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Gastrointestinal bleeding as an extrapulmonary effect of COVID-19 infection

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Abstract

Background: Coronavirus disease 2019 (COVID-19) is a worldwide pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which appear in Wuhan, Hubei Province, China, in late December 2019. On March 11, 2020, World Health Organization (WHO) considered it a global pandemic. Although pneumonia is the most common presentation of COVID-19, GIT is regarded as the most common site for the extrapulmonary manifestation of COVID-19 which includes vomiting, nausea, diarrhea, abdominal pain, and gastrointestinal (GI) hemorrhage. In covid-19, GI bleeding can result from multiple factors, isolated or combined This study aimed to evaluate GI bleeding as an extrapulmonary complication among patients with COVID-19 infection. Materials and methods: This study is completed in Merjan Medical City, Babylon, Iraq. So the mild cases of COVID-19 that do not need hospital admission are excluded from this study. It was a retrospective observational study that included a sample of 1106 inpatients who have been admitted from June 2020 to March 2021. The population of the study includes every admitted patient who has been diagnosed with COVID-19 by PCR and/or Chest CT scan. Other investigations used in this study include CBC, CRP, serum creatinine, and blood urea. Results: Melena was the commonest type of GI bleeding and diabetes was the commonest comorbidity. Comorbidities and positive CRP have existed in most patients with GI bleeding. Platelet count and PCV are significantly lower in cases of COVID-19 with GI bleeding. There was a significant association between plasma, Favipiravir, Remdesivir, Methylprednisolone, and unfractionated heparin and GIT bleeding. Unfortunately, RCU admission and mortality are the increase in all types of GI bleeding. Conclusion: Melena was the commonest type of GI bleeding, although all types of GI bleeding were seen in COVID-19 infection. The major risk factors for GI bleeding were: older age, lower SOP2, higher CT involvement, associated co-morbidities, and lower platelets count. The use of certain treatments like convalescent plasma, Remdesivir, and pulse methylprednisolone was associated with an increased risk of bleeding in a patient with COVID-19 infection.

Keywords

Coronavirus, COVID-19, infection, GI bleeding

Gastrointestinal (GI) bleeding, which can happen from any portion of the intestine, is still a serious medical issue. The most typical reason for upper GI hemorrhage hospitalization is ulcers (1). Most clinical trials of treatment for upper GI bleeding concentrate on ulcer disease. According to a population-based audit of upper GI bleeding in the Western world, there are 103 cases of acute bleeding per 100,000 adult adults each year (2).

Coronavirus disease 2019 (COVID-19), a worldwide pandemic resulting from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which appeared in Wuhan, Hubei Province, China, in late December 2019 (3, 4). On March 11, 2020, World Health Organization (WHO) considered it a global pandemic (5, 6). This infection is regarded as the most global health crisis since 1918 when the pandemic of influenza occurred. SARS-CoV-2 is an RNA virus which means it is capable to develop genetic mutations over time resulting in new mutant variants (7). Till June 22, 2021, according to the

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WHO, there are four variants of this virus have been detected: Alpha, Beta, Gamma, and Delta (7, 8).

Clinical manifestation of Covid-19 varies from severe cases present with multi-organ failure and septicemia to mild cases that are diagnosed accidentally with no symptoms. Although COVID-19 infection presentation is mostly pneumonia (9), the gastrointestinal tract (GIT) is regarded as the most common site for the extrapulmonary manifestation of COVID-19, which includes diarrhea, abdominal pain, nausea, vomiting, and GI hemorrhage. In covid-19, GI bleeding could be due to multiple factors, isolated or combined (10).

COVID-19 patient with gastrointestinal bleeding has been increasing in number around the world. In several cases, an endoscopy was done and detect congestion, erosion, and/or scattered bleeding of different sites of the mucosal membrane. In COVID-19 patients with hypoalbuminemia or increased prothrombin time, and critical cases, the occult gastrointestinal bleeding risk is more and the prognosis is worse (11).

In hospitalized patients with COVID-19 infection, the occurrence of bleeding from the gastrointestinal tract ranges from 2% to 13%,(12, 13). In patients with moderate-to-severe acute respiratory distress syndrome due to COVID-19 infection, the bleeding ulcer was detected in a lot of patients (14). In another study, gastroduodenal ulcers and rectal ulcers were the most common endoscopic findings in upper (48.4%) and lower (36.4%) endoscopies that cause GI bleeding (15).

