PUBLICAÇÃO OFICIAL DO NÚCLEO HOSPITALAR DE EPIDEMIOLOGIA DO HOSPITAL SANTA CRUZ E PROGRAMA DE PÓS GRADUAÇÃO EM PROMOÇÃO DA SAÚDE - DEPARTAMENTO DE BIOLOGIA E FARMÁCIA DA UNISC

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Original Article

Gastrointestinal manifestations in Covid-19 infected patients admitted to the intensive care unit

Manifestações gastrointestinais em pacientes infectados por Covid-19 internados em unidade de terapia intensiva
Manifestaciones gastrointestinales en pacientes infectados con Covid-19 ingresados en la unidad de cuidados intensivos

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ABSTRACT

Background and Objectives: Covid-19 can affect more than just the respiratory system, potentially leading to gastrointestinal dysfunction, including impaired intestinal motility and nutrient absorption, particularly in critically ill patients. The objective of this study was to estimate the prevalence of gastrointestinal (GI) manifestations and investigate their association with clinical outcomes among patients with Covid-19 hospitalized in the Intensive Care Unit (ICU) of a university hospital in the interior of Rio Grande do Sul, Brazil. **Methods:** This retrospective cohort study included 395 medical records of patients admitted to the ICU of a hospital in Santa Cruz do Sul, Brazil, between March 1, 2020, and June 30, 2021. Patients were identified using ICD-10 codes related to Covid-19. The presence of at least one documented gastrointestinal manifestation during the ICU stay was considered the primary exposure. The manifestations evaluated were diarrhea, nausea, vomiting, abdominal pain, abdominal distension, and constipation. Enteral nutrition was analyzed separately and was not considered a gastrointestinal manifestation. **Results:** Among the gastrointestinal manifestations evaluated, constipation was the most frequent (41.8%), followed by diarrhea (12.4%), abdominal distension (10.9%), abdominal pain (9.6%), nausea (5.3%), and vomiting (4.8%). The presence of gastrointestinal manifestations was not significantly associated with mortality or mechanical ventilation. However, it was associated with greater use of antibiotic therapy (OR 1.596; 95% CI 1.063–2.397; p = 0.024). Diarrhea was inversely associated with mortality and mechanical ventilation, while nausea was inversely associated with mortality. **Conclusion:** Gastrointestinal manifestations were frequent in patients with Covid-19 admitted to the ICU, and constipation was the most common manifestation. Although the overall presence of gastrointestinal manifestations was not significantly associated with mortality or mechanical ventilation, some individual manifestations showed associations with clinical outcomes. Despite its limitations, this study suggests that recognizing gastrointestinal manifestations early may help clinicians identify and manage them in critically ill patients.

Keywords: *Gastrointestinal diseases. Critical illness. Covid-19. Intensive care units. Enteral nutrition.*

RESUMO

Justificativa e Objetivos: A Covid-19 pode afetar além do sistema respiratório, levando a distúrbios de ingestão e motilidade intestinal/má absorção, especialmente em pacientes críticos. O objetivo deste estudo foi estimar a prevalência de manifestações gastrointestinais (GI) e investigar sua associação com desfechos clínicos em pacientes com Covid-19 hospitalizados na Unidade de Terapia Intensiva (UTI) de um hospital universitário no interior do Rio Grande do Sul, Brasil. **Métodos:** Estudo de coorte retrospectivo incluindo 395 prontuários médicos de pacientes internados em UTI, identificados por meio de códigos da CID-10 relacionados à Covid-19 e admitidos em um hospital de Santa Cruz do Sul, de 1º de março de 2020 a 30 de junho de 2021. A presença de pelo menos uma manifestação gastrointestinal documentada durante a hospitalização na UTI foi considerada a exposição principal. As manifestações avaliadas foram diarreia, náusea, vômitos, dor abdominal, distensão abdominal e constipação. A nutrição enteral foi analisada separadamente e não foi considerada uma manifestação gastrointestinal. **Resultados:** Entre as manifestações gastrointestinais avaliadas, a constipação foi a mais frequente (41,8%), seguida por diarreia (12,4%), distensão abdominal (10,9%), dor abdominal (9,6%), náusea (5,3%) e vômitos (4,8%). A presença de manifestações gastrointestinais não esteve significativamente associada à mortalidade ou à ventilação mecânica. Entretanto, esteve associada a maior uso de antibioticoterapia (OR 1,596; IC 1,063–2,397; p = 0,024). A diarreia apresentou associação inversa com mortalidade e ventilação mecânica, enquanto náusea apresentou associação inversa com mortalidade. **Conclusão:** Manifestações gastrointestinais foram frequentes em pacientes com Covid-19 internados na UTI, sendo a constipação a manifestação mais comum. Embora a presença geral de manifestações gastrointestinais não tenha apresentado associação significativa com a mortalidade ou a ventilação mecânica, algumas manifestações isoladas mostraram associação com desfechos clínicos. Apesar das limitações do estudo, esses achados podem contribuir para o reconhecimento precoce e o manejo de manifestações gastrointestinais em pacientes em estado crítico.

