Gastrointestinal and Hepatic Manifestations in Patients with Covid-19

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Abstract

Background: Gastrointestinal symptoms and Liver injury have been frequently described in patients with COVID-19.In this study, we aim to study the prevalence of Gastrointestinal symptoms and Liver injury and their impact on disease severity and clinical outcomes.

Methods: This is a descriptive, cross sectional observational study done in 195 patients admitted to Bir Hospital with Corona virus Disease-19(COVID-19) from May 2021 to July 2021. Patients presenting symptoms and liver function tests (LFTs) were noted at admission. Gastrointestinal symptoms were defined as the presence of one of Nausea, Vomiting, Abdominal pain or Diarrhea. Liver injury was defined as elevation of Total Bilirubin > 1mg/dl or Alanine transaminase (ALT) >40U/L, Aspartate Transaminase(AST) >40U/L or Alkaline Phosphatase(ALP)>135 U/L. Patients were followed during hospitalization and outcomes assessed at discharge.

Results: Gastrointestinal symptoms were present in 32.3% among which Nausea (27.7%) was the commonest. There was no significant association of Gastrointestinal symptoms with duration of hospital stay, ICU admission or mortality. Liver injury was present in 72.8% patients and significantly more in those with GI symptoms than without GI symptoms. Patients with liver injury had a significantly longer hospital stay (8.92 ± 3.7 days vs 6.70±3.2 days, p=0.004), higher ICU admissions (38.02% vs 7.54% p=0.000018) and mortality (23.23% vs 1.88%, p=0.001) compared to patients with normal LFTs.

Conclusion: Gastrointestinal symptoms and Liver Injury are common in patients with COVID-19. Liver injury at admission is associated with severe disease and higher mortality. More attention should be given in the care of such patients to avoid poor outcomes.

Introduction

Ever since the first case of confirmed COVID-19 infection was detected in Nepal in January 2020[1], it continues to remain a major health concern and has infected more than one million individuals with 11999 deaths[2]. COVID-19 infection primarily involves the lungs with most infected persons presenting with fever and cough as the predominant symptoms[3]. However, Gastrointestinal symptoms are also common with studies describing at least one GI symptom in as much as one third of patients diagnosed with COVID-19[4].Moreover, patients with GI symptoms were found to have more severe disease[5]. GI symptoms in COVID are attributed to virus entry into the GI tract epithelium via ACE-2 receptors with subsequent direct injury to the epithelium[6].There could also be alteration in the intestinal flora and gut mucosal immunity leading to digestive symptoms[5].

Apart from GI symptoms, liver injury is also common in patients

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with COVID-19. Several studies have shown elevated levels of liver enzymes, Alanine Transaminase (ALT) and Aspartate Transaminase (AST) with higher levels more prevalent in patients with severe disease. Liver injury in COVID-19 is attributed to viral infection in liver cell, immune mediated injury or Drug induced liver injury[7].

GI symptoms and liver injury though quiet common among COVID-19 patients, there is scarce data from Nepal. In this study, we aim to characterize the GI symptoms and Liver function abnormalities in patients of COVID-19 in hospitalized patients and correlate with disease severity and clinical outcomes.

Methodology

This is a single center descriptive, hospital based observational study. 195 consecutive adult patients (18 years and above) with a positive RT-PCR for SARS COV-2 from Nasopharyngeal or Oropharyneal swabs admitted to Bir hospital COVID wards and ICU in the months of May to July 2021 were included. Informed consent was taken from the patients and Ethical board approval was taken from the Institutional Review Board, NAMS before the start of the study. Sample size was calculated using the formula $N = Z2p(1-p)/e2$ where $Z = 1.96$ at 95% confidence interval; $p = 0.15$(15 % prevalence in previous study); e = margin of error, 5%.

