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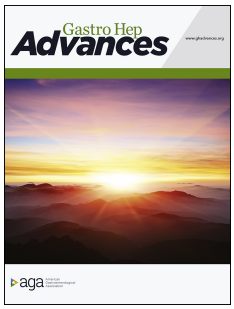

Clinical and Endoscopic Outcomes in COVID-19 Patients with Gastrointestinal Bleeding

Hassan Ashktorab, Tiziano Russo, Gholamreza Oskrochi, Giovanni Latella, Sara Massironi, Martina Luca, Lakshmi G. Chirumamilla, Adeyinka O. Laiyemo, Hassan Brim

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Clinical and Endoscopic Outcomes in COVID-19 Patients with Gastrointestinal Bleeding

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Abstract

Background & Aims: Over 404 million people worldwide have been infected with COVID-19, 145 million in the United States (77 million) and Europe (151 million) alone (as of Feb. 10th, 2022). This paper aims to analyze data from studies reporting Gastrointestinal bleeding (GIB) and/or endoscopic findings in COVID-19 patients in Western countries.

Methods: We conducted a systematic review of articles on confirmed COVID-19 cases with GIB in Western countries published in PubMed and Google Scholar databases from June 20th, 2020, to July 10th, 2021.

Results: A total of 12 studies reporting GIB and/or endoscopic findings in 808 COVID-19 patients in Western countries were collected and analyzed. Outcomes and comorbidities were compared with 18,179 non-GIB COVID-19 patients from Italy and the United States. As per our study findings the overall incidence of GIB in COVID-19 patients was found to be 0.06%. When compared to non-GIB cohort, death rate was significantly high in COVID-19 patients with GIB (16.4% vs. 25.4%, $p<0.001$, respectively). Endoscopic treatment was rarely necessary, and blood transfusion was the most common GIB treatment. Most common presentation in GIB patients is melena (n=117, 47.5%). Peptic, esophageal, and rectal ulcers were the most common endoscopic findings in upper (48.4%) and lower endoscopies (36.4%), respectively. The GIB cohort had worse outcomes and higher incidence of hypertension (61.1%), liver disease (11.2%), and cancer (13.6%) when compared with non-GIB cohort. Death was strongly associated with hypertension ($p<0.001$, $r=0.814$), hematochezia ($p<0.001$, $r=0.646$) and EGD ($p<0.001$, $r=0.591$) in COVID-19 patients with GIB.

Conclusion: Overall, the incidence of GIB in COVID-19 patients is similar to that estimated in the overall population with melena being the most common presentation. The common endoscopic

findings in GIB COVID-19 patients were ulcers, esophagitis, gastritis, and colitis. Patients with GIB were more prone to death than non-GIB COVID-19 patients.

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Introduction

SARS-CoV-2 virus has infected over 404 million people worldwide, many of them developed the coronavirus disease-2019 (COVID-19) [1]. SARS-CoV-2 associates with a wide variety of manifestations, partly because there are several variants in the world due to mutations but also because of geographic and population's specificities and differences. The most common COVID-19 symptoms are fever, cough, dyspnea, sore throat, rhinorrhea, anosmia, dysgeusia, fatigue, and myalgia [2]. However, gastrointestinal (GI) symptoms (nausea, diarrhea, vomiting, abdominal pain, and anorexia) are also commonly reported [2, 3]. A specific GI manifestation that has been identified in 3-12% of COVID-19 patients is gastrointestinal bleeding (GIB) [4-6].

Coagulopathy is a major concern in COVID-19 patients[7]. Endothelial dysfunction and hypercoagulability are likely associated with a strong immune response of the host towards the virus, which generates a cytokine storm and subsequent complications[7]. Therefore, anti-coagulants and thromboprophylaxis are frequently used in the treatment of COVID-19. Coagulopathies, adoption of anti-coagulant therapies, and other viral effects make COVID-19 patients more prone to develop gastrointestinal bleeding [6]. In particular, the virus is thought to cause both direct and indirect damage, via a "double-hit" mechanism [8]. Direct damage refers to the GI mucosal injury with consequent immune response and inflammation, and indirect damage is the subsequent hypoxic stress that stems from coagulopathy [9]. Little is known about the underlying conditions that increase the risk of developing GIB.

In normal circumstances, it is recommended that patients developing upper GI bleeding (UGIB) undergo endoscopy within 24 hours from presentation [9]. However, the COVID-19 pandemic has led to several changes in the allocation of resources and performance of such procedures, both to free health care providers to deal with patients infected by the virus and to

limit the risk of infection in health care facilities. A study from Northern Italy reported that most of the endoscopic procedures that were supposed to take place in March 2020 were either postponed or cancelled [10]. Another study from central Italy reported similar findings, with the number of patients admitted for urgent upper endoscopy in March-May 2020 dropping 50% from the same period pre-lockdown [11]. Finally, a nation-wide Italian study showed a statistically significant decrease in upper and lower endoscopies during the COVID-19 pandemic, mainly due to patients avoiding exposure to the virus in hospital settings [12]. Consequently, post-UGIB endoscopy survival was shown to be reduced during the COVID-19 pandemic [13].

In this review, we analyze and discuss the results of studies including mainly patients from western countries that report GIB and endoscopic findings in COVID-19 patients. We report the current consensus and available information on different types of treatments, and investigate the differences in underlying conditions and outcomes between COVID-19 patients with and without GIB.

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Methods

Search strategy and selection criteria: We conducted a systematic literature search of published articles using PubMed and Google Scholar databases from June 20th, 2020, to July 10th, 2021. We used the following search words: COVID-19, COVID-19 GI bleeding, hematemesis, hematochezia, melena COVID-19 gastrointestinal bleeding, COVID-19 endoscopic findings, COVID-19 endoscopy, COVID-19 clinical characteristics, COVID-19 comorbidities, COVID-19 underlying conditions, COVID-19 outcome, COVID-19 Italy, COVID-19 Unites States. The protocol of this systematic review and analysis for COVID-19 patients' data is in accordance with the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) guidelines [14].

Selection and identification of relevant literature: Using the listed inclusion and exclusion criteria, we first sorted the GI bleeding and endoscopy COVID-19 studies by title and abstract; then we compiled the papers by relevance and conducted a new selection process by a thorough review of the data (Fig. 1). We incorporated studies that reported GI bleeding and/or endoscopic findings in COVID-19 patients. Then we selected articles on non-GIB COVID-19 patients from Italy and the United States for comparison. From the selected papers, tables were generated for each dataset on Microsoft Excel. These tables included the following information for each study (when available): general information about the study (year, location, hospital or city, state and country, publication date), confirmed cases, GI bleeding (general, upper, lower), indication to gastroscopy/GI bleeding manifestation (melena, hematochezia, anemia, hematemesis, etc.), number and type of endoscopies, main upper and lower endoscopy findings, COVID-19 treatments, GI bleeding treatments, outcome (re-bleeding, hospitalizations, ICU transfers, deaths), respiratory support (supplemental oxygen, non-invasive ventilation/CPAP, intubation), general signs and symptoms, GI symptoms, comorbidities. We compared clinical manifestations,

comorbidities, treatment, and outcomes between COVID-19 patients with GIB vs. non-GIB COVID-19 patients

Inclusion criteria: The following inclusion criteria were adopted to validate article selection: any study including patients with confirmed diagnosis of COVID-19 (PCR positive) with specified gastrointestinal bleeding or endoscopic findings; any study with 5 or more patients; any study with all or the majority of patients from Western countries; no distinction with regard to sex, age, severity of disease, inpatient or outpatient management, data collection date, treatment and outcome. Confirmed diagnosis of COVID-19 (RT-PCR) patient without GIB are included for comparison with GIB patients.

Exclusion criteria: The following exclusion criteria were adopted to filter out incomplete data: studies where cases were not confirmed by PCR; studies with less than 5 patients; studies which did not distinguish between COVID-19 with GIB and COVID-19 patients without GIB; systematic reviews and meta-analyses. Studies from Eastern countries were also excluded to have more homogeneous data.

