Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Digestive and Liver Disease 54 (2022) 580–582

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Correspondence

Gastrointestinal sequelae among COVID-19 patients after discharge and their predictors

Dear Editor,

Although severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is considered primarily a respiratory pathogen, its impact on other organs including the gastrointestinal (GI) tract has been well documented [1]. The GI symptoms can be noted at presentation, or during the course of illness and can sometimes be the only symptoms [2]. While ample data exist on the prevalence of GI symptoms among coronavirus disease 2019 (COVID-19) patients, there is limited information on the long-term GI sequelae in these cases. Hence, this prospective study was conducted to look at the prevalence of GI sequelae on follow-up in patients of COVID-19 and factors predicting it.

All consecutive patients of established COVID-19 positive cases presenting to a tertiary care center in India between July and October 2020 were prospectively assessed. Detailed symptomatology was documented including respiratory and gastrointestinal (GI) symptoms. Prior co-morbidities, drug history and medical history were documented. Patients having any pre-existing GI diseases or having GI symptoms one month prior to onset of COVID-19 were excluded. All patients, on admission, underwent blood cytology, biochemical parameters and serum inflammatory markers estimation. Clinical severity of COVID-19 was classified into mild, moderate and severe as per NIH guidelines [3]. Outcome measures such as need for ICU, oxygen requirement, need for ventilation and mortality were noted.

After discharge, the patients were followed up after 1 month and 3 months. The follow-up visits were primarily through teleconsultation via video-conferencing using smart phones unless the physician felt the need for physical examination. A detailed documentation of the various symptomatology, duration and severity was performed, specifically GI symptoms such as nausea, vomiting, diarrhea, abdominal pain/discomfort, GI bleeding etc. GI sequelae were defined as GI symptoms that were present on 3-month follow-up but were absent within one month of the initiation of COVID symptoms. The study was approved by the Institute Ethics committee.

All the data was entered into a spreadsheet and analysed using the SPSS (version 21.0, SPSS Inc; Chicago, USA) software. Continuous variables were expressed as mean with standard deviation or median with interquartile range. Dichotomous variables were compared using the Chi-square test or the Fischer's exact test. Multivariable logistic regression was carried out to look for the predictors for gastrointestinal sequelae The p value of less than 0.05 were taken as statistically significant.

Of the 244 patients screened, 41 were excluded (23 – incomplete data; 18 – pre-existing GI disease) and 203 patients had all the details documented during admission. Of them, 89 patients (53 males; 59.6%) consented for follow-up and thus included for the final analysis (Fig 1). Among them, 14 patients (15.7%) had GI sequelae on 3-month follow-up while 75 (84.3%) did not. The GI symptoms that persisted on follow-up included abdominal pain/discomfort – 8; constipation – 9; loose stools – 3; nausea and vomiting – 1 and persistence of loss of appetite – 2.

Comparing patients with and without GI sequelae on 3-month follow up, it was noted that the baseline characteristics such as age, sex and pre-existing comorbidities were similar between the two groups (Table 1). Patients with GI sequelae had initially more severe disease ($p = 0.011$), higher need for oxygen supplementation (78.6% vs 36.0%; $p = 0.006$) and ICU stay (35.7% vs 5.3%; $p = 0.004$). All patients with GI sequelae had both respiratory and GI symptoms during admission while none of the patients having initially only GI symptoms had any GI sequelae ($p = 0.04$). GI sequelae were noted in a higher proportion of patients receiving steroids during hospitalization (78.6% vs 37.3%; $p = 0.007$), while the intake of NSAIDs and other drugs were similar.

Laboratory investigations performed during hospitalization were comparable between the two groups, except for higher fibrinogen levels (5.30 vs 4.04 g/L; $p = 0.03$) and higher ALT levels (54.5 vs 33.0 U/L; $p = 0.014$) in the GI sequelae group (Supplementary Table 1). On multivariable regression analysis, (Table 2) severe COVID-19 infection (aOR 8.17; $p = 0.047$), need for oxygen supplementation (aOR 7.53; $p = 0.035$), ICU stay (aOR 5.89; $p = 0.034$) and steroids administration (aOR 7.27; $p = 0.04$) during hospitalization were significant predictors of subsequent GI sequelae, when adjusted for age, sex and symptomatology profile during admission.

