Gastrointestinal Manifestations and Health Outcomes in Patients with COVID-19 Infection in a Tertiary Hospital

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Abstract

Objectives: to determine the frequencies of gastrointestinal manifestations and identify associations with outcomes among COVID-19 patients admitted in a tertiary hospital. Furthermore, it sought to determine conditions and risk factors that can be attributed to the development of these gastrointestinal symptoms.

Materials and Methods: This was a retrospective cohort of 1212 adult patients admitted at the Philippine General Hospital from April to September 2020 for COVID-19 infection. Data were gathered from an established database and chart review. Frequencies of observations were tabulated and expressed in percentages. Analytical statistics via the Fisher's Exact test was used to determine associations.

Results: A total of 597 observations of gastrointestinal symptoms was noted: diarrhea (16.4%), anorexia (13.3%), ageusia/dysgeusia/hypogeusia (7.7%), vomiting (4.5%), abdominal discomfort (4.7%), nausea (1.7%), and gastrointestinal bleeding (0.7% - [melena 0.5%, hematochezia 0.16%, hematemesis 0.08%]). Most of these patients had moderate COVID infection (38.37%). Gastrointestinal bleeding was significantly associated with the need for oxygen support (p = 0.009), invasive ventilation (p = 0.002), invasive ventilation (p= 0.001), ICU admission (p = 0.006) and mortality (p= 0.006). Anorexia was significantly associated with the need for oxygen support (p = <0.001), invasive ventilation (p= <0.001), renal replacement therapy (p = 0.003), ICU admission (p = <0.001) and mortality (p = <0.001). Vomiting was significantly associated with need for invasive ventilation (p = 0.023) and renal replacement therapy (p = 0.003).

Conclusion: Gastrointestinal manifestations can present among patients with COVID-19 infection and can affect overall prognosis.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) is an infectious disease caused by a new strain of coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) and was unknown before an outbreak was documented in Wuhan, China last December 2019.[1] Since its inception, many countries had been affected, crippling economic machineries and taking away lives. During the time of this writing, across 5 continents, at least a 103 million confirmed cases with at least 2.2 million deaths had already been documented.[2] The Philippines has not been spared and as of January 27, 2021, a total of at least 524 thousand cases with 10 thousand deaths had been recorded.[3] These figures are still continuing to grow.

It has been widely reported that respiratory symptoms, such as fever, dry cough and dyspnea, are the most frequent manifestations of COVID-19 infection. However, the incidence of less common features like diarrhea, nausea, vomiting, ageusia/dysgeusia/hypogeusia, abdominal discomfort and gastrointestinal bleeding have as well been documented; these varies significantly among different study populations, presenting frequently with early and mild onset followed by the typical respiratory symptoms.[4]

Gastrointestinal Manifestations of COVID-19

Emerging data suggest that the gastrointestinal tract and the liver might also be affected by SARS-CoV-2, on the basis that gastrointestinal epithelial cells and

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liver cells express angiotensin-converting enzyme 2 (ACE2), the major receptor of SARS-CoV-2.[5] Furthermore, patients can present with a multitude of gastrointestinal manifestations such as anorexia, vomiting and abdominal pain as a systemic viral response. Diarrhea can also be present, which was the most common symptom in both adults and children. Although the specific mechanisms involved in diarrhea pathogenesis are not entirely known, viral infection is likely to cause an alteration of intestinal permeability, resulting in enterocyte malabsorption.[6]

Data on Frequency of Gastrointestinal Manifestations of COVID-19

Two systematic reviews and meta-analysis were published showing data on the frequency of gastrointestinal manifestations of COVID-19.

A study done by Cheung, et. al.[7] reviewing 60 studies with data on GI symptoms (4243 patients) had shown that the pooled prevalence of GI manifestations was 18%. The most common symptom was anorexia (27%), followed by diarrhea (12%), nausea and vomiting (10%), and abdominal pain (9%). Prevalence of GI symptoms was 17% in patients with severe disease compared with 12% in those with non-severe disease and was similar among adults, children, and pregnant women.

In a much earlier systematic review and meta-analysis published in The Lancet Gastroenterology & Hepatology Journal, Ren Mao and colleagues[8] analyzed data from 35 studies that included 6686 patients with COVID-19. In 29 studies (6064 cases) reporting gastrointestinal symptoms in patients with COVID-19, the pooled prevalence of digestive symptoms was 15% (95% CI 10–21), the most common of which were nausea or vomiting, diarrhea, and anorexia. Of note, the authors report that around 10% of patients presented only with gastrointestinal symptoms and without respiratory features.

