

Gastrointestinal Complications in Sarscov-2 Infection: An Integrative Review



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ABSTRACT: The novel coronavirus causes varied symptomatology and several complications, among them, stand out those of the gastrointestinal tract. In order to discuss gastrointestinal complications in SARS-COV-2 infected patients and their outcomes, we've developed an integrative literature review, using Pubmed and BVS databases. The following descriptors were used: covid-19, Sars-cov-2, gastrointestinal Tract, and Complications. The selected studies presented patients with covid-19 and gastrointestinal complications. The majority of the 13 articles included were case reports, in Europe, mostly men at the age of 60 or more. As for complications, ischemia, gastrointestinal bleeding, and pneumatosis, arterial narrowing and thrombosis stands out. In diagnoses, commonly exam was the reverse polymerase-transcriptase chain reaction; treatment varied between conservative and surgical resection. It's evident the importance of good practice, early diagnosis and treatments, avoiding at its most the worsening of the condition. However, whereas is such a recent subject matter, further studies need to be made.

KEYWORDS: SARS Virus. Intestinal Diseases. Coronavirus Infections, Gastrointestinal complications, Gastrointestinal Tract.

I. INTRODUCTION

The new coronavirus (SARSCoV-2) is a positive single-stranded, enveloped RNA virus. It had its first reported case in Wuhan, Hubei Province, People's Republic of China¹ at the end of 2019 and, since then, it has spread rapidly and overwhelmingly, configuring a pandemic. Currently, more than 72,196,732 cases have been reported worldwide, including 1,630,521 deaths of individuals with COVID-19². Brazil is one of the countries that have suffered from the effects of this disease, totaling 6,970,034 cases and 182,799 deaths³. Furthermore, its clinical manifestations vary significantly, from asymptomatic individuals to those with complications that go beyond classic symptoms such as fever, headache, myalgia, respiratory secretions, diarrhea⁴, since in addition to its tropism for the airways and lung tissue, complications have already been described kidney, liver and gastrointestinal tract (GIT).

Upon entering the individual's body, the virus binds to the angiotensin 2 converting enzyme (ACE2) receptor, allowing access to the target cell and its replication. Thus, it is capable of triggering an immune response in the host, with the first symptoms and clinical manifestations, including those related to GIT, appearing. This is because cells that have these receptors are led to produce inflammatory mediators, activating immune cells, which release cytokines (such as interleukin [IL]-2, IL-6, IL-17 and tumor necrosis factor [TNF]), that act on the local and systemic manifestations of COVID-19⁵. Furthermore, this receptor is found on alveolar cells, but also on epithelial cells throughout the TGI⁶. Thus, SARS-CoV-2 can cause digestive symptoms by direct viral invasion into target cells and/or immune-mediated tissue and target organ damage.

The most frequent complications related to the gastrointestinal tract are intestinal ischemia, gastrointestinal bleeding and intestinal pneumatosis, in addition to arterial narrowing and thrombosis. Therefore, treatment can be a conservative or surgical approach, which may or may not lead to death.

In view of these considerations, it is considered relevant to seek theoretical support for a better understanding of the fact, and therefore, this review aimed to discuss the main complications in the gastrointestinal tract in patients with COVID-19, as well as the possible associated outcomes.

Gastrointestinal Complications in Sarscov-2 Infection: An Integrative Review

II. METHODS

An integrative literature review was conducted, according to the reference of Mendes, Silveira and Galvão⁷. Initially, the research question was elaborated and, subsequently, the search for articles in the PubMed and BVS databases was carried out. The descriptors used were: covid-19, sars-cov-2, gastrointestinal tract and complications, found in MeSH. There was no temporal delimitation, as the theme is an emerging pandemic; with regard to language, the delimitation was for articles in English, Portuguese and Spanish. As inclusion criteria, the following were delimited: studies of the type report or case series, cross-sectional, cohort, retrospective that reported the occurrence of gastrointestinal complications in adult patients infected by sars-cov-2. Studies that did not demonstrate the occurrence of gastrointestinal complications in patients infected with sars-cov-2, articles not available in full, research carried out on experimental models, as well as those developed in special populations such as children, pregnant women or the elderly, were excluded. Afterwards, the initial reading of the title and abstract of the articles was carried out to select those that met the inclusion criteria and, then, to carry out the full reading and collect the data relevant to the research.

