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TECHNICAL NOTES

Gastrointestinal perforation and vascular thrombosis in patients with corona virus disease-19: A life-threatening problem

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Introduction

The current pandemic of corona virus disease 19 (COVID-19) due to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has shown an ebb and flow pattern due to its emerging variants of concern (VOC) causing repeated waves of the pandemic. The SARS-CoV-2 is predominantly a respiratory tropic virus leading to a spectrum of pulmonary illnesses ranging from mild upper respiratory tract symptoms to severe life-threatening pulmonary complications such as acute respiratory distress syndrome (ARDS) from which the virus derives its name. Using its spike (S) protein, the SARS-CoV-2 attaches to the angiotensin-converting enzyme-2 (ACE-2) receptor. Another host protease, the transmembrane serine protease (TMPRSS 2 and 4) helps cleave the viral S protein and facilitates internalization of the virus inside host cells [1]. Since the ACE-2 receptor is expressed widely throughout the gastrointestinal (GI) tract, including the esophagus, stomach, small and large intestine, liver, and pancreas, not surprisingly, GI manifestations are not uncommon [2, 3]. Up to 20% of patients with COVID-19 might have GI symptoms including dysgeusia, nausea, vomiting, and diarrhea [4]. However, severe GI complications are rare [5].

In this issue of the *Journal*, Chaugale et al. and Hashim and colleagues present unusual severe presentation of COVID-19 such as intestinal perforation and mesenteric ischemia [6, 7]. These complications, albeit rare, deserve to be explored in more detail. Intestinal perforation and mesenteric ischemia are potentially life-threatening and need a high degree of suspicion for an early diagnosis and effective treatment. This narrative review explores the epidemiology, pathogenesis, clinical presentation, and management of these severe GI complications of COVID-19.

Search strategy

A systematic review of literature was done on PubMed using "intestinal perforation" OR "mesenteric ischemia" AND "COVID-19" as keywords. The detailed search strategy is as follows: ("perforant"[All Fields] OR "perforants"[All Fields] OR "perforate"[All Fields] OR "perforated"[All Fields] OR "perforates"[All Fields] OR "perforating"[All Fields] OR "perforation"[All Fields] OR "perforations"[All Fields] OR "perforative"[All Fields] OR "perforator"[All Fields] OR "perforator s"[All Fields] OR "perforators"[All Fields] OR "mesenteric ischemia"[All Fields]) AND ("COVID 19"[All Fields] OR "COVID 19"[MeSH Terms] OR "COVID 19 vaccines"[All Fields] OR "COVID 19 vaccines"[MeSH Terms] OR "COVID 19 serotherapy"[All Fields] OR "COVID 19 serotherapy"[Supplementary Concept] OR "COVID 19 nucleic acid testing"[All Fields] OR "COVID 19 nucleic acid testing"[MeSH Terms] OR "COVID 19 serological testing"[All Fields] OR "COVID 19 serological testing"[MeSH Terms] OR "COVID 19 testing"[All Fields] OR "COVID 19 testing"[MeSH Terms] OR "SARS-CoV-2"[All Fields] OR "SARS-CoV-2"[MeSH Terms] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "NCOV"[All Fields] OR "2019 NCOV"[All Fields] OR ("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "COV"[All Fields] AND 2019/11/01:3000/12/31[Date - Publication]).

The above strategy yielded 295 articles screened independently by both authors. Only papers published in the English language were reviewed. The references of these articles were further searched for relevant literature.

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Epidemiology

Patients with COVID-19 have been reported to develop many severe GI complications, including pancreatitis, Ogilvie syndrome, ileus, and perforation [8]. Non-COVID critically ill patients admitted with ARDS have also been reported to develop similar complications. However, in a propensity score–matched analysis by El Moheb et al., it has been shown that patients with COVID-19 are more likely to develop severe GI complications as compared to those without COVID-19 (74% vs. 37%; $p < .001$; incidence rate ratio, 2.33 [95% confidence interval, 1.52–3.63]) [8].

