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Research Article

Gastrointestinal Bleeding In COVID-19 Infection: A case-control study

COVID-19 Enfeksiyonunda Gastrointestinal Kanama: Vaka- Kontrol Çalışması

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Abstract

Aim: Since the gastrointestinal tract contains ACE-2 receptors, gastrointestinal symptoms, including gastrointestinal bleeding (GIB), are frequently seen during COVID-19 infection. In addition, the risk of GIB increases not only due to the virus but also to the drugs used during the treatment of infection. In this study, we aimed to determine the frequency of GIB in patients being treated due to COVID-19 infection in the intensive care unit (ICU), and to examine the effects of anticoagulant, antiaggregant, corticosteroid, antibiotic, and antiviral treatments on bleeding risk.

Material and Methods: This retrospective study included a total of 189 patients hospitalized due to the COVID-19 infection in the intensive care unit. Patients were analyzed according to the presence of GIB. The duration and doses of treatment with steroid, pulse steroid, anticoagulant, antiaggregant, and proton pump inhibitors were also analyzed. Intubation need and mortality rates were compared between GIB and without GIB.

Results: GIB developed in 34 (18%) patients followed in the COVID-19 -ICU. Patients with GIB had longer use of steroids and anticoagulants than those without GIB ($p<0.001$ and $p=0.005$). The mortality rate was higher in those with GIB (73.5% vs 51%, $p=0.027$)

Conclusion: It has been shown that the risk of GIB in patients hospitalized in the COVID-19 ICU is associated with the duration of anticoagulant and steroid therapy. Therefore, we think that patients receiving these treatments should be followed up for the risk of GIB.

Keywords: COVID-19, gastrointestinal bleeding, intensive care unit, anticoagulant, proton pump inhibitor

Öz

Amaç: Gastrointestinal sistem, ACE-2 reseptörü içermesinden dolayı COVID-19 enfeksiyonu sırasında gastrointestinal kanama dahil olmak üzere gastrointestinal semptomlar sıklıkla görülür. Ayrıca sadece virüs nedeniyle değil enfeksiyonun tedavisinde kullanılan ilaçlar nedeniyle de gastrointestinal kanama riski artmaktadır. Bu çalışmada COVID-19 nedeni ile COVID-19 yoğun bakım ünitesinde tedavi edilen hastalarda gastrointestinal kanama sıklığının saptanması ve antikoagülan, antiagregan, kortikosteroid, antibiyotik ve antiviral tedavilerin kanama riski üzerine etkilerini incelemeyi amaçladık.

Materyal ve Metot: Çalışma retrospektif bir çalışmadır. Çalışmaya COVID-19 yoğun bakım ünitesinde takip edilen 189 hasta dahil edilmiştir. Hastalar gastrointestinal kanama varlığına göre analiz edildi. Hastaların steroid, pulse steroid, antikoagülan, antiagregan ve proton pompa inhibitörü tedavisi alıp almaması, tedavi süresi ve tedavi dozları incelendi. Gastrointestinal kanama olan ve olmayan hastalarda entübasyon ihtiyacı ve mortalite oranları karşılaştırıldı.

Bulgular: COVID-19 yoğun bakımda takip edilen hastaların 34 (%18)'ünde gastrointestinal kanama geliştiği gözlendi. Gastrointestinal kanaması olan hastaların, kanaması olmayanlara göre daha uzun süre steroid ve antikoagülan tedavi kullanımına sahip olduğu gözlendi ($p<0.001$ ve $p=0.005$). Gastrointestinal kanama geçirenlerde mortalite oranı daha yüksek izlendi (%73.5 vs %51, $p=0.027$)

Sonuç: COVID-19 yoğun bakım ünitesinde yatan hastalarda gastrointestinal kanama geçirme riskinin, antikoagülan ve steroid tedavisinin süresi ile ilişkili olduğu gösterilmiştir. Bu nedenle, bu tedavileri alan hastaların gastrointestinal kanama açısından takip edilmesi gerektiğini düşünmekteyiz.

Anahtar Kelimeler: COVID-19, gastrointestinal kanama, yoğun bakım ünitesi, antikoagülan, proton pompa inhibitörü

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) started in Wuhan in December 2019 and caused 5.5 million deaths as of January 2022, according to World Health Organization (WHO) data (1). It has been observed in several studies that COVID-19 does not only affect the respiratory system but also affects extrapulmonary systems such as the cardiovascular, central nervous, and gastrointestinal systems (2-4).

