to 21 days (aOR 0.73 [0.64]) and 28 days (aOR 0.76 [0.67–0.85]), while a 7-day follow-up had slightly lower odds of GIB compared to 14 days (aOR 0.61 [0.53–0.71]).

To assess for potential misclassification of patients with incidental or previous SARS-CoV-2, we performed a sensitivity analysis (Table 4) to assess model robustness for lower, upper, and

TABLE 2 Logistic regression models for GIB by targeted therapies in adults hospitalized with COVID-19, April 1, 2020 to June 30, 2022.

Variable	Unadjusted odds ratio (95% confidence interval)	*p* Value	Adjusted odds ratio (95% confidence interval)	*p* Value
Age at COVID-19 diagnosis	1.00 (1.00, 1.01)	<0.001	[a]	[a]
Sex				
Male	Reference		[a]	[a]
Female	0.79 (0.72, 0.85)	<0.001	[a]	[a]
Race/ethnicity				
White non-Hispanic	Reference		[a]	[a]
Black or African American non-Hispanic	0.97 (0.87, 1.07)	0.5	[a]	[a]
Hispanic or Latino any race	0.72 (0.63, 0.83)	<0.001	[a]	[a]
Other/unknown	0.92 (0.80, 1.05)	0.2	[a]	[a]
Acute COVID-19 epoch				
Prevaccine (<December 10, 2020)	0.89 (0.80, 1.00)	0.051	[a]	[a]
Pre-Delta (December 10, 2020 to June 14, 2021)	Reference		[a]	[a]
Delta (June 15, 2021 to December 21, 2021)	1.02 (0.91, 1.16)	0.7	[a]	[a]
Omicron (>December 21, 2021)	1.26 (1.12, 1.42)	<0.001	[a]	[a]
Comorbidities				
Documented history of smoking	1.72 (1.50, 1.95)	<0.001	[a]	[a]
Obesity	1.03 (0.95, 1.12)	0.4	[a]	[a]
History of GI bleed or peptic ulcer	10.8 (9.94, 11.8)	<0.001	[a]	[a]
Pulmonary embolism or DVT	1.71 (1.49, 1.95)	<0.001	[a]	[a]
Atrial fibrillation	1.46 (1.31, 1.62)	<0.001	[a]	[a]
Heart failure	1.57 (1.41, 1.74)	<0.001	[a]	[a]
Chronic obstructive pulmonary disorder	1.37 (1.25, 1.50)	<0.001	[a]	[a]
Chronic kidney disease	1.36 (1.25, 1.49)	<0.001	[a]	[a]
Diabetes (with and without complications)	1.69 (1.55, 1.85)	<0.001	[a]	[a]
Cancer (any malignancy except skin)	1.21 (1.11, 1.32)	<0.001	[a]	[a]
COVID-19 vaccination before infection	1.21 (1.04, 1.39)	0.011	[a]	[a]
Medication Exposure During COVID-19 hospitalization				
Remdesivir	0.50 (0.44, 0.57)	<0.001	0.48 (0.42, 0.54)	<0.001
Dexamethasone	0.37 (0.33, 0.41)	<0.001	0.35 (0.31, 0.39)	<0.001
Baricitinib	0.56 (0.39, 0.78)	0.001	0.57 (0.39, 0.80)	0.002
Antiplatelet medications	0.48 (0.42, 0.56)	<0.001	0.40 (0.35, 0.46)	<0.001
Antivitamin K medications	0.83 (0.60, 1.12)	0.3	0.62 (0.45, 0.85)	0.004
Injectable anticoagulants	0.26 (0.24, 0.28)	<0.001	0.22 (0.20, 0.24)	<0.001
Direct-acting oral anticoagulants	0.43 (0.35, 0.53)	<0.001	0.35 (0.29, 0.43)	<0.001
NSAIDs	0.27 (0.22, 0.34)	<0.001	0.31 (0.25, 0.38)	<0.001
H2 blockers	0.43 (0.36, 0.50)	<0.001	0.43 (0.36, 0.50)	<0.001
Proton pump inhibitors	1.40 (1.28, 1.53)	<0.001	0.92 (0.84, 1.01)	0.082

Abbreviations: DVT, deep vein thrombosis; GI, gastrointestinal; IGIB, gastrointestinal bleeding; NSAID, nonsteroidal anti-inflammatory drug.

