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SYSTEMATIC REVIEW

Infectious diseases

Bowel ischemia in COVID-19: A systematic review

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Abstract

Background: Gastrointestinal complications of COVID-19 have been reported over the last year. One such manifestation is bowel ischaemia. This study thus aims to provide a more holistic review of our current understanding of COVID-19-induced bowel ischaemia.

Method and Results: A meticulous search was performed using different keywords in PubMed and Google Scholar. Fifty-two articles were included in our study after applying inclusion and exclusion criteria and performing the qualitative assessment of the studies. A total of 25 702 patients were included in our study after the completion of the qualitative assessment.

Discussion: The common symptoms of GIT in COVID-19 patients are as diarrhoea, vomiting, nausea and abdominal pain. The mechanism of bowel ischaemia is associated with the formation of emboli which is related to COVID-19's high affinity for angiotensin-converting enzyme-2 on enterocytes, affecting the superior mesenteric vessels. Clinically, patients present with abdominal pain and vomiting. CT angiography of the abdomen and pelvis showed acute intestinal ischaemia (mesenteric). Management is usually initiated with gastric decompression, fluid resuscitation, and haemodynamic support. Surgical intervention is also sought.

Conclusion: Intestinal ischaemia presenting in patients with COVID-19 has to be considered when symptoms of severe abdominal pain are present. More research and guidelines are required to triage patients with COVID-19 to suspect intestinal ischaemia and to help in diagnosis and management.

1 | INTRODUCTION AND BACKGROUND

The world has not been the same after the universal spread of the COVID-19 pandemic which dawned in Wuhan, China at the end of 2019. COVID-19 has been known to be transmitted through respiratory droplets. The manifestations of SARS-CoV-2 are so variable ranging from being asymptomatic to severe respiratory distress syndrome (ARDS).[1] It has affected millions of people all over the world because of its rapid aerosol transmission. This compelled the World Health Organization (WHO) to declare COVID-19 as a health emergency on 30 January 2020. Later, declaring it as a full-blown pandemic on 11 March 2020. COVID-19 has various systemic manifestations that are vital to understanding and preventing significant morbidity and mortality. SARS-CoV-2 creates a habitat for a prothrombotic state in the human body and causes arterial, venous, and catheter-related thrombosis.[2] This hypercoagulable state leads to a variety of manifestations on the cardiovascular system, nervous system, renal and gastrointestinal systems. Arterial thrombosis caused by COVID-19 includes limb and mesenteric ischaemia, stroke, and acute coronary syndrome.[3-5]

Plenty of other gastrointestinal complications were reported in COVID-19 patients like ileus, hepatic necrosis, acalculous

cholecystitis as well. There is very high mortality in bowel ischaemia and limited data available make it very essential to predict and prevent COVID-19-related bowel ischaemia. Our study specifically focuses on bowel ischaemia as a gastrointestinal complication of Coronavirus. Apart from hypercoagulation, several other mechanisms like inflammation, vasculopathy and immobilisation have been proposed to explain the occurrence of GI ischaemia, but the exact cause is still very unclear.[2]

The clinician should have a high index of suspicion to prevent such a deadly complication. Our systematic review aims at exploring the occurrence, course, symptomatology and outcome of bowel ischaemia in COVID-19. This will help clinicians to predict this specific complication and treat it in the earliest possible way to reduce significant morbidity and mortality.

Review Criteria

- We gathered information with the help of an electronic search using PubMed and Google Scholar by using keywords either in combination or alone.
- Keywords used were "COVID-19," "Bowel ischemia," "Mesenteric ischemia," and "pathophysiology," "Management," "Sequelae."
- Articles went through our inclusion and exclusion criteria mentioned in the methods section to decide whether to include them in our review.
- Clinical Appraisal tools were later applied to each of the articles by the authors for quality analysis.

Message for the clinic

- We intend to provide an insight to the clinician so that an early diagnosis of bowel ischaemia is made and none of the cases are missed.
- We have included even very rare presentations of bowel ischaemia and methods of their diagnosis to guide the clinician in their management.
- Bowel ischaemia should not be taken lightly as it has a very high mortality rate. It requires the immediate attention of the clinician while managing the patient of COVID-19.

2 | METHODS

2.1 | Electronic search

Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guideline was strictly followed for the conduct of our systematic review. The authors SP, RS, DV systematically searched PubMed and Google Scholar using an advanced search strategy to find relevant articles for our study. The keywords used for the search strategy were "COVID-19," "Bowel ischemia," "Mesenteric ischemia," "pathophysiology," "Management," and "Sequelae." The keywords were used either alone or in combination. In addition, many publications were identified using the "Snowball Method," that is, articles were identified from reference lists of relevant articles.

