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GASTROINTESTINAL MANIFESTATIONS AND THEIR ASSOCIATION WITH NEUROLOGIC AND SLEEP PROBLEMS IN LONG COVID-19 MINORITY PATIENTS: A PROSPECTIVE FOLLOW-UP STUDY

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Abstract

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Author's contributions: HA designed the study, HA, SC, and HB wrote the manuscript, JMC, reviewed and edited the paper; SRC, GC, MI, ZM, PW, MR, NS, SM, AN, MD, AE, VR, EE, TT, MA, OE, L, K, YAOO, CD, OD, B, AS, DCL, EH, SP, KR, BCW, RK, ZK, LCG collected and analyzed the clinical data. GO performed statistical analysis. All authors read and approved the final manuscript.

Conflict-of-interest statement: The authors declare no conflicts of interest.

Ethics approval: This study was approved by Howard University institutional review board (approval number IRB-12-MED-76)

Background: Long COVID is a condition post SARS-CoV-2 infection with persistent or recurring symptoms affecting multiple organs, and may involve viral persistence, changes to the microbiome, coagulopathies, and alterations to neuro-immune interactions. These factors can disrupt the Gut-Brain Axis, which is a complex system involving bidirectional communication between the central nervous system and the gastrointestinal (GI) system. As a result of these disruptions, individuals with long COVID may develop post-infectious functional GI disorders, which can cause a range of symptoms affecting the digestive system.

Aim: To understand frequency of GI manifestations of Long COVID and to determine association with sleep or neurological symptoms in a predominantly minority population.

Methods: We included patients with positive SARS-CoV-2 PCR (n=747) who were hospitalized from Feb. 2020 to May 2021 at Howard University Hospital and followed between 6–12 months from discharge. GI, sleep, and neurological symptoms (via the Montreal Cognitive Assessment (MoCA) scoring system) were assessed using a standardized questionnaire. Linear regression analysis, Chi-square and Fisher's exact test were utilized to determine the statistical significance of correlations of GI/Neuro/COVID.

Results: The mean age of patients was 58, with 51.6% females and a predominant African American ethnicity (73.6%, n=550). A total of 108 patients died during their initial hospital stay, with the remaining 639 patients followed-up. Three hundred fifty (350) patients responded to the questionnaire (57 patients died during the follow-up period). Overall, 39 (13.3%) patients reported GI-related symptoms, out of which 19 (6.4%) had persistent symptoms and 20 (6.8%) developed new onset GI symptoms. Nausea and vomiting were the most common 24/39 (61.5%), followed by abdominal pain 7/39 (18%), diarrhea 5/39 (12.8%), and others 3/39 (7.6%). Patients who presented with vomiting during acute SARS-CoV-2 infection were more likely to have Long COVID GI manifestations (P=0.023). Use of ACE inhibitors, abnormal lymphocyte count and elevated ferritin are other variables that showed significant associations with Long COVID GI manifestations (P=0.03, 0.006 and 0.03, respectively). During follow-up, a total of 28 (9.5%) patients reported difficulty with sleep and 79 (27%) patients had abnormal MoCA assessment. With further analysis, there was a trend between presenation of GI symptoms on admission with abnormal MoCA assessment, and an association between abnormal LFTs and history of liver disease during hospitalization with subsequent sleep problems. Baseline characteristics, clinical comorbidities, other laboratory values, hospital length of stay, mechanical ventilation, medications during hospitalization, re-admission and Flu or COVID-19 vaccination have not shown any association with Long COVID GI symptoms in our cohort.

Conclusion: Dyspeptic symptoms were common GI manifestations in the acute and post COVID periods. GI symptoms, abnormal LFTs and a history of liver disease during the acute infectious phase associates with abnormal MoCA and sleep problems during follow-up. Further large population studies are needed to determine if COVID-19 leads to a GI symptoms-associated Long COVID phenotypes and other symptoms through the Gut-Brain-Axis.

