

Upper gastrointestinal system bleedings in COVID-19 patients: Risk factors and management/a retrospective cohort study

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ABSTRACT

BACKGROUND: Upper gastrointestinal system bleeding (UGIB) that occurs with the effect of coagulopathy due to COVID-19 disease itself and drugs such as LMWH and steroids used in the treatment negatively affects the outcomes. In this study, we aimed to examine the frequency of gastrointestinal system bleeding in COVID-19 patients, risk factors, effect on outcomes, and management.

METHODS: Institutional center (a third-level pandemic center) database was searched for patients hospitalized for COVID-19 between March 11, 2020, and December 17, 2020, retrospectively. Patients with UGIB symptoms/signs were included in the study. Age, gender, body mass index (kg/m²), hospital department where bleeding was diagnosed, previous bleeding history, comorbidities, and medication were steroid, anticoagulant, low weight molecule heparin, and proton-pump inhibitor; endoscopic findings/treatment, transfusion, and mortality rates were evaluated. Patients were divided into two groups as survivors and non-survivors and parameters were compared.

RESULTS: Forty-five of a total 5484 patients under COVID-19 treatment had upper gastrointestinal bleeding (0.8%). The average age of the patients was 70.1 years and 73% bleeders were male. Nineteen patients (44%) underwent endoscopy. The most common etiologies of bleeding were gastric/duodenal ulcer (n=9), erosive gastritis (n=4), and hemorrhagic gastritis (n=3). Active bleeding requiring intervention was detected in only one patient; therapeutic band ligation was applied to only 1 (2%) of all patients. The most common etiologies of bleeding were gastric/duodenal ulcer (n=9), erosive gastritis (n=4), and hemorrhagic gastritis (n=3). In terms of statistical significance, it was observed that the rate of steroid treatment (77% vs. 39%) and the number of days of steroid treatment were higher in non-survivor group.

CONCLUSION: UGIB is less common in COVID-19 patients compared to other hospitalized patients. However, it significantly increases mortality. Mortality risk increases even more in patients using steroids. These risks should be considered in patients under COVID-19 treatment. The majority of the bleeding patients does not require endoscopic treatment and should be managed conservatively. It is worth considering reducing unnecessary endoscopies in the pandemic.

Keywords: Bleeding; COVID-19; gastrointestinal; steroid.

INTRODUCTION

Although the predominant symptoms of COVID-19 infection are fever and respiratory symptoms, the disease also

has effects on many systems such as the gastrointestinal, neurological, genitourinary, and hematological systems. The few published pathology reports of patients with COVID-19 have shown findings of adult respiratory distress syndrome

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(ARDS) and evidence of small vessel occlusion.^[1,2] Wang et al.^[3] reported that of a total of 16.67% mostly critically ill patients with a high risk for thrombotic events, 17.3% were diagnosed with deep vein thrombosis. Patients with COVID-19 pneumonia also have a high risk of pulmonary embolism (PE) in small branches of the pulmonary arteries and arterial thrombosis.^[4,5] As thrombotic events have been shown in many studies, low-molecular-weight heparin (LMWH) prophylaxis and its early initiation have been recommended and accepted.^[6] The recommended dose of LMWH is still controversial, but it has now become standard in COVID-19 treatment, although during the treatment process, various life-threatening bleeding events have also been observed. The majority of bleeding in COVID-19 patients is seen in the gastrointestinal system. In addition, studies have been published showing that glucocorticoid use contributes positively to treatment, especially in severely ill patients, by preventing a cytokine storm and providing immune modulation.^[7-9] In line with these studies, glucocorticoids have begun to be widely used in COVID-19 patients. However, there is a known wide spectrum of adverse events related to glucocorticoid use and they may cause upper gastrointestinal system bleeding (UGIB).^[10]

UGIB occurring with the effect of coagulopathy due to COVID-19 itself and the drugs such as LMWH and steroids used in the treatment, can have a negative effect on the outcomes. The aim of this study was to examine the frequency of gastrointestinal system bleeding in COVID-19 patients, the risk factors, effects on outcomes, and management.