2.2 | Eligibility criteria

The eligibility criteria that we applied for the studies to be included in our review article were: Laboratory-confirmed SARS-CoV-2/COVID-positive cases, cases reporting a diagnosis of AMI/bowel ischaemia, articles published in English language. Animal trial studies, in vitro studies, articles with no abstracts were excluded.

2.3 | Study selection and quality assessment

The authors MW, CP and UA evaluated the title and abstracts of the articles extracted from databases and ascertained the studies based on predominant eligibility criteria. Quality assessment of the selected studies was done using standardised quality appraisal tools based on the type of study. The authors RA, NB, DS, RS, SP, CP and MW did the quality assessment of the studies. The standard tools used were:

Observational studies: New-Castle Ottawa Scale

Systematic Reviews/Meta-Analysis: AMSTAR Checklist

Case Reports and Case Series: Joanna Briggs Institute Checklist

Narrative Reviews: SANRA

Studies were ranked as good, fair and poor quality based on the assessment scores of the studies.

2.4 | Data extraction

A standardised data abstraction form was adopted to extract the data from databases. The authors DV, SP and RA extracted the data manually. Any difference in opinion was resolved through mutual discussion among the authors. The following information was extracted: authors, year of publication, no of cases or participants in the study, study design, laboratory findings and treatment procedure adopted for the management, complication and outcome in the patients following the treatment.

3 | RESULTS

An initial search of the databases yielded 180 826 articles using advanced search strategies which included Medical Subjects Heading [MeSH] as well. The articles were then screened by applying eligibility criteria as discussed above which left us with 92 articles and 180 734 articles were excluded. Ninety-two articles were screened

and 32 articles were removed because of irrelevant or insufficient information or not having a full-text article or abstract. Sixty articles were then assessed for eligibility.

The eligibility was determined by the use of various critical appraisal tools as mentioned above. Fifty-two articles qualified for the critical appraisal assessment and were included in our study. Eight articles were excluded for not qualifying the critical appraisal assessment.

Figure 1 below shows the PRISMA flow diagram mentioning the result of our study.[6]

A total of 25 702 patients were included in our study from 10 observational studies, three systematic reviews, meta-analysis, and 24 case reports. Fever was the most predominant presenting complaint reported. Most of the studies reported the presence of acute abdomen, nausea, loss of appetite, diarrhoea along with sore throat, cough, confusion and sepsis in severely ill patients.

3.1 | Diagnostic findings

All the cases included in our study were laboratory-confirmed SARS-CoV-2 positive. We tried to explore the diagnostic findings suggesting bowel ischaemia. Most of the cases did not report any laboratory findings supporting the diagnosis of bowel ischaemia. Some studies reported elevation of D-dimer and lactate dehydrogenase. Table 1