III. RESULTS

It were found 113 articles in PubMed and 84 in the BVS, after removing the duplicates there were 183 in total, for title and abstract analysis, after this step 164 were excluded for not meeting the inclusion criteria, leaving 13 studies for full reading, data collection and analysis, as shown in Figure 1.

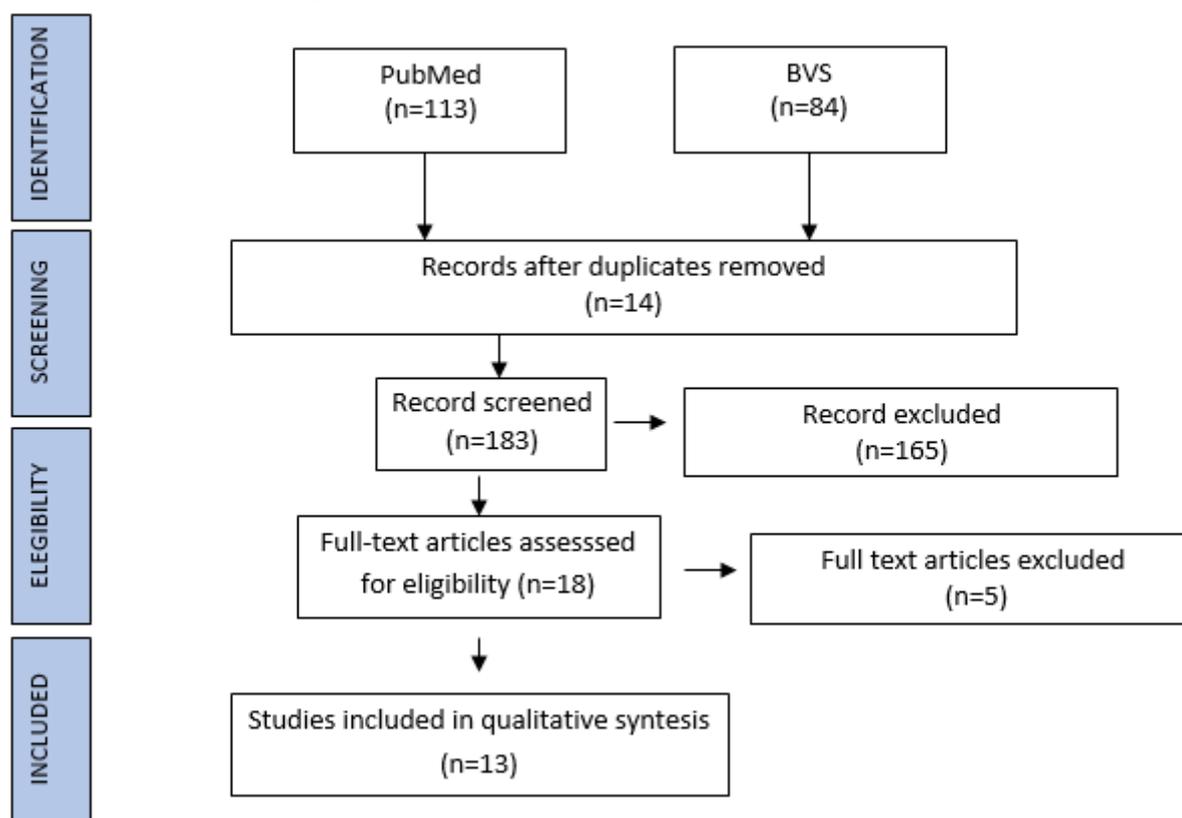


Figure 1 – Flowchart of study selection

Among the studies included, most were presented as a case report (69% - 9 articles), three studies are retrospective and one article as a case series. The main region of occurrence of the studies was Europe, with 10 studies from this continent, followed by two Asian studies, one from China and one from Qatar, and a North American study. A total of 176 patients were included in the studies, of which the majority were female (n=119). Regarding age, in six studies the patients were over 60 years old, in three over 50 and in 2 over 40, one study did not report the age of the patients.

Azouz et al.⁸ presented the case report of a 56-year-old patient who progressed to an intestinal resection of 2 meters of small bowel. The patient was admitted with an acute ischemic stroke due to right middle cerebral artery occlusion. An angiotomography was performed and showed lesions suggestive of COVID-19, a diagnosis confirmed by PCR+. Later, the patient progressed to abdominal pain and vomiting. A CT scan confirmed a thrombus in the aortic arch associated with occlusion of the superior mesenteric artery, with no signs of aortic atherosclerosis. With these findings, the patient underwent an endovascular

Gastrointestinal Complications in Sarscov-2 Infection: An Integrative Review

thrombectomy and laparotomy, requiring bowel resection. The authors report that patients with COVID -19 are predisposed to thromboembolic diseases due to their state of excessive inflammation, hypoxia and in some cases disseminated intravascular coagulation, in addition, they point out that recent studies have shown that the virus targets endothelial cells, which results in endothelial dysfunction.