Most of the literature on mesenteric ischemia in COVID-19 is in the form of case reports or series without mention of the denominator, making it difficult to get an idea about the frequency of this complication. The best approximation can be made from studies reporting abdominal imaging findings among patients with COVID-19 (Table 1) [9–13]. In a systematic review on mesenteric ischemia in COVID-19 by Serban et al., they reported that acute mesenteric ischemia among patients hospitalized to intensive care unit (ICU) varied between 0.22% and 10.5% [14]. These findings need to be interpreted with caution because, in these studies, abdomino-pelvic imaging was done only in the presence of clinical clues in the form of GI symptoms and not routinely. Hence, these studies largely overestimate the true prevalence. Moreover, the listed studies include hospitalized patients with COVID-19; the same frequency might not hold for all patients with COVID-19. In this issue of the *Journal*, Hashim and colleagues have reported two such cases with GI thrombotic complications among the 3583 cases hospitalized with COVID-19 at their center [7]. Hence, mesenteric ischemia secondary to COVID-19 is likely a rare complication. Intestinal perforation among patients with COVID-19 is also a rare occurrence. Various studies reporting the incidence of GI perforation among patients with COVID-19 have been summarized in Table 2. The varying incidence from 0.5% to 2.8% might be due to different patient characteristics and different treatments offered as these are likely to impact the frequency, as discussed later [9, 10, 15, 16].

Pathogenesis

The exact pathogenesis of COVID-19-induced vascular thrombosis is not clear. The purported mechanism of COVID-19-induced vascular thrombosis has been invoked using Virchow's triad [17]. In a subset of patients infected with SARS-CoV-2, the virus proliferation continues unabated either due to inadequate immune response or excessive viral load leading to infection of the endothelium of the systemic vasculature [17]. The SARS-CoV-2 attaches avidly to the endothelium via ACE-2 receptor, which is abundantly expressed on its surface, infecting them and leading to endothelial damage and endotheliitis [18]. There is an associated increase in pro-inflammatory cytokines such as interleukin-1 (IL-1), IL-6, and tumor necrosis factor-alpha (TNF-α), and other procoagulant factors such as factor VIII and von Willebrand factor (vWF) leading to a state of hyperviscosity [19, 20]. Presence of increased microvesicles released from monocytes and platelets carrying tissue factor and phospholipid procoagulant moieties and

Table 1 Frequency of abdominal ischemic complications among hospitalized patients with corona virus disease 19

Author	Sample size	Findings	Comments
Bhayana et al. (2020) [9]	412	Bowel wall thickening in 12/412 (2.9%) Pneumatosis in 4/412 (0.97%) Portal venous gas in 4/412 (0.97%)	CT done on clinical suspicion only in 42 patients
Kaafarani et al. (2020) [16]	141	5 (3.5%) had bowel ischemia	Two of them had perforation secondary to microvascular mesenteric thrombosis
Goldberg-Stein et al. (2020) [10]	141	Bowel thickening in 12 (8.5%) Arterial thrombosis in 3 (2.12%)	80 patients had some finding on abdominal CT
O'Shea et al. (2021) [11]	308	Bowel ischemia or infarction in 4 (1.3%)	CT done on clinical suspicion only in 56 patients
Shiralkar et al. (2020) [12]	10	Colonic thickening in 2 (20%)	CT done on clinical suspicion only
Norsa et al. (2020) [13]	1500+	Intestinal ischemia in 7	Exact denominator not mentioned in study
Hashim et al. (2022) [7]	3583	2 (0.05%) had ischemia or infarction	Of the two reported cases only 1 had intestinal ischemia, and the other had aortic thrombus and solid organ infarction
Chaugale et al. (2022) [6]	-	2 out of 10 reported cases had intestinal gangrene	Both patients had the classically described pattern of microvascular thrombosis Denominator not mentioned in study