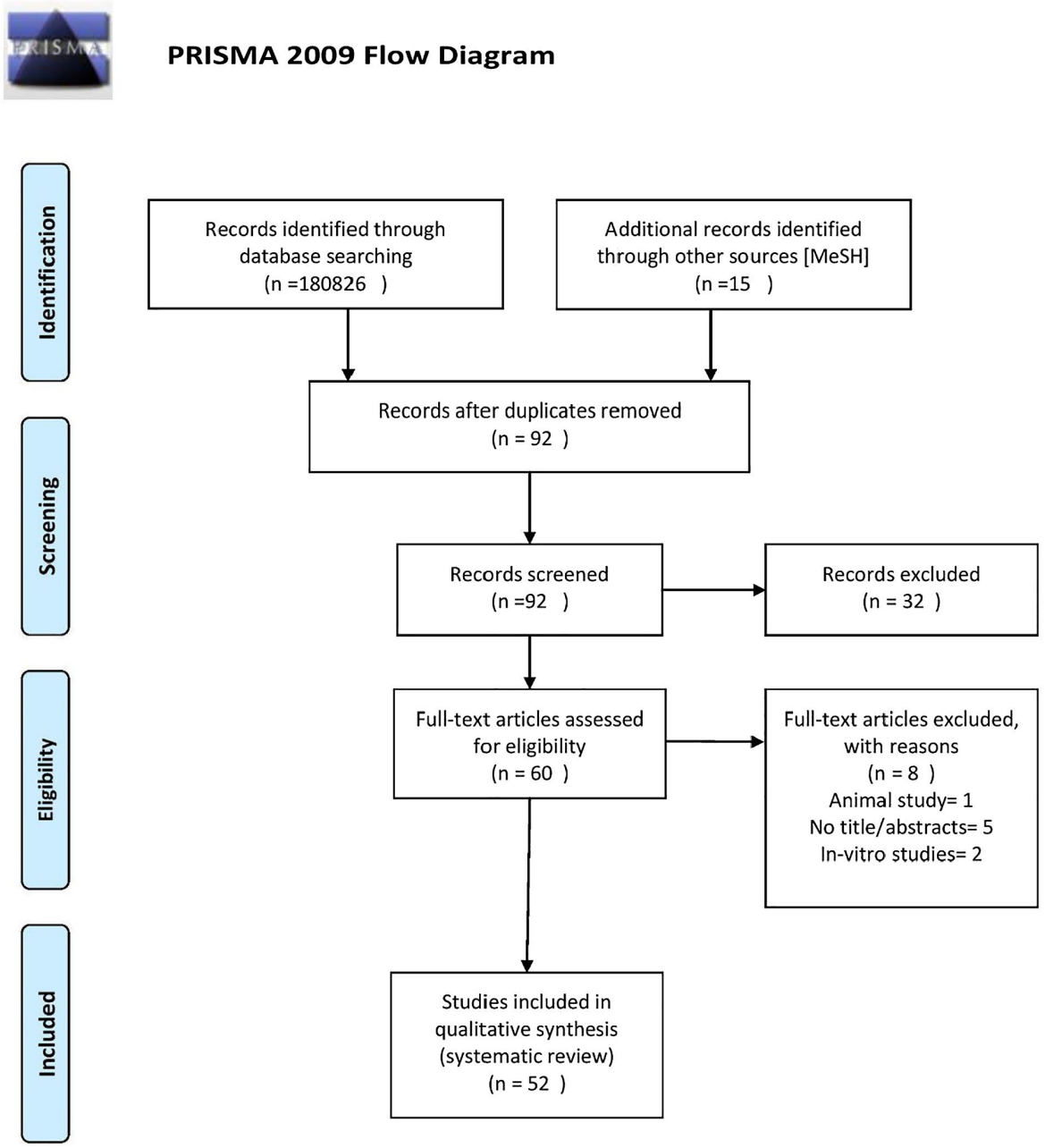

FIGURE 1 PRISMA 2009 flow diagram

TABLE 1 Studies depicting presentation and lab values, specifically D-dimer and LDH values, of COVID-19 patients

Reference	Author	Year of publication	Type of study	n	SARSCoV2 status
[4]	Kaur P et al	2020	Case report	1	Positive
[5]	Singh B et al	2020	Case report	1	Positive
[7]	Wang D et al	2020	Retrospective single-centre case series	138	Positive
[8]	Guan W et al	2020	Retrospective cohort study	1099	Positive
[9]	Pan L et al	2020	Descriptive, cross-sectional, multicentre study	204	Positive
[10]	Cheung KS et al	2020	Systematic review and meta-analysis	59	Positive
[12]	Han C et al	2020	Retrospective cohort study	206	Positive
[13]	Mao R et al	2020	Systematic review and meta-analysis	6064	Positive
[14]	Noda S et al	2021	Case report	1	Positive
[15]	Laski D et al	2021	Case report	1	Positive
[16]	Zeng W et al	2021	Systematic review	5285	Positive
[17]	Chen N et al	2020	Retrospective, single-centre study	99	Positive
[18]	Kim JY et al	2020	Case report	1	Positive
[19]	Tang A et al	2020	Case report	1	Positive
[22]	Singh B et al	2021	Systematic review	13	Positive
[23]	Rodriguez-Nakamura RM et al	2020	Case report and literature review	2	Positive
[25]	Ignat M et al	2020	Case series	3	Positive
[26]	Paul T et al	2021	Case report	1	Positive
[27]	Swami GA et al	2021	Case report	1	Positive
[28]	Calcagno E et al	2021	Case report	1	Positive
[32]	Holleb P et al	2021	Case report	1	Positive
[34]	Gartland M et al	2020	Case report	1	Positive
[35]	JHQ Pang et al	2020	Case report	1	Positive
[36]	Al Argan RJ et al	2021	Case series	3	Positive
[37]	Varshney R et al	2021	Case report	1	Positive
[38]	Drakos, P. et al	2021	retrospective cohort study	218	Positive
[33]	Cheung S et al	2020	Case report	1	Positive
[39]	Krothapalli N et al	2021	Case report	1	Positive
[40]	Bannazadeh M et al	2021	Case report	1	Positive
[41]	Alharthy A et al	2020	Case report	1	Positive
[43]	Tang N et al	2020	Retrospective cohort study	449	Positive
[44]	Dinoto E et al	2021	Case report	1	positive
[45]	Balani P et al	2021	Case report	1	Positive
[47]	Shaikh DH et al	2021	Case report	1	Positive

Abbreviations: IQR, interquartile range; n, no. of patients; N/A, not available.

