Prevalence and Characteristics of Gastrointestinal Symptoms and Hepatic Manifestation in Covid-19 Infection in Tertiary Care Center

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ABSTRACT

Introduction: Although the primary clinical manifestation of COVID-19 is pulmonary disease, but there are increasing data to support the gastrointestinal and hepatic involvement. **Aims:** We aimed to see the prevalence and characteristics of gastrointestinal symptoms and hepatic manifestation in COVID-19 infection. **Methods**: This is a hospital based descriptive cross-sectional study which was carried out in medicine department of Nepalgunj Medical College. Consecutive patients of COVID-19 cases confirmed by polymerase chain reaction were included. The presenting complaints, laboratory parameters, clinical events were noted. The primary objective was to determine the prevalence of gastrointestinal manifestation and hepatic dysfunction and their correlation with severity of pneumonia. **Results:** Total patients enrolled in the study were 205. Majority of patients presented with respiratory symptoms 67.8%. Both respiratory and gastrointestinal symptoms were observed in 29.3% cases. Isolated gastrointestinal symptoms were observed in 2.9% cases. Common gastrointestinal symptoms were anorexia 14.1%, anorexia and nausea in 6.3%, pain abdomen in 3.9% and diarrhea in 2.4% cases. Hepatocellular type hepatic dysfunction reported in 53.2% cases. Rise in alanine aminotransferase (58.2% vs. 23.6%), aspartate aminotransferase (51.6% vs. 20.6%), alkaline phosphatase (44% vs. 15%), total bilirubin (76.6% vs12.5%) found significantly high in severe pneumonias compared with pneumonia only. Both gastrointestinal and hepatic dysfunctions were more common in severe cases (87.9% and 58.7%) than in mild disease (1% and 27%). **Conclusion**: One third of the patients of COVID-19 can have gastrointestinal symptoms and hepatic dysfunction. Around 3% of patients presented with isolated gastrointestinal symptoms. Thus, unexplained gastrointestinal symptoms in contacts of COVID-19 may demand polymerase chain reaction test to confirm the disease. Both gastrointestinal and hepatic dysfunction was more prevalent in severe pneumonia.

***Keywords**:* COVID-19, diarrhea, gastrointestinal, hepatic dysfunction, pneumonia

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INTRODUCTION

The virus known as severe acute respiratory syndrome corona virus 2 (SARS-CoV-2), which causes the disease corona virus disease 2019 (COVID-19), in a very short time period became a global pandemic.[1] After the first outbreak reported from China, in December 2019, the World Health Organization (WHO) has declared a pandemic on March 11, 2020.[2,3] The clinical presentation of COVID-19 is predominantly respiratory in nature. Involvement of the gastrointestinal tract and the hepatic system is now being frequently reported during the course of the disease.[4] The information on extra-pulmonary manifestations, however, has been scarce in our country. Indeed, the first case of COVID-19 in the United States presented with gastrointestinal (GI) manifestation.[5] Several studies also have reported the incidence of liver injury with abnormal levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST).[6,7,8,9] Therefore, the aim of this study was to systematically characterize the prevalence and features of GI and hepatic manifestations and their correlation with severity of the COVID 19.

METHODS

This hospital based descriptive cross-sectional study was carried

out in medicine department of Nepalgunj Medical College, Kohalpur, Nepal. All confirmed COVID-19 case diagnosed by polymerase chain reaction of nasopharyngeal or throat swab taken during time period of October 2020 to February 2021 were included. Patient's demographics, presenting symptoms, duration of symptoms, associated co-morbidities were noted. Routine laboratory investigations like complete blood count, liver function test, renal function test, random blood glucose, CRP, D-Dimer, chest x-ray were done. Severity of COVID-19 was as per the national guidelines for community-acquired pneumonia and the diagnosis and treatment plan for the new corona virus in China.[10,11] Severe pneumonia was defined by the presence of any of the following conditions: i) significantly increased respiration rate (RR): RR ≥ 30 times/minute ii) hypoxia: oxygen saturation (resting state) ≤93% iii) blood gas analysis: partial pressure of oxygen/fraction of inspired oxygen(PaO2) /FiO2) ≤300 mmHg (millimeters of Mercury) or iv) the occurrence of respiratory or other organ failure that requires intensive care unit (ICU) monitoring and treatment, or shock.

The exclusion criteria included co-infection with any viral hepatitis (Hepatitis B, Hepatitis C), presence of other chronic liver diseases (autoimmune hepatitis, alcoholic liver disease, nonalcoholic fatty liver disease), receiving long-term medication associated with liver dysfunction; having malignancy. Liver test abnormalities were defined as the elevation of the following liver enzymes in serum: ALT>40 U/L, AST>40 U/L,gamma-glutamyltransferase (GGT) >49 U/L, alkaline phosphatase (ALP) >135 U/L, and total bilirubin (TBIL)>1 mg/dl. Rise in ALT/AST three times or more leveled as hepatocellular type liver injury, rise in ALP two times or more leveled as cholestatic type and both rise in ALT/AST three times or more and ALP two times or more leveled as mixed type liver injury.