Among studies involving cohorts of patients with COVID-19 infection, the latest study looking into the same interest was done by Lijing, et.al.,[9] which included 204 patients with confirmed COVID-19 cases. They found out that 103 of these individuals presented with digestive symptoms, such as lack of appetite (79%), diarrhea (34%), vomiting (4%), and abdominal pain (2%). They reported of six patients with only digestive manifestations present during the whole course of the disease.

Presently, no data has been published in the local settings regarding the frequency and characteristics of gastrointestinal manifestations among Filipino COVID-19 patients.

Clinical Implications of Gastrointestinal Manifestations of COVID-19

There are contradictory results among studies in terms of association of presence of gastrointestinal symptoms with more severe COVID-19 illness.[10] A systematic review of four studies by Gul, et. al.[11] showed that the presence of gastrointestinal symptoms were equivocally related with mortality (pooled OR 0.91, 95% CI 0.49-1.68) and shows a trend to the development of ARDS (pooled OR 2.94, 95% CI 1.17-7.40). Additional studies are needed to clarify this.

RESEARCH QUESTION

Among adult patients diagnosed with COVID-19 infection, how frequent are gastrointestinal manifestations and how do the presence of these manifestations affect the over- all prognosis and health outcomes of infected patients?

OBJECTIVES

General Objectives:

To determine the frequency of gastrointestinal manifestations among COVID-19 patients and correlate these with health outcomes among patients admitted in the Philippine General Hospital from April 1, 2020 to September 30, 2020

Specific Objectives:

1. To determine the frequency and characteristics of the gastrointestinal symptoms of patients with COVID-19 infection, specifically:
   a. Nausea and Vomiting

b. Anorexia

c. Dygeusia/Ageusia/Hypogeusia

d. Diarrhea

e. Abdominal pain/discomfort

f. Gastrointestinal bleeding presenting as coffee-ground vomiting, melena, hematochezia or hematemesis

2. To determine prior conditions and risk factors that can be attributed and correlated to the development of gastrointestinal symptoms among these patients, specifically:
   a. Comorbidities: heart disease, hypertension, diabetes, chronic lung diseases, (asthma and COPD), chronic liver disease, active tuberculosis, chronic kidney disease, HIV infection, prior stroke/neurologic diseases and malignancies.
   b. Smoking, alcohol intake and illicit drug use

3. To determine association between the presence of gastrointestinal manifestations and health outcomes among these patients, specifically:
   a. Need for Oxygen Support
   b. Need for Invasive ventilation/Intubation c. Need for ICU admission
   c. Need for Renal Replacement Therapy e. Mortality

METHODOLOGY

Study Design and Setting

This was a retrospective cohort study of patients admitted at the COVID wards of the Philippine General Hospital admitted from April 1, 2020 to September 30, 2020.

Data were gathered through an established database and chart review of medical records of adult patients with laboratory-confirmed COVID-19 infection admitted at the designated COVID wards of the Philippine General Hospital.

Study Population and Sampling

A total of 1212 patients were included in this study. Purposive sampling was utilized for the inclusion of patients in this study. Eligibility of the included patients was guided by the following criteria:

Inclusion criteria: Adult patients aged $\geq$ 18 years old with laboratory – confirmed COVID-19 positive test admitted at the Philippine General Hospital form April 1, 2020 to September 30, 2020

Exclusion criteria: pediatric patients

Definition of Terms

a. Previous Classification of Disease Severity use by Chinese Center for Disease Control and Prevention[12]

   Mild to moderate – patients with mild symptoms up to mild pneumonia
   Severe – patients with dyspnea, hypoxia, or >50% lung involvement on imaging
   Critical – patients with respiratory failure, shock, or multiorgan system dysfunction

DATA COLLECTION AND STATISTICAL ANALYSIS

Data Collection and Monitoring

a. Data Collection Instruments – The data were collected by handpicking data by the principal investigator and co-investigators from an existing COVID-19 database collated and anonymized by the Department of Medicine, Division of Infectious diseases. In case there was no data or the data is incomplete on the signs/symptoms and laboratories in the database, the patients' charts were retrieved for review upon request for de-anonymization of the database from the department. Other laboratory tests which may not be available on the chart will be retrieved via OpenMRS™ software that is provided readily by the hospital to all authorized physicians.