[a]No./total no. (%).

Age (years)	Presenting symptoms	D-dimer	LDH
43	Shortness of breath and acute right leg pain	>20 (reference: <0.5)	718 U/L (reference: 140-271 U/L)
77	Shortness of breath and pain, discoloration, and swelling of the left leg	2.77 (reference: <0.5)	392 U/L (reference: 140-271 U/L)
56 (mean age)	Fever, fatigue, and dry cough	203 U/L (125-243) [IQR]	261 U/L [125-243] [IQR]
47 (mean age)	Fever and cough, diarrhoea	No of patients with D-dimer ≥0.5 mg/L - 46.4%[a]	No of patients with LDH ≥250 U/L - 41.0%
52.9 (mean age)	Digestive manifestations, including lack of appetite, diarrhoea, vomiting, and abdominal pain	N/A	N/A
58.5 (mean age)	Fever, cough, dyspnoea, diarrhoea, vomiting, abdominal pain/discomfort	N/A	N/A
62.5 (mean age)	Diarrhoea	N/A	N/A
N/A	Nausea, vomiting, diarrhoea, loss of appetite, abdominal pain, fever	N/A	N/A
17	Abdominal pain, vomiting and fever	2.2 mcg/mL, normal ≤0.5 mcg/mL	N/A
39	Fever, pain in upper abdomen, nausea, vomiting	N/A	N/A
N/A	Diarrhoea, abdominal pain	N/A	N/A
55.5 (mean age)	Fever, cough, shortness of breath. Muscle ache, diarrhoea	0.9 (normal range 0.0-1.5)	336.0 (normal range 120.0-250.0)
35	Fever, chills, myalgia	N/A	561 U/L (highest value recorded)
10	Asymptomatic	N/A	N/A
56 (mean age)	Nausea, vomiting, fever, abdominal pain	N/A	N/A
43.5 (mean age)	Case 1 - Severe gastric pain Case 2 - spontaneous abdominal pain	Case 1 - 1450 mcg/L Case 2 – 14 407 mcg/L	N/A
50.3 (mean age)	Case 1 - Abdominal pain Case 2,3 - ARDS	N/A	N/A
66	Fever, cough, loss of smell and taste	N/A	N/A
54	Fever, cough	1245 ng/mL (normal - <250 ng/mL)	745 IU/L (n = 50-250)
36	Abdominal pain	N/A	N/A
54	Nausea, vomiting, abdominal pain, diarrhoea	N/A	N/A
47	Fever, shortness of breath	N/A	N/A
30	Abdominal pain associated with vomiting	D-dimer >20.0 μg/mL	N/A
59.33(mean age)	Case 1 - Dry cough and fever Case 2 - Shortness of breath Case 3 - Abdominal pain	Case 1 - 0.6 Case 2 - 0.41 Case 3 - 1.66 (Normal - ≤0.5 μg/mL)	Case 1 - 434 Case 2 - 442 Case 3 - 617 (Normal - (81-234) U/L)
50	Abdominal pain and constipation	N/A	N/A
59.8 (mean age)	Listed as acute gastrointestinal injury	Increased based on grading of acute gastrointestinal injury	N/A
55	Nausea, vomiting, generalised abdominal pain	3.4 nmol/L	N/A
76	Shortness of breath	2159 ng/L (normal - <250 ng/mL)	N/A
55	Severe abdominal pain	2400 ng/L (normal - <250 ng/mL)	N/A
54	Fever, cough, dyspnea, diarrhoea	4.1 μg/mL; reference range, 0 to 0.5 μg/mL	997 U/L; reference range, 100-190 U/L)
65.1 (mean age)	Diarrhoea, acute abdomen	1.94 Reference - 0 to 0.5 μg/mL)	N/A
84	Acute abdomen	6937 ng/mL (normal - <250 ng/mL)	431 U/L (n = 50-250)
37	Abdominal pain, vomiting	3.1 Reference - 0 to 0.5 μg/mL	N/A
73	Acute abdomen, distension of abdomen	2757 (normal - <250 ng/mL)	236 (normal = 50-250)

below summarises the presenting complaints and laboratory findings in various studies.

