

Gastrointestinal Bleeding: Prevalence, Etiology, and Outcomes in COVID-19 Inpatients

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ABSTRACT

Background:

The current study aimed to investigate the prevalence, risk factors, endoscopic findings, and outcome of gastrointestinal bleeding in COVID-19 hospitalized patients.

Materials and Methods:

This study is a retrospective review of COVID-19 hospitalized patients with gastrointestinal bleeding from a large university hospital in southeast Iran. This study was conducted over one year from April 2020 to March 2021.

Results:

Out of 3563 COVID-19 inpatients with approximately equal sex distribution (52.5% of men and 47.5% of women), 80 (2.24%) patients with a mean age of 58.01 ± 20.71 were identified with signs of gastrointestinal bleeding, including; melena (48.8%), hemoglobin drop (42.5%), fresh blood hematemesis (31.3%), rectorrhagia (20%) and coffee ground emesis (10%). 52 patients (65%) had signs of gastrointestinal bleeding on admission, and 28 patients (35%) developed gastrointestinal bleeding during their hospital admissions, most of whom were men (63.8%). Endoscopic characteristics were; gastric erosion (27.7%), gastric ulcer (23%), duodenal ulcer (21.5%), esophageal ulcer (12.3%), and esophageal erosion (6.1%) in upper gastrointestinal endoscopy. On colonoscopy, hemorrhoids (25%), mass lesions (16%), fissures (8.3%), diverticular lesions (8.3%), and polyps (8.3%) were the most common findings. The overall mortality of the patients in the present study was 36.2%. However, gastrointestinal bleeding-related deaths were 7.5%.

Conclusion:

Gastrointestinal bleeding was identified in 2.24% of hospitalized COVID-19 patients, with gastroduodenal ulcers and erosions as the most common symptoms.

Keywords: COVID-19, Gastrointestinal Tract, Hemorrhage, Endoscopy, Colonoscopy, Iran

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INTRODUCTION

The coronavirus disease-2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been a significant public health problem worldwide and has turned into a global pandemic since December 2019 (1,2). Although respiratory manifestations of COVID-19 are most widely known, recent data shows implications in extrapulmonary sites, especially with the involvement of gastrointestinal (GI) tract (3–5). The most common GI symptoms of COVID-19 include abdominal pain, nausea, vomiting, and diarrhea, with an incidence rate of 2-18.6%. This rate in critically ill patients has been reported to be as high as 36-50.5% (6,7). GI bleeding (GIB) has various causes, which can be presented in patients with COVID-19, and so far, there is limited information about this complication in such patients (8,9). However, in various studies, the prevalence of GIB in hospitalized COVID-19 patients has been estimated to be between 2% and 13% (8).

Although the clinical spectrum of COVID-19 is not yet fully understood, some studies have reported the high incidence of peptic ulcer disease (PUD) as the most common cause of bleeding in patients with moderate-to-severe acute respiratory distress syndrome caused by COVID-19 (10,11). Various mechanisms may be involved in the pathogenesis of PUD, including direct COVID-19 damage to gastric epithelial cells due to the abundant expression of the angiotensin-converting enzyme (ACE) 2 receptors on the luminal epithelial cells of the GI, and active mucosal inflammation because of overproduction of inflammatory cytokines or cytokine storms (10).

Currently, by using prophylactic drugs, stress-related mucosal damage (SRMD) and subsequent GIB happen infrequently in critically ill patients, and their prevalence is estimated 0.6-4% (12). However, GIB in critically ill patients is a herald of poor outcomes, as in the study of Cook and colleagues, a mortality rate of 50% in patients with GIB was reported in the intensive care unit (ICU) (13).

The prevalence, exact cause, risk factors, associated conditions, and effect on mortality in COVID-19 patients complicated with GIB are unclear. Therefore, this study aimed to assess the prevalence, risk factors, endoscopic findings, and outcomes associated with GIB in hospitalized patients with COVID-19.