[a]Each multivariable model in Table 2 contains 1 drug/drug class and all demographic/comorbidity measures. Full model specifications for each drug/drug class are available in Supporting Information: eTable S–1.

TABLE 3 Logistic regression models for lower and upper GI bleed by combined therapies in adults hospitalized with COVID-19, April 1, 2020 to June 30, 2022.

Variable	Lower GI bleed adjusted odds ratios (95% confidence interval)	*p* Value	Upper GI bleed adjusted odds ratios (95% confidence interval)	*p* Value	Upper or lower GI bleed adjusted odds ratios (95% confidence interval)	*p* Value
Age at COVID-19 diagnosis	1.01 (1.01, 1.01)	<0.001	1.00 (0.99, 1.00)	0.048	1.00 (1.00, 1.00)	0.5
Sex						
Male	Reference		Reference		Reference	
Female	0.80 (0.71, 0.90)	<0.001	0.70 (0.63, 0.78)	<0.001	0.76 (0.70, 0.83)	<0.001
Race/ethnicity						
White non-Hispanic	Reference		Reference		Reference	
Black or African American non-Hispanic	0.93 (0.79, 1.09)	0.4	0.99 (0.86, 1.15)	>0.9	1.01 (0.90, 1.13)	0.8
Hispanic or Latino any race	0.82 (0.67, 1.00)	0.055	0.80 (0.66, 0.96)	0.016	0.85 (0.73, 0.98)	0.023
Other/unknown	0.90 (0.73, 1.10)	0.3	0.97 (0.81, 1.16)	0.8	0.97 (0.84, 1.12)	0.7
Acute COVID-19 epoch						
Prevaccine (<December 10, 2020)	0.87 (0.74, 1.02)	0.095	0.86 (0.74, 1.00)	0.05	0.89 (0.79, 1.00)	0.048
Pre-Delta (December 10, 2020 to June 14, 2021)	Reference		Reference		Reference	
Delta (June 15, 2021 to December 21, 2021)	1.03 (0.86, 1.22)	0.8	1.02 (0.87, 1.20)	0.8	1.04 (0.91, 1.18)	0.6
Omicron (>December 21, 2021)	1.08 (0.91, 1.28)	0.4	1.10 (0.94, 1.29)	0.2	1.07 (0.94, 1.21)	0.3
Comorbidities						
Documented history of smoking	1.15 (0.94, 1.40)	0.2	1.43 (1.20, 1.69)	<0.001	1.28 (1.11, 1.46)	<0.001
Obesity	1.40 (1.23, 1.59)	<0.001	1.19 (1.05, 1.33)	0.004	1.27 (1.16, 1.39)	<0.001
History of GI bleed or peptic ulcer	10.1 (8.92, 11.5)	<0.001	9.88 (8.78, 11.1)	<0.001	10.2 (9.32, 11.2)	<0.001
Pulmonary embolism or DVT	1.17 (0.96, 1.42)	0.12	1.15 (0.95, 1.39)	0.15	1.13 (0.97, 1.31)	0.11
Atrial fibrillation	1.04 (0.88, 1.23)	0.6	0.97 (0.83, 1.15)	0.8	1.03 (0.91, 1.17)	0.6
Heart failure	1.03 (0.86, 1.22)	0.8	0.90 (0.76, 1.06)	0.2	0.97 (0.85, 1.10)	0.6
Chronic obstructive pulmonary disorder	1.11 (0.97, 1.28)	0.13	0.89 (0.78, 1.02)	0.091	0.99 (0.89, 1.09)	0.8
Chronic kidney disease	1.06 (0.91, 1.23)	0.5	1.32 (1.15, 1.51)	<0.001	1.20 (1.08, 1.34)	<0.001

