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Acute intestinal ischemia in patients with COVID-19: single-centre experience and literature review

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Abstract. – OBJECTIVE: Acute Intestinal ischemia (AII) may involve the small and/or large bowel after any process affecting intestinal blood flow. COVID-19-related gastrointestinal manifestations, including AII, have been attributed to pharmacologic effects, metabolic disorders in ICU patients and other opportunistic colonic pathogens. AII in COVID-19 patients may be due also to "viral enteropathy" and SARS-CoV-2-induced small vessel thrombosis. A critical appraisal of personal experience regarding COVID-19 and AII was carried out comparing this with a systematic literature review of published series.

PATIENTS AND METHODS: A retrospective observational clinical cohort study and a systematic literature review including only COVID-19 positive patients with acute arterial or venous intestinal ischemia were performed. The primary endpoint of the study was the mortality rate. Secondary endpoints were occurrence of major complications and length of hospital stay.

RESULTS: Patient mean age was 62.9±14.9, with a prevalence of male gender (23 male, 72% *vs*. 9 female, 28%). The mean Charlson Comorbidity Index was 3.1±2.7. Surgery was performed in 24/32 patients (75.0%), with a mean delay time from admission to surgery of 6.0 ±5.6 days. Small bowel ischemia was confirmed to be the most common finding at surgical exploration (22/24, 91.7%). Acute abdomen at admission to the ED (Group 1) was observed in 10 (31.2%) cases, while 16 (50%) patients developed an acute abdomen condition during hospitalization (Group 2) for SARS-CoV-2 infection.

CONCLUSIONS: Our literature review showed how intestinal ischemia in patients with SARS-CoV-2 has been reported all over the world. The majority of the patients have a high CCI with multiple comorbidities, above all hypertension and cardiovascular disease. GI symptoms were not always present at the admission. A high level of suspicion for intestinal ischemia should be maintained in COVID-19 patients presenting with GI symptoms or with incremental abdominal pain. Nevertheless, a prompt thromboelastogram and laboratory test may confirm the need of improving and fastening the use of anticoagulants and trigger an extended indication for early abdominal CECT in patients with suggestive symptoms or biochemical markers of intestinal ischemia.

Key Words:
COVID-19, Intestinal ischemia, Acute care surgery, Pandemic.

Abbreviations

AII: acute intestinal ischemia; SARS-CoV2: severe acute respiratory syndrome coronavirus 2; COVID-19: Corona Virus Disease 19; CRP: C-Reactive Protein; PCT: procalcitonin; ED: emergency department; WMD: weighted mean difference; CI: confidence interval; OR: odds ratio; ASA: American Society of Anesthesiologists; ICD-9™: International Classification of Diseases versions 9; LOS: Length of in-hospital Stay; CECT: Contrast Enhancement Computerized Tomography; IQR: Interquartile Range; OAD: Oral Anticoagulant Drugs; BMI: Body Mass Index; WBC: White Blood Cells Count; CCI: Charlson Comorbidities Index; C-D: Clavien – Dindo classification.

Introduction

Acute Intestinal ischemia (AII) may involve the small and/or the large bowel after any process affecting intestinal blood flow, such as arterial

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occlusion, venous occlusion, arterial vasospasm, hypovolemia and cardiogenic shock[1-3]. Risk factors for AII include any condition reducing perfusion of the bowel, or predisposing to mesenteric arterial embolism, arterial and venous thrombosis, or vasoconstriction[4-7]. Since the beginning of the SARS-CoV-2 outbreak, alongside the most common clinical manifestations such as fever, cough and dyspnoea, other clinical presentations have been described[8-11]. All these clinical pictures are linked to the demonstrated ability of the virus to affect multiple organs and tissues. COVID-19-related gastrointestinal manifestations, including AII, have been attributed to pharmacologic effects, metabolic disorders in ICU patients and other opportunistic colonic pathogens. AII in COVID-19 patients may be due also to "viral enteropathy" and SARS-CoV-2-induced small vessels thrombosis[12-15]. Knowing the extension of the intestinal microcirculation, the possibility of endothelial and thrombotic damage in this district must always be considered.

Study Aim

The aim of this study is to provide an insight on acute intestinal ischemia in COVID-19 patients, in order to better understand its pathophysiological mechanism, outcome, and possible treatment. To do this, we critically appraised our experience and compared it with the results obtained by a systematic literature review of published series. Furthermore, we compared AII COVID-19 patients with a personal cohort of AII COVID-19 negative patients.

Patients and Methods

Description of the Personal Series

A retrospective observational clinical cohort study was conducted. Medical charts of patients with SARS-CoV-2 infection and acute intestinal ischemia (AII) admitted to the Fondazione Policlinico Universitario A. Gemelli IRCCS (FPG) in Rome from March 2020 to December 2020 were reviewed. FPG has been designated Hub for COVID-19 patients in the Lazio region. Since the beginning of the pandemic, FPG has treated over 4000 COVID-19 patients[16]. Patient data were retrieved from the electronic health records using the International Classification of Diseases versions 9 (ICD-9™) [codes: 557.0 and/or 557.1 and/or 557.9]. Only COVID-19 positive patients with radiologically, intraoperatively, or histopathologically confirmed acute arterial or venous intestinal ischemia were included. Patients with chronic bowel ischemia, mechanically induced intestinal ischemia (e.g., postoperative bowel obstruction, volvulus, incarcerated hernia) or inflammation-induced intestinal ischemia (e.g., necrotizing pancreatitis, toxic megacolon), recent history of abdominal aortic aneurysm repair, viscera-vascular interventions vasculitis-induced ischemia or concomitant conditions requiring surgical treatment were excluded.

All clinical records were reviewed in terms of demographics and clinical variables, procedure details and peri-operative outcomes. Demographic variables included age, gender distribution, body mass index (BMI), American Society of Anaesthesiology (ASA) classification and comorbidities. Comorbidity was recorded if the condition was under medical treatment at the time of admission, or if any previous treatment for the condition was described in the admission report. The Charlson Comorbidity Index (CCI)[17] was utilized for classification.

Procedure details included operative time, type of procedure, length of hospital stay (LOS), 30-days post-operative complications classified according to Clavien-Dindo (C-D) and mortality, if COVID-19 infection could be logically associated to the fatal event[18].

A formal institutional review board approval was not required because of the un-interventional retrospective design; however, a signed consent for the data treatment and storage for scientific purpose was obtained from all patients at the hospital admission.

