Clinical Characteristics and Outcomes of COVID-19 Patients with Gastrointestinal Manifestations Seen in a Tertiary Hospital: A Retrospective, Cohort Study

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Abstract

Significance: Patients with Coronavirus Disease 2019 (COVID-19) usually have respiratory symptoms. However, some patients present with gastrointestinal (GI) symptoms. Studies on the association of clinical outcomes and GI symptoms are conflicting. Attention to atypical symptoms like digestive symptoms is important for extensive identification, implementation of efficient quarantine protocols and ultimate control of COVID-19 transmission. Findings can also contribute to Philippine data on the management of COVID-19.

*Objectives:*This study aims to determine the association of GI symptoms with severity of COVID-19 infection and mortality in COVID-19 patients.

Methods: In this retrospective, single-center, cohort, data from 348 adults with confirmed-COVID-19 patients admitted in Manila Doctors Hospital from March 1, 2020 to August 31, 2020 were reviewed. Demographic profile, disease severity and clinical outcomes were summarized and the association of GI symptoms and disease severity was determined using logistic regression.

Results: Of the 348 patients, 38.5% had GI symptoms. Diarrhea was the most common symptom (50%). Patients with GI symptoms were older (54.42±17.92 vs 47.7±17.49, p<0.01), had higher values of AST (44.1±57.39 vs 32.1±39.2, p=0.017), ALT (57.23±67.92 vs 44.72±43.95, p=0.029), creatinine (166.19±325.43 vs 99.8±158.32, p=0.014), BUN (6.59±10.21 vs 4.49±5.92, p=0.015), and quantitative CRP (17.12±41.33 vs 7.08±23.38, p=0.005), lower procalcitonin (0.32±0.6 vs 0.8±2.85, p=0.009) and albumin (25.85±14.89 vs 20.14±17.33, p< 0.01), and higher incidence of bilateral pneumonia (63% vs 50%, p=0.006). These patients had moderate (p=0.003) and critical (p=0.049) severity on admission. During hospitalization, those with GI symptoms had higher cases of critical illness (28% vs 21%, p=0.0480), but no statistical difference in death (19% vs 14%, p=0.1510) compared to those without GI manifestations.

Conclusion: Gastrointestinal manifestations are common in COVID-19. GI symptoms were associated with moderate and critical disease but were not associated with higher death rates.

Keywords: COVID-19, SARS-CoV-2, gastrointestinal manifestations, gastrointestinal symptoms

Introduction

In December 2019, cases of pneumonia of unknown etiology were first reported in Wuhan City, Hubei Province, China. In January 2019, this virus was isolated and sequenced as a novel coronavirus, now known as the Severe Acute Respiratory Distress Syndrome Coronavirus 2 (SARS-Cov2). Within a few months, the outbreak had spread across China then worldwide, crippling global health and economies. (1) By March 2020, this disease called Coronavirus Disease 2019 (COVID-19) was declared a pandemic by the World Health Organization. COVID-19 has a wide spectrum of manifestations, from mild cough to severe respiratory failure that can be potentially fatal. It has a tropism for the respiratory tract with most infected patients presenting with fever and cough. As the pandemic continued to evolve, several cases have shown that extra-pulmonary symptoms including gastrointestinal (GI) symptoms are just as common, with incidence varying among different populations.

Studies have suggested that up to 50% of COVID-19 patients will present with at least one GI symptom, with diarrhea as the most common GI manifestation. (2) In the Philippines, there are patients who would come to the hospital not for the classic symptoms of COVID-19 but for abdominal pain, bloating or diarrhea. These patients sometimes test positive for the novel coronavirus.

Angiotensin converting enzyme 2 receptor (ACE2), abundant in lungs, GI tract and kidneys, is thought to be responsible for SARS-CoV-2 entry into the host cells. (3, 4) SARS-CoV-2 has also been identified in fecal specimens, and the potential for viral transmission through endoscopic procedures by close contact had been described. (5) Several studies have reported the relationship of GI symptoms with longer illness duration, disease severity, ICU stay and death. (6, 7, 8) There is growing interest in whether GI symptoms are associated with severe COVID-19 disease. Therefore, in this study, we aim to explore GI manifestations of COVID-19 in the Filipino population, including clinical characteristics and associated outcomes especially disease severity.

