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## Body Imaging

## Ischemic gastrointestinal complications of COVID-19: a systematic review on imaging presentation

Pedram Keshavarz<sup>a,f</sup>, Faranak Rafiee<sup>a</sup>, Hadiseh Kavandi<sup>b</sup>, Sogand Goudarzi<sup>c</sup>,  
Firouzeh Heidari<sup>d</sup>, Ali Gholamrezanezhad<sup>e,\*</sup>

<sup>a</sup> Department of Radiology, Medical Imaging Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

<sup>b</sup> Connective Tissue Diseases Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

<sup>c</sup> Division of Cardiovascular Medicine, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, United States

<sup>d</sup> Endocrinology and Metabolism Research Center (EMRC), Vali-Asr Hospital, Tehran University of Medical Sciences, Tehran, Iran

<sup>e</sup> Department of Radiology, Keck School of Medicine, University of Southern California (USC), Los Angeles, CA, United States

<sup>f</sup> Department of Radiology, Tbilisi State Medical University (TSMU), Tbilisi, Georgia



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## ABSTRACT

**Background:** Limited data is available addressing gastrointestinal (GI) ischemia in coronavirus disease 2019 (COVID-19). We reviewed the clinical and radiologic features of GI ischemia and its related complications in thirty-one COVID-19 patients reported in literature.

**Methods:** A systematic literature review was performed using a search strategy on all studies published from January 1, 2020, to June 13, 2020, and updated on September 6, 2020, on databases from PubMed, Scopus, Embase, Web of Science, and Google Scholar. Every study with at least one presentation of COVID-19-related GI ischemia complication and one GI imaging finding was included.

**Results:** In total, twenty-two studies and thirty-one patients with the mean age of  $59 \pm 12.7$  (age range: 28–80) years old were included, of which 23 (74.2%) patients were male, 7 (22.5%) female, and one unknown gender. The significant GI imaging findings include mesenteric arterial or venous thromboembolism, followed by small bowel ischemia. Nine patients (29%) presented with arterial compromise due to superior mesenteric thromboembolism, resulting in bowel ischemia. Also, 6 patients (19.3%) demonstrated occlusive thrombosis of the portal system and superior mesenteric vein. More than two-thirds of patients (20, 64.5%) required laparotomy and bowel resection. Eventually, five (16.1%) patients were discharged, of whom four cases (12.9%) readmitted. Five (16.1%) patients remained ICU hospitalized at the report time and 12 (38.7%) patients died.

**Conclusion:** Macrovascular arterial/venous thrombosis is identified in almost half of COVID-19 patients with bowel ischemia. Overall mortality in COVID-19 patients with GI ischemia and radiologically evident mesenteric thrombotic occlusion was 38.7% and 40%, retrospectively.

## 1. Introduction

Since December 2019, the outbreak of the coronavirus disease 2019 (COVID-19) in Wuhan, China has become the leading cause of respiratory illnesses worldwide.<sup>1,2</sup> From the latest world health organization (WHO) updated on November 1st, 2020, over 46 million cases of COVID-19 across 216 countries have been confirmed.<sup>3</sup>

COVID-19 manifestations are mostly respiratory with related complications ranging from mild non-pneumonic illnesses to respiratory failure.<sup>4–6</sup> However, several extrapulmonary presentations, including

gastrointestinal (GI) symptoms, such as anorexia, diarrhea, vomiting, nausea, abdominal pain, and GI bleeding have been recently reported in COVID-19 patients.<sup>7–9</sup> Due to the prominence of the pulmonary presentations, extrapulmonary manifestations can be easily missed and overlooked, resulting in a delayed diagnosis of COVID-19 in patients with primary GI manifestations.<sup>9</sup> Severe GI complications have been observed in critically ill patients with a higher frequency.<sup>7,10</sup> Numerous GI complications, such as ileus, extensive hepatic necrosis, acute acalculous cholecystitis, and bowel ischemia have been reported in COVID-19 patients, particularly those admitted to intensive care unit (ICU).<sup>11</sup>

\* Corresponding author at: Department of Radiology Division of Emergency Radiology, Keck School of Medicine, University of Southern California, 1500 San Pablo Street, Los Angeles, CA 90033, United States.

E-mail address: [ali.gholamrezanezhad@med.usc.edu](mailto:ali.gholamrezanezhad@med.usc.edu) (A. Gholamrezanezhad).

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GI ischemia is an uncommon medical condition and results from any etiology that leads to bowel hypoperfusion.<sup>12,13</sup> Recent studies suggest that the possible coagulopathy or vasculopathy caused by COVID-19 may increase the risk of thromboembolic events and associated ischemia.<sup>14–16</sup> Most of the published reports, however, include extremity venous thrombosis and pulmonary embolism.<sup>15,17–19</sup> Thromboembolic events in the GI system, including mesenteric ischemia, are specifically important, because they constitute a potentially fatal clinical emergency with a high rate of mortality.<sup>20–22</sup>

Limited data is available addressing GI ischemia in the setting of COVID-19.<sup>23,24</sup> Also, the exact underlying pathologic mechanism is not clear. Different pathophysiological mechanisms, such as inflammation, vasculopathy, immobilization, endothelial dysfunction, and hypercoagulable state have been considered to explain GI ischemia in COVID-19 patients.<sup>25</sup> However, it is still unclear whether arterial thromboembolic events are direct complications of COVID-19 or simply a coincident. Considering the high mortality rate of GI ischemia, clinicians are encouraged to have a very high clinical suspicion index and low threshold for cross-sectional imaging and clinical screening of GI symptoms in the era of COVID-19 due to the possible risk of GI ischemia progression and its related complications that may require emergent surgical intervention. As comprehensive and inclusive data are not currently available to declare GI complications in COVID-19 patients, we systematically reviewed imaging findings and the outcome of confirmed COVID-19 patients with GI ischemic complications.

