



# Exploring the gastrointestinal tract in SARS-CoV-2 infection: route of infection, manifestations, and impacts on the clinical course of patients with COVID-19



## Explorando o Trato Gastrointestinal na Infecção por SARS-CoV-2: Via de Infecção, Manifestações e Impactos na Evolução do Pacientes com COVID-19

Jéssica Inojosa Aguiar  Larissa Di Paula Souza Pires 

Pedro Henrique Leite Lima  Fábio Menezes de Melo 

<sup>1</sup> Faculdade de Medicina de Olinda. Olinda, Pernambuco, Brazil.

<sup>2</sup> Universidade Federal de Pernambuco. Recife, Pernambuco, Brazil.

### Abstract

The Severe Acute Respiratory Syndrome Coronavirus-2 virus (SARS-CoV-2) infection may lead to respiratory symptoms and dysfunctions in the gastrointestinal tract (GIT), including abdominal pain, diarrhea, nausea, and vomiting episodes. Also, growing evidence suggests an oral-fecal route of transmission in SARS-CoV-2 infection. Thus, this integrative review discussed the influence of SARS-CoV-2 infection on the GIT function. An automatic search was performed in the PubMed and Scielo databases, and studies were screened according to eligibility criteria and by reading the title and abstract. Ten studies meeting the inclusion criteria described symptoms in the GIT related to SARS-CoV-2 infection. Also, other abdominal symptoms were described, such as involvement of the liver and viral RNA in the feces of infected patients. Thus, further studies are needed to elucidate the underlying mechanisms of SARS-CoV-2 infection, manifestations in the GIT, and disease progression.

**Keywords:** SARS-CoV-2; COVID-19; Coronavirus; Gastrointestinal diseases.

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### Corresponding Author:

Jéssica Inojosa Aguiar

E-mail:

[jess.aguiar@hotmail.com](mailto:jess.aguiar@hotmail.com)

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## Resumo

Evidências mostraram que a infecção pelo SARS-CoV-2, além de desencadear sintomas respiratórios, pode promover anormalidades e manifestações no trato gastrointestinal (TGI), como dor abdominal, diarreia, náuseas e episódios eméticos. Estudos sugerem uma possível rota de infecção oral-fecal através do TGI após a infecção pelo SARS-CoV-2. Este estudo realizou uma revisão integrativa sobre a influência da infecção pelo SARS-CoV-2 no TGI. Uma busca automática nas bases de dados PubMed e Scielo foi conduzida e 10 estudos atenderam aos critérios estabelecidos, compreendendo a amostra final. As manifestações do TGI relacionadas ao COVID-19 foram observadas em todos os estudos incluídos nesta revisão. Além disso, outras condições associadas ao TGI, como envolvimento hepático e presença de RNA viral nas fezes, foram relatadas. Estudos adicionais são necessários para elucidar os mecanismos subjacentes à infecção por SARS-CoV-2, manifestações do TGI e agravamento do quadro.

**Palavras-chave:** SARS-CoV-2; COVID-19; Coronavírus; Gastroenteropatias.

## INTRODUCTION

The Coronavirus disease 2019 (COVID-19) is caused by the Severe Acute Respiratory Syndrome Coronavirus-2 virus (SARS-CoV-2). Considering its high rate of spread, the World Health Organization (WHO) declared the pandemic in March 2020. Since then, COVID-19 emerged as a global public health emergency, leading to numerous severe cases and a high mortality rate<sup>1</sup>.

COVID-19 presents several clinical conditions, ranging from asymptomatic and mild to severe. The most common signs and symptoms of COVID-19 occur in the respiratory system (e.g., dry cough, dyspnea, hyposmia, and pulmonary infiltrates) but also include general symptoms, such as fever, headache, and myalgia<sup>1</sup>. Moreover, patients infected with SARS-CoV-2 may experience symptoms and dysfunctions in the gastrointestinal tract (GIT), such as abdominal pain, diarrhea, nausea, and vomiting<sup>2</sup>. The involvement of the GIT during SARS-CoV-2 infection suggests an oral-fecal route of transmission since the virus can infect epithelial cells of the esophagus, stomach, duodenum, and rectum glands. Also, studies have indicated that feces from patients with COVID-19 are potentially infectious<sup>3-6</sup>.