Conduction of the Meta-Analysis

Literature Search Strategy

A systematic review was performed according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement (Figure 1) to identify articles reporting acute intestinal ischemia in COVID-19 patients. A literature search was performed through MEDLINE (PubMed), Embase and Google Scholar from March 2020 to December 2020. The following keywords and/or medical subject heading (MeSH) terms were used in combination: "acute mesenteric ischemia", "intestinal ischemia", bowel necrosis", "Abdominal Visceral Infarction", "gastro-intestinal manifestation" "COVID-19", "SARS CoV-2". A manual search was also per-

formed in the reference lists of relevant articles to find potential additional studies. The search was carried out using English language terms and was limited to Western languages in the Latin alphabet. No restriction was adopted to exclude any specific study type.

Inclusion and Exclusion Criteria

Inclusion criteria: all patients with radiologically, intraoperatively, or histopathologically confirmed acute arterial or venous intestinal ischemia were included. Only the papers focusing on Acute Intestinal Ischemia (AII) in COVID-19 patients among adult populations were included. Studies were included if they reported outcomes of AII. Whenever the same group of authors presented multiple papers through years, the most comprehensive paper was considered, and the real number of treated patients reported.

Exclusion criteria: patients with chronic intestinal ischemia, mechanically induced intestinal ischemia (e.g., postoperative obstruction, volvulus, incarcerated hernia) inflammation-induced intestinal ischemia (e.g., necrotizing pancreatitis, toxic megacolon), recent history of abdominal aortic aneurysm repair, viscera-vascular interventions, and patients with vasculitis-induced ischemia were excluded. Studies conducted on animals were not considered. The search was limited to English language papers but not restricted according to study type.

Study Outcomes

The primary endpoint of the study was the intra-hospital mortality rate. Secondary endpoints were occurrence of major complications (need of ventilation, sepsis, multiple organ dysfunction/failure), and length of hospital stay. The length of hospital stay (LOS) was calculated from Emergency Department (ED) admission to hospital discharge or death. Occurrence of death was considered if COVID-19 infection could be logically related to the fatal event. COVID-19 positive patients were compared with a personal cohort of COVID-19 negative patients.

Data Extraction and Quality Assessment

All articles were reviewed and discussed by four different reviewers (P.F., G.C., A.L.G and G.S.) and any discrepancies as to the opportunity to include reported data were resolved in a consensus meeting. The following criteria were identified and analysed: patient age and gender, body mass index (BMI), ASA classification, comorbidity, operative time, type of procedure, length of hospital stay (LOS), 30-days post-operative complication arranged by Clavien-Dindo (C-D) and mortality.

Statistical Analysis

Continuous variables were analysed by the weighted mean difference (WMD) and 95% confidence interval (CI). Categorical variables were evaluated using the odds ratio (OR) and 95% CI. When variables were reported in the papers as median and range or interquartile range, they have been converted to mean and standard deviation (SD) according to Hozo.11. The degrees of heterogeneity between the studies were assessed by the I^2. An I^2 value of 40% or lower was considered as trivial or not important heterogeneity and an I^2 value of 75% or higher as considerable heterogeneity. When I2 value was higher than 50%, pooled estimates were obtained using a random effects model with the generic inverse variance method. As concerns *p*-value of Q index (chi-square test of heterogeneity) a p-value<0.10 was considered significant otherwise a conventional level of p-value<0.05 was accepted as statistically significant. All statistical analysis and forest and funnel plot regarding meta-analysis were carried out and generated using the Jamovi Software (Version 1.2.22) integrated with the plug-in module for the R Statistical software. (The Jamovi project (2019) retrieved from https://www.jamovi.org and R Core Team (2018). R: A Language and environment for statistical computing retrieved from https://cran.r-project.org/.).

Results

Personal Series

A total of 2 patients affected by COVID-19 and AII fulfilled the inclusion criteria. The mean age of patients was 72±7.1. As to clinical signs on admission to the ED, one patient needed mechanical ventilation due to an ongoing septic shock and acute abdomen. In this patient, the Contrast Enhanced Computer Tomography (CECT) highlighted a superior mesenteric artery thrombosis, with signs of small bowel ischemia.

Based on these findings a damage control surgery was performed with simple resection of the ischemic gut without anastomoses followed by open abdomen procedure. Time from onset of symptoms to surgery was 199.8 minutes. After 48 hours, during the second look, a small bowel anastomosis and abdominal wall primary closure were performed. During the post-operative period, the patient experienced an ischemic stroke. After medical treatment, he was discharged on 57th postoperative day with a residual paraplegia. The second patient was transferred from another hospital because of deterioration of respiratory conditions. During hospitalization, he presented abdominal pain and distension, nausea, and vomiting. Abdominal CECT highlighted a superior mesenteric artery thrombosis, with signs of small bowel ischemia and splenic and hepatic infarctions (Figure 2). Based on these findings he underwent explorative laparotomy, which showed ischemia of both small and large bowel. In this case, based on intraoperative findings there was no room for resection, and the patient died few hours after surgical exploration. The delay from the onset of symptoms to the surgical exploration was of 720 minutes. Clinical and intraoperative data are reported in Tables I and II.

Results of Literature Review

Using the described search strategy, 151 items were identified. After removing duplicates and screening titles and abstract, 144 full text papers were evaluated. 117 papers were further eliminated with reasons thus 27 studies were considered eligible (Figure 1). Finally, our series and 25 relevant studies were selected which enrolled 32 patients[19-43]. With regard to the retrieved studies, 6 of these were conducted in Italy[19,25,28,33,36,41], 5 in USA[21,24,29,32,39], 3 in UK[27,30,33], 3 in France[20,26,31], 1 in Singapore[34], 1 in India[40], 1 in Kuwait[37], 1 in