MATERIALS AND METHODS

Study population and ethical issues

This study is a retrospective review of the charts of adult patients with COVID-19 (>18 years) hospitalized due to GIB in a large hospital under the supervision of the University of Medical Sciences in Kerman, Southeast Iran, between April 2020 and March 2021. The study was approved by Kerman Medical University Ethics Review Board (Ethical approval number: IR.KMU.AH.REC.1400.095).

Inclusion and exclusion criteria

Inclusion criteria were subjects whose age is >18 years, have a positive result for SARS-CoV-2 infection by polymerase chain reaction (PCR) from nasal swabs, and also show at least one sign or symptom of GIB (hematemesis, hematochezia, melena, coffee ground emesis, and hemoglobin drop by two g/dL in 24 hours). The exclusion criteria included patients with equivocal PCR tests and patients with missing data on their recorded medical documents.

Data collection

Demographics (age and sex), comorbidities, and known risk factors for GIB (such as the previous history of PUD, GIB, inflammatory bowel disease (IBD), end-stage renal disease (ESRD), diverticulitis, use of medications such as antiplatelets, anticoagulants, steroids, and non-steroidal anti-inflammatory drugs (NSAIDs), GIB manifestations, time of GIB presentation (on admission vs. during hospitalization), length of hospital stay, endoscopic intervention (upper and or lower GI endoscopy), endoscopic findings (site and type of lesion), need for ICU admission and mechanical ventilation and final outcome of the patients (in-hospital mortality or discharge) were collected by reviewing medical documents. However, no interventional radiology or surgical procedures were performed in this study, and also the analysis for medications (antiplatelet, anticoagulation, steroids, or NSAIDs) as risk factors for GIB was not evaluated.

Statistical analysis

All data were analyzed using the Statistical Package for the Social Sciences (SPSS), version 22 (IBM). Descriptive

statistics were reported as rates and means with standard deviations (SD) or counts and proportions. All analyses were based on non-missing data, and missing data were not imputed.

RESULTS

Patient characteristics

During the study period, a total number of 3563 adult patients (>18 years old) were hospitalized due to COVID-19 infection, among which files of 80 patients were examined according to the inclusion criteria. The mean age of the patients was 58.01 ± 20.71 years, and the distribution between men and women is listed in [Table 1](#).

Outcomes of GI mortality and bleeding in COVID-19 patients

The prevalence of GIB in all patients) 3563 (with this disease was 2.24%. GIB signs and symptoms were revealed as one of the primary manifestations in 27.5% of patients. The prevalence of GIB manifestations included

Table 1. Characteristics of gastrointestinal bleeding in patients with COVID-19

Sex	No (%)
Male	51 (63.8%)
Female	29 (36.3%)
Time of 1 st episode of GIB	No (%)
Before admission	52 (65%)
During admission	28 (35%)
GIB Manifestations	No (%)
Melena	39 (48.8%)
Hemoglobin drop	34 (42.5%)
Hematemesis	25 (31.3%)
Hematochezia	16 (20%)
Coffee ground emesis	8 (10%)
ICU admission	No (%)
No	58 (72.5%)
Yes	22 (27.5%)
Mechanical Ventilation	No (%)
No	58 (72.5%)
Yes	22 (27.5%)
Final outcome	No (%)
Discharge	51 (63.8%)
In-hospital death	29 (36.2%)

melena, hemoglobin drop, fresh blood hematemesis, rectorrhagia, and coffee ground emesis as reported in [Table 1](#). Other outcomes related to GIB in COVID-19 patients are summarized in [Table 1](#).

Endoscopic and colonoscopic characteristics in COVID-19 patients with GIB

Among all patients with GIB, 56 patients (70%) had undergone gastroscopy, three patients (3.8%) had a colonoscopy, and nine patients (11.3%) had both gastroscopy and colonoscopy. However, the gastroscopy of 12 patients (15%) were canceled due to their instability, and near-arrest conditions. GI endoscopic findings revealed that the most common site of pathology was the stomach. Gastric erosion and gastric ulcer, as well as duodenal and esophageal ulcers, were the most prevalent findings of this study ([Table 2](#)). Meanwhile, the antrum of

