ORIGINAL RESEARCH

Endoscopic findings are not different in patients with upper gastrointestinal bleeding with COVID-19

COVID-19'lu üst gastrointestinal sistem kanamalı hastalarda endoskopik bulgular farklı değildir

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Background and Aims: Coronavirus disease-2019 is an emerging disease of global public health concern. We aimed to evaluate the demographic data, clinical properties, risk factors and endoscopy findings of coronavirus disease-2019 patients with upper gastrointestinal system bleeding. **Materials and Method:** Patients who underwent endoscopy for upper gastrointestinal bleeding between July 2, 2020 and January 29, 2021 and were diagnosed with severe acute respiratory syndrome coronavirus-2 confirmed by polymerase chain reaction were included in the study. In this retrospective study patients with gastrointestinal bleeding were compared as 1:2 case-control. Coronavirus disease-2019 patients who underwent endoscopy for upper gastrointestinal bleeding and the control group were compared retrospectively in terms of demographic data, comorbid diseases, bleeding symptom, drugs administered, laboratory parameters, time between bleeding symptom and endoscopy, endoscopy findings, gastrointestinal bleeding treatment, and mortality rates. **Results:** Forty Covid-19 patients (23 males, mean age ± SD, 65.92 ± 12.97) and 80 non-Covid-19 control patients (43 males, mean age ± SD, 66.17 ± 15.61) who underwent endoscopy for upper gastrointestinal bleeding were compared. The most common bleeding symptom was melena in both groups (50% vs 60%). Hospitalization in intensive care unit (47.5% vs 20%, P = 0.004) and need for mechanic ventilation (22.5% vs 5%, p = 0.006), use of corticosteroids were more common in coronavirus disease-2019 group (30% vs. 2.5%, p = 0.000). The need for erythrocyt replacement were not different between the groups [median (min - max) 1.5 (0 - 13) vs 0.5 (0 - 22), p = 0.397]. Use of low molecular weight heparin was statistically more common in coronavirus disease-2019 group (32.5% vs 5%, p=0.00). Time elapsed until the performance of endoscopy in terms of hours was significantly longer in coronavirus disease-2019 group (62.97 ± 84.59 vs. 21.85 ± 33.91, p = 0.006). The most common endoscopic finding was gastroduodenal ulcer in both groups. No significant differences were seen in terms of rebleeeding rates. Mortality rate was statistically higher in coronavirus disease-2019 group (37.5% vs 8.8%, p = 0.000). **Conclusions:** Until more precise guidelines for the management of gastrointestinal bleeding in COVID-19 patients are developed, a case-by-case decision should be made on whether to perform endoscopy and the timing of the procedure, after multidisciplinary assessments are made in terms of patient status, response to medical therapy, treatment resources, and assessment of risks.