After enrollment, the participants symptoms, signs, vital parameters, demographic data, comorbidities, laboratory data including Liver Function Tests(Total Bilirubin, Alanine Tranasminase(ALT),Aspartate Transaminase(AST),Alkaline Phosphatase(ALP) were collected in a structured proforma at the time of admission. Disease severity was defined according the National Institute of Health (NIH) Covid-19 treatment guidelines into Mild, Moderate, Severe and Critical illnesses.[8]

1. Mild Illness: Individuals who have any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but who do not have shortness of breath, dyspnea, or abnormal chest imaging.

2. Moderate Illness: Individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have saturation of oxygen (SpO2) ≥94% on room air at sea level.

3. Severe Illness: Individuals who have SpO2 <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 mmHg, respiratory frequency >30 breaths per minute, or lung infiltrates >50%.

4. Critical Illness: Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.

GI symptoms included presence of at least one of Nausea, Vomiting, Diarrhea and Abdominal pain at the time of presentation. Diarrhea was defined as the passage of 2-10 loose or watery stools a day[9]. Liver injury was defined as abnormal Liver Function tests with a value of Total Bilirubin > 1mg/dl or ALT > 40U/L, AST> 40U/L or ALP> 135 U/L[10]. The patients were given appropriate treatment according to their severity of illness. Outcomes included mortality during hospital stay, ICU admissions and in-hospital mortality in relation to GI symptoms and Liver Function Test abnormalities.

Data analysis was done using Statistical Package for Social Sciences (SPSS), version 20.0 (IBM Corp., Armonk, N.Y., USA). Categorical variables were expressed as frequency and percentage and compared using the Pearson's chi square test while continuous variables expressed as mean ± SD compared by unpaired t test. A two sided p value of < 0.05 was considered statistically significant.

Results

195 patients who fulfilled inclusion criteria were included in the study. The median age was 48 years with a range of 18 to 79 years. 119 (61%) of the study population were males. Most Patients (n=132, 67.69%) presented with Non Gastrointestinal (Non GI) complaints. Fever (66.2%), Cough (61.5%), Fatigue (28.7%) and Nausea (27.7%) were the most common presenting complaints. Overall, 63 patients(32.3%) presented with GI symptoms most commonly Nausea (n=54, 27.7%) followed by vomiting(n= 31,15.9%), Abdominal Pain (n=23,11%) and Diarrhea(n=18,9.2%). 6 patients presented with GI symptoms only. More number of males presented with GI symptoms (n=40, 63.49%) compared to females (n= 23, 36.5%).There were 60 patients (30.76%) with comorbid conditions, among whom 23(38.33%) presented with GI symptoms. Diabetes (n=21, 35%) and Hypertension (n=11, 18.33%) were the most common. [Table 1]

Most of the patients had Moderate disease (n=122, 62.56%) at presentation. 38(19.48%) patients had severe disease and 23(11.79%) were critical [Table 2]. 142 patients has abnormal LFTs of whom 126 patients (64.6%) and 129 patients (66.15%) had elevated ALT and AST respectively. ALP was found to be elevated in 43 patients (22.05%). Total Bilirubin was elevated in 35(17.94%) patients. The mean value of ALT was 71.91 U/L and AST was 75.01U/L in the whole cohort respectively. 60(30.76%) patients had ALT and 62(31.79%) patients had AST elevated to more than 2 times of ULN. A significantly higher number of patients with GI symptoms had abnormal LFTs than patients without GI symptoms (92% vs 63.6%; p=0.00003) [Table 3]

Overall 60 patients required admission to ICU among which 13 of the 19 patients admitted with GI symptoms died compared to 21 deaths among 41 patients who were admitted with non-GI symptoms (p=0.421).The average length of hospital stay in the whole sample was 8.32 days (SD ±3.743) with no significant difference between patients with GI or without GI symptoms.(9.86±3.96 vs 7.58 ± 3.40 days; p= 0.124)[Table 4]

Patients with abnormal LFTs had more severe illness (P=0.000003), a significantly longer duration of hospital stay (8.92±3.7 days vs 6.70±3.2 days, p=0.004), significantly higher ICU admissions (38.02% vs 7.54%, p=0.000018) and mortality (23.23% vs 1.88%, p=0.001) compared to patients with normal LFTs. [Table 5].