Methodology

A.Study Design

This is a retrospective, single-center, cohort study of patients eighteen years old and above with RT-PCR-confirmed COVID-19 admitted at Manila Doctors Hospital from March 1, 2020 to August 30, 2020. Sample size computation for this descriptive study was done in Epi Info version 7.1.4.0 with the following assumptions: (1) the total population size of COVID19 patients admitted from March 1, 2020 to August 30, 2020 was 377; (2) the outcome, gastrointestinal problem occurs in up to 50.5% (10); (3) the desired precision is 5%. The computed sample size at <5% margin of error was 191. Patients who were diagnosed with pneumonia but had no COVID-19 RT-PCR test done, with known GI disease, and those who were transferred to another hospital for further management were excluded from this study.

B. Operational Definitions

o Gastrointestinal (GI) manifestations included one or more of the following: loss of/decreased appetite, nausea, vomiting, abdominal pain, bloating, diarrhea and GI bleeding. Diarrhea was defined as passage of ≥3 stools per day. Symptoms were noted before admission and within 3 days of admission.

o GI Symptomatic were COVID-19 patients who presented with ≥ 1 GI symptoms prior to admission and within 3 days of admission.

o GI Asymptomatic were COVID-19 patients who did not present with any GI symptom prior to admission.

o COVID-19 Confirmed was a patient with laboratory-confirmed COVID-19 test through RT-PCR in a national or subnational reference laboratory or a DOH-certified laboratory testing facility. (9)

C. Description of Outcome Measures

o COVID-19 RT-PCR Confirmed Infection were classified clinically into disease severity based on the PSBIM Interim Management Guidance for COVID-19, Version 3.1 (9)

1. Mild COVID-19 Infection had disease with signs and symptoms such as fever, cough, fatigue, anorexia, myalgia, sore throat, nasal congestion, headache, diarrhea, nausea, vomiting, anosmia or aguesia, and with no signs of pneumonia or hypoxia.

2. Moderate COVID-19 Infection had disease with signs of non-severe pneumonia (e.g. fever, cough, dyspnea or difficulty breathing), respiratory rate 21-31 breaths per minute, Oxygen Saturation >92% on room air.

3. Severe COVID-19 Infection had severe pneumonia or severe acute respiratory infection with fever, cough, dyspnea, respiratory rate >30 breaths per minute, severe respiratory distress or Oxygen Saturation =/< 92% on room air.

4. Critical COVID-19 Infection had disease with onset within 1 week of known clinical insult (pneumonia) or new/worsening respiratory symptoms, progressing infiltrates on CXR or chest CT, with respiratory failure not fully explained by cardiac failure or fluid overload and/or the following:

o Sepsis: life-threatening organ dysfunction caused by a dysregulated host response to suspected/proven infection, with signs of organ dysfunction such as altered mental status, difficult or fast breathing, low oxygen saturation, reduced urine output, fast heart rate, weak pulse, cold extremities or low blood pressure, skin mottling, or laboratory evidence of coagulopathy, thrombocytopenia, acidosis, high lactate or hyperbilirubinemia

o Septic Shock: persisting hypotension despite volume resuscitation requiring vasopressors to maintain Mean Arterial Pressure (MAP) of 65 mmHg and above and serum lactate level > 2 mmol/L. (9)

o Acute Respiratory Distress Syndrome (ARDS) was defined severe lung injury within 1 week of a clinical insult or new/worsening respiratory symptoms with progressive infiltrates on Chest X-Ray and Chest Tomography not fully explained by heart failure or fluid overload, and a PaO2/FiO2 ratio of 300 mmHg or less. (9)

o Acute Kidney Injury was defined as an acute deterioration of kidney function manifested by an increase in serum creatinine at least 1.5x from baseline within 48 hours and/or decrease in urine output to < 0.5 ml/kg/hr for > 6 hours.

o Acute Cardiac Injury was defined as a rise on high sensitivity troponin with at least 1 value above the 99th percentile of the upper reference limit and at least one or more of the following: symptoms of ischemia, new electrocardiographic evidence of ischemia, new pathological Q waves, new regional wall motions on imaging in an ischemic territory and coronary thrombus on angiography. (10)

o Clinical outcomes were defined as:

o Mortality was defined as a patient that has died during care or hospitalization.