b. Data Management – Data were encoded by the principal investigator through the use of the data collection forms and the dummy tables. Appropriate patient code were assigned to each individual patient to ensure anonymity.

c. Data Protection Plan – In the event that de-anonymization of the database were needed for further data collection, all records retrieved that link an individual patient to a specific information were kept in confidence and were not released. Only the investigators of this study had access to the data. In case of breach in privacy and confidentiality, reports were forwarded to the PGH Data Privacy Officer for mitigation.

d. Data Archiving – Data were kept under lock and key by the principal investigators and co-investigators. Data will be stored for at least 1 year from the publication of this paper. Data were encoded in word and excel formats. These are encrypted and stored in dedicated hard drives only accessible by the principal investigator of this study.

Statistical Analysis

Frequencies of observations were tabulated and expressed in percentages. To determine associations, the Fisher exact test was used for statistical analysis given that the data were not normally distributed. All statistical analyses were performed using SPSS 22.0. The significance level recognized was at a P value of < 0.05.

ETHICAL CONSIDERATIONS

The study was conducted upon the approval of the Technical Review Board (TRB) of Department of Internal Medicine and PGH-Expanded Health Research Office (EHRO).

Informed Consent

Since the research presented no more than minimal risk due to its nature being only a retrospective review, informed consent for this study was waived for the chart review part. This was approved by the UP-Medicine Research Ethical Board (UPMREB) after application and assessment by the said board.

A request for a waiver of consent was requested from the UPMREB panel for this study for the following reasons, in accordance with the National Ethical Guidelines for Health and Health-Related Researches, provisions 17.1-17.4, page 16:

- The research presents no more than minimal risk.
- The waiver or alteration will not adversely affect the rights and welfare of the participants.
- This research cannot be practicably carried out without the waiver of informed consent.

Autonomy

Collection of the data through chart review as well as its interpretation were not foreseen to directly affect the patient's welfare. More importantly, ensuring confidentiality in handling patient's data was consistently implemented throughout the study. Reference numbers were assigned to cases reviewed to maintain patient's anonymity.

Beneficence

Despite the absence of direct benefit to included subjects in the study, determining the clinical profile, presence of gastrointestinal manifestations and possibly establishing clinical associations to morbidity and mortality among laboratory confirmed COVID-19 positive patients shall significantly guide clinicians in the prioritization and formulation of a comprehensive diagnostic and management plan for future patients involved. No financial compensation were offered for participation.

Disclosure of Conflict of Interest

The investigators declared that there were no competing interests existing.

RESULTS

Characteristics of Study Participants and Frequencies of Gastrointestinal Manifestations

The baseline characteristics of the participants included in this study are seen in table 1. A total of 597 observations of gastrointestinal symptoms were reported with diarrhea (16.4%) being the most frequent symptom. All gastrointestinal symptoms were reported by 370 patients comprised mostly of those patients classified as moderate COVID infection (38.38%).

Table 1. Clinical characteristics of patients with COVID-19 included

Characteristics	N=1212
Sex	
Male	637 (52.56%)
Female	575 (47.42%)
Comorbidities	
Hypertension	582 (48.02%)
Diabetes Mellitus	310 (25.58%)
Heart Disease	165 (13.62%)
Chronic Kidney disease	107 (8.83%)
Chronic Liver Disease	11 (0.91%)
COPD	29 (2.40%)
Asthma	87 (7.18%)
Active TB	34 (2.81%)
HIV	7 (0.58%)
Malignancies	69 (5.69%)
Neurologic	83 (6.90%)
Vices	
Smoker	258 (21.29%)
Significant Alcohol Use	287 (23.68%)
Illicit Drug Use	22 (1.82%
Severity of Illness:	
Mild	203 (16.75%)
Moderate	487 (40.18%)
Severe	182 (15.02%)
Critical	340 (28.05%)
Outcomes:	
Need for ICU Admission	459 (37.87%)
Need for O2 Support	661 (54.54%)
Need for Invasive Ventilation/Intubation	241 (19.98%)
Need for Renal Replacement Therapy	113 (9.32%)
Discharged/Recovered	993 (81.93%)
Expired	219 (18.06%)