## 2. Materials and methods

### 2.1. Search strategies

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines.<sup>26</sup> We firstly searched PubMed (MEDLINE), Scopus, Embase (Elsevier), Web of Science, and Google Scholar databases from January 1, 2020, to June 13, 2020, and updated on September 6, 2020, for studies on COVID-19 that reported the GI ischemia complications. Keywords for the literature search included “coronavirus disease,” “coronavirus infections,” “COVID-19”, “2019-nCoV”, “abdominal pain”, and “intestinal ischemia”. The full list of the keywords used is provided in Appendix A. Fig. 1 shows the flow diagram of the study selection process.

### 2.2. Eligibility criteria

All studies published in the English language that included COVID-19 cases confirmed via reverse transcription-polymerase chain reaction (RT-PCR) or nasopharyngeal swabs, reported at least one presentation of GI ischemia complication, and with at least one GI imaging finding were eligible for inclusion. Correspondence or letters fulfilling the above criteria were also included in this study. Duplicates, conference abstracts, and studies without available full text were excluded.

### 2.3. Data extraction and quality assessment

Two authors independently extracted the data and then continued to cross-check the results. Disagreements were resolved by consensus. The

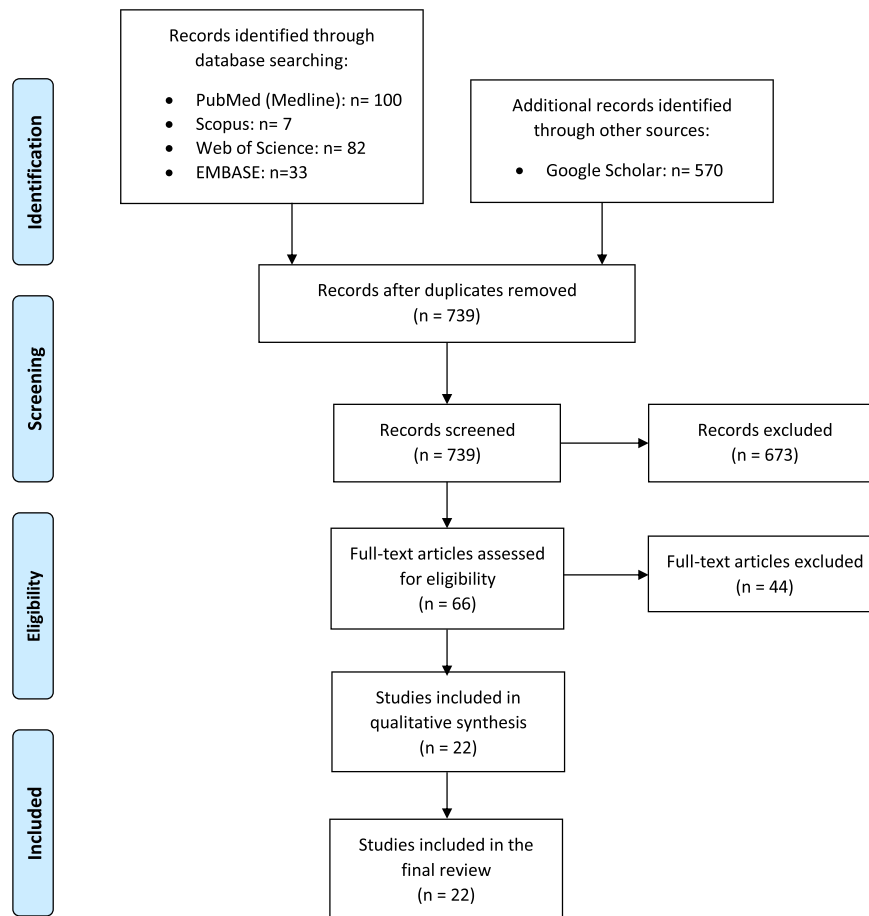
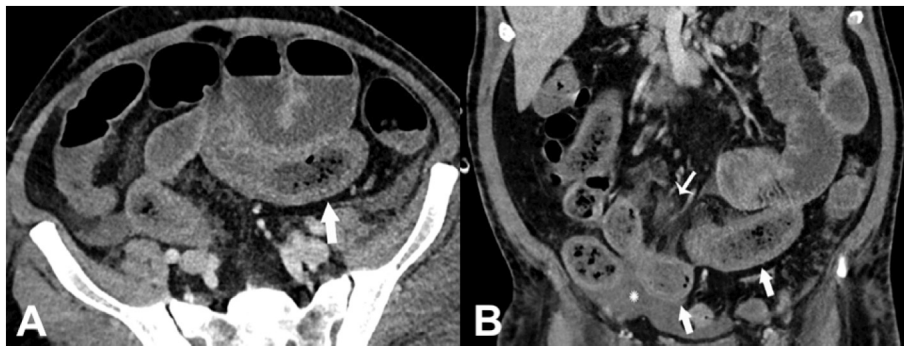
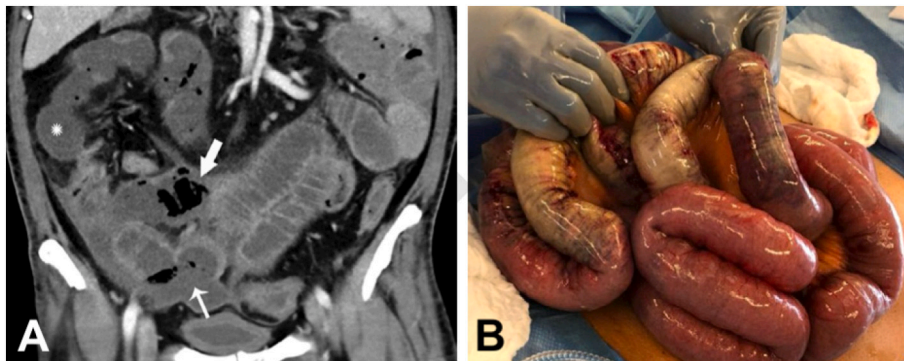


