Research Article

Hepatic and Gastrointestinal Manifestations of COVID-19

Sami Ullah Mumtaz[1], Tayyeba Komal[2], Zafar Niaz[3], Somia Iqtadar[4], Iqra Waheed[5], Sajid Abaidullah[6]

[1]Assistant Professor, Department of North Medicine, KEMU/ Mayo Hospital, Lahore; [2]M.Phil Trainee Microbiology, King Edward Medical University, Lahore; [3]Assistant Professor, Department of North Medicine, KEMU/ Mayo Hospital, Lahore; [4]Associate Professor, Department of North Medicine, KEMU/ Mayo Hospital, Lahore; [5]Ex-Data Manger, PIPO, Mayo Hospital, Lahore; [6]Professor and Head of North Medicine, KEMU/ Mayo Hospital, Lahore .

Abstract

Background: Coronavirus disease (COVID-19) is a global challenge affecting more than 45 million people with a significant mortality.

Objective: To determine the frequency of hepatic and gastrointestinal manifestations in patients of COVID-19.

Methodology: This was a cross sectional study conducted at King Edward Medical University (KEMU), Mayo Hospital, Lahore for three months. After ethical approval of the study, 230 COVID-19 positive cases of ages 15 to 80 years were included in the study. Complete history & examination regarding hepatic & gastrointestinal symptoms were noted. Liver function tests & prothrombin time (PT) were sent to pathology laboratory at the time of presentation & results were noted. Data was analyzed using SPSS version 26. Descriptive continuous variables like age, bilirubin, Aminotransferases & PT were taken as mean ± standard deviation. Categorical variables like gender, hepatic & GI symptoms were taken as frequency and percentages.

Results: In 230 patients, the most common gastrointestinal symptom at presentation was diarrhea 34 (14.8%), anosmia 10 (4.3%), nausea & vomiting, abdominal pain 8 (3.5%) each, dysgeusia & right hypochondrial pain 4(1.7%) & Hiccup malaise, anorexia 2 (0.9%). No patient presented with jaundice. Among hepatic manifestations, 8.7% patients had elevated bilirubin levels while Aspartate aminotransferase (AST) was raised in 40% of cases, Alanine aminotransferase (ALT) in 11.3%, Alkaline phosphatase in 1.7%, Gamma-glutamyl transferase (GGT) in 54.8% of cases. 8 (3.5%) cases showed decrease albumin levels and 6.1% cases had prolonged Prothrombin Time (PT).

Conclusion: Hepatic & gastrointestinal symptoms were present as the main presenting symptoms of COVID-19 in many patients. So, careful history must be taken for these extra-pulmonary symptoms to avoid any delay in treatment & progression of disease with complications.

Corresponding Author | Dr. Sami Ullah Mumtaz, Assistant Professor, Department of North Medicine, KEMU/ Mayo Hospital, Lahore. **Email:** drsumumtaz@gmail.com

Key Words: COVID-19, Pandemic, Liver Function Tests, Gastrointestinal, Manifestations.

Introduction

Coronavirus disease (COVID-19) pandemic was first identified in Wuhan city of Hubei province of China, which later on has involved 215 countries so far.[1] It was caused by novel SARS-COV2 corona-virus with Huanan seafood wholesale market as the possible point of origin.[2] Since then this disease has infected almost more than 45 million people worldwide, with over 140,00,000 cases in the United States alone.[3] In Pakistan, it has affected around 300,000 people with a mortality of over 5000 people.[3]

COVID-19 is a disease of acute onset with wide range of disease severity from mild to severe & critical disease having a case fatality risk of 2%. Damage to the alveoli with progressive respiratory failure is the usual cause of mortality in these patients with severe to critical disease.[4] In past two decades, coronaviruses epidemic of Middle East Respiratory Syndrome (MERS-COV) had 37% mortality rate & Severe Acute Respiratory Syndrome (SARS-COV) had 10% affecting more than 10,000 population together.[5]

SARS-COV-2 responsible for COVID-19 belongs to coronaviridae family of enveloped viruses, with an unusually large positive sense single stranded RNA genome with the surface containing club shaped spikes.[7] Multiple trials are going on to discover definitive treatment modalities of this novel disease as well as for its vaccine.