Statistical Analysis: The collected data was used to calculate the most common endoscopic findings in the included COVID-19 patients' studies. Different GIB presentations, common symptoms, comorbidities, treatment strategies, respiratory support, and outcomes were combined and analyzed by weighted analysis methods where applicable. Variables reported in only one study were excluded from statistical analysis. Correlation coefficients were calculated together with regression analysis to establish associations between comorbidities and mortality. The effect of symptoms was reported using weighted analysis where weights were related to the size of the reported study. Differences in comorbidities and outcome between COVID-19 patients with and

without GI bleeding were computed. SPSS (SPSS Inc., Chicago, IL, USA) was used for this analysis.

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Results

Upper GIB occurred more often than lower GIB

The studies reporting GIB included a total of 808 patients (Table 1). Six of these studies reported the incidence of patients with GIB in their overall COVID-19 population which amounts to 0.06%. Within the selected 808 patients with endoscopic findings from the 12 studies, 92.7% displayed GIB. Not all studies specified the type or presence of GIB. Among 633 patients, the bleeding was localized in the upper GI tract in 66.0% (418) of patients, and in the lower GI tract in 24.8% (157). The remaining 9.2% (58) had unspecified GIB location.

From the 808 patients in all the studies reporting GIB, the mean age was 69.7 years compared to 62.3 in the control group (Tables 1 and 2). The control population consists of a large general COVID-19 cohort of which the characteristics are presented in Table 2 (Non-GIB cohort). In the GIB cohort, 62.4% were males and 37.6% were females, while the distribution in the control cohort was 52.6% and 47.4%, respectively. In the GIB cohort, men are older than in the control group ($p<0.001$).

GIB was strongly correlated with GI symptoms, diabetes, cancer, hypertension, and heart disease but not with anti-coagulants

Several symptoms, comorbidities, and treatments were associated with GIB. Positive associations were found with diarrhea ($p<0.001$, $r=0.884$), loss of taste ($p<0.001$, $r=0.791$), nausea ($p<0.001$, $r=0.734$), and vomiting ($p<0.001$, $r=0.651$). Negative associations with shortness of breath ($p<0.001$, $r=-0.770$) and fever ($p<0.001$, $r=-0.524$) were noted. As for comorbidities, positive correlations were found between GIB and diabetes ($p<0.001$, $r=0.915$), cancer ($p<0.001$, $r=0.844$), hypertension ($p<0.001$, $r=0.754$), and cardiac disease ($p<0.001$, $r=0.714$).

Melena was the most common form of reported GIB manifestation

Endoscopic procedures were performed for varied reasons (Table 1). Only 9 out of the 12 studies reporting GIB also reported information regarding endoscopies. Most procedures were carried out due to GIB. The known GIB manifestations and reasons for endoscopy were melena (47.5%), hematochezia (37.8%), anemia (21.0%), hematemesis (16.7%), diarrhea (8.1%), and coffee-ground emesis (7.8%) (Fig.2). Performed endoscopic procedures were esophagogastroduodenoscopy (EGD) (81.7%), colonoscopy (20.9%), Endoscopic retrograde cholangiopancreatography (ERCP) (9.2%), sigmoidoscopy (8.7%), and enteroscopy (3.8%).

Ulcer was the main finding in both upper and lower endoscopies

The upper and lower endoscopies revealed a wide spectrum of findings (Table 1). The upper endoscopy findings were the following: peptic ulcer (48.4%), esophagitis or esophageal ulcer (17.6%), erosive or hemorrhagic gastritis (16.6%), gastropathy or duodenopathy (9.9%), Mallory-Weiss tears (6.3%), esophageal varices (5.5%), and Dielafuoy lesions (2.9%) while 23% of upper endoscopies had no abnormal findings (Fig. 3a). As for the lower endoscopies, the most reported findings were rectal ulcer (36.4%), hemorrhagic, lymphocytic, or microscopic colitis (30.7%), colon ischemia (29.8%), diverticular bleeding or diverticulosis (25.0%), hemorrhoids (15.6%), and blood without source (11.7%; Fig. 3b). In 20.5% of cases, no abnormal findings were identified.

Endoscopic treatment was rarely necessary to treat GIB

In the cohort of 808 GIB patients, endoscopic treatment (in the form of cautery, clips and others) was only performed in 6% of the cases (Table 1). In the remaining 94%, treatment for bleeding was either medical only or not performed. The most frequent non-endoscopic treatments for GI bleeding were the following: transfusions (55.2%), proton pump inhibitor (47.7%), vasopressor support (44.9%), H2 receptor blockers (15.2%), and interventional radiology (8.9%; Fig. 4).

Different kinds of COVID-19 treatments were also reported as follows: azithromycin or other antibiotics (71.2%), anti-coagulants, low molecular weight heparin, or thromboprophylaxis (59.6%), hydroxychloroquine (52.1%), steroids (43.5%), anti-platelets (43.3%), Remdesivir (11.6%), and Tocilizumab (11.4%; Supplementary Fig.1).

The GIB cohort had higher incidence of hypertension, liver disease, and cancer

The GIB cohort and the control cohort had different incidences of comorbidities (Fig. 5a), most of which were significant. The GIB cohort had a higher incidence of hypertension (61.1% vs. 58.4%, $p<0.001$), liver disease (11.2% vs. 6.8%, $p<0.001$) and cancer (7.7% vs. 1.5%, $p=0.006$). The control group, on the other hand, had higher prevalence of respiratory disease (16.9% vs. 10.9%, $p<0.001$), obesity (31.5% vs. 13.7%, $p<0.001$), smoking (67.6% vs. 21.4%, $p<0.001$), and chronic kidney disease (20.0% vs. 13.4%, $p<0.001$).

Death, ICU transfer, ventilation, and intubation were more common in the GIB cohort

Death had an incidence of 25.4% in the GI bleeding cohort, versus 16.4% in the control group ($p<0.001$) (Tables 1&2). Worth noting that most patients in both cohorts were hospitalized (92.6% in GIB and 99.6% in Control cohort). ICU transfer, however, was much higher in the GIB cohort, with an incidence of 39.9% versus 17.2% in the control group. Respiratory support rates were also different, with supplemental oxygen being more common in the control group (57.3% vs. 38.3% in GIB) as opposed to non-invasive ventilation (40.5% in the GIB vs. 25.5% in the controls) and intubation (35.6% vs. 23.2%) (Fig. 5b). There was also a 5.9% incidence of re-bleeding in the GIB cohort. All these differences in outcomes were significant ($p<0.001$).

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Death was positively associated with hypertension, EGD, and hematochezia in GIB patients

Several associations with death were found in the GIB cohort. Among all the comorbidities, death was strongly associated with hypertension ($p<0.001$, $r=0.814$). Other strong positive correlations with death were EGD ($p<0.001$, $r=0.591$), and hematochezia ($p<0.001$, $r=0.646$).

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Discussion

Gastrointestinal bleeding (GIB) has been identified in some COVID-19 patients as a GI manifestation. In this systematic review, we analyzed the findings of 12 studies which reported GIB and endoscopic findings in COVID-19 patients. These studies included 808 patients. The data retrieved from the GIB cohort was compared with a control group consisting of 18,179 COVID-19 mostly hospitalized patients. GIB was found to have an incidence of about 0.06% in COVID-19 patients. This rate was calculated from the studies from which we extracted and constructed our GIB cohort. This rate is slightly greater than the incidence in the overall population, which is estimated around 0.05% (0.06% for upper GIB and 0.03% for lower GIB)[15]. In our cohort, as in the overall population, bleeding in the upper GI tract occurred more often than in the lower GI tract. Because not all the analyzed studies provided a specific subdivision of upper and lower GIB, we could not calculate an exact ratio, but from the available data it is approximately 7:3. Additionally, males were found to be more susceptible to GIB than females. This is also confirmed by the studies, which state that both upper and lower GIB are more common in men than women[15, 16]. As such, it seems unlikely that COVID-19 affects GIB or its upper/lower distribution since the profile in the general population fits the one in the GIB COVID-19 cohort. It is worth noting however that COVID-19 associates with coagulopathies and veinous thromboembolism and that many patients receive anti-coagulants as part of their treatment regimen. While anti-coagulants' use is known to associate with bleeding disorders, including in the GI tract, such an association was not confirmed in our cohort. Consequently, neither COVID-19 nor anti-coagulants' use can be suspected to be causative of GIB in the analyzed cohort.