TABLE 3 (Continued)

Variable	Lower GI bleed adjusted odds ratios (95% confidence interval)	*p* Value	Upper GI bleed adjusted odds ratios (95% confidence interval)	*p* Value	Upper or lower GI bleed adjusted odds ratios (95% confidence interval)	*p* Value
Diabetes (with and without complications)	0.87 (0.76, 0.99)	0.042	1.11 (0.99, 1.26)	0.082	0.97 (0.88, 1.07)	0.5
Cancer (any malignancy except skin)	1.11 (0.95, 1.29)	0.2	0.99 (0.85, 1.15)	0.9	1.05 (0.93, 1.17)	0.4
Primary vaccination before infection	0.81 (0.66, 0.99)	0.048	0.63 (0.51, 0.78)	<0.001	0.74 (0.64, 0.87)	<0.001
Medication exposure during COVID-19 hospitalization						
Remdesivir	0.96 (0.78, 1.18)	0.7	1.25 (1.04, 1.51)	0.017	1.09 (0.94, 1.26)	0.2
Dexamethasone	0.62 (0.52, 0.74)	<0.001	0.68 (0.58, 0.81)	<0.001	0.67 (0.58, 0.76)	<0.001
Baricitinib	0.77 (0.40, 1.35)	0.4	1.47 (0.95, 2.18)	0.068	1.16 (0.79, 1.65)	0.4
Antiplatelet medications	0.72 (0.59, 0.88)	0.002	0.77 (0.63, 0.93)	0.009	0.74 (0.64, 0.86)	<0.001
Antivitamin K medications	1.00 (0.62, 1.53)	>0.9	1.33 (0.85, 1.98)	0.2	1.16 (0.83, 1.60)	0.4
Injectable anticoagulants	0.36 (0.30, 0.42)	<0.001	0.25 (0.21, 0.29)	<0.001	0.30 (0.26, 0.33)	<0.001
Direct-acting oral anticoagulants	0.75 (0.56, 1.00)	0.055	0.77 (0.57, 1.03)	0.092	0.77 (0.62, 0.96)	0.024
NSAIDs	0.54 (0.40, 0.72)	<0.001	0.39 (0.29, 0.52)	<0.001	0.44 (0.35, 0.54)	<0.001
H2 blockers	0.71 (0.55, 0.90)	0.007	0.85 (0.67, 1.05)	0.14	0.82 (0.69, 0.97)	0.022

Abbreviations: DVT, deep vein thrombosis; GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug.

