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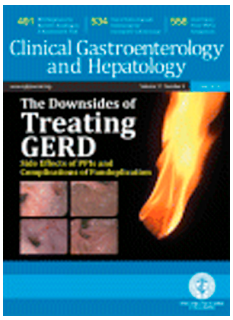

Gastrointestinal sequelae three and six months after hospitalization for Coronavirus Disease 2019

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Introduction

Gastrointestinal (GI) symptoms are highly prevalent in Coronavirus Disease 2019 (COVID-19) ranging from 17.6% to 53% [1-4]. The proposed mechanism for GI symptoms involves SARS-CoV-2 virus binding to the host cell's angiotensin-converting enzyme 2 (ACE2) receptor, commonly found in gastrointestinal tract epithelial cells[5].

With an increasing population of patients recovering from acute infection, there is now interest in understanding post-COVID-19 sequelae. Our study aims to report gastrointestinal sequelae 3 and 6 months after hospitalization for COVID-19 infection.

Methods

This is a multicenter, retrospective study of hospitalized adult patients (18 years and older) who tested positive for COVID-19 infection from March 1st, 2020 to January 24th, 2021 across 12 hospitals comprising the Northwell Health System in New York. Patients were included if 1) tested positive for SARS-CoV-2 nasal swab PCR 2) were hospitalized with GI manifestations on initial presentation 3) had 3 and/or 6 months follow up as an outpatient post-hospitalization or repeat hospitalization. Further description of methods included in supplemental material.

Results

During the study period, 17,462 COVID-19 patients were hospitalized. Of the 17,462 patients, 3,229 (18.5%) also had GI manifestations. A total of 715 (22.1%) patients had 788 (24.4%) distinct GI manifestations and also had 3 and/or 6 months outpatient follow up data post-discharge. Patient characteristics are in Table 1.

Initial GI symptoms were as follows: gastroenteritis in 414 (52.5%), GI bleeding in 161 (20.4%), malnutrition in 181 (23.0%) and idiopathic pancreatitis in 4 (0.5%) patients. Gastroenteritis resolved in 323 (90.5%) patients at 3 months and 210 (89.4%) at 6 months. GI bleeding resolved in 138 (92.0%) patients at 3 months and 89 (94.7%) at 6 months. Inability for weight regain remains present in 81

(50.6%) patients at 3 months and 33 (32.4%) at 6 months. Pancreatitis attributed to a viral etiology resolved in all patients at 3 months and 6 months.

For patients with malnutrition, median weight on admission was 156.4 pounds [IQR 131.7- 193.0]. Median weight loss for patients at 3 months was -4.9 pounds [IQR -16.7 to +6.6] and at 6 months -2.2 pounds [-19.6 to 11.8] respectively. Interestingly, 81 (59.1%) patients were unable to gain weight at 3 months and 44 (56.4 %) were unable to gain weight at 6 months. For patients with malnutrition unable to gain weight at follow up, median weight loss was -14.7 pounds [IQR -26.6 to -7.9] at 3 months and -17.8 pounds [IQR -35.2 to -6.5] at 6 months.

Discussion

We report the following important findings from 3 and 6 month follow up regarding GI symptoms and COVID-19 disease:

- GI manifestations of COVID-19 disease are common (18.5% in our cohort).
- Most initial presentations of GI bleeding, gastroenteritis and pancreatitis associated with COVID-19 infection resolve by 3 months follow up.
- Malnutrition is the most persistent GI sequelae without resolution at 3 and 6 months follow up intervals. A significant portion of patients with these complaints may have difficulty gaining weight long term (i.e. a median 14.7 pound weight loss remained for these patients at 6 months follow up).

Our study provides reassurance that most individuals with the onset of GI bleeding or gastroenteritis associated with COVID-19 infection will have resolution of these symptoms. Our study highlights the need to pay particular attention to COVID-19 patients who suffer from malnutrition during their initial hospitalization. Many of these patients may have on-going malnutrition or weight loss despite resolution of COVID-19 infection. Therefore it may be imperative to establish malnutrition screening practices in post-COVID 19 patients who have recovered from acute infection [6,7].