Since upper GIB was more common than lower GIB, it follows that the most common type of endoscopy was EGD and the most common bleeding presentation was melena, which mainly occurs when the bleeding lesions are located above the ligament of Treitz[15, 17]. Hematemesis,

which was the fourth most common presentation in the papers included in the study, confirms that the bleeding is mostly located in the upper GI tract and that the hemorrhage is large, often leading to the loss of large amounts of blood and ultimately to anemia[17]. Altogether, melena and hematemesis usually derive from peptic ulcers, esophagitis, varices, Mallory-Weiss tears, and other upper GI etiologies. Finally, hematochezia, which was the second most common presentation, indicates lower GIB.

Endoscopic findings revealed that ulcers were the most common lesions in both upper and lower GIB patients, followed by varied inflammations such as esophagitis, gastritis, and colitis. It is unclear whether the GI damage present in these patients is caused or exacerbated by SARS-CoV-2. At least from the inflammatory conditions, the viral infection might have been a factor, if not the trigger. Since we do not have access to these patients' medical records prior to infection, it is difficult to rule whether the co-occurrence is causative, cumulative, or coincidental.

In patients where the association might be judged as causative, the virus might lead to GIB through direct mucosal damage followed by a strong immune response and indirect consequences of viral-induced hypoxia and coagulopathy[8]. Indeed, SARS-CoV-2 can bind to the angiotensin-converting enzyme 2 (ACE2) receptors present on cells as the main route of access[18]. These receptors are abundant on the epithelial cells lining not only the lungs, but also the GI tract. By binding to these receptors, the virus reduces their action, increasing the concentration of angiotensin II, which is a vasoconstrictor. This leads to thrombosis, oxidative stress, and inflammation[18]. Disturbances in the capillaries can also cause hypoxia, which triggers cytokines release, creating a positive feedback loop that leads to more capillary dysfunction and more severe hypoxia[18]. As for the mucosal damage and immune response, we know that SARS-CoV-2 activates T cell lymphocytes, which induce an abnormal release of pro-inflammatory cytokines such as IL-1, IL-6, and IFN-γ[19]. This immune response can lead to organ damage and could be associated

with some of the aforementioned endoscopic findings. For instance, IL-6 and TNF-α (directly correlated with the severity of COVID-19) have been shown to contribute to the onset and maintenance of ulcers in later stages of tissue inflammation[20]. A similar mechanism could be taking place in the GI tract to cause peptic ulcers.

Steroids' use was positively associated with GIB, a finding consistent with the previous study by Narum et al.[21]. Interestingly, among all the patients who exhibited GIB and/or underwent endoscopy, only 6% required an endoscopic treatment. This means that 94% of the patients fully recovered with medical treatment or no treatment at all. The medical treatments mostly consisted of blood transfusions, proton pump inhibitors, and vasopressor support, which are used routinely to deal with blood loss and to reduce stomach acid production, whether or not a COVID-19 background is present[22].

Overall, the GIB cohort exhibited worse outcomes than the control group. This is reflected by the higher incidence of ventilation, intubations, ICU transfers, and deaths. Furthermore, our analysis showed a direct correlation between death and both EGD (p= 0.000, r=0.591) and hematochezia (p=0.0001, r= 0.646). It was reported that patients undergoing endoscopy secondary to upper GIB in the COVID-19 era (regardless of whether or not they are infected) were more likely to die than before the pandemic[13]. These results were attributed to two main factors: patients' avoidance of hospitals to reduce exposure to virus during the pandemic and hospital staff and resources relocation to respond to more severe COVID-19 cases, thus leading to a reduction and delay in endoscopic procedures, leading to the exacerbation of patients' conditions[13].

The reduced survival in GIB patients could also be linked to comorbidities. According to our analysis, in the GIB cohort, death was positively associated with hypertension. Hypertension was found to be directly correlated with GIB, and more prevalent in the GIB cohort than in the control group. According to a recent meta-analysis, high blood pressure was independently

associated with increased mortality in COVID-19 patients[23]. A specific mechanism connecting hypertension with COVID-19-related death was not identified. Of note, many anti-hypertensive drugs can increase the expression of ACE2, thus increasing the number of entry points for the virus. By contrast, other researchers proposed a diametrically opposite reasoning, stating that hypertensive patients might have reduced ACE2 expression, which would lead to a higher concentration of angiotensin upon binding with SARS-CoV-2, and consequent COVID-19 development[23].

Other variables that were associated with GIB or had a higher incidence in the GIB cohort were GI symptoms (diarrhea, nausea, vomiting), loss of taste, diabetes, liver disease, cancer, and heart disease. Diabetes has been associated with increased incidence of GI bleeding in diabetic ketoacidosis patients[24]. Patients with liver cirrhosis are known to be at higher risk of GIB from different lesions, including gastroesophageal varices, which were identified in this analysis[25]. Same goes for cancer patients, who are often subjects to GIB[26]. Of note, the studies included in the analysis did not specify the types of cancer detected in their cohorts. Finally, heart disease is normally considered a risk factor for GIB because these patients take anti-coagulants or anti-platelets medications[27, 28]. However, in our data analysis, no correlation between the use of anti-coagulants/anti-platelets and GIB was found.

The main limitation of this study is certainly the heterogeneity of the data reported in the included studies. Indeed, all collected data was in aggregated format. This means that calculations reporting associations between variables, such as correlations with GIB and death, have a more potential statistical error than would be yielded by an analysis of de-identified single patients' data. Moreover, the studies were published by different authors, who differently decided 1) what data to collect, 2) how to collect it, and 3) what information to share. Some papers did not report the reason for the endoscopy. Not every research article (except Massaroni et al.) mentioned the reason

for the endoscopy. Massironi et al.[29] evaluated GIB for the COVID-19 positive patients including all patients who were managed in seven hospitals in Lombardy, Northern Italy, and underwent endoscopic examination between Feb. 1st and Apr. 20th, 2020: among these patients, GIB was detected in 20/24 EGD and 20/20 colonoscopies. Reasons for EGD were melena in 10 (42%), anemia in eight (33.4%), and hematemesis in two (8.3%). Reasons for colonoscopies were bloody diarrhea in five (25%), hematochezia in eight (40%), melena with negative EGD in four (20%), and anemia in three (15%). The main findings at EGD consisted of esophagitis in five cases (20.8%) (two Los Angeles grade B, two Los Angeles grade C, and one Los Angeles grade D), bulbar ulcer in five (20.8%) (two Forrest II a, two Forrest II c, and one Forrest I b), erosive gastritis in four (16.6%), neoplasm in two cases (8.3%), Mallory Weiss in one case (4.1%). The main findings at colonoscopy were segmental colitis associated with diverticulosis (SCAD) in five (25%), ischemic colitis in four (20%), diffuse hemorrhagic colitis with a mild edematous mucosa and multiple red mucosal spots in one case, and neoplasm in one. For other studies, it was difficult to estimate what percent of suspected GIB patients have endoscopically confirmed GIB. Furthermore, for this reason, the analysis of several comorbidities, treatments, and symptoms was made impossible by the fact that not all authors reported the same variables.

GI bleeding in patients with SARS-CoV-2 poses unique challenges, particularly for endoscopists and other healthcare staff, because of the potential for aerosol spread. Not every GIB may have been reported at the pandemic's peak. Due to the risk of transmission of the virus, shortage of medical facilities, avoidance of preventive care and overwhelming burden on the healthcare workers, there was a significant delay in patient care. All these factors may have cumulatively underestimated the presence of these bleeds and significantly delayed patients' care. It was difficult to judge the nature of GI symptoms. We could not evaluate the severity and duration

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of GI symptoms from the currently available data. Additionally, some GI symptoms might not be caused by SARS-CoV-2 infection.

