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Acute Mesenteric Ischemia in Patients with COVID-19: Review of the literature

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Abstract: The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in a global health emergency. In addition to common respiratory symptoms, some patients with COVID-19 infections may experience a range of extra-pulmonary manifestations, such as digestive system involvement. Patients with COVID-19 have been reported to suffer from acute mesenteric ischemia (AMI) that is associated with disease-related severity and mortality. However, in the context of COVID-19, the exact cause of AMI has yet to be clearly defined. This review provides a comprehensive overview of the available data and elucidates the possible underlying mechanisms linking COVID-19 to AMI, in addition to highlighting therapeutic approaches for clinicians. Finally, given the severe global impact of COVID-19, we emphasize the importance of coordinated vaccination programs.

Keywords: COVID-19 ■ SARS-CoV-2 ■ Gastrointestinal disorders ■ Acute mesenteric ischemia ■ Therapy

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Abbreviations: AMI, acute mesenteric ischemia; NOMI, non-occlusive mesenteric ischemia; MVT, mesenteric venous thrombosis; SMA, superior mesenteric artery; EVT, endovascular therapy; PTA, percutaneous transluminal angioplasty.

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INTRODUCTION

COVID-19 is a serious respiratory disease caused by SARS-CoV-2, and the ongoing outbreak of this disease was declared a global pandemic by the World Health Organization on March 11, 2020. As of June 15, 2021, there have been 175 million confirmed cases, including 3.8 million deaths. Although the majority of COVID-19 patients experience relatively mild disease, some experience critical illness associated with high rates of vascular events that often prove fatal.[1] Many COVID-19 patients have been found to present in a highly hypercoagulable state that places them at significantly elevated risk of complications including venous and arterial thromboembolism.[2] Such thrombotic events have the potential to impact many vessels and vascular systems, potentially resulting in rare and poorly documented conditions such as acute mesenteric ischemia (AMI) that warrant further study.

While rare, AMI is classified as a surgical emergency that can present in the form of arterial thrombosis, arterial embolism, venous thrombosis, or non-occlusive mesenteric ischemia (NOMI).[3] Obstruction of arterial blood flow is the primary cause of AMI, and mortality rates can be as high as 80% in individuals suffering from obstructive AMI who do not undergo revascularization. Rapid diagnosis and treatment are key determinants of patient survival, with early diagnosis being linked to an up to 50% reduction in patient mortality.[4] The relationship between COVID-19 infections and AMI incidence has yet to be studied in detail, and the present article was therefore written to provide a comprehensive overview of what is known regarding the interplay between these two potentially fatal conditions.

AMI INCIDENCE

AMI is thought to affect approximately 120 per million individuals each year,[5] with two-thirds of these cases arising as a consequence of thromboembolic occlusive mesenteric ischemia, whereas the remaining cases occur as a result of NOMI or mesenteric venous thrombosis (MVT).[6] AMI resulting from acute occlusion of the superior mesenteric artery (SMA) is the most common form of this condition, occurring at an annual rate of 86/100,000.

AMI incidence rises with age, most commonly affecting individuals over 75 years of age. Mesenteric ischemia rates can also rise in patients suffering from certain conditions associated with hypercoagulability, including COVID-19 (0.13%), with rates rising even higher in individuals admitted to the intensive care unit (ICU; 0.7%) and in individuals suffering from acute respiratory distress syndrome (ARDS; 4.3%).[7,8]

PATHOLOGY

As discussed above, AMI is traditionally stratified into four subtypes according to disease etiology. However, this classification system has been updated in response to morphological insights gleaned from more advanced CT scans of obstructed arteries in AMI patients, enabling clear differentiation between arterial and venous mesenteric ischemia. The mesenteric vascular system is interconnected and highly complex, being composed of the celiac artery, SMA, and inferior mesenteric artery, with the connections between these vessels serving to protect patients from catastrophic visceral malperfusion due to the loss of any individual vessel.[3]

Arterial AMI is associated with embolic occlusion in roughly half of cases, while the embolic or thrombotic occlusion of previously stenotic mesenteric vessels accounts for just 20 - 35% of cases, and direct arterial inflammation occurs in < 5% of cases.[3] MVT is the most common cause of venous mesenteric ischemia and can be readily detected by contrast-enhanced CT. While severe COVID-19 is known to be linked with coagulopathy in many patients, thus elevating their risk of AMI, the specific relationship between these two diseases remains poorly understood.

