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Prevalence of Gastrointestinal Symptoms in Severe Acute Respiratory Syndrome Coronavirus 2 Infection: Results of the Prospective Controlled Multinational GI-COVID-19 Study

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INTRODUCTION: **Gastrointestinal (GI) symptoms in coronavirus-19 disease (COVID-19) have been reported with great variability and without standardization. In hospitalized patients, we aimed to evaluate the prevalence of GI symptoms, factors associated with their occurrence, and variation at 1 month.**

METHODS: **The GI-COVID-19 is a prospective, multicenter, controlled study. Patients with and without COVID-19 diagnosis were recruited at hospital admission and asked for GI symptoms at admission and after 1 month, using the validated Gastrointestinal Symptom Rating Scale questionnaire.**

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RESULTS: **The study included 2036 hospitalized patients. A total of 871 patients (575 COVID+ and 296 COVID−) were included for the primary analysis. GI symptoms occurred more frequently in patients with COVID-19 (59.7%; 343/575 patients) than in the control group (43.2%; 128/296 patients) ($P < 0.001$). Patients with COVID-19 complained of higher presence or intensity of nausea, diarrhea, loose stools, and urgency as compared with controls. At a 1-month follow-up, a reduction in the presence or intensity of GI symptoms was found in COVID-19 patients with GI symptoms at hospital admission. Nausea remained increased over controls. Factors significantly associated with nausea persistence in COVID-19 were female sex, high body mass index, the presence of dyspnea, and increased C-reactive protein levels.**

DISCUSSION: **The prevalence of GI symptoms in hospitalized patients with COVID-19 is higher than previously reported. Systemic and respiratory symptoms are often associated with GI complaints. Nausea may persist after the resolution of COVID-19 infection.**

INTRODUCTION

The clinical course of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, known as coronavirus-19 disease (COVID-19), can range from asymptomatic to rapidly progressing and life-threatening disease. Severe COVID-19 is characterized by hypoxemia, respiratory insufficiency, and eventually multiple organ failure (1). SARS-CoV-2 may also infect the gastrointestinal (GI) tract (2), for which it has a marked tropism. The virus binds to angiotensin-converting enzyme 2 receptors, which are abundantly expressed on epithelial cells, causing local and systemic inflammation (3,4). GI tract involvement is associated with nausea, vomiting, abdominal pain, and diarrhea (5). Stool shedding of SARS-CoV-2 RNA in approximately 50% of patients with COVID-19 confirms that the GI tract is a target organ of the virus and raises concerns about possible oral-fecal spread of the disease (6). A meta-analysis (7) of 29 studies, including 4,805 patients with COVID, reported a pooled prevalence of nausea/vomiting and diarrhea of 4.6% and 7.4%, respectively. However, the results were highly heterogeneous, with symptom prevalence ranging between 3.4% and 17.0% (8,9). In addition, most studies were mainly obtained from the same COVID-19 clusters; they were frequently uncontrolled, retrospective or observational, and data were collected without the aid of validated questionnaires. Thus, attempts to evaluate the prevalence of GI symptoms in COVID-19 and the risk of GI symptoms for respiratory failure or mortality based on these data have led to inconclusive results (10). We conducted a global, multicenter, controlled study to determine the prevalence of GI symptoms in hospitalized patients with COVID-19 compared with a non-COVID control group. In addition, we assessed risk factors for the development of COVID-19–related GI symptoms and the persistence of GI symptoms 1 month after the initial assessment.

METHODS

Oversight

This study was promoted by GB, GM, CC, and VS at the Department of Medical and Surgical Science, University of Bologna, Italy, and IRCCS S. Orsola in Bologna, Italy. The study was endorsed by the United European Gastroenterology, the European Society of Neurogastroenterology and Motility, and the Rome Foundation. All patients were clinically evaluated according to standard clinical practice. The study was conducted according to the Declaration of Helsinki for clinical studies and approved by each local ethics committee (approval identification number: 399/2020/Oss/AOUBo). Written informed consent was obtained from all subjects.

Patients

Eligible patients were ≥18 and ≤85 years of age, with or without a diagnosis of COVID-19 confirmed according to the World Health Organization definition (laboratory-confirmed SARS-CoV-2

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infection) (11) with symptoms severe enough to deserve hospital admission, and consecutively recruited from May to September 2020. Patients under mechanical ventilation at enrollment or who were unable to report the required data or to sign informed consent, or who were diagnosed with concurrent cancer, were excluded from the study. Control group was composed of hospitalized patients for reasons other than COVID-19, disease/disorders of gastroenterological, traumatic, and surgical pertinence, prospectively enrolled within study timeframe for the majority in Internal Medicine and in a minority in Gastroenterology Units within participating centers (see Supplementary Tables, Supplementary Digital Content 1, http://links.lww.com/AJG/C272).

Study design

The study was performed in 36 centers in 12 countries: Italy, Bangladesh, Egypt, Israel, India, Macedonia, Romania, the Russian Federation, Serbia, Spain, Sweden, and Turkey. The country and center selection was based on the availability of interested country principal investigators contacted either directly by the coordinating center or responding spontaneously to advertisements of the study posted on the United European Gastroenterology, European Society of Neurogastroenterology and Motility, and Rome Foundation websites. Hospitalized patients with or without COVID-19 were prospectively and consecutively enrolled at hospital admission and followed up for 30 days to define disease outcome. The enrollment time frame lasted from 1 to 3 months for each center. Each center was asked to enroll 25 patients with and 25 without COVID-19.

