Origional Article

FUNCTIONAL BOWEL DISORDERS AFTER COVID-19

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ABSTRACT

Background: To assess gut-brain interaction disorders and gastrointestinal symptoms after COVID-19 hospitalisation.

Material and Methods: This prospective study was done on Medical wards and ICUs of Jinnah Hospital Lahore, Mayo Hospital Lahore, DHQ Hospital Gujranwalla, and Hijaz Hospital Lahore from April 1, 2020–December 31, 2021.We enrolled 1284 patients (both COVID-19 and non-COVID-19) who met the inclusion criteria and followed them for 1, 6, and 12 months after hospital discharge. Validated questionnaires measured depression, anxiety, and gastrointestinal symptoms. 881 patients were included in the primary analysis after excluding those with preexisting GI symptoms or surgery. (270 controls, 611 COVID-19).

Results: Out of 805 (62.7%) of the remaining 1035 had COVID-19, and 162 (94 COVID-19 and 68 control) were excluded due to history of existing gastrointestinal symptoms or surgery in the past. 873 subjects without pre-existing confounders were assessed and followed up for primary and secondary aim analysis. 746 patients completed 6-month and 603 patients completed 12-month follow-up evaluations. In primary aim analysis, mean age was 48.9 ±20.1 years for control group and 52.9±14.2 for COVID patients (p=0.47). 62.1% of control and 58.7% of COVID cases were male (p=0.54). BMI in control group was 24.8±7.5 and in COVID cases it was 23.9±7.6 (p=0.6). COVID-19 patients had more gastrointestinal symptoms at enrollment (65.5% vs 38.5%, p<0.0015). Controls (15.5%) have more constipation than COVID-19 patients (9.1%) at 12 months (p=0.029). ROME IV-defined IBS was higher in COVID-19 patients (4.0% vs. 0.3%, p=0.035). IBS was linked to allergies, dyspnoea, and proton pump inhibitors.At 6 months, the rate of depression among COVID-19 patients was higher than that of controls.

Conclusion: At 12 months, patients hospitalised with COVID-19 had less number of hard stools and constipation than controls. COVID-19 patients had significantly more IBS than controls.

Keywords: COVID-19, Nasopharyngeal swab, ROME IV, Irritable Bow syndrome.

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INTRODUCTION

In June 2022, the WHO reported over 5 million COVID-19 cases and over 6 million deaths worldwide. There is a wide range of possible symptoms associated with COVID-19, from asymptomatic to potentially fatal.[1] Elderly and sick people are more likely to get serious illnesses. New virus variants cause cyclical peaks despite vaccination.[2]

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The newly emerging COVID-19', which is characterised by symptoms like dyspnea, fatigue, arthralgia, cognitive disturbances, chest pain and compromised quality of life after SARS-CoV-2 infection, is straining healthcare systems worldwide. [2,3] A meta-analysis of 57 studies, found long-term sequelae of respiratory impairment, neuropsychiatric disorders, functional impairments and presence of constitutional symptoms in COVID-19 survivors. Abdominal pain, diarrhoea, anorexia, nausea and vomiting were long-term digestive symptoms.[4,5] The background mechanism of these symptoms includes virus-induced prothrombotic state, gut dysbiosis, cellular injury and enteric nervous system dysfunction [6-9] In addition, these so-called "long COVID-19 symptoms" may be similar to post-infection (PI) disorders of the interaction between the gut and the brain (DGBI). Post-infectious IBS is most strongly linked with acute gastroenteritis caused by bacterial or viral pathogens (PI-IBS).[10] Fewer studies have looked at IBS and other DGBI caused by viruses than have looked at those caused by bacteria. Due to limited follow-up, small sample size, lack of controls, and retrospective study design, the long-term effects of these disorders are unknown.[11] The objective of this study is to compare hospitalised patients with COVID-19 to non-COVID to see which group had a higher prevalence of gastrointestinal symptoms.