COVID-19 patients often present with hypercoagulability arising due to systemic inflammation, endothelial activation, hypoxia, and immobilization, significantly increasing their risk of MVT. Preliminary pathological evidence suggests that the thrombosis of small mesenteric vessels, rather than an embolic event, may occur in these patients.[9] Dysregulated or damaged endothelial cells can further promote vascular thrombosis associated with von Willebrand Factor (vWF) release from Weibel-Palade bodies. The ability of SARS-CoV-2 to target endothelial cells is believed to be attributable to the fact that these cells express angiotensin-converting enzyme 2 (ACE2), which is a receptor for the virus.[9,10] In addition, ACE2 is expressed on enterocytes, resulting in bowel damage that can also coincide with lymphoid follicle atrophy within the small intestine. This, in turn, has the potential to increase mucosal permeability, allowing gas from the bowel to pass into the bowel wall, thereby giving rise to venous gas.[11] These factors suggest that COVID-19 complicated by AMI is more likely to arise due to a thrombotic event, rather than an embolic event.

CLINICAL PRESENTATION AND DIAGNOSTIC EXAMINATIONS

Acute occlusion of the SMA is the most prevalent cause of AMI,[12] with emboli of cardiac origin being associated with the rapid development of symptoms including poorly localized abdominal pain.[13] Such pain is typically disproportional to what would be expected upon examination, and it exhibits a general epigastric distribution.[14] The location of the occlusion within the mesenteric arteries and individual anatomical differences ultimately drive differences in the severity and mode of clinical presentation, with some patients exhibiting tenderness with palpation that may result in the consideration of diagnoses other than AMI.[15]

Thrombosis occurs in over half of all patients suffering from acute SMA occlusion, representing a form of progressive atherosclerotic occlusive disease. The clinical presentation of such cases is more complex than that of embolic AMI, with severity depending upon the extent of the arterial obstruction, collateral artery compensatory blood flow, and the acuteness of presentation, which can vary from poorly defined abdominal pain, diarrhea, or vomiting to fulminant bowel ischemia.[4,16]

In some cases, acute thrombosis of the superior mesenteric vein and its branches can occur, extending to the portal vein and thereby causing MVT. In patients suffering from acute MVT, mild intestinal edema may progress to arterial spasms and transmural bowel infarction over the course of days to weeks, whereas subacute MVT may progress more gradually and present with less severe pain.[4,16]

COVID-19 symptoms have the potential to overlap with gastrointestinal symptoms of AMI, masking this condition in those suffering from infection-related coagulopathy. AMI concurrent with COVID-19 has been described in 18 patients in whom symptoms ranged from asymptomatic to generalized abdominal pain, vomiting, fever, diarrhea, epigastric pain, or worsening systemic status (Table 1). COVID-19 patients are more likely to present with thrombosis. In published cases, 9 patients developed AMI due to thrombosis whereas just 5 exhibited clear evidence of embolic events. In four of these five patients, venous gas was identified as the cause of embolism, while just one patient presented with arterial thromboembolism. In 6 patients, the artery alone was involved, while venous involvement was evident in five patients, and 2 exhibited both arterial and venous involvement.

Other sites of thrombosis concurrent with AMI reported in published COVID-19 cases included splenic[20,30], renal infarction[20,28], digital necrosis of both feet[20], portal vein thrombosis[23,28,30,32], right middle cerebral artery[26], aortic arch[26], descending thoracic[25,28], abdominal aorta [28], and right pulmonary artery[30] thromboses. The most commonly reported site of concurrent thrombosis in COVID-19 patients with intestinal thrombosis was the lung.[11,17,18,20,22,23,25,27-30] Other disease-related effects

Table 1. The clinical manifestations, treatment modalities, and outcomes of the patients with AMI and COVID-19.