Gastrointestinal bleeding (GIB) is one of the common causes of emergency consultations in COVID-19. It is thought that many mechanisms cause this situation. Firstly, the SARS-CO-2 virus enters the cell through the ACE-2 receptor. Since the ACE-2 receptor is found in the lungs, gastrointestinal tract, heart, and kidneys, these systems may be affected (5). Gastrointestinal system findings include diarrhea, nausea, vomiting, abdominal pain, abnormal liver function tests, and GIB (6,7). GIB is not common but may be seen in patients with COVID-19 infection (7). Secondly, the drugs used in the treatment increase the risk of bleeding. It is known that corticosteroids, which are drugs used in the treatment of COVID-19, may also increase the risk of bleeding and perforation (8). In addition, anticoagulant therapy is commonly used according to the clinical status and laboratory findings of the patients due to the increased thromboembolic risk of COVID-19 infection (9). That is also an additional factor increasing the risk of GIB (10).

In this study, we aimed to analyze the frequency of GIB in patients diagnosed with COVID-19 treated in an intensive care unit, and compare the duration and doses of corticosteroid, anticoagulant, antiaggregant, antibiotic, and antiviral therapy.

MATERIAL AND METHOD

Study Design and Settings

This retrospective study was approved by the Health Science Ethics Committee of Muğla Sıtkı Koçman University (14.04.2021- 60). This study was conducted with patients hospitalized in the intensive care unit due to COVID-19 infection. It was carried out in a COVID-19 intensive care unit with a capacity of 14 patients in a secondary hospital. The study included a total of 189 patients between September 1, 2020, and February 1, 2021. Indications for the intensive care unit were planned according to the patient management guide of the Ministry of Health (11).

Selection of the Participants

Patients over the age of 18 were included. Both COVID-19 polymerase chain reaction (PCR) positive and negative patients who were admitted to the intensive care unit with typical radiological findings of COVID-19 were also included. The exclusion criteria in this study were the patient's referral to an external center for any reason or due to the inability to follow up on the last condition of the patient. GIB symptoms are accepted as hematemesis, melena, hematochezia, and presence of the fecal occult blood.

Measurements and Outcomes

Patients hospitalized in the COVID-19 intensive care unit were examined in terms of PCR results and thorax CT findings. Comorbidities and previous GIB of the patients were noted. The duration ve doses of steroid, pulse steroid, anticoagulant, antiaggregant, antibiotic, and antiviral treatments given to the patients were examined. INR, hemoglobin, and platelet counts were examined on the day of hospitalization and the day of GIB. Hospitalization days, length of the intensive care stay, and mortality status were examined.

Statical Analysis

In the summary of data, descriptive statistics are tabulated as mean±standard deviation or median, minimum and maximum depending on the distribution for continuous (numerical) variables. Categorical variables were summarized as numbers and percentages. The normality of numeric variables; was checked with Shapiro-Wilk, Kolmogorov-Smirnov, and Anderson-Darling Tests.

In the comparison of two independent groups; the Independent Samples T-Test was used when numerical variables showed normal distribution, and the Mann Whitney U test was used they show no normal distribution.

Pearson Chi-Square was used in 2x2 tables with expected cells 5 and above, Fisher's Exact Test was used in tables with expected cells below 5, and Fisher Freeman Halton test was used in RxC tables with expected cells below in the comparison of differences between categorical variables according to groups.

Statistical analyzes "Jamovi project (2020), Jamovi (Version 2.0.0) [Computer Software] (Retrieved from https://www.jamovi.org) and JASP (Version 0.14.1.0) (Retrieved from https://jasp-stats.org) programs and the level of significance was taken into account as 0,05 (p-value) in statistical analysis.

RESULTS

A total of 189 patients were included in the study. The study group consisted of 108 male (57.1%) and 61 female (42.9%) patients with a mean age of 67.6±16.1 years. Previous GIB was positive in three patients (1.6 %). Hypertension was present in 105 patients (55.6 %) and was the most common comorbid disease. Positive COVID-19 PCR results and typical thorax CT findings for COVID-19 were detected in 118(62.1%) and 180 (95.2%) patients, respectively (Table 1).

GIB was developed in 34 (18%) of patients in the study. GIB developed in 8.5 days (2-37 days) after hospitalization. The median values of INR, hemoglobin, and platelet count on the day of admission were within the normal range. As laboratory tests, were performed on the day of bleeding, INR and platelet count were found to be within the normal range. The median hemoglobin value was 8.5g/dL (Table 2).