DISCUSSION

In this study, we found a high prevalence of GI symptoms and Liver injury (based on elevated liver enzymes) in hospitalized COVID-19 patients at presentation. However, only Liver injury at presentation was significantly associated with severe illness, ICU admission and mortality.

Our study showed more than one fourth of patients had GI symptoms at presentation. Various studies done in COVID-19 Patients have reported a prevalence of GI symptoms ranging from 3% to 50%.[5,11,12]. Pan et al. reported digestive symptoms in 50.5 % in his cohort of 204 patients among which Anorexia was most frequent(78.6%) diarrhea was present in 34% cases.[5] However we did not report Anorexia as a GI symptom due to its non-specific nature. Our study showed nausea (27.7%) as the predominant GI symptom which is similar to the study done by S.Poudel in a cohort of hospitalized patients who reported overall prevalence of GI symptoms in 24.5% with Nausea and vomiting as the commonest presenting GI symptom seen in 23% patients.[13] This could probably explain by the high prevalence of abnormal LFTs seen in our study cohort. Hajifathalian et al.[14] and Pan et al.[5] reported diarrhea as the commonest GI symptom

present in one third of their study population. However, diarrhea was an uncommon symptom in our study seen only in 9.2% of patients. A metaanalysis done by Ren Mao et al. which included 35 studies comprising 6686 patients showed a pooled prevalence of GI symptoms of 15% with nausea/vomiting, diarrhea and anorexia as the main symptoms.[15]

In our study we did not observe a significant association with age, sex, comorbid conditions and clinical outcomes including hospital stay, ICU admission and mortality between patients with GI and without GI symptoms. This is similar to some previous other studies which have evaluated the association between GI symptoms and disease severity and outcomes[12,16]. However, some studies have shown contrasting results. In the metaanalysis by Ren Mao et al. , patients with GI symptoms were found to have increased risk of severe or critical disease(OR 2.96 [95% CI 1.17-7.48] ;p=0.02) in contrast to our study which showed no difference. Study done by Hajifathalian et al in adult COVID-19 patients with severe disease showed a significant lower rate of ICU admission and death in patients with GI symptoms compared to those who presented without GI symptoms[17].In one study, patients with severe COVID-19 had abdominal pain significantly compared to non-severe patients[18].

In our study cohort, we found that 72.8 % of COVID-19 patients had abnormal Liver Function Tests, notably elevation of ALT and AST in two third of patients. Previous studies done in COVID-19 patients have shown LFT abnormalities ranging from 19%-76.3%%[10,17]. The percentage of LFT abnormalities was 93.33% in patients requiring ICU admission and 97% of those with abnormal LFTs died which was significant compared to patients with normal LFTs. We observed a high frequency of LFT abnormalities in our study cohort than most previously reported studies though we had very few number of patients with diagnosed liver disease. This suggest liver injury in COVID might be due to direct viral entry and infection of liver cells mediated via SARS COV-2 receptors which are abundantly expressed in the liver[19].

Patients with liver injury also had longer length of hospital stay, more ICU admissions and higher mortality compared to patients who had normal liver enzymes at presentation similar to previous studies. Fan et al. in his retrospective review of 148 adult COVID patients found that patients abnormal LFTs at presentation had longer mean hospital stays (15.09 ±4.79) than patients with normal LFTs (12.76±4.14 days) [p=0.21].[20] D Yadav et al. in a metaanalysis of 32 studies including 6993 COVID 19 patients also reported that liver injury was associated with a higher mortality compared to those patients without liver injury OR: 1.74; 95% CI: 1.10 to 2.74; I2 = 25%; P= 0.02).[21]

Elevation of bilirubin and Alkaline Phosphatase was uncommon in our study. Other studies have also reported a lower prevalence of elevated ALP compared to ALT and AST[20]. Liver injury was significantly common in patients with GI compared to patients without GI symptoms. No significant difference was found in relation to age, sex and comorbid conditions unlike Abdelrehman et al. who found significantly higher number of diabetic patients with abnormal LFTs[22] and Cai et al. who reported higher proportion of abnormal LFTs in older patients and males[10].