Ethical approval was taken from Institutional Review Committee (IRC), NGMC and written informed consent was taken from each patient. Data collected in structured proforma were entered in Microsoft Excel 2007 and statistical analysis was done with SPSS 20 software. Chi-Square test or Fisher exact testwas used for comparisons between categorical variables. Values were expressed as mean±SD, a 95% confidence interval was taken and P values of <0.05 was considered to be statistically significant.

RESULTS

Total patients with confirmed COVID-19 enrolled in the study were 205. Among them 126(61.5%) were male and 79 (38.5%) were female with male preponderance.Demographic profile and clinical presentation of the patients are given in table I. Respiratory symptoms were the predominant presenting complaint noted among 139(67.8%) individuals. Fever was predominant initial clinical presentation among 115(56.1%) cases. Other major respiratory symptoms were fever, cough 34(16.6%), fever, cough and shortness of breath 23(11.2%) and only cough 22(10.7%). Both respiratory and gastrointestinal symptoms were observed among 60(29.3%) cases. Isolated gastrointestinal symptoms were observed in 6(2.9%) cases. Among gastrointestinal symptoms, anorexia was most common 29(14.1%). Other gastrointestinal symptoms were anorexia, nausea 13(6.3%), pain abdomen 8(3.9%). Diarrhea was noted in 5 cases (2.4%). On the basis of severity of pneumonia, no evidence of pneumonia was reported in 109(53.2%), pneumonia in 31(15.1%) and severe pneumonia in 65(31.5%) cases. Hepatocellular type of liver injury pattern was found in 109(53.2%) cases.

RESPIRATORY SYMPTOMS	Frequency	Percent (%)
Cough	22	10.7
Cough, SOB	2	1
Fever	115	56.1
Fever,Cough	34	16.6
Fever,Cough,SOB	23	11.2
Fever,SOB	2	1
None	6	2.9
SOB	1	0.5
Total	205	100
GI SYMPTOMS		
Anorexia	29	14.1
Anorexia,Anosmia	1	0.5
Anorexia,Nausea	13	6.3
Anorexia,Nausea,Pain abdomen	1	0.5
Anorexia,Nausea,Vomiting	1	0.5
Anosmia	4	2
Diarrhoea	5	2.4
Nausea	2	1
Nausea,Vomiting	2	1
None	139	67.8
Pain abdomen	8	3.9
Total	205	100
ISOLATED SYMPTOM		
Respiratory only	139	67.8
GI only	6	2.9
Both	60	29.3
Total	205	100
PNEUMONIA		
No pneumonia	109	53.2
Pneumonia	31	15.1
Severe pneumonia	65	31.7
Total	205	100
LIVER INJURY		
Hepatocellular	109	53.2
Normal	96	46.8
Total	205	100

*SOB-shortness of breath, GI-gastrointestinal

Table I. Demographic and clinical characteristics

Liver function abnormalities in the form of transaminitis were noted among infected individuals. Rise in AST was found in 126 (61.5%) more common than ALT which was seen in 110 (53.7%).

ALT	Frequency	Percent (%)
> 40	110	53.7
<= 40	95	46.3
Total	205	100
AST		
> 40	126	61.5
<= 40	79	38.5
Total	205	100
ALP		
> 135	100	48.8
<= 135	105	51.2
Total	205	100
TBIL		
> 1	64	31.2
<= 1	141	68.8
Total	205	100

*ALT-alanine aminotransferase, AST-aspartate aminotransferase, ALP-alkaline phosphate, TBIL-total bilirubin

Table II. Liver function test abnormality

Significant correlation between severity of pneumonia with patients having GI symptoms, liver injury and comorbidities was found. No significant relation was noted between gender and severity of pneumonia. (Table III)

Gender	No pneumonia	Percent	Pneumonia	Percent	Severe pneumonia	Percent	Total	p
F	43	54.4	14	17.7	22	27.8	79	0.544
M	66	52.4	17	13.5	43	34.1	126	
GI symptom								
Yes	7	10.6	1	1.5	58	87.9	66	<0.001
No	102	73.4	30	21.6	7	5.0	139	
Comorbidity								
Yes	7	11.3	3	4.8	52	83.9	62	<0.001
No	102	71.3	28	19.6	13	9.1	143	
ALT								
> 40	20	18.2	26	23.6	64	58.2	110	<0.001
<= 40	89	93.7	5	5.3	1	1.1	95	
AST								
> 40	35	27.8	26	20.6	65	51.6	126	<0.001
<= 40	74	93.7	5	6.3	0		79	
ALP								
> 135	41	41.0	15	15.0	44	44.0	100	0.001
<= 135	68	64.8	16	15.2	21	20.0	105	
TBIL								
> 1	7	10.9	8	12.5	49	76.6	64	<0.001
<= 1	102	72.3	23	16.3	16	11.3	141	
Liver injury								
Hepatocellular	18	16.5	27	24.8	64	58.7	109	<0.001
Normal	91	94.8	4	4.2	1	1.0	96	