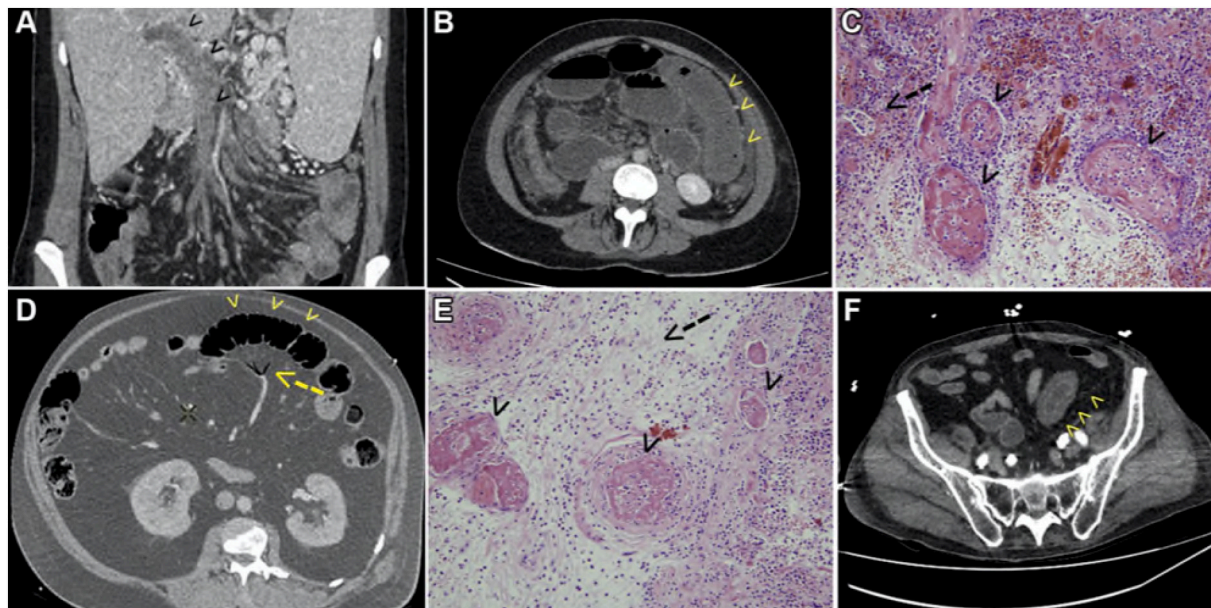
Fig. 1. Flow diagram of study selection process.



**Fig. 2.** Axial (A) and coronal (B) CT of the abdomen and pelvis with IV contrast in a 57-year old man (patient no. 3) with a high clinical suspicion for bowel ischemia. There was generalized small bowel distension and segmental thickening (arrows), with adjacent mesenteric congestion (thin arrow in B), and a small volume of ascites (\* in B). Findings are nonspecific but suggestive of early ischemia or infection. Images obtained from Bhayana et al.<sup>23</sup> Radiology, published online May 11, 2020, copyright (2020), and permission to use granted by Ashley E. Daly, Senior Manager, Journal Rights & Communications Publications, Radiological Society of North America (RSNA).

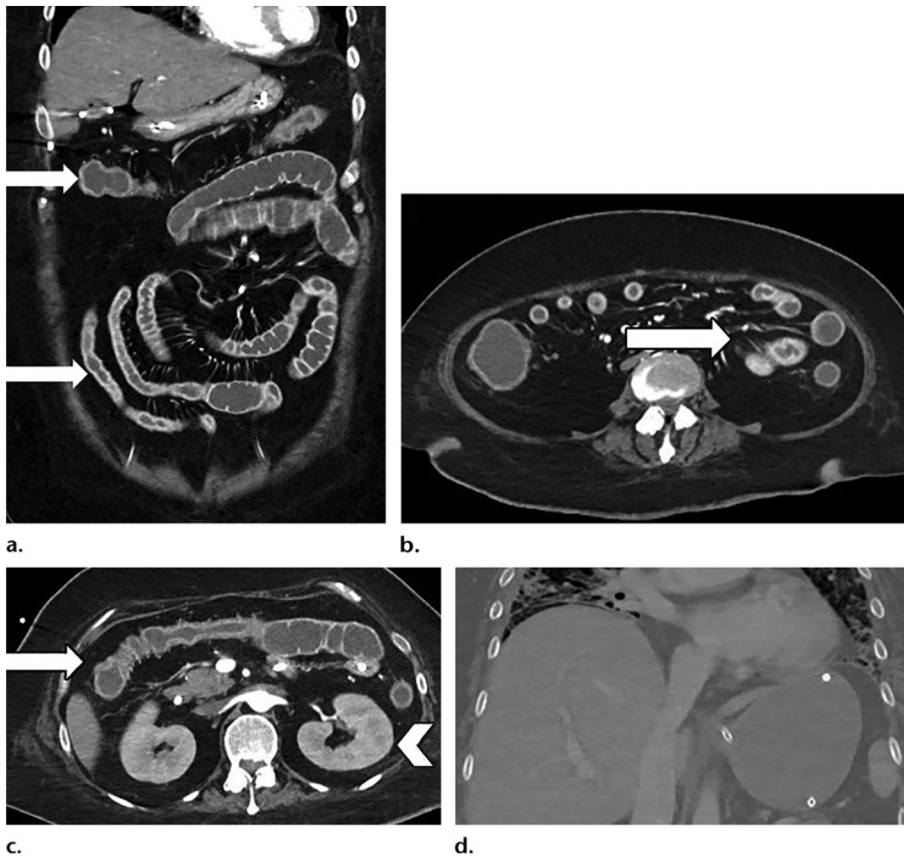


**Fig. 3.** Coronal (A) CT of the abdomen and pelvis with IV contrast in a 47-year-old man (patient no. 4) with abdominal tenderness demonstrates typical findings of mesenteric ischemia and infarction, including pneumatosis intestinalis (arrow) and non-enhancing bowel (\*). Frank discontinuity of a thickened loop of small bowel in the pelvis (thin arrow) is in keeping with perforation. These findings were confirmed at laparotomy (B), with the additional observation of atypical yellow discoloration of bowel. Images obtained from Bhayana et al.<sup>23</sup> Radiology, published online May 11, 2020, copyright (2020), and permission to use granted by Ashley E. Daly, Senior Manager, Journal Rights & Communications Publications, Radiological Society of North America (RSNA). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)