Key words: Covid-19, gastrointestinal bleeding, anticogulant

Giriş ve Amaç: Kovid-19 hastalığı, küresel halk sağlığı endişesi yaratan yeni ortaya çıkan bir hastalıktır. Üst gastrointestinal sistem kanaması olan Kovid-19 hastalarının demografik verilerini, klinik özelliklerini, risk faktörlerini ve endoskopi bulgularını değerlendirmeyi amaçladık. **Gereç ve Yöntem:** 2 Temmuz 2020 - 29 Ocak 2021 tarihleri arasında üst gastrointestinal sistem kanaması nedeniyle endoskopi yapılan ve polimerize zincir reaksiyon ile doğrulanmış ağır akut solunum sendrom-koronavirüs-2 tanısı konan hastalar çalışmaya alındı. Gastrointestinal sistem kanaması olan Kovid-19'lu hastalar retrospektif olarak karşılaştırıldı. Üst gastrointestinal sistem kanaması nedeniyle endoskopi yapılan Kovid-19 hastaları ile kontrol grubu retrospektif olarak demografik veriler, komorbid hastalıklar, kanama semptomu, uygulanan ilaçlar, laboratuvar parametreleri, kanama semptomu ile endoskopi arasındaki süre, endoskopi bulguları, gastrointestinal kanama tedavisi ve ölüm oranları açısından karşılaştırıldı. **Bulgular:** Üst gastrointestinal sistem kanaması nedeniyle endoskopisi yapılan 40 Kovid-19 hastası (23 erkek, ortalama yaş ± SD, 65.92 ± 12.97) ve 80 Kovid-19 hastalığı olmayan kontrol (43 erkek, ortalama yaş ± SD, 66.17 ± 15.61) hastası karşılaştırıldı. Her iki grupta da en sık görülen kanama semptomu melena idi (%50'ye karşı %60). Yoğun bakım ünitesinde yatış (%47.5'e karşı %20, p = 0.004) ve mekanik ventilasyon ihtiyacı (%22.5'e karşı %5, p = 0.006), kortikosteroid kullanımı (%30'a karşı %2.5, p = 0.000) Kovid-19 hastalığı grubunda daha yaygındı. Eritrosit replasmanı ihtiyacı gruplar arasında farklı değildi [medyan (min - maks) 1.5 (0-13) vs 0.5 (0-22), p = 0.397]. Düşük moleküler ağırlıklı heparin kullanımı Kovid-19 hastalığı grubunda istatistiksel olarak daha yaygındı (%32.5'e karşı %5, p = 0.00). Endoskopi performansına kadar geçen süre, saat olarak Kovid-19 hastalık grubunda anlamlı olarak daha uzundu (62.97 ± 84.59 vs. 21.85 ± 33.91, p = 0.006). Her iki grupta da en sık görülen endoskopik bulgu gastroduodenal ülserdi. Tekrar kanama oranları açısından anlamlı bir fark görülmedi. Ölüm oranı Kovid-19 hastalığı grubunda istatistiksel olarak daha yüksekti (%37.5'e karşı %8.8, p = 0.000). **Sonuç:** Kovid-19 hastalarında gastrointestinal sistem kanamalarının yönetimine ilişkin daha kesin kılavuzlar geliştirilinceye kadar, hastanın durumu, medikal tedaviye yanıt, tedavi kaynakları ve risklerin değerlendirilmesi açısından multidisipliner değerlendirmeler yapıldıktan sonra, endoskopi yapılıp yapılmayacağına ve işlemin zamanlamasına vaka bazında karar verilmelidir.

Anahtar kelimeler: Kovid-19, gastrointestinal kanama, antikogülan

INTRODUCTION

Coronavirus disease 2019 (Covid-19), an infectious disease caused by coronavirus 2 (SARS-CoV-2) is characterized by severe acute respiratory failure (1). The typical presentation of coronavirus disease is pulmonary infiltrations associated with fever, cough, and dyspnea (2). Even though the involvement of the respiratory system is the most common manifestation, gastrointestinal tract can be affected as well. Gastrointestinal tract symptoms include nausea, vomiting, diarrhea, abdominal pain, and gastrointestinal bleeding (3). Some observational studies suggest that the risk of gastrointestinal (GI) bleeding may be increased in patients with Covid-19 (4-6). The first-line treatment of acute gastrointestinal bleeding is an endoscopic approach after appropriate resuscitation. Endoscopic guidelines mostly recommend endoscopy procedures should be performed within the first 24 hours in acute upper GI bleeding (7). But endoscopic procedures carry a high risk for health care workers due to aerosol production (8). Due to the risk of transmission, there seems to be a trend towards the conservative treatment of Covid-19 positive patients with GI bleeding consisting of pharmacotherapy, transfusion, and close hemodynamic monitoring (6,9,10). As a result, gastrointestinal pathologies have not been clarified yet in Covid-19 positive patients with GI bleeding. We aimed to present demographic, clinical data, risk factors, and endoscopy findings in patients with Covid-19 positive GI bleeding who underwent endoscopy in a tertiary center retrospectively.