Additional studies investigated the relationship between the SARS-CoV-2 infection and manifestations in the GIT. Some patients presented the symptoms previously mentioned, anorexia, and digestive bleeding. Also, those with severe COVID-19 were more likely to develop abdominal pain and changes in biomarkers of liver function, suggesting the involvement of the GIT and a worse prognosis<sup>6</sup>.

In this sense, studies investigating the impact of SARS-CoV-2 infection on the GIT are

essential for understanding the clinical condition and decision-making for effective therapeutic approaches. Thus, this integrative review aimed to identify the GIT role as a route of SARS-CoV-2 infection, prevalence of gastrointestinal manifestations related to the infection, and its impact on the health of adults and older people.

## METHODS

This integrative literature review (semi-systematic) was conducted between April 2022 and January 2023 with no meta-analysis.

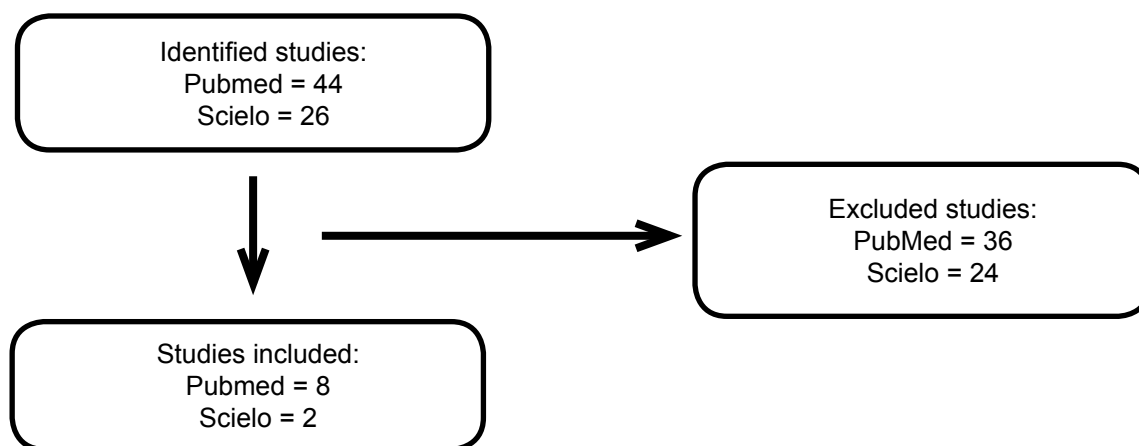
## RESEARCH QUESTION

What is the influence of SARS-CoV-2 infection on the GIT (including route of infection, manifestations, and impacts on the clinical course) of patients?

## SEARCH STRATEGY

The following descriptors (DeCS and MeSH) were used as search strategy in the PubMed and Scielo databases: “SARS-CoV-2”, “COVID-19”, “coronavirus”, “gastroenterology”, “gastrointestinal symptoms”, and their equivalents in Portuguese and Spanish. Inclusion criteria comprised free access to the full text, specific focus on gastrointestinal manifestations in patients with COVID-19, published between January 2020 and December 2022, and availability in Portuguese, English, or Spanish. Opinion articles, studies exclusively addressing pediatric cases, narrative reviews, dissertations, theses, preprints, and duplicates were excluded.

Seventy studies were identified after the automatic search and application of the inclusion and exclusion criteria (44 in PubMed and 26 in Scielo). Titles and abstracts were read, and 60 studies were excluded. Thus, ten studies (eight from PubMed and two from Scielo) were selected for full reading and considered in this review. Figure 1 shows the flowchart of studies selection.



**Figure 1.** Flowchart of studies selection

## RESULTS

The ten studies included were published in English, mostly ( $n = 7$ ) in 2020; only one study was published in 2021, and two in 2022. Most studies were conducted in China, followed by the United States of America. The average age of patients in the studies was 40 years; one included patients over 18 years, and one included children and adolescents over 10 years. Five studies were meta-analyses, four were cohort studies, and one was a multicenter cross-sectional study. Chart 1 presents characteristics of the included studies (i.e., title, author and year of publication, objective, and main findings and conclusion). Also, Chart 2 describes the sample of each study, highlighting the prevalence of manifestations in the GIT of patients with COVID-19, especially diarrhea, nausea, vomiting, abdominal pain, and anorexia.