Assessment

Study data were simultaneously collected from each center using an e-Case report form on the REDCap platform. All demographics, medical history, laboratory and imaging tests, and other clinical data, including the presence of GI symptoms according to the Gastrointestinal Symptoms Rating Scale (GSRS) questionnaire at admission and a 1-month follow-up, were reported with descriptive statistics. All data present in the inpatient medical record were used for the study, including demographics, clinical parameters, age, sex, weight, height, body mass index, physical activity, alcohol intake, country of residence, ethnicity, medical history, chronic medication intake, routine blood examination, results of nasal/oropharyngeal swab for the diagnosis of COVID-19 infection, results of imaging examinations, and therapies administered during hospitalization. At admission, patients were assessed for the presence of COVID-19–related symptoms, including current or previous (1 week before hospitalization) GI symptoms, using the GSRS, which consists of 15 items including common upper and lower GI symptoms graded on a 7-item Likert-like scale (12). To assess the presence of chronic GI symptoms leading to overestimation of results, the presence of GI symptom onset at least 6 months before the hospitalization was assessed with the GSRS. After enrollment, all patients were subsequently contacted by telephone interview at 1 month to reassess GSRS and hospitalization outcomes (mechanical ventilation or need of ICU after interview, death, or main discharge diagnosis).

End points

The primary end point of this study was the assessment of the prevalence of GI symptoms in hospitalized patients with COVID-19 compared with a non-COVID control group.
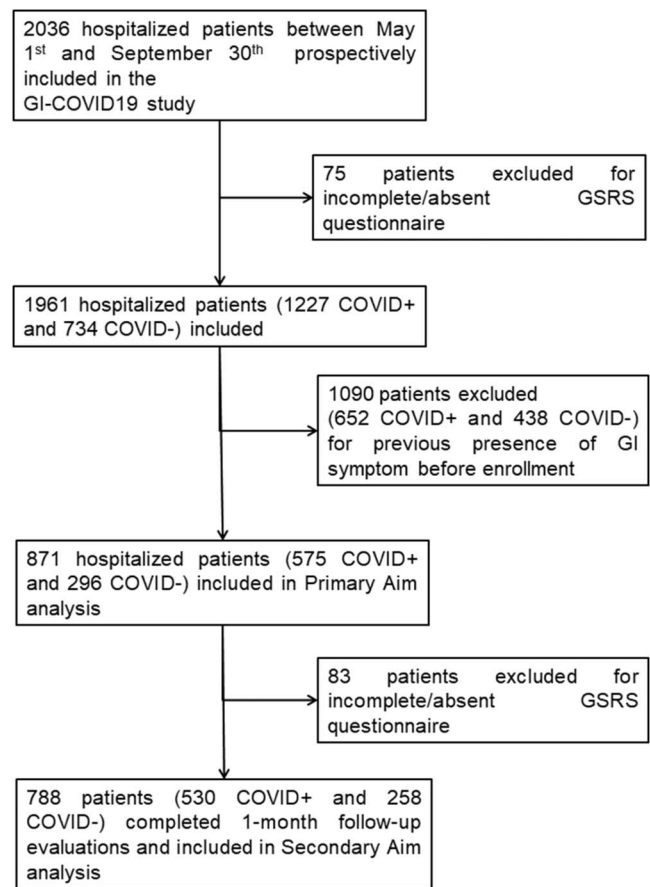

Figure 1. Flowchart of the selection of patients enrolled in the study. COVID-19, coronavirus-19 disease; GSRS, Gastrointestinal Symptoms Rating Scale.

Secondary end points included the identification of risk factors for the development of COVID-19–related GI symptoms and the persistence of GI symptoms 1 month after the initial assessment. Exploratory end points included symptom prevalence, univariate and multivariate analyses of predictive factors associated with GI symptoms, and symptom follow-up of the entire study cohort (1,961 patients).

Statistical analysis

Continuous variables were reported as means and SD, and categorical variables as numbers and percentages. The presence of chronic GI symptoms was defined as the presence of at least 1 GSRS item with any degree of severity, except borborygmi, flatus, and eructation, for which the presence of at least 1 other GSRS item in association was required. Primary and secondary aim analyses were conducted after excluding subjects with chronic GI symptoms. Patients without COVID-19 diagnosis were used as control group for the primary study outcome. Data recorded at admission were compared using the χ^2 test, Fisher test, and Student t-test when appropriate. These data were then tested as predictors of GI symptoms in patients with COVID-19 at admission and at questionnaire 1 month after initial assessment using logistic regression uni- and multivariate analyses. The estimated odds ratios with their 95% confidence intervals were calculated. The results obtained from the multivariate

Table 1. Demographics and anamnestic characteristics of patients included in the GI-COVID-19 study