This prospective evaluation of COVID-19 recovered patients on 3-months follow up showed that severe disease at baseline was associated with GI sequelae later on. Additionally, patients having GI sequelae had higher requirements for oxygen support and ICU admission. Administration of steroids was associated with a greater risk of GI sequelae.

The interest in the extra-pulmonary manifestations of COVID-19 has been steadily growing and the commonest of them is involvement of the GI tract. Most studies report GI manifestations to the tune of 2% - 57% [1]. However, limited data exist on GI sequelae that might be present in COVID-19 recovered patients on follow-up. In a recent study, Rizvi et al. [4] have described the resolution of the initial GI manifestations in more than 90% of the cases on 3 and 6-month follow-up in a retrospective study of a large cohort of patients. In our prospective study we observed that GI sequelae persist in around 16% of the patients, on 3-month follow-up.

https://doi.org/10.1016/j.dld.2022.02.002

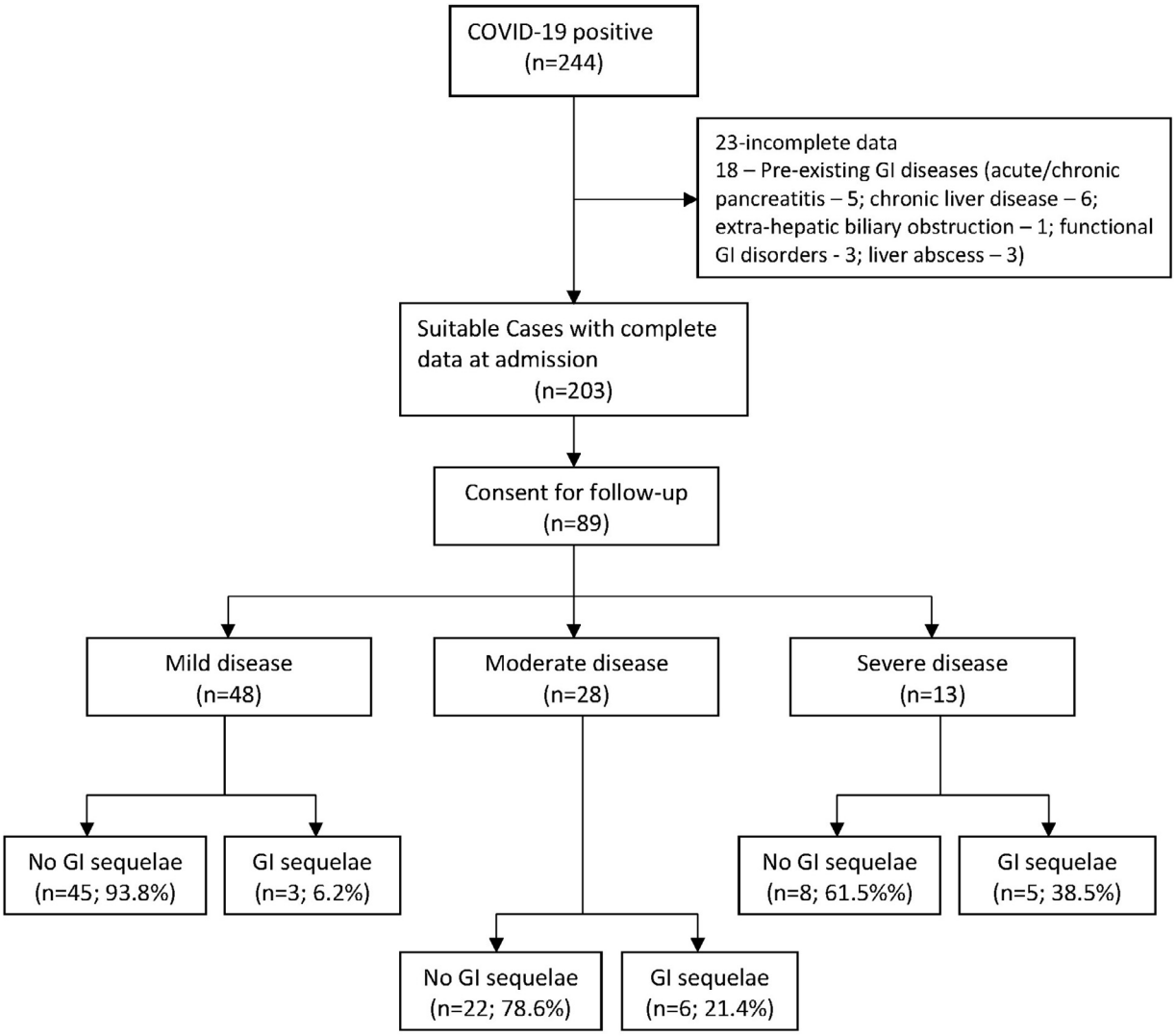

Fig. 1. Study flowchart.

Table 1
Comparison between patients with/without gastrointestinal sequelae on follow up.

Parameters	No GI manifestations on follow up (n = 75)	GI manifestations on follow up (n = 14)	p value
Age in years (mean±SD)	41.15±16.0	43.86±13.9	0.56
Sex Male	46 (61.3%)	7 (50%)	0.43
Female	29 (38.7%)	7 (50%)	
Co-morbidities	33 (44.0%)	8 (57.1%)	0.36
Diabetes	22 (29.3%)	5 (35.7%)	0.75
Hypertension	18 (24.0%)	4 (28.6%)	0.74
Chronic kidney disease	6 (8.0%)	2 (14.3%)	0.61
Presentation during admission			