**Chart 1.** Characteristics of the included studies

Title	Author (Year)	Objective	Conclusion
Gastrointestinal symptoms of 95 cases with SARS-CoV-2 infection	Lin et al. (2020)	To study the gastrointestinal symptoms in patients infected with SARS-CoV-2.	The GIT may be a route of infection and a target organ for SARS-CoV-2.
Clinical characteristics of COVID-19 patients with digestive symptoms in Hubei, China: a descriptive, cross-sectional, multicenter study	Lei et al. (2020)	To identify the prevalence and outcomes of digestive symptoms in patients with COVID-19.	Digestive abnormalities (e.g., diarrhea) were common in patients with COVID-19, especially in hospitalization.
COVID-19 and the gastrointestinal tract: what do we already know?	Almeida et al. (2020)	To review the relationship of the SARS-CoV-2 infection with gastrointestinal tract and liver diseases and possible oral-fecal transmission.	COVID-19 affected the GIT, resulting in specific symptoms, changes in blood tests, and viral RNA in feces.
COVID-19 gastrointestinal manifestations: a systematic review	Silva et al. (2020)	To analyze the prevalence of gastrointestinal symptoms, increase in serum levels of biomarkers of liver function, and associated factors in patients infected with SARS-CoV-2.	Gastrointestinal symptoms were observed during SARS-CoV-2 infection (i.e., diarrhea, nausea, vomiting, and abdominal pain), and most patients were categorized as severely ill. Thus, gastrointestinal symptoms were common in patients with COVID-19, and a possible hepatic involvement was observed.
COVID-19 and its effects on the digestive system and endoscopy practice	Aguila et al. (2020)	To describe the effects of the SARS-CoV-2 virus on the GIT.	Gastrointestinal symptoms varied and usually preceded pulmonary symptoms. The most common GIT symptoms were anorexia, nausea, vomiting, diarrhea, and abdominal pain.

Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study	Chen et al. (2020)	To elucidate the epidemiological and clinical characteristics of COVID-19 associated with pneumonia, including systemic symptoms, such as myalgia, headache, confusion, chest pain, and gastrointestinal symptoms (e.g., diarrhea, nausea, and vomiting).	Older patients with other risk factors presented an increased risk for COVID-19 associated with pneumonia. Also, 11% of patients showed gastrointestinal symptoms.
Prevalence and characteristics of gastrointestinal symptoms in patients with severe acute respiratory syndrome coronavirus 2 infection in the United States: a multicenter cohort study	Redd et al. (2020)	To characterize the prevalence and features of gastrointestinal manifestations associated with SARS-CoV-2 infection and evaluate gastrointestinal-specific health outcomes in a cohort study	Two thirds of patients with COVID-19 reported at least 1 gastrointestinal symptom, with loss of appetite and diarrhea being the most common.
Gastrointestinal and hepatic abnormalities in patients with confirmed COVID-19: a systematic review and meta-analysis	Zarifian et al. (2021)	To identify the prevalence of gastrointestinal and hepatic manifestations in patients with COVID-19.	Gastrointestinal and hepatic manifestations were common in patients with COVID-19, and pre-existing conditions may affect their prevalence. Diarrhea and mild liver disorders were relatively common in individuals with COVID-19, regardless of comorbidities.
Gastrointestinal symptoms and fecal shedding of SARS-CoV-2 RNA suggest prolonged gastrointestinal infection	Natarajan et al. (2022)	To define the characteristics of SARS-CoV-2 infection in the GIT and its impact on human health in the short and long term.	Gastrointestinal symptoms were associated with fecal shedding of SARS-CoV-2 RNA. The persistence of viral RNA in feces for a long period compared with respiratory samples indicated a possible manifestation and relationship of viral infection with the GIT, leading to a potentially prolonged infection.
Are gastrointestinal symptoms associated with a higher risk of mortality in COVID-19 patients? A systematic review and meta-analysis	Wang et al. (2022)	To investigate the relationship between gastrointestinal symptoms and mortality from COVID-19.	Gastrointestinal symptoms were not associated with increased mortality from COVID-19. However, the prognostic value of these symptoms in COVID-19 still requires investigation.

SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus-2 virus; GIT: gastrointestinal tract; COVID-19: coronavirus disease.