MATERIAL AND METHODS

In this prospective study in which 1284 patients of both genders, aged between 15 to 80 years hospitalised with or without COVID-19 (WHO-defined COVID-19 diagnosis –Positive Nasopharyngeal swab for COVID-19 PCR), were enrolled upon admission from April 2020 to December 2021 and reassessed for their symptoms at 1, 6, and 12 months. All patients gave written consent and were evaluated according to clinical symptoms. Patients with concurrent cancer or mechanical ventilation were excluded. The control group included patients from Jinnah, Mayo, and Hijaz hospitals' internal medicine units and ICUs who were hospitalised for reasons other than COVID-19. Demographic characteristics, medical history, laboratory data, and the Gastrointestinal Symptoms Rating Scale (GSRS) were recorded at admission and follow-up(1, 6, and 12 months).

GSRS is a 1-week recall tool for IBS and peptic ulcer disease that grades 15 common gastrointestinal symptoms on a 7-point scale. It was used to assess patients for COVID-19-related-gastrointestinal symptoms. Patients who had symptoms within the previous six months of hospitalization were also screened out using the GSRS. These patients were called and interviewed at follow-up to calculate GSRS and Hospital Anxiety and Depression Scale (HADS). [12] Depression and anxiety are rated as follows by the HADS: 0–7, normal; 8–10, borderline abnormal; 11–21, abnormal. The Rome IV Diagnostic Questionnaire for Functional Gastrointestinal Disorders in Adults was used to diagnose DGBI at 6 and 12 months.[13]

The primary endpoints were DGBI and long-term gastrointestinal symptoms after COVID-19. After finding a statistically significant difference between groups, the secondary endpoints assessed predictive factors of PI DGBI. Exploratory endpoints included DGBI, long-term gastrointestinal symptoms, anxiety, and depression at the 12-month follow-up.

Means and standard deviations were reported for quantitative data, while frequencies and percentages were used to describe qualitative data. Primary and secondary aim analyses were performed after excluding patients with prior gastrointestinal symptoms or recent surgery. Prior gastrointestinal symptoms

included at least two GSRS items starting at least six months before hospitalisation. COVID-19-negative patients made up the control group. Admission and follow-up data were compared using the Mann-Whitney U test, Fisher's test and Student's t-test. At a follow-up of 12 months,

Histograms described the data about DGBI, anxiety, and depression and logistic regression analysis (univariate and multivariate) predicted the occurrence of GSRS and DGBI. We estimated the Odds ratio, 95% Confidence interval, and p values. SPSS 24 performed all analyses.

RESULTS

1284 hospitalised patients were consecutively enrolled from April 01, 2020, to December 2022. 249 patients were excluded because they did not follow the study protocol (died), had missing questionnaire data, or were diagnosed with cancer during follow-up. 805 (62.7%) of the remaining 1035 had COVID-19, and 162 (94 COVID-19 and 68 control) were excluded due to prior gastrointestinal symptoms or recent surgery. 873 subjects without pre-existing confounders were evaluated and followed up for primary as well as secondary study goals. 746 patients completed 6-month and 603 patients completed 12-month follow-up evaluations. At enrollment, COVID-19 patients had a higher rate of gastrointestinal symptoms compared to control (59.3% vs 39.7%), $p<0.001$(Table 2). They had higher rates of nausea, diarrhoea, loose stools and urgency. At 1 month, COVID-19 patients had high rates of acid regurgitation and nausea. At the 6 and 12-month follow-up, these patients had low rates of hard stools and constipation compared to the control group. No other GSRS results differed between groups.

At the 6-month follow-up, both groups had similar rates of epigastric pain, post-prandial distress syndrome, functional dyspepsia, IBS and functional diarrhoea (table 2) but COVID-19 patients had a higher depression rate than controls: borderline abnormal, 9.9% versus 4%, and abnormal, 4.2% versus 2.7% ($p=0.014$). COVID-19 patients had significantly higher IBS (4% vs 0.3%, $p=0.035$) (figure 2, table 2) and other DGBI rates than controls at 12 months. Post-COVID IBS patients had significantly higher baseline rates of antibiotic intake, cough, dyspnoea, and headache during hospitalisation in the previous 3 months. In post-hoc analysis, clinical and demographic data at baseline, 6-months, and 12-months were tested as independent predictors of IBS diagnosis for the study cohort selected for primary aim evaluations. COVID-19, allergies, and PPI use predicted IBS in the post-hoc analysis of the entire study cohort. Univariate analysis showed that comorbidities, cough and dyspnea at enrollment, PPI intake, antibiotic intake within three months before hospital admission, anxiety at the six-month follow-up, and in-hospital antibiotic administration were predictive factors for IBS in COVID-19 patients (table 3). Three variables were found significant in multivariate analysis: allergies, chronic PPI use, and dyspnoea.Figure 4 shows a nomogram of risk factors for IBS at 12 months.