MATERIALS and METHODS

In this single tertiary care center (Ankara City Hospital, Turkey), retrospective study patients with GI bleeding were compared as 1:2 case-control. The Covid-19 group was defined as upper GI bleeding Covid-19 patients confirmed with polymerase chain reaction (PCR) positivity and the control group was defined as upper GI bleeding patients who were confirmed not to have Covid-19 using laboratory, clinical, and imaging data. Endoscopy was performed on all patients in both groups. Patients in the endoscopy database from July 6, 2020, when the first Covid-19 positive case was received, to January 29, 2021, who underwent endoscopy for upper gastrointestinal bleeding were included in the study. Endoscopy patients with upper GI bleeding were selected from this endoscopy database. Patient files were searched and demographic data, data about comorbid diseases, GI bleeding symptom, medications used especially antiplatelet and anticoagulant drugs, laboratory parameters, the time period between the bleeding symptom and endoscopy procedure, endoscopic findings, treatments for GI bleeding (medical, endoscopic, radiologic, surgery) were extracted from electronic medical records. The endpoint of the study was the discharge or exit of the patients. Over acute upper GI bleeding was accepted as symptoms such as hematemesis, melena, hematochezia, blood in a nasogastric tube, blood coming from ostomy site, syncope, or drop of hemoglobin more than 2 units. Covid-19 positivity was defined as Covid-19 PCR positivity in nasopharyngeal swabs. The control group was selected from upper GI bleeding patients to whom endoscopy was performed and with no previous history of Covid-19 disease and with no fever, cough, and respiratory difficulty at the time of endoscopy. Patients in the control group were Covid-19 PCR negative, an antibody against Covid-19 was negative (Immunoglobulin G + Immunoglobulin M), and they did not have any Covid-19 findings radiologically Covid-19 PCR negativity was accepted only if the test was performed within the 24 hours before endoscopy. Patients younger than 18 years of age, with suboptimal endoscopy reports and pregnant patients were excluded.

Endoscopic classification of upper GI bleeding was defined according to international guidelines

(11,12). Endoscopic treatments were recorded. Radiologic and surgical treatments were recorded in patients with endoscopic treatment failure. General mortality rates were recorded.

Ethics

This study was conducted with the permission of the Ministry of Health of Turkish Government. Ethics board permission was granted from Ankara Yıldırım Beyazıt University Faculty of Medicine with the reference number 26379996150/40. The data entry was made without using any identity information (i.e., name) thereby patient anonymity was assured.

Statistics

In this retrospective study, discrete variables such as the need for ventilation and the rate of intensive care unit admission were presented in terms of absolute values and percentages. Continuous variables, such as ferritin, hemoglobin, hematocrit levels were expressed and summarized based on mean, standart deviation (SD), median and interquartile range values. Frequencies were expressed per hundred (%) separately for Covid-19 and non-Covid-19 patients with 95% confidence interval (CI). For the comparison of Covid-19 and non-Covid-19 patients (i.e., control group), the χ^2 test and cross-tab analysis were utilized to analyze the frequency differences in discrete variables. In particular, frequencies for the use of low molecular weight heparin and mortalities (i.e., mortality rates) were compared using Chi-square tests and cross-tabs analysis. On the other hand, Student t test were conducted to compare Covid-19 patients with non-Covid-19 patients in terms of hemoglobin levels, Hematocrit levels, lymphocyte count, platelet count, international normalised ratio (INR), blood urea nitrogen (BUN), creatinine, blood cell count, ferritin levels. In all comparisons, statistical significance was accepted if the p-value was < 0.05.

All analyses were conducted with the SPSS (v.24) statistical software package (IBM Corp., Armonk, NY). After the analyses were conducted, post-hoc analysis of "observed power" was made by using the obtained sample and effect size. For the comparisons of ferritin levels and white blood cell counts, the power of the analysis was found to be more than 0.80 threshold level. For instance, using an alpha level of .05, an effect size of .76, and sample sizes of 40 and 59 for Covid-19 and non-Covid -19 patient groups respectively, we found the post hoc statistical power to be .98 using G*power analysis.

