Original Article

Gastrointestinal and hepatobiliary manifestations of COVID-19 infection: A single centre study from Pakistan

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ABSTRACT

BACKGROUND: Coronavirus disease was a global challenge affecting around 229 countries with over 700 million confirmed cases with significant morbidity and mortality.

OBJECTIVE: To determine the prevalence and spectrum of gastrointestinal and hepatobiliary manifestations in COVID-19 patients, including liver function test abnormalities and clinical features, within the Pakistani population.

METHODOLOGY: This was a cross-sectional study conducted at North Medical Ward, Mayo Hospital, Lahore for three months. After ethical approval of the study, 200 COVID-19 RT-PCR positive cases of ages 15 to 80 years were included in the study. Complete history & examination regarding hepatobiliary symptoms were noted. Liver function tests & prothrombin time were sent to pathology laboratory & results were noted. Data was analyzed using SPSS-26. Chi-square tests and t-tests were used to compare categorical and continuous variables, respectively. Quantitative variables like age, bilirubin, Aminotransferases & Prothrombin time were taken as mean ± standard deviation. Qualitative variables like gender, hepatobiliary symptoms were taken as frequency and percentages.

RESULTS: The most common symptom at presentation was diarrhea 30 (15.0%) followed by fatigue, pruritic and anorexia 17 (8.5%), nausea, vomiting and abdominal pain 15 (7.5%), body petechiae & purpura in 13(6.5%), Right hypochondrial pain 11(5.5%) & Hiccup and dark colour urine 1(0.5%). On laboratory findings,17(8.5%) patients had elevated bilirubin levels while AST was raised in 79(39.5%) of cases, ALT in 23(11.5%), Alkaline phosphatase in 6(3.0%), GGT in 95(47.5%) of cases. 8 (4.0%) cases showed decrease albumin level and 12(6.0%) cases had prolonged PT levels.

CONCLUSION: Gastrointestinal and Hepatobiliary manifestations are frequent in COVID-19 patients and should be closely monitored. Recognition of these symptoms could help mitigate delays in diagnosis and treatment, particularly in asymptomatic or non-respiratory patients.

KEYWORDS: COVID-19, Pandemic, Liver Function Tests, Hepatobiliary, Manifestations.

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INTRODUCTION

A novel coronavirus disease (COVID-19) outbreak was reported in seafood market in Wuhan city of China since end of December 2019, which has subsequently affected 229 countries so far.[1,2] Since then, this disease has infected almost 700 million people worldwide. In Pakistan, it has been known to cause over 1.5 million infections. While respiratory symptoms are predominant, hepatobiliary manifestations have also been reported but remain under-explored in local studies.[3]

In general, COVID-19 is an acute resolved disease but severe disease onset might result in death due to massive alveolar damage and progressive respiratory failure.[4] Although most coronavirus infections amount for mild respiratory illnesses, expression of the ACE2 gene a receptor for the SARS-CoV-2 virus with in the gastrointestinal tract suggests the digestive system is a potential targeted infection for COVID-19 making patients with an affected hepatobiliary system susceptible to this novel infection. Very limited data are available on the prevalence of COVID-19 among patients with pancreatic or biliary conditions although pancreatic manifestations of the disease are rare.[5]

The pathogen responsible for COVID-19 disease has been isolated from a family of enveloped, positive sense RNA viruses, characterized by club shaped spikes that project from their surface, an unusually large RNA genome and a unique replication strategy.[7] Multiple trials are going on to discover definitive treatment modalities of this novel disease as well as for its vaccine.

The pandemic of COVID-19, caused by the virus SARS-CoV-2 can be either asymptomatic or with mild to moderate symptoms leading to acute respiratory distress syndrome. Common symptoms of the disease include fever, flu, sore throat, cough, myalgia & less common symptoms are sputum production, & headache. Gastrointestinal and hepatobiliary involvement can range from asymptomatic liver enzyme elevation to more pronounced clinical manifestations. Identifying such patterns, especially in the Pakistani population is vital for guiding clinical management and understanding the regional impact of the disease. More specifically the hepatobiliary symptoms include anorexia, malaise, abdominal pain, nausea, vomiting, dark colored urine, clay-colored stools, pruritis & diarrhea. Jaundice has also been reported.[6] Liver chemistry abnormalities are also common and include elevation of aspartate transferase (AST), alanine transferase (ALT), alkaline phosphatase, gamma glutamyl transferase (GGT) and total bilirubin.[6]

The hepatobiliary system can be affected through multiple mechanisms, including direct viral cytopathic effects, immune dysregulation, and drug-induced liver injury. This study aims to explore the prevalence, clinical features, and laboratory

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abnormalities associated with hepatobiliary 770involvement in COVID-19 patients in Pakistan. [7]

In this study we will determine the frequency of these symptoms in our population as little local data is available about the disease & diagnosis can be missed due to non-respiratory symptoms.