Table 2. Frequencies of GI Manifestations

	N = 597
Anorexia	161 (13.3%)
Ageusia/Dysgeusia/Hypogeusia	94 (7.7%)
Nausea	21 (1.7%)
Vomiting	55 (4.5%)
Diarrhea	199 (16.4%)
Abdominal Discomfort	58 (4.7%)
GI Bleeding	9 (0.7%)
Coffee-ground vomiting	0
Hematemesis	1 (0.08%)
Melena	6 (0.5%)
Hematochezia	2 (0.16)

Table 3. Over-all frequency of patients presenting with GI symptoms and over-all COVID disease severity of these patients stratified from mild to critical

	N = 370
Mild	71 (19.2%)
Moderate	142 (38.38%)
Severe	58 (15.68%)
Critical	99 (26.75%)

Association of Health Determinants/Risk Factors with Gastrointestinal Symptoms

Table 4.1 shows the different p-values showing associations between the different surveyed health determinants/risk factors and the different surveyed GI manifestations reported for this study with values <0.05 considered as significant associations.

The following associations were observed:

- DIARRHEA - A history of illicit drug use, HIV infection, cancer and neurologic disease were significantly associated with the presentation of diarrhea.

- NAUSEA - A history of hypertension, chronic kidney disease and neurologic disease were significantly associated with the presentation of nausea.

- VOMITING - Chronic kidney disease was significantly associated with the presentation of vomiting.

- ABDOMINAL PAIN/DISCOMFORT - Diabetes Mellitus, HIV infection as well as malignancy were significantly associated with the presentation of abdominal pain/discomfort.

- MELENA - A history of heart disease and chronic kidney disease were significantly associated with the presentation of melena.

Table 4. Cross-table reference for health determinants/risk factors with the different GI manifestations

		DIARRHEA (-)	DIARRHEA (+)	p-value	NAUSEA (-)	NAUSEA (+)	p-value	VOMITING (-)	VOMITING (+)	p-value	ANOREXIA (-)	ANOREXIA (+)	p-value	ABDOMINAL PAIN / DISCOMFORT (-)	ABDOMINAL PAIN / DISCOMFORT (+)	p-value
SMOKER	(-)	785	169		937	17		915	39		825	129		908	46	
	(+)	228	30	0.018	254	4	1.000	242	16	0.176	226	32	0.680	246	12	1.000
ALCOHOL BEVERAGE DRINKER	(-)	764	161		908	17		889	36		805	120		883	42	
	(+)	249	38	0.101	283	4	0.797	268	19	0.072	246	41	0.552	271	16	0.526
ILLICIT DRUG USE	(-)	991	199		1169	21		1135	55		1030	160		1132	58	
	(+)	22	0	0.037*	22	0	1.000	22	0	0.620	21	1	0.344	22	0	0.621
DM	(-)	749	153		887	15		858	44		788	114		851	51	
	(+)	264	46	0.424	304	6	0.801	299	11	0.429	263	47	0.286	303	7	0.013*
HPN	(-)	527	103		624	6		604	26		560	70		596	34	
	(+)	486	96	1.000	567	15	0.045*	553	29	0.493	491	91	0.022	558	24	0.346
HEART DISEASE	(-)	868	179		1028	19		1000	47		908	139		996	51	
	(+)	145	20	0.115	163	2	0.757	157	8	0.840	143	22	1.000	158	7	0.846
CHRONIC LIVER DISEASE	(-)	1004	197		1180	21		1146	55		1040	161		1145	56	
	(+)	9	2	0.699	11	0	1.000	11	0	1.000	11	0	0.377	9	2	0.094
CHRONIC KIDNEY DISEASE	(-)	919	186		1090	15		1062	43		956	149		1054	51	
	(+)	94	13	0.273	101	6	0.007*	95	12	0.002*	95	12	0.654	100	7	0.344
COPD	(-)	985	198		1162	21		1129	54		1026	157		1127	56	
	(+)	28	1	0.071	29	0	1.000	28	1	1.000	25	4	1.000	27	2	0.646
ASTHMA	(-)	946	179		1107	18		1071	54		977	148		1073	52	
	(+)	67	20	0.098	84	3	0.187	86	1	0.175	74	13	0.623	81	6	0.300
ACTIVE TB	(-)	983	195		1158	20		1126	52		1023	155		1122	56	
	(+)	30	4	0.639	33	1	0.453	31	3	0.197	28	6	0.440	32	2	0.676
HIV	(-)	1011	194		1184	21		1150	55		1045	160		1149	56	
	(+)	2	5	0.002*	7	0	1.000	7	0	1.000	6	1	1.000	5	2	0.040*
CANCER	(-)	947	196		1123	20		1092	51		994	149		1094	49	
	(+)	66	3	0.004*	68	1	1.000	65	4	0.549	57	12	0.277	60	9	0.004*
NEUROLOGIC DISEASE	(-)	934	195		1112	17		1079	50		983	146		1075	54	
	(+)	79	4	0.002*	79	4	0.050*	78	5	0.419	68	15	0.181	79	4	1.000