RESULTS

Fourty Covid-19 positive patients with upper GI bleeding in whom endoscopy was performed and 80 non- Covid-19 controls with upper GI bleeding and endoscopy performed during the same period were selected for this retrospective study. Basic demographic data of both groups are presented in Table 1.

The most common bleeding symptom was melena in both groups. According to Chi-Square Analysis, the rate of intensive care unit admission and the need for mechanical ventilation were found to be more prevalent in Covid-19 group. Besides, the use of corticosteroids was more frequently observed in the Covid-19 group compared to non-Covid-19 patients. The use of low molecular weight heparin (LMWH) was statistically more common in the Covid-19 group (32.5% vs 5%, p = 0.00). Remarkably, there were no significant differences in terms of packed red blood cell replacement between the groups [median (min-max) 1.5 (0-13) for Covid-19 group vs 0.5 (0-22), p = 0.397 for non-Covid-19 group]. Besides packed red blood cell replacements, statistically significant differences were not obtained between two groups for minimum or maximum hemoglobin levels, hematocrit levels, lymphocyte count, platelet count, INR, BUN, creatinine.

Table 1 Demographic and clinical data of with Covid-19 GI bleeding patients and non-Covid-19 GI bleeding patients.

	Group 1 (n = 40)	Group 2 (n = 80)	p value
Gender (Female/Male)	17/23	37/43	0.697
Age (years)	65.92 ± 12.97	66.17 ± 15.61	0.931
Comorbidity, n (%)	33 (82.5)	67 (83.8)	1
Hypertension	50 (50)	38 (47.5)	0.049
Diabetes	19 (47.5)	26 (32.5)	0.162
Coronary arter disease	6 (15)	21 (26.3)	0.246
Cancer	7 (17.5)	10 (12.5)	0.644
Cirrhosis	2 (5)	7 (8.8)	0.370
Chronic renal failure	6 (15)	7 (8.9)	0.237
Neurological disease	5 (12.5)	17 (21.3)	0.359
COPD	5 (12.5)	2 (2.5)	**0.04**
Congestive heart failure	2 (5)	0 (0)	0.109
Other	1 (2.5)	11 (13.8)	**0.045**
History of peptic ulcer, n (%)	5 (12.5)	6 (7.5)	0.282
Use of corticosteroids, n (%)	12 (30)	2 (2.5)	**0.000**
Bleeding symptom, n (%)			
Melena	20 (50)	48 (60)	0.471
Hematemesis	10 (25)	25 (31.25)	0.619
Hematochesia	4 (10)	3 (3.75)	0.167
Drop of hemoglobin	2 (5)	0 (0)	0.109
Blood in NG tube	3 (7.5)	1 (1.25)	0.107
Blood in ostomy	1 (2.5)	1 (1.25)	0.557
Syncope	0 (0)	2 (2.5)	0.443
Hospitalization in intensive care unit, n (%)	19 (47.5)	16 (20)	**0.004**
Oxygen treatment, n (%)			
Room air	20 (50)	69 (87.3)	**0.000**
Low flow	6 (15)	5 (6.3)	**0.111**
High flow	5 (12.5)	2 (2.5)	**0.040**
Mechanical ventilation	9 (22.5)	4 (5)	**0.006**
ES replacement median (min - max)	1.5 (0-13)	0.5 (0-22)	0.397
Medical treatment for bleeding, %			0.354
PPI infusion	37 (92.5)	75 (93.8)	
PPI + somatostatin infusion	2 (5)	5 (6.2)	
PPI x 2	1 (2.5)	0 (0)	
Rebleeding, %	6 (15)	4 (5)	0.068
Exitus, %	15 (37.5)	6 (7.5)	**0.000**

COPD: Chronic obstructive pulmonary disease, NG: Nasogastric, ES: Erythrocyte suspension, PPI: Proton pump inhibitor.