Descritores: *Doenças gastrointestinais. Doenças críticas. Covid-19. Unidades de terapia intensiva. Nutrição enteral.*

RESUMEN

Justificación y Objetivos: La Covid-19 puede afectar más allá del sistema respiratorio, y provocar trastornos de la ingesta, de la motilidad intestinal y de la absorción, especialmente en pacientes críticos. El objetivo de este estudio fue estimar la prevalencia de manifestaciones gastrointestinales (GI) e investigar su asociación con desenlaces clínicos en pacientes con Covid-19 hospitalizados en la Unidad de Cuidados Intensivos (UCI) de un hospital universitario del interior de Rio Grande do Sul, Brasil. **Métodos:** Estudio de cohorte retrospectivo que incluyó 395 historias clínicas de pacientes con Covid-19 ingresados en la UCI de un hospital universitario de Santa Cruz do Sul entre el 1 de marzo de 2020 y el 30 de junio de 2021, identificados mediante códigos de la CIE-10. La presencia de al menos una manifestación gastrointestinal documentada durante la hospitalización en la UCI se consideró la exposición principal. Las manifestaciones evaluadas fueron diarrea, náuseas, vómitos, dolor abdominal, distensión abdominal y estreñimiento. La nutrición enteral se analizó por separado y no se consideró una manifestación gastrointestinal. **Resultados:** Entre las manifestaciones gastrointestinales evaluadas, el estreñimiento fue el más frecuente (41,8%), seguido de diarrea (12,4%), distensión abdominal (10,9%), dolor abdominal (9,6%), náuseas (5,3%) y vómitos (4,8%). La presencia de manifestaciones gastrointestinales no se asoció significativamente con la mortalidad ni con la ventilación mecánica. Sin embargo, se asoció con un mayor uso de antibioticoterapia (OR 1,596; IC del 95%: 1,063–2,397; p = 0,024). La diarrea presentó una asociación inversa con la mortalidad y la ventilación mecánica, mientras que las náuseas presentaron una asociación inversa con la mortalidad. **Conclusión:** Las manifestaciones gastrointestinales fueron frecuentes en los pacientes con Covid-19 ingresados en la UCI, y el estreñimiento fue la más común. Aunque la presencia general de manifestaciones gastrointestinales no se asoció de manera significativa con la mortalidad ni con la ventilación mecánica, algunas manifestaciones individuales mostraron asociaciones con los resultados clínicos. A pesar de las limitaciones del estudio, estos hallazgos pueden contribuir al reconocimiento y manejo tempranos de las manifestaciones gastrointestinales en pacientes en estado crítico.

Palabras Clave: *Enfermedades gastrointestinales. Enfermedades críticas. Covid-19. Unidades de cuidados intensivos. Nutrición enteral.*

INTRODUCTION

SARS-CoV-2 infection, which caused the Covid-19pandemic, is primarily characterized by respiratory symptoms and fever.[1] However, critically ill patients may also experience gastrointestinal manifestations.[1,2]

The severity of gastrointestinal symptoms can range from mild to severe, depending on the underlying disease process. The main manifestations include diarrhea, weight loss, flatulence, bloating, and abdominal pain.[4]

During the Covid-19 pandemic, intensive care units (ICUs) became overcrowded, with many patients requiring advanced nutrition. It is notable that intensive care patients often experience a hypermetabolic state, which is a critical phase for the preservation of organ function, and require early nutritional therapy. Furthermore, critical illness may be associated with alterations in intestinal barrier integrity, which may facilitate bacterial translocation and contribute to complications, particularly in highly contaminated environments such as ICUs.