The strengths of our study include the largest cohort of patients with follow up data of COVID-19 associated GI symptoms to date, a diverse patient population across multiple hospitals in Long Island,

Manhattan, Queens, and Staten Island making results more generalizable, and manual chart review to confirm GI findings on admission and follow up visits. Moreover, patients were diagnosed with malnutrition by a dedicated nutrition service. Limitations of our study lie inherently in the retrospective design. Other considerations include our follow up data being restricted to our network facilities (though they are quite expansive spanning across Long Island and New York City) and 6 month follow up is not yet available for a number of patients who developed COVID-19 infection later in the study interval.

In conclusion, GI symptoms of malnutrition, weight loss, and anorexia may persist for several months after COVID-19 infection and may require further medical attention, while GI bleeding, gastroenteritis, and pancreatitis are likely to resolve after initial presentation.

References

1. Cheung, K.S., et al. Gastroenterology, 2020. 159(1): p. 81-95.
2. Elmunzer, B.J., et al. Clin Gastroenterol Hepatol, 2020;19: 1355-1365
3. Trindade AJ et al. J Intern Med. 2021;289(6):887-894.
4. Inamdar S et al. Gastroenterology. 2020;159(6):2226-2228.e2
5. Qi, F., et al. Biochem Biophys Res Commun, 2020. 526(1): p. 135-140.
6. Larrazabal, R.B., Jr., et al. Clin Nutr ESPEN, 2021. 42: p. 98-104.
7. Vitale, E., et al. Endocr Metab Immune Disord Drug Targets, 2021. Online ahead of print. doi: 10.2174/1871530321666210114154401

Table 1: Results Summary of Patients with COVID-19 Infection with GI Symptoms at 3 and/or 6 Months Follow Up

Patient Demographics	Median [IQR] or N (%)
Total # Patients (+) COVID-19 N	17462
#Pts with GI Symptoms N (%)	3229 (18.5%)
#Pts with GI Symptoms + Follow up N (%)	715 (22.1%)
#Distinct GI Symptoms in Pts	788 (24.4%)
#Pts with 3 Month Follow Up N (%)	627 (88.7%)
#Pts with 6 Month Follow Up N (%)	404 (56.5%)
Median Age Years [IQR]	66 [IQR 55-76]
Female N (%)	336 (46.9%)
Race / Ethnicity	
• Caucasian N (%)	325 (46%)
• African American N (%)	161 (23%)
• Hispanic N(%)	121 (17%)
• Asian N (%)	50 (7%)
• Native American, Alaskan, Hawaiian	5 (0.5%)
Length of Stay (Days)	9 [IQR 5-17]
Mechanical ventilation	101 (14.1%)
BIPAP	36 (5.0%)
Vasopressors	106 (14.8%)
Irritable bowel syndrome (IBS)	7 (1.0%)
Inflammatory bowel syndrome (IBD)	14 (2.0%)
GI Symptoms	
Gastroenteritis N (%)	414 (52.5%)
• Resolution at 3 Month N (%)	323 (90.5%)
• Resolution at 6 Month N (%)	210 (89.5%)
GI bleeding N (%)	161 (20.4%)
• Resolution at 3 Month N (%)	138 (92.0%)
• Resolution at 6 Month N (%)	89 (94.7%)
Malnutrition N (%)	181 (23.0%)
• Present at 3 Month N (%)	81 (53.6%)
• Present at 6 Month N (%)	33 (32.4%)
Pancreatitis N (%)	4 (0.5%)
• Resolution at 3 Month N (%)	4 (100%)
• Resolution at 6 Month N (%)	4 (100%)
Endoscopy for GI Bleeding	
Underwent endoscopy	19 (11.8%)
• Upper endoscopy	15 (9.3%)
• Lower Endoscopy	4 (2.5%)
Underwent intervention	4 (2.5%)

Findings	
• Gastric and duodenal ulcers	4 (21.1%)
• Gastritis, duodenitis	4 (21.1%)
• Angioectasias	3 (15.8%)
• Rectosigmoid ulcers	1 (5.3%)
• Diverticulosis	1 (5.3%)
• Hemorrhoids	2 (10.5%)
• Normal	4 (21.1%)
Weight Measurements	
Median Weight on Admission Lbs [IQR]	156.4 [131.7 - 193]
Median Weight Loss 3 Month Lbs [IQR]	-4.9 [-16.7 to +6.6]
Median Weight Loss 6 Month Lbs [IQR]	-2.2 [-19.6 to 11.8]
Pts Unable to Gain Weight	
• 3 Month N (%)	81 (59.1%)
• 6 Month N (%)	44 (56.4%)
• Median Weight Loss 3 Month Lbs [IQR]	-14.7 [-26.6 to -7.9]
• Median Weight Loss 6 Month Lbs [IQR]	-17.8 [-35.2 to -6.5]
Pts with Malnutrition	
Malnutrition + mechanical ventilation	36 (19.9%)
Malnutrition + BIPAP	11 (6.1%)
Malnutrition + vasopressors	41 (22.7%)