**Fig. 4.** Abdominal CT scan and pathological findings in SARS-CoV-2 infected patients. (A) CT scan shows mesenteric and portal vein thrombosis (arrowheads) in a young female patient (patient no. 12) with essential thrombocythemia, as a first sign and prior to respiratory symptoms revealing the COVID-19. (B) CT scan shows bowel infarction in the first bowel loop (arrowheads) 5 days after admission of the patient no. 12, prompting emergency laparotomy and bowel resection. (C) Pathological findings of patient no. 12 (hematoxylin and eosin stain, 200 magnification): small bowel necrosis; arrowheads show microthrombi in the lamina propria and the submucosa; arrow shows glandular necrosis. (D) CT scan shows signs of bowel ischemia (arrowheads) and mesenteric venous gas (arrow) in the proximal jejunum in a 56-year-old male patient (patient no. 13) with acute respiratory distress syndrome during COVID-19. (E) Pathological findings of patient no. 13 (hematoxylin and eosin stain, 200 magnification): small bowel necrosis; arrowheads show micro-thrombi; and arrow shows edema and inflammatory infiltrates in the submucosa. (F) CT scan shows an inflammatory bowel loop with thickening and edema (arrowhead) in a 67-year-old male (patient no. 14) with acute respiratory distress syndrome during COVID-19. Images obtained from Ignat.<sup>27</sup> Surgery published on July 1, 2020, Vol. 168 (1) P14–16 (copyright 2020), and permission to use granted by Elsevier and Copyright Clearance Center.





**Fig. 5.** Cough and shortness of breath in a 46-year-old woman (patient no. 22) with diabetes mellitus who was initially diagnosed with COVID-19. The patient's condition clinically deteriorated, and the use of mechanical ventilation, extracorporeal membrane oxygenation (ECMO), and pressor support was required. The clinical course was complicated by acute toxic metabolic encephalopathy, pneumonia, acute respiratory distress syndrome, cardiogenic shock, acute kidney injury, and secondary adrenal insufficiency. Coronal (a) and axial (b, c) contrast-enhanced CT images show multifocal small and large bowel wall thickening (arrows) creating a ribbonlike appearance, likely related to small vessel ischemia. Note the altered enhancement of the kidneys (arrowhead in c) in the setting of acute kidney injury and multifocal peripheral airspace opacities at the lung bases on the coronal CT image (d). Images obtained from Olson et al.<sup>29</sup> Radiology published online on July 10, 2020, Vol. 40, No. 5, copyright (2020), and permission to use granted by Ashley E. Daly, Senior Manager, Journal Rights & Communications Publications, Radiological Society of North America (RSNA).

following data from each study were extracted: name of the first author, study country, study design, the patient's age, gender, initial clinical presentations, imaging findings, operative procedure, course of the disease (such as ICU admission), and outcome. Furthermore, we reported a series of imaging findings from included studies<sup>23,27–29</sup> (Fig. 2–6) (formal permissions obtained from the copyright holder). Quality of the included studies was assessed using the National Institutes of Health (NIH) quality assessment tool for case series/reports<sup>30</sup> and the modified version of the Newcastle-Ottawa Quality Scale (NOS) for cohort studies.<sup>31</sup> (Supplementary Tables 1&2).

### 3. Results

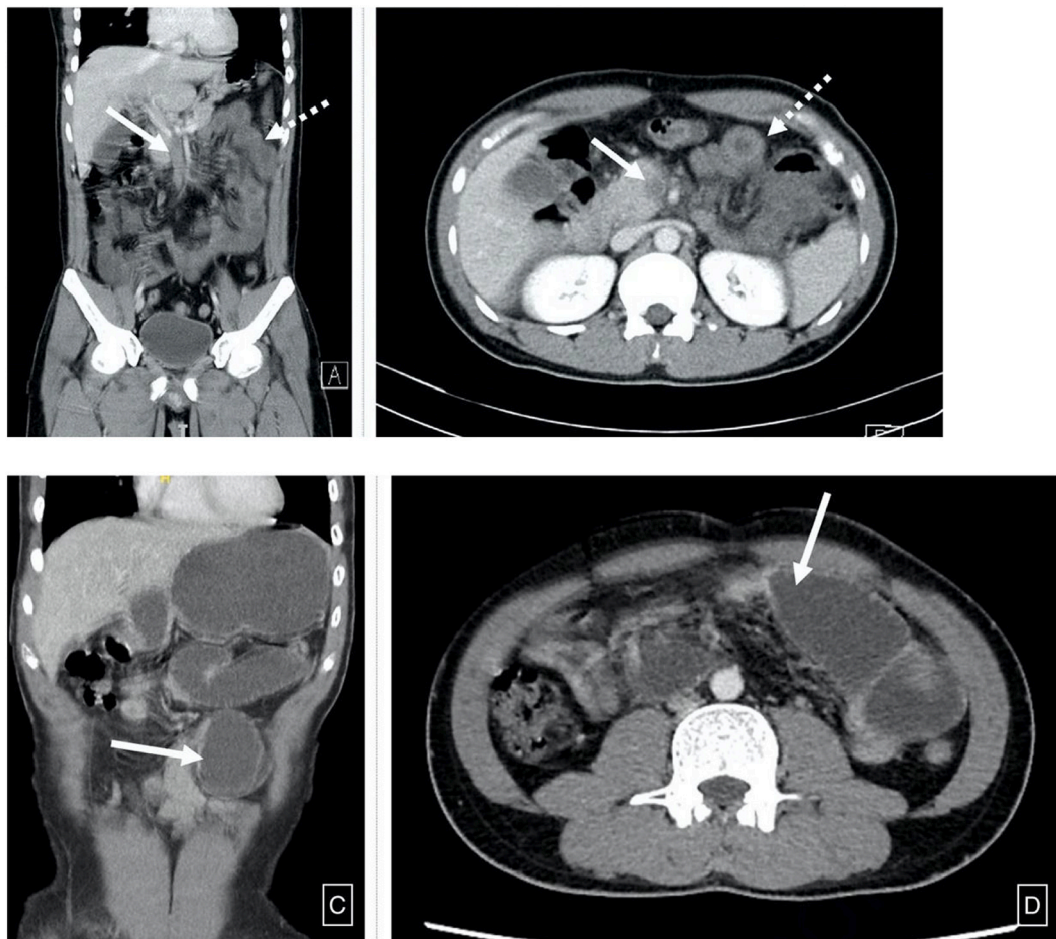
A total of 792 articles were recognized in the initial search. After removing duplicates, 739 were screened by titles and abstracts. Next, unrelated articles were excluded and the remaining 57 were retrieved for full-text evaluation. In our search, we found twenty-two studies, including three cohort studies, three case series, twelve case reports, and four correspondence to the editors related to GI ischemia complications in patients with COVID-19. Thirty-one patients with the mean age of  $59 \pm 12.7$  (age range: 28–80; age IQR: 51–70) years old were included, of which 23 patients were male (74.2%), 7 (22.5%) female, and one unknown gender. Table 1 summarizes the clinical characteristics, imaging findings, operative procedures, and outcomes of these patients.