Independent sample t-tests revealed that white blood cell count and ferritin levels were statistically higher in the Covid-19 group. Albumin levels were statistically lower in the Covid-19 group (Table 2). Time spent until endoscopy procedure (hours) (defined as the time from emergency department

Table 2 Laboratory findings of Covid-19 GI bleeding patients and non-Covid-19 GI bleeding patients

	Group 1 (n = 40)	Group 2 (n = 80)	p value
Hgb max, g/dL	11.94 ± 0.37	11.53 ± 0.25	0.358
Hgb min, g/dL	7.93 ± 0.41	7.99 ± 0.26	0.895
Htc	25.72 ± 1.36	26.19 ± 0.82	0.759
White blood cell count, 103 µL^{-1}	14628 ± 2797	8471 ± 599	**0.037**
Lymphocyte, 10^3 µL-^{1}	1255 ± 341	1686 ± 247	0.316
Platelet count, 10^3 µL-^{1}	228350 ± 26205	239116 ± 12194	0.671
INR	4.21 ± 2.89	1.52 ± 0.17	0.360
BUN, mg/dL	91.77 ± 9.46	74.58 ± 6.47	0.132
Cr, mg/dL	1.53 ± 0.21	1.24 ± 0.13	0.237
D-Dimer, ng/mL	4.28 ± 1,28	3.73 ± 0,99	0,736
Ferritin, (µg/L)	781.39 ± 180	164.26 ± 36.39	**0.002**
LDH (U/L)	339.48 ± 25.28	279.15 ± 37.96	0.189
C-reactive protein (g/L)	0.77 ± 0.12	0.45 ± 0.11	0.062
Albumin (g/L)	30.86 ± 1.19	34.91 ± 0.8	**0.006**

Hgb: Hemoglobin, Htc: Hematocrit, INR: International normalized ratio, BUN: Blood urea nitrogen, Cr: Creatinine, LDH: Lactic dehydrogenase.

admission to endoscopy in outpatients and time from the first appearance of bleeding symptoms to endoscopy in already hospitalized patients) was significantly longer in Covid-19 patients.

There were no significant differences in terms of endoscopy findings between Covid-19 and the non-Covid-19 group. The most common endoscopic finding was a gastroduodenal ulcer in both groups. Due to a low number of cases, other endoscopic findings could not be compared but 2 cases of candida esophagitis were detected in the Covid-19 group and erosive gastritis was numerically more common (17.5% vs 7.5%). There were no differences in terms of Forrest classification of gastroduodenal ulcers. Similarly, there were no differences in terms of endoscopic management between the groups (Table 3). No differences were not noted in terms of medical treatment of upper GI bleeding (p = 0.354). Two patients needed surgical treatment for GI bleeding. No surgical treatment was needed for patients in the non-Covid-19 group but 1 patient underwent embolization by interventional radiology. The rate of rebleeding did not differ between the groups. Mortality rate of Covid-19 patients were significantly higher than non-Covid-19 group (37.5% vs 7.5%, p = 0.000) (Table 1). The cause of mortality was due to GI bleeding in only 1 patient out of 15 in the Covid-19 group while in the non-Covid-19 group 4 out of 6 patients died due to upper GI bleeding.

DISCUSSION

Endoscopy guidelines recommend that, upper GI endoscopy be performed in the first 24 hours upon admission (7). This approach enables to determine to cause of bleeding, estimate the risk of rebleeding/mortality, and apply therapeutic measures if necessary. A therapeutic approach to GI bleeding has been affected during the Covid-19 pandemic. In clinical practice, this 24-hour recommendation can be ignored due to some reservations. This delay might be due to respiratory failure and difficulty of oxygenation of the patients with accompanying

Table 3 Endoscopic outcomes of Covid-19 and non-Covid-19 patients with upper GI bleeding.