Another case report, this one carried out in Italy, with a 59-year-old male patient, who needed bowel resection, in this case 15 centimeters of the small bowel were resected due to ischemia. The patient, hypertensive, arrived with fever, progressive dyspnea and a confirmed diagnosis of bilateral interstitial pneumonia caused by COVID-19. On the fifth day after admission, he had worsening acute abdominal pain with nausea and grade 3 arterial hypertension (160 / 115mmHg). Blood tests showed a 30-fold increase in D-dimer levels, leukocytosis and lymphopenia. A contrast-enhanced CT scan of the chest and abdomen revealed classic features of COVID-19: air fluids in the small intestine, mesenteric edema, and free peritoneal fluid. Through an emergency laparotomy, a segmental ischemia of the small bowel was found; then performing resection with subsequent lateral anastomosis. Peritoneal fluid was analyzed using PCR for COVID-19, with a negative result. The patient died due to multi-organ failure on the fourth postoperative day⁹.

According to Cheung¹⁰, reporting a case that occurred in the United States, a 55-year-old male patient, diagnosed by PCR +, had high-grade narrowing of the proximal superior mesenteric artery, in addition to multifocal alveolar opacities; he performed a 20 cm resection of necrotic small intestine and administration of heparin due to hypercoagulation.

Another case report, carried out in Italy, with a 62-year-old female patient with low rectal cancer (under treatment, with chemotherapy and radiotherapy, and previously laparoscopic low anterior resection, hand-stitched coloanal anastomosis and loop ileostomy protection) and no comorbidity, diagnosis by PCR +, portrayed bowel ischemia and vaginal cervix fistula; performed abdominoperineal resection and colostomy for reconstruction of the posterior vaginal wall¹¹.