The most common initial presentations were fever (10, 32.2%), dry cough (9, 29%), and shortness of breath (8, 25.8%). Additionally, GI symptoms were compromised of abdominal pain (19, 61.3%) and nausea and vomiting (10, 32.2%). The significant GI imaging findings of these patients were comprised of mesenteric arterial or venous thromboembolism, followed by imaging signs of small bowel ischemia. Moreover, 11 patients (35.4%) required direct ICU admission. Nine patients (29%) demonstrated arterial compromise, resulting in bowel

ischemia with evident superior mesenteric artery thromboembolism. Six patients (19.3%) demonstrated occluding thrombi in the portal system or superior mesenteric vein. In the remaining patients, no filling defect on imaging was identified to suggest occlusion of the large to medium size abdominal vasculature.

Eventually, five (16.1%) patients were discharged from the hospital, of whom 4 patients (12.9%) were readmitted. Five other patients (16.1%) remained hospitalized in ICU at the time of publication of the reports, and 12 (38.7%) patients died. The outcome is unknown/not reported in 9 patients (29%). Laparotomy and partial bowel resection were performed in twenty patients, of whom six patients died within few days after resection, eight patients transferred to ICU after the operation, and one patient (no. 12) was successfully discharged after resection of 80 cm long segment jejunal ischemia and 7 days of ICU stay. The outcome of the other five patients was not reported/published in the included articles. Patient no. 15 had a past medical history of diabetes type 2, obesity, arterial hypertension, and hepatic cirrhosis (non-alcoholic steatohepatitis) and presented with extensive thromboembolic involvement of superior mesenteric vein and associated pneumatosis intestinalis. He died 12 hours after small bowel resection due to refractory septic shock. Patient no. 18 had a past medical history of diabetes type 2 and hypertension; twelve days after admission to the ICU, the follow-up CT scan demonstrated a cecal perforation with left colonic pneumatosis. Laparotomy then confirmed fecaloid peritonitis, gangrenous cecal perforation, and diffuse small bowel and colon ischemia. The patient died a few days after the operation.

Patient no. 2 had an unremarkable past medical history, except for mild hypertension. Laparotomy and bowel resection (15-cm) with side-to-side manual anastomosis were performed to treat his ischemic bowel, but he died due to the multiorgan failure on the 4th postoperative day. Patient no. 6 improved clinically after 7th days of antiviral therapy after confirmed COVID-19 pneumonia and then discharged from the hospital.



**Fig. 6.** A computed tomography scan of the abdomen and pelvis revealed A, B: Superior mesenteric vein thrombosis (bold arrow) and diffuse mural thickening (dotted arrow), C, D: High grade small bowel obstruction with a transition point (bold arrow) seen in mid jejunum. Images obtained from Pang et al.<sup>28</sup> *Annals of Vascular Surgery* available online on August 28, 2020, (copyright 2020), and permission to use granted by Elsevier and Copyright Clearance Center.

He was readmitted with severe clinical conditions like fever and several episodes of diarrhea without any signs of an acute abdomen. A contrast-enhanced abdominopelvic CT revealed arterial thrombosis involving SMA and bowel distension. Subsequently, intestinal resection with stapled side-to-side anastomosis was performed for the management of his intestinal ischemia. He was discharged uneventfully after surgery with regular GI function. Surgical exploration found the necrotic bowel extending from the ligament of Treitz to the transverse colon with perforation of the terminal ileum in patient no. 7.

In total, 12 patients (38.7%) of the population included in our systematic review died from mesenteric ischemia. All of these cases demonstrated moderate to severe GI symptomatic presentation, of whom 11 patients (35.5%) died within a few days after bowel resection due to refractory septic shock or multiorgan failure. The only case who was treated non-surgically and died, was case no. 10, because the surgery consultants believed the surgery is of no added value. The contrast-enhanced abdominopelvic CT scan of this patient revealed ischemic colitis evident by thickening of the distal sigmoid colon along with pockets of gas within the mesenteric vessels. Reportedly, the patient was managed conservatively with bowel rest and antibiotic therapies; His hospital stay was complicated by cardiac arrest on day 5 of admission. He expired in 20 min despite advanced cardiovascular life support (ACLS).