Although gastrointestinal manifestations in patients with Covid-19 have been increasingly recognized, there is still heterogeneity in the literature regarding the frequency and clinical characterization of gastrointestinal manifestations, especially among critically ill patients. Furthermore, studies evaluating the impact of gastrointestinal manifestations on clinical outcomes among patients admitted to intensive care units remain limited, particularly in the Brazilian context. [1,3,5] The objective of this study was to estimate the prevalence of gastrointestinal (GI) manifestations and investigate their association with clinical outcomes among patients with Covid-19 admitted to the intensive care unit (ICU) of a university hospital in the interior of Rio Grande do Sul.

METHODS

This retrospective observational cohort study was conducted from March 1, 2020, to June 30, 2021, in the ICU of Hospital Santa Cruz, located in Santa Cruz do Sul, Rio Grande do Sul, Brazil. The study population consisted of patients with a documented diagnosis of Covid-19 who were admitted to the ICU during the study period and whose gastrointestinal manifestations and other predefined clinical variables were evaluated. All patients admitted to the ICU during the study period and identified using International Classification of Diseases, 10th Revision (ICD-10), codes related to Covid-19 were initially screened for eligibility. Of these, 19 patients were transferred to another institution, and 4 had medical records with incomplete predefined data required for the analysis and were therefore excluded. The final study population comprised 395 eligible patients. The ICD-10 codes were selected based on guidance from the attending physicians in the institution's ICU. Subsequently, all medical records identified through these codes were reviewed to confirm the presence of a documented diagnosis of Covid-19. The study did not collect specific information regarding the laboratory method used to establish the diagnosis of Covid-19, such as reverse transcription polymerase chain reaction (RT-PCR) or antigen testing. Therefore, the type of diagnostic test used for confirmation of Covid-19 was not available for analysis.

Data were retrospectively obtained from medical records provided by the institution, with access to and use of the data duly authorized for research purposes. Data collection was conducted from September 28, 2022, to March 2, 2023. The gastrointestinal manifestations assessed included diarrhea, nausea, vomiting, abdominal pain, abdominal distension, and constipation. The primary exposure was defined as the presence of at least one documented gastrointestinal manifestation during ICU hospitalization. Data on age, sex, comorbidities, medication use, antibiotic use and classes, mechanical ventilation, enteral nutrition, and in-hospital mortality were also collected. The outcomes assessed included the need for mechanical ventilation and in-hospital mortality. The use of enteral nutrition was collected and analyzed separately as a clinical variable and was not considered a gastrointestinal manifestation. Information regarding enteral nutrition intolerance was not systematically collected and, therefore, could not be analyzed.

For analytical purposes, patients were classified according to whether they had at least one documented gastrointestinal manifestation during their ICU stay. Gastrointestinal manifestations were identified based on documentation in the medical records by the attending clinical team. No standardized symptom-specific diagnostic criteria were applied retrospectively. Enteral nutrition was analyzed separately from gastrointestinal manifestations.

Data were analyzed using JASP software. Categorical variables were compared using the chi-square test, and odds ratios (ORs) with 95% confidence intervals (CIs) were calculated from contingency tables. A partial Pearson correlation analysis was performed to assess the association between proton pump inhibitor (PPI) use and gastrointestinal manifestations, controlling for heart disease and alcohol use.

This study was conducted in accordance with the ethical standards established by Resolutions No. 466/2012, No. 510/2016, and No. 580/2018 of the National Health Council of Brazil. The research project was approved by the Research Ethics Committee (Opinion No. 5,707,499) under the Certificate of

Presentation for Ethical Consideration (CAAE) No. 58112622.2.0000.5343 on October 18, 2022.