D. Description of Study Procedure, Data Collection and Ethical Considerations

This is a retrospective, cohort study of patients with confirmed COVID-19 infection and who were admitted in Manila Doctors Hospital (MDH) from March 1, 2020 to August 31, 2020. Approval from the MDH Institutional Review Board (IRB), Ethics Review Board and the Data Privacy Officer for clearance to access patients' records was acquired. The epidemiological data, baseline characteristics, laboratory data, treatment and outcome measures (disease severity and mortality) were obtained by review of the patients' medical records/charts. Clinical outcomes were noted including discharge/expiry of each patient. Patient anonymity and data confidentiality were ensured by encoding patient data on the data collection forms with an assigned patient number. All information were written in the data collection form with only patient codes in place to safeguard the privacy and anonymity of the patients involved. A waiver of informed consent was requested from the IRB panel since the study has no more than minimal risk to privacy with the retrieval of information from past records. All these were in accordance to the National Ethical Guidelines of Health and Health-Related Research 2017. The research did not receive any financial support from any pharmaceutical company that may benefit from this study. No financial compensation or direct benefits were given to patients involved in this study.

E. Data Analysis

All data were encoded using Microsoft Excel and imported into Stata/SE software Version 12.0 for statistical analysis. Prevalence of GI manifestations was measured in terms of proportion of patients having the condition over the total number of COVID-19 patients. For the demographic, clinical and laboratory profile, a descriptive statistics were employed with mean and standard deviation for the age and other continuous type of data and frequency and percent for categorical data such as sex, comorbidities and other data. For the comparative analysis between COVID-19 patients with GI symptoms and those without GI symptoms, several analyses were used. In the case of categorical data, t-test for two proportions for comparing for the difference of the two percentages, Fisher Exact tests for 2x2 tables and Chi-square test for independence for m x n tables were used.

For association analysis, Binary Logistic Regression analysis was used. A binomial logistic regression, predicts the probability that an observation falls into one of two categories of a dichotomous dependent variable using the gastrointestinal manifestation parameters, in this case the following outcomes: severity of COVID19, expiration and discharge based on one or

more independent variables that can be either continuous or categorical which are your demographic and clinical variables. This is used to determine risk factors associated with an outcome. A p-value of less than 0.05 is considered significant.

Results

From March 1, 2020 to August 31, 2020, there were a total of 377 adult patients who tested positive for COVID-19 and who were admitted at MDH (Figure 1). Twenty-nine patients did not meet the inclusion criteria: 20 patients had known GI disease (GI cancer, cirrhosis, chronic hepatitis, fatty liver, GERD), 7 patients transferred to another hospital hence outcomes were not completely followed up, and 2 patients were pediatric cases. Three hundred forty-eight (348) patients were, thus, included in the study. Of the 348 patients, 134 patients presented with GI symptoms.