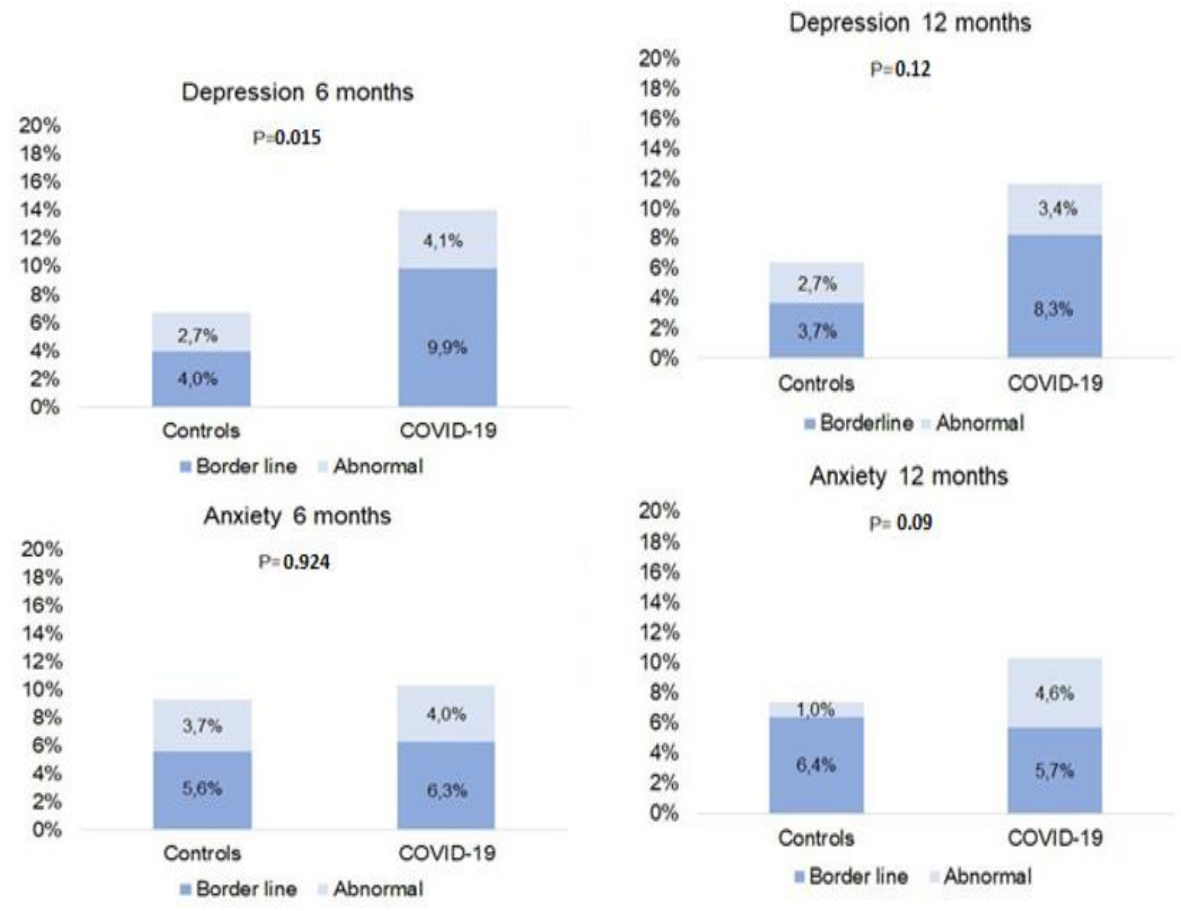

Figure 1: HADS measurements done in follow up period in patients with COVID-19 and controls.

