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Original article

Morbidity and Mortality in COVID-19 Patients With and Without Gastrointestinal Symptoms

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Abstract

Objective: Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) causes a wide range of symptoms, including gastrointestinal manifestations such as nausea, vomiting, diarrhea, and abdominal pain. This study aimed to evaluate whether the presence or absence of these gastrointestinal symptoms could be associated with more severe disease progression, defined as death, the need for intensive care unit (ICU) management, mechanical ventilation, or bacterial coinfection. **Patients and Methods:** An analytical observational cohort study was conducted with confirmed COVID-19 patients with gastrointestinal symptoms and a comparison group without gastrointestinal symptoms. Patients included were over 18 years old, presented with symptoms suggestive of COVID-19, and had the diagnosis confirmed by a polymerase chain reaction test. **Results:** A total of 414 patients who met the selection criteria were analyzed, and it was found that mortality was influenced only by age, while mechanical ventilation and the need for ICU management were related to liver function profile. However, no difference in severity was found between patients with gastrointestinal symptoms and those without. **Conclusions:** Gastrointestinal symptoms alone do not represent a risk for the progression of SARS-CoV-2 disease, however, levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and direct bilirubin (DB) should be included in the initial assessment of these patients, as they provide prognostic value according to the results of our study.

Keywords

COVID-19, Clinical Symptoms, Intensive Care Unit, Mechanical Ventilation, Mortality, Bacterial Infections.

INTRODUCTION

The number of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) cases during the COVID-19 pandemic has exponentially increased, with over 260,522,651 confirmed cases worldwide and 5,187,665 reported deaths, according to the World Health Organization (WHO)[1,2]. This infection typically presents with a wide range of symptoms, from asymptomatic individuals to severe cases that primarily affect the respiratory system, as well as other systems such as the gastrointestinal system[3]. Gastrointestinal symptoms include diarrhea (3%–34%), nausea (1%–17%), vomiting (1%–4%), abdominal pain (2%–5%), gastrointestinal bleeding (0%–13%), and even liver failure[4-6].

Several studies propose a link between the presence of angiotensin-converting enzyme 2 (ACE-2) receptors and gastrointestinal symptoms, as these receptors are present throughout the gastrointestinal epithelium and serve as an

entry point for SARS-CoV-2. This receptor also influences the expression of neutral amino acid transporters in the intestine, altering the composition of the microbiota and leading to inflammation of the mucosa[7,8]. While this receptor is highly expressed in type II alveolar cells in the lungs, which explains the primary clinical manifestations, it is also found in high concentrations in the gastrointestinal tract (keratinocytes of the esophagus, epithelial cells of the stomach, intestinal cells, and colonocytes). Recent studies have shown that SARS-CoV-2 can directly bind to cholangiocytes via this receptor, causing liver damage, which explains its role in liver function test abnormalities during infection[9,10].

Some studies suggest that patients with gastrointestinal symptoms may experience worse clinical outcomes, with evidence that COVID-19 patients with gastrointestinal symptoms are up to seven times more likely to progress to acute respiratory distress syndrome and liver failure. Additionally, up to 50% of those who seek medical care may present with elevated liver enzymes (alanine aminotransferase [ALT], aspartate aminotransferase [AST], γ-glucuronosyltransferase [GGT]) and mild bilirubin elevation during the course of the disease[11]. This is significant because the true impact of gastrointestinal symptoms on the natural history of COVID-19 remains unclear, but their presence has been directly associated with a poorer prognosis[9,10,12].

MATERIALS AND METHODS

An observational, analytical cohort study was conducted, comparing a study group of COVID-19-positive patients with gastrointestinal symptoms and a comparator group without gastrointestinal symptoms. This study was approved by the Corporate Ethics Committee of Fundación Santa Fe de Bogotá and adheres to the principles of the Declaration of Helsinki[13] and Resolution 008430 of 1993 of the Republic of Colombia's Ministry of Health for observational studies[14].