Contrast-enhanced abdominopelvic CT scan of patient no. 13 revealed mesenteric venous gas and small bowel ischemia. The histopathologic evaluation confirmed the inflammatory necrosis of the mucosa, which was entirely replaced by phantom cells after laparotomy

and bowel resection. This patient was suffering from multi-organ failure and was still admitted in ICU at the time of the submission of the manuscript. Patient no. 16 had a past medical history of diabetes type 2, hypertension, renal failure (stage III), coronary artery disease, and myocardial infarction. Subsequent to laparotomy, resection of the ischemic bowel loop, and splenectomy, he was discharged from the ICU, but readmitted due to recurrent mild abdominal pain.

In our systematically reviewed population, radiologically detectable mesenteric arterial thrombosis was detected in 9 patients (29%) and venous thrombosis in 6 patients (19.3%). In 16 patients (51.6%) no evident macroscopic thrombi were detected on contrast-enhanced CT abdomen and pelvis. The frequency of the radiologic findings of bowel ischemia in the reported cases (total of 41 imaging signs in 31 patients) are as follows: thrombosis in the arterial system (SMA and/or aorta) in 10 patients (24%), thrombosis in a portal system in 6 patients (14.6%), bowel wall unenhancement in 6 cases (14.6%), bowel wall thickening in 6 cases (14.6%), pneumatosis intestinalis in 5 cases (12%), mesenteric edema and stranding in 4 patients (9.7%), portal venous gas in 2 patients (4.8%), and pneumoperitoneum indicating perforation in 2 cases (4.8%).

#### 4. Discussion

Life-threatening GI complications of COVID-19 infection mainly encompass ischemic infarction of the small and large bowel loops. In our study, radiologically detectable arterial/venous thrombosis was identified in almost half of patients with ischemic bowel. This study amplifies

**Table 1**  
Characteristics of twenty patients with COVID-19 infection according to gastrointestinal ischemia complications.

Patient no./sex/age(y)	First author	Country	Initial symptoms	Imaging findings (Abdominal and pelvic CT scan)	Surgery procedure	Outcome
P1/NR/56	Azouz et al. <sup>54</sup>	France	Abdominal pain and vomiting	Intraluminal thrombus of the aortic arch, SMA thromboembolism, dilation and unenhancement of small bowel loops (ischemia)	Endovascular thrombectomy, laparotomy (resection of 2 m of small bowel)	NR
P2/M/59	Bianco et al. <sup>45</sup>	Italy	Bilateral pneumonia, acute abdominal pain with nausea	Air-fluid levels in the small bowel loops associated with mesenteric edema, mild peritoneal free fluid, segmental small bowel ischemia	Laparotomy	Death
P3/M/57	Bhayana et al. <sup>23</sup>	USA	NR	Generalized small bowel distension and segmental thickening, adjacent mesenteric congestion, mild free fluid (ischemia)	Exploratory laparotomy	NR
P4/M/47	Bhayana et al. <sup>23</sup>	USA	Abdominal pain	Pneumatosis intestinalis and non-enhancing bowel, mesenteric ischemia and infarction, concomitant small bowel perforation	Exploratory laparotomy	NR
P5/M/52	Bhayana et al. <sup>23</sup>	USA	NR	Portal venous gas, suggesting small bowel infarction	Exploratory laparotomy	NR
P6/M/52	Beccara et al. <sup>55</sup>	Italy	Cough, fever, two episodes of diarrhea, vomiting, abdominal pain	Thrombosis of SMA branches, bowel distension	Intestinal resection with stapled side-to side anastomosis	Discharged, readmitted, and discharged
P7/M/47	Gratland et al. <sup>24</sup>	USA	Cough, SOB, fever, hypoxia, respiratory distress, increased abdominal pain	Small bowel ischemia with perforation	Exploratory laparotomy	Death
P8/M/60	Vulliamy et al. <sup>56</sup>	England	Loss of sensation and power in legs, cough, fever, tachypnoea and tachycardia	Acute thrombotic occlusion of the infrarenal aorta extending into the common iliac arteries	Thromboembolctomy	NR
P9/M/75	Vulliamy et al. <sup>56</sup>	England	Abdominal pain, vomiting, worsening of the cough, SOB	Intraluminal thrombus of descending thoracic aorta with embolic occlusion of SMA	Catheter-directed thrombolysis, laparotomy (resection of 150 cm of ischemic small bowel)	NR
P10/M/73	Chun et al. <sup>57</sup>	USA	Fever, nonproductive cough, SOB, bloody diarrhea, sudden left lower quadrant cramping pain	Mucosal hyperenhancement with mass-like thickening of the distal sigmoid colon, regional air within the mesenteric vessels (ischemic colitis)	Managed conservatively	Death
P11/M/70	Farnia et al. <sup>58</sup>	Italy	Diffuse abdominal pain, nausea, fever, cough, pharyngodynia, positive Blumberg sign	Occlusion of SMA, small bowel wall thinning and absence of contrast enhancement (ischemia)	NR	Death
P12/F/28	Ignat et al. <sup>27</sup>	France	Sudden increased abdominal pain and vomiting	Superior mesenteric and portal vein thrombosis followed by segmental small bowel ischemia	Bowel resection, temporary laparostomy (second-look procedure 48 h later); double jejunostomy and abdominal wall closure	Discharged
P13/M/56	Ignat et al. <sup>27</sup>	France	Acute respiratory distress	Mesenteric venous gas in proximal jejunum, small bowel ischemia	Bowel resection, laparostomy (second-look procedure and double ostomy 48 h later)	Hospitalized (ICU)
P14/M/67	Ignat et al. <sup>27</sup>	France	Acute respiratory distress	Single inflammatory bowel loop with wall thickening and edema, inflammatory segmental ileitis	NR	Hospitalized (ICU)
P15/M/62	Norsa et al. <sup>59</sup>	Italy	Abdominal pain and bilious vomiting	Thromboembolism of superior mesenteric vein, jejunal overdistension and unenhancement, pneumatosis intestinalis (ischemia)	Small intestine resection	Death
P16/M/72	Besutti et al. <sup>60</sup>	Italy	Dry cough, SOB, severe abdominal pain	Thrombi in SMA and thoracic descending aorta, decreased or absent wall enhancement of small bowel loops (ischemia), associated splenic and renal infarcts	Resection of the ischemic bowel loop and splenectomy	Discharged and readmitted
P17/M/76	Almeida et al. <sup>61</sup>	Spain	Pneumonia, several episodes of hematochezia	Necrotizing pancreatitis, colonic wall thickening, absent of wall enhancement and mesenteric stranding (colonic ischemia)	NR	Death
P18/M/68	Almeida et al. <sup>61</sup>	Spain	Bilateral pneumonia, abdominal pain, paralytic ileus with signs of peritoneal irritation	Cecal perforation, pneumatosis of left colon	Laparotomy, peritoneal lavage and ileostomy	Death
P19/M/56	Almeida et al. <sup>61</sup>	Spain	Respiratory failure, abdominal distension with pain and guarding	Pneumoperitoneum, colonic pneumatosis	NR	Death
P20/M/46	Dane et al. <sup>47</sup>	USA	Fever, SOB, epigastric pain, weakness	Partial thrombosis of abdominal aorta and celiac trunk extending into common hepatic artery, SMA thrombosis, left sided renal and splenic infarcts	NR	NR
		USA	NR		NR	NR