This study aimed to evaluate GI bleeding as an extrapulmonary complication among patients with COVID-19 infection.

Patients and Method

This study is completed in Merjan Medical City, Babylon, Iraq. So the mild cases of COVID-19 that do not need hospital admission are excluded from this study. It was a retrospective observational study that included the files of 1106 inpatient samples who have been admitted from June 2020 to March 2021. The population of the study includes every admitted patient who has been diagnosed with COVID-19 by PCR and/or Chest CT scan. Chest CT scan results had been assessed by a radiologist, pulmonologist, and internist.

The definition of GI Bleeding includes any evidence of melena, coffee-ground vomiting, hematemesis, maroon stool, or hematochezia.

The variables that have been collected from the files to be analyzed in the study included: age, gender, presence of GI bleeding, type of GI bleeding (melena, hematemesis, coffee ground vomiting), presence of comorbidities and SPO2 at admission, and the lowest level of SPO2 reached during the hospital stay.

Other investigations used in this study include complete blood count (CBC), CRP, serum creatinine, and blood urea, by using locally available techniques at the hospital laboratories. Files that lacked necessary data were excluded from the study.

The treatment used in hospitals included plasma, Remdesivir, Favipiravir, injectable methylprednisolone, dexamethasone, unfractionated heparin, and enoxaparin. The treatment of COVID-19 was according to the Iraqi health ministry guidelines line and individual health variations of patients.

The study included any interventional need for bleeding and the fate of the patient (resolved, died, or admitted to RCU). The variables have been collected from patients' files. All the data has been submitted into a designed online form by the research team.

Since the study was retroactive and archive-based, informed consent was not required, and the Babylon health institution accepted and permitted the entire project.

Data Analysis

Statistical analysis had been carried out using SPSS version 25. Categorical variables were presented as frequencies and percentages. Continuous variables were presented as (Means ± SD). Student t-test was used to perform a means comparison between the two groups. Pearson chi-square and Fisher's exact test were done to find the relationship between categorical variables. A p-value of ≤ 0.05 was reflected as significant.

Results

Table 1 includes patients' distribution according to (age, gender, and smoking habit) (N=1106).

Study variables	Statistic	
Age (years)	(53.60 ± 15.30)	(14.0 - 96.0)
Gender		
Male	685	61.9%
Female	421	38.1%
Total	1106	100.0%
Smoking		
Smoker	95	8.6%
Non-smoker	1011	91.4%
Total	1106	100.0%

Table 2 includes patients' distribution according to comorbidities including (diabetes mellitus, hypertension, chronic kidney disease, gastric or duodenal ulcer, heart disease, and liver disease). The total sample included in the study shows more co-morbidities with diabetes being the commonest. Also shows the distribution of patients according to intervention including (chest tube, blood transfusion, interventional treatment, and non-specific treatment) (N:1106).

Study variables	Number	%
Comorbidities		
Present	510	46.1%
Absent	596	53.9%
Total	1106	100.0%
Type of comorbidities		
Diabetes mellitus	134	26.28%
Chronic kidney disease	5	0.98%
Heart disease	19	3.72%
Hypertension	122	23.92%
Gastric or duodenal ulcer	3	0.59%
Liver disease	2	0.39%
Multiple comorbidities	225	44.12%
Total	510	100.0%
Intervention		
Present	97	8.8%
Absent	1009	91.2%
Total	1106	100.0%
Type of intervention		
Anti-ischemic drugs	19	19.6%
Chest tube	19	19.6%
Blood transfusion	12	12.4%
Interventional treatment	8	8.2%
Non-specific treatment	39	40.2%
Total	97	100.0%

Figure 1 shows patients' distribution according to fate including (death, RCU admission, and cure). Only (N=199, 18%) of patients died and (N=30, 2.7%) of patients admitted to RCU and the majority of patients (N=877, 79.3%) get complete cures.

Table 3 includes patients' distribution according to presence and type of GIT bleeding (Melena, Hematochezia, fresh blood vomiting, coffee-ground vomiting, and melena and fresh blood vomiting) and according to intervention need and associated abdominal pain(N: 1106).