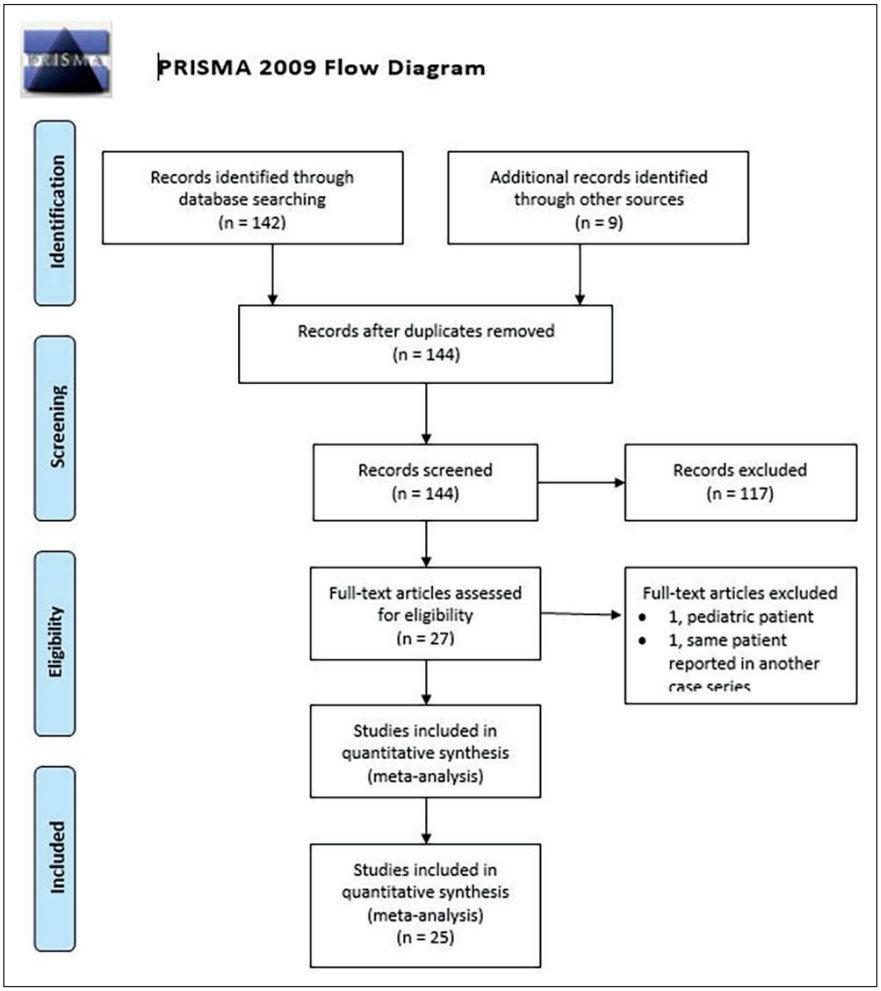

Figure 1. PRISMA flow-chart.

Table I. Characteristics of the studies included in the systematic review.

Reference	Month of publication	Nationality	Number of cases	Mean age (y)	Female gender (%)
Beccara L et al[19]	April 2020	Italy	1	52	0
De Barry O et al[20]	April 2020	France	1	79	1 (100)
Gartland R et al[21]	April 2020	USA	1	47	0
Ucpinar BA et al[22]	April 2020	Turkey	1	82	1 (100)
Azouz E et al[23]	May 2020	France	1	56	0
Chan KH et al[24]	May 2020	USA	1	73	0
Farina D et al[25]	May 2020	Italy	1	70	0
Ignat M et al[26]	May 2020	France	2	61.5 ± 7.8	0
Vulliamy P et al[27]	May 2020	UK	1	75	0
Bianco F et al[28]	June 2020	Italy	1	59	0
Cheung S et al[29]	July 2020	USA	1	55	0
English W et al[30]	July 2020	UK	1	40	0
Seeliger B et al[31]	July 2020	France	3	51.3 ± 21.4	2 (66.7)
Aiello P et al[32]	August 2020	USA	1	73	0
Besutti G et al[33]	August 2020	Italy	1	72	0
Fan BE et al[34]	August 2020	Singapore	1	30	0
Almafreji I et al[35]	September 2020	UK	1	83	0
Giuffrè M et al[36]	September 2020	Italy	2	76 ± 11.3	2 (100)
Lari E et al[37]	September 2020	Kuwait	1	38	0
Sehhat S et al[38]	September 2020	Iran	1	77	0
Singh B et al[39]	September 2020	USA	1	82	1 (100)
Karna ST et al[40]	October 2020	India	1	61	1 (100)
Norsa L et al[41]	October 2020	Italy	1	62	0
Rodriguez-Nakamura RM et al[42]	October 2020	Mexico	2	43.5 ± 2.1	1 (50)
Paul T et al[43]	November 2020	Qatar	1	66	0
Our Series	-	Italy	2	72 ± 7.1	0

Qatar[43], 1 in Mexico[42], 1 in Iran[38] and 1 in Turkey[22]. 18 (72%) studies were case reports while 7 (28%) were case series. All the studies were single centre studies, reporting on patients treated between April and November 2020.

Patients' Characteristics

Patients mean age was 62.9±14.9, with a prevalence of male gender (23 male, 72% *vs.* 9 female, 28%). 81.8% of patient present at least 1 comorbidity (Table III). The mean Charlson Comorbidity Index was 3.1±2.7 and the most common comorbidity was hypertension (12/26, 46%) followed by diabetes (9/26, 34.6%), cardiovascular disease (5/26, 19.2%) and chronic kidney disease (5/26, 19.2%) (Table I). Regarding clinical presentation, 27/32 (84.4%) patient had respiratory symptoms with radiological pulmonary involvement in 26/27 (96.3) cases. On the contrary, only 14/32 (43.7%) patients had gastrointestinal symptoms at the admission to the ED. Moreover, 10/32 (31.2%) patients had an acute abdomen at the admission and 16/32 50% developed an acute abdomen during COVID-19 hospitalization. Interesting enough, 2/32 (6.2%) patients presented a clinical picture of acute abdomen after the first hospitalization for COVID-19, 4 days and 1 week after discharge respectively (1.28) (Table IV and Table V).

Laboratory Data

The mean SpO_2 was 89.6 ±5.8, the mean WBC was 12.9±5.2 $\times 10^9$/L with a CRP mean value of 154.1±96.9 mg/L. Lactate level was elevated with mean value of 2.9±1.9 mmol/L as well as D-dimer 6108.9±6178.7 ng/ml (Table II).

Radiologic Findings

All but two patients (93.7%) underwent CECT of the abdomen. The most common findings were small bowel ischemia (17/30, 56%) and mesenteric artery thrombosis (8/30, 26.7%). Colonic ischemia was detected in 5/30 (16.7%), such as intestinal wall pneumatosis (5/30, 16.7%). Mesenteric/portal vein thrombosis was found in 5/30 (16.7%). Perforation was depicted at the CECT also in 5/30, 16.7% (Table V).

Table II. Patients' comorbidities.