	Group 1 (n = 40)	Group 2 (n = 80)	p value
Endoscopy findings			0.276
Gastric ulcer, n (%)	5 (12.5)	11 (13.75)	
Duodenal ulcer, n (%)	9 (22.5)	18 (22.5)	
Gastroduodenal ulcer, n (%)	1 (2.5)	4 (5)	
Erosive gastritis, n (%)	7 (17.5)	6 (7.5)	
Varix, n (%)	2 (5)	5 (6.25)	
Mallory Weis tear, n (%)	0 (0)	1 (1.25)	
Pangastropathy, n (%)	9 (22.5)	12 (15)	
Candida esophagitis, n (%)	2 (5)	0 (0)	
Other, n (%)	2 (5)	13 (16.25)	
AD, n (%)	1 (2.5)	2 (2.5)	
No visible source, n (%)	2 (5)	8 (10)	
Ulcer, Forrest classification, n	15	33	0.429
Forrest 1a, n (%)	0 (0)	1 (3)	
Forrest 1b, n (%)	1 (6.7)	4 (12)	
Forrest 2a, n (%)	4 (26.6)	2 (6)	
Forrest 2b, n (%)	1 (6.7)	3 (9)	
Forrest 2c, n (%)	2 (13.4)	8 (24)	
Forrest 3, n (%)	7 (46.6)	15 (46)	
Endoscopic intervention, n	40	80	0.339
None, n (%)	32 (80)	59 (73.75)	
Injection, n (%)	3 (7.5)	3 (3.75)	
Cautery, n (%)	1 (2.5)	1 (1.25)	
Hemoclip, n (%)	3 (7.5)	3 (3.75)	
Injection, cautery, n (%)	0 (0)	6 (7.5)	
Injection, hemoclip, n (%)	0 (0)	3 (3.75)	
APC, hemoclip, n (%)	0 (0)	1 (1.25)	
EBL, n (%)	1 (2.5)	2 (2.5)	

AD: Angiodysplasia, APC: Argon plasma coagulation, EBL: Endoscopic band ligation

cardiopulmonary complications or upper GI endoscopy being a highly aerosol producing procedure causing risk of transmission (13). This observation has been confirmed in our study. The time period between emergency department admission in outpatients and appearance of first bleeding symptom in hospitalized patients and endoscopy was significantly longer in the Covid-19 group. Gonzales R et al. have shown that endoscopy was performed 30% less in Covid-19 patients with upper GI bleeding (14). On the other hand daily, GI endoscopy

practice has also been affected in non-Covid-19 patients in pandemic and these changes are anticipated to last in the near future. Gastroenterological procedures are decreased with the advent of the pandemic. Lantinga MA et al. have reported that gastroscopic procedures have been decreased 57% (15). This trend seems to be also affecting non-Covid-19 patients with GI bleeding. But in our study, we have shown that upper GI endoscopy was performed within 21.85 ± 33.91 hours in non-Covid-19 patients with GI bleeding.

When we evaluated the data of both Covid-19 and non-Covid-19 patients with upper GI bleeding in this single-center retrospective case-control study we saw the most common etiology was gastroduodenal ulcer. We searched the endoscopic data of 40 Covid-19 patients in this study. To our knowledge, this is one of the highest numbers of Covid-19 patients with upper GI bleeding and reports of endoscopic procedures. When we searched the current literature we could see case series or fewer patients with endoscopic procedures (6,16,17). None of these studies included a comparison with non-Covid-19 GI bleeding patients. Gonzales et al. performed endoscopy in 39 Covid-19 patients with upper GI bleeding in the emergency department before hospitalization. Peptic ulcer was the most common finding in these patients with a 46.2% rate. They compared endoscopic findings with the non-Covid-19 GI bleeding group and found no significant difference (14). We also did not find a significant difference in terms of endoscopic findings between Covid-19 and non-Covid-19 groups. Generally, the most common reason for upper GI bleeding has been reported to be peptic ulcer disease (approximately 32-36%) in the literature. The other commonly reported reasons are gastritis or gastric erosions (18-22%) and duodenitis (13%) (18). In our study, we also found similar findings in Covid-19 and non-Covid-19 groups.