Prospective studies that use patients' medical records prior to COVID-19 and follow their symptoms and prognosis post-infection are needed to establish the potential role of COVID-19 in the onset of GI bleeding and whether such an infection would speed up GIB occurrence in patients with predisposing conditions or worsen the outcome when GIB is preceding the infection. Studies describing the percent of patients who had been consulted for GIB or those who had suspected GIB but could not get an upper endoscopy along with the number of days healthcare was delayed in patients with suspected GIB are required. The role of anti-coagulants needs also further investigation as it is part of COVID-19 patients' treatment and known to cause GIB.

In conclusion, we found that the incidence of GIB in COVID-19 patients is similar to that estimated in the overall population, with men being more susceptible than women and melena being the most common presentation. Nonetheless, patients with GIB were more likely to die than non-GIB COVID-19 control patients. Common endoscopic findings in GIB COVID-19 patients were ulcers, esophagitis, gastritis, and colitis. GIB was not found to be associated with anti-coagulants' use. There was a higher incidence and association of GI symptoms, diabetes, heart disease, hypertension, liver disease and cancer in the GIB cohort. The latter three were positively associated with death in the GIB cohort.

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Table 1: **Demographics and clinical characteristics of patients with COVID-19 reporting GI bleeding**

Study (n=808)	Gonzalez[30]	Kuftinec[31]	Martin[6]	Massironi[29]	Mauro[32]	Melazzini[33]	Rustgi[34]	Trindade[5]	Vanella[35]	Holzwanger[36]	Ierardi[37]	Cavaliere[38]	Total % (N)
Total # of patients	83	24	41	38	23	5	146	314	106	11	11	6	100 (808)
Mean age	77	65.2	68.7	69	75	73	67.4	70	68	64	65	67.8	69.7
Male	61.4 (51)	83.3 (20)	66 (27)	73.7 (28)	78.3 (18)	80 (4)	53.4 (78)	59.6 (187)	70.8 (75)	55 (6)	63.6 (7)	50 (3)	62.4 (504)
Female	38.6 (32)	16.7 (4)	34 (14)	26.3 (10)	21.7 (5)	20 (1)	46.6 (68)	40.5 (127)	29.2 (31)	45 (5)	36.4 (4)	50 (3)	37.6 (304)
GI bleed	100 (83)	54.2 (13)	100 (41)	86.8 (33)	100 (23)	100 (5)	100 (146)	100 (314)	59.4 (63)	100 (11)	100 (11)	100 (6)	92.7 (749)
UGIB	100 (83)	-	75.6 (31)	39.5 (15)	100 (23)	-	-	68.2 (214)	38.7 (41)	-	45.5 (5)	100 (6)	66 (418)
LGIB	-	-	24.4 (10)	21.1 (8)	-	-	-	31.9 (100)	20.8 (22)	100 (11)	54.5 (6)	-	24.8 (157)
Reason for Endoscopy/ GI bleeding manifestation (n=382)													
Melena	68.7 (57)	-	48.8 (20)	34.2 (13)	52 (12)	100 (5)	35.3 (6)	-	-	-	-	66.7 (4)	47.5 (117)
Hematochezia	-	-	26.8 (11)	18.4 (7)	-	-	41.2 (7)	-	-	100 (11)	-	-	37.8 (36)
Anemia	-	4.2 (1)	-	34.2 (13)	-	100 (5)	17.6 (3)	-	-	-	-	-	21 (22)
Hematemesis	32.5 (27)	-	4.9 (2)	7.9 (3)	22 (5)	-	11.8 (2)	-	-	-	-	33.3 (2)	16.7 (41)
Coffee-ground emesis	-	-	4.9 (2)	-	13 (3)	-	-	-	-	-	-	-	7.8 (5)
Diarrhea	-	4.2 (1)	-	10.5 (4)	-	-	-	-	-	-	-	-	8.1 (5)
Endoscopy (n=298)													
EGD	100 (39)	75 (20)	66.7 (10)	63.2 (28)	100 (18)	-	82.4 (14)	85 (17)	67 (76)	-	-	-	81.7 (222)
Colonoscopy	-	29.2 (8)	6.7 (1)	52.6 (23)	-	-	35.3 (6)	10 (2)	25.5 (29)	-	-	-	20.9 (69)
Enteroscopy	-	-	-	-	-	-	5.9 (1)	-	0.9 (1)	-	-	-	3.8 (2)
Sigmoidoscopy	-	-	26.7 (4)	-	-	-	11.8 (2)	5 (1)	-	-	-	-	8.7 (7)
ERCP	-	8.3 (2)	-	-	-	-	-	-	9.4 (11)	-	-	-	9.2 (13)
Main UGI findings (n=241)													
Peptic Ulcer	46.2 (18)	55.6 (10)	80 (16)	20.8 (5)	44 (8)	75 (3)	28.5 (4)	64.7 (11)	25.3 (22)	-	-	-	48.4 (97)
Esophagitis/Esophageal ulcer	28.9 (11)	-	30 (6)	20.8 (5)	-	-	14.3 (2)	5.8 (1)	42.5 (37)	-	-	-	17.6 (62)
Esophageal varices	2.6 (1)	5.6 (1)	-	-	-	-	7.1 (1)	-	-	-	-	-	5.5 (3)
Erosive gastritis or Hemorrhagic gastritis	-	5.6 (1)	-	16.6 (4)	22 (4)	-	28.6 (4)	11.7 (2)	16.1 (14)	-	-	-	16.6 (29)
Mallory-Weiss tear	-	-	-	4.1 (1)	11 (2)	-	7.1 (1)	5.8 (1)	-	-	-	-	6.3 (5)
Dieulafoy lesions	-	-	-	-	11 (2)	-	-	-	1.1 (1)	-	-	-	2.9 (3)
Gastropathy/ Duodenopathy	-	-	-	-	-	25 (1)	-	-	9.2 (8)	-	-	-	9.9 (9)
Normal	-	5.6 (1)	-	25 (6)	6 (1)	-	-	-	29.9 (26)	-	-	-	23 (34)
Main LGI findings (n=71)													
Rectal ulcer	-	14.3 (1)	60 (3)	-	-	-	33.3 (3)	-	-	-	-	-	36.4 (7)
Colitis-hemorrhagic/lymphocytic/Microscopic	-	-	20 (1)	20 (4)	-	-	-	33.3 (1)	-	-	-	-	30.7 (6)
Hemorrhoids	-	42.9 (3)	-	-	-	-	11.1 (1)	-	-	-	-	-	15.6 (4)