This study has certain limitations. First, this is a single hospital based study with a small sample size done in admitted patients and many patients were sicker requiring ICU admission, so the results may not be applicable to patients with milder disease and to larger population. Second, we did not monitor the patients to follow the trend of LFT abnormalities and its effect on outcomes. Third, we did not consider the effect of medications used before admission.

Conclusion

GI symptoms and LFT abnormalities are common in COVID patients. Patients with liver injury are at increased risk of severe disease and mortality compared to patients with normal LFTs. So, more attention should be given to the care of these patients who present with abnormal LFTs. Besides, few patients may present only with GI symptoms and clinicians should be aware regarding possible COVID infection in these patients.

Conflict of Interest: None

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Table 1: Baseline Demographic Profile

Characteristics	GI symptoms(n=63)	Non GI symptoms(n=132)	Total(n=195)
Age(years) Mean± SD	50.49±12.92	48.23±13.78	48.96±13.52
Sex, n(%)			
Male	40(63.5)	79(59.8)	119(61)
Female	23(36.5)	53(40.1)	76(39)
Comorbidities*,n(%)	23(36.5)	37(28.03)	60(30.76)
GI Symptoms, n(%)			
Nausea	54(85.7)		27.7
Vomiting	31(49.2)		15.9
Abdominal Pain	23(36.5)		11.8
Diarrhoea	18(28.6)		9.2
Non GI symptoms,n(%)			
Fever		129(97.7)	66.2
cough		120(90.9)	61.5
Fatigue		56(42.4)	28.7
SOB		51(38.63)	26.2
Headache		45(34.09)	23.1

*Comorbities include Diabetes Mellitus, Hypertension, Coronary Artery Disease, Chronic liver disease , Chronic Airway Disease, Thyroid Disorder

Table 2: Incidence of GI and Non GI symptoms and LFT with Disease Severity

Disease severity

	Mild	Moderate	Severe	Critical	Total	P value
Symptoms,n(%)						
GI	3(4.76)	40(63.49)	10(15.87)	10(15.87)	63	0.524
Non GI	9(6.81)	82(62.12)	28(21.21)	13(9.84)	132	
LFT,n(%)						
Normal	8(15.09)	42(79.24)	3(5.66)	0(0)	53	0.000003
Abnormal	4(2.81)	80(56.33)	35(24.64)	23(16.19)	142	

Table 3: Incidence of GI and Non GI symptoms with LFT

	GI(n=63)	Non GI(n=132)	Total(n=195)	p value
LFT				
Normal	5(7.93)	48(36.36)	53(32.3)	
Abnormal	58(92.06)	84(63.63)	142(72.82)	0.00003

Table 4: Association of GI and Non GI symptoms with clinical outcomes

	GI(n=63)	Non GI(n=132)	Total(n=195)	p value
Duration of hospital stay(Days ±SD)	9.86±3.967	7.58±3.409	8.32±3.74	0.124
ICU admission,n(%)	19(30.15)	41(31.06)	60(30.76)	0.898
Outcome				
Death	13(20.63)	21(15.9)	34(17.43)	0.416

Table 5 : Association of LFT with clinical outcomes

	LFT		Total(n=195)	p value
	Normal(n=53)	Abnormal(n=142)		
Duration of hospital stay(Days ±SD)	6.7±3.28	8.92±3.73	8.32±3.74	0.004
ICU admission,n(%)	4(7.54)	56(38.02)	60(30.7)	0.000018
Outcome				
Death	1(1.88)	33(23.23)	34(17.43)	0.001