Study variables	Number	%
GIT bleeding		
Present	32	2.9%
Absent	1074	97.1%
Total	1106	100.0%
Type of GIT bleeding		
Melena	20	62.5%
Hematochezia	4	12.5%
Fresh blood vomiting	4	12.5%
Coffee-ground vomiting	2	6.25%
Melena and Fresh blood vomiting	2	6.25%
Total	32	100.0%
Intervention		
Blood transfusion	9	28.1%
No intervention	23	71.9%
Total	32	100.0%
Associated symptoms		
Abdominal pain	16	50.0%
No abdominal pain	16	50.0%
Total	32	100.0%

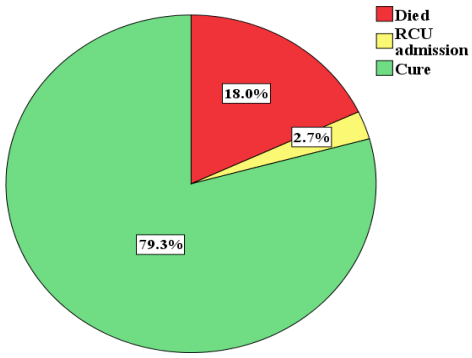

Figure 1: Distribution of patients with COVID-19 according to fate (N=1106)

Table 4: The mean study variables' differences including (age, SPO2 on admission, lowest SPO2, CT involvement, Platelet count, and PCV (HCT)) according to GIT bleeding including (present and absent). There were significant differences between the study variables' means according to GIT bleeding.

Study variables	GIT bleeding	N	Mean	SD	t-test	
Age (years)	Present	32	67.78	7.95	9.853	<0.001*
	Absent	1074	53.17	15.27		
SPO2 on admission (%)	Present	32	0.78	0.15	-4.419	<0.001*
	Absent	1071	0.89	0.08		
Lowest SPO2 (%)	Present	32	0.65	0.23	-4.536	<0.001*
	Absent	1070	0.84	0.12		
CT involvement (%)	Present	30	0.64	0.23	4.353	<0.001*
	Absent	1039	0.46	0.22		
Platelet count	Present	25	160.12	57.15	-7.915	<0.001*
	Absent	472	262.13	129.28		
PCV (HCT)	Present	25	36.28	8.47	-2.093	0.047*
	Absent	502	39.87	5.89		

*P value ≤ 0.05 was significant.

Table 5 shows the association between study variables including (gender, smoking habit, comorbidities, C-reactive protein, respiratory rate, associated symptoms, and interventions required) and GIT bleeding including (present and absent). There was a significant association between comorbidities-associated symptoms and interventions required and GIT bleeding. (N:1106)

Study variables	GIT bleeding		Total	X^2	P-value
	Present	Absent			
Gender Male Female Total	18 (56.3) 14 (43.7) 32 (100.0)	667 (62.1) 407 (37.9) 1074 (100.0)	685 (61.9) 421 (38.1) 1106 (100.0)	0.452	0.502
Smoking Smoker Non-smoker Total	4 (12.5) 28 (87.5) 32 (100.0)	91 (8.5) 983 (91.5) 1074 (100.0)	95 (8.6) 1011 (91.4) 1106 (100.0)		0.347 f
Comorbidities Present Absent Total	28 (87.5) 4 (12.5) 32 (100.0)	482 (44.9) 592 (55.1) 1074 (100.0)	510 (46.1) 596 (53.9) 1106 (100.0)	22.71	<0.001*
C-reactive protein Positive negative Total	24 (75.0) 8 (25.0) 32 (100.0)	744 (69.3) 330 (30.7) 1074 (100.0)	768 (69.4) 338 (30.6) 1106 (100.0)	0.48	0.488
Associated symptoms Yes No Total	16 (50.0) 16 (50.0) 32 (100.0)	88 (8.2) 986 (91.8) 1074 (100.0)	104 (9.4) 1002 (90.6) 1106 (100.0)		<0.001* f
Respiratory rate 12-18 18-30 >30 Total	0 (0.0) 7 (53.8) 6 (46.2) 13 (100.0)	39 (21.9) 97 (54.5) 42 (23.6) 178 (100.0)	39 (20.4) 104 (54.5) 48 (25.1) 191 (100.0)		0.075 f
Interventions Yes No Total	9 (28.1) 23 (71.9) 32 (100.0)	88 (8.2) 986 (91.8) 1074 (100.0)	97 (8.8) 1009 (91.2) 1106 (100.0)		0.001* f

*P value ≤ 0.05 was significant.

