Gastrointestinal manifestations and outcomes of hospitalised patients with COVID-19 disease

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Abstract

Background: COVID-19 infection usually presents with respiratory symptoms. Many hospitalised patients of COVID-19 present with gastrointestinal symptoms which can alter the clinical outcomes of patients.

Objectives: To characterise the gastrointestinal manifestations of COVID-19 patients requiring hospitalisation and their correlation with disease severity and clinical outcomes.

Methods: This was a single centre prospective, observational, cohort study done at Kathmandu Medical College, a tertiary health care centre after ethical clearance. All consecutive hospitalised patients with COVID-19 disease admitted during May and June 2021 were included in the study after ethical clearance. Diagnosis of COVID-19 infection was done by RT-PCR. Gastrointestinal symptoms of abdominal pain, aguesia, nausea/vomiting, and diarrhoea were recorded on hospital admission and outcomes accessed at discharge. Data were analysed using SPSS v.24.

Results: A total of 196 consecutive adult patients with COVID-19 infection were included in study. Gastrointestinal symptoms were recorded in 48 (24.5%) patients. The most frequent symptom was nausea/vomiting (23, 11.7%) followed by aguesia (19, 9.7%), diarrhoea (14, 7.1%), and abdominal pain (8, 4.1%). There was no significant association between duration of hospital stay and presence of gastrointestinal symptoms (10.15 vs 10.95 days; p = 0.481). No significance was seen on association of gastrointestinal symptoms with ICU admission and mortality but requirement of mechanical ventilation was significantly higher in patients without symptoms (10.4 vs 23.6%; p = 0.048).

Conclusion: Significant proportion of patients with COVID-19 infection can have gastrointestinal manifestations. Presences of these symptoms do not have any association with the final clinical outcome of the patient.

Key words: Coronavirus disease 2019; Disease severity; Gastrointestinal manifestation.

INTRODUCTION

It has already been more than two years and the global health challenge with coronavirus disease 2019 (COVID-19) is still not over.[1] General systemic symptoms like fever, myalgia, fatigue along with respiratory manifestations like, cough and shortness of breath are the principal presenting features of COVID-19 infections.[2,3] But, COVID-19 is considered a systemic hyper-inflammatory disease affecting not only the respiratory system, but also many other organs including gastrointestinal (GI) tract. Due to the massive expression of COVID-19 receptor that is Angiotensin Converting Enzyme Type-2 (ACE2) throughout the GI tract and liver; GI system not only can act as a potential route for the virus transmission but also as the site of symptoms origin.[4-7] It is also plausible theoretically that a portion of patients may present with GI tract symptoms only.

Most of the previous studies done on COVID-19 and its extrapulmonary symptoms are retrospective and quite

often not particularly designed for addressing GI specific clinical features.[2,8-12] Nevertheless, still very limited data is available on this field, especially from Nepal.

This study was conducted with an aim to characterise the gastrointestinal manifestations of COVID-19 patients requiring hospitalisation and their correlation with disease severity and clinical outcomes.

METHODOLOGY

This is a single centre prospective, observational, cohort, study. All consecutive patients with moderate to severe COVID-19 disease admitted during the months of May and June 2021 at Kathmandu Medical College Teaching Hospital (KMCTH), Sinamagal, Kathmandu, Nepal were included. Diagnosis of COVID-19 infection was done by RT-PCR with swabs taken from both nasopharyngeal and oropharyngeal regions. All the hospitalised patients of age 18 years and above were included in this study.[13] While, patients with negative RT-PCR but positive COVID-19 antigen or antibody status with or without clinical and radiological evidence of COVID-19 infection were excluded from the study. This study was performed in accordance with the Declaration of Helsinki. Data collection was started after approval from the institutional research committee of Kathmandu Medical College (Ref. 2005202102). The identity of the respondents and their response including all associated data were preserved confidentially and used for research purpose only. Sample size was calculated using the formula, sample size (N) = $Z^2p(1-p)/e^2$; where Z = 1.96 at 95% confidence interval; p = 0.114 (11.4% prevalence in previous study); e = 0.05 (5% margin of error). The present study consisted of 196 convenient sample.

All the patients who gave written consent for enrollment were evaluated for their symptoms and signs as well radiological and laboratory findings. Demographic, clinical, laboratory, treatment and outcome data were collected using the proforma. All the clinical and investigational findings related to the GI system were noted and followed up till the patients were discharged or expired with usual medical care and without any extra intervention. The clinical course of patients and related morbidity and mortality data with GI manifestations were evaluated.

