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Intestinal ischemia in COVID-19 patients: A case series

Tobias Van De Winkel, Ward Janssens, Nouredin Messaoudi, Martijn Schoneveld, Jasper Stijns, Ellen Van Eetvelde, Yanina JL Jansen

ABSTRACT

Introduction: COVID-19 is associated with increased coagulability, resulting in thromboembolic complications, such as intestinal ischemia. Diagnosis of bowel infarction can be challenging due to the severity of illness and the laboratory changes associated with the COVID-19 infection itself.

Case Series: In a retrospective monocentric study, we performed an in-depth analysis of the clinical course of intestinal ischemia in COVID-19 patients. Biochemical analysis of coagulation status and predictors of ischemia was performed. We identified five patients with intestinal ischemia, between March 2020 and January 2021. Mean time-to-onset of intestinal ischemia from COVID-diagnosis was 31 days (range 16–56). Intestinal ischemia was confirmed by contrast-enhanced computed tomography (CT) scan. D-dimer, Fibrinogen, C-reactive protein (CRP), and lactate dehydrogenase (LDH) were elevated prior to the ischemic event, but no recurrent pattern could be distinguished in our case series. Lactate levels demonstrated a marked increase at the time of ischemia in our series. No consistent findings were made for prothrombin time (PT) and activated partial thromboplastin time (aPTT) and creatin kinase. Extent of bowel ischemia varied between limited to the ileocecal region (two patients), additional ischemia of small and large bowel (two patients) and extensive ischemia of entire intestinal tract (one patient). Four patients (80%) required an ileostomy. Planned relook surgery was performed in three patients (60%). Three (60%) patients died.

Conclusion: In the five days prior to an intestinal ischemic event in COVID-19 patients, we did not identify a clear pattern in commonly used markers for coagulation status and ischemia. However, lactate levels showed a recurrent pattern of clear increase leading up to the ischemic event and rapid normalization after surgery. Unfortunately, our patient numbers were too small to draw definitive conclusions.

Keywords: Bowel ischemia, COVID-19, Intestinal ischemia

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INTRODUCTION

The Coronavirus disease 2019 (COVID-19) pandemic has rapidly spread throughout the world, infecting over 480 million patients and causing over 6.1 million deaths to date [1]. Apart from the acute respiratory distress syndrome, COVID-19 is associated with an increased risk of thromboembolic complications, resulting in, e.g., cerebrovascular disease, pulmonary embolism, limb ischemia, and intestinal ischemia [2, 3].

The pathophysiology of COVID-19 related coagulopathy is attributed to several factors such as endothelial damage, tissue hypoxia, and a hyperinflammatory state and is still a matter of debate [2, 4]. The interaction of the SARS-CoV-2 virus with the angiotensin-converting enzyme 2 receptor on endothelial cells causes endothelial inflammation and consequently microvascular coagulopathy [5]. Furthermore angiotensin 2 is known to be a potent vasoconstrictor and increases expression of tissue factor and plasminogen activator inhibitor, further facilitating a hypercoagulable state. Another factor is the overproduction of a variety of proinflammatory cytokines (such as interleukin 6 (IL-6), IL-17A, and tumor necrosis factor) resulting in a so-called cytokine storm response. These proinflammatory cytokines play a role in abnormal clotting and platelet activation and in downregulation of anticoagulant pathways [3]. Finally, the presence of microorganisms directly causes activation of complement pathways resulting in complement-mediated microvascular injury [4]. This hypercoagulable state results a variety of thromboembolic complications, among which intestinal ischemia [3]. Severe cases of COVID-19 are associated with a profound septic shock, requiring admission to the intensive care unit and, as a part of standardized therapy, administration of vasoactive agents such as noradrenalin. As a result, splanchnic perfusion is reduced. When blood flow is reduced by 75% for more than 12 hours, this may result in intestinal ischemia [6]. Therefore, it is a combination of hypoperfusion of the splanchnic bed due to vasoconstrictive agents and shock, and an increased coagulability which results in intestinal ischemia in COVID-19 patients.