Table 6 shows the association between types of treatment including (anti-platelet, Plasma, Favipiravir, Remdesivir, Methylprednisolone, Dexamethasone, Unfractionated heparin, and Enoxaparin) and GIT bleeding including (present and absent). There was a significant association between Plasma, Favipiravir, Remdesivir, Methylprednisolone, and Unfractionated heparin and GIT bleeding (N:1106).

Type of treatment	GIT bleeding		Total	X^2	P-value
	Present	Absent			
Anti-platelet use					
Yes	0 (0.0)	66 (6.1)	66 (6.0)		0.254 f
No	32 (100.0)	1008 (93.9)	1040 (94.0)		
Total	32 (100.0)	1074 (100.0)	1106 (100.0)		
Plasma					
Yes	24 (75.0)	111 (10.3)	135 (12.2)		<0.001* f
No	8 (25.0)	963 (89.7)	971 (87.8)		
Total	32 (100.0)	1074 (100.0)	1106 (100.0)		
Favipiravir					
Yes	14 (43.7)	217 (20.2)	231 (20.9)	10.42	0.001*
No	18 (56.3)	857 (79.8)	875 (79.1)		
Total	32 (100.0)	1074 (100.0)	1106 (100.0)		
Remdesivir					
Yes	21 (65.6)	202 (18.8)	223 (20.2)	42.31	<0.001*
No	11 (34.4)	872 (81.2)	883 (79.8)		
Total	32 (100.0)	1074 (100.0)	1106 (100.0)		
Methylprednisolone					
Yes	20 (62.5)	170 (15.8)	190 (17.2)	47.57	<0.001*
No	12 (37.5)	904 (84.2)	916 (82.8)		
Total	32 (100.0)	1074 (100.0)	1106 (100.0)		
Dexamethasone					
Yes	30 (93.8)	965 (89.9)	995 (90.0)		0.763
No	2 (6.2)	109 (10.1)	111 (10.0)		
Total	32 (100.0)	1074 (100.0)	1106 (100.0)		
Unfractionated heparin					
Yes	28 (87.5)	357 (33.2)	385 (34.8)	40.315	<0.001*
No	4 (12.5)	717 (66.8)	721 (65.2)		
Total	32 (100.0)	1074 (100.0)	1106 (100.0)		
Enoxaparin					
Yes	23 (71.9)	737 (68.6)	760 (68.7)	0.153	0.696
No	9 (28.1)	337 (31.4)	346 (31.3)		
Total	32 (100.0)	1074 (100.0)	1106 (100.0)		

*P value ≤ 0.05 was significant.

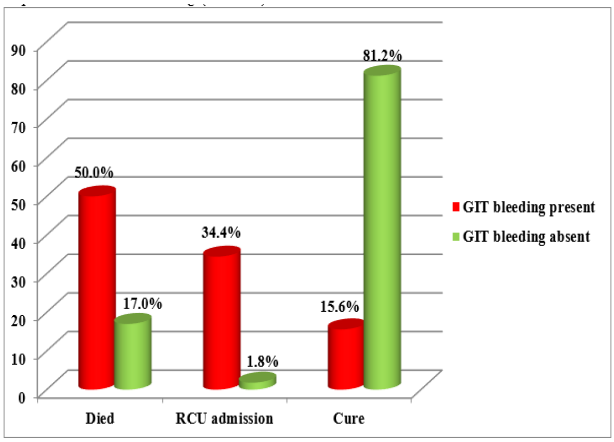

Figure 2 shows the fate of patients with GIT bleeding including (deaths, RCU admission, and cure) where 50% died,34.4% need RCU admission, and 15.6% cure while in patients with no GIT bleeding only 17 % died,1.8% need RCU admission and 81.2% cure. So there was a significant association between the fate of patients and GIT bleeding (N=1106).

Discussion

Gastrointestinal bleeding represents one of the important COVID-19 infection complications, particularly in presence of antithrombotic medications that are used as treatment or prophylaxis in a patient with COVID-19 infection (16). The risk of Gastrointestinal bleeding is increased in patients with COVID-19 infection (17, 18). This complication is particularly in presence of antithrombotic medications that are used as treatment or prophylaxis in a patient with COVID-19 infection. According to this observational study, we found different types of GI bleeding but the most frequent type is upper GIT bleeding. Although the bleeding affects 32 patients from a total of 1106 patients with COVID-19 infection (2.9%), it represents most patients that were died or admitted to RCU.