	COVID-19–negative, n (%) or mean (SD)	COVID-19–positive, n (%) or mean (SD)	P
Age	51.9 (18)	50.7 (15.9)	0.364
Sex (male)	183 (63.3)	333 (58.5)	0.175
BMI	27.1 (5.6)	27.5 (5.1)	0.137
Smoke			<0.001
No	138 (47.8)	399 (69.9)	
Current	74 (25.6)	57 (10)	
Former	77 (26.6)	115 (20.1)	
Alcohol consumption	62 (21.6)	85 (14.9)	0.015
Physical activity (at least 30 min 3 times/week)	85 (29.8)	161 (30.3)	0.896
Comorbidities			
Neurological	20 (6.8)	15 (2.6)	0.003
Cardiovascular	119 (40.2)	176 (30.6)	0.005
Respiratory	35 (11.8)	39 (6.8)	0.011
Liver	18 (6.1)	20 (3.5)	0.075
Kidney	23 (7.8)	24 (4.2)	0.026
Diabetes	70 (23.7)	93 (16.2)	0.007
Metabolic other than diabetes	39 (13.2)	57 (9.9)	0.145
Musculoskeletal	8 (2.7)	13 (2.3)	0.687
Psychiatric	10 (3.4)	5 (0.9)	0.007
Gynaecological	4 (1.4)	1 (0.2)	0.029
Urological	23 (7.8)	9 (3.3)	0.004
Rheumatological	10 (3.4)	13 (2.3)	0.330
Allergies	12 (4.1)	17 (3)	0.392
Autoimmune	13 (4.4)	20 (3.5)	0.504
Neoplastic	14 (4.7)	12 (2.1)	0.030
Psychological	11 (3.7)	8 (1.4)	0.026
Hematological	12 (4.1)	8 (1.4)	0.013
Chronic medication intake with GI effect	156 (55.5)	228 (41.6)	<0.001
Proton pump inhibitors	86 (29.1)	76 (13.2)	<0.001
Nonsteroidal anti-inflammatory drugs	35 (11.8)	35 (6.1)	0.003
Steroids	18 (6.1)	7 (1.2)	<0.001
Metformin	19 (6.4)	34 (5.9)	0.767
Serotonin selective reuptake inhibitors	10 (3.4)	11 (1.9)	0.182
Antipsychotic	6 (2)	3 (0.5)	0.037
Iron	8 (2.7)	5 (0.9)	0.035
Fibrates	2 (0.7)	6 (1)	0.590
ACE-I	38 (12.8)	56 (9.7)	0.163
Beta-blockers	54 (18.2)	80 (13.9)	0.093

Table 1. (*continued*)

	COVID-19–negative, n (%) or mean (SD)	COVID-19–positive, n (%) or mean (SD)	P
Angiotensin-2 antagonist	21 (7.1)	56 (9.7)	0.193
Lithium	—	—	
Carbamazepine	3 (1)	1 (0.2)	0.083
Furosemide	29 (9.8)	10 (1.7)	<0.001
5-ASA	3 (1)	11 (1.9)	0.317
Rifaximin	3 (1)	0	0.016
Opiates	5 (1.7)	2 (0.4)	0.036
Anticholinergics	1 (0.3)	1 (0.2)	0.632
Verapamil	3 (1)	3 (0.5)	0.406
Levothyroxine	15 (5.1)	21 (3.7)	0.320
Cholestyramine	1 (0.3)	0	0.163
Chemo-therapeutics	2 (0.7)	3 (0.5)	0.776
Monoclonal antibodies	2 (0.7)	3 (0.5)	0.776
Digoxin	0	1 (0.2)	0.473
Dopaminergic agents	2 (0.7)	2 (0.4)	0.498
H2 blockers	3 (1)	1 (0.2)	0.083
Benzodiazepines	17 (5.7)	11 (1.9)	0.002
Tricyclic antidepressant	3 (1)	2 (0.4)	0.218
Antibiotics in the past 3 mo	105 (36.2)	132 (23)	<0.001
Probiotics in the past 3 mo	30 (10.4)	43 (7.5)	0.152

5-ASA, acid 5 amino-salicylic; BMI, body mass index; COVID-19, coronavirus 19–associated disease; GI, Gastrointestinal; n: number.

analysis were translated into graphic form, using a nomogram for logistic regression. *P* values less than 0.05 (2-tailed) were considered statistically significant. Survival among the groups of patients with and without GI symptoms was calculated using the Kaplan-Meier method and compared through the log-rank test. All analyses were performed using STATA statistical software (Stata Corp., College Station, TX). This study is registered with ClinicalTrials.gov, NCT04691895.

RESULTS
Patients
From May 1 to September 30, 2020, a total of 2,036 hospitalized patients were consecutively enrolled in the study from the 36 recruiting centers. Of these, 75 patients were excluded for incomplete or absence of questionnaire data. Of the remaining 1,961 patients, 1,227 (62.6%) had a diagnosis of COVID-19. A total of 1,090 patients had pre-existing GI symptoms (652 in the COVID population and 438 in the control group) and were excluded from the primary and secondary aim analyses (Figure 1). Data of subjects without pre-existing GI symptoms (871 patients: 575 COVID-19 and 296 controls) were subsequently used to evaluate primary and secondary study aims. Demographic and clinical characteristics of patients included in the study are reported in Table 1. The control group di-

agnoses are detailed in the Supplementary Text (see Supplementary Digital Content 1, http://links.lww.com/AJG/C272). Overall, 17 patients died at the 1-month follow-up, of whom 11 had COVID-19 (3 without and 8 with GI symptoms) and 6 were controls ($P = 0.868$). For the exploratory end points, demographics, clinical history data, symptom prevalence, univariate and multivariate analyses of predictive factors associated with GI symptoms, and symptom follow-up of the

entire study cohort (1,961 patients) are reported in Supplementary Tables 1–4 (see Supplementary Digital Content 2, 3, 4, and 5, respectively, http://links.lww.com/AJG/C272).