Supplemental Methods

Institutional review board approval was obtained for this study. ICD-10 codes for the following gastrointestinal symptoms were used to screen patients for initial GI manifestations: gastrointestinal bleeding (upper GI bleed, lower GI bleed, melena, hematochezia, hematemesis, bright red blood per rectum), gastroenteritis (abdominal pain/diarrhea/nausea/vomiting), malnutrition (including severe, moderate, mild protein calorie malnutrition per nutrition assessments, and anorexia), and pancreatitis. These GI manifestations were selected for the following reasons: gastroenteritis symptoms have been well described as a component of the acute presentation of COVID-19, GI bleeding has been well described in the COVID-19 literature[1,2], critical and prolonged COVID-19 hospitalization courses may result in malnutrition, and acute pancreatitis has been described as an entity associated with COVID-19 infection[3,4]. Pancreatitis was diagnosed based on the Atlanta classification. Clinical information was collected from electronic medical records using a standardized data collection sheet. We included malnutrition in the study as we have been anecdotally seeing patients with prior COVID-19 who are unable to have weight regain.

Patient charts were reviewed manually to confirm presence of GI manifestations at admission, GI bleeding and malnutrition during course of initial COVID-19 hospitalization and evaluate symptoms at 3 and 6 months follow up visits. 3 month follow up criteria included outpatient visit or repeat hospitalization 3 months after initial hospitalization date (up to 6 months), and similarly 6 month follow up was considered 6 months after initial hospitalization date. Upon manual chart review the following were excluded: those with anemia not secondary to GI bleeding, pancreatitis secondary to non-viral etiologies, and those patients with multiple gastroenteritis symptoms were consolidated (ie if abdominal pain, nausea, and vomiting all present, patient was counted for this symptom one time in the gastroenteritis category). Our population cohort had a rate of IBS and IBD at 1% and 2% respectively and thus were not excluded from the study. While there are a total number of patients in the study, some patients experienced two or more unique GI manifestations (ie if GI bleeding and malnutrition both occurred in the same patient, this was counted as two distinct GI manifestations however one patient in the study overall).

Resolution of each symptom was determined via chart review – for gastroenteritis symptoms it is the resolution of abdominal pain, nausea, vomiting, diarrhea on subsequent follow up, for GI bleeding is the absence of repeat episode of GI bleeding on follow up, for pancreatitis is it absence of recurrence of another acute pancreatitis episode/sequelae of pancreatitis, and for malnutrition based on the ability to have weight regain (the only objective marker that can be abstracted easily).

For those patients with symptoms of malnutrition, anorexia, and weight loss, weight assessments at admission, 3 and 6 months were documented. In addition those with malnutrition were documented as such on initial hospitalization via a nutrition consult by a board certified nutritionist. Descriptive statistical analysis was performed.

1. Trindade AJ, Izard S, Coppa K, et al. Gastrointestinal bleeding in hospitalized COVID-19 patients: a propensity score matched cohort study. J Intern Med. 2021;289(6):887-894.
2. Martin TA, Wan DW, Hajifathalian K, et al. Gastrointestinal Bleeding in Patients With Coronavirus Disease 2019: A Matched Case-Control Study. Am J Gastroenterol. 2020;115(10):1609-1616.
3. Inamdar S, Benias PC, Liu Y, et al. Prevalence, Risk Factors, and Outcomes of Hospitalized Patients With Coronavirus Disease 2019 Presenting as Acute Pancreatitis. Gastroenterology. 2020;159(6):2226-2228.e2.
4. Dirweesh A, Li Y, Trikudanathan G, et al. Clinical Outcomes of Acute Pancreatitis in Patients With Coronavirus Disease 2019. Gastroenterology. 2020;159(5):1972-1974.