Due to varying factors such as scarce scientific reports and difficulties in diagnosing intestinal ischemia in critically ill COVID-19 patients, an estimation of the incidence of intestinal ischemia as a complication of COVID-19 is hard to make [7]. The prognosis of bowel ischemia in COVID-19 patients largely depends upon extent of ischemia and timing of diagnosis and treatment. However, reported overall mortality is high around 50%, even going up to 100% in patients older than 65 years [8]. Prophylactic anticoagulants decrease the mortality rate in hospitalized COVID-19 patients, resulting in inclusion of anticoagulants in standard care protocols [9].

The hypercoagulable state in COVID-19 patients leads to an increased frequency of intestinal ischemia with 208 published cases globally to date [7,8,10–49]. Little data are available on the clinical course and possible predictive parameters of intestinal ischemia in COVID-19. In a monocentric retrospective study, we evaluated the occurrence and clinical course of intestinal ischemia in COVID-19 patients.

CASE SERIES

We performed a single-center retrospective observational study at the University Hospital Brussels. All COVID-19 patients, hospitalized between March 2020 and January 2021, were screened for the presence of intestinal ischemia. All patients with confirmed intestinal ischemia on contrast enhanced abdominal CT or surgical protocol were included. Analysis of patient characteristics [age, mass, body mass index (BMI)] and evolution of COVID-19 infection [date of onset of symptoms, date of diagnosis by polymerase chain reaction (PCR), date of admission, CT-score at admission, severity at admission by admission to ward vs. intensive care unit (ICU), date of admission to ICU, date of discharge if applicable] was performed. Details on medical treatment were analyzed with a special interest in anticoagulant therapy (start of treatment, type and dose of anticoagulant therapy, date and reason for therapy changes if applicable), corticosteroids (start of treatment, type and dose of corticosteroid, date and reason for therapy changes if applicable), and for vasopressor agents at 24 h pre-diagnosis of intestinal ischemia. We conducted biochemical analysis of coagulating status [D-dimers, fibrinogen, prothrombin time (PT), and activated partial thromboplastin time (aPTT)] and ischemia [C-reactive protein (CRP), creatin kinase, lactate dehydrogenase and lactate] for the interval from five days before to five days past the ischemic event. To measure D-dimer levels on sodium citrate tube blood sample immunoassay was performed. To measure fibrinogen levels, PT and aPTT on sodium citrate tube blood sample turbidimetry was used. Photometry was applied to determine CRP, creatine kinase (CK), and LDH levels. Amperometry was used to determine lactate levels on arterial blood gas sample. Finally, we registered diagnosis of intestinal ischemia by date of symptom onset, CT findings and surgical diagnosis during exploratory surgery, and if applicable relook surgery.

All hospitalized COVID-19 patients were treated according to standard treatment protocol based on the scientific knowledge of the COVID disease at the time. Respiratory support ranging from nasal oxygen admission to sedation and mechanical ventilation was started following WHO-guidelines targeting a SpO_2 between 90% and 96%. Antiviral medication (Remdesivir) to limit viral replication in the early stages of infection was administrated only to the critically ill, due to limited availability, if hospitalization was no later than 10 days after onset of symptoms (200 mg on 1st day, 100 mg on following days). To suppress the cytokine storm caused by massive inflammatory activation following COVID-19 infection administration of corticosteroids was incorporated by means of Dexametasone-Na-phosphate 10 mg intravenous (IV) at least for 10 days. Finally, antithrombotic treatment to counter the observed hypercoagulating state was started, using Tinzaparin in intermediate dosage (100 IU/kg).

All data are represented in a descriptive manner, no statistical analysis was performed. The study was conducted in accordance with international standards of Good Clinical Practice, and the protocol was approved by the independent ethics committee or the University

Hospital Brussels (number EC-2021-074). No written consent has been obtained from the patients as there is no patient identifiable data included in this case series.

Between March 6, 2020 and December 31, 2020, 907 patients were hospitalized due to COVID-19 infection of which 220 were admitted to the ICU. A total of five (0.6%) patients were diagnosed with intestinal ischemia as a complication of COVID-19 infection. All cases occurred during the second wave of the pandemic, between September and November 2020 in previously relatively young and healthy patients.