No	Age, years	Gender	Comorbidities[a]	Symptoms at presentation[b]	Imagine findings[c]		Prophylactic anticoagulation[d]	Therapy[e]			Anticoagulation at discharge[f]	Other site of thrombosis	Current state
					A/V	T/E		Anticoagulation	EVT	Surgery			
1[17]	55	Male	Hypertension	nausea, vomiting and abdominal pain	A	T	NA	Y, heparin	N	Y	NA	NA	NA
2[18]	52	Male	NA	diarrhoea, vomiting and abdominal pain	A	T	Y, LMWH 4000U/d	Y, LMWH plus aspirin 100mg/d	N	Y	Y	NA	Discharged
3[19]	70	Male	NA	abdominal pain, nausea and fever	NA	NA	NA	N	N	N	/	NA	Died
4[20]	58	Male	NA	dyspnea and abdominal pain	A	NA	NA	N	N	Y	/	splenic, renal infarction and digital necrosis of both feet	In hospital
5[21]	69	Male	Untreated vitiligo	abdominal pain, n ausea and diaphoresis	NA	T	NA	Y, enoxaparin 1 mg/kg twice a day	N	Y	Y, rivaroxaban 10mg/d	NA	Discharged
6[22]	42	Female	Extreme obesity	abdominal pain and constipation	V	T	NA	N	N	Y	/	NA	Died
7[23]	79	Female	N	fever, epigastric abdominal pain and diarrhea	V and A	T	NA	N	N	Y	/	right-portal vein thrombosis	Died
8[11]	47	Male	Anxiety, OSA, obesity	distended abdomen and diarrhoea	V	pneumatosis	NA	Y, UFH (APTT: 2.0–2.5)	N	N	NA	NA	Discharged

(*continued on next page*)

Table 1 (*continued*)

No	Age, years	Gender	Comorbidities[a]	Symptoms at presentation[b]	Imagine findings[c]		Prophylactic anticoagulation[d]	Therapy[e]			Anticoagulation at discharge[f]	Other site of thrombosis	Current state
					A/V	T/E		Anticoagulation	EVT	Surgery			
9[24]	30	Male	N	abdominal pain and vomiting	V	T	NA	Y[#], LMWH firstly, then enoxaparin	N	Y, recurrence	Y, enoxaparin	NA	Discharged
10[25]	75	Male	N	abdominal pain and vomiting	A	E	NA	N	Y	Y, progression	NA	descending thoracic aorta	NA
11[26]	56	NA	N	abdominal pain and vomiting	NA	T	NA	N	Y	Y	NA	right middle cerebral artery, aortic arch	NA
12[27]	82	Female	Hypertension, NIDDM	abdominal distension and tenderness	NA	pneumatosis	Y, heparin	Y, heparin	N	Y	NA	NA	discharged
13[28]	75	Male	Diverticular disease and hypertension	abdominal pain	A	NA	NA	Y, heparin	Y	Y, progression	NA	descending thoracic, abdominal aorta and left kidney	NA
14[29]	40	Male	Obesity	abdominal distension	NA	intramural gas	NA	Y, UFH 5000 U, three times a day	N	Y	NA	NA	NA
15[30]	38	Female	N	abdominal pain, nausea and vomiting	V	NA	NA	Y, heparin	N	Y	/	portal, splenic and right pulmonary artery	In hospital
16[31]	61	Female	Diabetic and hypertensive	abdominal pain with distention	A	T	Y, enoxaparin	Y[&]	N	Y, progression	/	NA	Died

(*continued on next page*)

Table 1 (*continued*)