*Chi square test, fisher exact test

Table III. Correlation of severity of pneumonia with GI symptoms, Liver injury and co morbidities

DISCUSSION

In our study, most of the patients presented with respiratory symptoms (67.8%). Fever was initial presenting feature reported in majority (56.1%). Among respiratory symptoms, fever and cough noted in 16.6%, fever, cough with shortness of breath in 11.2% and only cough in 10.7% cases. As lung epithelium is the primary target of virus, after entry into human host cells, it attacks the ACE2 receptors in the lung where intracellular viral replications starts along with activation of both innate and adaptive immune response occurs which leads to harmful tissue damage, both locally and systemically due to release of cytokine and various inflammatory markers.[12] Various other studies also reported fever ,cough and shortness of breath were the most common presenting features in infected individuals.[2,9,10,13]

Earlier it was thought that COVID-19 is primarily respiratory illness but with due course of time extra- pulmonary symptoms including gastrointestinal and hepatic dysfunction also reported. In our study 29.3% cases have GI symptoms along with respiratory symptoms and 6 cases (2.9%) have isolated GI symptoms. Common GI symptoms observed in our study were anorexia 14.1%, pain abdomen 3.9%, nausea 6.3% , diarrhea 2.4% and loss of smell in 2% cases. GI symptoms like anorexia, nausea , pain abdomen, diarrhea, vomiting also reported by various other studies.[14,15,16] Studies also shown that cases having GI symptoms preceding respiratory symptoms with some having isolated GI symptoms in absence of respiratory symptoms.[17,18] The proposed mechanism for GI manifestations in COVID-19 infection is presence of ACE2 receptors in GI tract especially in proximal and distal enterocytes.[19] SARS-CoV-2, exert direct cytopathic effect on enterocytes via ACE2 receptors resulting cellular dysfunction and increased permeability which in turn can lead to most of GI symptoms like anorexia, nausea ,pain abdomen and diarrdoea.[20] Another proposed mechanism is hypoxia induced necrosis and cellular injury mostly in severe cases resulting in enterocyte dysfunction.[21] In our study, hepatic dysfunction reported in 53.2% cases as evidence by raised transaminase (ALT, AST) which is predominantly hepatocellular type. Rise in ALT(58.2% vs. 23.6%), AST(51.6% vs. 20.6%), ALP(44% vs. 15%), total bilirubin (76.6% vs 12.5%) found significantly high in severe pneumonias compared with pneumonia. One of the earliest study conducted by Huang C et al from Wuhan reported transaminitis in COVID-19 patients and number was even higher in severe cases (62% vs 25%) as compared to non severe cases.[8] Hepatic dysfunction as evident by raised ALT, AST, ALP and total bilirubin was also reported by various other observational studies.[2,8,9,22,23] As compared to other studies[1,8,24,25], our study also reported both GI and hepatic dysfunction were more common in severe cases (87.9% and 58.7%) versus mild disease (1% and 27%) respectively. Hepatic dysfunction is also due to presence of virus specific ACE2 receptors on hepatocytes (cholangiocytes>hepatocytes).[26] Rise in transaminase is directly due to hepatocytes injury and indirectly liver injury from overwhelming release of inflammatory cytokines (cytokine storm) or ischemia.[6] Other possible mechanism may be due to intake of hepatotoxic drugs or undiagnosed underlying chronic liver disease. Another concern raised by

several authors about fecal-oral transmission.[19,25] In addition stool samples can remain positive even after a negative throat swab.[2] Only focused on respiratory symptoms may miss or delay the diagnosis as the features are non-specific which might be responsible for significant exposure and increased risk of transmission in home, communities and even among healthcare workers. So, during ongoing pandemic atypical presentation especially GI symptoms and hepatic abnormalities should not be ignored before confirmatory result came.

LIMITATIONS

Our study included patients hospitalized in tertiary care center, is a single center study. For better generalization of results may need further multicenter studies. In our study, GI and hepatic dysfunction are associated with severity but final outcome like length of hospital stay or mortality was not followed. GI symptoms are nonspecific, underlying GI disease like acid peptic disease, GERD etc also have similar symptoms.Hepatic dysfunction in the form of transaminitis might be due to over the counter drugs like paracetamol for fever or other hepatotoxicor herbal medicine, undiagnosed liver disease like NAFLD, ALD.

CONCLUSION

Typical presentation of SARS-CoV-2 infection is mostly respiratory in nature but atypical or extra-pulmonary features like GI or liver injury are also frequently reported. Thus, it is important for all, including healthcare workers (HCW) to be vigilant during ongoing pandemic in considering COVID-19 even in the atypical patients. Early recognition of GI and hepatic abnormalities not only help in reducing community and nosocomial transmission but also guides physicians regarding safe and effective clinical practice during the ongoing pandemic.

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