All five (0.6%) patients were male with a mean age of 60 years (range 53–65), a mean weight of 87 kg (range 71–110) and mean BMI of 29 kg/m² (range 27–34). Two (40%) patients had an impaired renal function, one (20%) patient had a medical history of multiple myeloma, and one (20%) patient had a history of cold agglutinin disease for which low dose corticosteroids were chronically administered. Baseline characteristics are portrayed in Table 1. Mean time between diagnosis of COVID-19 and admission to the ICU was four days (range 0–6). Four (80%) patients required respiratory support, three of them (60%) by intubation and mechanical ventilation, two (40%) upon admission and two (40%) prior to the ischemic insult. Standard treatment protocol was followed in all cases on admission to the ICU. For the patient with cold agglutinins, morbus Waldenstrom was diagnosed as the culprit and immunotherapy (rituximab 375 mg/m²) were associated to the standard treatment and normothermia was kept at all times. Mean time to onset of intestinal ischemia from COVID diagnosis was 31 days (range 16–56) and from hospital admission was 27 days (range 10–52). At the onset of intestinal ischemia, two (40%) patients were non-sedated and diagnosis was made on clinical findings (stomach ache, vomiting, and early signs of septic shock). In all other patients, a septic shock with lactate acidosis associated with varying abdominal factors (increased intra-abdominal pressure, diarrhea) warranted further investigation. In all cases intestinal ischemia was confirmed by contrast-enhanced CT scan. Three patients (60%) required vasoactive agents (noradrenalin) 24 h prior to intestinal ischemia with a mean dose of 0,28 µg/kg/min (range 0.1–0.45) and two (40%) patients were receiving corticosteroids 24 h prior to ischemia, as part of the treatment of deteriorating shock. All patients were treated with 10 days of corticosteroids as per protocol. One patient was receiving low molecular weight heparin as per protocol at the time of onset. Two patients received full dose anticoagulation (due to cold-agglutinin and due to VV-ECMO). In two patients, anticoagulation was intermittently stopped (one due to spontaneous nose bleeding and one due to minor surgical intervention). An overview of pre-ischemia variables is portrayed in Table 2.

Table 1: Baseline patient characteristics

Patient	Age	Sex	Comorbidity (CCI)	Chronic medication (none=0/antico =1/ antiplatelet=2)
1	62	M	5	2
2	65	M	2	0
3	58	M	2	0
4	64	M	5	2
5	53	M	1	2

Table 2: Pre-ischemia variables, d = days, anti-coA = anticoagulants, ICU = intensive care unit

Patient	Time from COVID-diagnosis to onset (d)	Time from admission to onset (d)	Time from ICU-admission to onset (d)	Use of vasopressor before onset	mechanical ventilation 24h before onset	Cortico at onset	Antico at onset 1= prophylactic 2= therapeutic 3= intermittent
1	20	20	14	1	1	1	1
2	56	52	32	1	1	0	2
3	16	10		0	0	0	3
4	17	17	17	1	0	1	2
5	44	38	38	0	1	0	3
Mean	30.6	27.4	25.25	0.6	0.6	0.4	2.2

D-dimer levels were elevated in all patients admitted to the ICU between 1 and 5 days prior to the ischemic event with a mean value of 4335 ng/mL (range 1139–15730; normal value <500 ng/mL). The fifth patient, not administered to the ICU at diagnosis of intestinal ischemia had marginally increased D-dimer levels prior to the event (550–565 ng/mL). Fibrinogen levels were mildly elevated in four patients (80%) during the five days prior to ischemia (range 443–1000; normal value 180–400 mg/dL). In one patient fibrinogen levels remained normal from five days prior to five days after the ischemic insult. Mean CRP level in our series at the time of ischemia was 209 mg/L (range 8.5–442; normal value <5 mg/L). C-reactive protein was only mildly elevated in two patients (40%) despite the presence of necrotic bowel. Only in two patients (40%), an incremental increase of CRP levels was observed in the five days prior to diagnosis of intestinal ischemia (Figure 1). A different pattern was found in lactate analysis, where a marked increase was found at the time of ischemia in four patients (80%) with a mean level of 5.1 mmol/L (range 2.7–7.3; normal value 0.7–2.1 mmol/l) (Figure 2). Lactate dehydrogenase levels were elevated in all patients at the time of ischemia (mean 1480 U/L; range 330–5288; normal value <250 U/L), though no clear pattern of progression could be determined between five days prior to five days after the ischemic insult (Figure 3). No consistent findings were made for PT, aPTT, and for creatin kinase with values ranging between normal and elevated between five days prior and five days after the event, between different patients and for each patient separately.