CT computed tomography

Table 2 Frequency of bowel perforation associated with corona virus disease 19

Author	Sample size	Findings	Comments
Estevez-Cerda et al. (2021) [15]	905	10 (1.1%) had gastrointestinal perforations	Two of these patients had perforation related to mesenteric thrombosis Tocilizumab was given to 2 of those with perforation
Kaafarani et al. (2020) [16]	141	3 (2.1%) had gastrointestinal perforations	Two of them had perforation secondary to microvascular mesenteric thrombosis
Bhayana et al. (2020) [9]	412	2 (0.48%) had gastrointestinal perforations	Both had perforation secondary to microvascular mesenteric thrombosis
Goldberg-Stein et al. (2020) [10]	141	4 (2.8%) had gastrointestinal perforations	These patients had free air in peritoneum, no histopathological details available
Chaugale et al. (2022) [6]	-	8 out of 10 reported cases had intestinal perforation	Denominator not mentioned in study

neutrophil extracellular traps (NETs) released from activated neutrophils has also been hypothesized to contribute to the hyperviscosity [20]. The unabated increase in the levels of cytokines leads to a cytokine storm eventually leading to multi-organ failure. Thrombin formed as a result of the unchecked coagulation cascade itself promotes inflammation via its action on protease-activated receptor-1 [21]. Additionally, hospitalization and immobilization contribute to vascular stasis. Furthermore, mesenteric ischemia may occur as a result of hemodynamic compromise secondary to severe COVID-19 [15]. These mechanisms may act individually or in combination to result in mesenteric ischemia (Fig. 1) [19].

Whether GI perforations arise secondary to intestinal ischemia or direct injury to the bowel mucosa as a result of widespread ACE-2 expression is still debatable [15]. Dexamethasone and tocilizumab are two drugs that have been proven to be helpful in a subset of patients with COVID-19 [22, 23]. Steroid use has long been associated with an increased risk of GI perforation [24, 25]. Tocilizumab has also been associated with the risk of GI perforation when used for patients with rheumatoid arthritis [26]. Although GI perforation has been reported among patients with COVID-19 on tocilizumab, yet causality has not been proven [27]. Baricitinib is a Janus kinase (JAK) inhibitor approved for the treatment of COVID-19, which has been associated with an increased risk of GI perforation and thrombosis [28]. Although case series report an association between baricitinib and these complications among patients with COVID-19, its causative role is not firmly established [15].

Clinical presentation

Clinical presentation of acute mesenteric ischemia in COVID-19 varies from typical presentation as an acute abdomen to an incidentally detected abnormality found on cross-sectional imaging done because of increasing vasopressor requirement [29].

In a systematic review of 89 patients with acute mesenteric ischemia due to COVID-19 by Serban et al., the mean age of patients was 59.3 ± 12.7 years with slight male preponderance (61%) [14]. Most (70%) patients were hospitalized in ICU, and the mean time from onset of COVID-19 to the diagnosis of ischemia was 9.6 ± 8.3 days [14]. A high body mass index (BMI) was a risk factor for mesenteric ischemia. Among the clinical symptoms, abdominal pain was the most common symptom and was present universally. Fever was not a helpful pointer of the complication since most hospitalized patients with COVID-19 either already have fever or are receiving antipyretics. Other GI symptoms such as nausea, anorexia, vomiting, and intolerance to feed are non-specific and poorly sensitive and are present in only 30% to 40% of patients with mesenteric ischemia [14]. Rarely, bleeding per rectum might be the presenting complaint [30]. In another study by Hwabejire et al. reporting their 1-year experience of 20 patients with COVID-19-associated mesenteric ischemia, the mean age was 58 ± 7 years with 65% being males [29]. The mean time from admission to the diagnosis of mesenteric ischemia was 13 ± 6 days. Almost half the patients (45%) had improvement in respiratory function by the time abdominal complications developed and increase in vasopressor requirement (80%), abdominal distension (70%), and increase in the post-prandial gastric residue (50%) were the major clinical features, which triggered targeted abdominal imaging.

The clinical characteristics of patients with GI perforation have been described by Estevez-Cerda et al. [15]. In their series, the mean age of presentation was 61 years, 70% being male [15]. The mean BMI was 29.2 kg/m^2 [15]. Of these patients, 30% had diabetes, and 40% were hypertensive. The mean time from admission to perforation diagnosis was 10.6 days. Half of these patients were on vasopressor support, and nearly 80% were on mechanical ventilation [15]. In a study by Kaafarani et al., all three patients (100%) with perforation had ileus for which targeted cross-sectional imaging showed perforation [16]. These findings are similar to those reported by

Chaugale et al. in this issue of the *Journal* in which most patients with perforation were males (75%) and beyond the 6th decade of life (88%) [6]. The most common symptom was abdominal pain (90%) followed by vomiting (40%) and inability to pass stool and flatus (40%).