GI symptoms during COVID-19 infection

The overall prevalence of at least 1 GI symptom in the study population was 54.1% (471/871 patients). GI symptoms occurred more frequently in patients with COVID-19 (59.7%; 343/575
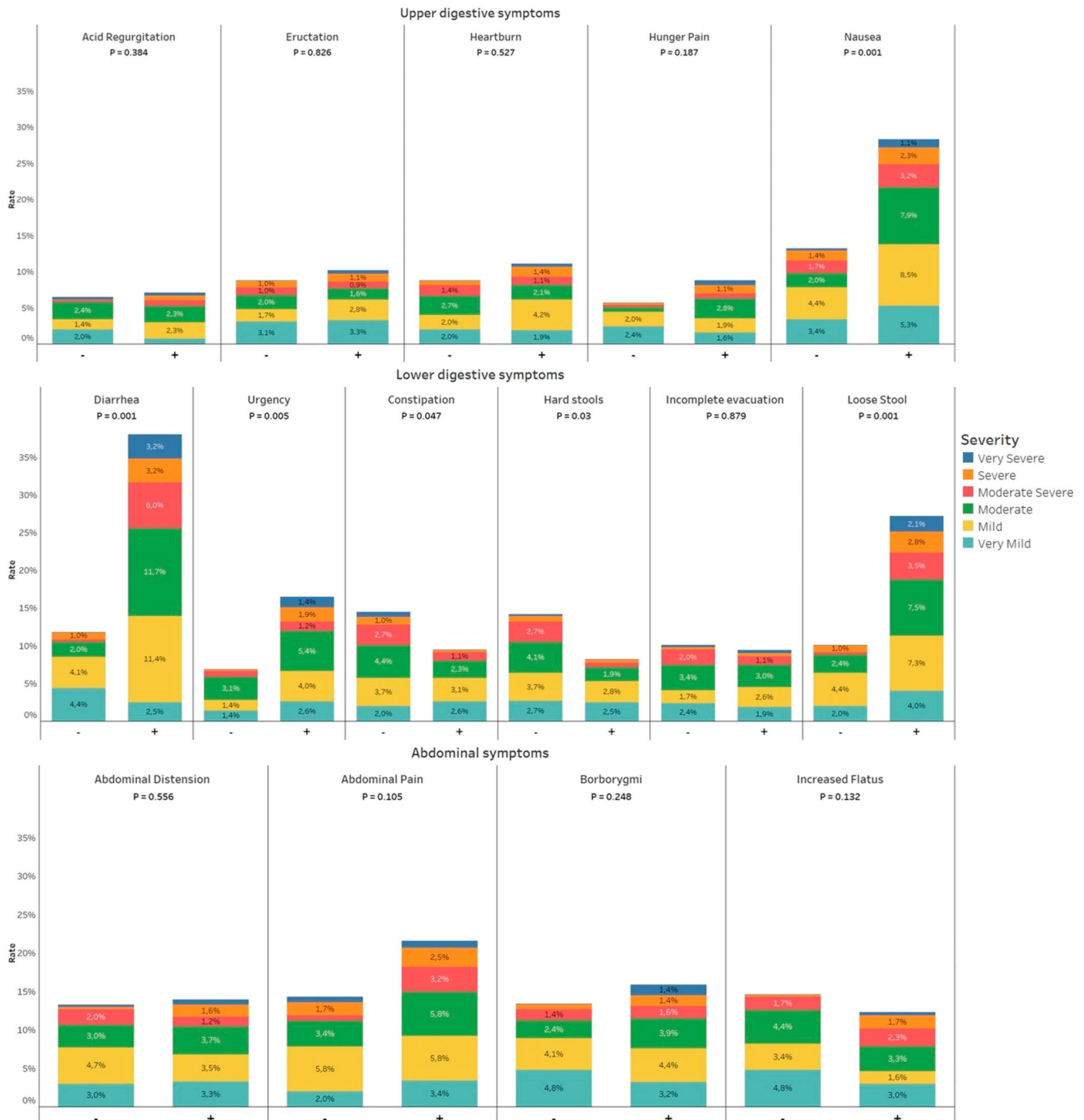
Figure 2. Gastrointestinal symptoms within the Gastrointestinal Symptom Rating Scale questionnaire complained by patients without (−) and with (+) COVID-19 diagnosis.

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Table 2. Baseline laboratory and clinical characteristics of hospitalized patients with COVID-19 enrolled

	No GI symptoms, n (%) or mean (SD)	GI symptoms, n (%) or mean (SD)	P
Blood tests			
WBC ($\times10^3$/mm^3)	6.5 (3.8)	6.2 (3)	0.445
Hb (g/dL)	13.4 (1.9)	13.3 (1.8)	0.440
Neutrophils ($\times10^3$/mm^3)	6.9 (11.7)	7.2 (12.4)	0.806
Lymphocyte ($\times10^3$/mm^3)	3.4 (7.8)	3.4 (8.4)	0.143
Platelet ($\times10^3$/mm^3)	228 (95.8)	218 (88)	0.435
INR	1.1 (0.4)	1.1 (0.2)	0.843
Creatinine (mg/dL)	1.2 (1.7)	1.1 (1.2)	0.006
AST (U/L)	35 (30)	41 (37)	0.061
ALT (U/L)	37 (31)	43 (53)	0.450
Total bilirubin (mg/dL)	0.8 (1.5)	0.9 (2.3)	0.700
GGT (U/L)	72 (175)	66 (88)	0.337
Ferritin (ng/mL)	392 (632)	438 (468)	0.020
IL-6 (pg/mL)	68 (114)	52 (83)	0.549
C-reactive protein (mg/dL)	20 (37)	17 (35)	0.311
Oropharyngeal/nasal swab for SARS-CoV-2 positivity	213 (92.2)	330 (96.5)	0.024
Common symptoms			
Fever	136 (58.6)	262 (76.4)	<0.001
Fatigue	117 (50.4)	210 (61.2)	0.010
Cough	126 (54.3)	206 (60.1)	0.171
Myalgia	69 (29.7)	141 (41.1)	0.005
Dyspnea	52 (22.4)	122 (35.6)	0.001
Runny nose	7 (3)	36 (10.5)	0.001
Headache	32 (13.8)	121 (35.3)	<0.001
Anosmia	38 (16.4)	104 (30.3)	<0.001
Dysgeusia	34 (14.7)	93 (27.1)	<0.001
High-resolution computed tomography			
Pattern COVID-19–like	115 (81)	183 (86.7)	0.145
In-hospital treatments			
Antibiotics			
Azithromycin	68 (29.3)	116 (33.8)	0.255
Penicillins	33 (14.2)	45 (13.1)	0.704
Tetracyclines	9 (3.9)	11 (3.2)	0.666
Cephalosporins	53 (22.8)	88 (25.7)	0.442
Quinolones	22 (9.5)	36 (10.5)	0.692
Lincomycin	0	1 (0.3)	0.410
Macrolides	6 (2.6)	13 (3.8)	0.428
Sulfonamides	0	2 (0.6)	0.244