OBJECTIVE:

To determine the prevalence and spectrum of gastrointestinal and hepatobiliary manifestations in COVID-19 patients, including liver function test abnormalities and clinical features, within the Pakistani population.

METHODOLOGY:

This was a cross-sectional study, conducted at the North Medical Ward, Mayo Hospital, Corona isolation ward, Lahore between 1st June and 31st August 2020. After ethical approval of the study from institutional review board, King Edward Medical University Lahore, 200 patients were enrolled with informed consent. Patients of ages 15 to 80 years of either sex with COVID PCR positive status were included in the study. All patients with ages below 15 years & above 80 years & prior liver or biliary diseases like cholangiocarcinoma, acute or chronic hepatitis, chronic liver disease etc were excluded. Demographic details including name, age, gender, address & contact number were recoded. Complete history & examination of each enrolled patient regarding hepatobiliary symptoms 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 Pathology laboratory. These tests results were then recorded in the predesigned proforma in standard SI Units. Data was analyzed using SPSS-26. Chi-square tests and t-tests were used to compare categorical and continuous variables, respectively. Quantitative variables like age, bilirubin, Aminotransferases, Alkaline phosphatase, gamma glutamyl transferase (GGT), albumin & PT were recorded as mean ± standard deviation. Qualitative variables like sex and hepatobiliary symptoms were taken as frequency and percentages.

RESULTS

The mean age of patients positive for COVID-19 was 34.16±16.70 years. There were 94 (47%) males and 106 (53%) females. We found that 46(23.0%) Covid positive patients had hepatobiliary symptoms without any respiratory feature, while 14(7.0%) cases had both hepatobiliary and respiratory symptoms.

The most common hepatobiliary symptom at presentation was diarrhea 30 (15.0%). Others include fatigue, pruritic and anorexia 17 (8.5%), nausea, vomiting and abdominal pain 15 (7.5%), body petechiae & purpura in 13(6.5%), Right hypochondrial pain 11(5.5%) & Hiccup and dark color urine 1(0.5%). No patient presented with jaundice or clay colored stool. (Table 1) Among 200,113(56.5%) patients had non-hepatobiliary symptoms (Table 1)

Table1: Gastrointestinal and hepatobiliary manifestation of COVID-19 Infection.

Symptoms	Percentage (%)
Diarrhea	30 (15.0%)
Nausea & vomiting, Abdominal Pain	15 (7.5%)
Right hypochondrial pain	11 (5.5%)
Hiccup, Fatigue, Pruritis, Anorexia	17 (8.5%)
Body Petechiae, Purpura,	13 (6.5%)
Dark Colored Urine	1 (0.5%)
Clay colored stools, Jaundice	0(0.0%)
Non-hepatobiliary Symptoms	113(56.5%)

On laboratory findings, mean bilirubin level of patients was 0.77±0.39 IU/ml, mean AST and ALT were 42.3±22.7 & 43.6±21.9, respectively, mean alkaline phosphate was 95.3±30.0, mean GGT was 46.4±33.7, mean total protein level was 6.7±0.4 mg/dl, mean albumin was 3.8±0.4 mg/dl and mean PT of patients was 11.85±1.4 sec. 17(8.5%) patients had elevated bilirubin levels while AST was raised in 79(39.5%) of cases, ALT in 23(11.5%), Alkaline phosphatase in 6(3.0%), GGT in 95(47.5%) of cases. 8 (4.0%) cases showed decrease albumin level and 12(6.0%) cases had prolonged PT levels. (Table-2).

Table 2: Laboratory findings of COVID-19 Patients (LFTS & PT)

Lab test with Normal Values Range	Mean±SD	Normal	Abvove Normal	Below Normal
Bilirubin(0.3-1.2mg/dl)	0.77±0.3	183 (91.5%)	17(8.5%)	0 (0%)
AST(10-40IU/L)	42.3±22.7	121 (63.5%)	79 (39.5%)	0 (0%)
ALT(7-56IU/L)	43.6±21.9	177 (88.5%)	23 (11.5%)	0 (0%)
Alkaline phosphate(44-147IU/L)	95.3±30.0	194 (97.0%)	6 (3.0%)	0 (0%)
GGT(5-40 IU/L)	46.4±33.7	104 (52.0%)	95 (47.5%)	1 (0.5%)
Total Protein(6-8.3g/dL)	6.7±0.4	200 (100%)	0 (0%)	0 (0%)
Albumin(3.5-5.5g/dL)	3.8±0.4	192 (96.0%)	0 (0%)	8 (4.0%)
PT(11-13.5Sec)	11.85±1.48	141 (70.5%)	12 (6.0%)	47 (23.5%)

DISCUSSION

In this study, we found that hepatobiliary manifestations are a common complaint in patients presenting with COVID-19. The purpose of the study was to detect these extra-pulmonary symptoms so that earlier treatment can be initiated to avoid any further complication.