4 | DISCUSSION

4.1 | General GI manifestations of COVID-19

Patients infected with COVID-19 have shown GI symptoms (2%-10%); however, those numbers, in reality, appear to be much higher.[7,8] About 50.5% of patients reported various gastrointestinal signs and symptoms during a study of COVID-19 patients in China.[9] A meta-analysis consisting of 60 studies and 4243 patients demonstrated a pooled prevalence of GI symptoms of 16.1% and 33.4% in studies from China and other countries, respectively.[10] In another meta-analysis including 47 studies and 10 890 unique patients, GI symptoms were present in less than 10% of patients, but rates were higher in studies outside of China.[11] GI symptoms as a result of COVID-19 were suggested to be more common in females according to Han et al (65.7% in females and 51.1% in males), but no alternate studies showed similar figures.[12] COVID-19 presents as anorexia (21%), diarrhoea (9%), nausea/vomiting (7%), and abdominal pain/discomfort (3%) when presenting in the GI.[13] A minority of patients present with an acute abdomen with aetiologies such as acute pancreatitis, acute appendicitis, intestinal obstruction, bowel ischaemia, haemoperitoneum, abdominal compartment syndrome, bowel perforation, hepatic necrosis, acalculous cholecystitis, and colitis. Very rare GI presentations of the COVID-19 have also been noted like mesenteric adenopathy[14] and pneumatosis intestinalis.[15]

There is a strong relationship between the severity of COVID-19 and gastrointestinal symptoms which can be illustrated by: (1) 40% of severe COVID-19 positive patients have gastrointestinal symptoms; (2) Abdominal pain is associated with 2.8-fold increase in the risk of severe COVID-19.[16]

Like other respiratory virus infections, the majority of patients with COVID-19 present with acute respiratory symptoms.[17,18] Many times COVID-19 patients are asymptomatic so there are very high chances of these cases being missed out which need more investigation like stool PCR.[19] Diarrhoea, nausea and vomiting while being common GI symptoms in general did not seem to be present in COVID-19 in initial studies.[20] However, with the growing number of studies on COVID-19, up to 48.5% (204 patients) in China reported presenting with GI symptoms. They presented with symptoms such as anorexia, diarrhoea, vomiting and abdominal pain.[9]

Patients with underlying digestive diseases and COVID-19 infection may present with a severe infection in chronic liver diseases such as viral hepatitis B or C.[21] Sometimes damage to the alimentary canal leads to inflammation that causes malabsorption and damage to the mucosal integrity of the canal, activation of the enteric nervous system, and an imbalance in the secretion of the alimentary canal. Usually, the symptoms are self-limited but, at times surgery may be required depending on the extent of the damage.

4.2 | Pathophysiology

Studies indicate the involvement of multiple mechanisms in the causation of acute mesenteric ischaemia (AMI) in COVID-19 patients.

Firstly, the SARS-CoV-2 virus has a high affinity and tropism for angiotensin-converting enzyme-2 (ACE2) receptors on enterocytes. This can lead to the tropism of the virus into the enterocytes causing direct damage to the bowel tissue.[22] This binding of the virus to the ACE2 receptors decreases the breakdown of ACE2 which increases IL-6 levels, leading to the development of a cytokine storm. Endothelial cells increase the expression of tissue factor and plasminogen activator inhibitor-1 because of the hypercoagulability caused by angiotensin 2.[23] Second, a viral infection of the endothelial cells can lead to their inflammation and dysfunction. This endothelial damage increases the formation of procoagulant factors like factor VIII, von Willebrand factor secreted by the Weibel Palade bodies, and fibrinogen. The hypercoagulable state in COVID-19 can cause thrombosis of small mesenteric vessels and bowel ischaemia.[24] This mucosal ischaemia can lead to a considerable spread of the virus from the bowel to other organ systems causing a rapid clinical deterioration in the patient's condition.[25] Venous thromboembolism is more commonly observed than arterial thrombosis in patients with COVID-19.[26] Hypercoagulability can also be a result of the circulating microvesicles that can originate from platelets, monocytes or neutrophil extracellular traps released from activated neutrophils.[22] Lastly, patients with severe COVID-19 pneumonia might require vasopressors like norepinephrine and high-dose epinephrine to treat shock and haemodynamic instability. The resulting vasoconstriction and decreased mesenteric blood circulation can lead to non-occlusive mesenteric ischaemia.[26] Figure 2 below summarises the mechanism involved in AMI. Table 2 below summarises the pathophysiological mechanism involved.