Table 4. continued

		AGEUSIA / HYPO / DYSGEUSIA			HEMATEMESIS			COFFEE-GROUND VOMITING			MELENA			HEMATOCHEZIA		
		(-)	(+)	p-value	(-)	(+)	p-value	(-)	(+)	p-value	(-)	(+)	p-value	(-)	(+)	p-value
SMOKER	(-)	879	75		953	1		954	0		950	4		952	2	
	(+)	239	19	0.896	258	0	1.000	258	0	no test	256	2	0.613	258	0	1.000
ALCOHOL BEVERAGE DRINKER	(-)	854	71		924	1		925	0		921	4		923	2	
	(+)	264	23	0.899	287	0	1.000	287	0	no test	285	2	0.632	287	0	1.000
ILLICIT DRUG USE	(-)	1099	91		1189	1		1190	0		1184	6		1188	2	
	(+)	19	3	0.240	22	0	1.000	22	0	no test	22	0	1.000	22	0	1.000
DM	(-)	833	69		901	1		902	0		896	6		901	1	
	(+)	285	25	0.806	310	0	1.000	310	0	no test	310	0	0.347	309	1	0.446
HPN	(-)	587	43		629	1		630	0		627	3		628	2	
	(+)	531	51	0.237	582	0	1.000	582	0	no test	579	3	1.000	582	0	0.500
HEART DISEASE	(-)	964	83		1047	0		1047	0		1044	3		1045	2	
	(+)	154	11	0.642	164	1	0.136	165	0	no test	162	3	0.036*	165	0	1.000
CHRONIC LIVER DISEASE	(-)	1107	94		1200	1		1201	0		1195	6		1199	2	
	(+)	11	0	1.000	11	0	1.000	11	0	no test	11	0	1.000	11	0	1.000
CHRONIC KIDNEY DISEASE	(-)	1019	86		1105	0		1105	0		1102	3		1103	2	
	(+)	99	8	1.000	106	1	0.088	107	0	no test	104	3	0.011*	107	0	1.000
COPD	(-)	1089	94		1182	1		1183	0		1177	6		1181	2	
	(+)	29	0	0.161	29	0	1.000	29	0	no test	29	0	1.000	29	0	1.000
ASTHMA	(-)	1038	87		1124	1		1125	0		1119	6		1123	2	
	(+)	80	7	0.836	87	0	1.000	87	0	no test	87	0	1.000	87	0	1.000
ACTIVE TB	(-)	1085	93		1177	1		1178	0		1173	5		1176	2	
	(+)	33	1	0.511	34	0	1.000	34	0	no test	33	1	0.157	34	0	1.000
HIV	(-)	1111	94		1204	1		1205	0		1199	6		1203	2	
	(+)	7	0	1.000	7	0	1.000	7	0	no test	7	0	1.000	7	0	1.000
CANCER	(-)	1052	91		1142	1		1143	0		1137	6		1142	1	
	(+)	66	3	0.358	69	0	1.000	69	0	no test	69	0	1.000	68	1	0.111
NEUROLOGIC DISEASE	(-)	1042	87		1129	1		1129	0		1124	5		1127	2	
	(+)	76	7	0.831	82	1	0.068	83	0	no test	82	1	0.347	83	0	1.000

Association of Gastrointestinal Manifestations with In-Hospital Health Outcomes

The Fisher Exact test was used to determine associations between the presence of gastrointestinal symptoms and the outcomes that were studied,

specifically the need of oxygen support, need for invasive ventilation, need for renal replacement therapy, need for ICU admission and mortality. The subsequent tables show the different p-values showing these associations.