RESULTS

A total of 418 patients were initially selected. Of these, 19 were transferred and 4 were excluded due to incomplete data, resulting in a final sample of 395 patients. Among the included patients, 181 (45.8%) died in the hospital, while 214 (54.2%) were discharged.

Regarding the baseline characteristics, the mean age was 59.6 ± 14.3 years among patients with gastrointestinal manifestations and 56.4 ± 14.2 years among those without these manifestations (p = 0.725). The proportion of male patients was 58.0% among those with gastrointestinal manifestations and 49.1% among those without gastrointestinal manifestations (p = 0.079). No statistically significant differences were observed between the groups with respect to obesity, diabetes mellitus, hypertension, pulmonary disease, kidney disease, psychiatric disorders, or smoking status. However, cardiopathy was less frequent among patients with gastrointestinal manifestations than among those without gastrointestinal manifestations (15.5% vs. 27.8%; OR = 0.477, 95% CI: 0.292–0.781; p = 0.003), whereas alcohol use was more frequent in the former group (30.1% vs. 19.6%; OR = 1.766, 95% CI: 1.106–2.819; p = 0.022). (Table 1).

Table 1. Clinical and demographic characteristics of patients with Covid-19 admitted to the intensive care unit of Hospital Santa Cruz, Santa Cruz do Sul, Brazil, 2020–2021.

Variable	GIM present *N (%)*	GIM absent *N (%)*	*OR*	*IC*	*P*
Age (years) (SD)	59,6 (14.3)	56,4 (14.2)			0.725
Sex (male)	123 (58.0)	90 (49.1)	1.428	0.959-2.126	0.079
Diabetes-mellitus	58 (27.3)	48 (26.2)	1.059	0.678-1.656	0.436
Chronic lung disease	33 (15.5)	42 (22.9)	0.619	0.373-1.027	0.062
Obesity	81 (38.2)	63 (34.4)	1.178	0.78-1.778	0.436
Systemic arterial hypertension	115 (54.2)	105 (57.3)	0.881	0.591-1.312	0.532
Heart disease	33 (15.5)	51 (27.8)	0.477	0.292-0.781	0.003
Kidney disease	15 (7.0)	22 (12.0)	0.557	0.28-1.109	0.092
Psychiatric illness	45 (21.2)	30 (16.3)	1.374	0.824-2.292	0.222
Smoking	39 (18.3)	29 (15.8)	1.197	0.706-2.028	0.503
Alcoholism	64 (30.1)	36 (19.6)	1.766	1.106-2.819	0.022

Abbreviation: GIM = gastrointestinal manifestations.

Regarding clinical outcomes and interventions, no statistically significant differences were observed between the groups in terms of mortality, enteral nutrition use, or mechanical ventilation. However, fever and antibiotic use were more frequent among patients with gastrointestinal manifestations than among those without gastrointestinal manifestations (55.1% vs. 38.7%; OR = 1.943, 95% CI: 1.300–2.904; p = 0.001; and 65.5% vs. 54.3%; OR = 1.596, 95% CI: 1.063–2.397; p = 0.024, respectively). Proton pump inhibitor use before ICU admission was also more frequent among patients with gastrointestinal manifestations than among those without gastrointestinal manifestations (30.1% vs. 19.6%; OR = 1.766, 95% CI: 1.106–2.819; p = 0.017).

Among the gastrointestinal manifestations evaluated, constipation was the most frequent, occurring in 165 patients (41.8%), followed by diarrhea in 49 patients (12.4%), abdominal distension in 43 (10.9%), abdominal pain in 38 (9.6%), nausea in 21 (5.3%), and vomiting in 19 (4.8%) (Table 2).

Table 2. Clinical complications associated with gastrointestinal dysfunction in patients with Covid-19 admitted to the intensive care unit of Hospital Santa Cruz, Santa Cruz do Sul, Brazil, 2020–2021.

Variable	GIM present* *OR (CI)*	*P*
Antibiotic use	1,596 (1,063 - 2,397)	0,024
Need for mechanical ventilation	0,947 (0,615-1,457)	0,803
Enteral nutrition	1,451 (0,973-2,165)	0,068
Death	0,81 (0,544-1,205)	0,298

Abbreviation: OR = odds ratio; CI = confidence interval; GIM: gastrointestinal manifestations.