Keywords

African Americans; Long-COVID; PASC; Gastrointestinal manifestations; Sleep problems; mini-MoCA

Introduction:

The COVID-19 pandemic has affected many individuals globally, with over 750 million confirmed cases and a mortality of 6.9 million people as reported by the World Health Organization as of April 2023 (1). Despite the recovery of most patients, a subset of individuals with acute COVID-19 are reporting persistent symptoms or developing new ones without clear explanation.

The diagnosis of Long COVID, also referred to as COVID Long-Hauler, post-acute sequelae of SARS CoV-2 infection (PASC), long-term effects of COVID, and chronic COVID, is not yet well defined. In July 2021, Long COVID was recognized as a condition that could result in disability under the Americans with Disabilities Act (ADA). Various national organizations have provided working definitions, with the World Health Organization (WHO) defining it as symptoms occurring 3 months after COVID-19 infection and lasting for 2 months or more without an alternative explanation (2). The Centers for Disease Control and Prevention (CDC) defines PASC as new, returning, or ongoing health problems at least 4 weeks after infection with the virus (3). The National Institute of Health (NIH) defines PASC as a failure to recover from acute COVID-19 or persistent symptoms for more than 30 days from the onset of infection (4). The duration of recovery after an acute symptomatic infection varies widely, with estimates ranging from two weeks to three months, and is dependent on factors such as age, comorbidities, and illness severity. Long COVID involves multiple organs including respiratory, neurologic, and digestive system and can present with conditions that are hard to explain.

It is well recognized that acute SARS CoV-2 infection can affect the gastrointestinal (GI) system and liver (5,6,7) Based on robust research and recent evidence, GI symptoms were also noted to be part of Long-COVID and commonly present with loss of appetite, dyspepsia, irritable bowel syndrome, loss of taste, and abdominal pain (8). Angiotensin-converting enzyme 2 (ACE2) serves as a functional receptor target for SARS-CoV-2 entry and is highly expressed in the intestinal epithelial cells, more than four times compared to other organs (9). Studies have shown viral shedding, detection of RNA in the feces even after respiratory samples tested negative postulating that they can survive a wide pH range and the mucus layer in the GI tract might preserve the viral RNA to retain its infectivity (10). This has been the basis for wastewater detection strategies to identify physical sites of infected individuals or groups.

The GI track is also connected with bidirectional effects with the central nervous system, influencing the behavior of the host through the Gut-Brain Axis. The vagus nerve, expressing Toll-like receptors and neurotransmitter receptors at their end, receives stimulus from the intestinal metabolites, bacterial pathogens and hormones to serve as a pathway for relaying information to the nervous system. Disruption of the gut flora can damage the intestinal barrier, increasing inflammatory responses and allowing the pathogens to enter the blood and lymphatic system eventually reaching other organs. It was also hypothesized that retrograde invasion of viruses can happen through the intestinal vagus nerve and olfactory nerve causing sensory symptoms in COVID-19 patients (11). Overall, the GI tract directly or indirectly acts as a portal for neuroinvasion of SARS-CoV-2 potentially leading to Long-

COVID GI and CNS manifestations. Interestingly, there is also bidirectional influences between digestive symptoms and sleep disturbances, particularly in patients with acid reflux disease (GERD), abdominal pain and irritable bowel syndrome (IBS) (12). Theoretically, imbalances of the gut flora in COVID patients could potentially develop or aggravate sleep problems but so far, there are no studies looking at this correlation.

Minority groups, particularly African Americans, face significant social and economic disparities and have a higher disease burden related to COVID-19 compared to the general population (13,14,X). Despite this, studies examining the long-term effects of COVID-19 in these communities are scarce and the available data provides limited insight into the long-term outcomes for such patients. This study prospectively followed patients admitted for COVID-19 at our institution to gain a deeper understanding of the long-term gastrointestinal symptoms and their relationship with neurological and sleep problems, within the unique social context of these communities.