Presence of GI symptoms required, having at least one of the following: nausea, aguesia, vomiting, abdominal pain, or diarrhoea at the time of admission. Patients with known pre-existing liver, pancreas, other GI diseases were excluded from the study. GI symptoms were recorded on admission only, precluding the influence of medical therapy and external factors. Diarrhoea was defined as passage of loose (Bristol Scale >4) stools more than three times per day.[14,15]

Normally distributed continuous variables were expressed in mean ± SD, whereas other continuous variables were expressed in median (IQR). Categorical variables were expressed as percentage. The association between presence of GI symptoms and demographic profiles were examined using Student's t-test for continuous variables and Pearson's Chi-square test for categorical variables. All statistical tests were two tailed and p-value of <0.05 was considered statistically significant. Data were entered and analysed with IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, N.Y., USA).

RESULTS

A total of 196 consecutive adult patients with COVID-19 infection requiring hospital admission and fulfilling the inclusion criteria were included in the study. For the purpose of data analysis patients were divided into two groups that is those with and those without GI symptoms. There was slight male preponderance (82, 58.16%) in samples with the mean age of 55.9 ± 16.84 years (Table 1).

Gastrointestinal symptoms were present in 48 (24.5%) patients at the time of presentation. There was no significant difference in age with presence of GI symptoms. Among the patients with GI symptoms, majority were females though it was not statistically significant (p = 0.08).

There was no clinically significant association between underlining comorbid conditions like diabetes, systemic hypertension, chronic kidney disease, cirrhosis of liver, or hypothyroidism and presence of GI symptoms. Likewise, there was no impact of regular alcohol intake (p = 0.587) or smoking habits (p = 0.536) on GI symptoms.

The most frequent GI symptom at presentation to hospital was nausea/vomiting (23, 11.7%) followed by aguesia (19, 9.7%), diarrhoea (14, 7.1%), and abdominal pain (8, 4.1%). Many of the patients had more than one GI symptom at the time of presentation. There was no significant difference in duration of hospital stay among the patients with or without GI symptoms (10.15 ± 8.9 vs 10.95 ± 6.09 days; p = 0.481) with average stay being 10.76 ± 9.5 days.

In terms of disease severity, defined as requirement of mechanical ventilation, intensive care unit (ICU)

admission or death; there was no significant difference in requirement of ICU admission (p = 0.423) and death (p = 0.852) but patients with GI symptoms had significantly less requirement of mechanical ventilation than those without symptoms (10.4% vs 23.6%; p = 0.048) (Table 2).

Patients with diarrhoea had longest hospital stay (12.07 ± 14.56 days) followed by abdominal pain (10.5 ± 6.39 days) and least with aguesia (9.11 ± 2.9 days). However, none of these symptoms had any significant impact on duration of hospital stay (Table 3).

Table 1: Baseline demographic profile

Characteristics	GI symptoms (N = 48)	No GI symptoms (N = 148)	Total (N = 196)	p-value
Age (years) Mean ± SD	54.94 ± 17.91	56.22 ± 16.53	55.9 ± 16.84	0.649
Sex, n (%)				
Male	20 (41.67)	94 (63.51)	114 (58.16)	0.08
Female	28 (58.33)	54 (36.49)	82 (41.84)	
Comorbidities, n (%)				
Diabetes	10 (20.8)	28 (18.9)	38 (19.4)	0.771
Hypertension	11 (22.9)	38 (25.7)	49 (25)	0.701
CKD	4 (8.3)	2 (1.2)	6 (3.1)	0.015
Obesity	2 (4.2)	8 (5.4)	10 (5.1)	0.735
CLD	1 (2.1)	-	1 (0.5)	0.078
Hypothyroidism	3 (6.3)	15 (10.1)	18 (9.2)	0.412
CAD	1 (2.1)	3 (2)	4 (2.1)	0.966
COPD	1 (2.1)	4 (2.7)	5 (2.6)	0.828
Smoking, n (%)	10 (20.8)	25 (16.9)	35 (17.9)	0.536
Regular alcohol consumption, n (%)	8 (16.7)	20 (13.5)	28 (14.3)	0.587
Duration of hospital stay (Days), Mean ± SD	10.15 ± 8.9	10.95 ± 6.09	10.76 ± 9.5	0.481
GI Symptoms, n (%)				
Aguesia	19 (39.58)		9.7%	
Diarrhoea	14 (29.16)		7.1%	
Nausea/vomiting	23 (47.91)		11.7%	
Abdominal pain	8 (16.67)		4.1%	

Data are expressed in mean ± SD and percentage – n/N (%), p-value of <0.05 taken as significant.
Abbreviations: CKD – chronic kidney disease; CLD – chronic liver disease; CAD – coronary artery disease; COPD – chronic obstructive pulmonary disease; GI – gastrointestinal

Table 2: Clinical characteristics and outcomes, n (%)

Characteristics	GI symptoms	No GI symptoms	Total	p-value
Severe Disease				
ICU admission	12 (25)	46 (31.1)	58 (29.6)	0.423
Mechanical ventilation	5 (10.4)	35 (23.6)	40 (20.4)	0.048
Death	7 (14.6)	20 (13.5)	27 (13.8)	0.852
Total	**48**	**148**	**196**	