Table 1: Demographics of patients in primary aim analysis in the study

	Control group, **n (%) or Mean±SD n= *264***	COVID-19, **n (%) or Mean±SD n=**609	**P value**
Age	48.9±20.1	52.9±14.2	0.47
Sex, male	159 (62.1)	358(58.7)	0.54
BMI	24.8±7.5	23.9±7.6	0.06
Smoker			0.001
Current	72 (27.3)	59 (9.8)	
Former	66 (25)	112 (18.4)	
Physical exercise (at least 45 minutes three times per week)	90 (34)	152 (24.9)	0.88
Comorbidities			
Neuropsychiatric	30 (11.4)	22 (3.6)	<0.01
Cardiovascular	105 (40)	174 (28.6)	0.001
Pulmonary	31 (11.7)	41 (6.7)	0.013
Hepatic	16 (6)	20 (3.3)	0.046
Renal	20 (7.6)	28 (4.59)	0.082
Diabetes	60 (22.7)	88 (14.4)	0.004
Allergies	13 (4.9)	18 (2.95)	0.157

Autoimmune	11 (4.2)	17 (2.8)	0.302
Blood disorders	11 (4.2)	8 (1.13)	0.011
Chronic medication intake with GI effect			
PPI	69 (26.1)	75 (12.3)	0.002
NSAIDs	33 (12.5)	33 (5.4)	0.001
Steroids	13 (4.9)	7 (1.1)	0.002
Metformin	16 (6)	31 (5.1)	0.585
SSRI	9 (3.4)	11 (1.8)	0.154
Antipsychotic	4 (1.5)	3 (0.5)	0.126
Thyroxine	11 (4)	19 (3.1)	0.454
Rifaximin	3 (1)	0	0.008
5-ASA	3 (1)	5 (0.8)	0.665
Probiotics in the last 3 months	28 (10.6)	46 (7.5)	0.126
Antibiotics in the last 3 months	91 (34.6)	132 (21.5)	<0.001

Table 2: Prevalence of anxiety, DGBI, and depression at the follow-ups among patients who met the study's eligibility criteria for the primary aim analysis

	Follow up at 6-Month			***Follow-up at 12 month***		
	Control group **n (%) n=*211***	COVID-19 **n (%) n=*535***	**P value**	Control group **n (%) n=*178***	COVID -19 **n (%) n=*425***	**P value**
Anxiety			0.92			0.098
Borderline abnormal	13 (6.16)	30 (5.6%)		13 (7.3%)	26 (6.1%)	
Abnormal	7 (3.31)	19 (3.6%)		1 (0.56%)	19 (4.4%)	
DGBI						
Functional dyspepsia	4 (1.9)	11 (2)	0.53	4 (2.1)	16 (3.7)	0.31
Postprandial distress syndrome	4 (1.9)	10 (1.9)	0.76	4 (2.1)	18 (4.2)	0.13
Epigastric pain	1(0.4)	4 (0.74)	0.25	3 (1.9)	9 (2.1)	0.48
Chronic nausea and vomiting syndrome	3 (1.3)	6 (1.1)	0.77	3 (1.9)	2 (0.5)	0.14
Functional diarrhoea	0	1 (0.2)	0.52	0	1 (0.2)	0.51
Cyclic vomiting syndrome	1 (0.5)	0	0.12	—	—	—
IBS	2 (0.94)	3 (0.56)	0.58	1 (0.3)	17 (4%)	0.035
HADS						
Depression				0.0150.1		
Borderline abnormal	10 (4.7)	55 (10.3)		8 (4.5)	35 (8.2)	
Abnormal	6 (2.8)	22 (4.1)		4 (2.3)	16 (3.7)	

Table 3: Logistic regression analysis to identify factors associated with occurrence of IBS at 12 months follow-up in COVID-19 patients in the primary aim analysis group.

	Univariate	P value	Multivariate	P value
	Odd ratio (95% CI)		Odd ratio (95% CI)	
Clinical course				
Dyspnoea	4.167 (1.369 to 12.680)	0.012	4.157 (1.336 to 12.934)	0.013
Cough	4.935 (1.091 to 22.321)	0.038		
Anxiety (at 6 months according to HADS)	2.091 (0.994 to 4.357)	0.052		
Antibiotic administration during				
Hospitalization	3.975 (0.861 to 16.951)	0.076		
Coexisting conditions/Comorbidities				
Allergies	6.221 (1.229 to 32.148)	0.025	10.123 (1.765 to 56.881)	0.008
Hepatic diseases	4.846 (0.989 to 23.734)	0.051		
Chronic medication intake				
PPI	4.031 (1.301 to 11.49)	0.017	4.826 (1.457 to 17.026)	0.011
Antibiotic use in the last 3 months	3.168 (1.061 to 9.320)	0.036		