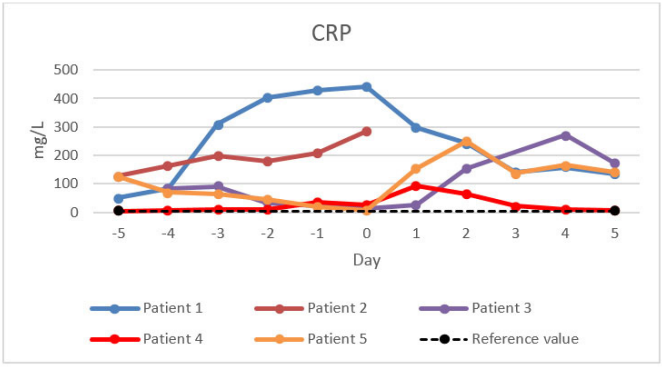

Figure 1: C-reactive protein levels around ischemic events.

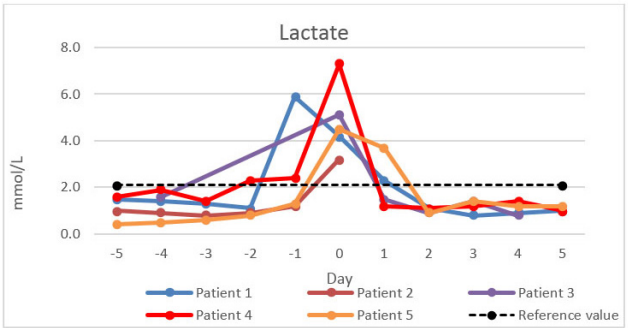

Figure 2: Lactate levels around ischemic events.

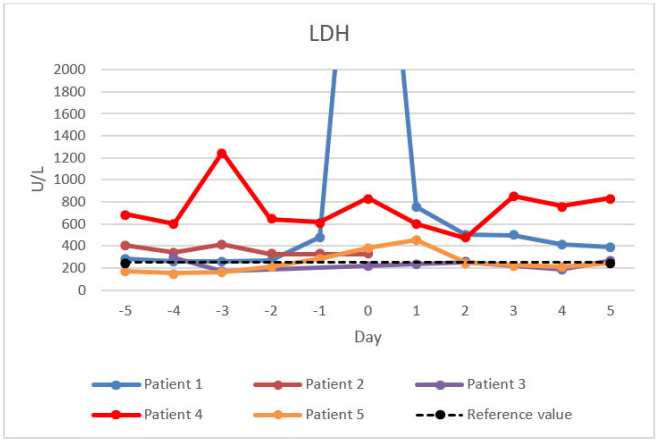

Figure 3: LDH levels around ischemic events.

All patients underwent a diagnostic laparoscopy and/or laparotomy. In one patient extensive enteric ischemia of the entire small bowel and colon was observed during laparotomy. In the other four patients (80%) the distal part of small bowel and the ileocecal transition were involved. One of these patients had a second segment of ischemia at the level of the small bowel and in one of these patients the ischemia extended down to the sigmoid colon. Thrombosis of the superior mesenteric artery was observed in two (40%) patients. Due to the extent of bowel ischemia and thus the need for exploratory surgery, thrombolysis was not retained as a therapeutic option.