Evaluation

Contrast-enhanced computed tomography (CECT) of the abdomen, preferably computed tomography (CT) angiogram, is the investigation of choice in patients with suspected mesenteric ischemia. In a systematic review of 75 patients describing the abdominal imaging findings in patients with COVID-19-associated mesenteric ischemia, Ojha et al. showed that small bowel ischemia (46.7%) was more common than large bowel ischemia (37.3%) [31]. Arterial thrombi were present only in a quarter of patients, while venous involvement was seen in 20%. Solid-organ infarcts (19%), ascites (17%), and pneumoperitoneum (11%) were other prominent findings. Mural thickening and bowel wall edema were seen in 50% of patients. The most common pattern of ischemia was non-occlusive mesenteric ischemia (NOMI) (68%) [31]. Although CT scan is the gold standard investigation, it is crucial to appreciate that many patients with COVID-19-associated mesenteric ischemia are often too sick to mobilize for a CT scan. A simple bedside X-ray of the abdomen is very helpful in identifying pneumatosis intestinalis (42%) and portal venous gas (33%) [29]. An important caveat is that pneumatosis intestinalis could be an incidental finding in patients on mechanical ventilation [30].

In some studies, large mesenteric vessels such as celiac artery, superior mesenteric artery, and inferior mesenteric artery have been largely (92%) patent [29]. This pattern is consistent with the intraoperative findings of a well-vascularized mesentery and histopathological finding of an inflammatory ischemic injury of the small submucosal and lamina propria vessels resulting in fibrin thrombi in these vessels [29]. This pattern is consistent with NOMI described in other studies and is largely different from thromboembolic mesenteric occlusion in any critically ill patient [29].

In a series of patients with COVID-19-associated GI perforations, 8 (80%) were diagnosed on CT, 60% having pneumoperitoneum [15]. Two (20%) were diagnosed on plain X-ray showing air under the diaphragm [15].

An increasing white blood cell (WBC) count has been described as a non-specific marker of acute mesenteric ischemia. Hwabejire et al. have reported that 90% of patients show an increasing WBC count 48-h before the diagnosis, and one-third even show a doubling of WBC during the same duration [29].

D-dimer (97%) and C-reactive protein (79%) are acute phase reactants that may be non-specifically raised among patients with mesenteric ischemia [31]. Lactate levels are insensitive and might also be raised non-specifically [29].

Management

The basic principles of management of acute abdomen in such a setting remain the same as in a non-COVID setting; these include fluid resuscitation, broad-spectrum antibiotics, resection of necrotic bowel, and revascularization if necessary [30]. In a systematic review, Ojha et al. showed that the majority (65%) of patients received surgical treatment [31]. Endovascular management has not been used frequently in these patients with COVID-19-associated mesenteric ischemia probably because the predominant pathology is NOMI. Rest were either managed conservatively (30%) or with endovascular management (5%) [31]. There was a 33% mortality among those managed surgically compared to 50% mortality in those managed conservatively [31]. Hwabejire et al. have described the surgical procedures undertaken in detail [29]. In their experience, 85% of patients need bowel resection on first exploratory laparotomy. Often in sick patients with doubtful bowel viability, it is difficult to demarcate healthy bowel from bowel with impending gangrene; in such cases, a second-look exploratory laparotomy helps [30]. For the same reason, they reported leaving the abdomen open in nearly two-thirds of the patients [29]. One-third of those who returned for 2nd look laparotomy needed re-resection in their experience. The decision to do a primary re-anastomosis vs. diversion stoma needs to be individualized based on the patient's general condition and demarcation, and condition of the residual bowel. It has been reported that only half of the patients could successfully undergo primary re-anastomosis, rest requiring a diversion stoma [29]. Although therapeutic anticoagulation in the form of low molecular weight heparin (LMWH) or unfractionated heparin (UFH) is given to these patients, its role has been questioned. In the series by Hwabejire et al., they reported that nearly 40% developed thromboembolic complications despite being on a therapeutic dose of anticoagulation [29].