DISCUSSION

This prospective study compared the cohort of hospitalised COVID-19 patients to a control group of non-COVID patients. After hospitalisation, patients were followed for 12 months and adjusted for previous gastrointestinal symptoms, surgery, and medication use. This study revealed that the majority of gastrointestinal symptoms improved after being hospitalised for primary disease. These patients had more IBS and less constipation/hard stool than controls at 12 months but did not differ from control in GSRS domains. These findings contradict previous reports. COVID-19 survivors had more loose stools and no constipation at 6 months, according to one of the studies. [14] These patients are more likely to use laxatives and have constipation, according to large retrospective matched-controlled studies.[15,16] The COVID-19 group had a higher incidence of IBS (4%) than the control group, but it was lower than previously reported, which is up to 16% according to Rome IV criteria at 6 months .[16, 21] Our stringent patient selection may explain these discrepancies. Another study found an IBS rate of 6.4%, which is very close to our post-COVID-19 rate.[17] Post-COVID-19 GI symptoms have been studied in several previous studies but these studies have limitations due to small sample size, short follow-up time and retrospective and cross-sectional design. They had not deployed Rome IV criteria and had not adjusted analyses for the pre-COVID gastrointestinal symptoms. Additionally, they have not omitted the confounders of study [18] The risk of IBS in COVID-19 patients is higher if they have a history of allergies, dyspnoea and chronic PPI use. These patients had higher levels of depression and anxiety at followup. Our findings supported the link between post-COVID-19 IBS and allergies, immune dysregulation, and mucosal homeostasis.[19] The presence of dyspnea at baseline is also predictive of IBS following COVID-19. COVID severity may cause chronic intestinal symptoms.[20] PPIs may alter gut microbiota and this may cause post-COVID-19 gastrointestinal symptoms COVID-19 patients have reduced

microbial diversity, greater colonization of Bacteroides and substantially reduced butyrate-producing bacteria.[21] Alteration in enteroendocrine cell function, gut motility and permeability, and serotonin metabolism may be involved in microbiota changes and cause the persistence of symptoms. This viral infection can infect the ileum and colon due to more affinity with ACE2 receptor, thus it may cause de novo IBS (as viral gastroenteritis outbreaks cause IBS). Amplification of viral nucleic acids and immune activation have been found in the ileum of these patients up to six months after acute infection. Other studies have found an augmentation of the cytotoxic T-cell number in these patients.[22] In contrast to other PI-IBS, which typically peak soon after the acute infection, the peak of post-COVID-19 IBS occurs 6- 12 months later.[23] There are a few caveats to our study. First, there may be some other confounding factors that were not considered here. Additionally, the 12-month follow-up and use of GSRS to assess pre-hospitalization symptoms also affected our results as they might introduce a recall bias and have affected the outcomes. Second, we might not have been able to detect statistically significant DGBI in the COVID-19 patients as we excluded subjects who had pre-hospitalization gastrointestinal symptoms, thereby increasing the likelihood of type II error. In addition, there are some random drop-outs at each time-point, but this may not have affected our endpoints. Third, the control group of hospitalized patients had more comorbidities and medications at baseline than COVID-19 patients, which may have affected our results. Our study suffered overfitting variable bias due to a very low number of IBS patients. We selected variables based on pathophysiological reasons to partially overcome this limitation. Due to hospital access restrictions, patients were interviewed by phone at follow-up, potentially introducing questionnaire bias. Finally, our study only included inpatients from only three hospitals; this means that our results may not apply to the general public or to those who are not hospitalized. In conclusion, COVID-19 is linked to an increase in chronic gastrointestinal symptoms and IBS. Given the global distribution of disease, new-onset gut-brain interaction disorders are expected. To understand the mechanisms of these symptoms and find new remedies, more research is neede.

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AUTHOR'S CONTRIBUTION

AZ: Research proposal development, Data collection, analysis, article writing and aeviewing
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FI: Analysis, Article writing and reviewing
AZ: Data collection, analysis and article writing
AM: Analysis, article writing and review

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