Materials and Methods:

Study population:

The study analyzed patients who tested positive for SARS-CoV-2 via PCR and were admitted to Howard University Hospital between February 2020 and May 2021 as part of a single-center prospective and longitudinal cohort study (Y). We identified a total of 747 patients (Fig. 1). The chart review and follow-up of these patients was approved by the Institutional Review Board (IRB) at Howard University (IRB-12-MED-76). Baseline demographic, clinical, laboratory, and pathological data were collected from the electronic medical records (EMR) and information gathered during the follow-up interviews were coded into an encrypted excel file.

Inclusion criteria: We included patients with a confirmed diagnosis of COVID-19 (PCR positive) who were hospitalized during the study timeline. No distinction was made concerning sex, age, disease severity, treatment, and outcome.

Exclusion criteria: We excluded patients with negative PCR results for COVID-19, and patients under the age of 18.

Follow-up protocol:

The study protocol involved inviting patients who were alive at the time of discharge to participate in a follow-up interview, which was scheduled to occur between 6 to 12 months post-discharge. We developed a standardized questionnaire to assess symptoms related to gastroenterology, neurology (using the mini-MoCA), and sleep problems. This questionnaire was developed through review by faculty members and fellows in the Divisions of Gastroenterology, Neurology, and Sleep Medicine at Howard University in Washington, D.C. Feedback received was incorporated to refine the questionnaire until a final version was agreed upon. The patients were followed up by attending doctors and the follow up data was collected to assess symptoms.

Statistical Methods:

Data analysis was performed using both Microsoft Excel and SPSS software. Linear regression analysis, Chi-square test, and Fisher's exact test were applied, as appropriate, to identify associations of risk factors and demographic factors with the outcome. A p-value of <0.05 was considered to indicate statistical significance in this study.

Results:

Demographics of hospitalized COVID-19 patients:

The study enrolled 747 SARS-CoV-2 PCR positive patients who were hospitalized. The patients had a mean age of 58 years old, with 51.6% being female. Most subjects were African American (74%, n=550), followed by Hispanics (16%, n=121), Caucasians (6%, n=43), and others (4%, n=33). One hundred eight (108) patients died during their initial hospital stay, while 639 patients were followed up. Out of the 358 patients who answered the telephone call, 350 completed the questionnaire. During the follow-up period, 57 patients died (Fig. 1).

Long-COVID gastrointestinal symptoms:

In this study, 39 patients (13.3% (39 out of 293)) reported GI related symptoms. Of these, 19 (6.4%) had persistent symptoms and 20 (6.8%) developed new onset symptoms. The most common symptoms were nausea with vomiting, reported by 24 patients (61.5%), vomiting alone in 20 patients (51%) followed by loss of appetite in 10 patients (26%), abdominal pain in 7 patients (18%), diarrhea in 5 patients (12.8%), and other GI symptoms in 3 patients (7.6%). Results showed that vomiting during the acute phase of COVID-19 was significantly associated with long-lasting overall GI manifestations (P=0.023), while other acute GI symptoms such as loss of appetite, nausea, abdominal pain, and diarrhea were not (Table 1).

Laboratory testing: The use of ACE inhibitors, abnormal lymphocyte count, and elevated ferritin levels were found to be significant predictors of Long-COVID GI manifestations (p=0.03, 0.006, and 0.03, respectively) (Table 1). The study did not find a significant association between Long-COVID GI manifestations and underlying comorbidities such as hypertension, diabetes, chronic kidney disease, cardiac disease, gastroesophageal reflux disease/peptic ulcer disease, and liver disease. Additionally, medications commonly used during COVID hospitalization, including azithromycin, ceftriaxone, remdesivir, and steroids, were not found to influence Long-COVID GI manifestations. The use of mechanical ventilation and length of hospital stay during acute COVID-19 were also not found to be significant predictors of Long-COVID GI manifestations.