Study Population

Patients over 18 years of age who presented to the emergency department with symptoms suggestive of COVID-19 and were confirmed with a polymerase chain reaction (PCR) test were included, regardless of whether they were managed as outpatients or hospitalized, and whether or not they had gastrointestinal symptoms at the time of admission (abdominal pain, nausea, vomiting, diarrhea, or elevated liver function tests). Initial liver function measurements were also considered for those patients who required hospitalization, with most measurements taken before admission to the intensive care unit (ICU).

Patients who did not have a confirmatory test for the virus or were diagnosed with a test other than PCR were excluded, as well as those who initially consulted through telemedicine or home care.

Data Systematization and Analysis

This ambispective cohort study collected data retrospectively from the admission of the first positive patient reported at Fundación Santa Fe de Bogotá on March 6, 2020, and prospectively until September 2021. The information was extracted from the medical records of patients admitted through the emergency department who were confirmed to have COVID-19 via PCR testing, regardless of the severity of the disease or whether hospitalization was required. The data collection included sociodemographic variables, relevant personal medical history (including a history of liver disease), source or exposure to the infection, presence of nausea/vomiting, diarrhea, abdominal pain, and clinical outcomes, considering mortality, ICU stay, bacterial coinfection, and the need for mechanical ventilation.

Statistical Analysis

Sample size calculation was performed using OpenEpi software[15], estimating that the percentage of COVID-19 patients without gastrointestinal symptoms (unexposed) would be 8.14%, while the percentage with gastrointestinal symptoms (exposed) would be 22.97%. A standard deviation of 0.5, a significance level of 5%, and a power of 80% were used in the calculation. A 10% loss rate was factored in, requiring an initial inclusion of 65 exposed patients and 194 unexposed patients. However, due to the patient volume, a total sample size of 414 patients was achieved, of whom 105 had gastrointestinal symptoms.

For the statistical analysis, categorical variables were described using frequency and percentages, and continuous variables were presented with frequency, mean, median, interquartile range, and the Shapiro-Wilk test to assess normal distribution. Bivariate analysis was conducted to determine if the presence of gastrointestinal symptoms was a risk factor for worse outcomes using the chi-square test and Fisher's exact test. Outcomes with a p-value <0.2 were included in the multivariate analysis, using a multivariate logistic regression model to identify independent predictors. The multivariate analysis was conducted using a multiple logistic regression model. Factors that significantly explained the outcome were those with a p-value <0.05, along with their odds ratio (OR) and 95% confidence interval (CI). Analyses were performed using Real Statistics software, version 7.9, August 2021.

RESULTS

A total of 414 patients who met the selection criteria were analyzed (178 women and 236 men), aged between 18 and 94 years. Of these, 105 patients presented with at least one gastrointestinal symptom at the time of admission, such as diarrhea, nausea, vomiting, or abdominal pain, and had outcomes including bacterial co-infection (12/402), need for mechanical ventilation (102/312), ICU admission (157/257), or death (19/395) (**Table 1**).

Table 1. Demographic Description of the Study Population (n = 414)

Variable		%	n
Sex	Female	42.99	178
	Male	57.24	236
Mechanical ventilation		24.63	102
ICU		37.92	157
Mortality		4.58	19
Bacterial co-infection		2.89	12
Gastrointestinal symptoms	Diarrhea	11.83	49
	Vomiting	2.65	11
	Nausea	6.28	26
	Abdominal pain	8.21	34
		Average	SD
Age	n =414	54.51	17.97282532
BMI (kg/m^2)	n = 414	26.72	4.605037009
ALT (U/L)	n = 298	123.44	846.6107765
AST (U/L)	n = 298	82.19	343.6445574
Direct bilirubin (mg/dL)	n = 263	0.22	0.294993885
ALP (U/L)	n = 104	117.21	78.326
GGT (U/mL)	n = 7	159	36.42043547

ALT: alanine aminotransferase; AST: aspartate aminotransferase; SD: standard deviation; ALP: alkaline phosphatase; GGT: γ-glutamyltransferase; BMI: body mass index; ICU: intensive care unit. Author's own research.