In clinical practice, Covid 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 [8]. In our study, patients also presented with hepatobiliary symptoms without respiratory symptoms. So, clinicians and gastroenterologists should pay attention to these extra pulmonary symptoms of Covid-19, as lesser attention to these initial findings can contribute to transmission inside family or community.[9]

By reviewing the literature, it was found that there are several reasons of Covid-19 to cause hepatobiliary symptoms. SARS-CoV-2 is similar to SARS-CoV and can bind to angiotensin converting enzyme 2 (ACE-2) receptors that causes liver damage by upregulation of ACE-2 expression in the liver tissue.[10] The high proportion of cases with liver injury suggests that hepatic dysfunction plays a critical role in multisystem organ dysfunction. It is caused by compensatory proliferation of hepatocytes derived from bile duct epithelial cells. It also damages digestive system directly or indirectly by an inflammatory process.[11]

Through different studies, it was found that viral nucleic acid is detected in stool samples of 53% of Covid positive patients.[12] In a study by Zhang and colleagues reported that the majority of fatal COVID-19 cases (up to 78%) had clinical evidence of liver injury. [13]

In the liver, single-cell transcriptome analysis from several studies (involving both human tissues and organoid cultures) has confirmed the presence of ACE2 receptor and TMPRSS2 in liver parenchymal cells and cholangiocytes.[14-16] Hepatic complications of COVID-19 may not be directly related to the infection itself but may be caused by the various therapies that are used to prevent or combat the disease. [17]

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Shih AR and colleagues in their study found out that ischemic enterocolitis was the most common related gastrointestinal manifestation; consequence of COVID-19 and liver injury was related to consequences of severe systemic viral infection.[18]

Liondthard S et.al concluded that COVID-19 causes Secondary Sclerosing Cholangitis in a substantial proportion of critically ill patients in contrast to our study where we didn't find any case of Secondary Sclerosing Cholangitis.[19]

In a study by Mushannen M on 161,689 patients with COVID-19 infections, 683 developed hepatobiliary complications possibly related to COVID-19 infection. They distributed these patients into different categories: 61 patients with cholangitis, 1 patient with acalculous cholecystitis, 5 patients with choledocholithiasis, 11 patients with hepatitis, 140 patients with steatosis, 22 patients with cirrhosis, 3 patients with acute liver failure, 29 patients with liver inflammation by imaging, 41 patients with hepatomegaly, and 370 patients with unspecified hepatobiliary disease. Of these, 6 patients died.[20]

There are certain limitations of our study. Firstly, this was a study with limited sample size and single centered that can affect reliability as well as generalizability. Secondly, we did not test for RNA or ACE2 levels in hepatocytes samples of Covid positive patients.

CONCLUSION

In conclusion gastrointestinal and hepatobiliary symptoms are not uncommon in patients with COVID-19. Patients having coronavirus disease can present only with gastric or hepatobiliary symptoms such as diarrhea, vomiting, nausea and abdominal pain without any respiratory symptoms; such patients' diagnosis may be delayed. So,

attention should be given to these initial extra-pulmonary features to avoid disease progression & complications.

REFERENCES:

1. Jin X, Lian JS, Hu JH, Gao J, Zheng L, Zhang YM, et al. epidemiological, clinical, virological characteristics of 74 cases of coronavirus infection disease 2019(COVID-19) with gastrointestinal symptoms. GUT. 2020; 69(6): 1002-1009.

2. Gao QY, Chen YX, Fang JY. 2019 novel coronavirus infection and gastrointestinal symptoms. J Digestive Dis. 2020; 21(3): 125-126.

3. Leo C, Kaushal S, Yeo D. Enteric involvement of coronaviruses: is faecal-oral transmission of SARS-COV-2 possible? Lancet Gastroenterol Hepatol. 2020; 5(4): 335-337.