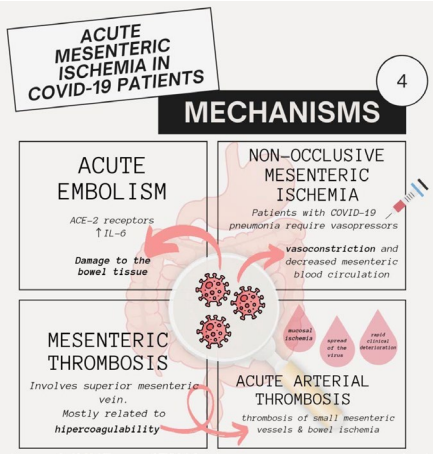

FIGURE 2 Flow chart of mechanisms of acute mesenteric ischaemia in COVID-19. ACE-2, angiotensin-converting enzyme 2; IL-6, interleukin-6

TABLE 2 Pathophysiology involved in bowel ischaemia

Author	Year	Type	Purpose of study	Place of study	Conclusion
Singh B et al[22]	2021	Letter to the editor	To identify the possible mechanisms and diagnostic pathways for AMI in Severe Coronavirus-19 infection.	USA	Detailed understanding of the occurrence of AMI in COVID-19 patients will aid in carrying out appropriate diagnostic tests at an early stage and making swift decisions regarding the intensity of thromboprophylaxis to decrease the risk of morbidity and mortality
Rodriguez N et al[23]	2020	Case report and literature review	2 cases of COVID-19-induced ischaemia leading to acute mesenteric thrombosis. The SCARE criteria have been utilised to report the work in the study	Mexico	Suspicion for rare pathologies like mesenteric thrombosis in COVID-19 should be raised in patients who present with an unclear clinical picture
Parry A et al[24]	2020	Letter to the editor	To identify the possible mechanisms and diagnostic pathways for AMI in Severe Coronavirus-19 infection	India	Suitable diagnostic tests at an early stage of COVID-19 can be helpful in making swift decisions regarding the intensity of thromboprophylaxis to decrease the risk of morbidity and mortality linked with the disorder
Ignat M et al[25]	2020	Case series	To describe the clinical and the CT features of 3 patients presenting with an acute abdomen induced by SARS-CoV-2 infection	France	If a patient with COVID-19 worsens and the cause is undetermined, abdominal CT can be considered. Exploratory laparotomy and bowel resection may be deemed necessary in the event of small bowel involvement
Paul T et al[26]	2020	Case report		Qatar	Severe COVID-19 pneumonia should raise concern for a hypercoagulable state. Diagnosing and treating such patients early in the disease course has shown better outcomes

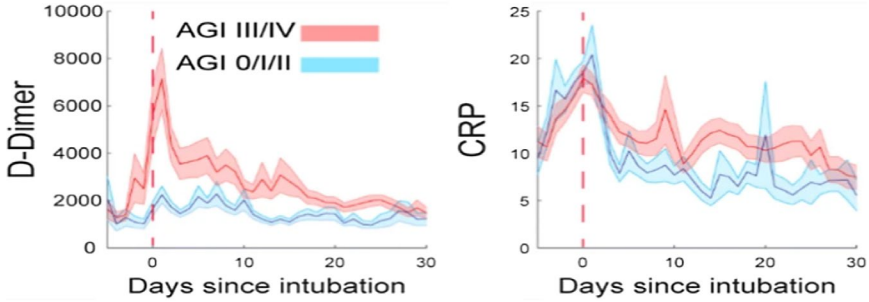

FIGURE 3 Co-relation of AGI with D-dimer and CRP

4.3 | Diagnosis, sequela and prognosis

The SARS-CoV-2 virus has been found to cause pneumonia as well as a variety of other symptoms in the gastrointestinal, cardiovascular, and nervous systems as part of a multi-inflammatory syndrome, which is becoming more widely recognized as a part of the disease spectrum. Coagulopathy associated with COVID-19 has become a major contributor to high mortality and morbidity, with ischemic bowel disease being one of the outcomes.[27] Because clinical factors are ineffective at predicting or suspecting coagulopathy and associated consequences, it is critical to be aware of imaging symptoms of COVID-19 coagulopathy sequelae.[28] The following imaging findings are often documented on CT abdomen of COVID-19 positive patients with GI symptoms:thrombosis of vessels, pneumoperitoneum, gut wall thickening, fluid-filled dilated colon, pneumatosis, mesenteric ischemia, and intussusception.[29]