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Diverticular bleeding/diverticulosis	-	8.6 (1)	20 (1)	25 (5)	-	-	11.1 (1)	33.3 (1)	-	-	-	-	25 (9)
Colon ischemia	-	-	-	20 (4)	-	-	-	-	33.3 (9)	-	-	-	29.8 (13)
Blood without source/LGIB without other abnormalities	-	14.3 (1)	-	-	-	-	-	-	11.1 (3)	-	-	-	11.7 (4)
Normal	-	14.3 (1)	-	30 (6)	-	-	-	-	18.5 (5)	-	-	-	20.5 (12)
COVID-19 Treatments (n=719)													
Anticoagulants/LMWH/Thromboprophylaxis	-	-	70.7 (29)	76 (29)	78 (18)	100 (5)	43.2 (63)	61.9 (194)	54.8 (58)	73 (8)	90 (10)	-	59.6 (414)
Steroids	-	-	-	35.9 (14)	-	-	33.6 (49)	54.3 (170)	28 (30)	-	-	-	43.5 (263)
Remdesivir	-	12.5 (3)	-	11 (4)	-	-	-	-	-	-	-	-	11.6 (7)
Tocilizumab	-	16.7 (4)	-	8 (3)	-	-	-	-	-	-	-	-	11.4 (7)
Hydroxychloroquine	-	66.7 (16)	-	47 (18)	-	-	58.9 (86)	-	41.4 (44)	-	-	-	52.1 (164)
Azithromycin or other antibiotics	-	-	-	-	-	-	58.2 (85)	-	89.1 (94)	-	-	-	71.2 (179)
Ritonavir/Lopinavir/ Antivirals	-	-	-	26 (10)	-	-	-	-	45.9 (49)	-	-	-	40.6 (59)
Antiplatelet	-	-	48.8 (20)	-	30 (7)	-	-	43.8 (138)	-	36 (4)	-	-	43.3 (168)
GI Bleeding Treatments (n=664)													
Endoscopic interventions	14.5 (12)	41.7 (10)	17.1 (7)	-	26.1 (6)	20 (1)	4.1 (6)	-	-	-	-	-	6.3 (42)
Medical only	85.5 (71)	58.3 (14)	82.9 (34)	-	73.9 (17)	80 (4)	95.9 (140)	100 (314)	-	100 (11)	100 (11)	100 (6)	93.7 (622)
Interventional radiology	-	-	-	-	8.7 (2)	-	2.1 (3)	-	-	9 (1)	100 (11)	-	8.9 (17)
Transfusions	-	-	73.2 (30)	-	-	-	69.2 (101)	45.9 (144)	-	64 (7)	-	66.7 (4)	55.2 (286)
Proton pump inhibitor	-	-	90.2 (37)	-	95.7 (22)	-	-	37.6 (118)	-	-	-	100 (6)	47.7 (183)
H2 receptor blocker	-	-	14.6 (6)	-	-	-	-	15.2 (48)	-	-	-	-	15.2 (54)
Vasopressor support	-	66.7 (16)	-	-	4.3 (1)	-	-	-	-	82 (9)	-	-	44.9 (26)
Outcome (n=808)													
Rebleeding	-	-	12.2 (5)	-	17 (4)	20 (1)	1.4 (2)	-	-	9 (1)	9 (1)	-	5.9 (14)
Hospitalized	86.7 (72)	100 (24)	100 (41)	97 (37)	100 (23)	-	-	100 (314)	67 (71)	100 (11)	-	-	92.6 (593)
ICU Transfer	10.8 (9)	100 (24)	46.3 (19)	21 (8)	-	-	44.5 (65)	45.7 (144)	33 (35)	90.9 (10)	-	-	39.9 (313)
Death	26.5 (22)	29.2 (7)	24.4 (10)	13 (5)	22 (5)	20 (1)	35.6 (52)	-	21.7 (23)	3 (0)	-	-	25.4 (125)
Respiratory Support (n=249)													
Supplemental Oxygen (NC/VM/NRB)	-	-	34 (14)	28.9 (11)	47.8 (11)	-	-	-	-	-	-	83.3 (5)	38.3 (41)
Non-invasive ventilation/CPAP	-	83.3 (20)	34 (14)	23.7 (9)	35 (8)	-	-	-	-	-	-	-	40.5 (51)
Intubated (invasive ventilation)	-	-	46.3 (19)	23.7 (9)	-	-	-	-	33 (35)	73 (8)	-	16.7 (1)	35.6 (72)
Signs and Symptoms (n=409)													
Fever	36.1 (30)	-	61 (25)	73.7 (28)	-	100 (5)	-	-	-	-	-	100 (6)	54.3 (94)
Shortness of breath	39.8 (33)	-	54 (22)	70.3 (27)	-	100 (5)	-	-	81.1 (73)	-	-	100 (6)	64.1 (179)
Cough	30.1 (25)	-	64 (26)	42.1 (16)	-	100 (5)	-	-	-	-	-	-	43.2 (72)
Loss of taste (ageusia)	2.4 (2)	-	5 (2)	-	-	-	-	-	-	-	-	-	2.5 (4)
Loss of smell (anosmia)	2.4 (2)	-	-	-	-	-	-	-	-	-	-	-	1.6 (2)

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Abdominal pain	30.1 (25)	-	2 (1)	-	-	-	-	-	27.8 (25)	-	-	-	24 (55)
Nausea	-	-	-	12.5 (5)	-	-	28.1 (41)	-	17.8 (16)	-	-	-	22.3 (65)
Vomiting	37.3 (31)	-	-	15.2 (6)	-	-	21.2 (31)	-	14.4 (13)	-	-	-	22.2 (83)
Diarrhea	27.7 (23)	-	27 (11)	34.2 (13)	-	-	30.1 (44)	-	15.6 (14)	-	-	-	26 (108)
Anorexia	-	-	17 (7)	-	-	-	-	-	11.1 (10)	-	-	-	12.7 (19)
Comorbidities/ Risk factors (n=766)													
Respiratory disease	-	-	12 (5)	-	-	-	-	-	10.5 (11)	-	-	-	10.9 (16)
Hypertension	68.7 (57)	-	66 (27)	48.6 (18)	70 (16)	80 (4)	-	62 (195)	52.4 (55)	-	-	-	61.1 (373)
Cardiac disease	-	-	24 (10)	42.1 (16)	39 (9)	-	-	-	16.2 (17)	-	-	-	25 (52)
Metabolic, Diabetes	34.9 (29)	-	37 (15)	31.6 (12)	48 (11)	-	-	35.6 (112)	21.9 (23)	-	-	-	33.4 (202)
Obesity	13.3 (11)	-	-	23.5 (9)	9 (2)	-	-	-	11.4 (12)	-	-	-	13.7 (34)
Smoking	8.4 (7)	-	-	28.1 (11)	-	-	27 (39)	-	-	-	-	-	21.4 (57)
H/O IBD	-	-	5 (2)	4 (2)	-	-	-	0.6 (2)	-	-	-	-	1.4 (6)
H/O Liver disease	12 (10)	-	5 (2)	16.2 (6)	-	-	-	-	-	-	-	-	11.2 (18)
H/O GERD/PUD	5 (4)	-	-	-	-	-	-	2.9 (9)	-	-	-	-	3.3 (13)
Chronic Kidney Disease	24.1 (20)	-	22 (9)	-	17 (4)	-	-	8.9 (28)	14.3 (15)	-	-	-	13.4 (76)
Cancer	-	-	27 (11)	-	13 (3)	-	-	-	8.6 (9)	-	-	-	13.6 (23)
Prior Anticoagulant Therapy	-	-	39 (16)	-	-	-	43.2 (63)	-	-	-	-	-	42.3 (79)
Prior steroids therapy	-	-	15 (6)	-	-	-	33.6 (49)	-	-	-	-	-	29.5 (55)
Prior proton pump inhibitors	-	-	-	-	-	-	63.7 (93)	37.6 (118)	-	-	-	-	45.9 (211)
Cirrhosis	-	-	-	-	9 (2)	-	-	-	8.6 (9)	-	-	-	8 (11)
Prior GI bleed	-	-	-	-	-	-	-	2.9 (9)	-	9 (1)	-	-	3.1 (10)

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Table 2: Demographics and clinical characteristics of patients with COVID-19 not reporting GI bleeding