Surgery consisted of extended resection of terminal ileum and ascending colon with construction of a terminal ileostomy in three patients (60%), in one (20%) case in combination with arterial embolectomy and in two (40%) cases in combination with small bowel anastomosis after additional segmental small bowel resection during second look. One of these patients developed ongoing ischemia, requiring relook surgery three times, finally resulting in resection of cecum, ascending and descending colon. One patient required more extensive resection of ischemic bowel resulting in a subtotal colectomy. Due to the extent of intestinal ischemia no resection was performed in one patient. Four patients (80%) required construction of an ileostomy and planned relook surgery was performed in three patients (60%). Anastomotic or stump leakage occurred in two out of four patients (50%) who underwent bowel resection, requiring relook surgery for secondary suture of the leakage.

Three patients died resulting in an overall mortality of 60%. One patient died shortly after surgery in light of therapeutic abstinence due to massive intestinal ischemia, two died after persistent acute respiratory distress syndrome (ARDS) and septic shock resulting in multiple organ failure at 14 and 19 days after surgery. The other two patients were discharged at 44 and 88 days after primary surgery.

DISCUSSION

Diagnosis of intestinal ischemia relies on a combination of clinical features, non-specific laboratory findings and imaging studies. Increased white blood cell (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 [50]. In COVID-19 patients, diagnosis of intestinal ischemia is more challenging due to changes of laboratory findings associated with the infectious disease itself. Although a total of 208 cases have been described, description of the clinical and biochemical course is limited. Due to the precarious respiratory and hemodynamic state of critically ill COVID-19 patients, diagnostic CT or exploratory surgery is not always feasible without jeopardizing the patient's already fragile condition. Therefore, more data concerning diagnostic approach of intestinal ischemia in COVID-19 patients are needed.

Norsa et al. reported a prevalence of intestinal ischemia in COVID-19 hospitalized patients of 0.7% [24]. This is confirmed by our case series, with an overall incidence of intestinal ischemia of 0.55%. Fifty-eight published cases reported on timing of the ischemic insult. Hwabejire et al. reported a mean time to onset from admission of 12 days [8]. In our patient population, intestinal ischemia occurred at a late stage in the disease (median of onset 31 days after diagnosis of COVID-19 and median of onset 27 days after admission to the hospital). Mortality due to intestinal ischemia in COVID-19 patients varied widely. Wang et al. and Miyara et al. reported a mortality rate of 39% [25, 51]. Two published literature reviews suggest a postoperative mortality of 23.8% and 62.5% [20, 26]. In our series, three out of five patients died resulting in a mortality of 60%. A possible explanation for the wide range of observed mortality is the dependence of survival on timely diagnosis and adequate treatment, which can be challenging especially in the critically ill, sedated patients [21, 26, 27, 50].

An analysis of the evolution of commonly used biomarkers of ischemia and coagulation status, in patients with COVID-19 developing intestinal ischemia has not been published. Some case series and case reports, focus on the presence of elevated D-dimers, lactate, and LDH. However, often these data are lacking or only data on these parameters on the date of patients' admission to the hospital or intensive care unit are reported. In an attempt to identify a good biomarker of intestinal ischemia in COVID-19 patients we analyzed the evolution of biomarkers in the 10 day period surrounding the ischemic event.

Multiple articles reported on D-dimers as a biomarker for hypercoagulability and intestinal ischemia due to the finding that D-dimer is a highly sensitive marker for the prothrombotic state caused by COVID-19 [7]. Although elevated D-dimer levels are common in severe sepsis and disseminated intravascular coagulation, Sarkar et al. reported a different profile of laboratory findings in coagulopathy secondary to COVID-19 infection with a more profound rise in D-dimer levels and a normal or slightly elevated PT and aPTT [2]. This pattern is confirmed by our series (D-dimer mean 5404 ng/mL; PT mean 13.03 s; aPTT 58 s). D-dimers are increased in 36–46% of COVID-19 patients and a higher D-dimer count is associated with more critical patients and is inversely correlated with survival [21, 24, 26, 52]. Norsa et al. reported an elevation of D-dimers in 81% of patients at diagnosis of intestinal ischemia in COVID [24]. The reported threshold of D-dimer elevation for initiation of coagulopathy varies between publications from two times the normal value, up to a 14-fold rise [21, 52]. We found a mean nine-fold elevation in D-dimer levels at the diagnosis of intestinal ischemia in our series. Sun et al. reports a sensitivity of 0.94 and a specificity of 0.5 for D-dimer levels in detecting intestinal ischemia, outside the scope of COVID-19 [53].