No	Age, years	Gender	Comorbidities[a]	Symptoms at presentation[b]	Imagine findings[c]		Prophylactic anticoagulation[d]	Therapy[e]			Anticoagulation at discharge[f]	Other site of thrombosis	Current state
					A/V	T/E		Anticoagulation	EVT	Surgery			
17[32]	28	Female	ET	abdominal pain and vomiting	V/A	T	N	Y	N	Y, progression	NA	Portal vein	Discharged
18[32]	56	Male	Hypertension, obesity and diabetes	ARDS	V	Gas	N	N	N	Y	/	NA	In hospital

EVT, endovascular therapy; A, artery; V, vein; T, thrombosis; E, embolus; NIDDM, non-insulin dependent diabetes mellitus; NA, not available; N, none; Y, yes; LMWH, low molecular weight heparin; OSA, obstructive sleep apnea; UFH,unfractionated heparin; ARDS, acute respiratory distress syndrome; ET, essential thrombocytosis.

[a] *Complications of patients with AMI and COVID-19 at diagnosis*

[b] *Primary symptoms mainly caused by AMI in COVID-19 patients*

[c] *Responsible vessels may include the artery or the vein, and may present with thrombosis or embolus*

[d] *Prophylactic anticoagulation strategy for patients with COVID-19 before the confirmation of AMI.*

[e] *The anticoagulation strategy after the diagnosis of AMI.*

[f] *The anticoagulation strategy after discharge.*

[#] *Initially, he was administered twice-daily LMWH (1 mg/kg). After a 17-day length of stay, he was discharged with a planned treatment with LMWH for 3 months. One month later, he presented with abdominal pain and vomiting and received twice-daily enoxaparin.*

[&] *UFH, (5000 u i.v., followed by a 1000 u/h infusion), ecosprin and clopidogrel.*

reportedly include cytopenia,[25,27] splenic and renal infarction,[20] acute ischemic stroke,[20,26] essential thrombocythemia, acute respiratory distress syndrome, and multiple organ failure[32. ‘

AMI patients without COVID-19 are likely to present with symptoms including leukocytosis, elevated D-dimer levels, metabolic acidosis, and elevated serum lactate levels. No specific diagnostic test for AMI has been identified to date, with D-dimer primarily being useful as an exclusionary test given that normal D-dimer levels are likely to exclude the potential acute thromboembolic occlusion of the SMA.[33,34] Measuring fluid levels, electrolyte levels, and acid-base status can guide the evaluation of some AMI patients.[3] For individuals suffering from concurrent COVID-19 and AMI, elevated D-dimer, CRP, and lactate levels may be detected, but these results are non-specific as they may also occur in severe COVID-19 patients not suffering from AMI. D-Dimer levels, in particular, are likely to be elevated, eliminating the value of this exclusionary test.[35] Other studies have described elevated fibrinogen levels.[36] Zhang et al.[37] and Aktokmakyan et al.[38] posited that antiphospholipid antibodies may participate in these thrombotic events associated with AMI incidence in selected cases. However, all of these tests remain relatively non-specific, and the most effective means of achieving a timely diagnosis is through a review of clinical symptoms and imaging findings, thus requiring the extensive experience and awareness of attending clinicians.

Early abdominal CT scans may fail to detect AMI even with contrast. While reduced or absent bowel wall enhancement is a highly specific finding associated with intestinal ischemia (96%), the associated sensitivity is poor (16-62%).[39] On CT scans, wall thickening, edema, and dilation of the bowel (>3 cm) suggest the potential for AMI. Portomesenteric venous gas has been detected in 3-14% of AMI cases, while 6-28% of patients exhibit pneumatosis intestinalis.[39] Although pneumatosis is very specific for bowel ischemia, its sensitivity is very low. In severe COVID-19 patients with AMI, only a depleted intestinal stromal framework may remain such that venous gas incidence is as high as 15%, which is higher than that in AMI patients without COVID-19.

Ultrasound imaging limits patient radiation exposure, but also yields nonspecific imaging findings. CT angiography (CTA) of the mesenteric vessels should therefore be conducted.[36] Such imaging is often conducted in COVID-19 patients to detect the occurrence of pulmonary embolism, but an extension of these scans to simultaneously cover the chest and abdomen would be beneficial as a means of excluding suspected AMI despite the higher associated radiation dose.