Study	Mamatha Balla et al.[39]	Incerti et al.[40]	Schettino et al.[41]	Colaneri et al.[42]	Aghemo et al.[43]	Vena et al.[44]	Total % (N)
Total # of patients	217	17086	190	44	325	317	100 (18179)
Mean age	63.13 (137)	62 (10593)	67 (127)	67.5 (30)	67 (218)	71 (225)	62.3
Male	47 (102)	51.9 (8868)	66.84 (127)	63.64 (28)	68.62 (223)	67.19 (213)	52.6 (9561)
Female	53 (115)	48.1 (8218)	33.16 (63)	36.36 (16)	31.38 (102)	32.81 (104)	47.4 (8618)
Respiratory Support							
Supplemental Oxygen (NC/VM/NRB)	-	-	80.95 (154)	38.64 (17)	45.99 (149)	-	57.3 (320)
Non-invasive ventilation/CPAP	-	-	40 (76)	-	7.69 (25)	35.02 (111)	25.5 (212)
Intubated (Invasive ventilation)	-	-	11.05 (21)	-	34.59 (112)	18.93 (60)	23.2 (193)
Severity/Hospitalizations/Outcome							
Hospitalized	100 (217)	100 (17086)	88.57 (168)	100 (44)	100 (325)	86.75 (275)	99.6 (18115)
ICU Transfer	-	-	13.21 (25)	6.82 (3)	17.85 (58)	20.5 (65)	17.2 (151)
Death	10.6 (23)	15.8 (2700)	21.58 (41)	4.5 (2)	21.85 (71)	43.64 (138)	16.4 (2975)
Comorbidities/Risk factors/Medical history							
Respiratory disease	39.17 (85)	17 (2905)	-	4.55 (2)	10.15 (33)	5.68 (18)	16.9 (3043)
Hypertension	70.97 (154)	58.6 (10012)	58.95 (112)	34.09 (15)	51.38 (167)	47 (149)	58.4 (10609)
Cardiac disease	41.94 (91)	26.6 (4545)	19.47 (37)	25 (11)	17.85 (58)	-	26.5 (4742)
Metabolic, Diabetes	43.32 (94)	33.8 (5775)	21.58 (41)	15.91 (7)	22.46 (73)	15.46 (49)	33.2 (6039)
Obesity	57.14 (124)	-	18.52 (35)	8.5 (4)	25.1 (82)	-	31.5 (244)
Smoking	38.25 (83)	-	-	-	87.23 (283)	-	67.6 (366)
A fib/Arrhythmia	-	-	6.32 (12)	-	10.46 (34)	-	8.9 (46)
H/O Liver disease	7.3 (16)	-	-	4.55 (2)	-	-	6.8 (18)
Chronic Kidney Disease	-	20.7 (3537)	3.16 (6)	2.27 (1)	8.95 (29)	6.94 (22)	20 (3595)
Cancer	8.3 (18)	12.3 (2102)	3.16 (6)	-	-	3.47 (11)	12 (2137)
Stroke	-	10.5 (1794)	6.84 (13)	-	-	-	10.5 (1807)
Oncologic	-	-	-	13.64 (6)	-	3.79 (12)	5 (18)
Other Neurological disease and Mental disorder	-	10.2 (1743)	6.32 (12)	-	-	8.83 (28)	10.1 (1783)

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Figure Legends:

Figure 1: PRISMA Flow diagram

Figure 2. Clinical manifestations/ Reason for Endoscopy in the GIB patients with COVID-19.

Figure 3: Endoscopic gastrointestinal findings in the GIB patients. **A**: Upper gastrointestinal findings in the GIB patients. **B**: Lower gastrointestinal (LGI) findings in the GIB patients.

Figure 4: Non- surgical Treatments for Gastrointestinal Bleeding in patients with COVID-19

Figure 5: Comparing comorbidities, outcomes, and respiratory support between GIB and Non-GIB COVID-19 patients. A. Differences in comorbidities among the GIB and non-GIB patients. B. Differences in respiratory support and outcomes among GIB and non-GIB COVID-19 patients.

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Figure 1. PRISMA Flow diagram- Study selection

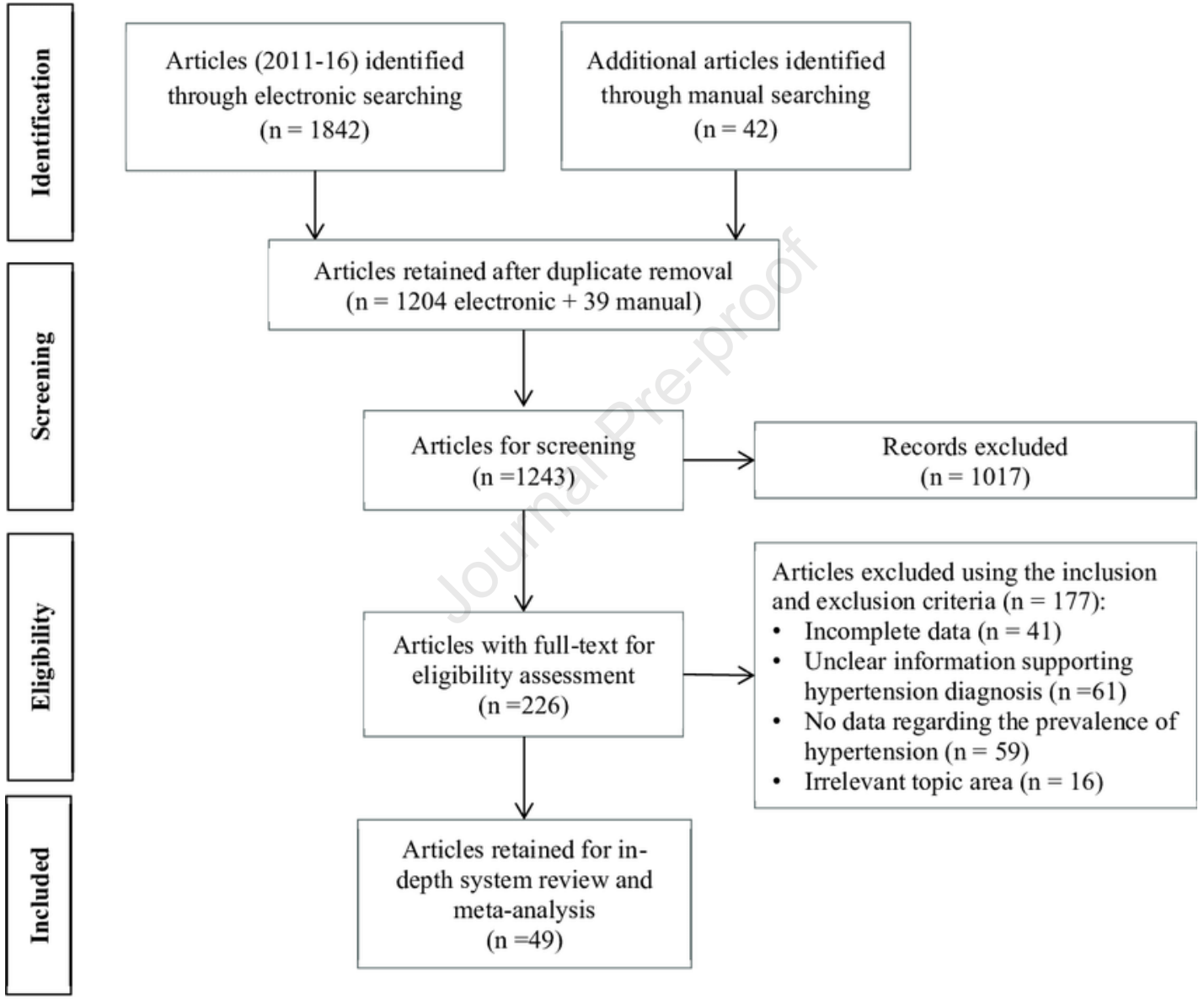

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Figure 2. Clinical manifestations/ Reason for Endoscopy in the GIB patients with COVID-19.