Serban et al. reported serum lactate to be a non-specific biomarker of tissue hypoperfusion which elevates only after ischemic damage has arisen. A value of higher than 2 mmol/L is nonetheless associated with increased mortality [7]. Lactate levels at onset of ischemia were reported in only 9 cases and ranged between 0.6 and 3.3 mmol/L. We found an overall higher level of serum lactate with a mean of 5.1 mmol/L, suggesting a later diagnosis, possibly due to the diagnostic difficulty in critically ill and sedated patients. Another commonly used biomarker for ischemia is LDH. It is also reported as an independent risk factor of severe COVID-19 [4, 7]. Zhou et al. found an association between elevated LDH levels and risk of death [54]. In six cases reporting on LDH levels, elevation above normal was reported in all cases. In our series we found a mild increase of LDH in 80% of cases.

No consistent findings were made for PT, aPTT and for creatin kinase in our case series. Data on PT, aPTT, and creatin kinase are lacking in literature. As a result, for our population, we can conclude that a rise in D-dimers, LDH, and lactate in the setting of COVID-19 is not a specific marker for intestinal ischemia. However, a rise in D-dimers, lactate, and LDH warrants early suspicion of and investigation for intestinal ischemia in COVID-19 patients to reduce mortality. Unfortunately, our patient numbers were too small to draw definitive conclusions and more data are needed to help guide diagnosis and rapid treatment of ischemia in COVID-19 patients.

Reporting on the affected area of bowel is scarce and the relative frequency of affected bowel varies between different articles [8, 10–16, 19, 20]. It is noteworthy that in our series the distal part of the small bowel was ischemic in 100% of cases, suggesting a thromboembolic cause of ischemia to be the more likely. Hypoperfusion due to shock and vasoconstrictors would result in bowel ischemia concentrated at the so-called watershed areas of the bowel (splenic flexure or Griffiths point and rectosigmoidal junction or Sudek's point) [21]. In our

series 60% of patients received Noradrenalin 24 h before onset of ischemia and in two patients anticoagulation was halted days prior to onset. In our small series, we believe that the vasoactive agents are more likely a result than a cause of bowel ischemia.

By international consensus, as recorded in treatment guidelines by both the WHO and the NIH, corticosteroids are incorporated in the standard care protocol for COVID-19 [55, 56]. Although no evidence suggests an increased risk in intestinal ischemia due to steroid therapy, increased risk of gastrointestinal perforation and an increased mortality and morbidity in the context of bowel perforation and bowel surgery has been described [39]. In our series, two patients developed anastomotic or stump leakage after surgery, one of whom was receiving corticosteroids at the time of ischemia. Although no conclusions can be made in this regard due to the low patient numbers, corticosteroid treatment can be a factor in surgical decision making (e.g., planned second look, intestinal anastomosis versus ileo- or colostomy) to reduce mortality and morbidity risk.

CONCLUSION

In the diagnosis of intestinal ischemia in COVID-19 patients biomarkers provide a useful tool. Of all biomarkers analyzed in our series (PT, aPTT, LDH, CK, CRP, lactate, D-dimers, fibrinogen) only lactate levels showed a recurrent pattern of clear increase leading up to the ischemic event and rapid normalization after surgery. Although other biomarkers are useful in risk assessment and outcome prediction in intestinal ischemia as mentioned above, lactate levels appear to be the most important biomarker for diagnosis of occurring ischemia in COVID-19 patients. Unfortunately, our patient numbers were too small to draw definitive conclusions and more data are needed to help guide diagnosis and rapid treatment of ischemia in COVID-19 patients.

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Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.