MATERIALS AND METHODS

Study Design, Setting, and Population

This observational, retrospective, cohort study was conducted in a tertiary level training and research hospital, also designated as a tertiary level pandemic center. Approval for the study was granted by the Ministry of Health of Turkey (December 15, 2020/13_18_18) and the Institutional Review Board (2020/Number). Verbal and written consent for the use of the data was routinely obtained from all patients at the time of hospital admission.

A retrospective scan was made of the institutional database for patients hospitalized because of COVID-19 infection during the 9-month period from the date of the first COVID-19 case in Turkey on March 11, 2020, to December 17, 2020. Patients with bleeding symptoms who had UGIB were identified and included in the study.

The study was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and followed the guidelines of the strengthening the reporting of observational studies in epidemiology report.

Data Collection

The clinical data recorded included age, gender, height, weight, BMI (kg/m²), hospital department where bleeding was diagnosed (hospitalization with bleeding, ward, and intensive care unit), history of previous UGIB, accompanying comorbidities (hypertension, diabetes mellitus, coronary artery disease, respiratory diseases, oncological diseases, neurological diseases, kidney diseases, gastrointestinal system diseases, and endocrine diseases), and antiplatelet therapy.

COVID-19 severity classification (no pneumonia, mild-moderate pneumonia, and severe pneumonia) and respiratory support classification (non-nasal cannula, non-breather face mask, HFNO (high-frequency nasal oxygen), and invasive mechanical ventilation) were recorded. The disease severity classification was made according to the Ministry of Health of the Republic of Turkey COVID-19 guidelines.^[11]

The laboratory values recorded at baseline and as the lowest and highest values during hospitalization included hemoglobin, hematocrit, platelet count, prothrombin time, INR, partial thromboplastin time, D-Dimer, and fibrinogen values. The lowest values were recorded for hemoglobin, hematocrit, platelet count, and the highest values for other laboratory values.

UGIB findings were classified as absent, hematemesis, melena, or hematemesis plus melena. The esophagogastroduodenoscopy (EGD) characteristics of those who did not undergo EGD, those who underwent EGD but were not diagnosed (no specific bleeding focus was seen, there were signs of previous bleeding), and those who underwent EGD and were diagnosed (inactive bleeding focus was observed) were classified as patients who underwent endoscopic therapeutic procedures.

The patients were separated into two groups as survivors and non-survivors. In each group, the patients using LMWH, steroids, and proton-pump inhibitor and the number of days the drugs were used were determined. Patients using PPI were classified as 40 mg/day and 80 mg/day. The amounts of erythrocyte suspension (ES) and fresh frozen plasma (FFP) used as blood components were recorded as units. The two groups of survivors and non-survivors were also classified as patients with and without EGD. The length of stay in hospital was recorded in days and admission to the intensive care unit.

Statistical Analysis

The conformity of continuous variables to normal distribution was tested with the Shapiro–Wilk test. Continuous variables with normal distribution were presented as mean ± standard deviation (SD), and continuous variables not conforming to normal distribution were presented as median (interquartile range 25–75) values. Categorical variables were presented

as number (n) and percentage (%). Laboratory data were compared using the paired samples T-test and the Wilcoxon signed-ranks test. The Mann–Whitney U-test was used for comparison of continuous variables between paired groups, and the Fisher's exact test or Pearson Chi-square tests were used for intergroup comparisons of discrete variables. $P < 0.05$ was considered statistically significant.

RESULTS

A total of 5484 patients were hospitalized because of COVID-19 within the specified study period. Of these, 45 (0.8%) patients were identified with UGIB and the clinical data of these 45 patients were evaluated. The patients comprised 73% of males and 27% of females with a mean age of 70.1 years and mean BMI of 25.4 (overweight) (Table 1). Examination for UGIB was seen to be in clinics in the majority of patients (53%, $n=24$), and 8 (17%) patients were admitted to the emergency department with the complaint of UGIB. A history of UGIB was determined in 3 (7%) patients and 39 (87%) had at least one comorbidity. The three most common comorbidities were hypertension ($n=16$, 36%), diabetes mellitus ($n=13$, 29%), and coronary artery disease ($n=12$, 27%). No gastrointestinal system disease other than a history of bleeding was determined in 7 patients (16%). Long-term antiplatelet therapy was determined in 10 (22%) of the patients with upper GIS bleeding (Table 1).