**Chart 2.** TSample size and prevalence of gastrointestinal abnormalities in patients during SARS-CoV-2 infection

Author (Year)	Total Patients	Patients with Gastrointestinal Symptoms	Patients with Diarrhea	Patients with Nausea And Vomiting	Patients with Abdominal Pain	Patients with Anorexia
Lin et al. (2020)	95	58 (61.0%)	14 (24.2%)	10 (17.9%)	Not reported	10 (17.9%)
Lei et al. (2020)	204	103 (50.5%)	35 (34.0%)	4 (3.9%)	2 (1.9%)	81 (78.6%)
Almeida et al. (2020)	2,352	815 (34.0%)	399 (48.0%)	352 (41.0%)	76 (9.0%)	264 (32.0%)
Silva et al. (2020)	18,246	1,841 (30.5%)	2,115 (11.5%)	1.158 (6.3%)	424 (2.3%)	Not reported
Aguila et al. (2020)	4,243	747 (17.6%)	90 (12.0%)	77 (10.2%)	69 (92.0%)	200 (26.8%)
Chen et al. (2020)	99	58 (58.6%)	2 (2.0%)	1 (1.0%)	Not reported	Not reported
Redd et al. (2020)	318	195 (61.3%)	107 (33.7%)	Nausea: 84 (26.4%) Vomiting 49 (15.4)	46 (14.5%)	110 (34.8%)
Zarifian et al. (2021)	13,251	Não relatado	10,652 (80.3%)	Nausea: 5,089 (38.4%) Vomiting: 4,567 (34.5%)	2342 (17.6%)	3871 (29.2%)
Natarajan et al. (2022)	113	54 (49.0%)	29 (26.0%)	36 (31.85%)	13 (12.0%)	Not reported
Wang et al. (2022)	55,245	8,535 (15.5%)	1,341 (12.2%) (considering 10,983 patients)	525 (7.3%) (considering 7,175 patients)	92 (1.8%) (considering 5,012 patients)	Not reported

## DISCUSSION

This review had an integrative and comprehensive approach to analyze the relationship between SARS-CoV-2 infection and GIT, identifying the main signs and symptoms in the GIT related to the infection. Thus, this study contributed to the understanding of clinical manifestations of COVID-19, providing information for its early identification in patients, updating the scientific knowledge, and improving the healthcare related to COVID-19.

After fully reading the selected studies, they were categorized into three distinct dimen-

sions: GIT as a route of transmission for SARS-CoV-2 (i.e., presence and persistence of viral RNA in feces indicated the GIT as a potential route for viral transmission); main gastrointestinal manifestations and abnormalities related to the SARS-CoV-2 infection (i.e., diarrhea, nausea, vomiting, abdominal pain, and anorexia related to the viral infection); and impact of manifestations in the GIT on the evolution and outcomes of patients with COVID-19 (i.e., clinical impact of gastrointestinal abnormalities on disease evolution, including possible complications, worsening of the clinical condition, and adverse outcomes). These dimensions allowed a comprehensive and structured understanding of the available information, provided insights into the GIT role in SARS-CoV-2 infection, and its possible influence on the clinical outcomes of patients with COVID-19.

### **GIT as a route of transmission for SARS-CoV-2**

Some studies have addressed the involvement of the GIT in patients with COVID-19 and suggested a fecal-oral route of infection since the SARS-CoV-2 may infect epithelial cells of the GIT, increasing its potential for dissemination and contamination within the body<sup>3,4</sup>. Also, the virus may damage these cells when infecting the GIT, resulting in gastrointestinal inflammation and dysfunction<sup>3,4</sup>. Thus, these findings suggested that SARS-CoV-2 transmission is not restricted to the respiratory tract but may also occur through infected feces.

Lin et al.<sup>5</sup>, Almeida et al.<sup>9</sup>, and Natarajan et al.<sup>15</sup> corroborated the hypothesis of a fecal-oral route of transmission of SARS-CoV-2. These studies identified the presence of viral RNA in the feces of patients with COVID-19, reinforcing the GIT as a potential route of transmission. Also, they described that the viral RNA in feces may persist longer than in samples from the respiratory tract. Thus, considering the prolonged manifestations and viral shedding in feces even after the resolution of respiratory symptoms, SARS-CoV-2 infection may impact the GIT. These findings reinforced the need to consider the GIT as a potential source and route of transmission for SARS-CoV-2 and appropriate hygiene measures to prevent viral spread, such as washing hands and correctly disposing of fecal waste<sup>17</sup>.