(continued on next page)

Table 1 (continued)

Patient no./sex/age(y)	First author	Country	Initial symptoms	Imaging findings (Abdominal and pelvic CT scan)	Surgery procedure	Outcome
P21/M/51	Olson et al. <sup>29</sup>			Diffuse gastric wall thickening and pneumatosis with surrounding inflammation and portal vein thrombus and gas, esophagogastrosopic image shows gastric ischemia		
P22/F/46	Olson et al. <sup>29</sup>	USA	NR	Multifocal small and large bowel wall thickening creating ribbonlike appearance, likely related to small vessel ischemia	NR	NR
P23/M/55	Cheung et al. <sup>62</sup>	USA	Fever, generalized abdominal pain, diarrhea, nausea	Low density clot causing high grade narrowing of the proximal SMA	Laparotomy, SMA thromboembolectomy (resection of 8 in. of necrotic small bowel followed by primary anastomosis)	Discharged and readmitted
P24/F/79	De Barry et al. <sup>46</sup>	France	Fever, epigastric abdominal pain, diarrhea, SOB	Spontaneous hyperdensity in the right portal vein (right portal vein thrombosis), proximal thrombosis of SMA, ischemia of caecum and small intestine	Thrombolysis and thrombectomy of the SMA	Death
P25/M/49	English et al. <sup>63</sup>	UK	Fever, SOB, cough	Hyperperfusion of the distal small bowel with intramural gas, ischemic distal small bowel	Laparotomy, laparoscopy	Hospitalized (ICU)
P26/M/56	Seelinger et al. <sup>64</sup>	France	NR	Small bowel ischemia was detected	Open small bowel resection, second look and double barrel ileostomy 48 h later	Hospitalized (ICU)
P27/F/70	Seelinger et al. <sup>64</sup>	France	NR	Sigmoid ischemia was detected, rectosigmoidoscopy found ulcerative and ischemic changes	Open rectosigmoid resection (Hartmann)	Hospitalized (ICU)
P28/F/61	Karna et al. <sup>65</sup>	India	NR	Thrombosis of distal SMA with dilated jejunoileal loops and normal enhancing bowel wall	Laparotomy	Death
P29/F/80	Neto et al. <sup>66</sup>	Brazil	Fever, cough, SOB, diffuse abdominal pain, stiffness	Extensive pneumoperitoneum	Laparotomy, rectosigmoidectomy with terminal colostomy	Death
P30/F/61	Hoyo et al. <sup>67</sup>	Spain	Severe acute abdominal pain, vomiting	Portal vein thrombosis, complete thrombosis of the splenoportal axis, mesenteric and splenic ischemia were observed in second CT scan	NR	Death
P31/M/30	Pang et al. <sup>28</sup>	Singapore	Colicky abdominal pain, vomiting	Superior mesenteric vein thrombosis with diffuse mural thickening and fat standing of multiple jejunal loops	Laparotomy	Discharged, readmitted, and discharged

Noted. NR: Not reported, M: Male, F: Female, SOB: Shortness of breath, SMA: Superior mesenteric artery, ICU: Intensive care unit.

the importance of the macro- and microvascular involvement in the pathophysiology of the bowel ischemia in the background of SARS-CoV-2 infection.

According to genome sequence analysis, COVID-19 belongs to the *Betacoronavirus* genus, which also includes the severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) coronaviruses.<sup>32,33</sup> GI manifestations were reported in about one-third of hospitalized MERS patients according to the study in Saudi Arabia.<sup>34</sup> The most frequent GI tract symptoms were diarrhea, followed by nausea, vomiting, and abdominal pain.<sup>35</sup> More severe extrapulmonary manifestations and complications, such as GI complications, were reported in three ICU admitted MERS patients with respiratory failure. One patient developed ischemic bowel with pneumatosis intestinalis on CT, requiring hemicolectomy.<sup>36</sup> Laparotomy findings for the other two patients were not significant. Also, elevated aminotransferase levels were present in some patients during hospitalization, which indicated liver damage.