Regarding clinical outcomes, diarrhea was inversely associated with mechanical ventilation (OR 0.482, 95% CI 0.266–0.876; p = 0.015) and mortality (OR 0.532, 95% CI 0.282–1.002; p = 0.030). Nausea was also inversely associated with mechanical ventilation (OR 0.415, 95% CI 0.175–0.985; p = 0.045) and in-hospital mortality (OR 0.184, 95% CI 0.053–0.634; p = 0.004). No statistically significant associations were observed between vomiting, abdominal pain, abdominal distension, or constipation and either mortality or the need for mechanical ventilation.

Regarding enteral nutrition, diarrhea (OR 0.498, 95% CI 0.262–0.947) and nausea (OR 0.198, 95% CI 0.055–0.658) were inversely associated with its use. No statistically significant associations were observed between vomiting, abdominal pain, abdominal distension, or constipation and enteral nutrition. Abdominal distension was positively associated with

antibiotic use (OR 2.575, 95% CI 1.238–5.358; p = 0.010), as was constipation (OR 1.676, 95% CI 1.041–2.392; p = 0.015). No statistically significant associations were observed between antibiotic use and diarrhea, nausea, vomiting, or abdominal pain. Enteral nutrition was strongly associated with antibiotic use (OR 8.161, 95% CI 5.045–13.201; p < 0.001) and mechanical ventilation (OR 10.213, 95% CI 5.674–18.383; p < 0.001) (Table 3).

Table 3. Association between gastrointestinal manifestations, enteral nutrition, and clinical outcomes in patients with Covid-19 admitted to the intensive care unit of Hospital Santa Cruz, Santa Cruz do Sul, Brazil, 2020–2021.

Variables	ATB use OR (CI)	MV OR (CI)	EN OR (CI)	Death OR (CI)
Diarrhea	1.152 (0.629-2.109)	0.482 (0.266-0.876) †	0.498 (0.262-0.947)	0.532 (0.282-1.002) ◊
Nausea	0.797 (0.336 -2.1889)	0.415 (0.175-0.985) ǁ	0.198 (0.055- 0.658)	0.184 (0.053-0.634) ○
Vomiting	2.805 (0.921-8.545)	0.804 (0.313-2.065)	0.886 (0.348-2.251)	0.853 (0.336-2.169)
Abdominal pain	0.857 (0.44-1.668)	0.76 (0.381-1.157)	0.608 (0.302-1.227)	0.585 (0.29-1.18)
Abdominal distension	2.575 (1.238-5.358)¶	1.817 (0.866-3.962)	1.623(0.863-3.088)	1.569 (0.829-2.968)
Constipation	1.676 (1,041-2.392)†	1.282 (0.835-1.967)	0.839 (0.561 -1.255)	0.859 (0.575 – 1.286)
EN	8.161 (5.045 - 13.201)‡	10.213 (5.674 - 18.383)‡	NA	NA

Abbreviation: ATB = antibiotic; MV = mechanical ventilation; EN = enteral nutrition; OR = odds ratio; CI = confidence interval; ¶ = p 0,01; † = p 0,015; ‡ = p <0,001; ǁ = p 0,045; = p 0,009; ◊ = p 0,03; ○ = p 0,004. NA = not applicable.

Finally, a partial correlation analysis was performed to assess the relationship between proton pump inhibitor use and gastrointestinal manifestations while controlling for cardiopathy and alcohol use. A statistically significant positive correlation was observed (partial Pearson's r = 0.115; p = 0.023) (Table 4).

Table 4. Association between Proton Pump Inhibitor (PPI) use and gastrointestinal manifestations.

Variables		PPI	GIM
PPI	Pearson`s r	-	
	p-value	-	
GIM	Pearson`s r	0.115	-
	p-value	0.023	-

Abbreviation: PPI = proton pump inhibitor; GIM = gastrointestinal manifestations. Enteral nutrition was analyzed separately and was not considered a gastrointestinal manifestation.