The symptom complex of the disease range from asymptomatic to variety of symptoms. Most patients present with fever, sore throat, cough, flu, and myalgia & less commonly with sputum production, & headache. As the disease is progressing, involvement of other body systems like gastrointestinal & hepatobiliary have also been reported. Almost 50% of the patients also have associated digestive symptoms which vary from abdominal pain to diarrhea and indigestion.[8,9] The gastrointestinal symptoms include diarrhea, abdominal pain, nausea, vomiting, malaise, anorexia, dysgeusia & anosmia. Jaundice has also been reported.[6] Deranged liver function tests like raised levels of bilirubin, aminotransferases, alkaline phosphatase, gamma glutamyl transferase (GGT) and PT have also been reported.[6]

The hepatic & gastrointestinal manifestations of COVID19 are due to strong affinity of SARS-COV-2 for angiotensin converting enzyme-2 (ACE-2) receptors located in esophagus, small intestine, liver & bile duct epithelial cells.[10] So far disease severity has not been established due to gastrointestinal involvement however hepatic involvement is attributed as important predictor of severe disease.[7]

Since no local data is available about the non-respiratory symptoms of the disease & diagnosis can be missed. So, the objective was to determine the frequency of hepatic and gastrointestinal manifestations of COVID-19 in a tertiary care hospital of Lahore.

Methods:

It was a cross sectional study performed in Corona isolation wards of King Edward Medical University (KEMU) affiliated Mayo Hospital, Lahore for three months i.e 15th April to 15th July 2020. Ethical approval of the study was taken from institutional review board KEMU vide letter No 455/RC/KEMU. Two thirty patients with COVID-19 were enrolled after informed consent. Patients of ages 15 to 80 years of either gender with real time Polymerase chain reaction (RT-PCR) positive status were included in the study. All patients with prior hepatic or gastrointestinal diseases like inflammatory bowel disease, colorectal carcinoma, liver abscess, acute or chronic hepatitis and chronic liver disease were excluded. Demographic details including name, age, gender, address were recoded. Complete history & examination of each enrolled patient was done & recorded in a predesigned proforma. Then 2ml venous blood sample of every covid-19 positive patient was sent, each for Liver function tests & prothrombin time (PT) to KEMU Pathology laboratory.

These tests results were then recorded in the predesigned proforma in standard SI Units. Data analysis was performed using SPSS, version 26. Mean and standard deviation (SD) were presented for descriptive continuous variables (such as Age bilirubin, AST, ALT, Alkaline phosphatase, gamma glutamyl transferase (GGT), albumin & PT) and frequencies with percentages for categorical variables (like gender, hepatic & gastrointestinal symptoms). Statistical significance for categorical type and continuous type variables was tested, using chi-square test and t-test respectively.

Results

The mean age of patients positive for COVID-19 was 38.17±14.80 years. There were 108 (47%) males while 122 (53%) females. In our study, it was also found that 40(17.39%) COVID-19 positive patients had gastrointestinal & hepatic symptoms while 12(5.2%) cases had both gastrointestinal and respiratory symptoms.

The most common GI symptom in this study was diarrhea in 34 (14.8%).Others include anosmia in 10 (4.3%), nausea & vomiting, abdominal pain in 8 (3.5%), dysgeusia in 4(1.7%), Right hypochondrial pain in 4(1.7%) & hiccup malaise, anorexia in 2 (0.9%). No patient presented with jaundice. (Table 1)Many patients of GI symptoms also had respiratory symptoms (Table 2)The non-GI symptoms in our study were fever 96 (42.1%), followed by cough 62 (27.2%), fatigue 58 (25.4%), sore throat 46 (20.2%), shortness of breath 22 (9.6%), flu 18 (7.9%), headache 12 (5.3%), myalgia 8 (3.5%) & body ache 4 (1.8%).

On laboratory findings Liver function derangements were observed in patients with or without GI symptoms. Among GI symptoms patients, bilirubin was raised in 4(6.9%) while AST was raised in 16(27.6%), ALT in 4(6.9%), Alkaline phosphatase in 4(6.9%), GGT in 22(37.9%) of patients. Similarly albumin was low in 2(3.4%) & PT was prolonged in 32 (55.2%) in GI symptoms patients. on the other side, in non-GI symptoms patients bilirubin was raised in 16 (9.3%), AST 76 (44.2%), ALT 22 (12.8%) & GGT 104 (60.5%).Low albumin was seen 6 (3.5%) & prolonged PT in 46 (26.7%). (Table-3).

Table 1: *Frequency of GI & Hepatic Manifestations of Patients (n=230)*

Age (years)	38.17±14.80
Gender	
Male	108 (47%)
Female	122 (53%)
Symptoms at presentation	F%
Diarrhea	34 (14.8%)
Anosmia	10 (4.3%)
Nausea & vomiting	8 (3.5%)
Abdominal pain	8 (3.5%)
Right hypochondrial pain	4 (1.7%)
Dysgeusia	4 (1.7%)
Hiccup	2 (0.9%)
Malaise	2 (0.9%)
Anorexia	2 (0.9%)
Jaundice	0(0.0%)

Table 2: *Comparison of Symptoms in Patients With or Without GI & Hepatic Symptoms*