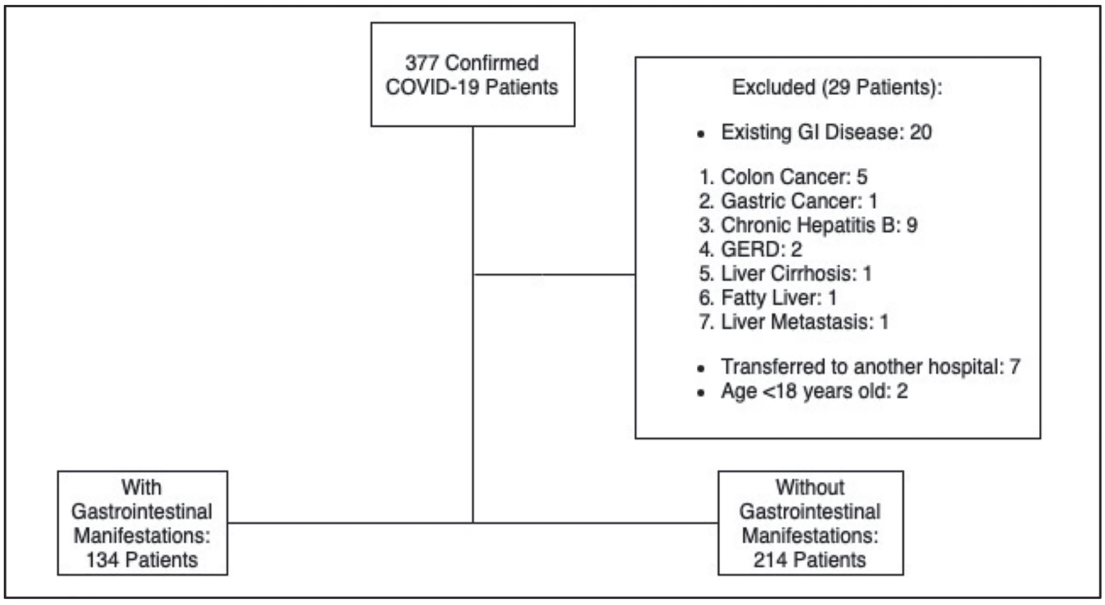

Figure 1. Flow of the Study

Demographic profile of patients is shown in Table 1. There was no statistical difference in COVID-19 patients with and without GI symptoms in terms of sex, although COVID-19 patients were mostly male. COVID-19 patients with GI symptoms were older with a mean age of 54.42±17.92 ($p<0.01$). There were also more patients with GI symptoms and with comorbidities such as hypertension (59% vs 40%, $p<0.01$), diabetes (28% vs 20%, $p=0.038$), post-cerebrovascular disease (7% vs 3%, $p=0.040$) and chronic kidney disease (10% vs 4%, $p=0.11$). There was no significant difference in the duration from illness to onset of admission in both groups (GI symptomatic = 7.53±5.4 days vs GI asymptomatic = 6.34±9.13).

Table 1. Demographic profile and baseline laboratory results of patients on admission. Mean values of laboratory results were based on the total number of patients who had respective laboratory study done.

	GI Symptomatic N = 134	GI Asymptomatic N = 214	P-value
Sex			
Male	77(57%)	116(54%)	0.276
Female	57(43%)	98(46%)	0.276
Age, years (mean ± SD)	54.42±17.92	47.7±17.49	<0.01
Comorbidities			
Cardiovascular Disease			
Hypertension	79(59%)	85(40%)	<0.01
Heart Disease	17(13%)	20(9%)	0.163
Other CVS Disease	2(1%)	4(2%)	0.396
Endocrine Disease			
Diabetes	38(28%)	43(20%)	0.038
Thyroid Problems	4(3%)	5(2%)	0.355
Other Endocrine Disease	0(0%)	2(1%)	0.131
Dyslipidemia	9(7%)	10(5%)	0.207
Lung Disease	13(10%)	18(8%)	0.340
Nervous System Disease			
Post CVD	9(7%)	6(3%)	0.040
Kidney Disease			
On Maintenance Dialysis	7(5%)	5(2%)	0.075
Chronic Kidney Disease not on Maintenance Dialysis	14(10%)	9(4%)	0.011
Others	1(1%)	0(0%)	0.103
Duration from Illness Onset to Admission (mean ± SD)	7.53±5.4	6.34±9.13	0.062
BASELINE LABORATORY VALUES			
White Blood Count	7.59±3.2	7.64±4.71	0.455
Neutrophils	69.6±14.62	64.62±17.98	0.002
Lymphocytes	20.14±11.27	21.67±11.65	0.112
Monocytes	8.2±3.94	8.41±4.64	0.325
Eosinophils	0.72±1.16	1.22±1.82	0.001
Basophils	0.08±0.78	0.01±0.12	0.185
Platelet Count	259.17±105.33	267.56±143.52	0.265
Hemoglobin	134.91±24.21	132.98±30.45	0.256
Hematocrit	40.35±7.86	40.16±9.16	0.418
Aspartate Aminotransferase (AST)	44.1±57.39	32.1±39.2	0.017
Alanine Aminotransferase (ALT)	57.23±67.92	44.72±43.95	0.029
INR	0.3±0.49	0.28±0.49	0.336
Creatinine	166.19±325.43	99.8±158.32	0.014
Blood Urea Nitrogen (BUN)	6.59±10.21	4.49±5.92	0.015
HS C-Reactive Protein	39.1±54.51	35.88±65.96	0.311
C-Reactive Protein (Quantitative)	17.12±41.33	7.08±23.38	0.005
Procalcitonin	0.32±0.6	0.8±2.85	0.009
Lactate Dehydrogenase	250.34±185.36	245.97±226.7	0.422
D-Dimer	1142.47±2743.87	798.87±2204.83	0.111
Ferritin	462.42±491.79	374.49±491.01	0.052
Albumin	25.85±14.89	20.14±17.33	<0.01
Total Bilirubin	2.74±6.23	2.42±10.25	0.358
Direct Bilirubin	1.09±3.71	1.27±8.33	0.396
Indirect Bilirubin	5.18±29.23	1.15±2.94	0.056
Imaging with Unilateral Pneumonia	25(19%)	30(14%)	0.124
Imaging with Bilateral Pneumonia	85(63%)	106(50%)	0.006