4. World Health Organization Coronavirus disease 2019 (COVID-19) pandemic. 2020. https://www.who.int/emergencies/diseases/novel-coronavirus-2019.

5. McNabb-Baltar J, Jin DX, Grover AS, et al. Lipase elevation in patients with COVID-19. Am J Gastroenterol 2020; 115:1286–8.

6. Zhang J, Wang S, Xue Y. Fecal specimen diagnosis 2019 novel coronavirus-infected pneumonia. J Med Virol. 2020; 92(6): 680-682.

7. Luo S, Zhang X, Xu H. Don't overlook digestive symptoms in patients with 2019 novel coronavirus disease (COVID-19). Clin Gastroenterol Hepatol. 2020; 18(7): 1636-1637.

8. Cha MH, Regueiro M, Sandhu DS. Gastrointestinal and hepatic manifestations of COVID-19: A comprehensive review. World J Gastroenterol. 2020; 26(19):2323-32.

9. Sultan S, Altayar O, Siddique SM, Davidkov P, Feverstein JD, Lim JK, et al. AGA institute rapid review of the

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gastrointestinal and liver manifestations of COVID- 19, Meta-analysis of international data and recommendations for the consultative management of patients with COVID-19. Gastroenterology. 2020; 159:320-34.

10. Musa S. Hepatic and gastrointestinal involvement in coronavirus disease 2019 (COVID-19): What do we know till now? Arab J Gastroenterol. 2020; 21:3-8.

11. Pan L, Mu M, Yang P, Sun Y, Wang R, Yan J, et al. Clinical characteristics of COVID-19 patients with digestive symptoms in Hubei, China: A descriptive, cross-sectional, multi-center study. Am J Gastroenterol. 2020; 115:766-73.

12. Lee IC, Huo TI, Huang YH. Gastrointestinal and liver manifestations in patients with COVID-19. J Chin Med Assoc. 2020:1-3(www.ejcma.org).

13. Weber S., Mayerle J., Irlbeck M., Gerbes A.L. Severe liver failure during SARS-CoV-2 infection. Gut. 2020;69:1365–1367.

14. Pirola C.J., Sookoian S. SARS-CoV-2 virus and liver expression of host receptors: putative mechanisms of liver involvement in COVID-19. Liver Int. 2020;40.

15. 63.Qi F., Qian S., Zhang S., Zhang Z. Single cell RNA sequencing of 13 human tissues identify cell types and receptors of human coronaviruses. Biochem Bioph Res Co. 2020;526:135–140.

16. 64.Yang L., Han Y., Nilsson-Payant B.E., et al. A human pluripotent stem cell-based platform to study SARS-CoV-2 tropism and model virus infection in human cells and organoids. Cell Stem Cell. 2020;27:125–136.

17. Shih AR, Misdraji J. COVID-19: gastrointestinal and hepatobiliary manifestations. Hum Pathol. 2023 Feb;132:39-55.

18. Shih AR, Misdraji J. COVID-19: gastrointestinal and hepatobiliary manifestations. Hum Pathol. 2023 Feb;132:39-55.

19. Leonhardt S, Jürgensen C, Frohme J, Grajecki D, Adler A, Sigal M, Leonhardt J, Voll JM, Kruse JM, Körner R, Eckardt KU, Janssen HJ, Gebhardt V, Schmittner MD; Pa-COVID-19 collaborative study group; Frey C, Müller-Ide H, Bauer M, Thibeault C, Kurth F, Sander LE, Müller T, Tacke F. Hepatobiliary long-term consequences of COVID-19: dramatically increased rate of secondary sclerosing cholangitis in critically ill COVID-19 patients. Hepatol Int. 2023 Dec;17(6):1610-1625.

20. Mushannen, Malik MD[1,*]; Lebbe, Ahamed Akmal[2]; Aboulwafa, Ali[3]; Bayraktar, Nuran[3]; Sarkar, Shaunak[3]; Ayoub, Sama[3]; Abdalla, Marwan[3]; Mushannen, Beshr[3]; Khalil, Aya[3]; Mohammed, Ibrahim MD[4]; Yagan, Lina MD[5]; Zakaria, Dalia PhD[3]. S1705 Hepatobiliary Sequelae of COVID-19: Investigating Post-Infection Complications. The American Journal of Gastroenterology 119(10S):p S1241, October 2024.

Author's Contribution:

SUM: Conceived and designed the study, involved in data collection, performed statistical analysis and writing the manuscript.

RH, TK, SI, ZN, SA: Collected the data, critical review and preparation of manuscript.

All authors have read, approved the final manuscript and are responsible for the integrity of the study.