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Original Research Article

Alteration of Liver Function Tests in COVID-19: A Correlation with Clinical Severity

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Abstract

Introduction: Coronavirus disease-19 (COVID-19) can cause a spectrum of clinical features ranging from being asymptomatic to flu-like syndrome, pneumonia, multi-organ failure and death. Liver damage in COVID-19 has been attributed to the direct attack by SARS-CoV-2, drug toxicity in COVID-19 therapy, acute inflammatory damage and hypoxia caused by pneumonia

Aim: The present study was aimed to understand whether COVID-19 causes significant alterations of liver function tests and what is the correlation between liver function tests and clinical severity.

Material and methods:

A cross-sectional study was conducted at Vardhaman Institute of Medical Sciences, Pawapuri, Bihar, India from July 2020 to May 2021 after receiving approval from the Institutional Ethics Committee. Two hundred COVID-19 patients, 18 years and above were selected and categorized into asymptomatic cases, mild cases, moderate cases and severe cases on the basis of clinical and radiological criteria. Venous blood sample was tested for Serum Bilirubin, Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Alkaline phosphatase (ALP) and Prothrombin time (PT). Obtained data was statistically analyzed using SPSS.

Results: Out of two hundred cases, 19% of cases were classified in the asymptomatic group, 41% in the mild group, 29% in the moderate group and only 11% in the severe group. Mean serum bilirubin in the severe group was 4.4±2.7mg/dl. The mean ALT in the moderate and severe group was 197±44 U/L, 964±243U/L and mean AST 293±87U/L, 1172±301U/L respectively. PT was found 17.77±2.78 seconds and 23±3.45 seconds in the moderate and severe groups respectively. These alterations in Liver function test parameters were found statistically significant when compared among different severity groups.

Conclusion: COVID-19 is associated with hepatic injury and alteration in liver functions. Liver enzymes can be used as markers of severity of COVID-19.

Keywords: Coronavirus disease-19, Liver function tests, Markers of severity.

Introduction

Coronavirus disease-19 (COVID-19) pandemic is the most devastating event for mankind in recent times. It has jeopardized human activity globally. World Health Organization (WHO) declared a pandemic of Coronavirus disease-2019 (COVID-19) in March 2020. On 12th May 2021, there were 2,29,92,517 confirmed cases of COVID 19 including 2,49,992 deaths in India and 158,651,638 confirmed cases of COVID 19 in world. [1]

Only a little is known about COVID-19 pathogenesis, natural history and its sequalae. Clinically COVID-19 can cause a spectrum of clinical features ranging from being asymptomatic to flu-like syndrome, pneumonia, multi-organ failure and death. [2] Based on clinical severity, cases of COVID-19 has been divided into asymptomatic, mild, moderate and severe disease; *Asymptomatic disease*: no symptoms; *Mild disease*: uncomplicated upper respiratory tract infection with mild symptoms such as fever, cough, sore throat, nasal congestion, malaise, headache without evidence of breathlessness or Hypoxia (normal saturation); *Moderate disease*: pneumonia and no signs of severe disease, with the presence of clinical features of dyspnea and or hypoxia, fever, cough, including SpO2 90 to 94% on room air, respiratory rate 24 to 30/ min; *Severe disease*: severe pneumonia with clinical signs of Pneumonia plus one of the following; respiratory rate >30 breaths/min, severe respiratory distress, SpO2 < 90% on room air [3,4].