Table 5. Cross-table reference of GI manifestations with need for oxygen support

| | | NEED FOR O2 SUPPORT | | | | | |
| | | (-) | | (+) | | Total | |
		Count	Row %	Count	Row %	Count	p-value
Diarrhea	(-)	456	45.0%	557	55.0%	1013	
	(+)	95	47.7%	104	52.3%	199	0.485
Nausea	(-)	542	45.5%	649	54.5%	1191	
	(+)	9	42.9%	12	57.1%	21	0.830
Vomiting	(-)	533	46.1%	624	53.9%	1157	
	(+)	18	32.7%	37	67.3%	55	0.054
Anorexia	(-)	512	48.7%	539	51.3%	1051	
	(+)	39	24.2%	122	75.8%	161	<0.001*
Abdominal Pain / Discomfort	(-)	522	45.2%	632	54.8%	1154	
	(+)	29	50.0%	29	50.0%	58	0.501
Ageusia / Hypo / Dysgeusia	(-)	505	45.2%	613	54.8%	1118	
	(+)	46	48.9%	48	51.1%	94	0.518
Gastrointestinal Bleeding	(-)	551	45.8%	653	54.2%	1204	
	(+)	0	0.0%	8	100.0%	8	0.009*
Hematemesis	(-)	551	45.5%	660	54.5%	1211	
	(+)	0	0.0%	1	100.0%	1	1.000
Coffee-ground Vomiting	(-)	551	45.5%	661	54.5%	1212	
	(+)	0	0.0%	0	0.0%	0	no test
Melena	(-)	551	45.7%	655	54.3%	1206	
	(+)	0	0.0%	6	100.0%	6	0.035*
Hematochezia	(-)	551	45.5%	659	54.5%	1210	
	(+)	0	0.0%	2	100.0%	2	0.504

The manifestations of anorexia (p = <0.001) and gastrointestinal bleeding (p = 0.009) were significantly associated with the need for oxygen support among the population included in this study. Sub-analysis of gastrointestinal bleeding showed that melena (p= 0.035) was significantly associated with this outcome. (Table 5)

Table 6. Cross-table reference of GI manifestations with need for invasive ventilation or intubation

		NEED FOR INVASIVE VENTILATION OR INTUBATION					
		(-)		(+)		Total	
		Count	Row %	Count	Row %	Count	p-value
Diarrhea	(-)	804	79.4%	209	20.6%	1013	
	(+)	167	83.9%	32	16.1%	199	0.146
Nausea	(-)	956	80.3%	235	19.7%	1191	
	(+)	15	71.4%	6	28.6%	21	0.282
Vomiting	(-)	934	80.7%	223	19.3%	1157	
	(+)	37	67.3%	18	32.7%	55	0.023*
Anorexia	(-)	861	81.9%	190	18.1%	1051	
	(+)	110	68.3%	51	31.7%	161	<0.001*
Abdominal Pain / Discomfort	(-)	928	80.4%	226	19.6%	1154	
	(+)	43	74.1%	15	25.9%	58	0.240
Ageusia / Hypo / Dysgeusia	(-)	891	79.7%	227	20.3%	1118	
	(+)	80	85.1%	14	14.9%	94	0.228
Gastrointestinal Bleeding	(-)	969	80.5%	235	19.5%	1204	
	(+)	2	25.0%	6	75.0%	8	0.001*
Hematemesis	(-)	971	80.2%	240	19.8%	1211	
	(+)	0	0.0%	1	100.0%	1	0.199
Coffee-ground Vomiting	(-)	971	80.1%	241	19.9%	1212	
	(+)	0	0.0%	0	0.0%	0	no test
Melena	(-)	970	80.4%	236	19.6%	1206	
	(+)	1	16.7%	5	83.3%	6	0.002*
Hematochezia	(-)	970	80.2%	240	19.8%	1210	
	(+)	1	50.0%	1	50.0%	2	0.358

The manifestations of vomiting (p = 0.023), anorexia (p = <0.001) and gastrointestinal bleeding (p= 0.001) were significantly associated with the need for invasive ventilation among the population included in this study. Sub-analysis of the gastrointestinal bleeding showed that melena (p=0.002) was significantly associated with this outcome. (Table 6)

Table 7. Cross-table reference of GI manifestations with need for renal replacement therapy