Reference	Comorbidities							Mean charlson comorbidity index
	Number of cases	Hypertension (%)	Cardiovascular (%)	Respiratory (%)	Diabetes (%)	Chronic kidney disease (%)	Others (%)	
Beccara L et al[19]	1	0	0	0	0	0	0	1
De Barry O et al[20]	1	0	0	0	0	0	0	3
Gartland R et al[21]	1	0	0	0	1 (100)	0	0	1
Ucpinar BA et al[22]	1	1 (100)	1 (100)	0	0	1 (100)	0	6
Azouz E et al[23]	1	0	0	0	0	0	0	1
Chan KH et al[24]	1	1 (100)	0	0	0	1 (100)	0	5
Farina D et al[25]	1	0	0	0	0	0	0	3
Ignat M et al[26]	2	1 (50)	1 (50)	1 (50)	2 (100)	0	0	3 ± 1.4
Vulliamy P et al[27]	1	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Bianco F et al[28]	1	1 (100)	0	0	0	0	0	1
Cheung S et al[29]	1	1 (100)	0	0	0	0	0	1
English W et al[30]	1	0	0	0	0	0	0	0
Seeliger B et al[31]	3	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Aiello P et al[32]	1	1 (100)	1 (100)	0	1 (100)	1 (100)	0	7
Besutti G et al[33]	1	1 (100)	1 (100)	0	1 (100)	1 (100)	0	8
Fan BE et al[34]	1	0	0	0	0	0	0	0
Almafreji I et al[35]	1	1 (100)	1 (100)	0	1 (100)	1 (100)	0	9
Giuffrè M et al[36]	2	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Lari E et al[37]	1	0	0	0	0	0	0	0
Sehhat S et al[38]	1	1 (100)	0	0	0	0	0	3
Singh B et al[39]	1	1 (100)	0	0	1 (100)	0	0	5
Karna ST et al[40]	1	1 (100)	0	0	1 (100)	0	0	3
Norsa L et al[41]	1	1 (100)	0	0	1 (100)	0	1 (100)	6
Rodriguez-Nakamura RM et al[42]	2	0	0	0	0	0	1 (50)	0 ± 0
Paul T et al[43]	1	0	0	0	0	0	0	2
Our Series	2	0	0	1 (50)	0	0	0	3 ± 1.4

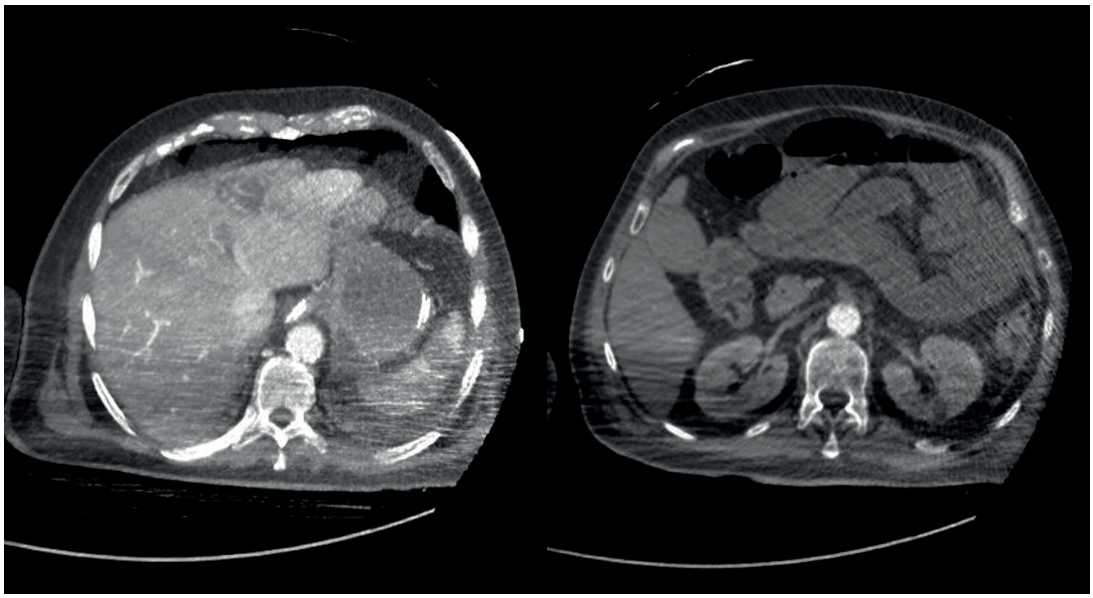

Figure 2. Abdominal CECT highlighted a superior mesenteric artery thrombosis, with signs of small bowel ischemia and splenic and hepatic infarctions.

Treatment Details and Outcome

Table VI summarizes treatment and outcomes. Surgery was performed in 24/32 patients (75.0%), with a mean time delay from admission to surgery of 6.0±5.6 days. Small bowel ischemia was confirmed to be the most common finding at surgical exploration (22/24, 91.7%) but with only two cases of perforation (2/24, 8.3%). The second most frequent surgical finding was large bowel ischemia (7/24, 29.2%). In agreement with these findings, small bowel resection was the most common surgical procedure performed (19/24, 75%) followed by 5/24 (20.8%) large bowel resections and only by 3/24 (12.5%) thrombectomies. Open abdomen for a second look was reported in only 6/24 cases (25%). According to CD classification, the post-operative morbidity rate > 3 was of 14/19 (73.7%), while mortality rate was of 10/16 (62.5%).

Comparison Between Patients with Acute Abdomen at the ED Admission vs. Patients with Acute Abdomen During Hospitalization

Acute abdomen at admission to the ED in patients with SARS-CoV-2 infection confirmed by reverse transcriptase-polymerase-chain-reaction (Group 1) was observed in 10 (31.2%) cases. On the other hand, 16 (50%) patients developed an acute abdomen condition during hospitalization (Group 2) for SARS-CoV-2 infection. The mean age was 59.70±19.2 for Groups 1 and 64.13 ±16.0 for Group 2 patient, *p*-value=0.25.

Laboratory values showed that Lactate level was slightly higher in patients with acute abdomen at admission (Group 1) compared to those with no acute abdomen (Group 2): 3.7±1.9 mmolL *vs.* 1.2±0.2 mmolL respectively, *p*-value>0.05 (Figure 3). While there was no significant difference in terms of WBC (Group 1 59.7±19.2 $\times 10^9$L *vs.* Group 2 11.8±9.7 $\times 10^9$L), CRP (Group 1182.7±104.6 mgL *vs.* Group 2 176.1±109.2 mgL) and D-Dimers (Group 1 6906.0±7269.6 ngmL *vs.* Group 2 3943.1±5032.1 ngmL) (Figure 3).

Moreover, there was no significant difference in terms of Charlson Comorbidities index between the two groups, with a mean value of 2.89±3.2 for Group 1 and of 3.09±2.5 for Group 2, *p*-value>0.05 (Figure 3). Table VII summarizes clinical features and outcomes of both groups. There was no difference in terms of fever, respiratory symptoms, radiological pulmonary involvement, and rate of small bowel ischemia. Regarding large bowel ischemia, a slighter higher rate was observed in patients with acute abdomen at admission to the ED (Group 1: 3 patients, 33% *vs.* Group 2: 2 patients, 13.3%, OD 3.250, 95% confidence interval 0.425-24.844, *p*-value>0.05). Moreover, there was no difference in terms of surgical procedures performed and outcomes.