Table 2. Characteristics of endoscopic and colonoscopic findings related to gastrointestinal bleeding in patients with COVID-19

Upper GI endoscopy findings	No (%)
Normal	14 (21.5%)
Stomach	36 (55.3%)
Erosion	18 (27.7%)
Ulcer	15 (23%)
Telangiectasia	1 (1.55)
Polyp	1 (1.5%)
Mass	1 (1.5%)
Duodenum	19 (29.2%)
Ulcer	14 (21.5%)
Erosion	4 (6.1%)
Nodularity	1 (1.5%)
Esophagus	19 (29.2%)
Ulcers	8 (12.3%)
Varices	5 (7.7%)
Mass	2 (3%)
Erosion	2 (3%)
Distal esophagitis	2 (3%)
Candidiasis	1 (1.5%)
Lower gastrointestinal endoscopy findings	No (%)
Normal	4 (33.3%)
Hemorrhoid	3 (25%)
Mass	2 (16.6%)
Fissure	1 (8.3%)
Diverticulum	1 (8.3%)
Polyp	1 (8.3%)

the stomach was the most involved site (in 14 patients or 21.5% of gastroscopies), and then diffuse gastric lesions in ten patients (15.3%). The body, pylorus, pre-pylorus, fundus, and cardia were involved in 7 (12.5%), 6 (9.2%), 5 (7.7%), and 3 (4.6%) of the patients. Finally, in GI colonoscopy, hemorrhoid was found as the most common type of lesion (Table 2).

Comorbid diseases in COVID-19 patients with GIB

Comorbid diseases and their related in-hospital mortality are shown in Table 3. The most common comorbidity was hypertension. In-hospital mortality in patients without underlying diseases- presumed as COVID-19-related mortality- was calculated at 7.5%.

DISCUSSION

COVID-19 is known to present respiratory symptoms, but many of its extra-pulmonary manifestations are observed and reported worldwide. GIB was one of the clinical features that were initially reported as a rare manifestation. However, by increasing the number of performed studies about COVID-19, multiple cases were reported showing that 2-13% of hospitalized COVID-19 patients will develop GIB (14).

In this study, the risk of GIB related to COVID-19 was calculated to be 2.4 %, a low global prevalence level (2-13%) (14). The results of this study align with a meta-analysis by Marasco and colleagues, who estimated the

Table 3. Frequency of comorbid diseases and their related mortality in patients with COVID-19 with gastrointestinal bleeding

Comorbid disease	No (%)	No of mortalities (%)
Hypertension	21 (26.3%)	7 (8.75%)
Diabetes mellitus	20 (25%)	9 (11.25%)
Pulmonary disease	12 (15%)	6 (7.5%)
Renal failure	11 (13.75%)	6 (7.5%)
Previous gastrointestinal bleeding	9 (11.3%)	3 (3.75%)
Coronary artery and heart diseases	9 (11.3%)	6 (7.5%)
Liver cirrhosis	6 (7.5%)	3 (3.75%)
Cerebrovascular disease	4 (5%)	2 (2.5%)
Other diseases	23 (28.8%)	5 (6.25%)
No comorbidities	21 (26.25%)	6 (7.5%)

overall prevalence of GIB in COVID-19 patients to be 2% (14). Some studies show that the reported prevalence of GIB in patients with critical conditions has been reported to vary from 1.5% to 5.5% compared with the patients who do not have critical conditions (0.005% to 0.04%) (15–17). These findings, along with our study, indicate the need for special care in early diagnosis and early action in COVID-19 patients.

Although the prevalence of COVID-19 infection at the time of our study was approximately equal in both sexes (47.5% of women and 52.5% of men), the results of our study showed that the prevalence of GIB in men was almost twice as high as in women (63.8% and 36.2%, respectively). This is consistent with the results of many similar studies in patients with COVID-19. For example, in the study by Mauro and colleagues, men accounted for 78.2% of GIB inpatients, and in the study by Martin and co-workers, men accounted for 66% of cases (8,11).