Table 1. Demographic and clinical characteristics of patients

	All patients (n=189)
Age†	67.6±16.1
Gender‡	
Male	108 (57.1)
Female	81 (42.9)
Previous gastrointestinal bleeding. yes‡	3 (1.6)
Comorbidites‡	
Diabetes mellitus	69 (36.5)
Hypertension	105 (55.6)
Coronary Artery Disease	59 (31.2)
Chronic Obstructive Respiratory Disease	17 (9.0)
Asthma	10 (5.3)
Chronic Kidney Disease	24 (12.7)
Cancer	12 (6.3)
COVID 19 PCR positive‡	118 (62.4)
COVID 19 Thorax CT positive‡	180 (95.2)

†:mean ± standard deviation‡: n (%)

Table 2. Features of GIB

		All patients (n=189)
Presence of GIB ‡		34 (18.0)
Day of hospitalization where GIB develop§		8.5 [2.0–37.0]
Laboratory findings §		
Hospitalization day	INR	1.1 [0.8–3.6]
	Hemoglobin (g/dL)	12.3 [6.1–151.0]
	Platelet count (x10^9)	216.0 [24.0–662.0]
Day of the GIB	INR	1.0 [1.0–1.1]
	Hemoglobin (g/dL)	8.5 [5.9–11.5]
	Platelet count (x10^9)	206.5 [26.0–547.0]

‡: n (%), §: median [min-max]

The details of treatment were presented in Table-3. While steroid treatment was used in 82.5% of the patients, pulse steroid treatment was needed in 33 patients (17.5%). Anticoagulant and antiaggregant treatments were used in 92.6% and 11.6% of patients. Proton pump inhibitors (PPI) drugs were administered to 183 patients (96.8%). PPIs were used in 59% of these patients daily.

The median duration of hospitalization and intensive care unit stay were 12 and 7 days. At the end of the treatment, the overall mortality rate was 55% (Table 4).

Patients with and without GIB were compared in Table 5 in terms of demographic and general characteristics. No significant difference was detected between the two groups.

Table 3. Distribution of treatment

	All patients (n=189)
Steroid treatment ‡	156 (82.5)
Steroid treatment day	9.5 [1.0 – 35.0]
Pulse steroid treatment‡	33 (17.5)
Pulse steroid treatment day	4.0 [1.0–9.0]
Anticoagulant treatment‡	175 (92.6)
Anticoagulant treatment day	11.0 [1.0–55.0]
Anticoagulant dosage‡	
0.4 ml, 1/day	1 (0.6)
0.4 ml, 2/day	35 (19.9)
0.6 ml, 1/day	82 (46.6)
0.6 ml, 2/day	22 (12.5)
0.8 ml, 1/day	35 (19.9)
0.8 ml, 2/day	1 (0.6)
Antiaggregant treatment ‡	22 (11.6)
Antiaggregant treatment day	5.5 [1.0–31.0]
Proton pump inhibitor treatment‡	183(96.8)
Proton pump inhibitor treatment day	11.0 [1.0–62.0]
Proton pump inhibitor treatment dosage‡	
1/day	61 (33.3)
2/day	110 (60.1)
3/day	10(5.5)
4/day	2 (1.1)
Regular daily use PPI treatment ‡	111 (59.0)
Antiviral ‡	169 (89.4)
Antibiotic ‡	187 (98.9)

‡: n (%), §: median [min-max]

Table 4. Treatment outcomes and mortality details

	All patients (n=189)
Need for intubation‡	109 (57.7)
Total days of hospitalization§	12.0 [0.0–65.0]
Intensive care unit length of stay (days) §	7.0 [1.0–48.0]
Intubation in the presence of GIB‡	**15 (50.0)**
Prognosis‡	
Survivor	85 (45.0)
Exitus	104 (55.0)

‡: n (%), §: median [min-max]

There was a significant difference between the groups in terms of hospitalization hemoglobin value (p=0.022). The median hospitalization hemoglobin value of patients with GIB was significantly lower than those without GIB (11.4 and 12.6 g/dL)(Table 6).