Table 2. (*continued*)

	No GI symptoms, n (%) or mean (SD)	GI symptoms, n (%) or mean (SD)	P
Glycopeptides	7 (3)	10 (2.9)	0.944
Aminoglycosides	7 (3)	9 (2.6)	0.778
Carbapenems	8 (3.5)	19 (5.5)	0.245
Antimycotic	3 (1.3)	9 (2.6)	0.290
COVID-19–targeted therapies			
Remdesivir	9 (3.9)	34 (9.9)	0.007
Chloroquine	4 (1.7)	0	0.015
Hydroxychloroquine	125 (53.9)	193 (56.3)	0.572
Oseltamivir	2 (0.9)	13 (3.8)	0.031
Lopinavir/ritonavir	29 (12.5)	27 (7.9)	0.066
Tocilizumab	16 (6.9)	39 (11.4)	0.074
Corticosteroids	39 (16.8)	88 (25.7)	0.012
Outcomes			
Need for ICU	19 (8.6)	44 (13.1)	0.097
Need for mechanical ventilation	14 (6.3)	22 (6.6)	0.910
Death	3 (1.4)	8 (2.4)	0.392
Survival (d)	35 (10.4)	33.8 (13.6)	<0.001

ALT, alanine amino-transferase; AST, aspartate amino-transferase; COVID-19, coronavirus 19–associated disease; GGT, gamma-glutamyl transferase; GI, Gastrointestinal; Hb, hemoglobin; ICU, intensive care unit; IL, interleukin; INR, international normalized ratio; n, number; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WBC, white blood cells.

patients) than in the control group (43.2%; 128/296 patients) ($P < 0.001$). Patients with COVID-19, as compared with the control group, reported higher rates of nausea (28.2% vs 13.2%, $P < 0.001$), diarrhea (37.9% vs 11.9%, $P < 0.001$), loose stool (27.3% vs 10.2%, $P < 0.001$), and urgency (16.6% vs 6.8%, $P = 0.005$) and lower rates of constipation (9.4% vs 14.6%, $P = 0.047$) and hard stools (8.2% vs 14.2, $P = 0.030$) (Figure 2). Rates of GI symptom intensity scores in the study population are reported in Figure 2. The country distribution of the most prevalent GI symptom, namely, diarrhea, is reported in Supplementary Figure 1, Panel A (see Supplementary Digital Content 6, http://links.lww.com/AJG/C271).

Risk factors associated with GI symptoms in patients with COVID-19

Clinical and laboratory data of the study population are detailed in Table 2. COVID-19 patients with GI symptoms, as compared with those without, had higher prevalence of symptoms such as fever (76.4% vs 58.6%, $P < 0.001$), fatigue (61.2% vs 50.4%, $P = 0.010$), myalgia (41.4% vs 29.7%, $P = 0.005$), dyspnea (35.6% vs 22.4%, $P = 0.001$), runny nose (10.5% vs 3%, $P = 0.001$), headache (35.3% vs 13.8%, $P < 0.001$), anosmia (30.3% vs 16.4%, $P < 0.001$), and dysgeusia (27.1% vs 14.7%, $P < 0.001$). When all COVID-positive patients were evaluated, patients with GI symptoms had higher levels of ferritin (mean 438 vs 392 ng/mL,

$P = 0.020$) and lower levels of creatinine (mean 1.1 vs 1.2 mg/dL, $P = 0.006$). The needs for high-resolution chest computed tomography, mechanical ventilation, and ICU support were not statistically different between patients with and without GI symptoms. Similarly, Kaplan-Meier curves for 30-day survival showed no survival differences between patients with and without GI symptoms (log-rank test $P = 0.338$; see Supplementary Figure 2; see Supplementary Digital Content 7, http://links.lww.com/AJG/C271).

Among factors associated with GI symptoms identified in univariate analysis, only 7 variables survived the multivariate analysis (see Supplementary Table 5, Supplementary Digital Content 8, http://links.lww.com/AJG/C272), namely, female sex, fever, headache, anosmia, runny nose, aspartate aminotransferase levels, and antibiotic intake within the 3 months before hospital admission. A nomogram assessing the individual risk of factors associated with GI symptoms is presented in Figure 3.