Although the fecal-oral route was not considered the main route of infection for SARS-CoV-2, this possibility should be analyzed. However, detecting viral RNA in feces may not indicate effective virus transmission, and no robust epidemiological evidence was found to support this hypothesis. Also, possible biases in the studies should be considered<sup>18</sup>. Studies included in this review were conducted before the occurrence of new SARS-CoV-2 variants (e.g., Delta and Omicron), which are currently prevalent in many regions. Thus, these variants might present distinct characteristics, such as different tropisms and rates of viral elimination in the GIT<sup>5,9,15</sup>, and further studies are needed to understand their impact on the GIT.

### **Main gastrointestinal manifestations and abnormalities related to the SARS-CoV-2 infection**

The prevalence of gastrointestinal symptoms in patients infected with SARS-CoV-2 varied



considerably among the studies included in this review, ranging between 15.5% and 61.3% (Chart 2). This variation may be attributed to several factors, mainly due to the nature of COVID-19 evolution in each patient but also the study design, methodology, and population characteristics.

All studies in this review addressed the prevalence of symptoms in GIT (e.g., diarrhea, nausea, and vomiting) of patients infected with COVID-19. However, the approach of the studies varied on other symptoms; 30% and 40% did not report the prevalence of abdominal pain and anorexia related to COVID-19, respectively. The absence of these data may be attributed to several reasons, such as differences in study designs, emphasis on other predominant symptoms, and limitations in data availability. Although this absence may be a limitation in the studies, their findings showed a high prevalence of manifestations in the GIT related to the SARS-CoV-2 infection.

The presence of symptoms in the GIT of patients with COVID-19 affected their quality of life and recovery. For example, diarrhea and vomiting may lead to further complications, such as dehydration and nutritional dysfunctions<sup>19</sup>, and abnormalities in the GIT may indicate a more serious clinical condition<sup>20</sup>. Thus, the findings highlighted the importance of a systemic and global evaluation of patients with COVID-19, considering its negative impact on the GIT.

### **Impact of manifestations in the GIT on the evolution and outcomes of patients with COVID-19**

Silva et al.<sup>10</sup> and Zarifian et al.<sup>14</sup> identified that patients with manifestations in the GIT during SARS-CoV-2 infection also presented changes in biomarkers of liver injury and function. Although no causal relationship has been established between the manifestations in GIT and liver damage, studies suggested that these biomarkers indicate damage by viral infection<sup>10,14</sup>. Thus, the relationship of SARS-CoV-2 infection with manifestations in the GIT and changes in liver function still needs to be investigated.

Wang et al.<sup>16</sup> showed that gastrointestinal symptoms during COVID-19 were not associated with an increased mortality rate. However, they emphasized that the prognostic value of the manifestations in the GIT should be investigated in further studies. Although some limitations (e.g., selection bias) should be considered when elucidating the results, this was a preliminary study, highlighting the need for further prospective observational studies to understand the role of gastrointestinal symptoms during the COVID-19 evolution. Thus, this study contributed to the understanding of the topic, but future studies need to confirm and expand these findings<sup>1</sup>.

### **Limitations and strengths**

Despite the biases from an integrative review, strengths can be observed, such as the relevant databases for search to establish a solid foundation for the analysis. Also, this review followed a rigorous methodological process, defining and following inclusion and exclusion criteria to ensure the reliability of the findings. Moreover, it addressed an emerging and relevant topic,



adding valuable perspectives on the possible relationship between SARS-CoV-2 infection and manifestations in the GIT.

## CONCLUSION

The results of this review emphasized the influence of SARS-CoV-2 infection on manifestations in the GIT, such as diarrhea, nausea, vomiting, abdominal pain, and anorexia. Also, the presence of viral RNA in the feces of infected patients indicated the potential for a fecal-oral route of infection. However, some gaps still need to be addressed, and further studies should expand the understanding of the GIT role in the transmission and pathogenesis of SARS-CoV-2. Thus, future studies will allow to identify the manifestations in the GIT related to the SARS-CoV-2 infection, adequate management of symptoms, and develop therapeutic interventions for general support of the patient. In addition, the possible oral-fecal route of infection highlighted the importance of adopting adequate hygiene and sanitation measures to prevent viral spread and the need for further prevention strategies.

## CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

## AUTHOR CONTRIBUTIONS

**JIA:** conceptualization, data curation, supervision, validation, review, writing of the original draft, and review. **LDPSP:** data curation, validation, review, and writing of the original draft. **PHLL:** data curation, validation, review, and writing of the original draft. **FMM:** conceptualization, data curation, validation, review, methodology, management, supervision, writing of the original draft, and review. All authors approved the final version.

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