DISCUSSION

The intestinal mucosa can be affected by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which can be associated with gastrointestinal symptoms and impaired nutrient absorption.[6] Studies on the prevalence of gastrointestinal manifestations in patients with Covid-19 remain limited, which is surprising, given that the gastrointestinal tract is responsible for the mechanical and chemical breakdown of food for absorption by the body, and has abundant angiotensin-converting enzyme II (ACE2) receptors, used by SARS-CoV-2 for cell binding and replication.[6,7,9]

One study reported that the first patient with Covid-19 in the United States experienced nausea, vomiting, cough, diarrhea, and abdominal pain during their hospitalization, reinforcing the data presented in the literature on the incidence of gastrointestinal manifestations in patients with this respiratory pathology.[10]

Laboratory analyses have shown that SARS-CoV-2 RNA has been detected in blood samples, raising questions about the possibility of fecal-oral transmission and gastrointestinal viral infection, which may persist even after clearance of the virus from the respiratory tract.[9,12]

It has also been observed that SARS-CoV-2 RNA can be detected in feces for an extended period, even after patients become asymptomatic and test negative for the virus in respiratory samples.[12,13] It has also been suggested that the gastrointestinal tract may be susceptible to SARS-CoV-2 infection due to the expression of ACE2 receptors in epithelial cells of the stomach, duodenum, rectum, and, to a lesser extent, in those of the esophagus. In addition to these manifestations, liver involvement has also been described as a possible consequence of Covid-19 infection, characterized by elevated transaminases, hypoproteinemia, and prolonged prothrombin time.[8]

In the present study, gastrointestinal manifestations were frequent among patients admitted to the intensive care unit. Among the 395 patients included in the final analysis, constipation was the most frequently reported manifestation (41.8%), followed by diarrhea (12.4%), abdominal distension (10.9%), abdominal pain (9.6%), nausea (5.3%), and vomiting (4.8%). The predominance of constipation is particularly relevant in critically ill patients, in whom immobility, opioid use, reduced oral intake, electrolyte disturbances, and prolonged hospitalization may contribute to altered bowel function.

In contrast to our findings, research in the medical literature has shown that, overall, the most common gastrointestinal manifestations in these patients were

diarrhea, nausea, vomiting, and abdominal discomfort.[11] Diarrhea appears to be one of the most frequently reported gastrointestinal manifestations in studies involving both adult and pediatric populations.[6,11] Differences in the frequency of individual manifestations may be related to differences in patient populations, disease severity, timing of assessment, and the criteria used to identify gastrointestinal manifestations.

In the present analysis, the overall presence of gastrointestinal manifestations was not significantly associated with mortality or mechanical ventilation. However, specific gastrointestinal manifestations showed distinct associations with clinical outcomes. Diarrhea and nausea were inversely associated with both mortality and the need for mechanical ventilation. These findings should be interpreted with caution, as the observational study design does not permit causal inferences. In critically ill patients, the presence or absence of individual gastrointestinal manifestations may be influenced by disease severity, treatments received, nutritional status, medications, and the timing of documentation. Therefore, the observed inverse associations should not be interpreted as evidence of a protective effect of diarrhea or nausea.

Several gastrointestinal manifestations were also associated with other clinical variables. Diarrhea and nausea were inversely associated with enteral nutrition, whereas vomiting, abdominal pain, abdominal distension, and constipation were not significantly associated with enteral nutrition. Abdominal distension and constipation were positively associated with antibiotic use. Enteral nutrition was also strongly associated with both antibiotic use and mechanical ventilation. These findings may reflect the complex interaction between gastrointestinal manifestations and the clinical course of critically ill patients. In particular, enteral nutrition and antibiotic therapy may be markers of disease severity and therapeutic management rather than direct consequences of gastrointestinal manifestations. Therefore, these associations should not be interpreted as evidence of a causal relationship.

The association between gastrointestinal manifestations and antibiotic use is also clinically relevant. In the present study, abdominal distension and constipation were positively associated with antibiotic use. Antibiotics are frequently prescribed to critically ill patients with Covid-19 because of suspected or confirmed bacterial coinfection or secondary infection. At the same time, antimicrobial exposure can alter the intestinal microbiota and potentially contribute to gastrointestinal symptoms. Thus, the direction of this association cannot be established from the present retrospective analysis.