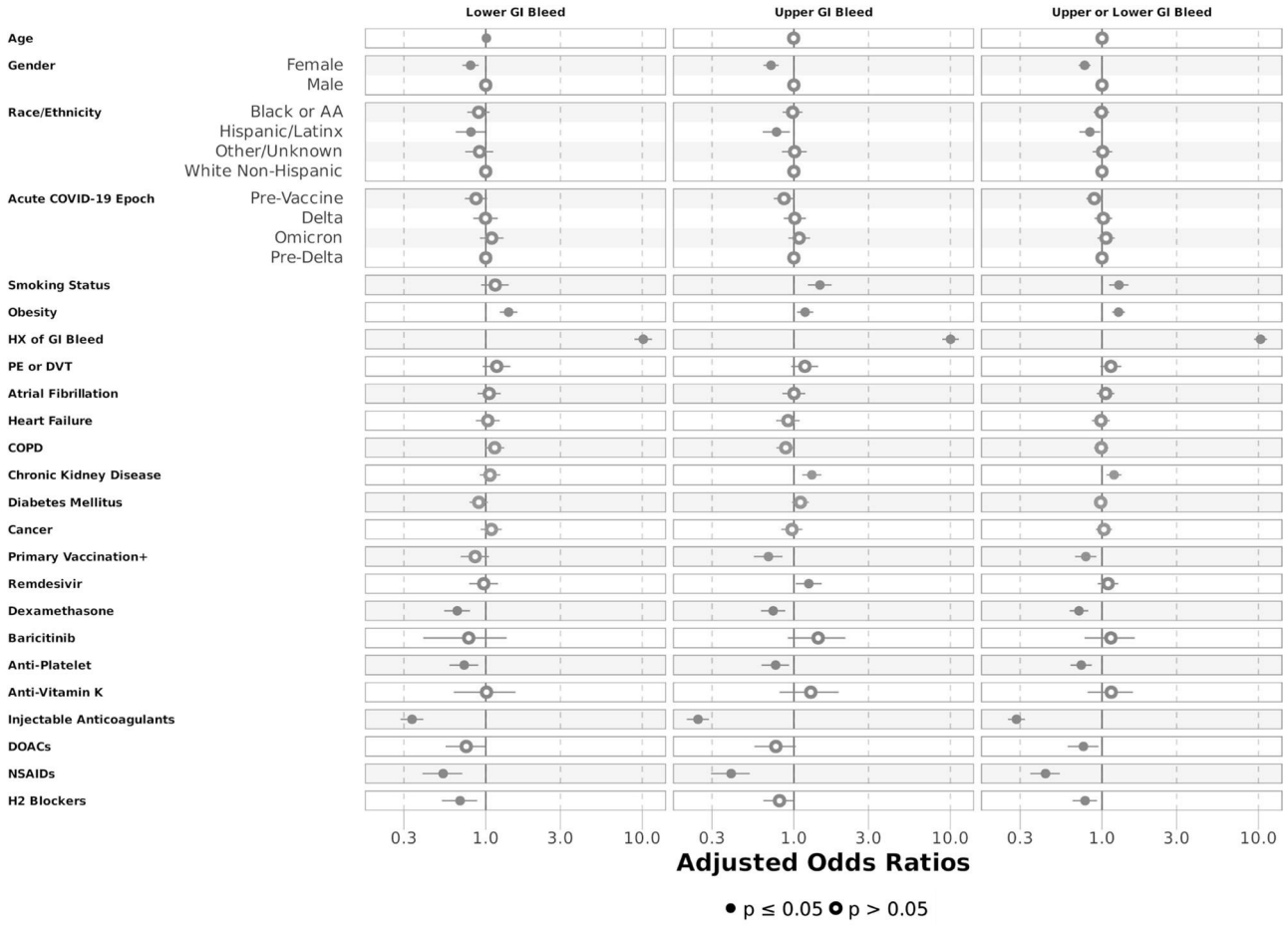

FIGURE 1 Multivariable logistic regression for lower gastrointestinal (GI) bleed, upper GI bleed, and combined upper or lower GI bleed during COVID-19 hospitalization. Covariate and outcome definitions are defined in detail in Supporting Information: eMethods S–1.

combined GIB findings, excluding patients with a purely clinical diagnosis of COVID-19 (i.e., without a confirmatory positive PCR or Ag test during hospitalization). In this cohort, no association was observed between baricitinib or remdesivir and lower, upper, or combined GIB but dexamethasone was again associated with lower odds of lower (aOR 0.71 [0.58–0.86]), upper (aOR 0.83 [0.68–0.99]), and combined GIB (aOR 0.67 [0.58–0.76]). Findings for other drugs were similar.

4 | DISCUSSION

In this retrospective analysis, we used the N3C database and concept sets reflecting upper and lower GI bleeding to evaluate the association of patient demographics, comorbidities, and selected medications commonly used to treat patients hospitalized with COVID-19 with the development of GIB within 14 days of initial encounter. Overall, our study found that 0.44% of patients admitted to the hospital with COVID-19 developed GIB, which is comparable to other studies involving COVID-19 patients.[3] and higher than prior studies indicate the incidence of GIB is in all hospitalized patients.[4] Development of GIB was associated with worse outcomes.