Table III. COVID-19 clinical manifestation and diagnosis at admission.

Reference	Number of cases	Fever (%)	Respiratory symptoms (%)	Gastrointestinal symptoms (%)	Asymptomatic (%)	Radiological pulmonary involvement (%)	Positive nasopharyngeal swab (%)
Beccara L et al[19]	1	1 (100)	1 (100)	0	0	1 (100)	1 (100)
De Barry O et al[20]	1	1 (100)	1 (100)	1 (100)	0	1 (100)	0
Gartland R et al[21]	1	1 (100)	1 (100)	0	0	n/a	1 (100)
Ucpinar BA et al[22]	1	1 (100)	1 (100)	0	0	1 (100)	1 (100)
Azouz E et al[23]	1	0	0	0	1 (100)	1 (100)	1 (100)
Chan KH et al[24]	1	1 (100)	1 (100)	1 (100)	0	1 (100)	1 (100)
Farina D et al[25]	1	1 (100)	1 (100)	1 (100)	0	1 (100)	0
Ignat M et al[26]	2	0	2 (100)	0	0	2 (100)	2 (100)
Vulliamy P et al[27]	1	0	1 (100)	1 (100)	0	1 (100)	n/a
Bianco F et al[28]	1	1 (100)	1 (100)	0	0	1 (100)	0
Cheung S et al[29]	1	0	0	1 (100)	0	1 (100)	1 (100)
English W et al[30]	1	1 (100)	1 (100)	0	0	1 (100)	1 (100)
Seeliger B et al[31]	3	3 (100)	3 (100)	1 (33.3)	0	3 (100)	2 (66.7)
Aiello P et al[32]	1	0	1 (100)	0	0	1 (100)	1 (100)
Besutti G et al[33]	1	0	1 (100)	0	0	n/a	1 (100)
Fan BE et al[34]	1	0	0	1 (100)	0	1 (100)	1 (100)
Almafreji I et al[35]	1	0	0	1 (100)	0	1 (100)	0
Giuffrè M et al[36]	2	2 (100)	2 (100)	0	0	n/a	2 (100)
Lari E et al[37]	1	0	1 (100)	1 (100)	0	1 (100)	1 (100)
Sehhat S et al[38]	1	0	1 (100)	0	0	1 (100)	1 (100)
Singh B et al[39]	1	1 (100)	1 (100)	0	0	n/a	n/a
Karna ST et al[40]	1	0	1 (100)	0	0	1 (100)	1 (100)
Norsa L et al[41]	1	0	0	1 (100)	0	0	0
Rodriguez-Nakamura RM et al[42]	2	1 (50)	2 (100)	2 (100)	0	2 (100)	1 (50)
Paul T et al[43]	1	1 (100)	1 (100)	0	0	1 (100)	1 (100)
Our Series	2	2 (100)	2 (100)	2 (100)	0	2 (100)	2 (100)

Table IV. Abdominal symptoms and imaging.

Reference	Number of cases	Acute abdomen at admission (%)	Acute abdomen during COVID-19 hospitalization (%)	Acute abdomen COVID-19 hospitalization after (%)	No abdominal pain (%)	Abdominal CT performed (%)	CT intestinal abnormalities					
							Small bowel ischemia (%)	Ischemic colitis (%)	Pneumatosis (%)	Mesenteric artery thrombosis (%)	Mesenteric/ portal vein thrombosis (%)	Perforation (%)
Beccara L et al[19]	1	0	0	1 (100)	0	1 (100)	0	0	0	1 (100)	0	0
De Barry O et al[20]	1	1 (100)	0	0	0	1 (100)	1 (100)	1 (100)	0	1 (100)	1 (100)	0
Gartland R et al[21]	1	0	1 (100)	0	0	1 (100)	1 (100)	0	0	0	0	1 (100)
Ucpinar BA et al[22]	1	0	1 (100)	0	0	1 (100)	0	0	1 (100)	1 (100)	0	0
Azouz E et al[23]	1	0	1 (100)	0	0	1 (100)	1 (100)	0	0	1 (100)	0	0
Chan KH et al[24]	1	1 (100)	0	0	0	1 (100)	0	1 (100)	0	0	0	0
Farina D et al[25]	1	1 (100)	0	0	0	1 (100)	1 (100)	0	0	0	0	0
Ignat M et al[26]	2	0	0	0	2 (100)	2 (100)	2 (100)	0	0	0	0	0
Vulliamy P et al[27]	1	1 (100)	0	0	0	1 (100)	0	0	0	1 (100)	0	0
Bianco F et al[28]	1	0	1 (100)	0	0	1 (100)	1 (100)	0	0	0	0	0
Cheung S et al[29]	1	0	0	1 (100)	0	1 (100)	0	0	0	1 (100)	0	0
English W et al[30]	1	0	1 (100)	0	0	1 (100)	1 (100)	0	1 (100)	0	0	0
Seeliger B et al[31]	3	0	3 (100)	0	0	2 (66.7)	2 (66.7)	0	0	0	0	0
Aiello P et al[32]	1	0	0	0	1 (100)	1 (100)	0	0	1 (100)	0	0	0
Besutti G et al[33]	1	0	1 (100)	0	0	1 (100)	1 (100)	0	0	0	0	0
Fan BE et al[34]	1	1 (100)	0	0	0	1 (100)	0	0	0	0	1 (100)	0
Almafreji I et al[35]	1	1 (100)	0	0	0	1 (100)	0	1 (100)	0	0	0	0
Giuffrè M et al[36]	2	0	2 (100)	0	0	2 (100)	0	2 (100)	0	0	0	2 (100)
Lari E et al[37]	1	1 (100)	0	0	0	1 (100)	1 (100)	0	0	0	1 (100)	0
Sehhat S et al[38]	1	0	1 (100)	0	0	1 (100)	0	0	0	0	0	0
Singh B et al[39]	1	0	1 (100)	0	0	1 (100)	0	0	1 (100)	0	0	0
Karna ST et al[40]	1	0	1 (100)	0	0	1 (100)	0	0	0	1 (100)	0	0
Norsa L et al[41]	1	1 (100)	0	0	0	1 (100)	1 (100)	0	0	0	1 (100)	0
Rodriguez-Nakamura RM et al[42]	2	2 (100)	0	0	0	1 (50)	1 (100)	0	0	0	1 (100)	1 (100)
Paul T et al[43]	1	0	0	0	1 (100)	0						
Our Series	2	0	2 (100)	0	0	2 (100)	2 (100)	0	1 (50)	1 (50)	0	1 (50)

Table V. Laboratories value.