In our analysis, the use of proton pump inhibitors (PPIs) was associated with gastrointestinal manifestations. A statistically significant positive partial correlation was observed between PPI use and gastrointestinal manifestations (partial Pearson's $r = 0.115$; $p = 0.023$).

A retrospective study investigated the association between proton pump inhibitor (PPI) use and clinical outcomes in patients with Covid-19 and found that the exclusive use of intravenous PPIs during hospitalization was associated with a poorer prognosis.[14] The suppression of gastric acidity caused by PPIs may weaken an important physiological barrier against ingested pathogens and may contribute to alterations in the gastrointestinal microbiome.[17] In a review study, PPI use has been associated with alterations in the gastrointestinal microbiome and an increased risk of enteric infections, including *Clostridium difficile* infection.[17]

Finally, our analysis revealed a substantial mortality rate of 45.8% among patients hospitalized in the ICU with Covid-19. In comparison, an observational study involving 215 patients who remained in the ICU for more than 24 hours reported higher in-hospital and 1-year mortality rates among patients with gastrointestinal manifestations.[15] A systematic review and meta-analysis involving 12,797 patients concluded that mortality among patients with Covid-19 and gastrointestinal symptoms was similar to overall mortality, although most studies presented a risk of bias and low-quality evidence.[16]

It should be taken into account that the present study has a number of limitations. In addition to being conducted at a single institution, the data analyzed was from patients who were already hospitalized in the ICU, making it impossible to assess whether the gastrointestinal manifestations were the origin of the patient's clinical deterioration or merely a consequence of treatment and/or complications.

Although these findings are relevant, it is important to consider some limitations. The retrospective design and reliance on medical records may have led to underreporting and heterogeneity in the documentation of gastrointestinal manifestations. As this is a retrospective observational cohort study, it only points to associations rather than cause-and-effect relationships between gastrointestinal manifestations, medication use, and clinical outcomes. It is also important to emphasize that the lack of systematic documentation of RT-PCR results may have introduced misclassification bias in the diagnosis of Covid-19.

As critically ill patients are frequently sedated, mechanically ventilated, and receiving enteral nutrition, some gastrointestinal manifestations may reflect disease severity and therapeutic interventions rather than gastrointestinal involvement itself. Moreover, since the patients were already admitted to the intensive care unit, it was not possible to determine whether the

gastrointestinal manifestations preceded clinical deterioration or were a consequence of treatment and associated complications.

Gastrointestinal manifestations were frequent among hospitalized Covid-19 patients in intensive care units, with constipation being the most commonly reported manifestation. Although the overall presence of gastrointestinal manifestations was not significantly associated with mortality or mechanical ventilation, specific manifestations showed associations with clinical outcomes and therapeutic interventions. Abdominal distension and constipation were associated with antibiotic use, while diarrhea and nausea were inversely associated with enteral nutrition. These findings highlight the multifactorial nature of gastrointestinal manifestations in critically ill patients and reinforce the importance of their recognition and clinical assessment in this population.

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AUTHORS' CONTRIBUTIONS

Caroline Wallau Fontana contributed to the bibliographic research, writing the abstract, introduction, methodology, discussion, interpretation and description of results, preparation of tables, conclusions, review and statistics. **Ingrid Pilz** contributed to the bibliographic research, writing the abstract, introduction, methodology, discussion, interpretation and description of results, preparation of tables, conclusions, review and statistics. **Victória Ribeiro** contributed to the writing of the abstract, methodology, interpretation of results, conclusions, review and statistics. **Jordana Vargas Peruzzo** contributed to the writing of the abstract, methodology, interpretation of results, conclusions, review and statistics. **Eduardo Marmitt Adams** contributed to the writing of the abstract, methodology, interpretation of results, conclusions, review and statistics. **Candice Franke Krumel** contributed to the bibliographic research, writing the abstract, introduction, methodology, discussion, interpretation and description of results, preparation of tables, conclusions, review and statistics.

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