Demographics and common comorbidities of patients hospitalized with COVID-19 were analyzed for association with GIB (Table 3). Patients with significantly higher risk of GIB included those with obesity (aOR 1.27), PUD (aOR = 10.2), CKD (aOR = 1.20), and patients with tobacco use disorder (aOR = 1.28). Obesity, CKD, and tobacco use disorder have been described as a risk factor for developing severe COVID-19 infection, potentially explaining some of these findings. Women (aOR = 0.76), patients vaccinated against COVID-19 (aOR = 0.74), and Latinx patients (aOR = 0.85) were observed to have a significantly lower risk of GIB. This finding is beyond the scope of this paper and deserves further investigation.

Medication analysis found numerous significant associations with in-hospital combined upper and lower GIB. Upon univariable analysis with GIB (Table 2), PPIs carried an unadjusted OR = 1.40, however, this association does not persist upon multivariate analysis (aOR 0.92). Medications with negative association with in-hospital GIB (Table 3) included dexamethasone (aOR 0.67), antiplatelet medications (aOR 0.74), injectable anticoagulants (aOR 0.30), DOACs (aOR 0.77), NSAIDs (aOR 0.44), and H2 Blockers (aOR 0.82). Notably, DVT prophylactic doses of heparin or enoxaparin are included in the injectable anticoagulant group. Provider's estimation of risk of bleeding and indication for anticoagulation influence which

TABLE 4 Logistic regression models for lower, upper GI bleed, and combined GI bleed by targeted therapies in adults hospitalized with COVID-19 with a PCR or lab Ag-positive, April 1, 2020 to June 30, 2022.

Variable	Lower GI bleed adjusted odds ratios (95% confidence interval)	*p* Value	Upper GI bleed adjusted odds ratios (95% confidence interval)	*p* Value	Combined GI bleed adjusted odds ratios (95% confidence interval)	*p* Value
Age at COVID-19 diagnosis	1.01 (1.01, 1.01)	<0.001	1.00 (0.99, 1.00)	0.2	1.00 (1.00, 1.00)	0.5
Sex						
Male	Reference		Reference		Reference	
Female	0.83 (0.73, 0.95)	0.006	0.70 (0.62, 0.79)	<0.001	0.76 (0.70, 0.83)	<0.001
Race/ethnicity						
White non-Hispanic	Reference		Reference		Reference	
Black or African American non-Hispanic	0.94 (0.79, 1.12)	0.5	1.01 (0.86, 1.18)	0.9	1.01 (0.90, 1.13)	0.8
Hispanic or Latino any race	0.85 (0.67, 1.06)	0.2	0.84 (0.68, 1.03)	0.11	0.85 (0.73, 0.98)	0.023
Other/unknown	0.83 (0.65, 1.06)	0.14	0.95 (0.76, 1.17)	0.6	0.97 (0.84, 1.12)	0.7
COVID-19 epoch						
Prevaccine (<December 10, 2020)	0.92 (0.77, 1.11)	0.4	0.82 (0.69, 0.97)	0.022	0.89 (0.79, 1.00)	0.048
Pre-Delta (December 10, 2020 to June 14, 2021)	Reference		Reference		Reference	
Delta (June 15, 2021 to December. 21, 2021)	0.95 (0.77, 1.15)	0.6	0.98 (0.82, 1.18)	0.9	1.04 (0.91, 1.18)	0.6
Omicron (>December 21, 2021)	1.06 (0.88, 1.29)	0.5	1.03 (0.86, 1.23)	0.7	1.07 (0.94, 1.21)	0.3
Comorbidities						
Documented history of smoking	1.17 (0.93, 1.45)	0.2	1.54 (1.27, 1.85)	<0.001	1.28 (1.11, 1.46)	<0.001
Obesity	1.44 (1.25, 1.66)	<0.001	1.27 (1.11, 1.45)	<0.001	1.27 (1.16, 1.39)	<0.001
History of GI bleed or peptic ulcer	9.76 (8.46, 11.2)	<0.001	8.46 (7.39, 9.67)	<0.001	10.2 (9.32, 11.2)	<0.001
Pulmonary embolism or deep vein thrombosis	1.21 (0.97, 1.51)	0.09	1.05 (0.83, 1.31)	0.7	1.13 (0.97, 1.31)	0.11
Atrial fibrillation	1.06 (0.88, 1.27)	0.6	0.97 (0.81, 1.17)	0.8	1.03 (0.91, 1.17)	0.6
Heart failure	0.96 (0.79, 1.16)	0.7	0.85 (0.70, 1.03)	0.1	0.97 (0.85, 1.10)	0.6
Chronic obstructive pulmonary disorder	1.16 (0.99, 1.35)	0.06	0.88 (0.76, 1.02)	0.1	0.99 (0.89, 1.09)	0.8