Reference	Number of cases	Mean SpO_2 value (%)	Mean WBC value (x10^9/L)	Mean CRP value (mg/L)	Mean Lactate value (mmol/L)	Mean D-Dimer value (ng/mL)
Beccara L et al[19]	1	99	n/a	44	n/a	n/a
De Barry O et al[20]	1	86	12.6	125	5.4	n/a
Gartland R et al[21]	1	n/a	n/a	n/a	n/a	n/a
Ucpinar BA et al[22]	1	n/a	n/a	n/a	n/a	n/a
Azouz E et al[23]	1	n/a	n/a	n/a	n/a	n/a
Chan KH et al[24]	1	88	3.8	77	2	4226
Farina D et al[25]	1	95	15.3	149	n/a	n/a
Ignat M et al[26]	2	n/a	n/a	n/a	n/a	n/a
Vulliamy P et al[27]	1	88	18.1	n/a	n/a	3200
Bianco F et al[28]	1	n/a	n/a	n/a	n/a	n/a
Cheung S et al[29]	1	87	n/a	n/a	n/a	n/a
English W et al[30]	1	n/a	8.6	n/a	n/a	13750
Seeliger B et al[31]	3	n/a	n/a	n/a	n/a	1560 ± 1499.1
Aiello P et al[32]	1	n/a	16.7	n/a	n/a	n/a
Besutti G et al[33]	1	94	n/a	53.8	n/a	n/a
Fan BE et al[34]	1	n/a	n/a	n/a	n/a	20000
Almafreji I et al[35]	1	95	15.9	139	5.3	2959
Giuffrè M et al[36]	2	n/a	11.9±8.4	19,2 ± 13.6	n/a	845 ± 289.9
Lari E et al[37]	1	n/a	n/a	n/a	2.2	2100
Sehhat S et al[38]	1	n/a	4.2	86	n/a	n/a
Singh B et al[39]	1	n/a	n/a	n/a	n/a	n/a
Karna ST et al[40]	1	78	n/a	343	1.1	n/a
Norsa L et al[41]	1	n/a	n/a	n/a	n/a	> 75 × n.v.
Rodriguez-Nakamura RM et al[42]	2	90 ± 14.1	17.6 ± 1.7	303 ± 90.5	n/a	7928.5 ± 9162.0
Paul T et al[43]	1	n/a	n/a	n/a	n/a	n/a
Our Series	2	86 ± 4,2	17.2 ± 16,5	183.1 ± 28.1	1.3 ± 0.3	4521 ± 4712.2

Comparison Between COVID-19 Negative and Positive Patient with Acute Intestinal Ischemia

The COVID-19 literature cohort patients were compared with a personal series of 24 patients with AII ischemia. Table VIII summarizes clinical features and outcomes of both groups. Significative differences were found in terms of overall post-operative complication (COVID-: 9, 56.3% *vs.* COVID+ 2, 13.3%, *p*-value=0.023) and number of surgical procedures performed (COVID- 29, 100%, COVID+ 19, 79.2%, *p*-value=0.014). A slightly significant difference in terms of time to surgery, with a longer time in COVID-19 patient (COVID- 217.1±120.7 *vs.* COVID+ 388.4±399.7, *p*-value=0.575), was identified.

Discussion

Acute intestinal ischemia (AII) is a pathological condition caused by insufficient mesenteric blood flow with subsequent ischemia and possibly transmural necrosis of the bowel wall[1]. Despite it is a rare disease, AII is considered a life-threatening condition with high morbidity and a mortality rate up to 60-80%[2-7]. After the first COVID-19 outbreaks, SARS-CoV-2 infection still affects our daily life and more has to be discovered on the pathophysiological effect of this virus. The involvement of multiples organs with different severity of clinical manifestations has led several authors to propose that the main damage is not primarily in the pulmonary parenchyma, but at the level of the microcirculation[8-12]. According to Klok et al[44], among 184 COVID-19 patients in a Dutch ICU, 38% had coagulation abnormalities and almost one-third already had clots. In the light of these data, it has been assumed that COVID-19 targets blood vessels and that all clinical manifestations start from this type of damage. As stated by different authors, coagulopathy has been found as a prominent feature of COVID-19 and severe coagulation dysfunction may be associated with poor prognosis[13,14]. In their review, Shi et al[45] observed

Table VI. Surgical treatment and outcome.

Reference	Number of cases	Surgery performed (%)	Mean delay from admission to surgery (d)	Intraoperative finding			Surgical procedure performed				P.o. outcomes	
				Small bowel ischemia (%)	Large bowel ischemia (%)	Perforation (%)	Small bowel resection (%)	Colon resection (%)	Thrombectomy (%)	Open Abdomen (%)	Postoperative complications grade > 3 according to Dindo-Clavien classification (%)	Postoperative mortality (%)
Beccara L et al[19]	1	1 (100)	1	1 (100)	0	0	1 (100)	0	0	0	0	0
De Barry O et al[20]	1	1 (100)	0	1 (100)	1 (100)	0	1 (100)	1 (100)	1 (100)	0	1 (100)	1 (100)
Gartland R et al[21]	1	1 (100)	14	1 (100)	1 (100)	1 (100)	0	0	0	0	1 (100)	1 (100)
Ucpinar BA et al[22]	1	0										
Azouz E et al[23]	1	1 (100)	1	1 (100)	0	0	1 (100)	0	1 (100)	0	n/a	n/a
Chan KH et al[24]	1	0										
Farina D et al[25]	1	0										
Ignat M et al[26]	2	1 (50)	9	1 (100)	0	0	1 (100)	0	0	1 (100)	1 (100)	n/a
Vulliamy P et al[27]	1	1 (100)	0	1 (100)	0	0	1 (100)	0	0	0	n/a	n/a
Bianco F et al[28]	1	1 (100)	5	1 (100)	0	0	1 (100)	0	0	0	1 (100)	1 (100)
Cheung S et al[29]	1	1 (100)	n/a	1 (100)	0	0	1 (100)	0	1 (100)	0	n/a	n/a
English W et al[30]	1	1 (100)	9	1 (100)	0	0	1 (100)	0	0	1 (100)	0	0
Seeliger B et al[31]	3	3 (100)	12 ± 10.8	2 (66.7)	1 (33.3)	0	2 (66.7)	1 (33.3)	0	2 (66.7)	3 (100)	1 (50)*
Aiello P et al[32]	1	0										
Besutti G et al[33]	1	1 (100)	1	1 (100)	0	0	1 (100)	0	0	0	n/a	n/a
Fan BE et al[34]	1	1 (100)	n/a	1 (100)	0	0	1 (100)	0	0	0	0	0
Almafreji I et al[35]	1	1 (100)	5	1 (100)	1 (100)	0	0	1 (100)	0	0	1 (100)	1 (100)
Giuffrè M et al[36]	2	0										
Lari E et al[37]	1	1 (100)	0	1 (100)	0	0	1 (100)	0	0	1 (100)	n/a	n/a
Sehhat S et al[38]	1	1 (100)	11	1 (100)	1 (100)	0	1 (100)	1 (100)	0	0	1 (100)	1 (100)
Singh B et al[39]	1	1 (100)	18	0	1 (100)	0	0	1 (100)	0	0	0	n/a
Karna ST et al[40]	1	1 (100)	10	1 (100)	0	0	1 (100)	0	0	0	1 (100)	1 (100)
Norsa L et al[41]	1	1 (100)	0	1 (100)	0	0	1 (100)	0	0	0	1 (100)	1 (100)
Rodriguez-Nakamura RM et al[42]	2	2 (100)	3.5 ± 4.9	2 (100)	0	1 (50)	2 (100)	0	0	0	1 (50)	1 (50)
Paul T et al[43]	1	0										
Our Series	2	2 (100)	4.5 ± 6.4	2 (100)	1 (50)	0	1 (50)	0	0	1 (50)	2 (100)	1 (50)