Patients were classified according to the severity of COVID-19. The most common status was mild and moderate pneumonia in 21 (47%) patients and 4 (9%) had no pneumonia. In the respiratory support classification, 10 patients (22%) were followed up in room air without any support, the most frequent support was oxygen administration with nasal cannula ($n=16$, 36%) and invasive mechanical ventilation was applied to 18% of the patients ($n=8$).

Comparisons were made of the basal laboratory values measured at the time of hospital admission and the most abnormal values during hospitalization. A statistically significant decrease was observed in the comparisons of hemoglobin (11.2 vs. 7.2 mg/dl; $p < 0.001$), hematocrit (33.8–22.1%, $p < 0.001$), and platelet counts ($192\text{--}88 \times 103/\text{mm}^3$, $p < 0.001$). Of the other laboratory parameters, only the increase in fibrinogen values (479–482) was found to be significant (Table 2).

The most common upper GIS bleeding finding in patients was melena ($n=29$, 65%), and no bleeding finding was observed in 8 patients (18%). EGD was not performed in 56% of the patients ($n=25$). Of the 19 patients (44%) who underwent EGD, 16 were diagnosed by EGD, and three patients were not diagnosed by EGD. Therapeutic band ligation was applied to only 1 (2%) of all the patients (Table 3).

Patients with upper GIS bleeding were separated into two groups as survivors ($n=28$, 62%) and non-survivors ($n=17$,

Table 1. Patient demographics ($n=45$)

	Total (n=45)
	n (%)
Age (years) ^a	70.1 (14.8)
Gender, male	33 (73)
Height (cm) ^a	167.2 (6.5)
Weight (kg) ^a	71.0 (7.4)
Body mass index (kg/m ²) ^a	25.4 (2.8)
Department where bleeding was diagnosed	
Hospitalization with bleeding	8 (18)
Ward	24 (53)
Intensive care unit	13 (29)
History of previous gastrointestinal bleeding	3 (7)
At least one comorbidity	39 (87)
Comorbidity	
Hypertension	16 (36)
Diabetes mellitus	13 (29)
Coronary artery disease	12 (27)
Respiratory disease	9 (20)
Oncological disease	7 (16)
Neurological disease	8 (18)
Kidney disease	7 (16)
Gastrointestinal system diseases	7 (16)
Endocrin disease	4 (9)
Antiplatelet therapy	10 (22)
COVID-19 disease classification	
Uncomplicated patient (no pneumonia)	4 (9)
Mild to moderate pneumonia ($\text{SpO}_2 > 90$)	21 (47)
Severe pneumonia ($\text{SpO}_2 \leq 90$)	29 (42)
COVID-19 disease respiratory support classification	
Non	10 (22)
Nasal cannula	16 (36)
Nonbreathing mask	7 (16)
High frequency nasal oxygen	4 (9)
Invasive mechanical ventilation	8 (18)

^aMean (Standard deviation).

38%). The rate of steroid use (77–39%) and the number of days of steroid use were statistically significantly higher in the non-survivor group. There was no statistically significant difference between the two groups in the number of patients using LMWH and the number of days using LMWH. When the amounts of ES and FFP used as blood components were compared between the two groups, there was no difference in terms of ES amounts, and FFP amounts were found to be significantly higher in the non-survivor group ($p < 0.001$). The rate of patients hospitalized in the intensive care unit was

Table 2. Comparison of laboratory values

	Basal values	Abnormal values	p-value
	Median (IQR 25 th -75 th)	Median (IQR 25 th -75 th)	
Hemoglobin (g/dL) ^a	11.2 (2.7)	7.2 (1.8)	<0.001 ^c
Hematocrit (%) ^a	33.8 (7.7)	22.1 (5.3)	<0.001 ^c
Platelet (x10 ³ /mm ³)	192 (127–273)	88 (50–158)	<0.001 ^d
Protomobin Time (s.)	13.3 (12.3–14.8)	15.2 (12.4–20.3)	0.069 ^d
International normalized ratio	1.16 (1.05–1.28)	1.3 (1.04–1.72)	0.102 ^d
Parsiyel tromb. time (s.)	27.9 (24.2–32.1)	28.8 (23.1–36.7)	0.829 ^d
D-dimer (ng/mL)	1.8 (0.5–3.3)	2.3 (0.8–8.3)	0.809 ^d
Fibrinogen (mg/dL)	479 (420–665)	482 (253–620)	0.004 ^d

^aMean (Standard deviation); ^cPaired samples T test; ^dWilcoxon Signed Ranks tests. s.: Seconds.