Association of Long-COVID gastrointestinal symptoms with neurological and sleep problems:

Of the 125 patients who answered the sleep questionnaire, 22% (n=28) reported difficulty falling asleep or sleep disturbances. A mini-MoCA assessment was completed by 103 patients, of which 78% (n=79) were noted to have abnormal results after acute COVID and hospitalization. Among these patients, 8 of the 28 (29%) with sleep disturbances and 6 of 79

(8%) with abnormal mini-MoCA results also had Long-COVID GI manifestations. However, our analysis revealed no significant association between Long-COVID GI manifestations and either sleep disturbances (p=0.183) or abnormal mini-MoCA results (p=0.560).

Further analysis revealed a linear trend between acute GI symptoms at the time of admission and subsequent MoCA assessment results (77% vs. 23%). Additionally, the final bilirubin and INR values at the time of hospital admission and the presence of HbSAg were found to be significantly associated with sleep problems (p=0.043, p=0.048 & p=0.041, respectively). The data indicated a linear trend between sleep problems and history of liver disease (67% vs. 22%), abnormal albumin levels (35% vs. 15.6%), elevated AST levels (32.3% vs. 21%), and elevated ALT levels (41.2% vs. 22.2%).

DISCUSSION

The gastrointestinal tract is among the many organ systems manifesting extra-pulmonary complications of COVID-19. Although COVID-19 primarily presents as a lung infection, with most symptomatic patients experiencing fever and respiratory symptoms, the virus is known to cause gastrointestinal symptoms in a substantial number of patients. A systematic review by Silva et al. reported a prevalence of 30.5% for gastrointestinal symptoms in patients with acute COVID-19, with diarrhea being the most reported manifestation (11.5%) followed by nausea and vomiting (6.3%) (15). Further studies have supported these findings, with the range of prevalence varying between 11.4–61.1% (17). However, the onset and severity of these symptoms varied across studies (16,17). Zeng et al.'s meta-analysis revealed that the presence of diarrhea increases the risk of COVID-19 severity by nearly 2.8-fold, with regional variations observed (18). As the COVID-19 pandemic has progressed, attention has shifted to understanding the long-term sequelae of the viral infection, including digestive symptoms. In a prospective study by Meringer et al., 29% of patients reported gastrointestinal symptoms as part of PASC. Subsequent studies have indicated an increase in the prevalence of gastrointestinal symptoms in Long-COVID compared to the immediate effects of the virus, with a reported prevalence of 22% versus 12% (19, 20). Al-Aly et al. also noted a significant burden of esophageal disorders, dysphagia, and abdominal pain, raising questions about the effect of COVID-19 on gastrointestinal motility (21). In our study, dyspeptic symptoms were commonly reported with further analysis showing vomiting as a predictor of Long-COVID GI manifestations.

The Gut-Brain-Axis, which refers to bidirectional influences between the gastrointestinal system and the central nervous system, is well established in the scientific and clinical community. Recent studies on the effects of COVID-19 have shown that the virus can impact both systems simultaneously. For example, one study reported a similar prevalence of both neurological and gastrointestinal symptoms in COVID patients, with 36% of patients exhibiting both types of symptoms. This phenomenon may be due to several factors, including viral replication in the gastrointestinal tract, inflammation of the intestines, disruption of gut flora, and changes in the Blood-Brain Barrier (BBB) (22). Another recent study has further hypothesized that the occurrence of both neurological and gastrointestinal symptoms in COVID patients is not simply a coincidence but may instead be a result of the complex interplay between the Gut-Brain Axis and the effects of the

virus (23). Our study did not find a similar prevalence of Long-COVID gastrointestinal and neurological symptoms or an association between them. However, we did observe that patients who experienced acute COVID-19 gastrointestinal symptoms tended to have cognitive impairment during follow-up.