Estevez-Cerda et al. have reported the detailed surgical management of these patients with perforation in their series [15]. Among the three patients with ascending colon perforation, all required right hemicolectomy, and primary anastomosis. Among the four patients with proximal jejunal perforation, three underwent resection and anastomosis while one underwent primary repair. Among the two patients with terminal ileal perforation, both underwent resection and anastomosis [15]. In their experience, only one patient required the temporary closure of abdomen and relook laparotomy later due to questionable bowel viability on first look [15].

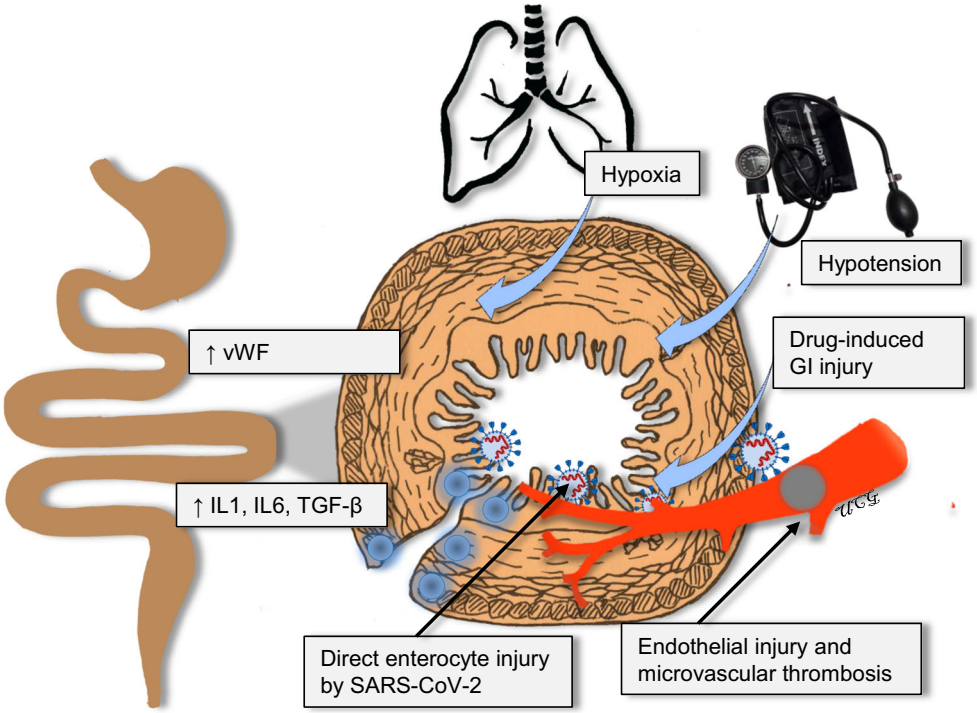

Fig. 1 Pathogenesis of mesenteric ischemia in corona virus disease 19: Microvascular thrombosis involving the submucosal vessels of the bowel arises due to a combination of direct endothelial injury due to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), hyperviscosity result from an inflammatory milieu and increased von Willebrand factor (vWF) levels, and vascular stasis. Direct injury of the bowel wall by SARS-CoV-2, hypoxemia, and hypotension play a contributory role resulting in commonly a pattern of injury characterized as non-occlusive mesenteric ischemia on cross-sectional imaging and pathology. *IL* interleukin, *TGF* transforming growth factor, *GI* gastrointestinal

Prognosis

The prognosis of COVID-19-associated mesenteric ischemia and GI perforation is grave. This high mortality might be partly because these complications often occur in patients with COVID-19 who have multiple comorbidities, hemodynamic compromise, and are often on mechanical ventilation and receiving a cocktail of drugs predisposing to these complications. In a systematic review of COVID-19-associated mesenteric ischemia, Ojha et al. reported an overall mortality of 43%, 33% in those managed surgically, and 50% in those managed conservatively [31]. Other surgical series have also described high mortality of 50%, increasing to 100% in those over 65 years of age [29]. The mortality is also dependent on the type of ischemic pattern. The NOMI pattern, which is by far the commonest pattern described in COVID-19, has higher mortality, close to 66%, compared to 20% in those with venous thrombosis [14]. A similar high mortality close to 50% has been demonstrated among patients with GI perforation [15].