Table 3. Classification of upper GIB findings and endoscopic characteristics

	Total (n=45)
	n (%)
Upper GIB findings	
Absent	8 (18)
Hematemesis	6 (13)
Melena	29 (65)
Hematemesis plus Melena	2 (4)
Endoscopy characteristics	
Don't have an endoscopy	25 (56)
Nondiagnostic endoscopic finding	6 (13)
Diagnostic endoscopic finding	13 (29)
Therapeutic procedure	1 (2)

GIB: Gastrointestinal system bleeding.

88% in the non-survivor group and 21% in the survivor group (Table 4).

DISCUSSION

The COVID-19 pandemic has resulted in more than 1.8 million deaths worldwide to date.^[12] Although the leading causes of mortality are respiratory disorders and thromboembolic pathologies, other superimposed on pathologies such as UGIB may also increase mortality and morbidity. COVID-19 itself and the anticoagulant and glucocorticoid treatment may induce the bleeding.^[13]

The reported prevalence of GI bleeding in critically ill patients is variable and has been reported to range from 1.5% to 5.5%.^[14] Investigating UGIB during COVID-19, González González et al.^[15] identified 83 UGIB in 74,814 (1.11%) COVID-19 patients who underwent EGD. This incidence

was lower compared with non-COVID-19 patients (1.78%) but the study only included patients who were applied with EGD. Trindade et al.^[16] reported 3% incidence of UGIB in hospitalized COVID-19 patients, and Mauro et al.^[17] found the incidence of UGIB in COVID-19 patients to be 0.47%. In the present study, the incidence of UGIB was 0.8% in COVID-19 inpatients, and all patients with symptoms were included even if EGD was not performed. This lower incidence may be related to hypercoagulopathy caused by COVID-19. However, in the present study, 17% of the patients had complaints of UGIB on first admission to hospital. Erdinc and Raina reported the case of a patient with spontaneous retroperitoneal hematoma coinciding with massive acute deep vein thrombosis as initial presentation of COVID-19.^[18] This dilemma suggests that the coagulopathy in COVID-19 is not only in the direction of hypercoagulopathy.^[12] The incidence in the present study was lower than the rates reported by González González et al. and Trindade et al., and this may have been attributable to the routine use of proton-pump inhibitors.

Trindade et al.^[16] stated that the use of anticoagulation, steroid, or antiplatelet agents was not a risk factor for GI bleeding in their cohort of hospitalized COVID-19 patients, and no relationship was determined with comorbidities, but the mortality rate of patients with GI bleeding during the hospitalization was higher. González González et al.^[15] also found a higher mortality rate in COVID-19 patients with UGB compared to non-COVID patients with UGB, but not compared to other COVID-19 patients. In the present study, 87% of patients had at least one comorbidity, and 78% of patients had no history of daily antiplatelet drug usage. The rate of use of LMWH as anticoagulant was 84% and steroids 53%. The use of steroids and duration of use were seen to be associated with higher mortality rates in the COVID-19 patients with UGIB (p<0.05). Patients treated in ICU had also higher mortality rates. However, these were not independent variables. Although the demographic characteristics and disease