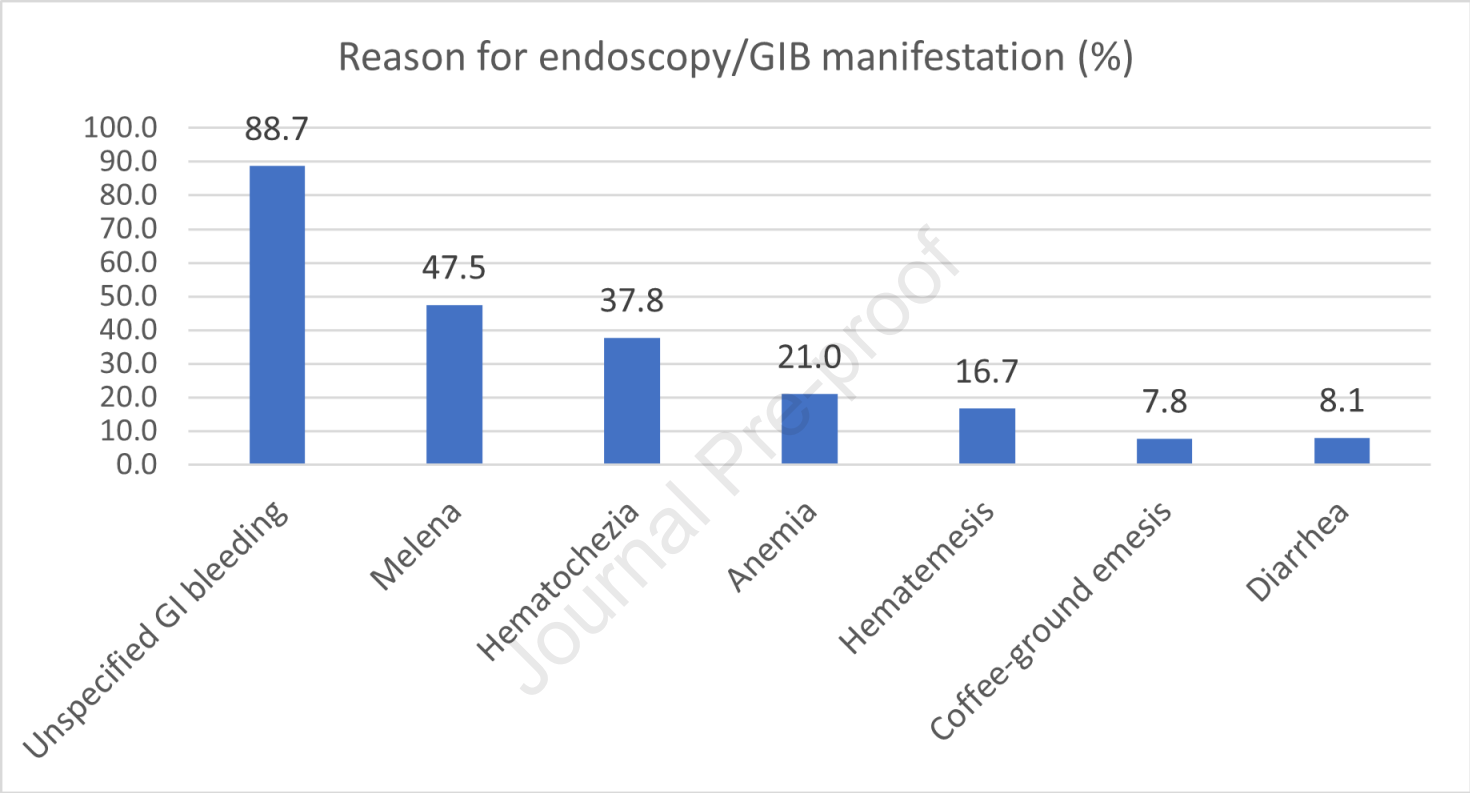

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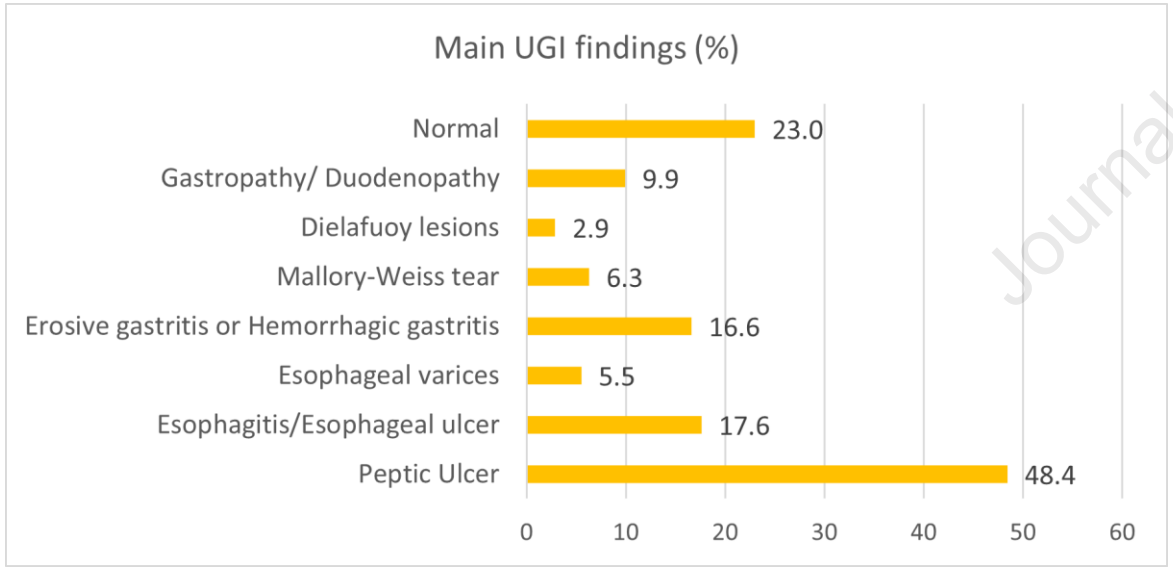
Figure 3: Endoscopic Gastrointestinal findings in the GIB patients. **A:** Main Upper Gastrointestinal findings in the GIB patients. **B:** Main lower Gastrointestinal (LGI) findings in the GIB patients

A



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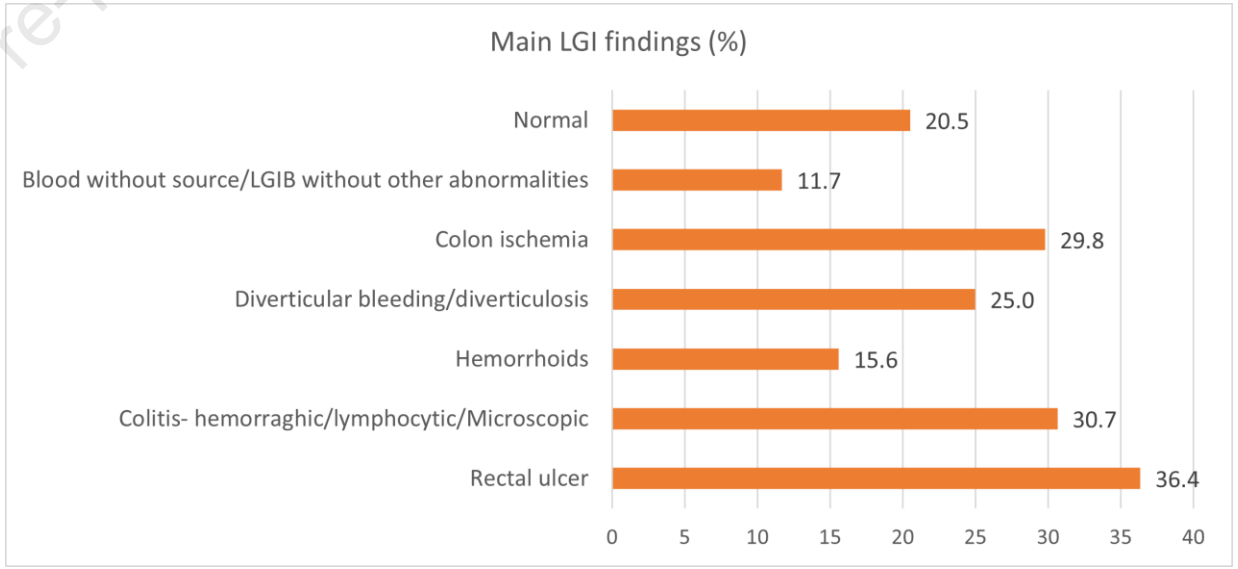

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Figure 4: Non- surgical Treatment for Gastrointestinal Bleeding in patients with COVID-19