As for Kieley¹², in a case report study, carried out in Dublin (Ireland), a 47-year-old male patient with a history of sleep apnea and anxiety (treatment with fluoxetine) had the diagnosis from CRP+, presented irregular opacities bilaterally in the chest by means of radiographic examinations, and treatment with augmentin (amoxicillin with clavulanate) and clarithromycin. On day 8 of symptoms, the patient had mild abdominal distension with diarrhea. The patient showed resistance to enteral feeding, and a starchy material was aspirated into the nasogastric tube. Contrast-enhanced computed tomography (CT) showed small bowel distension along with pneumatosis, fluid and free air in the cavity, and gas in the portal vein. The diagnostic hypothesis was of extensive mesenteric ischemia, which, as mentioned above, had complications of intestinal pneumatosis and acute abdomen, it was decided not to perform laparotomy, since the procedure would be small bowel resection, this being a very definitive decision and with poor prognosis according to the authors. Therefore, anticoagulant (heparin) was administered, since, in the article, the authors emphasized the use of anticoagulants (conservative approaches) when the patient was absent. signs of systemic deterioration. In addition to heparin, thromboplastin was administered together with the crystalloid solution, dobutamine (after removal of the nasogastric tube). The patient remained hemodynamically stable and an abdominal CT was performed after 4 days (on the 12th day of the patient's ICU), showing complete resolution of the intestinal pneumatosis, return to enteral feeding, extubation on the following day, and hospital discharge on the 14th day.

Another case report, carried out in Bergamo, Italy, with a 62-year-old male patient, diagnosed by CPA. On physical examination, the patient had a tense abdomen with tenderness to palpation, with no signs of peritonitis. Her symptoms worsened with acute abdominal pain associated with hypotension. CT showed, as a complication, active bleeding due to a ruptured aneurysm in the pancreaticoduodenal column, and, in addition, the patient had ulcerations in the ascending colon. As treatment, a selective embolization for the aneurysm was performed, with hospital discharge after 13 days without symptoms. However, 2 days later the patient was readmitted with repeated episodes of rectal bleeding. Abdominal CT and colonoscopy were performed, which showed edema and hyperemia of the submucosa of the ascending colon with ulcerations. Oxygen therapy, hydroxychloroquine, darunavir/cobicistat, in addition to the use of methylprednisolone, piperacillin and tazobactam were used, mainly due to the case of pro-inflammatory hypercoagulation and the reduction of ACE-2 receptors. The patient was still in the hospital at the time of article submission, but showed clinical improvements¹³.

In Paul¹⁴, there is a case report, carried out in Doha, Qatar, presenting a 66-year-old male patient with no previous comorbidities, admitted to the emergency department with fever, cough and loss of taste and smell in the last few three days, diagnosed from PCR+. She presented rapid deterioration of the condition, requiring admission to the Intensive Care Unit (ICU). After 13 days of hospitalization, associated with the pulmonary condition, he presented complications with bleeding from the gastrointestinal tract, with episodes of melena and intense bleeding from the rectum with the release of clots. During sigmoidoscopy, large clots, multiple ulcerations and regions of ischemia were found in the sigmoid colon. We opted for treatment with conservative support associated with blood transfusion. The authors' conclusion was that the patient had

Gastrointestinal Complications in Sarscov-2 Infection: An Integrative Review

coagulopathies, and had thromboembolic complications. After 40 days of hospitalization, the patient was discharged from the hospital.

Another case report, carried out by Meini¹⁵, in Florence - Italy, with a 44-year-old male patient, diagnosed by PCR+, with fever of 39°C, productive cough and chest pain. He underwent a series of tests, including contrast-enhanced computed tomography of the lung, without pulmonary findings, but as a collateral finding in the lower image, free intraperitoneal bullae and air collection in portions involving mainly the cecum and right colon were found, compatible with intestinal pneumatosis (intraural bowel gas). The patient was treated with ciprofloxacin and metronidazole and within a few days he was asymptomatic and the tests were repeated, showing no further changes. The authors' conclusion was that the complication was of multifactorial etiogenesis, however, it was probably associated with the damage of the intestinal wall and the intestinal microbiota generated by SARS-CoV-2 and they believe that the involvement of the colon testifies to the significant role of SARS-CoV-2 in the TGI, suggesting that clinicians should always focus on this device during history taking and physical examination.