(Continues)

TABLE 4 (Continued)

Variable	Lower GI bleed adjusted odds ratios (95% confidence interval)	*p* Value	Upper GI bleed adjusted odds ratios (95% confidence interval)	*p* Value	Combined GI bleed adjusted odds ratios (95% confidence interval)	*p* Value
Chronic kidney disease	1.06 (0.90, 1.25)	0.5	1.44 (1.24, 1.68)	<0.001	1.20 (1.08, 1.34)	<0.001
Diabetes (with and without complications)	0.87 (0.75, 1.01)	0.065	1.12 (0.98, 1.28)	0.11	0.97 (0.88, 1.07)	0.5
Cancer (any malignancy except skin)	1.16 (0.98, 1.37)	0.083	1.07 (0.91, 1.27)	0.4	1.05 (0.93, 1.17)	0.4
COVID-19 vaccination before infection	0.82 (0.65, 1.02)	0.086	0.67 (0.53, 0.83)	<0.001	0.74 (0.64, 0.87)	<0.001
Medication exposure during COVID-19 hospitalization						
Remdesivir	0.95 (0.76, 1.19)	0.7	1.25 (1.02, 1.52)	0.028	1.09 (0.94, 1.26)	0.2
Dexamethasone	0.71 (0.58, 0.86)	<0.001	0.83 (0.68, 0.99)	0.043	0.67 (0.58, 0.76)	<0.001
Baricitinib	0.94 (0.48, 1.64)	0.8	1.48 (0.92, 2.25)	0.083	1.16 (0.79, 1.65)	0.4
Antiplatelet medications	0.75 (0.59, 0.93)	0.011	0.76 (0.61, 0.94)	0.014	0.74 (0.64, 0.86)	<0.001
Antivitamin K medications	1.11 (0.67, 1.74)	0.7	1.55 (0.96, 2.36)	0.055	1.16 (0.83, 1.60)	0.4
Injectable anticoagulants	0.34 (0.28, 0.41)	<0.001	0.23 (0.20, 0.28)	<0.001	0.30 (0.26, 0.33)	<0.001
Direct-acting oral anticoagulants	0.77 (0.56, 1.05)	0.11	0.76 (0.54, 1.05)	0.11	0.77 (0.62, 0.96)	0.024
NSAIDs	0.61 (0.44, 0.83)	0.002	0.43 (0.31, 0.58)	<0.001	0.44 (0.35, 0.54)	<0.001
H2 blockers	0.72 (0.55, 0.94)	0.021	0.94 (0.73, 1.18)	0.6	0.82 (0.69, 0.97)	0.022

Abbreviations: GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug; PCR, polymerase chain reaction.

medications are administered, with discriminate use of all types of anticoagulants in those who were at high risk of GIB, confounding the interpretation of any observed association.