Liver damage in COVID-19 has been attributed to the direct attack by SARS-CoV-2, drug toxicity in COVID-19 therapy, acute inflammatory damage and hypoxia caused by pneumonia. A direct attack by SARS-CoV-2 on the liver includes the direct cytopathic effect on hepatocytes and cholangiocytes, and the effects of coagulopathy and endothelial aggression in small intrahepatic vessels. The mechanisms of direct hepatic destruction, in COVID-19, include its presence on the surface of endothelial cells in small blood vessels (endothelial layer of small blood vessels), and hepatocytes (2.6%), but especially on the surface of bile duct cells (cholangiocytes) (59.7%) of angiotensin 2 converting enzyme (ACE2) receptors, which are considered the cellular receptor for SARS-CoV-2. The expression level of these cholangiocyte receptors is also similar to that of lung type 2 alveolar cells, suggesting that the liver may be a potential target for SARS-CoV-2. Endothelial damage and coagulation dysfunction may be the major trigger in the pathogenesis of COVID-19 liver lesions. The hyper-inflammatory reaction of COVID-19 may cause liver damage. In the evolution of COVID-19, a massive release of pro-inflammatory cytokines is observed, with increasing interleukin (IL)-6, lactate dehydrogenase, C-reactive protein, and ferritin concentrations. This cytokine storm syndrome is accompanied by organ dysfunction, including progressive liver damage and liver failure. Hypoxia caused by respiratory failure in COVID-19 affects hepatocyte metabolism and may cause liver damage. [5,6]

The drugs used in the treatment of COVID-19 are also with hepatotoxic potential; Remdesivir, Favipiravir, Lopinavir-ritonavir, Antipyretics, especially paracetamol, Dexamethasone, Tocilizumab, Hydroxychloroquine, Azithromycin etc. [5,7]

Prothrombin time is regarded as an important indicator of COVID-19 severity and helps in predicting mortality.[8]

Elevation of ALT and AST is not uncommon in the Indian population due to the high prevalence of fatty liver disease,

alcoholic liver disease, several hepatic disorders and systemic diseases. Several studies done globally has documented the liver abnormalities and elevation of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) and alteration in Prothrombin time (PT) in COVID-19 patients. Whether COVID-19 causes significant alterations of liver function tests and its clinical significance among Indians remains to be elucidated. Hence this study was planned to study the true impact of COVID-19 on liver functions and its clinical implications.

Materials and methods:

This cross-sectional study was conducted at Vardhaman Institute of Medical Sciences, Pawapuri, Bihar, India from July 2020 to May 2021 after receiving approval from the Institutional Ethics Committee, vide letter No. 1015, dated 29.06.2020.

Inclusion criteria:

The diagnosis of COVID-19 was done through real-time reverse-transcription polymerase chain reaction (RT-PCR) on nasopharyngeal/oropharyngeal swabs as per the Indian council of medical research guidelines. Two hundred COVID-19 patients, 18 years and above were selected as cases.

Exclusion criteria:

Patients with a history of chronic liver diseases, hepatitis, diabetes mellitus, alcoholism, hepato-toxic drugs intake, pregnancy, oral contraceptives users and patients below 18 years of age were excluded from the study.

Informed consent was obtained from all the cases participating in this study. Routine general and systemic examination was performed on all the cases. A venous blood sample was obtained from the ante-cubital vein using all aseptic precautions. Serum was obtained after centrifugation of the samples and tested for Serum Bilirubin, Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Alkaline phosphatase (ALP). Prothrombin time (PT) was tested with venous blood taken in plastic tube containing 3.2% sodium citrate. Oxygen saturation was obtained by pulse-oximeter. Chest X-ray PA view and high-resolution computed tomography (HRCT) chest were done as and when required.

Based on the guidelines for the management of Covid-19 cases by the Health and Family Welfare Department of the Government of India, the cases were categorized into asymptomatic cases, mild cases, moderate cases and severe cases.[4]

Statistical analysis:

Statistical analysis was done using IBM SPSS statistics version 26. Qualitative data were expressed in frequencies and percentages and numeric data were expressed as mean and standard deviation. The student's t-test was applied to compare the continuous data of two groups. One-way analysis of variance (ANOVA) was used to compare continuous data of more than two groups. Post-hoc analysis was done to assess the differences between different groups. $P < 0.05$ was considered significant.