Recent research has highlighted the potential impact of COVID-19 on sleep patterns. In a prospective observational study, patients who had recovered from COVID-19 exhibited altered sleep architecture characterized by decreased total sleep and deep sleep, regardless of demographic background and symptom levels (24). In contrast, an international web-based survey of healthcare workers found that sleep problems and burnout were robustly associated with a greater risk of COVID-19 (25). Given the bidirectional link between gastrointestinal symptoms and sleep problems, we investigated the potential relationship between Long-COVID gastrointestinal manifestations and sleep patterns. However, our study did not identify any increased risk of sleep problems associated with Long-COVID GI symptoms. Based on our study results, it is noteworthy that patients with abnormal liver enzymes, a history of liver disease, and positive Hepatitis surface antigen are at an increased risk of experiencing sleep problems in the context of Long-COVID. The underlying pathophysiological mechanisms that drive this association remain unclear and warrant further investigation. Specifically, future research should explore any potential links between acute COVID-GI manifestations and disturbances in sleep patterns to gain a better understanding of the complex interplay between COVID-19, liver function, and sleep disorders.

According to latest updates from CDC, Black, Latino, and American Indian populations have a higher incidence of COVID-19 infection, hospitalization, and death compared to White non-Hispanic populations (26). This disparity is due to a combination of factors, including genetic predisposition to health conditions, societal factors such as work in crowded settings, and reduced access to primary and specialized care (X). The existing research on Long-COVID has highlighted the fact that the symptoms and severity of the disease can vary based on various factors such as age, gender, and location. However, despite the growing body of knowledge about the impact of Long-COVID, there is currently a significant gap in understanding the potential racial disparities that may exist. This is particularly true when it comes to understanding the gastrointestinal outcomes of Long-COVID and their potential impact in minority groups. Our study helps fill a critical gap in knowledge by focusing on the relationship between Long-COVID gastrointestinal manifestations and sleep/neurological alterations in a predominantly African American population.

It is important to note that our study has certain limitations that may impact the generalizability of our findings. Ours was a predominantly minority population and different populations may demonstrate different outcomes. Technical difficulties in contacting some patients, potential recall bias, and missing data were encountered in this study. These limitations may have influenced the accuracy and completeness of our data, which should be taken into consideration when interpreting our results. Small sample size may have failed to demonstrate some correlations between post Covid GI symptoms and sleep and neurologic

disturbance. Further studies with a larger and diverse cohort are necessary to validate our findings and improve our understanding of Long-COVID and its potential complications.

Conclusion:

Overall, the findings of our study suggest that gastrointestinal symptoms can be a significant long-term effect of COVID-19 in minority populations. Our results indicate that certain biomarkers, such as abnormal liver function tests and a history of liver disease during the acute infectious phase, may be useful in predicting who is at risk for developing these symptoms. Importantly, our study highlights the potential link between acute hospitalization GI symptoms and subsequent cognitive impairment and sleep problems in Long-COVID patients, emphasizing the importance of a potential Gut-Brain-Axis involvement in Long-COVID. Our study results is likely to contribute to the growing body of evidence on the potential long-term effects of COVID-19 on multiple organ systems, including the gastrointestinal and nervous systems, and lead to a better understanding of Long-COVID and the potential long-term consequences of the disease.

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Availability of data:

Available upon request.