Table 1 also shows the baseline laboratory values of the two groups on admission. Mean values were based on the total number of patients who had the respective laboratory examination done, since not all patients in the study had a complete panel of laboratory examinations. Patients with GI symptoms had higher values of AST (44.1±57.39 vs 32.1±39.2, p=0.017), ALT (57.23±67.92 vs 44.72±43.95, p=0.029), creatinine (166.19±325.43 vs 99.8±158.32, p=0.014), and blood urea nitrogen (6.59±10.21 vs 4.49±5.92, p=0.015), and quantitative C-reactive protein (17.12±41.33 vs 7.08±23.38, p = 0.005) compared to those without GI symptoms. Procalcitonin was lower in patients with GI symptoms (0.32±0.6 vs 0.8±2.85, p=0.009), while albumin was still lower than normal but higher than those without GI symptoms (25.85±14.89 vs 20.14±17.33, p< 0.01). There are also more patients with GI symptoms having bilateral pneumonia in imaging studies (63% vs 50%, p=0.006).

Overall, there was a total of 134 COVID-19 patients (38.5%) who have had at least one GI symptom as shown in Table 2. Of these patients, diarrhea (50%) was the most common symptom, followed by loss of appetite (40%), abdominal pain (14%), nausea/vomiting (7%), gastrointestinal bleeding (4%), bloating (2%) and constipation (2%).

Table 2. Distribution of Gastrointestinal Symptoms

	Gastrointestinal Symptoms	Frequency	%
N = 134 COVID (+) patients with 1 or more GI Symptoms	Diarrhea	67	50%
	Loss of / decreased appetite	54	40%
	Abdominal pain / discomfort	19	14%
	Nausea / vomiting	10	7%
	Gastrointestinal Bleeding	6	4%
	Bloating	3	2%
	Constipation	3	2%

In Table 3, mild disease on admission was noted more on those without GI symptoms (21.6% vs 42.52%, p<0.01), while moderate and critical infection on admission were noted more on those with GI symptoms (moderate 53.7% vs 39.25%, p=0.003; critical 17.9% vs 11.68%, p=0.049). Compared to COVID-19 patients without GI symptoms, there were also more patients with GI symptoms who had septic shock (19% vs 11%, p-value 0.017), acute kidney injury (11% vs 9%, p-value <0.01) and acute myocardial injury (5% vs 1%, p-value <0.02). There were also more patients with GI symptoms who had acute respiratory distress syndrome, but difference from those without GI symptoms was not statistically significant (p-value 0.107).

Table 3. Clinical Severity of COVID-19 on Admission and Complications During Course of Disease

Clinical Profile of COVID-19 Patients	GI Symptomatic N = 134	GI Asymptomatic N = 214	P-value
Disease Severity on Admission			
- Mild COVID-19	29(21.6%)	91(42.52%)	<0.01
- Moderate COVID-19	72(53.7%)	84(39.25%)	0.003
- Severe COVID-19	9(6.7%)	14(6.54%)	0.467
- Critical COVID-19	24(17.9%)	25(11.68%)	0.049
Complications During Admission			
Septic Shock	*25(19%)*	*23(11%)*	0.017
Acute Respiratory Distress Syndrome (ARDS)	*35(26%)*	*44(21%)*	0.107
Acute Kidney Injury	*15(11%)*	*19(9%)*	<0.01
Acute Myocardial Injury	*7(5%)*	*2(1%)*	<0.02