Mesenteric ischemia can be either acute (95% of the cases) or chronic (remaining 5% of the cases). Mesenteric ischemia is not detected by laboratory testing since they are neither sensitive nor specific.[30] Increased WBC count, metabolic acidosis, hemoconcentration, and elevated levels of lactate, D-dimer, liver enzymes, and amylase are some of the abnormal laboratory findings associated with ischemia. The first-line imaging test for suspected Acute and chronic mesenteric ischemia is multiplanar biphasic CT angiography of the abdomen and pelvis. Thin sections, multiplanar reformation, and three-dimensional rendering should all be used while performing CT angiography.[31] The initial sign of acute mesenteric ischemia (AMI) is a dynamic ileus, in which the intestine is dilated and frequently filled with fluid. This might be due to ischemia-induced aperistalsis or infarction-induced lack of contractility. The most prevalent sign in AMI is circumferential edematous intestinal wall thickening. When compared to other forms of mesenteric ischemia, in venous ischemia wall thickening is most noticeable,with a striated pattern that corresponds to the "target" & "halo sign". Edema or hemorrhage can cause the thickened intestinal wall to hypoattenuate or hyperattenuated respectively. In individuals with arterial AMI, the gut wall may also be thin. In individuals with AMI, bowel wall enhancement may be enhanced, reduced, or nonexistent. Mural hyperenhancement generally indicates that gut is viable and is associated with venous drainage problems, shock bowel, or acute arterial occlusion with reperfusion.[30]

One of the suggested mechanisms for paralytic ileus/small bowel obstruction is through the inflammatory process from the virus entry into the small intestine and leading to micro thrombosis of the microcirculation.[32] Studies have shown that in patients infected with coronavirus gastrointestinal involvement is seen in at least two-thirds of patients. Coagulation abnormalities and elevated D-dimer levels were noted in patients with COVID-19 and are related to a poor clinical outcome and a very high inpatient mortality rate.[33] A case report in a COVID-19-positive patient who had patent mesenteric vessels associated with catastrophic bowel necrosis suggested that it can be caused by microvascular thrombosis and inflammation. It is considered as one of the proposed mechanisms in such patients known to have hypercoagulability.[34] Another case report in a patient with COVID-19 has shown how superior mesenteric thrombosis can present as intestinal obstruction from congenital adhesion, which is a rare surgical condition. This patient had an acute presentation from small bowel stricture which can be one of the sequelae secondary to bowel ischaemia.[35] Cases have been reported in which COVID-19 led to gastric wall perforation, caecal perforation and sigmoid diverticulitis with perforation which were treated conservatively and surgically.[36] Varshney et al reported a case in which COVID-19 resulted in sigmoid and descending colonic gangrene further requiring colectomy.[37] Drakos et al performed Kaplan-Meier survival analysis, various other statistical tests and determined that the development of acute gastrointestinal injury (AGI) and intolerance to feeds during the initial days can serve as prognostic tools for predicting outcomes in critically ill COVID-19 ICU patients. Higher grades of AGI also correlated with the increased levels of D-dimer and C-reactive protein as shown in the Figure 3.[38]

4.4 | Management of bowel ischaemia in COVID-19

It has been documented that COVID-19 leads AMI.[33,39] This has often been attributed to the hypercoagulable state that the novel coronavirus puts the patient's body in, which eventually leads to bowel ischaemia.[40] The importance of early diagnosis and prevention cannot be stated enough. The cornerstone of management of such an acute emergency is the immediate restoration of blood flow, and removal of any necrotic bowel.[41,42]

This is an evolving topic and there are no clear guidelines specific to COVID-19-related bowel ischaemia when it comes to management. It is in the interest of healthcare providers to aid in the prevention of such severe complications as bowel ischaemia. Based on the understanding of the increased incidence of thrombotic events