Table 4. Comparison of clinical data of survivors and nonsurvivors

	Survivor n=28	Nonsurvivor (n=17)	p-value
	n (%)	n (%)	
Patients on LMWH	22 (79)	16 (94)	0.227 ^b
Patients on steroid	11 (39)	13 (77)	0.015 ^b
Patients on PPI			
40 mg/day	15 (53)	7 (41)	0.490 ^b
80 mg/day	13 (47)	10 (59)	
Days used LMWH ^a	3 (1–15)	7 (6–15)	0.118 ^c
Days used steroid ^a	0 (0–5)	2 (1–9)	0.044 ^c
Days used PPI ^a	4 (1.5–14.5)	7 (4–12)	0.095 ^c
Erythrocyte suspension (U) ^a	2 (0–4)	3 (2–5)	0.06 ^c
Fresh frozen plasma (U) ^a	0 (0–0.5)	2 (0–3)	0.001 ^c
Patients with endoscopy	15 (54)	5 (29)	0.114 ^b
Length of stay at hospital ^a	9.5 (5–21)	18 (10–22)	0.083 ^c
Patients in intensive care unit	6 (21)	15 (88)	<0.001 ^b

^aMedian (IQR 25th–75th); ^bχ² tests; ^cMann-Whitney U test. LMWH: Low-molecular-weight heparin; PPI: Proton pump inhibitor.

levels were similar; it is known that high-dose steroids are administered to patients with a worse clinical condition and to patients with excessive pulmonary involvement and progression.^[19] This naturally explains the difference in steroid usage and length of usage in patients with mortality. Similarly, it was not surprising that mortality developed in patients under intensive care. In patients with bleeding, the addition of transfusion-related pulmonary disorders^[20] added to already existing pulmonary disorders due to COVID-19 pneumonia can be thought to increase mortality in patients. It is difficult to clinically and radiologically differentiate transfusion-related acute lung injury in patients with severe COVID-19 pneumonia and pre-existing ARDS.

Mauro et al.^[17] reported 18 EGD of 23 patients in their study, and the most common macroscopic pathologies were peptic ulcer, erosive gastritis, and hemorrhagic gastritis, respectively. Only six patients had endoscopic treatment (33%). Martin et al.^[21] performed EGD to half of the patients with UGIB, and the most common pathology was gastric/duodenal ulcer. Endoscopic treatment was applied to 40% of the patients who underwent EGD. Trindade et al.^[6] reported that 20 of 314 (6%) patients with gastrointestinal bleeding underwent EGD, of which 85% (17/20) were upper endoscopies. The most common etiology for bleeding found on EGD was gastroduodenal ulceration. In the present study, EGD was applied to 42% (19/45) of the patients, and the most common etiologies of bleeding were gastric/duodenal ulcer (n=9), erosive gastritis (n=4), and hemorrhagic gastritis (n=3), similar to the other studies. None of the patients were actively bleeding except one with esophageal variceal bleeding and band ligation was applied in that case.

Most of the patients with bleeding do not seem to require endoscopic treatment, and it should be considered that unnecessary endoscopies should not be applied to pandemic patients to protect health care workers from contamination. In patients with bleeding, the addition of transfusion-related pulmonary disorders^[20] added to pre-existing pulmonary disorders due to COVID-19 pneumonia can be thought to increase mortality in patients. The most important limitation of this study was the absence of a control group. The retrospective nature of the study was also an important limitation. Further prospective controlled studies will shed light on better analysis of the results.

Conclusion

UGIB is less common in COVID-19 patients compared to other hospitalized patients. It can be suggested that most cases of UGIB in COVID-19 patients do not require endoscopic treatment and may be treated conservatively. It is worth considering reducing unnecessary endoscopies in pandemic patients to protect health care workers from contamination. Although patients do not primarily die of bleeding, it should be kept in mind that mortality increases in COVID-19 patients if UGIB develops. Nevertheless, there is a need for prospective controlled studies of COVID-19 patients with UGIB as the complex mechanisms remain unknown.

Ethics Committee Approval: This study was approved by the Gülhane Scientific Research Ethics Committee (Date: 14.01.2021, Decision No:2021-01).

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sign: Ü.A., U.K., C.T., Supervision: Ü.A., U.K., C.T., Resource: Ü.A., U.K., C.T., Data: Ü.A., U.K., C.T., Analysis: Ü.A., U.K., C.T., Literature search: Ü.A., U.K., C.T., Writing: Ü.A., U.K., C.T., Critical revision: Ü.A., U.K., C.T.