In a letter to the editor, also carried out in Bergamo, Italy, a 62-year-old male patient, the diagnosis obtained a PCR- of nasopharynx and bronchoalveolar lavage, however, positive for PCR ISH (in situ hybridization) in the intestinal mucosa, enabling a direct visualization of the virus in the tissue where the virus has established itself. The patient has comorbidities associated with obesity, hypertension, type 2 diabetes mellitus and liver cirrhosis. Laboratory tests revealed leukocytosis, marked levels of C-reactive protein, increased levels of D-dimer, in addition to changes in renal function and liver markers. It presented as a complication ischemia of the small intestine, in addition to thromboembolic filling defects in the inferior vena cava and superior mesenteric vein, being used as treatment the resection of the small intestine. The patient died about 12 hours after surgery due to refractory septic shock. The conclusion of the case was that the patient was in a state of hypercoagulation, with numerous coagulopathies¹⁶.

A case series carried out in China, with 6 patients, three males and three females, with a mean age of 68 years, reported that patients were admitted to the hospital with pneumonia as associated with COVID-19 (diagnosis by PCR+), fever, shortness of breath, infiltrate on chest X-ray and bleeding in the upper gastrointestinal tract, two of them with hematemesis and four had melena. Of the six patients, five were receiving supplemental oxygen and one patient with an endotracheal tube. All underwent conservative treatment with a positive response within 24 hours (drip of proton pump inhibitor, blood transfusion - performed in four patients who needed it, and frequent monitoring of vital signs), without endoscopy, with all cases having satisfactory resolution. As endoscopy was not performed, the authors state that the exact cause of gastrointestinal bleeding is uncertain, but they believe it is related to coagulation changes that occur in patients with COVID-19. They reinforce that as the patients in this case series evolved well in the first 24 hours, endoscopy can be discarded, but in case of lack of response in this period, it may indicate the need for endoscopy for correct resolution¹⁷.

A retrospective study in the United States, with 141 patients, with a mean age of 64 years, 41 males and 100 females and diagnosed using PCR+, identified 57% of patients with some type of abdominal-pelvic findings, with 53.8% of this number reporting abdominal pain, while those who did not obtain findings, abdominal pain occurred in 73.8% of patients. The 57% patients with abdominal-pelvic findings had: hepatomegaly (5%), periportal edema (1.2%); biliary dilation (10%); changes related to the gallbladder (15%); pancreatic duct dilation (3.8%); changes related to the spleen (8.8%); changes related to the kidneys (20%); changes related to the gastrointestinal tract (31.2%); changes related to the urinary bladder (22.5%); related to pelvic organs (5%); vascular changes (7.5%); peritoneal changes (23.8%); soft tissue changes (13.8%); retroperitoneal lymphadenopathy (5%); bone changes (6, 2%). Of the abdominopelvic changes, abnormalities in the gastrointestinal tract were the most common (31%), with abdominal pain as predictors of abdominopelvic findings. Low hemoglobin, younger ages, and statistically male gender were also independent predictors of such findings. In addition, this study correlated abdominopelvic findings as suggestive (64% of patients) pneumonia at the base of the lung caused by the coronavirus. In this study, 18% of the patients had solid organ infarction or vascular thrombosis related to the state of hypercoagulation, this study also correlated low hemoglobin levels with a more severe clinical picture in the coronavirus framework¹⁸.

Another retrospective study carried out by Norsa¹⁹, in Bergamo, Italy, with seven patients, showed that the main complication was intestinal ischemia. Two of them showed ischemic colitis with wall edema involving the entire large intestine and four of them had ischemia involving the small intestine, in addition to thromboembolic filling defects in the inferior and superior vena cava and mesenteric. D-dimer was tested in six patients, showing to be elevated in all of them. Thus, showing that gastrointestinal complications are signs of poor prognosis in patients with COVID, it was reported that four of them died, and mortality was 1.7 times higher than in the pre-COVID period-19. The authors' conclusion was that, in addition to the increased mortality rate, most patients had a state of hypercoagulability (D-dimer being the best marker for this state), which revealed a sign of poor prognosis. Furthermore, it was highlighted that the down-regulation of the angiotensin-2 converting enzyme (which

Gastrointestinal Complications in Sarscov-2 Infection: An Integrative Review

has proven to be a receptor for SARS-CoV-2) could be a hypothesis for the vascular damage caused and this receptor was found in the gastrointestinal epithelium of patients. Therefore, they suggested the prophylactic use of anticoagulants and computerized tomography as early as possible when there are suggestive symptoms.