Post-COVID-19 follow-up

GI symptoms at follow-up. A total of 1,138 patients with COVID-19 and 645 controls completed the symptom questionnaire 1 month after initial assessment (response rates of 92.7% and 87.9%, respectively). Of these, 788 patients (530 with COVID-19 and 258 from the control group had no symptoms before hospitalization) were considered for further analyses (response rates of 92.2% and 87.2%, respectively). The prevalence of diarrhea at a 1-month follow-up in patients with COVID-19 for each country participating in the study is reported in Supplementary Figure 1, Panel B (see Supplementary Digital Content 6, http://links.lww.com/AJG/C271).

At follow-up evaluation, nausea was significantly more prevalent in patients with COVID-19 than in the control group (8.3% vs 2.3%, $P = 0.038$). A borderline significantly higher prevalence was found for acid regurgitation (7.8% vs 3.1%, $P = 0.052$) (Figure 4). No other significant differences were found.

Factors associated with the presence of GI symptoms at 1 month after initial assessment identified in multivariate analysis are reported in Supplementary Table 6 (see Supplementary Digital Content 9, http://links.lww.com/AJG/C272). Among factors associated with nausea at 1 month after initial assessment identified in univariate analysis, only 4 variables survived the multivariate analysis (see Supplementary Table 7, Supplementary Digital Content 10, http://links.lww.com/AJG/C272), namely, female sex, body mass index, dyspnea, and C-reactive protein values. A nomogram assessing the individual risk of factors associated with nausea at 1 month is presented in Figure 5.

COVID-19 patients with symptoms at baseline. In COVID-19 patients with at least 1 GI symptom at baseline, we found a significant reduction in the presence or intensity rates of most symptoms, except for eructation, constipation, hard stools, incomplete evacuation, abdominal distension, and flatus (see Supplementary Figure 3, Supplementary Digital Content 11, http://links.lww.com/AJG/C271). In particular, significant variations were found for hunger pain (14.4% at baseline vs 6% at follow-up), nausea (46.3% vs 10.2%), heartburn (18.1% vs 9.5%), acid regurgitation (12.2% vs 9.9%), diarrhea (63.9% vs 12.1%), loose stools (46% vs 12.8%), urgency (28.5% vs 7.6%), abdominal pain (35.6% vs 12.7%), and borborygmi (25.9% vs 13.4%).

COVID-19 patients without symptoms at baseline. On the other hand, patients with COVID-19 without GI symptoms during the acute phase of SARS-CoV-2 infection developed GI symptoms at a 1-month follow-up in up to 9.8% of cases (see Supplementary Figure 4, Supplementary Digital Content 12, http://links.lww.com/AJG/C271). In particular, at a 1-month follow-up, we found a significant increase in the onset of eructation (4.7%), nausea (6%), acid regurgitation (4.7%), constipation (9.8%), hard stools (6.5%), abdominal pain (5.6%), and distension (9.3%).

DISCUSSION

The GI-COVID-19 study provides evidence that SARS-CoV-2 infection is associated with diarrhea, nausea, and other GI symptoms, including loose stools and urgency, compared with a noninfected control population. Female patients with fever, runny nose, anosmia, headache, increased aspartate aminotransferase
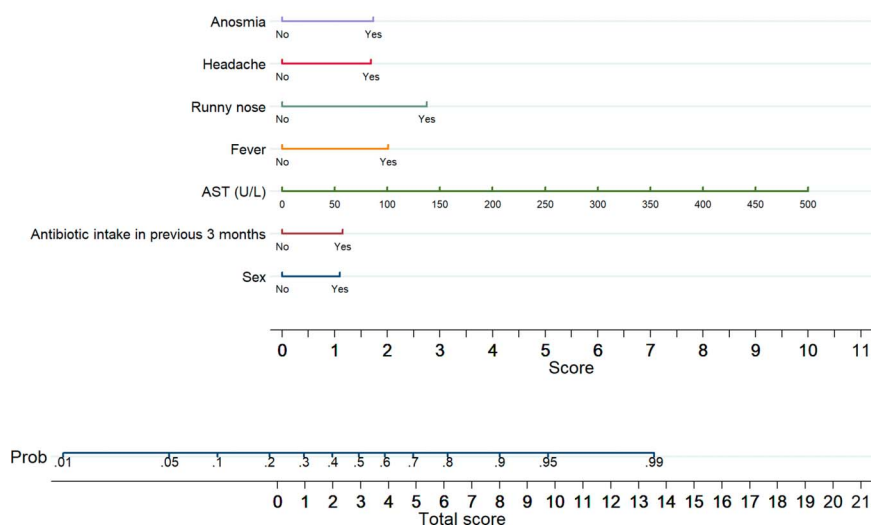