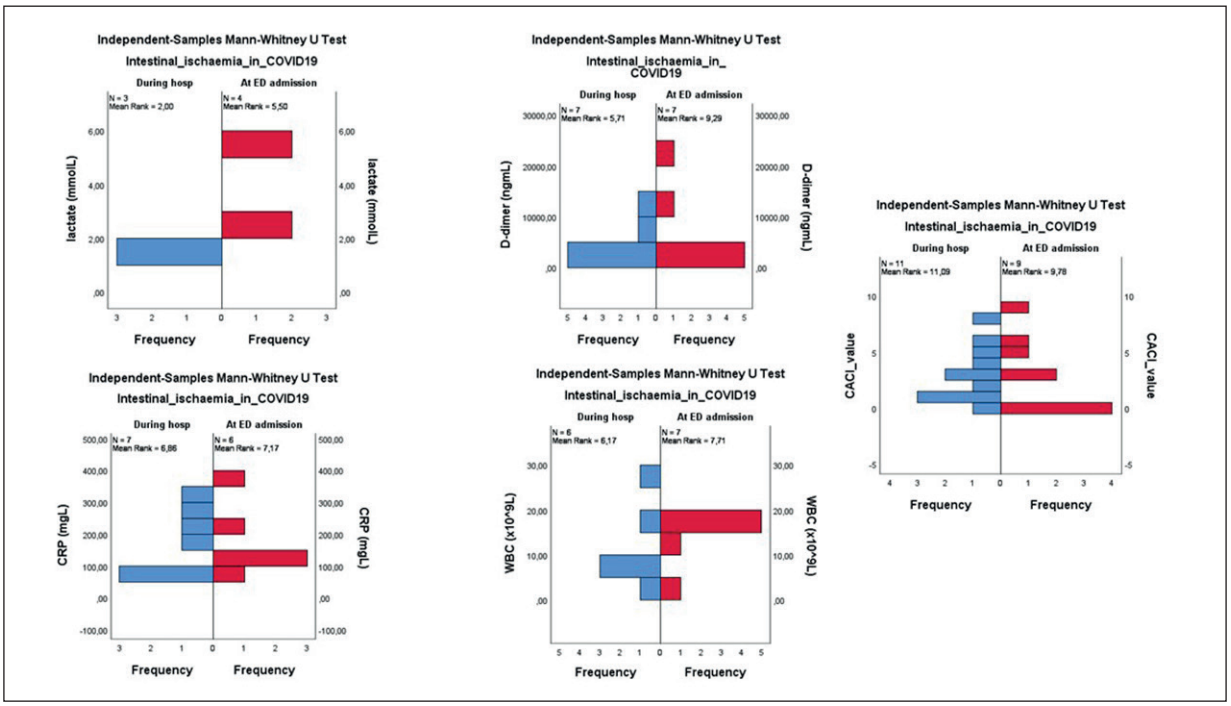

Figure 3. Comparison between patients with acute abdomen at the ED admission *vs.* patients with acute abdomen during hospitalization.

that the mechanisms underlying the coagulation dysfunction may be associated with inflammatory storm, uncontrolled inflammation-mediated endothelial injury, and renin angiotensin system (RAS) dysregulation. Lowenstein et al[46] reported an incidence of venous thromboembolic events in patients with COVID-19 admitted to intensive care that ranges from 20% to 35%, and deep venous thrombosis has been identified in 70% to 100% of patient who died from COVD-19. Furthermore, arterial thrombosis resulting in stroke or myocardial infarction occurred in up to 4% of

Table VII. Comparison between patient with acute abdomen at the ED admission *vs*. patient with acute abdomen during hospitalization.

	Total	At ED admission	During Hospitalization	*p*
CV comorbities	3 (15%)	1 (11.1%)	2 (18,2%)	> 0.05
Respiratory comorbidities	1 (3.8%)	0	1 (9.1%)	> 0.05
Chronic kidney disease	4 (15.4%)	2 (22.2%)	2 (18.2%)	> 0.05
Diabetes	6 (30%)	2 (22.2%)	4 (36.4%)	> 0.05
Hypertension	9 (45%)	3 (33.3%)	6 (54.5%)	> 0.05
Fever	16 (61.5%)	4 (40%)	12 (75.0%)	> 0.05
Respiratory symptoms	22 ()	7 (70.7%)	15 (93.%)	> 0.05
Radiological pulmonary involvement	20 ()	9 (90%)	11 (100%)	> 0.05
SB ischemia	14 (58.3%)	5 (55.6%)	9 (60%)	> 0.05
Large bowel ischemia	5 (20.8%)	3 (33.3%)	2 (13.3%)	> 0.05
Surgery performed	21 (80.8%)	8 (80.8%)	13 (81.3%)	> 0.05
SB resection	16 (76.2%)	7 (87.5%)	9 (69.2%))	> 0.05
Large Bowel resection	5 (23.8%)	2 (25%)	3 (23.1%)	> 0.05
Thrombectomy	2 (9.5%)	1 (12.5%)	1 (7.7%)	> 0.05
Open Abdomen	4 (19.0%)	1 (12.5%)	3 (23.1%)	> 0.05
P.O complications CD > 3	4 ()	4 (66.7%)	9 (81.8%)	> 0.05
Mortality	10 (66.7%)	4 (66.7%)	6 (66.7%)	> 0.05

Table VIII. Comparison between COVID19 positive e COVID19 negative patients.