Despite corticosteroids being associated with increased risk of GIB in hospitalized patients in general,[7] dexamethasone alone or in combination with remdesivir for treatment of COVID-19 in hospitalized patients was associated with significantly lower risk of combined upper and lower GIB (Table 3). This finding may be secondary to reduction in COVID-19-associated cytokine storm. Remdesivir is associated with upper GIB (aOR 1.25). The combination of remdesivir, dexamethasone, and baricitinib has a nonsignificant association with combined GIB (aOR = 1.25, Supporting Information: eTable S–3). Further study is justified to investigate underlying mechanisms of these findings.

As PPIs are used for treatment of acute GIB, chronic conditions including Gastroesophageal Reflux Disease and Barrett esophagus, as well as stress ulcer bleeding prophylaxis in the intensive care unit setting, sensitivity analyses were performed (Supporting Information: eTable S–4). Adjusted ORs of developing GIB were calculated by restricting the PPI usage variable to those who received PPIs within the first 2 days of hospitalization and excluding patients with a history of GIB or outpatient use of PPI. As anticipated, PPIs were more likely to be given to patients who developed GIB. The association between PPI and GIB is likely confounded by indication (i.e., continuation of chronic acid reduction regimen, prophylaxis in hospitalized patients, and treatment of acute GIB), and the predilection to GIB for patients who are chronically treated with PPI (including patients with chronic gastritis or PUD). We do not suspect a biological mechanism exposing hospitalized patients who are exposed to PPI to increased risk of GIB, rather our finding likely represents patients who developed acute GIB and were started on PPIs for treatment. H2 blockers (famotidine and ranitidine) were not associated with increased OR of GIB, potentially because first-line treatment of acute GIB is administration of a PPI rather than H2 blockers.

Limitations of this study include its retrospective nature; thus, no causal relationship can be determined, and correlations are prone to complex interactions. It is likely that some GI bleeding was not diagnosed (particularly very mild bleeding), and thus not represented in our data. Further limitation includes inconsistently available data, such as insurance status, demographic information, chronicity of diagnoses (e.g., PUD), comorbidities (e.g., BMI was documented in 60% of patients), dose and route of drug administration (improved documentation of intravenous vs. oral PPI administration could clarify correlation of PPIs and GIB in this study).

5 | CONCLUSION

In conclusion, for patients hospitalized with COVID-19, the use dexamethasone alone or in combination with remdesivir is associated with decreased risk of combined upper and lower GIB within 14 days of an admission. Remdesivir monotherapy is associated with an increased risk of upper GIB. Patients hospitalized with COVID-19 at higher risk of GIB include older patients, males, patients with obesity, PUD, CKD, and tobacco use disorder. Vaccinated and Hispanic patients appear less predisposed to GIB while hospitalized with COVID-19.

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Concept and design: Noah A. Wiedel, James McClay, Alexander Hewlett, Jin Ge, and Alfred Jerrod Anzalone. *Acquisition, analysis, or interpretation of data*: Alfred Jerrod Anzalone and Harlan Sayles. *Drafting of the manuscript*: Noah A. Wiedel, Jessica Larson, and Alfred Jerrod Anzalone. *Critical revision of the manuscript for important intellectual content*: All authors. *Administrative, technical, editorial, or material support*: Jana L. Wardian and Alfred Jerrod Anzalone. *Supervision*: Noah A. Wiedel.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

All diagnostic, medication, procedure, and laboratory concepts used in this study are available in Supporting Information: eMethods S–1. Raw code (R, SQL) is available upon request. N3C is a public resource maintained by NCATS to support COVID-19 research. To access patient-level data from the N3C consortium, institutions must have a signed Data Use Agreement executed with NCATS and investigators must complete mandatory training along with submitting a Data Use Request to N3C. Investigators can request access to the Enclave here (https://covid.cd2h.org/onboarding).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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