It was determined that steroid and anticoagulant drugs were used for significantly longer periods in patients with GIB than in patients without GIB (p<0.001 ve p=0.005)(Table 7). The dosage and frequency of the anticoagulant drug used did have no significant effect on GIB (p=0.261). The

Table 5. Comparison of patients with and without GIB in terms of demographic and general characteristics

	GIB (-) (n=155)	GIB (+) (n=34)	p
Age†	66.9 ± 15.9	70.7 ± 16.7	0.227
Gender‡			
Male	92 (59.4)	16 (47.1)	0.262
Female	63 (40.6)	18 (52.9)	
Previous GIB. yes‡	2 (1.3)	1 (2.9)	0.450
Comorbidities‡			
Diabetes mellitus	53 (34.2)	16 (47.1)	0.225
Hypertension	84 (54.2)	21 (61.8)	0.539
Coronary Artery Disease	46 (29.7)	13 (38.2)	0.441
Chronic Obstructive Respiratory Disease	14 (9.0)	3 (8.8)	0.999
Asthma	9 (5.8)	1 (2.9)	0.693
Chronic Kidney Disease	20 (12.9)	4 (11.8)	0.999
Cancer	10 (6.5)	2 (5.9)	0.999
COVID 19 PCR positive‡	99 (63.9)	19 (55.9)	0.499
COVID 19 thorax CT positive‡	147 (94.8)	33 (97.1)	0.999

†: mean ± standard deviation‡: n (%)

Table 6. Comparison of patients with and without GIB in terms of laboratory values during hospitalization

	GIB (-) (n=155)	GIB (+) (n=34)	p
INR §	1.1 [0.8–3.6]	1.1 [0.9–1.6]	0.702
Hemoglobin (g/dL)§	12.6 [6.1–151.0]	11.4 [6.1–16.5]	0.022
Platelet Count (x10^9)§	213. 0 [25.0–645.0]	234.5 [24.0–662.0]	0.758

§: median [min-max]

Table 7. Comparison of patients with and without GIB in terms of treatment characteristics.

	GIB (-) (n=155)	GIB (+) (n=34)	p
Steroid treatment‡	125(80.6)	31 (91.2)	0.224
Steroid treatment day	8.0 [1.0–30.0]	14.0 [2.0–35.0]	**<0.001**
Pulse steroid treatment‡	25 (16.1)	8 (23.5)	0.435
Pulse steroid treatment day	4.0 [1.0–9.0]	4.0 [1.0–8.0]	0.882
Anticoagulant treatment‡	142 (91.6)	33 (97.1)	0.471
Anticoagulant treatment day	10.0 [1.0–45.0]	14.0 [3.0–55.0]	**0.005**
Anticoagulant dosage‡			
0.4 ml. 1/day	1 (0.7)	0 (0.0)	0.261
0.4 ml. 2/day	27 (18.9)	8 (24.2)	
0.6 ml. 1/day	72 (50.3)	10 (30.3)	
0.6 ml. 2/day	17 (11.9)	5 (15.2)	
0.8 ml. 1/day	25 (17.5)	10 (30.3)	
0.8 ml. 2/day	1 (0.7)	0 (0.0)	
Antiaggregant treatment ‡	15 (9.7)	7 (20.6)	0.082
Antiaggregant treatment day	4.0 [2.0–31.0]	7.0 [1.0–11.0]	0.831
Proton pump inhibitor treatment ‡	149 (96.1)	34 (100.0)	0.594
Proton pump inhibitor treatment day	10.0 [1.0–46.0]	16.0 [2.0–62.0]	<0.001
Proton pump inhibitor treatment dosage ‡			
1/day	55 (36.9)	6 (17.6)	0.002
2/day	89 (59.7)	21 (61.8)	
3/day	4 (2.7)	6 (17.6)	
4/day	1 (0.7)	1 (2.9)	
Regular daily use PPI treatment ‡	90 (58.4)	21 (61.8)	0.870
Antiviral ‡	136 (87.7)	33 (97.1)	0.133
Antibiotic ‡	153 (98.7)	34 (100.0)	0.999

‡: n (%). §: median [min-max]

Table 8. Comparison of patients with and without GIB in terms of treatment outcomes				
		GIB (-) (n=155)	GIB (+) (n=34)	p
Need for intubation‡		82 (52.9)	27 (79.4)	**0.008**
Intubation in the presence of GIB‡		0 (0.0)	15 (51.7)	0,999
Total days of hospitalization (day)§		11.0 [0.0 – 51.0]	17.0 [3.0–65.0]	**<0.001**
Intensive care unit length of stay (day)§		6.0 [1.0 – 31.0]	13.5 [2.0–48.0]	**<0.001**
Prognosis‡				
	Survivor	76 (49.0)	9 (26.5)	**0.027**
	Exitus	79 (51.0)	25 (73.5)	

‡: n (%), §: median [min-max]

median duration of use PPI was found to be significantly higher in patients with GIB (16 days vs 10 days, p=0.002). In patients with GIB, the use of PPI drugs three times a day more preferred (17.6% vs 2.7% p=0.002). No significant differences were found between the groups regarding other treatments (Table 7).