Table 1: Demographic characteristics of the study population

	Asymptomatic (19%)	Mild (41%)	Moderate (29%)	Severe (11%)
Male(n=118)	32(27.11%)	46(38.98%)	26(22.03%)	14(11.86%)
Female(n=82)	6(7.31%)	36(43.90%)	32(39.02%)	8(9.75%)
Age(years)(mean±SD)	34.03±4.19	38.45±6.98	53.74±7.56	63.34±12.23

Table 2: Comparison of study parameters among different clinical severity groups

	Normal ranges	Asymptomatic	Mild	Moderate	Severe	p-value
Bilirubin(mg/dl)	0.0-1.0	0.9±0.4	1.6±0.8	2.3±1.1	4.4±2.7	<0.001
Alanine aminotransferase (ALT)(U/L)	29-33	27±13	59±18	197±44	964±243	<0.001
Aspartate aminotransferase (AST)(U/L)	10-40	41±07	77±23	293±87	1172±301	<0.001
Alkaline phosphatase (ALP)(U/L)	45-115	64±09	73±17	112±23	189±68	<0.007
Prothrombin Time (PT)(sec)	10-14	13.7±0.12	14.34±1.64	17.77±2.78	23±3.45	<0.001

Results:

The demographic characteristics of the study population are shown in Table-1. Out of two hundred cases,118(59%) were males and 82(41%) females. Based on the clinical and radiological criteria, 19% of cases were classified in the asymptomatic group, 41% in the mild group, 29% in the moderate group and only 11% in the severe group. The mean age of the asymptomatic group was 34.03±4.19 years, mild group 38.45±6.98 years, moderate group 53.74±7.56 years and severe group 63.34±12.23 years. Among males, distribution in the asymptomatic, mild, moderate and severe group was 27.11%, 38.98%, 22.03% and 11.86% respectively. Similarly, the distribution of females in the asymptomatic, mild, moderate and severe group was 7.31%, 43.90%, 39.02% and 9.75% respectively.

Mean serum bilirubin in the severe group was 4.4±2.7mg/dl. The mean ALT and AST in the moderate and severe group were 197±44 U/L, 964±243U/L and 293±87U/L, 1172±301U/L respectively. Similarly, PT was found 17.77±2.78 seconds and 23±3.45seconds in the moderate and severe groups respectively. These alterations in Liver function test parameters were found statistically significant when compared among different severity groups. (Table-2). Although ALP was also elevated in the severe group, it was found statistically not significant.

Discussion:

Coronaviruses have a broad host range and cause a wide variety of respiratory, gastrointestinal, and systemic diseases in humans. Liver enzyme abnormalities developed in as many as 50% of SARS-CoV-2-infected patients reported by various studies. In a study done by Wang et al, 41.0% of patients with COVID-19 presented with liver enzyme abnormality, with a prevalence of 23.5% even in the context of mild cases, confirming liver impairment is common in patients with COVID-19. The liver enzyme abnormality was associated with disease severity. [9]. In a study done by Chen et al, concentrations of alanine aminotransferase, aspartate aminotransferase, total bilirubin, alkaline phosphatase, and γ-glutamyl transpeptidase were markedly higher in deceased patients than in recovered patients. Fifty-two per cent of deceased patients and 16% who

recovered had abnormal aspartate aminotransferase concentrations (>40 U/L) [10]. In a study done by Araya S. et al prolonged prothrombin time and elevated INR were detected in more than 50% of severe and critical COVID-19 patients. [13]. In the present study, the significant rise in S. bilirubin, ALT, AST and PT among different severity COVID-19 disease groups was consistent with other studies [9,10,11,12,13]. This suggests that AST, ALT and PT are important indicators of the severity of COVID-19. The alteration in liver enzymes is associated with hypoxia and severe inflammation and corresponds with severe clinical symptoms [14]. Cytokine storms may be the important factor responsible for all these clinical symptoms and hepatic dysfunction. [15]. In the present study, the patients of the severe group had older age in comparison to other groups, which was found to be consistent with previous studies [11].

Underlying hepatic damage with severity of disease requires special attention during treatment using different kind of medications. This study has highlighted the critical issue in combating COVID-19 pandemic.

There were certain limitations of this study. This study was a single centric study conducted only on a small number of subjects. Only a few parameters were studied. This study couldn't find out the exact etiological factors responsible for alteration in liver enzymes. To resolve these issues a multicentric study on a large number of subjects requires to be conducted in future.

Conclusion:

COVID-19 is associated with hepatic injury and alteration in liver functions. Liver enzymes and prothrombin time can be used as markers of severity of COVID-19. Regular monitoring of liver function tests should be done at admission and during hospital stay.

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