According to this study's findings, bleeding is

more common in cases of more severe COVID-19 infection depending on the mean age, involvement of the chest on a CT scan, admission Spo2, and presence of co-morbidities, but only a minority of patients with GIT bleeding (9/32 patients) require blood transfusions. This may suggest that the severity of the disease rather than the bleeding itself is what causes the increased mortality and need for RCU. As a result, a larger study is required to assess the clinical severity of COVID-19 infection in cases where it occurs and to examine the factors that influence the development of GIT bleeding.

Critically sick patients have a high risk of GIT bleeding because of a variety of variables, including poor circulation, elevated levels of endogenous vasoconstrictors, and hypoperfusion of the GIT mucous membrane, which results in local ischemia (19). This may also assist to explain why, in this study, gastrointestinal bleeding impacted the majority of patients who passed away or were admitted to the RCU. Unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) are both used to treat venous thrombo-embolization, but there is debate over whether using UFH carries a higher risk of bleeding than using LMWH. However, some studies have found that UFH carries a higher risk of bleeding than enoxaparin (20).

Some theories suggest that GIT manifestation could result from mucosal lesions by direct viral effect since the virus is known to attach to receptors called ACE2 that are present in the absorptive mucosa in the parts of upper and lower GIT (21). This theory is still questionable and unclear since most of the reported cases and studies show that GIT bleeding usually occurs during hospitalization which goes more with the theory that GIT bleeding is related to the treatment or due to factors related to critical illness.

As Covid-19 is regarded as a major stress event, this stress may play a role in developing stress ulcers in critically ill covid-19 patients. The surprising fact about stress ulcers is that their major cause is splanchnic hypoperfusion in critically ill cases. These stressful states would cause sympathetic activation which would shift oxygen away from the GIT and drive it to more critical organs like the brain. This will cause ischemic mucosal damage, especially in presence of diffusion of pepsin and protons leading to drive more damage (22). Oxygen radicals that can result from hypoperfusion lead to the inhibition of protective prostaglandins (23). Also, reperfusion would cause sudden hyperemia which would bring more inflammatory mediators and result in more destruction (24).

GI Bleeding in covid-19 could occur as a result of Heparin-induced thrombocytopenia that could occur in less than 5% of patients treated with heparin (25). B lymphocytes produce antibodies called Anti-PF4 which are the first step in Heparin-induced thrombocytopenia. B cells are found in normal persons but in an inert state and this tolerance might be broken when exposed to heparin under some inflammatory conditions. In such conditions when the B cell gets activated, it will release Anti PF4. The immune complexes of PF4 connect to heparin and lead to stimulation and aggregation of the platelet. Anti-PF4 antibodies also stimulate procoagulant monocytes and endothelial cell activity (26). Thrombocytopenia (which can lead to bleeding) occurs due to increased destruction and clearance of platelets that are coated with antibodies and due to the coagulation process itself. The drugs that can have a role in the treatment of COVID-19 infection as steroids, some antibiotics, and anticoagulation recently, been shown to reduce mortality, but it is not clear whether these drugs lead to increase GI bleeding or not. A large cohort of hospitalized COVID-19 patients found that there is no significant increase in GI bleeding risk after the use of anticoagulation or antiplatelet agents. In hospitalized patients, there is increased mortality as a complication of gastrointestinal hemorrhage (27).

Although the bleeding affects 32 patients from a total of 1106 patients with COVID-19 infection (2.9%), it represents most patients that were died or admitted to RCU. In this study, the occurrence of bleeding is more in cases with more severe COVID-19 infection depending on mean age, chest CT involvement, Spo2 on admission, lowest Spo2, and presence of co-morbidities but the need for blood transfusion occur in the minority of patient (9/32) with GIT bleeding this can indicate that the cause of the increased mortality and need of RCU is the disease severity than the bleeding itself, so we need a larger study to achieve a clinical assessment of cases with COVID 19 infection with similar severity and study variables before and after the occurrence of GIT bleeding.

In acute GI bleeding, the risk-benefit assessment for mucosal examination in COVID- 19 cases is made more difficult because there is more need for protective tools and more risk of serious cases in those patients so there is limited information about the value of endoscopy in those patients.

There are cases of acute hemorrhagic colitis associated with SARS-CoV-2 viral infection; in general, the definitive effect of this virus as a cause of gastrointestinal bleeding is still required be more evaluated [12].