THERAPEUTIC INTERVENTIONS

The treatment and management of patients suffering from AMI focus on prompt diagnosis and revascularization prior to ischemic progression to intestinal gangrene. When symptoms persist or patients continue to deteriorate and exhibit signs of peritonitis, tissue death is most effectively minimized by performing immediate intestinal surgery or damage control surgery.[40] Managing patients suffering from both AMI and COVID-19 is challenging, as no consensus statements or guidelines are available, and COVID-19-associated hypercoagulability places patients at a very high risk of venous thromboembolism and arterial thrombosis.[41] Local direct vascular and endothelial injury have been linked to microvascular thrombosis and angiopathy in the lungs and other organs of COVID-19 patients.[2] However, owing to low patient counts and pandemic-related challenges, evidence regarding these patients is primarily limited to case reports and case series, making it difficult to draw definitive scientific conclusions. To attempt to overcome this issue, we herein reviewed the PubMed database for all studies published in English within the past 13 months, leading to the identification of 18 total AMI patients from whom findings are discussed further below.

For AMI patients not suffering from COVID-19, treatment can generally be directed based upon the severity of the presenting symptoms and on other patient-specific factors including evidence of AMI etiology, peritonitis, and hemodynamic instability. When not contraindicated, endovascular therapy (EVT) should be the primary treatment approach in stable patients with occlusive AMI before laparotomy is conducted, with viable treatment approaches including percutaneous aspiration, endovascular thrombolysis, and percutaneous transluminal angioplasty (PTA) with stenting.[4,42] In one recent meta-analysis, endovascular revascularization was shown to be superior to surgical treatment in arterial occlusive AMI patients with respect to both in-hospital mortality and overall morbidity.[43]

In contrast to occlusive AMI, NOMI is the result of severe intestinal hypoperfusion arising due to the redistribution of blood flow to vital organs such that the mesenteric arteries constrict. NOMI thus fails to induce significant mesenteric stenosis, cardiac output optimization, catheter-directed vasodilatory drug infusion, systemic anticoagulation therapy, and antibiotic treatment. However, laparotomy and necrotic bowel resection are essential in all patients exhibiting symptoms of clinical deterioration, including peritonitis, perforation, or hemodynamic instability irrespective of the underlying disease etiology.[44]

In cases of MVT without any evidence of peritonitis, anticoagulant therapy is the first-line treatment of choice. Unfractionated heparin is generally initially used for therapeutic intervention in these cases, followed by low molecular weight heparin (LMWH) and warfarin. In patients that remain symptomatic after anticoagulation, mechanical thrombectomy and/or transhepatic catheter-directed thrombolysis can be conducted to relieve the obstruction. As anticoagulation typically achieves favorable results within 24-48 h in these patients, surgery is generally not necessary. The prolonged anticoagulation treatment of these patients for 6 months may be appropriate when not contraindicated.[16]

Therapeutic principles for AMI patients are generally the same regardless of whether or not patients are suffering from COVID-19. Demographic features, clinical findings, treatment strategies, and outcomes for patients with AMI and COVID-19 are presented in Table 1. Of 18 analyzed patients, with the exception of one patient who was considered inoperable owing to their rapid clinical course, 10 were more likely to elect surgery as their initial treatment, of whom five underwent combination surgical evaluation and anticoagulant treatment. Just two of these 10 patients died. Of the remaining seven patients who were initially managed via nonsurgical approaches, two underwent catheter-directed thrombolysis and five underwent conservative treatment with unfractionated heparin, LMWH, or clopidogrel. Just one of these patients was successfully discharged, while five underwent subsequent surgery owing to worsening symptoms of intestinal ischemia. Two of these five patients were eventually discharged, while one died despite successful surgery. Together, these data suggest that in patients with AMI and COVID-19, clinicians typically perform surgery rather than anticoagulant therapy or EVT as a first-line treatment. Surgery may be associated with better patient outcomes than non-surgical treatments, even in patients without peritonitis symptoms. Indeed, nonoperative treatment of AMI in COVID-19 patients appears to be linked to high recurrence risk.