Only respiratory	14 (18.7%)	0 (0%)	**0.04**
Only GI	13 (17.3%)	0 (0%)	
Both	45 (60.0%)	14 (100%)	
Severity of COVID-19			
Mild	45 (60.0%)	3 (21.4%)	
Moderate	22 (29.3%)	6 (42.9%)	**0.011**
Severe	8 (10.7%)	5 (35.7%)	
Drugs received during therapy			
NSAIDs	49 (65.3%)	11 (78.6%)	0.33
Steroids	28 (37.3%)	11 (78.6%)	**0.007**
Remdesivir	18 (24.0%)	5 (35.7%)	0.36
Need for oxygen supplementation	27 (36.0%)	11 (78.6%)	**0.006**
ICU stay	4 (5.3%)	5 (35.7%)	**0.004**
Need for IMV	3 (4.1%)	1 (7.1%)	0.51
Need for dialysis	3 (4.0%)	2 (14.3%)	0.174

Abbreviations: GI Gastrointestinal; SD Standard deviation; COVID-19 Coronavirus disease 19; NSAIDs Non-steroidal anti-inflammatory drugs; ICU intensive care unit; IMV Invasive mechanical ventilation.

Table 2
Multivariable logistic regression for gastrointestinal sequelae.

Parameters	P value	aOR*	95% CI	
			Lower	Upper
Need for oxygen supplementation	0.035	7.53	1.15	49.06
Severe COVID-19 infection	0.047	8.17	1.03	64.65
Steroids	0.043	7.27	1.07	49.62
ICU stay	0.034	5.89	1.14	30.37

* Adjusted for age, sex and mode of presentation on initial admission
Abbreviations: aOR Adjusted Odds' ratio; CI Confidence interval; COVID Coronavirus disease 2019; ICU intensive care unit.

In another retrospective study, Weng at al. [5], however, found a high proportion of patients (44%) having GI sequelae on follow-up. Noviello et al. demonstrated that greater number of patients having diarrhea during the index admission had GI sequelae on follow-up [6]. In our study, of the patients who had GI symptoms at the onset ($n = 58$), 14 (24.1%) had GI sequelae on follow-up.