Observational studies suggested the beneficial effect of anticoagulant treatment on mortality rates in patients with Covid-19 related coagulopathy or a prominent increase in serum D-dimer levels (19). As a result, most hospitals integrated anticoagulant drugs into standard medical treatment. Likewise, LMWH use was significantly higher in Covid-19 patients. Anticoagulant drugs have been considered as risk factors for GI bleeding in the non-Covid-19 population. The risk of anticoagulant treatment for GI bleeding in Covid-19 patients has not been clarified yet. Trindade et al. suggested that the anticoagulant and antiplatelet drugs do not pose an increased risk of GI bleeding in Covid-19 patients (10,17). We also found that GI bleeding-related mortality was not high in Covid-19 patients despite the common use of LMWH. Likewise, rates of rebleeding were also similar in both groups.

Proton pump inhibitor (PPI) treatment had been given to all patients with a presumed diagnosis of GI bleeding. Although time period between admission/bleeding symptom to endoscopy was significantly higher in the Covid-19 group there were no significant differences in terms of the need for transfusion, endoscopic findings, rebleeding rates between Covid-19 and non-Covid-19 groups. Similarly, Mauro et al. did not find any difference in terms of mortality and rebleeding between the groups (groups were defined as patients to whom endoscopy was done in the first 24 hours, endoscopy was done after >24 hours, and patients who did not undergo endoscopic evaluation) (17). While deciding the timing of endoscopy a gastroenterologist should also consider the severity of the systemic involvement of Covid-19 disease, the presence or absence of significant respiratory involvement of the disease. Sedation and the endoscopic procedure itself may negatively affect respiratory functions. In patients, breathing room air or low flow oxygen endoscopy can be performed in the first 24 hours as guidelines recommend. On the other hand in patients receiving high flow oxygen or noninvasive positive pressure ventilation decision to perform endoscopy should be done after consideration of GI bleeding risk scores.

In this study of patients with GI bleeding, we found that Covid-19 patients had a significantly higher in-hospital mortality rate than the non-Covid-19 group. While only 1 out of 15 deaths in the Covid-19 group was due to GI bleeding this rate was 4 out of 6 in the non-Covid-19 group. Patients with GI bleeding in the Covid-19 group were shown to bleed during Covid-19 treatment, so they died from complications related to the Covid-19 disease. Our

hospital mortality rate in Covid-19 patients with GI bleeding was higher than mortality of Covid-19 patients without GI bleeding (Ates I et al. unpublished data). This may suggest that GI bleeding in Covid-19 patients is a complication advanced disease leading to a higher mortality rate. Further studies are needed to clarify whether GI bleeding has an effect on mortality rates in Covid-19 patients.

There are some limitations of our study. First of all, this is a retrospective study. Symptom evaluation of GI bleeding might have led to interobserver variations of definitions. Patients with melena were accepted as upper GI bleeding and a small fraction of these patients might be suffering from bleeding from middle or lower GI bleeding. Time to endoscopy was significantly different between the groups and medical treatment had been initiated in the meantime. This medical treatment might have changed the endoscopic findings. Another limitation of our study was the lack of data about the previous use of non-steroid antiinflammatory drugs (NSAIDs) and PPI. NSAIDs have long been known to be important in the etiology of peptic ulcer disease and most of our GI bleeding patients had a gastroduodenal ulcer.

We found similar etiologies in GI bleeding patients with or without Covid-19 infection. Although the time period between symptom/hospital admission till endoscopy was significantly longer in Covid-19 patients there were no significant differences in terms of the need for transfusion, rebleeding rates, and GI bleeding-related mortality rates from non-Covid-19 GI bleeding patients. Until definitive guidelines are developed decisions on whether to perform endoscopy and timing of the endoscopy should be made after multidisciplinary evaluation of the patient and after careful consideration of the patient's condition, response to medical treatment, risk evaluation. Finally, the decision should be individualized for each patient.

Ethics Committee: This study protocol was approved by Ethics Committee of Ankara Yıldırım Beyazıt University Faculty of Medicine (Date: 07.07.2021, and number 40). The study was complied with The World Medical Association Declaration of Helsinki.

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