		NEED FOR RENAL REPLACEMENT THERAPY					
		(-)		(+)		Total	
		Count	%	Count	%	Count	p-value
Diarrhea	(-)	919	90.7%	94	9.3%	1013	
	(+)	180	90.5%	19	9.5%	199	0.894
Nausea	(-)	1081	90.8%	110	9.2%	1191	
	(+)	18	85.7%	3	14.3%	21	0.434
Vomiting	(-)	1056	91.3%	101	8.7%	1157	
	(+)	43	78.2%	12	21.8%	55	0.003*
Anorexia	(-)	964	91.7%	87	8.3%	1051	
	(+)	135	83.9%	26	16.1%	161	0.003*
Abdominal Pain / Discomfort	(-)	1047	90.7%	107	9.3%	1154	
	(+)	52	89.7%	6	10.3%	58	0.816
Ageusia / Hypo / Dysgeusia	(-)	1011	90.4%	107	9.6%	1118	
	(+)	88	93.6%	6	6.4%	94	0.361
Gastrointestinal Bleeding	(-)	1093	90.8%	111	9.2%	1204	
	(+)	6	75.0%	2	25.0%	8	0.167
Hematemesis	(-)	1099	90.8%	112	9.2%	1211	
	(+)	0	0.0%	1	100.0%	1	0.093
Coffee-ground Vomiting	(-)	1099	90.7%	113	9.3%	1212	
	(+)	0	0.0%	0	0.0%	0	no test
Melena	(-)	1095	90.8%	111	9.2%	1206	
	(+)	4	66.7%	2	33.3%	6	0.101
Hematochezia	(-)	1097	90.7%	113	9.3%	1210	
	(+)	2	100.0%	0	0.0%	2	1.000

The manifestation of vomiting (p = 0.003) and decreased appetite (0.003) were significantly associated with the need for renal replacement therapy among the population included in this study. (Table 7)

Table 8. Cross-table reference of GI manifestations with need for ICU admission

		NEED FOR ICU ADMISSION					
		(-)		(+)		Total	
		Count	%	Count	%	Count	p-value
Diarrhea	(-)	624	61.6%	389	38.4%	1013	
	(+)	129	64.8%	70	35.2%	199	0.424
Nausea	(-)	741	62.2%	450	37.8%	1191	
	(+)	12	57.1%	9	42.9%	21	0.655
Vomiting	(-)	724	62.6%	433	37.4%	1157	
	(+)	29	52.7%	26	47.3%	55	0.156
Anorexia	(-)	690	65.7%	361	34.3%	1051	
	(+)	63	39.1%	98	60.9%	161	<0.001*
Abdominal Pain / Discomfort	(-)	719	62.3%	435	37.7%	1154	
	(+)	34	58.6%	24	41.4%	58	0.581
Ageusia / Hypo / Dysgeusia	(-)	688	61.5%	430	38.5%	1118	
	(+)	65	69.1%	29	30.9%	94	0.152
Gastrointestinal Bleeding	(-)	752	62.5%	452	37.5%	1204	
	(+)	1	12.5%	7	87.5%	8	0.006*
Hematemesis	(-)	753	62.2%	458	37.8%	1211	
	(+)	0	0.0%	1	100.0%	1	0.379
Coffee-ground Vomiting	(-)	753	62.1%	459	37.9%	1212	
	(+)	0	0.0%	0	0.0%	0	no test
Melena	(-)	752	62.4%	454	37.6%	1206	
	(+)	1	16.7%	5	83.3%	6	0.032*
Hematochezia	(-)	753	62.2%	457	37.8%	1210	
	(+)	0	0.0%	2	100.0%	2	0.143

The manifestations of anorexia (p = <0.001) and gastrointestinal bleeding (p = 0.006) were significantly associated with the need for ICU admission among the population included in this study. Sub-analysis of the gastrointestinal bleeding showed that melena (p= 0.032) was strongly associated with this outcome. (Table 8)