There may be many factors that account for the substantial discrepancy in therapeutic outcomes between COVID-19 patients and other AMI patients. For one, the mechanisms driving thrombogenesis in those suffering from COVID-19 are distinct from those in individuals with other forms of AMI owing to the disease-related activation of inflammatory signaling cascades and the immune system. Histological analyses of samples from COVID-19 patients have revealed the presence of severe endothelial inflammation in resected small bowel samples with confirmed SARS-CoV-2 presence in the intestinal mucosa as determined via an RNAscope-based approach.[45] AMI has been reported to occur in patients even when anticoagulant thromboprophylaxis is routinely administered. This may explain why the majority of conservatively treated COVID-19 patients have poor outcomes. Further complicating the relationship between COVID-19 and AMI is the fact that COVID-19 patients may be more likely to present with atypical symptoms such as abdominal pain, vomiting, or diarrhea that can mimic the consequences of serious pneumonia such that additional testing is only performed if these symptoms continue to worsen. Third, surgery can enable direct visualization of intestinal viability, enabling clinicians to accurately visualize necrotic tissue to reduce the risk of AMI underdiagnosis. As such, we suggest that the surgical removal of unsalvageable intestinal tissues be conducted in COVID-19 patients, given that such an intervention will likely yield good results.

There is a pressing need for the widespread distribution of vaccines against COVID-19. Studies of the related SARS-CoV virus, however, also suggest that disease severity may be increased due to antibody-dependent enhancement.[46] It will take significant time to develop vaccines that are both protective and safe, and these development efforts are currently underway throughout the world in the context of commercial competition.[47] Developing an efficacious COVID-19 vaccine within 12-24 months is extremely challenging, given that this process traditionally required 10-15 years to complete.[48] The first clinical trials of a COVID-19 vaccine were conducted by Moderna in the USA, dosing the first patient in its phase I study within 63 days of sequence selection[49]. Since then, multiple clinical trials have been registered and performed, with over 100 vaccine candidates in development throughout the world.

No single optimal approach to COVID-19 vaccination has been identified to date. Moderna, BioNTech/Pfizer, and Inovio are the leading companies preparing nucleic acid-based vaccines that have been shown to generate strong antibody responses. Vaccines that have advanced to clinical phase III trials include the AstraZeneca/Oxford AZD1222, Moderna mRNA1273, and Sinovac CoronaVac vaccines.[50] Achieving global herd immunity will be essential to stem the COVID-19 pandemic, and this will necessitate the distribution of these vaccines throughout the world. Ultimately, more than one efficacious vaccine will likely be developed, ensuring that reliable vaccines are available to vulnerable populations.

The data discussed in the present study are primarily derived from case reports and case series, resulting in a significant risk of publication bias. Additionally, uniform follow-up was not conducted in these studies, with authors having noted only clinical outcomes that were evident at the time of publication, potentially resulting in an overestimation of outcome data. Future large-scale prospective

studies are thus essential to validate and expand upon these findings.

CONCLUSIONS AND IMPLICATIONS

AMI is a severe, life-threatening condition that is challenging to diagnose, particularly in patients suffering from COVID-19 given that these individuals are in a hypercoagulable state and are suffering from pneumonia, which can also increase overall patient mortality rates. In COVID-19 patients undergoing CTA scans in an effort to detect pulmonary embolism for whom AMI cannot be excluded, extension scans covering the abdomen are thus likely to be beneficial. Early intervention for these patients is life-saving. As such, COVID-19 patients who are diagnosed with AMI should undergo prompt emergency surgery to relieve their pain and to minimize or eliminate the risk of further deterioration, while expediting the treatment of comorbidities.

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Since this is a review article, institutional approval and patient consent were not required.

CONSENT FOR PUBLISHING

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