Abbreviations: ICU – intensive care unit, GI – gastrointestinal

Table 3: GI symptoms and duration of hospital stay, mean ± SD

Characteristics	Present	Absent	p-value
Ageusia	9.11 ± 2.9	10.93 ± 7.14	0.271
Diarrhoea	12.07 ± 14.56	10.65 ± 5.9	0.456
Nausea/vomiting	9.22 ± 5.59	10.87 ± 6.91	0.272
Abdominal pain	10.5 ± 6.39	10.76 ± 6.89	0.918

DISCUSSION

COVID-19 infection predominantly produces upper and lower respiratory tract symptoms which can vary in regards to demographic profile and different virus variants.[3,13] Present study was done during the second wave of the COVID-19 which was predominantly due to the Delta variant. Though, the world is facing the new wave due to Omicron variant presently, but Delta variant is still occupying a significant proportion of the symptomatic COVID patients, probably will still be the threat to human health in coming future. Prevalence of different GI symptoms attributed to COVID-19 infection with their impact on outcomes of the patient was evaluated in this study. As, patients with known GI disease at baseline including chronic liver disease, pancreatitis and inflammatory bowel diseases were excluded from the study, all the new onset GI symptoms were attributed to the COVID-19 infection.

Different studies done on prevalence of GI symptoms with COVID-19 infection have shown variable results. Incidence of GI symptoms up to 79% have been reported in some studies.[14] In current study it was found that 48 (24.49%) patients had at least one GI manifestation which is in line with most of previous studies.[10,15,16] Nausea/vomiting was the predominant symptom in patients of this study which was similar with some previous studies.[12,17]

An early meta-analysis comprising 60 different studies which comprised 4243 patients with majority of studies from China, has shown the pooled prevalence of all gastrointestinal symptoms as 17.6% with anorexia being most common presenting symptom (26.8%), followed by diarrhoea (12.5%), nausea/vomiting (10.2 percent), and abdominal pain (9.2%).[18] However, the authors have not included anorexia as a gastrointestinal manifestation as it is highly non-specific and ubiquitous symptom.[10] A subsequent meta-analysis including more than 18,000 patients from different parts of the world suggested diarrhoea as the most common (11.5%) gastrointestinal symptom, followed by nausea and vomiting (6.3%) and abdominal pain (2.3%).[19]

In this study the authors found no significant association between age, sex, and comorbidities with presence GI symptoms in patient with COVID-19 disease (Table 1). Similarly, there was no significant association of severity parameters like duration of hospital stay, death, and mechanical ventilation with specific symptoms but requirement of mechanical ventilation was significantly higher in patients without GI symptoms (10.4 vs 23.6%; p = 0.048). Previous studies have found conflicting results on presence of GI symptoms and severity of outcomes. Study done by Ramachandran et al. and Reed and colleague have shown no association in clinical outcomes of patients with or without GI symptoms.[11,20] However, study done by Leal et al. had shown that presence of digestive symptoms was associated with less severe disease (28.3 vs 44%; p = 0.038) and also associated with decreased risk of mortality (11.7 vs 27.4%; p = 0.001).[10] Similarly, in a study done by Pan et al. from Wuhan, China patient with GI symptoms had a significantly longer time from onset of symptoms to admission than patients without GI symptoms (9 days vs 7.3 days).[21] Furthermore, they have also noted that as the severity and duration of COVID-19 increases, GI symptoms also increases.

This study showed that significant number of patients with COVID-19 disease can present with gastrointestinal complains. Although the specific mechanisms causing GI manifestations in patients with COVID-19 infections are not clear, there are different proposed theories. Due to the strong affinity of COVID-19 virus with ACE-2 that is highly expressed in GI tract, can result in direct bowel involvement with cytopathic effects producing GI symptoms.[4,7,22] Alteration of gut microbiota during COVID-19 infection with enrichment of pathogenic variants and depletion of beneficial commensals also has been proposed in different studies.[26,27] Altered intestinal permeability due to viral infection resulting in malabsorption also has been seen in COVID-19 infection.[11,27,28]

Present study has some limitations: firstly, sample size could be larger, though it is reasonably well sized to draw some conclusions and still have good sample size than most of previous similar studies. The authors have

included only those patients who require hospitalisation so, the result cannot be generalised to the patients with mild symptoms not requiring hospitalisation.

CONCLUSION

Infection with COVID-19 can have significant proportion of patients with GI symptoms as non-respiratory complains. This study has shown that, there is no significant association of age, sex, and presence of comorbidities along with smoking or regular alcohol consumption habits in developing GI symptoms. Also, GI symptoms were not associated with the poorer outcomes in the form increased duration of hospital admission, requirement of ICU admission and mortality which may signify that these symptoms could potentially be a bystander only, in patients with COVID-19 disease requiring hospitalisation due to different disease severity factors.

Conflict of interest: None
Source(s) of support: None

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