This study shows that certain medications that are used in the treatment of COVID-19 infection like remdesivir, convalescent plasma, pulse methylprednisolone, and heparin were associated with a higher risk of gastrointestinal bleeding but

the explanation for that may be the use of these medications for more severe and critical cases of COVID-19 infection, so we need other studies with control groups for proper evaluation of effects of these medications.

The authors recommend performing larger studies to include outpatients with mild states of disease. It is vital to keep all data for each patient to improve our registration system. We suggest another study with a trial of endoscopy to see the site & the cause of the GI bleeding.

Conclusions

All types of GI bleeding are expected complications seen with COVID-19 infection & should be always carried in mind melena is the commonest type of GI bleeding in cases of COVID-19 infection. Although there is increased overall mortality in all types of GI bleeding, in the majority of cases the bleeding is not so severe to need a blood transfusion, this may indicate that the reason behind the increased mortality is the disease severity than the bleeding itself. The major risk factors for GI bleeding are older age, lower SOP2, higher CT involvement, presence of co-morbidities, and lower PCV & platelets count. The use of convalescent plasma and Remdesivir (and less for favipiravir) separately or in combination may increase the risk of bleeding this may be due to the use of these types of treatment in more severe conditions. The use of pulse methylprednisolone increases the risk of bleeding more than the use of the usual dose of dexamethasone again may be due to the effect of the drug itself or the use of pulse steroid for the more serious state. The use of conventional heparin increases the risk of bleeding more than the enoxaparin

References

Weledji EP. Acute gastrointestinal bleeding: a review. 2020;3(3):e18.

van Leerdam ME, Vreeburg EM, Rauws EA, Geraedts AA, Tijssen JG, Reitsma JB, et al. Acute upper GI bleeding: did anything change? Time trend analysis of incidence and outcome of acute upper GI bleeding between 1993/1994 and 2000. The American journal of gastroenterology. 2003;98(7):1494-9.

Al-Agam A OA, Alzughaibi M, Makki H, Alhaideri AF. The Association of Depressive Symptoms With Plasma C-Reactive Protein in Patients With Major Depressive Disorder Under Treatment. Iranian Rehabilitation Journal. 2021;19(4):425-32.

Hayder AA. Al-Hindy MJM, Hayder O. Hashim BCG Vaccine in Preventing COVID-19 Epidemic Had to be Reviewed: Correlation does not imply causation. Australian Journal of Basic and Applied Sciences. 2020;14(11):58-63.

Amer Fadhil Alhaideri WAA, Azher Nema Mohammed Al-Agam, Mahir Abdulkadhum Alzughaibi, Hayder Abdul-Amir M. Al-Hindy, Mazin J. Mousa Hypovitaminosis D is A Biological Vulnerability for Depressive Symptoms in Major Depression at the era of COVID-19 Outbreak. Clinical Schizophrenia & Related Psychoses 2022.(5)

Amal Talib Al Saady, Abdulameer Abdulrasol, Zainab, Fadhil Obaid, Ali Abdul-Amir Makki Alhindy, Hayder, S. Al-Mumin, Amir. Prevalence of adverse effects from COVID-19 vaccine among Iraqi adults: A retrospective cross-sectional study. 2022;2022(3)-The International and Scientific Conference of Alnahrain College of Medicine and Colleges of Medicine in Iraq confronting COVID-19 Pandemic (ISMC-2022)).

Aleem A, Akbar Samad AB, Slenker AK. Emerging Variants of SARS-CoV-2 And Novel Therapeutics Against Coronavirus (COVID-19). StatPearls. Treasure Island (FL): StatPearls Publishing. Copyright © 2022, StatPearls Publishing LLC.; 2022.

Cascella M, Rajnik M, Aleem A, Dulebohn SC, Di Napoli R. Features, Evaluation, and Treatment of Coronavirus (COVID-19). StatPearls. Treasure Island (FL): StatPearls Publishing. Copyright © 2022, StatPearls Publishing LLC.; 2022.