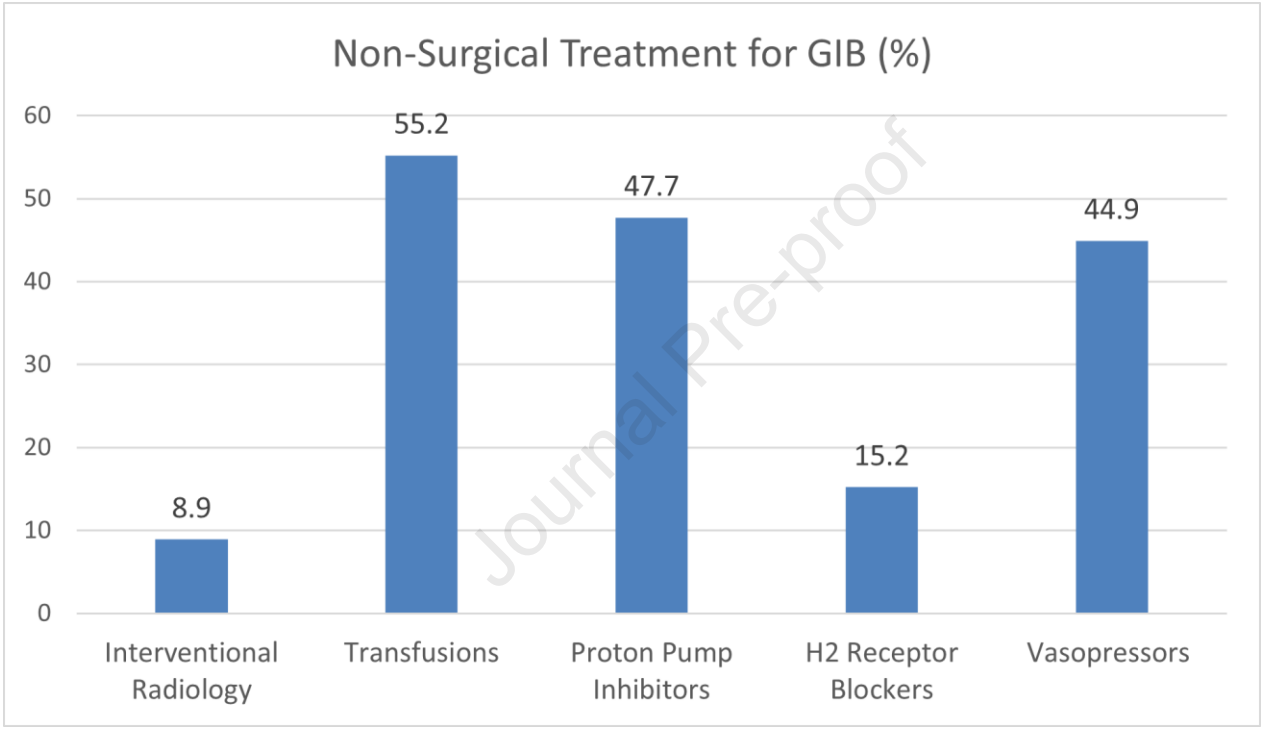

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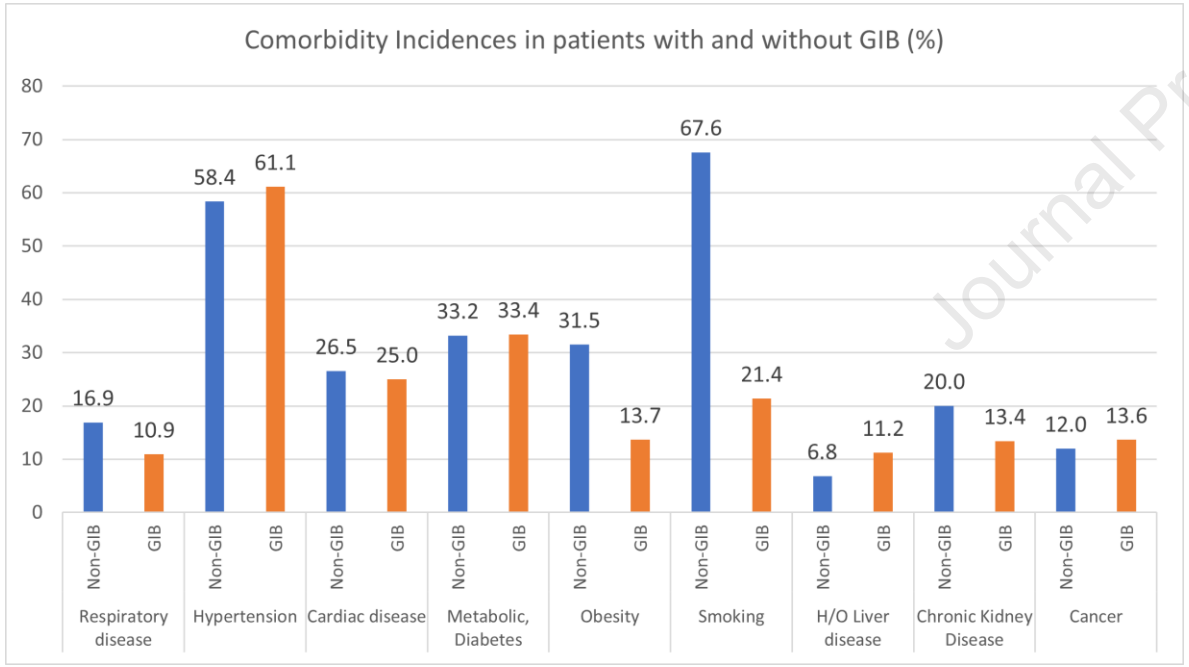
Figure 5: Comparing comorbidities, outcomes and respiratory support between GIB and Non- GIB patients exposed to COVID-19 **A.** Differences in comorbidities among the gastrointestinal bleeding and non-GIB patients. **B.** Differences in respiratory support and outcomes among gastrointestinal bleeding (GIB) and non-GIB patients exposed to COVID-19.

A



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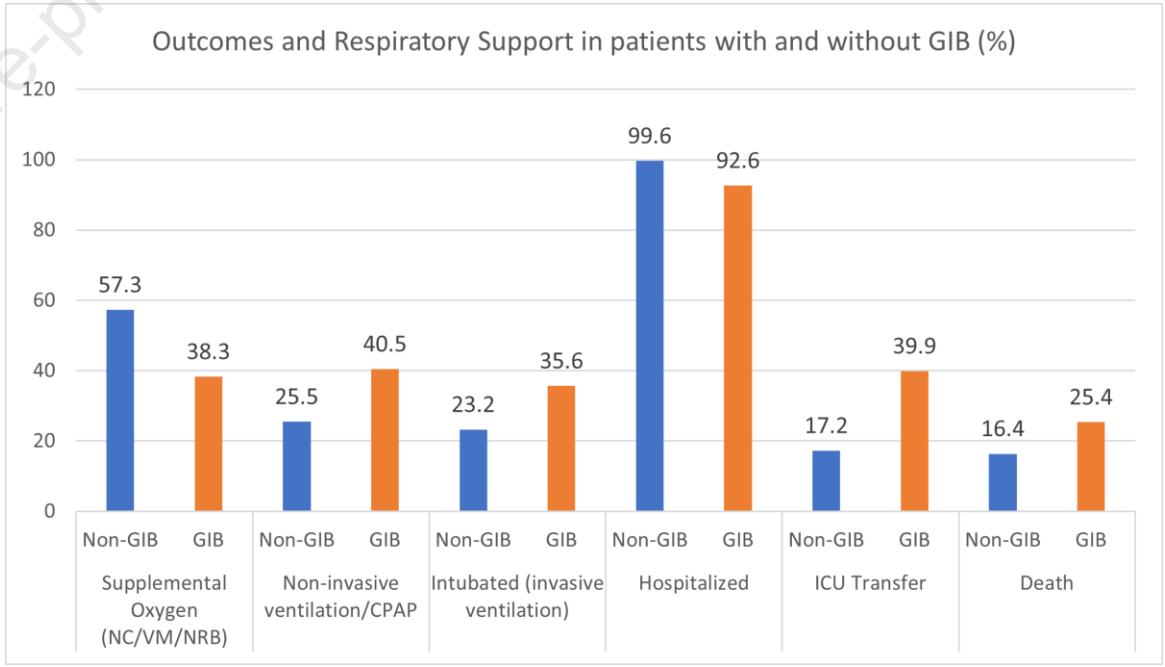

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