The factors predicting the persistence of GI sequelae would be an interesting observation. Rizvi et al. [4] did not look into these factors. Weng et al. [5], in their study, found that patients with GI sequelae had less severe disease (17% vs. 37%) compared to those who did not have GI sequelae. However, the authors agreed that this finding was "unexpected" from the pathophysiological perspective. In our prospective evaluation, we observed that GI sequelae were predicted by more severe disease, oxygen requirement and ICU admission. The fact that none of the patients having only GI symptoms had any GI sequelae but those with severe disease had them highlights the fact that it is probably hypoxia that drives the pathophysiology of GI symptom persistence. Hypoxia induced multi-organ damage is well known in COVID-19 infection and can lead to endothelial injury of the microvasculature of the intestine [7]. Additionally, severe COVID-19 may result in excess activation of hypoxia inducible factor (HIF)−1a leading to cytokine storm and destruction of epithelium [8]. This injury can plausibly explain the subsequent development of GI sequelae in these group of patients.

Various drugs used for the management of COVID-19 include NSAIDs, steroids, and remdesivir etc. These drugs are known to have GI side effects. We found that use of steroids was associated with GI sequelae, but not NSAIDs. This could be due to the drug itself or may be explained as an epiphenomenon as steroids are more likely to be used in patients with more severe disease.

The strengths of the study include prospective design, actual patient interview and examination rather than mere registry data and analysis of the possible factors predisposing to GI sequelae. However, small sample size from a single center are its limitations. Large multicenter studies with prospective follow-up design is needed to validate the findings of the study.

In conclusion, it's the severity of the disease rather than baseline GI symptoms that predisposes to development of GI sequelae on follow-up in patients recovered from COVID-19 infection.

Conflict of interest

None declared.

Writing assistance

Nil

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2022.02.002.

References

[1] Dhar J, Samanta J, Kochhar R. Corona virus disease-19 pandemic: the gastroenterologists' perspective. Indian J Gastroenterol 2020;39:220–31.
[2] Mao R, Qiu Y, He JS, et al. Manifestations and prognosis of gastrointestinal and liver involvement in patients with COVID-19: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol 2020;5:667–78.
[3] NIH COVID-19 treatment guidelines; 2021. [Available from: https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/ .
[4] Rizvi A, Patel Z, Liu Y, et al. Gastrointestinal sequelae three and six months after hospitalization for coronavirus disease 2019. Clin Gastroenterol Hepatol 2021. doi:10.1016/j.cgh.2021.06.046.
[5] Weng J, Li Y, Li J, et al. Gastrointestinal sequelae 90 days after discharge for COVID-19. Lancet Gastroenterol Hepatol 2021;6:344–6.
[6] Noviello D, Costantino A, Muscatello A, et al. Functional gastrointestinal and somatoform symptoms five months after SARS-CoV-2 infection: a controlled cohort study. Neurogastroenterol Motil 2022;34:e14187.
[7] Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet 2020;395:1417–18.
[8] Jahani M, Dokaneheifard S, Mansouri K. Hypoxia: a key feature of COVID-19 launching activation of HIF-1 and cytokine storm. J Inflamm (Lond) 2020;17:33.

Jayanta Samanta*
Department of Gastroenterology, Post Graduate Institute of Medical Education and Research, Chandigarh, India

Seerat Singh
Department of Internal Medicine, Post Graduate Institute of Medical Education and Research, Chandigarh, India

Sanjay Kumar, Megha Sharma, Rakesh Kochhar
Department of Gastroenterology, Post Graduate Institute of Medical Education and Research, Chandigarh, India

*Corresponding author at: Department of Gastroenterology, Post Graduate Institute of Medical Education and Research, Chandigarh, Chandigarh, India.
E-mail address: dj_samanta@yahoo.co.in (J. Samanta)