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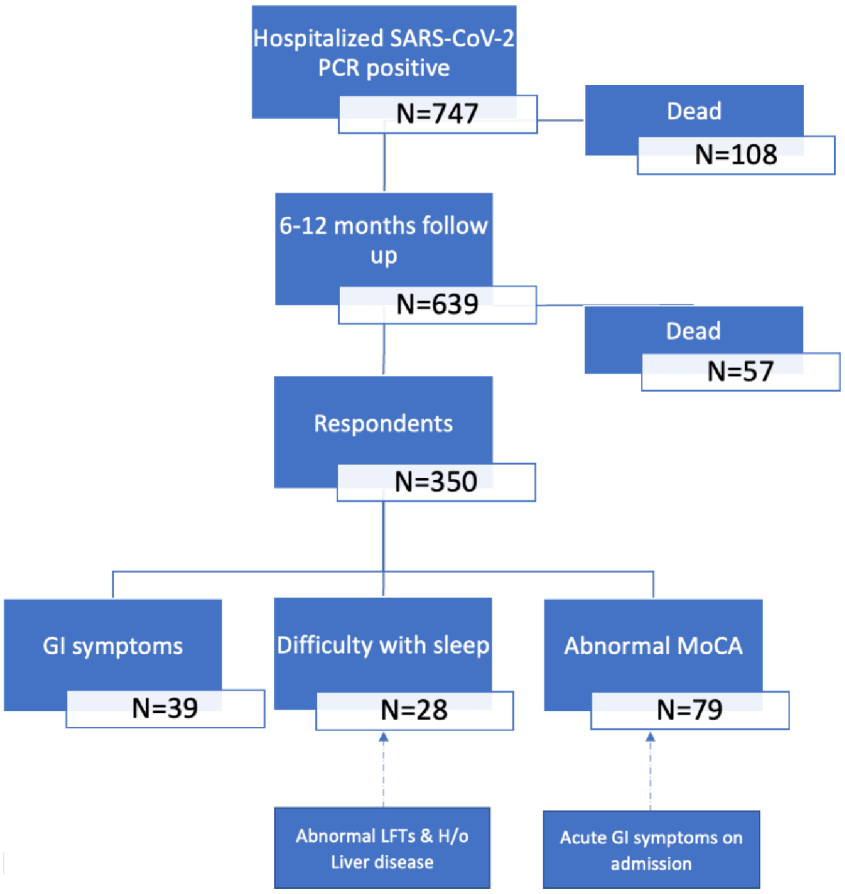

Fig – 1:

Study flow chart outlining the number of SARS-CoV-2 PCR positive patients included in the study with follow-up data.

Table – 1:

Statistical analysis of Initial hospital data with Long-COVID GI symptoms and comparison with Long-COVID Sleep and MoCA assessments.

	Patients with GI symptoms on follow up N (%)	Patients without GI symptoms on follow up N (%)	Chi-square/Fisher's exact test P<0.05
Initial symptoms during acute COVID-19 infection			
Loss of appetite	10 (26%)	62 (86%)	P=0.872
Nausea	9 (26%)	30 (83%)	P=0.647
Vomiting	20 (51%)	28 (74%)	P=0.023
Abdominal pain	7 (18%)	28 (85%)	P=0.902
Diarrhea	5 (13%)	51 (86%)	P=0.946
Clinical comorbidities			
H/o of GERD/PUD	6 (21%)	23 (79%)	P=0.231
H/o of Liver disease	2 (22%)	7 (78%)	P=0.409
H/o HTN	20 (13%)	136 (87%)	P=0.602
H/o DM	16 (16%)	81 (84%)	P=0.245
H/o CKD	3 (7%)	43 (93%)	P=0.188
H/o Cardiac disease	4 (8%)	48 (92%)	P=0.170
Abnormal Lab results during acute COVID-19 infection			
Ferritin	9 (26%)	25 (74%)	P=0.031
LDH	13 (27%)	36 (73%)	P=0.903
D-dimer	30 (14%)	181 (86%)	P=0.442
IL-6	6 (10%)	55 (90%)	P=0.075
CPK	13 (28%)	34 (72%)	P=0.732
Troponin	4 (36%)	7 (64%)	P=0.317
Lymphocyte	32 (12%)	225 (88%)	P=0.006
Medications during hospitalization			
Azithromycin	25 (16%)	127 (84%)	P=0.077
Ceftriaxone	21 (12%)	151 (88%)	P=0.586
Remdesivir	5 (13%)	33 (87%)	P=0.955
Steroids	14 (16%)	72 (84%)	P=0.359
ACEi	9 (24%)	28 (76%)	P=0.038
ARBs	4 (12%)	30 (88%)	P=0.806
Others			
Mechanical ventilation	3 (15%)	17 (85%)	P=0.791
Length of stay (>7days)	24 (13%)	158 (87%)	P=1.000
COVID vaccination	3 (9%)	29 (91%)	P=0.145
Long COVID-19 symptoms			
Sleep problems	8 (32%)	17 (68%)	P=0.183
Abnormal MoCA	6 (27%)	16 (72%)	P=0.560