Figure 3. Nomogram reporting a probability score for GI symptoms development in patients with COVID-19. COVID-19, coronavirus-19 disease; GI, gastrointestinal.
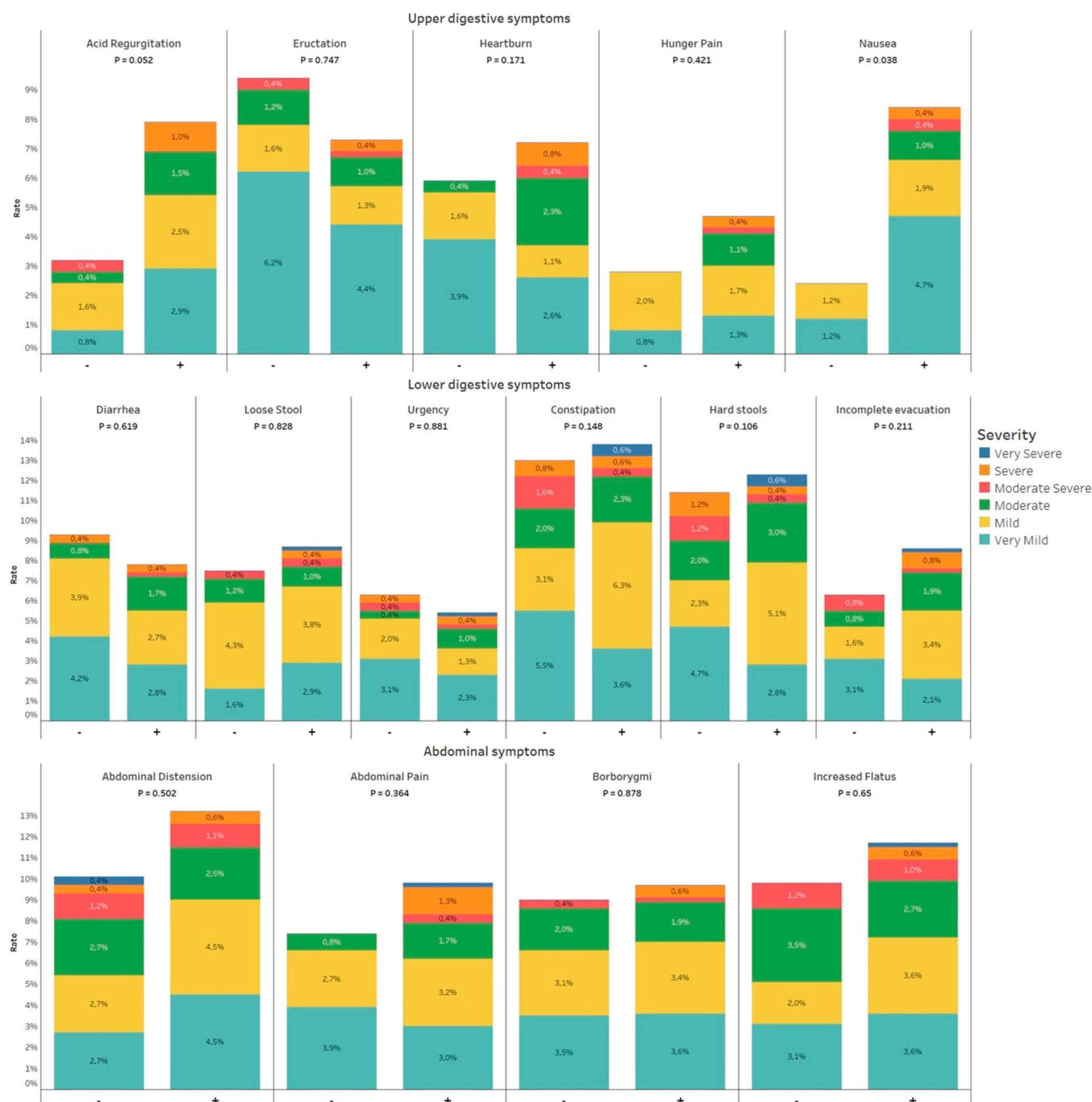
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Figure 4. Variations in gastrointestinal symptoms within the Gastrointestinal Symptom Rating Scale questionnaire complained by patients without (−) and with (+) COVID-19 diagnosis after the 1-month follow-up.

levels, and reporting antibiotic intake in the 3 months before hospital admission were at increased risk of GI symptoms. COVID-19 patients with GI symptoms had higher rates of systemic involvement, including fever, fatigue, myalgia, dyspnea, runny nose, headache, anosmia, and dysgeusia. However, the presence of GI symptoms did not increase the rate of ICU admission nor mortality. Although most GI symptoms declined at 1 month after the initial evaluation, the prevalence of nausea and acid regurgitation remained higher in the COVID-19 cohort of patients than in noninfected patients. Females with dyspnea, high body

mass index, and increased C reactive protein values were more likely to report nausea at a 1-month follow-up.

The novelty of the GI-COVID-19 study stems from its inclusion of a control population of noninfected patients, its multicenter design, and the analysis of new gastrointestinal symptoms developed after acute SARS-CoV-2 infection, all features that have often been previously neglected. We also investigated clinical features, such as stool consistency and urgency, that have a high impact on patients' quality of life and have only been reported in a small retrospective uncontrolled study (13). All the features mentioned above may at

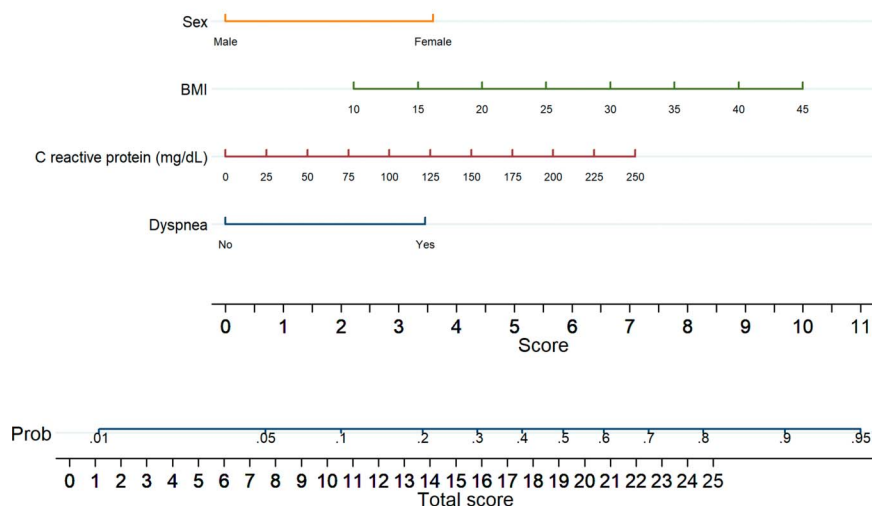## Probability of Nausea persistence in COVID-19 patients

Figure 5. Nomogram reporting a probability score for nausea at 1 month after initial assessment in patients with COVID-19. BMI, body mass index; COVID-19, coronavirus-19 disease.

least in part explain the higher prevalence of GI symptoms and diarrhea found in this study compared with pooled data reported in the literature (1,5,14), even when data were obtained from hospitalized patients or were adjusted for previous GI chronic diseases (15). Furthermore, our study included mostly western countries, in which comparative studies have found a higher prevalence of GI symptoms (15).