Binary logistic regression analysis was used to check for association of symptoms with outcomes of disease severity and death (Table 4). Odds ratio was adjusted for the known predictors of poor outcomes such as age and comorbidities such as hypertension, diabetes, chronic lung and kidney disease. In this analysis, those with abdominal pain were 3.194 times more likely to develop severe to critical disease (OR=3.194, p<0.05); this was statistically significant. Patients with GI bleeding were 6.892 times more likely to develop in to severe to critical severity (OR 6.892, p=0.171), but this finding was not significant. Significantly increased risk for death was noted in patients who had GI bleeding (OR=18.616, P<0.05). High risk for death was also noted in patients with (OR=2.901. P>0.05), loss of appetite (OR=2.102, P>0.05), abdominal pain (OR=1.674,P>0.05), and diarrhea (OR=1.053, P>0.05), but findings were not significant.

Table 4. Binary logistic regression analysis of gastrointestinal symptom and severe to critical COVID-19 and death, with adjustments for age and comorbidities.

	Odds Ratio	95% Confidence Interval Lower Limit	Upper Limit	P-value
Gastrointestinal Symptom and Risk of Having Severe to Critical COVID-19				
Loss of / decreased appetite	0.967	0.466	2.004	0.927
Nausea / vomiting	0.815	0.148	4.500	0.814
Bloating	-	-	-	-
Abdominal pain / discomfort	3.194	1.083	9.421	0.035
Diarrhea	0.910	0.455	1.820	0.790
Gastrointestinal Bleeding	6.892	0.436	108.997	0.171
Constipation	0.200	0.013	3.019	0.245
Gastrointestinal Symptom and Risk of Death				
Loss of / decreased appetite	2.102	0.986	4.479	0.054
Nausea / vomiting	0.272	0.022	3.323	0.308
Bloating	-	-	-	-
Abdominal pain / discomfort	1.674	0.496	5.645	0.406
Diarrhea	1.053	0.462	2.400	0.903
Gastrointestinal Bleeding	18.616	1.200	288.747	0.037
Constipation	2.901	0.255	32.944	0.390

In a comparative analysis using t-test for two proportions (Table 5), results revealed that among the disease severity, mild and critical COVID-19 showed significant difference in the distribution. In this case, for mild infection, more cases were noted for those without GI manifestations (44% versus 28%, P<0.01) and for critical disease, those with GI symptoms showed significantly higher cases (28% versus 21%, P=0.0480).

In terms of clinical outcomes, no statistical difference was noted in terms of patients being discharged in those with and without GI symptoms (81% versus 86%, P=0.151). There was no statistical difference in mortality (19% versus 14%, p=0.1510) for those with and without GI manifestations.

Table 5. Comparison of Disease Severity and Clinical Outcomes

	GI Symptomatic N = 134	GI Asymptomatic N = 214	P-value
Disease Severity			
Mild COVID-19	38(28%)	94(44%)	<0.01
Moderate COVID-19	51(38%)	65(30%)	0.0690
Severe COVID-19	7(5%)	11(5%)	0.4860
Critical COVID-19	38(28%)	44(21%)	0.0480
Clinical Outcome			
Discharged	109(81%)	183(86%)	0.1510
Expired	25(19%)	31(14%)	0.1510