Apart from causing well-known life-threatening pulmonary complications, the SARS-CoV-2 also causes critical GI complications, including perforation and ischemia, which are life-threatening, albeit rare. These complications often arise among hospitalized COVID-19 patients beyond their sixth decade and are multifactorial in origin. Prompt recognition among patients with new-onset abdominal pain, ileus, feeding intolerance, and worsening laboratory parameters is critical. Although CT scan is the investigation of choice, a simple bedside X-ray may suffice for certain patients too sick for transport to the radiology department. Most patients with ischemia have patent major vessels indicating a NOMI arising as a result of microvascular thrombosis documented in multiple series [9, 16, 29]. Perforation may occur de novo or in association with ischemic injury. There is no consensus on the management of these patients, but fluid resuscitation, broad-spectrum antibiotics, and surgical resection of the affected segment are the cornerstones of management. An individualized decision needs to be taken for primary closure or need for a relook laparotomy among patients with questionable viability on first surgery. Despite early recognition and surgical treatment, mortality remains unacceptably high among these patients.

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Author contribution AE: concept, literature review, and writing the first draft of the paper. UCG: concept, literature review, drawing the figure, and editing the paper. Both the authors approved the final version of the manuscript.

Declarations

Conflict of interest AE, and UCG declare no competing interests.

Ethics statement The study was performed conforming to the Helsinki declaration of 1975, as revised in 2000 and 2008 concerning human and animal rights, and the authors followed the policy concerning informed consent as shown on Springer.com.