	Overall		
	Covid -	Covid +	*p*
Number of patients	29	24	
Mean age (y)	68.9 ± 11.3	61.6 ± 17.5	0.208
Female gender (%)	10 (34.5)	9 (37.5)	0.820
Mean WBC value (×10^9/L)	17.0 ± 8.2	13.4±6.3	0.227
Mean Lactate value (mmol/L)	2.7 ± 2.2	3.1 ± 1.8	0.454
Pneumatosis (%)	10 (34.5)	3 (12.5)	0.108
Arterial occlusion (%)	5 (17.2)	5 (20.8)	1.000
Venous thrombosis (%)	3 (10.3)	4 (16.7)	0.688
Non occlusive thrombosis	21 (72.4)	15 (62.5)	0.635
Perforation (%)	5 (17.2)	4 (16.7)	1.000
Mean time to surgery (minutes)	217.1 ± 120.7	388.4 ± 399.7	0.575
Surgical treatment	29 (100)	19 (79.2)	**0.014**
Ileal resection	15 (51.7)	10 (52.6)	0.823
Ileo-colic resection	5 (17.3)	3 (15.7)	1.000
Colic resection	5 (17.2)	5 (26.3)	0.732
Explorative laparotomy	4 (13.7)	1 (5.3)	0.635
Post-operative Morbidity (CD 1-4)	9 (56.3)	2 (13.3)	**0.023**
Post-operative Morbidity CD > 2	2 (2.2)	2 (1.8)	1.000
Post-operative mortality (%)	13 (44.8)	13 (54.2)	0.688

CD = Clavien – Dindo classification

ICU COVID-19 patients. The Authors conclude that endothelial exocytosis plays a central role in the pathogenesis of severe COVID-19. Endothelial release of P-selectin and VWF activate two parallel pathways, leukocyte adherence and platelet aggregation, that lead to the cytokine storm and massive thrombosis characteristic of severe COVID-19[46]. Moreover, Venter et al[47] reported that structural pathologies found in platelets and erythrocytes, together with spontaneously formed amyloid micro-clots, may be central to vascular changes observed during COVID-19 progression. Thrombotic microangiopathy, diffuse intravascular coagulation and large-vessel thrombosis, as well as ground-glass opacities highlighted how cloth formation and subsequent thrombosis and/or ischemic events are directly linked to a poor prognosis[47,48].

Our literature review showed how intestinal ischemia in patients with SARS-CoV-2 has been reported all over the world[19-43]. Most of these patients with AII have a high CCI with multiple comorbidities first of which hypertension and cardiovascular disease. Clinical presentation was characterized by respiratory symptoms in most of the cases while GI symptoms were not always present at the admission. However, 10 patients had an acute abdomen at admission at the first diagnosis of SARS-CoV-2 infection, while 18 patients developed an acute abdomen during or after hospitalization. Contrast enhanced CT (CECT) scan remains the gold standard for the diagnosis of both SARS-CoV-2 related pneumonia and AII. Cumulating the data in our series and those from literature review intestinal ischemia in patients with SARS-CoV-2 infection reaches a morbidity rate of 73.7% and a mortality rate of 62.5% that rises to 81.8% and 66.7% respectively, if the signs of acute abdomen appear during hospitalization. It is possible, also, that GI symptoms at admission can also be a direct expression of an underlying intestinal ischemia. This last group of patients have a higher CCI and more frequently undergo bowel resection.

These findings advocate for a reactive approach with an early request for an abdominal CECT in patients with unexplained deteriorating status during COVID-19. CECT must specifically look for vascular damages and if these are present, an appropriate step-up medical treatment (immunoglobulins, corticoids) should be started to prevent gastro-intestinal complications. Exploratory laparotomy/laparoscopy and potentially bowel resection should be further considered, if signs of small bowel involvement are detected. An early screening of patients at higher thromboembolic risk since the first manifestations of SARS-CoV-2 infection, especially if with gastro-

intestinal involvement, could be useful to identify these events early. A low threshold of suspect for AII should be maintained. Moreover, it is interesting that from the comparison between COVID-19+ patient and COVID-19- patient with AII it seems that there is a statistically significant trend to reduce surgical procedure in COVID-19+ patient associated with a higher time to surgery. These findings can be explained on the one hand by the multisystemic impairment of COVID-19 that makes the patient not fit for surgery, but on the other hand by the difficulties in the management of these patients in terms of need of a dedicated OR, dedicated pathways and resources. The data here reported are relative to the "first wave" of the disease and there is hope that some of these management problems will resolve as the pandemic progresses.

Study Limitations

This retrospective study has several limitations. Firstly, all studies included in the analysis were case reports or case series. For these reasons, the effect estimates in the model are based only on low evidence studies. They are therefore subject to biases and confounding factors that may have influenced our model estimates. In the light of this, results and their analysis must be interpreted with care. The tendency is towards and underestimation of the full impact of COVID-19 regarding AII due to the difficulties in reporting during the COVID-19 "first wave"[49].

Conclusions

Our experience and the literature review suggest that a high level of suspicion for intestinal ischemia should be maintained in COVID-19 patients presenting with gastrointestinal symptoms or with incremental abdominal pain. Late diagnosis of this complication can account for an increased mortality risk. Nevertheless, a prompt performance of laboratory tests and a thromboelastogram may confirm the need of improving and fastening the use of anticoagulants. An abnormal thromboelastogram could trigger also an extended indication for early abdominal CECT in patients with suggestive symptoms or biochemical markers of intestinal ischemia. Moreover, hospitals should established dedicate pathways for COVID-19 patient in order to not delated surgical intervention.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Availability of Data and Materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Authors' Contribution

PF: Study conception and design, literature search, acquisition, interpretation and analysis of data, drafting and critically revising the article for important intellectual content and final approval of the version to be published. LD, CP, GP: literature search, acquisition, interpretation and analysis of data GC: acquisition, interpretation and analysis of data, drafting and critically revising the article for important intellectual content and final approval of the version to be published GA,VC: acquisition, interpretation and analysis of data PM: acquisition, interpretation and analysis of data ALG: drafting and critically revising the article for important intellectual content and final approval of the version to be published GS: drafting and critically revising the article for important intellectual content and final approval of the version to be published.

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