TABLE 3 Management strategies for bowel ischaemia secondary to COVID-19

Author	Year	Type	Purpose of study	Place of study	Conclusion
Cheung S et al[33]	2020	Case reports	COVID-19-induced thrombosis of the superior mesenteric artery.	USA	This case was managed with exploratory laparotomy, thrombectomy and resection of the ischaemic bowel
Krothapalli N et al[39]	2021	Case report and literature review	Discusses aetiology, clinical picture and laboratory findings of mesenteric ischaemia in COVID-19-positive patients and explains a case of it	USA	Surgical resection of the bowel is aided with gastric decompression and fluid resuscitation. This complication is best prevented by prophylactic thrombolytics
Bannazadeh M et al[40]	2021	Case report	Case report discussing the presentation of mesenteric artery thrombosis in a patient with COVID-19, 1 week after discharge	USA	Therapeutic enoxaparin for 3 months following bowel resection and end-to-end anastomosis will help
Alharthy A et al[41]	2020	Case report	To examine a case of COVID-19 presenting with acute abdomen and sepsis.	Saudi Arabia	Management mainly involves exploratory laparotomy, resection of the ischaemic area and anticoagulation in the post-op period. Based on renal function, enoxaparin is recommended for therapeutic anticoagulation
Kariyawasam JC et al[42]	2021	Review article	Presents the gastrointestinal manifestations of COVID-19	Sri Lanka	Cases of acute abdomen and GI bleeding may warrant surgical or endoscopic modalities for management
Tang N et al[43]	2020	Retrospective cohort study	To study the efficacy of low molecular weight heparin in decreasing the risk of disseminated intravascular coagulation and venous thromboembolism	China	Low molecular weight heparin appears to be the mainstay for therapeutic anticoagulation in severe COVID-19 patients with elevated D-dimer
Dinoto E et al[44]	2021	Case report	Introduces a case of mesenteric ischaemia which was followed by acute limb ischaemia in a patient with COVID-19	Italy	Endovascular management can be used as it has reduced mortality and morbidity rates. Different options exist such as mechanical thrombectomy, local thrombolysis and PTA stenting
Balani P et al[45]	2021	Case Report and literature review	Discusses early detection and management of bowel ischaemia in a patient with COVID-19	India	Catheter-directed thrombolysis with thrombus aspiration is a possible treatment modality for superior mesenteric thrombus if caught early
Mariette X et al[46]	2021	Research Letter	Follow-up article to a trial of tocilizumab in hospitalised patients of COVID-19 infection	France	Treatment of moderate-to-severe COVID-19 with elevated CRP levels can include the use of tocilizumab
Shaikh DH et al[47]	2021	Case report and literature review	To explain a case of COVID-19-related colitis along with distention and ischaemia	USA	Tocilizumab infusion can also be added after bowel resection to the management to treat COVID-19

in patients with COVID-19, the use of prophylaxis as well as out and out anticoagulation strategies have been tried and tested with favourable outcomes.[43] Screening with CT imaging and prothrombotic workup also plays a role in the early diagnosis of bowel ischaemia. Supportive and conservative therapy includes gastric decompression, fluid resuscitation, and hemodynamic support.[44,45] Also, early diagnosis and systemic thrombolysis have been shown to produce better outcomes in terms of bowel salvage.[44,45]

In terms of surgical interventions, exploratory laparotomy followed by bowel resection was often sought because of the acute presentation of the case. Another treatment modality involves an endovascular approach such as superior mesenteric artery (SMA) thrombectomy with stent repair, or catheter-directed thrombolysis with thrombus aspiration.[45] Tocilizumab, a monoclonal antibody acting against the IL-6 receptor, has been used to treat hospitalised patients with severe COVID-19.[46] Shaikh DH et al mentions its use as an infusion, in COVID-19-induced small bowel ischaemia, after a patient underwent surgical intervention. Good recovery was seen. In this case, it was also noted that convalescent plasma therapy along with tocilizumab infusion, was used post-op.[47] But, symptomatic and supportive care is the mainstay of therapy. In a general sense as well, more studies will help throw visibility on this unique but drastic complication of COVID-19 so that better treatment modalities may be identified. Table 3 presented below outlines the various management strategies involved in the treatment of bowel ischaemia secondary to COVID-19.

4.5 | Limitations

This study is not without its limitations. COVID-19 is still very much under investigation. Currently, there is not enough material for us to confidently establish causation and management of COVID-19-induced bowel ischaemia. Another point to note is that this is a retrospective study. While we are able to identify cases where AMI has occurred, we are unable to identify the baseline exposure status of such patients. Without this, we cannot point out the factors that lead to patients developing mesenteric ischaemia. Prospective studies in this direction will go a long way in understanding this complication. In addition, the pathophysiology of COVID-19-induced bowel ischaemia is not well-established. This is an important area of research that requires further exploration to help define this mechanism.

5 | CONCLUSION

Acute mesenteric ischemia does seem to be a rare complication of COVID-19. This review article underscores the importance of placing AMI in the workup of such a patient with COVID-19 presenting with manifestations of the gut, most commonly acute abdomen. Elevated lactate, LDH, and D-dimer levels can be considered while assessing a patient of COVID-19 with abdominal pain for mesenteric ischaemia. Ultimately, Computed Tomography of the abdomen helps clinch the diagnosis. However, more prospective studies are required to assess the laboratory diagnostics to help suspect as well as confirm bowel ischaemia in a patient with COVID-19. Immediate intervention may help provide better outcomes. It is important to acknowledge that adequate thrombolysis and hemodynamic support should be implemented as they may help maintain homeostasis thereby aiding in early diagnosis or even preventing this complication.

DISCLOSURES

No author has any conflicts of interest.

DATA AVAILABILITY STATEMENT

Data used in this study were a re-analysis of existing data, which are openly available at locations cited in the reference section. This data are publicly available to everyone at Pubmed Central [https://pubmed.ncbi.nlm.nih.gov/] and Google scholar [https://scholar.google.com/]. No datasets were generated or analysed during this study.

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