Intubation need, and length of stay in the intensive care unit were significantly higher in patients with GIB (Table 8). The mortality rate was 51% in patients without GIB, whereas 73.5 % in patients with GIB. The difference was statistically significant (p=0.027).

DISCUSSION

In our study, we examined the frequency of gastrointestinal bleeding and the relationship between antiaggregant, anticoagulant, corticosteroid, antibiotic, and antiviral therapy and GIB in COVID-19- ICU. In this study, GIB was observed in 34 patients (18%). The duration of corticosteroid and anticoagulant treatment was founded to be significantly longer in patients with GIB. In addition, we observed that there was a significantly longer duration of hospitalization in the intensive care unit and total hospitalization length of stay in those patients. The mortality rate was higher in the GIB group than in those without GIB.

In this study, we observed that the mean age of the patients was 67.6, 57.1% of the patients were male, and the most common comorbidity was hypertension followed by diabetes mellitus and coronary artery disease. These findings were similar to the results of the multicenter COVID-19-ICU study in our country. In this multicenter study, 58.6% of the male patients and 51.3% of them had hypertension, the most common comorbidity, and the other common comorbidities were diabetes mellitus and cardiac disease (12). Similarly, in Italy, the most common comorbidity was hypertension, and was more common in male patients. In addition, hypercholesterolemia was founded as the second most common disease in them. We could not comment on this subject, because we did not examine hypercholesterolemia, but other common comorbidities were similarly heart disease and diabetes mellitus (13).

We also found that 62.4 % of the patients had COVID-19 PCR positivity, and 95.2% had a COVID-19 appearance in thorax CT. According to a study conducted in Turkey, COVID-19 PCR positivity was observed at 65%, which is similar to ours (14). The number of studies that we can compare on this subject is limited since the exclusion criterion is COVID-19 PCR negative in most COVID-19 ICU studies.

In light of current literature, mortality due to COVID-19 has been reported as 55-61% in various studies (15,16). In our study, the mortality rate was observed at similar rates to 55 % in the COVID-19- ICU.

In our study, GIB was observed in 18% of the patients followed in the COVID-19- ICU. When the literature on COVID-19 was examined, it was observed that GIB ranged from 2-13% in patients followed up with COVID-19. The high rate of patients in our study may be due to the inclusion of patients followed in the ICU (6,17-20).

We know from previous studies that GIB is more common in patients with respiratory failure and coagulopathy in critically ill patients, and that stress ulcer bleeding is more common in patients hospitalized in intensive care units (21,22). Our patients are critically ill patients with respiratory distress and predisposition to coagulopathy, as they are treated in the intensive care unit due to COVID-19. For these reasons, an increase in the frequency of gastrointestinal bleeding may have been observed.

Studies have shown that patients receiving therapeutic doses of anticoagulants in COVID-19 patients tend to bleed more than patients receiving prophylactic doses of anticoagulants (23,24). In our study, no significant relationship was found between anticoagulant doses and bleeding, which may be due to the lower size of patients compared to other studies. In this study, it was observed that bleeding was more frequent in patients with a long duration of anticoagulant use.

A meta-analysis of 159 studies and 33253 patients showed that corticosteroid therapy increased the risk of gastrointestinal bleeding (8). In our study, it was observed that steroid use was not significantly associated with bleeding, and the day of steroid use was associated with bleeding. The reason for this can be explained by the use of PPI in 96.8% of our patients.

In addition, in this study, it was observed that the length of stay in the hospital and ICU of patients with GIB was

prolonged, and the mortality of patients with GIB was higher. It is seen that there is no significant relationship between GIB and mortality in the literature (25).

There are several limitations in our study. One of the limitations of our study is that endoscopy and colonoscopy were not performed on patients with a diagnosis of GIB. It is not possible to differentiate the patients as upper and lower GIB. In addition, the initial body weights of the patients were present and the body weight of the patients in the catabolic process was not followed up, and the anticoagulant doses of the patients were not adjusted according to weight. Also, intubated patients were examined in our study, and it was not possible to distinguish between patients who received noninvasive mechanical ventilation and those who did not receive oral intake, since the study was retrospective.

CONCLUSION

There is a risk of gastrointestinal bleeding due to COVID-19 and the drugs used in the treatment of this disease. Due to limitations in our study, this relationship was only shown with the duration of the anticoagulants and corticosteroids used. There is a need for studies conducted in centers with a higher size of patients, gastroenterologists, and endoscopy and colonoscopy to determine the relationship of other parameters associated with GIB.

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