In addition, most of the abovementioned large studies were lacking a control group. Only small single-center studies (16,17) have reported the prevalence of GI symptoms in COVID-19 compared with a control group of nonhospitalized patients, but symptoms were recorded without the use of validated questionnaires.

Limited data are available regarding factors associated with GI symptoms. Our results are in line with previous multivariate analyses (18,19), finding that female sex and systemic or respiratory illness increased the risk for GI symptoms (18). In addition, recent reports (20,21) found that age and fever were the only significant predictive factors for GI symptoms at hospital admission.

Interestingly, our study showed that antibiotic treatment in the 3 months before hospitalization was associated with GI symptom development. These data suggest that antibiotic-associated dysbiosis and increased intestinal permeability may contribute to GI symptom development in the context of COVID-19 infection (22,23). The contribution of dysbiosis to the pathogenesis of COVID-19 is also supported by previous evidence showing enrichment of opportunistic pathogens along with depletion of commensals (22). The increased relative abundance of *Streptococcus*, *Rothia*, *Veillonella*, *Erysipelatoclostridium*, and *Actinomyces* may play a pathogenic role in COVID-19 infection because it has been associated with the magnitude of systemic inflammation (22). Proton pump inhibitors (PPIs) may also contribute to dysbiosis (22,23). A previous meta-analysis (24) found that patients taking PPIs had an increased risk of SARS-CoV-2 infection and worse outcomes. In this study, we also found a significant association of PPIs with GI symptom occurrence in multivariate analysis of the entire study cohort. However, in the primary aim population, this association was not confirmed.

We confirmed the results of previous large series (25,26) and pooled data (27,28) reporting no differences in ICU admission or mortality between patients with and without GI symptoms. The overall 1-month mortality of 1.9% in patients with COVID-19, irrespective of GI symptoms, found in our study is slightly higher than that previously reported. This is likely due to the inclusion of hospitalized patients and an older population compared with previous studies.

Few longitudinal studies have assessed changes in digestive symptoms over time in patients with COVID-19 (26,29). Carvalho-Schneider et al. (29) found no differences in the rate of diarrhea from enrollment to the 2-month follow-up in a small group of patients. By contrast, Luo et al. (26) showed a rapid disappearance of diarrhea and other related symptoms at a 3-week follow-up and a slow and sporadic appearance of symptoms in patients without digestive symptoms at enrollment. In this study, persistence of symptoms at a 1-month follow-up was found in less than 17% of cases, whereas among COVID-19–positive patients without GI symptoms at admission, 9.8% developed GI symptoms at follow-up. The only symptoms that were persistently more frequent in patients with COVID-19 than controls at follow-up were nausea and acid regurgitation. The persistence of these symptoms may be related to the neuroinvasive potential of COVID-19, which may lead to the presence of the virus in the dorsal vagal complex and the area postrema (4).

We acknowledge that our study has some limitations. First, the primary and secondary outcomes might have been influenced by a number of different factors in the study population, including the effects of therapies, hospitalization, and comorbidities. However, our effort to compare the COVID-positive patients with a control population of hospitalized patients likely mitigated the influence of these factors on the end points. Besides, it should be underlined that our COVID-19 cohort included only hospitalized patients consequently having a moderate to severe disease course, who, in turn, have been reported to complain high rates of GI symptoms (18), thus leading to discrepancies in GI symptoms occurrence rates when compared with the outpatient setting.

Second, the study network, comprising several gastroenterology wards, might have introduced a selection bias and influenced the outcome; nonetheless, excluding patients with chronic GI symptoms from the primary and secondary analyses might have sufficed to overcome this limitation.

In conclusion, the finding that COVID-19 is associated with GI symptoms in a high proportion of infected patients and the persistence of some of these symptoms may increase awareness of the role of GI involvement in COVID-19. Future studies should investigate whether treatment of GI symptoms during the acute phase can prevent long-lasting GI symptoms in COVID-19.

Study Highlights

WHAT IS KNOWN

✓ SARS-CoV-2 may infect the gastrointestinal tract leading to nausea, vomiting, abdominal pain, and diarrhea.

✓ The attempts to evaluate the prevalence of gastrointestinal symptoms in SARS-CoV-2 infection gave high heterogeneous results.

WHAT IS NEW HERE

✓ Gastrointestinal symptoms occurred more frequently in patients with coronavirus-19 disease (COVID-19) (59.7%) than in the control group (43.2%).

✓ Patients with COVID-19 complained of higher presence or intensity of nausea, diarrhea, loose stools, and urgency as compared with controls.

✓ At a 1-month follow-up, nausea remained significantly increased in patients with COVID-19 over controls.

✓ Females with dyspnea, high body mass index, and C-reactive protein levels were more likely to report nausea at a 1-month follow-up.

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