Discussion

In this single-center retrospective cohort study of hospitalized patients with COVID-19, 38.5% of patients manifested with at least one gastrointestinal symptom. In a large observational cohort study in North America by Elmunzer et al, 53% (1052 of 1992 patients) patients experienced at least one GI symptom, but the overall proportion decreased to 47% after excluding patients on COVID-19 treatments that may be associated with GI side-effects such as antivirals and antimalarials. (11) Another meta-analysis of 23 published and 6 preprint studies (n=4,805) done in China noted that 12% of COVID-19 patients reported GI symptoms. (12) The prevalence of GI symptoms in this study was noted to be higher than those reported among COVID-19 patients in China, but lower than in Western countries. This may be due to possible under-reporting of GI symptoms as these studies in China were done during the earlier months of the pandemic prior to the recognition of GI symptoms as common symptoms in COVID-19 infection. Similarly, since this is a retrospective study of patients admitted during the early days of the pandemic in our country, it may be possible that other GI symptoms may have been under-documented as well. Moreover, Pan's study showed that patients with GI symptoms risk prompt recognition and delayed diagnosis of COVID-19. (6) In our study, patients with GI symptoms had significantly older mean age. There were also more patients with GI symptoms and with comorbidities such as hypertension, diabetes, post CVD and CKD compared to those without GI symptoms, suggesting that patients with GI symptoms also had established risk factors for disease severity, such as older age, diabetes, hypertension, cerebrovascular disease (7) There was no significant difference in the duration of onset of symptoms to admission in patients with and without GI symptoms in our study. This is in contrast to the study of Pan et al and Han et al, showing that COVID-19 patients with digestive symptoms have a longer time from symptom onset to time of admission versus patients without digestive symptoms probably due to the delay of diagnostic studies typically reserved first for patients with respiratory symptoms. (6, 14)

In our study, diarrhea stands as the most common symptom (50%). This is consistent with several studies noting diarrhea as the most common GI symptom. (2, 15) Several studies have suggested the role of the ACE2 receptors of SARS-CoV-2 infecting cells that was expressed both in the lungs and in the intestinal epithelial cells. A study by Lukassen et al showed that SARS-CoV-2 enter cells via ACE2 receptors. (16) High ACE2 expression throughout the GI tract especially in proximal and distal enterocytes makes the gastrointestinal tract vulnerable to SARS-CoV-2, resulting in cytopathic effects, causing GI symptoms especially diarrhea. (4) Aside from that, diarrhea and vomiting lead to electrolyte disturbances and interruption of normal intestinal flora. Cytokine storm in severe disease can also cause hypoxia-induced bowel injury contributing to GI symptoms. these factors possibly add to the worsening of the patient's condition. The "gut-lung axis" proposes that changes in the composition and function of the GI and respiratory flora impact the respiratory tract and the GI tract respectively through the common mucosal immune system and immune regulation. When inflammation occurs in the GIT, intestinal mucosa damage and bacterial imbalance occurs causing cytokines and bacteria to enter the respiratory tract further affecting pulmonary response and inflammation. (17)

In our study, patients with GI symptoms also manifested with higher values of liver enzymes, BUN, Creatinine and quantitative CRP and lower values of procalcitonin, compared to those without GI symptoms. In a study by Zhou et al, the presence of GI symptoms was associated with elevated CRP ($p=0.021$) and elevated ALT ($p=0.049$). (18) Similarly, several studies have also noted increased liver enzymes (AST, ALT, Bilirubin) are noted in 15% to 20% of patients. (6, 7, 19) A cohort by Chen et al also noted similar findings with higher levels of AST [27.0 (20.0–40.0) vs. 24.0 (18.0–38.0), $p = 0.008$], LDH [258.0 (200.0–355.0) vs. 227.0 (181.0–309.0)], CRP [30.8 (9.4–68.9) vs. 9.4 (2.4–54.1), $p < 0.001$] and procalcitonin [0.06 (0.04–0.14) vs. 0.05 (0.03–0.09), $p < 0.001$] in patients with GI symptoms compared to those without. (20) As an acute phase reactant, albumin levels in patients with GI symptoms were also lower than normal, albeit slightly higher than those without GI symptoms; no available literature yet is available to explain this finding being higher than those without GI symptoms. The elevated BUN and creatinine levels may be due to dehydration secondary to poor oral intake and GI losses from diarrhea and/or vomiting and the acute kidney injury from sepsis or from possible viral tropism, on top of the age-related comorbidities especially chronic kidney disease in patients with GI symptoms. (21) According to literature, ACE-2 expression is also high in cholangiocytes which is manifested by elevated bilirubins. (22) However, in our study, this elevation was not demonstrated as only a few patients had their bilirubins tested. Bilateral pneumonia in imaging studies were also more common in patients with GI manifestations. Chen at al also reported similar findings with the rate of bilateral pneumonia higher in patients with GI symptoms (83.8% vs 75.5%, p-value = 0.002]. (20) These results highlight the need for close monitoring of liver and kidney function in patients with COVID-19.