Notably, enteric involvement was also demonstrated in patients with SARS infection, an epidemic in 2002 to 2003.<sup>37,38</sup> GI symptoms in patients with SARS are overall the same as MERS.<sup>36</sup> Intestinal biopsy specimens from SARS patients showed significant active viral replication within the intestine cells.<sup>39</sup> Mildly elevated aminotransferase levels due to liver dysfunction and acute abdomen requiring exploratory laparotomy were also reported in several cases of SARS.<sup>40</sup>

By detecting anal swabs and fecal samples positive for COVID-19, the fecal-oral route of the disease transmission has been suggested.<sup>41,42</sup> Following the involvement of the GI tract mucosa by the virus, malabsorption, and diarrhea are the consequences of the infected enterocyte malfunction. Among the common presenting symptoms of the disease,

GI-related complaints are seen in up to 38% of patients, among which diarrhea, nausea/vomiting and abdominal pain are the most common complaints.<sup>43</sup>

The imaging characteristics of the patients presenting with GI dominant manifestations include distended fluid-filled bowel loops with post-contrast enhancement and surrounding fat stranding/mesenteric inflammation.<sup>44</sup> However, more severe cases of bowel wall necrosis leading to surgical resection have also been reported.<sup>45</sup> Reports of the GI complications following COVID-19 are evolving.<sup>27,46</sup> The most clinically significant imaging findings reported are pneumatosis intestinalis and portal venous gas, the two alarming signs of bowel ischemia. Although fluid-filled dilated loops have been frequently reported, this finding is associated with diarrhea, a common but nonspecific manifestation of the COVID-19 and other viral infections.<sup>23</sup>

In this study, nine patients demonstrated underlying radiologically detectable medium to extensive arterial thrombosis, and six patients were suffering from portal venous system thrombosis. An abdominal CT scan of patient no. 6 revealed thrombosis of far distal SMA branches. Moreover, in the category of radiologically visible arterial compromise, imaging finding of patient no. 11 was solely SMA occlusion by thromboembolism. Such arterial thromboembolic events, along with the mentioned six cases of the portal vein and superior mesenteric vein thrombosis, raise the suspicion of an underlying hypercoagulable state as a significant contributing factor in ischemic bowel disease in COVID-19 patients. Consistent with this review results, Dane et al. reported that solid organ infarction in COVID-19 patients follows vasculature patterns and may result from microthrombi.<sup>47</sup> Among the cases of bowel ischemia in the setting of COVID-19 in our systematic review, the most common non-thrombotic radiologic findings were bowel wall



unenancement (which is a specific sign for ischemia) and bowel wall thickening (which is probably the more sensitive sign of ischemia).

Multiple factors are described in the pathogenesis of thrombotic events in patients with COVID-19. These factors include endothelial inflammation, thrombin formation, complement activation and initiation of the immune response, which result in thrombotic complications, such as deep venous thrombosis and arterial ischemia.<sup>48–50</sup> Additionally, several contributing factors should be considered in the pathogenesis of bowel wall ischemia in COVID-19 patients, including ICU admissions, positive pressure ventilation, and viral enteritis. Microvascular thrombosis, non-occlusive mesenteric ischemia, and gross arterial and venous thrombosis have been suspected as culprits for fatal bowel wall necrosis. Furthermore, the COVID-19-associated coagulopathy in critically ill patients has been demonstrated and can result in microangiopathy, massive vessel thrombosis, and significant thromboembolic complications.<sup>23,45,51,52</sup>

Both macrovascular and microvascular thrombotic events are common in infected patients. It has been reported that the microvascular complications are detected in the early stages of the disease, and macrovascular events are frequently observed in severely ill patients. Now, it is well known that the hypercoagulable state induced by the COVID-19 infection results in micro and macrovascular complications.<sup>53</sup> In recent studies, it has been suggested that all hospitalized COVID-19 patients should undergo routine coagulation profile monitoring and thromboembolism prophylaxis.<sup>51</sup>

Contrast-enhanced abdominopelvic CT scan has a pivotal role in the early diagnosis of ischemic bowel disease. It should be considered in any cases of COVID-19 with prominent GI signs and symptoms, especially those admitted in ICU. This modality allows to detect associated vascular findings and identifying those patients who may benefit from percutaneous endovascular thrombectomy as well.<sup>54</sup> In our studied population, CT scan results revealed one patient (no. 14) with short segment bowel edema and diffuse wall thickening involving a single loop, concerning for inflammatory ileitis. Therefore, CT scan led the surgeon to a medical rather than surgical treatment approach. The patient underwent conservative management with a favorable outcome. Small or large bowel un-enhancement after contrast injection, along with pneumatosis intestinalis and portal venous gas, prompt lifesaving surgical intervention in the setting of acute bowel necrosis.<sup>24</sup> By the progression of the COVID-19 pandemic, new aspects of the disease morbidity are being sought. Meanwhile, spotting different clinical and imaging characteristics of these complications help the physicians prognosticate and take action to prevent unfavorable outcomes.<sup>68,69,70</sup>

To our knowledge, this review study represents all cases of arterial/venous thrombosis in COVID-19 patients with bowel ischemia to date; it implies that further research is needed to identify patients most at risk of acute GI ischemia according to the published reports of increased thrombo-occlusive and thromboembolic events in COVID-19. Moreover, a larger sample of cases is needed for specifying the early imaging findings of GI ischemia in patients with COVID-19. Additionally, standardized management guidelines and patient selection strategies are needed considering prophylactic anticoagulant regimen in these patients.

## 5. Conclusion

Macrovascular arterial/venous thrombosis can be depicted in almost half of COVID-19 patients with bowel ischemia. Overall mortality in COVID-19 patients with GI ischemia and radiologically evident mesenteric ischemia was 38% and 40%, retrospectively. Although many attributing factors are considered in the pathogenesis of bowel ischemia, factors such as hypercoagulable state, non-occlusive mesenteric ischemia, and microvascular thrombosis constitute the underlying pathology in the majority of COVID-19 patients with GI ischemic presentation.

## Abbreviations

COVID-19	Coronavirus disease 2019
GI	Gastrointestinal
ICU	Intensive care unit
SARS	Severe Acute Respiratory Syndrome
MERS	Middle East Respiratory Syndrome
SMA	Superior mesenteric artery

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Pedram Keshavarz: Investigation, Writing - original draft, Writing - review & editing, Data curation. Faranak Rafiee: Investigation, Writing - review & editing, Data curation. Hadiseh Kavandi: Writing - review & editing, Data curation. Sogand Goudarzi: Data curation, Writing - review & editing, Investigation. Firouzeh Heidari: Investigation, Data curation, Writing - review & editing. Ali Gholamrezaezhad: Data curation, Writing - original draft, Writing - review & editing, Conceptualization, Investigation.

## Declaration of competing interest

The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.clinimag.2020.11.054>.

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