In Strasbourg, France, a retrospective study was carried out with 13 patients, 6 women and 7 men, with a mean age of 64 years, all diagnosed using PCR+. Two scenarios were found: patients hospitalized for an acute abdominal condition where a COVID-19 co-infection was detected (group A) and patients hospitalized for a severe COVID-19 infection with a digestive complication that required emergency surgery (group B), with patients in the first group recovering better, with a lower mortality rate. The main pathologies found in group B were: perforated duodenal ulcer, sigmoid colon ischemia, retro and intraperitoneal hematoma. All cases of acute abdomen underwent surgery and there was only one death in each group. In this way, the authors stated that the acute abdomen generated from severe COVID-19 infection is a predictor of worse prognosis²⁰.

It is important to highlight that with regard to diagnosis, ten studies reported having performed the polymerase-reverse transcriptase chain reaction (RT-PCR) test with a positive result. One article describes that the RT-PCR result was negative, but in the analysis of the intestinal mucosa it was possible to detect the virus, and two studies do not describe the diagnostic confirmation methodology for covid-19.

As for complications, six studies reported the occurrence of intestinal ischemia, affecting a total of 16 patients, of which 5 required surgical resection, with a part of the intestine being removed, and eight died. Three studies reported the occurrence of gastrointestinal bleeding (n = 8 patients), which was treated with a conservative approach, without the need for surgical procedures, none of which evolved to death. Intestinal pneumatosis was a condition reported in two patients in two studies, none of which progressed to death. Other complications described were arterial narrowing and thrombosis.

IV. DISCUSSION

Although COVID-19 is a new disease, much has been described about its pathophysiology and affected systems, due to its great impact on the world population. Regarding the gastrointestinal tract, many studies, including literature reviews²¹ and systematic reviews²², have described the occurrence of symptoms such as diarrhea, abdominal pain, nausea, vomiting, anorexia and gastrointestinal bleeding, in addition to classic symptoms that include fever, dry cough and dyspnea.

However, complications involving the gastrointestinal system are still being studied, as there are more and more reports in patients with COVID-19. Thus, complications such as thrombosis and arterial narrowing, gastrointestinal ischemia and pneumatosis have already been described, but there is still a lot to discover about this subject, which makes some data inconclusive.

V. CONCLUSIONS

In order to respond to the proposed objective, all the complications evidenced in the different articles were analyzed, and it can be pointed out that the new coronavirus (SARSCoV-2) produces repercussions throughout the body, among which complications involving the gastrointestinal system are pointed out. Those include intestinal ischemia, gastrointestinal bleeding, arterial narrowing, thrombosis and intestinal pneumatosis – the predominant in the analyzed studies.

It is observed that most of the diagnosis is made possible through the examination of the polymerase-reverse transcriptase chain reaction (RT-PCR), and that the treatment can have a conservative or surgical approach, depending on the case. Furthermore, the occurrence of gastrointestinal disorders associated with the infection is associated with a poor prognosis.

We emphasize the importance of an effective clinic, which will detect symptoms early, with the aim of offering fast and safe treatment.

The studies are not conclusive and much remains to be investigated in this regard to determine effective conduct, especially with regard to the methodologies used in the studies and the risks of bias present. However, it is considered that the integration of knowledge from studies can greatly contribute to quality health care.

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Gastrointestinal Complications in Sarscov-2 Infection: An Integrative Review

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