Karim Abdul-Husseein H, Akram Al- Akkam, Karam, Karim Abdul-Husseein, Mustafa, Abdul-Amir Makki Al-Hindy, Hayder. The Liver Function Abnormalities in COVID-19 Patients and Their Association with Age and Sex: A Cross-Sectional Study %J Archives of Razi Institute. Archives of Razi Institute. 2022;(77)

Carvalho A ,Alqusairi R, Adams A, Paul M, Kothari N, Peters S, et al. SARS-CoV-2 Gastrointestinal Infection Causing Hemorrhagic Colitis: Implications for Detection and Transmission of COVID-19 Disease. The American journal of gastroenterology. 2020;115(6):942-6.

Zhao X, Tao M, Chen C, Zhang Y, Fu Y. Clinical Features and Factors Associated with Occult Gastrointestinal Bleeding in COVID-19 Patients. Infection and drug resistance. 2021;14:4217-26.

Tian Y, Rong L, Nian W, He Y. Review article: gastrointestinal features in COVID-19 and the possibility of fecal transmission. Alimentary pharmacology & therapeutics. 2020;51(9):843-51.

Qayed E, Deshpande AR, Elmunzer BJ. Low Incidence of Severe Gastrointestinal Complications in COVID-19 Patients Admitted to the Intensive Care Unit: A Large, Multicenter Study. Gastroenterology. 2021;160(4):1403-5.

Marasco G, Maida M, Morreale G, Licata M, Renzulli M, Cremon C, et al. Gastrointestinal Bleeding in COVID-19 Patients: A Systematic Review with Meta-Analysis. Canadian journal of gastroenterology & hepatology. 2021;2021:2534975.

Ashktorab H, Russo T, Oskrochi G, Latella G, Massironi S, Luca M, et al. Clinical and Endoscopic Outcomes in COVID-19 Patients With Gastrointestinal Bleeding. Gastro Hep Advances. 2022;1.99-487:(4)

Fadheel QJ, Naser RT, Al-Hindy HA-AJHN. Evaluation of Practice of Prescribing and Monitoring Anticoagulants Among Hospitalized Iraqi Patients. 2022;22(1):71-6.

Martin TA, Wan DW, Hajifathalian K, Tewani S, Shah SL, Mehta A, et al. Gastrointestinal bleeding in patients with coronavirus disease 2019: a matched case-control study. 2020.

Yang F, Shi S, Zhu J, Shi J, Dai K, Chen X. Analysis of 92 deceased patients with COVID-19. 2020;92(11):2511-5.

Bardou M, Quenot JP, Barkun A. Stress-related mucosal disease in the critically ill patient. Nature reviews Gastroenterology & hepatology. 2015;12(2):98-107.

Dolovich LR, Ginsberg JS, Douketis JD, Holbrook AM, Cheah G. A meta-analysis comparing low-molecular-weight heparins with unfractionated heparin in the treatment of venous thromboembolism: examining some unanswered questions regarding the location of treatment, product type, and dosing frequency. Archives of internal medicine. 2000;160(2):181-8.

Xu J, Chu M, Zhong F, Tan X, Tang G, Mai J, et al. Digestive symptoms of COVID-19 and expression of ACE2 in digestive tract organs. Cell death discovery. 2020;6:76.

Negro A, Villa G, Rolandi S, Lucchini A, Bambi S. Gastrointestinal Bleeding in COVID-19 Patients: A Rapid Review. Gastroenterology nursing: the official journal of the Society of Gastroenterology Nurses and Associates. 2022;45(4):267-75.

Silvagno F, Vernone A, Pescarmona GP. The Role of Glutathione in Protecting against the Severe Inflammatory Response Triggered by COVID-19. Antioxidants (Basel, Switzerland). 2020;9.(7)

Golabi S, Ghasemi S, Adelipour M, Bagheri R, Suzuki K, Wong A, et al. Oxidative Stress and Inflammatory Status in COVID-19 Outpatients: A Health Center-Based Analytical Cross-Sectional Study. Antioxidants (Basel, Switzerland). 2022;11.(4)

Sulakshana S, Nayak SS, Perumal S, Das BP. Heparin-Induced Thrombocytopenia in COVID-19: A Systematic Review. Anesthesia, essays, and research. 2021;15(4):341-7.

Maharaj S, Chang S. Anti-PF4/heparin antibodies are increased in hospitalized patients with bacterial sepsis. Thrombosis research. 2018;171:111-3.

Trindade AJ, Izard S, Coppa K, Hirsch JS, Lee C, Satapathy SK. Gastrointestinal bleeding in hospitalized COVID-19 patients: a propensity score matched cohort study. Journal of internal medicine. 2021;289(6):887-94.