Table 9. Cross-table reference of GI manifestations with mortality

| | | MORTALITY | | | | | |
| | | SURVIVOR | | NON-SURVIVOR | | Total | |
		Count	%	Count	%	Count	p-value
Diarrhea	(-)	822	81.1%	191	18.9%	1013	
	(+)	171	85.9%	28	14.1%	199	0.130
Nausea	(-)	977	82.0%	214	18.0%	1191	
	(+)	16	76.2%	5	23.8%	21	0.564
Vomiting	(-)	953	82.4%	204	17.6%	1157	
	(+)	40	72.7%	15	27.3%	55	0.074
Anorexia	(-)	879	83.6%	172	16.4%	1051	
	(+)	114	70.8%	47	29.2%	161	**<0.001***
Abdominal Pain / Discomfort	(-)	948	82.1%	206	17.9%	1154	
	(+)	45	77.6%	13	22.4%	58	0.382
Ageusia / Hypo / Dysgeusia	(-)	913	81.7%	205	18.3%	1118	
	(+)	80	85.1%	14	14.9%	94	0.486
Gastrointestinal Bleeding	(-)	990	82.2%	214	17.8%	1204	
	(+)	3	37.5%	5	62.5%	8	**0.006***
Hematemesis	(-)	992	81.9%	219	18.1%	1211	
	(+)	1	100.0%	0	0.0%	1	1.000
Coffee-ground Vomiting	(-)	993	81.9%	219	18.1%	1212	
	(+)	0	0.0%	0	0.0%	0	no test
Melena	(-)	991	82.2%	215	17.8%	1206	
	(+)	2	33.3%	4	66.7%	6	**0.012***
Hematochezia	(-)	992	82.0%	218	18.0%	1210	
	(+)	1	50.0%	1	50.0%	2	0.329

The manifestations of anorexia (p = <0.001) and gastrointestinal bleeding (p = 0.006) were associated significantly with mortality among the population included in this study. Sub-analysis of the gastrointestinal bleeding showed that melena (p= 0.012) was strongly associated with this outcome. (Table 9)

DISCUSSION

In terms of symptomatology, diarrhea was the most predominant symptom among the surveyed cohort. At present, it is proposed that SARS-CoV-2, which via the ACE2 receptor can infect and exert a direct cytopathic effect on enterocytes causing diarrhea. Adverse drug reactions can be another possible explanation. Some of the antivirals, antibiotics and immunomodulators, commonly prescribed to COVID-19 patients are known to cause diarrhea.[12] It is yet unclear as to what may be the reason behind this presentation among this surveyed cohort.

With the present data, it is still unclear as to how the different risk factors are associated with the presentation of the specific gastrointestinal manifestations. A further probe on the pathogenesis is needed to further elucidate the mechanisms behind these observed associations.

This study was able to perceive associations between the different gastrointestinal symptoms and in-hospital health outcomes. Most of the published literatures reported mostly on outcomes on ARDS development and mortality. This study was able to look into outcomes of the need for renal replacement therapy and ICU admission. It is hoped that this information be able to fill a gap of knowledge in this aspect.

Across the different literature, most of the studies have not reported of the presence of gastrointestinal bleeding as a gastrointestinal manifestation among infected COVID-19 patients.[12]

This study was able to document 8 observations of gastrointestinal bleeding. Yet due to a small number of observations, it would be premature to completely establish association between the presence of COVID-19 infection and the development of gastrointestinal bleeding. A multitude of factors may be able to explain for the development of gastrointestinal bleeding for the documented cases.

There are limitations to this study. It is based on a retrospective observational study of admitted patients in a tertiary COVID referral system hospital which receives a majority of moderate to critical cases. Mild cases may be underrepresented with these given data. However, given the paucity of literature in the local setting and conflicting results from available international studies on the prognostic significance of GI involvement amidst this unprecedented rapidly evolving pandemic, this study addresses an important issue of GI tract involvement by SARS-CoV-2 and its impact on clinical. Our findings will help local clinicians triage patients better in this resource-limited setting, especially with regards to hospital admission and level of care. Larger prospective studies are necessary to elucidate the complete natural history of this disease and to confirm our findings on an even larger scale.

CONCLUSION

To our knowledge, diarrhea is the most common gastrointestinal manifestation presented by COVID-19 patients included in this study. A history of illicit drug use, HIV infection, neurologic disease, hypertension, chronic kidney disease, malignancy and heart disease may foretell the development of specific gastrointestinal manifestations. The presence of anorexia, vomiting and gastrointestinal bleeding, specifically the presentation of melena, may herald poor clinical outcomes.

RECOMMENDATIONS

Since associations have been seen among the different variables considered in this study, the investigators recommends the following:

- That further investigations be done on the etiology and pathogenesis of the development of specific gastrointestinal manifestations associated with the different health determinants/risk factors identified in this study.

- That further investigations be done to further establish a robust correlation between health outcomes and gastrointestinal manifestations given that the observations for some GI manifestations were small for this study.

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