Among patients with COVID-19 who required mechanical ventilation as part of their treatment, the factors associated with this outcome were age (mean: 63.56 [33-87 years]; p = 0.025), BMI (27.80 [18.50-44.30 kg/m^2]; p = 0.001), ALT (252.09 [14.00-171.13 U/L]; p = 0.007), alkaline phosphatase (ALP) (71.37 [0.0-372.0]; p = 0.000), and direct bilirubin (DB) (0.23 [0.003-1.08]; p = 0.003). Regarding variables that could explain ICU admission, BMI (27.62 [18.40-46.7]; p = 0.015), ALT (186.66 [0.00-17,113]; p = 0.001), ALP (54.33 [372-0]; p = 0.000), and DB (0.23 [0.00-1.39]; p = 0.028) were found to be related to this outcome. As for the risk of concomitant bacterial co-infection with SARS-CoV-2, ALP (25.08 [0.00-156.00]; p = 0.048) and DB (0.30 [0.00-1.08]; p = 0.006) were associated with this outcome. Regarding the risk of death from COVID-19, the only factor found to be related was age (74.84 [60-94]; p = 0.002) (**Table 2**).

Regarding specific gastrointestinal symptoms such as nausea/vomiting, diarrhea, and abdominal pain, no association was found between their presence and severe disease outcomes, such as the need for ICU admission (p = 0.823), mechanical ventilation (p = 0.239), bacterial co-infection (p = 0.813), or death (p = 0.284). In other words, there were no individual factors explaining these proposed outcomes. Likewise, other measured variables, such as GGT levels, did not show any relationship with the outcomes.

When comparing patients with gastrointestinal symptoms to those without, no differences were found in severity outcomes, such as the need for ICU admission (p = 0.823), mechanical ventilation (p = 0.239), bacterial co-infection (p = 0.813), or death (p = 0.284). Thus, no individual factors could explain these outcomes (**Table 2**). Similarly, other variables, such as GGT levels, were not associated with the outcomes.

DISCUSSION

The multisystemic involvement caused by COVID-19 is a critical factor in the diagnosis, treatment, and overall clinical management of patients. Among other areas, the literature has focused on investigating whether gastrointestinal symptoms are associated with an increased risk of developing severe or critical illness and acute respiratory failure[16].

While the results of publications on this topic are inconclusive, some authors have indicated that there is no statistically significant difference in severe cases presenting with gastrointestinal symptoms compared to those without, whereas others, such as Wang and colleagues, found that the proportion of gastrointestinal symptoms was significantly higher in patients admitted to the ICU due to coronavirus infection[17]. Others have reported a link between the presence of gastrointestinal bleeding and abdominal pain with more severely ill patients[18], while Cai and colleagues demonstrated that liver injury occurred more frequently in patients with severe disease than in those with milder forms, with an incidence of up to 78% in patients who died from the virus[19]. However, none of these stud-

Table 2. Multivariable Logistic Regression Evaluating the Relationship Between Gastrointestinal Symptoms, Liver Function, and Outcomes