Symptoms at Presentation	GI Symptoms Present (n=58)	GI Symptoms Absent (n=172)	Chi²-Based p-value
Fever	16 (27.6%)	80 (46.5%)	(280.8) 0.011
Cough	10 (17.2%)	52 (30.2%)	(264.4) 0.054
Fatigue	8 (13.8%)	50 (29.1%)	(274.6) 0.021
Sore throat	12 (0.7%)	13 (19.8%)	(204.2) 0.879
Flu	2 (3.4%)	16 (9.3%)	(251.1) 0.151
Body ache	0 (0.0%)	4 (2.3%)	(243.7) 0.241
SOB	6 (10.3%)	16 (9.3%)	(209.7) 0.815
Headache	0 (0.0%)	12 (7.0%)	(268.1) 0.039
Myalgia	0 (0.0%)	8 (4.7%)	(257.5) 0.095

Table 3: *Hepatic Manifestations (LFTs & PT) In Patient With Or Without GI & Hepatic Symptoms*

Features	GI Symptoms Present (n=58)	GI Symptoms Absent (n=172)	Chi2-Values (P-values)
Nominal Features			
Raised Bilirubin	4 (6.9%)	16 (9.3%)	(224.4) 0.574
Raised AST	16 (27.6%)	76 (44.2%)	(272.4) 0.026
Raised ALT	4 (6.9%)	22 (12.8%)	(245.2) 0.22
Raised ALP	4 (6.9%)	0 (0%)	(300.9) 0.001
Raised GGT	22 (37.9%)	104 (60.5%)	(292.2) 0.003
Low protein	0 (0%)	0 (0%)	NA
Low Albumin	2 (3.4%)	6 (3.5%)	(182.8) 0.989
Prolonged PT	32 (55.2%)	46 (26.7%)	(301.0) 0. 000
Continuous Features			
	Mean ± SD	Mean ± SD	p-values based on t-test
AST	41.76±24.76	43.84±23.43	0.565
Bilirubin	0.73±0.40	0.75±0.37	0.743
ALT	40.55±12.68	43.33±23.46	0.392
Alkaline phosphate	98.10±39.56	90.34±27.38	0.099
GGT	46.48±49.74	46.30±22.90	0.97
Protein	7.04±0.43	6.87±0.37	0.003
Albumin	3.87±0.41	3.82±0.35	0.457
PT	11.45±1.65	12.03±1.25	0.005

Discussion

In this study of 230 COVID-19 cases, we found that hepatic & gastrointestinal manifestations can be the only presenting features in many patients. The purpose of our study was to detect these extra-pulmonary symptoms so that earlier treatment can be initiated to avoid any further complication.

In clinical practice, COVID-19 positive patients mainly present with respiratory symptoms but evidence of damage to other organ systems have also been reported. Especially critical patients are susceptible to multiorgan damage.[10] In our study, patients also presented with digestive symptoms without respiratory symptoms. So, clinicians should pay attention to these extra pulmonary symptoms of COVID-19, as lesser attention to these symptoms can result in spread of the disease in family as well community.[11]

By reviewing the literature, it was found that several mechanisms are present by which SARS-COV-2 cause's hepatic & GI manifestations. It binds to ACE-2 receptors present on enterocytes, hepatic-ytes & cholangiocytes.[12] It also damages digestive system directly by cytopathic process or indirectly by an inflammatory process.[13]

Through different studies, it was found that stool RNA is detected in 53% of the patients of COVID-19 presenting with diarrhea.[14] Secondly: this virus may cause damage to intestinal flora that can cause gastrointestinal symptoms. In another study, it was concluded that patients positive with hepatic & GI features rarely have any gastrointestinal & liver disorder.[15]

There are several studies that favor our results. A meta-analysis consisting of 4243 patients from 6 countries done by Cheung et al. concluded 17.6% patients with GI symptoms with 12.5 % having diarrhea.[16] Similarly in a 2nd meta-analysis of 59254 patients from 11 countries done by Borges et al. concluded GI symptoms in 9% of the COVID-19 patients.[17]

Similarly deranged LFTs in our study are supported by the literature. Deranged liver function was noted by Cai et al. in their study with severe disease patients of COVID-19 as we found in our study.[18] Another study of severe COVID-19 patients done by Chen et al. showed similar derangements in liver functions.[19]

There were certain limitations of our study. Firstly it is a study with limited sample size that can affect reliability as well as generalizability. Secondly, stool RNA of COVID-19 wasn't checked in our study. So, it is difficult to correlate the results.

Conclusion

It is concluded that hepatic & gastrointestinal manifestations are not uncommon in patients with COVID-19. Patients having coronavirus disease can present only with hepatic & gastrointestinal sympt-oms such as diarrhea, vomiting, nausea and abdomi-

nal discomfort without any respiratory symptoms; such patients' diagnosis may be delayed due to unusual symptoms. So, attention should be given to these initial extra-pulmonary features to avoid delay in treatment, progression of this disease & complications.

Ethical Approval: Given
Conflict of Interest: The authors declare no conflict of interest
Funding Source: None

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