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References

1. Zang R, Gomez Castro MF, McCune BT, et al. TMPRSS2 and TMPRSS4 promote SARS-CoV-2 infection of human small intestinal enterocytes. Sci Immunol. 2020;5:eabc3582.
2. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol. 2004;203:631–7.
3. Elhence A. Shalimar. COVID-19: beyond respiratory tract. J Dig Endosc. 2020;11:24–6.
4. Ghoshal UC, Ghoshal U, Mathur A, et al. The spectrum of gastrointestinal symptoms in patients with coronavirus disease-19: predictors, relationship with disease severity, and outcome. Clin Transl Gastroenterol. 2020;11:e00259.
5. Ghoshal UC, Ghoshal U, Dhiman RK. Gastrointestinal and hepatic involvement in severe acute respiratory syndrome coronavirus 2 infection: a review. J Clin Exp Hepatol. 2020;10:622–8.
6. Chaugale SB, Singhal V, Kapoor D, Singh A. Gastrointestinal complications (gangrene or perforation) after corona virus disease 2019 - a series of ten patients. Indian J Gastroenterol. 2022; 41: https://doi.org/10.1007/s12664-021-01218-z.
7. Hashim Z, Jaiswal S, Mohindra S. Thrombosis leading to acute abdomen in coronavirus disease 2019: a case series. Indian J Gastroenterol. 2022; 41. https://doi.org/10.1007/s12664-022-01260-5.
8. El Moheb M, Naar L, Christensen MA, et al. Gastrointestinal complications in critically ill patients with and without COVID-19. JAMA. 2020;324:1899–901.
9. Bhayana R, Som A, Li MD, et al. Abdominal imaging findings in COVID-19: preliminary observations. Radiology. 2020;297:E207–15.
10. Goldberg-Stein S, Fink A, Paroder V, Kobi M, Yee J, Chernyak V. Abdominopelvic CT findings in patients with novel coronavirus disease 2019 (COVID-19). Abdom Radiol (NY). 2020;45:2613–23.
11. O'Shea A, Parakh A, Hedgire S, Lee SI. Multisystem assessment of the imaging manifestations of coagulopathy in hospitalized patients with coronavirus disease (COVID-19). AJR Am J Roentgenol. 2021;216:1088–98.
12. Shiralkar K, Chinapuvvula N, Ocazionez D. Cross-sectional abdominal imaging findings in patients with COVID-19. Cureus [Internet]. Cureus; 2020 [cited 2022 Mar 20];12. Available from: https://www.cureus.com/articles/35834-cross-sectional-abdominal-imaging-findings-in-patients-with-covid-19
13. Norsa L, Bonaffini PA, Indriolo A, Valle C, Sonzogni A, Sironi S. Poor outcome of intestinal ischemic manifestations of COVID-19. Gastroenterology. 2020;159:1595–7.e1.
14. Serban D, Tribus LC, Vancea G, et al. Acute mesenteric ischemia in COVID-19 patients. J Clin Med. 2021;11:200.
15. Estevez-Cerda SC, Saldaña-Rodríguez JA, Alam-Gidi AG, et al. Severe bowel complications in SARS-CoV-2 patients receiving protocolized care. Rev Gastroenterol Mex (Engl Ed). 2021;86:378–86.
16. Kaafarani HMA, El Moheb M, Hwabejire JO, et al. Gastrointestinal complications in critically ill patients with COVID-19. Ann Surg. 2020;272:e61–2.
17. Leentjens J, van Haaps TF, Wessels PF, Schutgens REG, Middeldorp S. COVID-19-associated coagulopathy and antithrombotic agents-lessons after 1 year. Lancet Haematol. 2021;8:e524–33.
18. Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19.Lancet. 2020;395:1417–8.
19. Parry AH, Wani AH, Yaseen M. Acute mesenteric ischemia in severe coronavirus-19 (COVID-19): Possible mechanisms and diagnostic pathway. Acad Radiol. 2020;27:1190.
20. Panigada M, Bottino N, Tagliabue P, et al. Hypercoagulability of COVID-19 patients in intensive care unit: a report of thromboelastography findings and other parameters of hemostasis. J Thromb Haemost. 2020;18:1738–42.
21. Jose RJ, Manuel A. COVID-19 cytokine storm: the interplay between inflammation and coagulation. Lancet Respir Med. 2020;8:e46–7.
22. RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with COVID-19. N Engl J Med. 2021;384:693–704.
23. Soin AS, Kumar K, Choudhary NS, et al. Tocilizumab plus standard care versus standard care in patients in India with moderate to severe COVID-19-associated cytokine release syndrome (COVINTOC): an open-label, multicentre, randomised, controlled, phase 3 trial. Lancet Respir Med. 2021;9:511–21.
24. Fadul CE, Lemann W, Thaler HT, Posner JB. Perforation of the gastrointestinal tract in patients receiving steroids for neurologic disease. Neurology. 1988;38:348–52.
25. Arsura EL. Corticosteroid-association perforation of colonic diverticula. Arch Intern Med. 1990;150:1337–8.
26. Saad E, Awadelkarim A, Agab M, Babkir A. Tocilizumab-associated small bowel perforation in a young patient with rheumatoid arthritis: a lesson to remember during COVID-19 pandemic. J Med Cases. 2022;13:135–9.
27. Bulte JP, Postma N, Beukema M, et al. COVID 19 and the risk of gastro-intestinal perforation: a case series and literature review. J Crit Care. 2022;67:100–3.
28. Baricitinib: Drug information - UpToDate [Internet]. [cited 2022 Mar 23]. Available from: https://www.uptodate.com/contents/baricitinib-drug-information. Accessed 23 March 2022
29. Hwabejire JO, Kaafarani HMA, Mashbari H, et al. Bowel ischemia in COVID-19 infection: one-year surgical experience. Am Surg. 2021;87:1893–900.
30. Gupta A, Sharma O, Srikanth K, Mishra R, Tandon A, Rajput D. Review of mesenteric ischemia in COVID-19 patients. Indian J Surg [Internet]. 2022 [cited 2022 Mar 20]; Available from: https://doi.org/10.1007/s12262-022-03364-w.
31. Ojha V, Mani A, Mukherjee A, Kumar S, Jagia P. Mesenteric ischemia in patients with COVID-19: an updated systematic review of abdominal CT findings in 75 patients. Abdom Radiol [Internet]. 2021 [cited 2022 Mar 20]; Available from: https://link.springer.com/10.1007/s00261-021-03337-9