In terms of the type of lesion, ulcers, and erosions were the most common findings of the endoscopic results of our study, meaning that gastric erosion, gastric ulcer, duodenal ulcer, esophageal ulcer, and esophageal erosion, were the most common endoscopic findings. Likewise, the results of the study by Martin and colleagues showed that gastric and duodenal ulcers together accounted for 80% of the etiology of GIB in patients with COVID-19, and the meta-analysis done by Iqbal and others indicated that 47.5% of the endoscopic findings of patients were PUD (8,18). Similarly, the findings of our study are also supported by the results of studies done by Mauro et al. and Melazzini et al. (10,11). While the exact pathophysiology of ulcer and erosion in COVID-19 is still unclear, some hypotheses have been proposed. According to the known effect of acute stress on GI ulcers, acute stress has been suggested by some researchers as a risk factor (19). Some other researchers believe that due to the presence of ACE2 receptors in the GI mucosa, the SARS-CoV-2 directly damages the GI mucosa through interaction with these receptors and is responsible for the mechanism of the creation of the lesions. Moreover, active mucosal inflammation caused by cytokine storms has also been considered effective in the occurrence of these lesions (10,20). Finally, it is important to note that since coagulopathy is caused by COVID-19 and is treated

with thromboprophylaxis, this drug may also be effective in treating complications and bleeding of GI ulcers (21).

The most common colonoscopy finding was hemorrhoids in 25% of patients, in contrast to the findings of the study by Martin and colleagues, in which high rates of rectal ulcers were reported as a result of rectal tube insertion. Finally, their reported rectal tube usage showed a non-significant trend toward increased risk of lower GIB (8). This contrast is mainly because the rectal tube in our medical center is mainly used in patients with bad general and critical conditions who will not undergo colonoscopy. In the meta-analysis performed by Marasco with a large cohort of patients from different countries and the study done by Trindade et al. and Martin et al., GIB occurred mainly during hospital admissions (8,14,22). In contrast, in our study, the first bleeding episode (65%) occurred before hospitalization, fading the effect of in-hospital thromboprophylaxis on GIB. This is compatible with previous reports in which a non-significant trend toward increased risk of GIB was reported among in-hospital patients treated by therapeutic anticoagulation (8).

The overall mortality rate in our study was 36.2%, excluding the patients with multiorgan failure and poor conditions. The mortality rate in patients without comorbid diseases and related GIB was estimated to be 7.5%. It was shown that most deaths were in patients with underlying diseases. In a meta-analysis including eight studies with a collective 127 patients, pooled overall mortality was 19.1%, and pooled mortality secondary to GIB was 3.5% (18). In another study evaluating 56 COVID-19 patients with GIB, the overall 30-day mortality, and GIB-related deaths were 32% and 9%, respectively (23). Therefore, the results of these studies support our findings.

Strengths, limitations, and suggestions

The present study was one of the first studies to investigate the prevalence and pattern of GIB among patients with COVID-19 in Iran. Among the limitations of the present study, it can be mentioned that due to the retrospective nature of the study, only patients with a positive RT-PCR test for COVID-19 disease were included in the study, and given that the sensitivity of this test is about 77.7% and its specificity is about 98.8%, the exact prevalence might have been affected (24). Also, because our hospital

in Kerman is a tertiary-level of the care center and is the reference hospital for GI diseases in the whole province, there is another reason that may be effective in determining the exact prevalence. Therefore, for future research, it is recommended to conduct prospective studies to more accurately determine the prevalence of GIB with follow-up of patients and estimate the recurrence of bleeding in these patients, as well as a case-control study to investigate risk factors and the effect of GIB on disease prognosis.

In conclusion, this study presented findings on the pattern of GIB and its overall prevalence in patients with COVID-19. These findings can be used to adopt the best approaches for prevention, diagnosis, and treatment of GIB in patients with COVID-19 and provide the basis for further studies to promote useful interventions and a more accurate understanding of the pathophysiology of the disease.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest related to this work.

ETHICAL APPROVAL

The project received approval from the Ethics Committee of Kerman University of Medical Sciences, Kerman, Iran, under number IR.KMU.AH.REC.1400.095.

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