	Coeff b	*p*-Value	exp(b)	Lower	Upper
Logistic regression for mechanical ventilation					
- Intercept	-5.69	0.000	0.00		
- Age	0.04	0.000	1.04	1.02	1.06
- BMI (kg/m^2)	0.06	0.039	1.06	1.00	1.12
- ALT (U/L)	0.01	0.007	1.01	1.00	1.02
- ALP (U/L)	0.01	0.000	1.01	1.01	1.02
- Direct bilirubin (mg/dL)	-2.49	0.003	0.08	0.02	0.43
- Indirect bilirubin (mg/dL)	0.49	0.366	1.64	0.56	4.75
- AST (U/L)	0.00	0.317	1.00	0.99	1.00
- GGT (U/mL)	-0.01	0.142	0.99	0.98	1.00
- Gastrointestinal symptoms	-0.37	0.239	0.69	0.37	1.28
Logistic regression for ICU admission					
- Intercept	-6.22	0.000	0.00		
- Age	0.05	0.000	1.06	1.04	1.07
- BMI (kg/m^2)	0.07	0.015	1.07	1.01	1.13
- ALT (U/L)	0.02	0.001	1.02	1.01	1.03
- ALP (U/L)	0.01	0.000	1.01	1.00	1.01
- Direct bilirubin (mg/dL)	-1.70	0.028	0.18	0.04	0.83
- Indirect bilirubin (mg/dL)	0.41	0.444	1.51	0.53	4.30
- AST (U/L)	0.00	0.799	1.00	0.99	1.01
- GGT (U/mL)	0.00	0.569	1.00	0.98	1.01
- Gastrointestinal symptoms	-0.06	0.823	0.94	0.55	1.62
Logistic regression for bacterial co-infection					
- Intercept	-6.72	0.002	0.00		
- ALP (U/L)	-0.01	0.048	0.99	0.98	1.00
- Direct bilirubin (mg/dL)	4.67	0.006	106.35	3.83	2951.62
- Gastrointestinal symptoms	0.16	0.813	1.18	0.30	4.59
- BMI (kg/m^2)	0.07	0.278	1.07	0.94	1.22
- Age	0.03	0.168	1.03	0.99	1.07
- ALT (U/L)	0.00	0.988	1.00	0.99	1.01
- AST (U/L)	0.00	0.929	1.00	0.98	1.02
- GGT (U/mL)	-0.55	0.997	0.58	0.00	1.05
- Indirect bilirubin (mg/dL)	-2.48	0.092	0.08	0.00	1.49
Logistic regression for mortality					
- Intercept	-11.03	0.000	0.00		
- Age	0.10	0.000	1.10	1.05	1.16
- Direct bilirubin (mg/dL)	1.48	0.292	4.38	0.28	68.37
- Indirect bilirubin (mg/dL)	1.33	0.140	3.78	0.65	22.04
- BMI (kg/m^2)	0.05	0.452	1.05	0.93	1.19
- AST (U/L)	0.01	0.172	1.01	1.00	1.02
- GGT (U/mL)	0.01	0.373	1.01	0.99	1.03
- ALP (U/L)	-0.01	0.227	0.99	0.98	1.00
- ALT (U/L)	-0.02	0.085	0.98	0.96	1.00
- Gastrointestinal symptoms	-0.81	0.284	0.44	0.10	1.96

ALT: alanine aminotransferase; AST: aspartate aminotransferase; coeff b: b coefficient; exp(b): odds ratio; ALP: alkaline phosphatase; GGT: γ-glutamyltransferase; BMI: body mass index; ICU: intensive care unit. Author's own research.

ies considered gastrointestinal signs and symptoms as potential prognostic factors for unfavorable outcomes, such as mortality and acute respiratory distress syndrome (ARDS), in patients testing positive for SARS-CoV-2[20]. Another analysis found no significant differences in mortality between the two groups but did indicate that patients with gastrointestinal symptoms had a significant risk of developing ARDS[21].

In this study, none of the gastrointestinal symptoms, such as diarrhea, nausea, vomiting, or abdominal pain, were significantly associated with a specific outcome. However, liver function was related to certain outcomes. ALT was found to be associated with the risk of developing acute respiratory failure requiring mechanical ventilation, as well as the need for ICU admission. Importantly, these measurements were mostly taken before ICU admission, eliminating any confounding factors related to medications and ICU care. Additionally, there was a significant association between ALP and bacterial co-infection, mechanical ventilation, and ICU support requirements. Mortality, on the other hand, was the only outcome that showed no relationship with any gastrointestinal symptoms or liver function indicators. This finding aligns with international literature, where liver damage has been associated with disease progression but not with increased mortality[9,12,19]. Therefore, based on this study, it is recommended to include ALT, AST, and DB levels in the initial assessment of these patients, as they provide valuable prognostic information.

CONCLUSION

It is important to highlight that, when comparing patients with and without gastrointestinal symptoms, no statistically significant relationship was found regarding severe outcomes. However, a potential bias in this study is the inclusion of all patients, with or without gastrointestinal symptoms, as described, and not all had liver function measurements. This could be a limitation in terms of the total sample, although the number of patients with ALT and AST levels is still representative.

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