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ORIJİNAL ÇALIŞMA - ÖZ

COVID-19 hastalarında üst gastrointestinal sistem kanamaları: Risk faktörleri ve yönetimi / Geriye dönük bir kohort çalışması**Dr. Ümit Alakuş,¹ Dr. Umut Kara,² Dr. Cantürk Tasçı,³ Dr. Mehmet Eryılmaz⁴**¹Sağlık Bilimleri Üniversitesi, Gülhane Eğitim ve Araştırma Hastanesi, Genel Cerrahi Kliniği, Gastroenteroloji Cerrahisi Kliniği, Ankara²Sağlık Bilimleri Üniversitesi, Gülhane Eğitim ve Araştırma Hastanesi, Anesteziyoloji ve Reanimasyon Kliniği, Ankara³Sağlık Bilimleri Üniversitesi, Gülhane Eğitim ve Araştırma Hastanesi, Göğüs Hastalıkları Kliniği, Ankara⁴Sağlık Bilimleri Üniversitesi, Gülhane Eğitim ve Araştırma Hastanesi, Genel Cerrahi Kliniği, Ankara

AMAÇ: COVID-19 hastalığına bağlı koagülopatinin ve ve tedavide kullanılan DMAH ve steroid gibi ilaçların etkisiyle ortaya çıkan üst gastrointestinal sistem kanaması sonuçları olumsuz etkilemektedir. Bu çalışmada, COVID-19 hastalarında gastrointestinal sistem kanama sıklığı, risk faktörleri, yönetimi ile sonuçlara etkisi incelendi.

GEREÇ VE YÖNTEM: 11 Mart 2020 ve 17 Aralık 2020 tarihleri arasında COVID-19 nedeniyle hastaneye yatırılan hastalar için kurumsal merkez (üçüncü düzey bir pandemi merkezi) veri tabanı geriye dönük olarak tarandı. Üst gastrointestinal sistem kanaması semptomları/bulguları olan hastalar dahil edildi. Yaş, cinsiyet, vücut kitle indeksi (kg/m^2), kanamanın teşhis edildiği hastane departmanı, önceki kanama öyküsü, komorbiditeler ve ilaçlar (steroid, antikoagülan, düşük ağırlıklı molekülü heparin, proton pompa inhibitörü) endoskopik bulgu/tedavi, transfüzyon ve ölüm oranları değerlendirildi. Hastalar hayatta kalanlar ve hayatta kalmayanlar olarak iki gruba ayrılarak parametreler kıyaslandı.

BULGULAR: COVID-19 tedavisi altındaki toplam 5484 hastanın 45'inde üst gastrointestinal kanama vardı (%0.8). Hastaların yaş ortalaması 70.1 yıldır ve kanamaların %73'ü erkekti. On dokuz hastaya (%44) endoskopi yapıldı. Kanamanın en sık nedenleri mide/duodenal ülser ($n=9$), eroziv gastrit ($n=4$) ve hemorajik gastrit ($n=3$) idi. Sadece bir hastada müdahale gerektiren aktif kanama tespit edildi ve tüm hastaların sadece birine (%2) terapötik bant ligasyonu uygulandı. Kanamanın en sık nedenleri mide/duodenal ülser ($n=9$), aşındırıcı gastrit ($n=4$) ve hemorajik gastrit ($n=3$) idi. İstatistiksel anlamlılık açısından, hayatta kalmayan grupta steroid tedavi oranı (%77'ye karşı %39) ve steroid tedavi gün sayısının daha yüksek olduğu görüldü.

TARTIŞMA: COVID-19 hastalarında üst gastrointestinal sistem kanaması diğer hastanede yatan hastalara göre daha az görülmektedir. Bununla birlikte, ölüm oranını önemli ölçüde artırmaktadır. Steroid kullanan hastalarda ölüm riski daha da artmaktadır. COVID-19 tedavisi gören hastalarda bu riskler göz önünde bulundurulmalıdır. Kanayan hastaların çoğu endoskopik tedavi gerektirmez ve konservatif olarak tedavi edilmelidir. Pandemi gereksiz endoskopileri azaltmayı düşünmeye değer.

Anahtar sözcükler: COVID-19; gastrointestinal; kanama; steroid.

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