With regard to clinical profile, moderate and critical disease were significantly more common in patients with GI symptoms on admission in our study. However, in a study by Elmunzer et al, 74% of patients with GI symptoms presented with mild symptoms. (11). One explanation may be that patients with mild symptoms may have opted for home quarantine than admission

in our setting. There were more patients with GI symptoms presenting with septic shock (p=0.017), ARDS (p=0.107), AKI (p< 0.01) and AMI (p< 0.02). In a meta-analysis by Mao et al, patients with GI symptoms had an increased risk of ARDS (OR 2·96 [95% CI 1·17–7·48]; p=0·020) and liver injury (2·71 [1·52–4·83]; p=0·0007). (7) Similarly, COVID-19 patients with GI symptoms were more likely to require invasive ventilation compared to those patients without GI symptoms (6.76% vs 2.08%, p=0.034). (8) Hence, a higher incidence of complications such as septic shock, acute kidney injury and acute myocardial infarction was noted in patients with GI symptoms. In addition, patients with GI symptoms in our study were mostly middle-aged (mean age of 54 years old) and had more comorbidities than the GI asymptomatic population. Age and comorbidities may also play a factor in the elevation of laboratory markers and the vulnerability to complications compared to the other group due to the compromised immune system and a persistent pro-inflammatory state seen in these patients. (23, 24, 25)

Our study also reported the relationship of GI symptoms on the likelihood of severe-to-critical COVID-19 and death, without the established risk factors for severe disease such as age and comorbidities. In our study, patients with abdominal pain were significantly 3.194 times more likely to have severe to critical disease (OR=3.194, p<0.05). Similarly, abdominal pain was noted to be more common among those admitted to the ICU compared to those who were not admitted in the ICU (8.3% vs 0% respectively, p=0.02), according to Wang et al. (26) Patients with GI bleeding had the highest risk of death, compared to other GI symptoms in our study. It is important to note that these patients with GI bleeding were managed conservatively, due to the concerns about transmission risk during endoscopic procedures. This was different from other studies showing that GI bleeding on admission does not significantly affect mortality (OR 0.62, 95%CI 0.31-1.24, p=0.17) or need for mechanical ventilation (OR 0.50, 95%CI 0.21-1.17, p=0.10). (27) A possible explanation could be the high expression of ACE2 receptors in the GI tract.

It is important to note that COVID-19 mostly affects the lungs, hence, pneumonia is the most common presentation. However, with this study, we were able to note that most patients with moderate to critical COVID-19 pneumonia had GI manifestations on presentation. The association of GI symptoms on presentation with severity of COVID-19 disease is as much linked to the severity of pneumonia. This could be explained by the gut-lung axis, showing a bidirectional interaction between the lung mucosa and the gut microbiota. (30) GI symptoms in COVID-19 were linked to decreased diversity of gut microbiota, immune dysregulation and delayed viral clearance. Such dysbiosis in the GI tract is associated with increased morbidity and/or mortality because of worsened inflammation and decreased anti-inflammatory mechanisms both in the respiratory and GI systems. (31) Moreover, as most of our patients who are GI symptomatic were middle-aged with comorbidities and previous or established gut dysbiosis, hypertension, obesity, diabetes, chronic kidney disease and other age-related disorders is involved in the dysregulated immune response to SARS-CoV-2, more severe disease in patients with comorbidities can be expected. (25)

There are several limitations in our study such as the retrospective design, single-center hospital-based study, lack of validated definitions of GI symptoms, and the exclusion of non-hospitalized patients with possible mild to moderate disease. Nevertheless, our study provides valuable data on the overall burden of GI symptoms in the context of this pandemic. We recommend more studies with a rigorous design such as that of a prospective study with validated definitions of GI symptoms and possible inclusion of GI side effects of COVID-19 treatment.

In conclusion, gastrointestinal symptoms are common in patients with COVID-19, with diarrhea being the most common manifestation. A low threshold for testing may be advised in these patients. Gastrointestinal manifestations in patients with COVID-19 may be associated with moderate and critical illness but these symptoms were not associated with death.

Increasing awareness, comprehensive symptom definitions and a prospective study design including patients in the community or out-patient setting would provide better estimates on GI manifestations of this disease.

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