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Dr. Rajiv Nehra
Associate Professor,
Department of Biochemistry,
Govt. Medical College, Jalaun,
Uttar Pradesh, India

Dr. Dwijendar Nath
Principal Govt. Medical
College, Jalaun, Uttar Pradesh,
India

Corresponding Author:
Dr. Rajiv Nehra
Associate Professor,
Department of Biochemistry,
Govt. Medical College, Jalaun,
Uttar Pradesh, India

Hepatic response in COVID-19

Dr. Rajiv Nehra and Dr. Dwijendar Nath

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Abstract
Introduction: The world is facing a pandemic by a novel coronavirus termed COVID-19. Patients show symptoms of fever, respiratory discomfort and myalgia along with liver injury and GI symptoms such as abdominal pain, nausea, vomiting and diarrhoea. GI symptoms were also common during the previous outbreak of coronavirus family. Hepatic injury was assessed with abnormal serum levels of alanine aminotransferase, aspartate aminotransferase, total bilirubin, concentration of cytokine and acute phase protein.
Material and Methods: The present study was carried out in Govt. Medical College, Jalaun at Department of Biochemistry. The diagnosis of COVID-19 was made by at least one positive SARS-CoV-2 (RDRP) or Beta CoV (E-gene) or COVID-19 (E-gene/Orf1A) TrueNat test performed on nasopharyngeal swab samples. 10 ml of fasting venous blood was collected from the antecubital vein in a plain, fluoride and EDTA vacutainers. The blood sample was centrifuged and stored at 4 °C for Biochemical and immunological investigations. The study group consisted of four groups Normal (Group I) n=50 and COVID-19 positive patients (Total) (Group II) in two groups, Stable Patients (Group III) n=25 and Unstable patients (Group IV) n=25 are critically ill patients requiring ICU admission or intensive support of either sex aged between 40-65 years. The diagnosis of Liver disease was done by ultrasonographic examination of the liver. Serum levels of ALT, AST, Total Bilirubin, Cytokine (IL-6), malondialdehyde (MDA), reduced glutathione (GSH) and acute phase protein (CRP) were estimated.
Results: Mean value of ALT 20.10 ± 5.60, 110.34 ± 48.02, 158.6 ± 51.24* and 200.61± 58.35*, AST 28.50 ± 7.50, 104.20± 38.55*, 144.35 ± 46.60* and 193.15 ± 52.43* T. Bil 0.80 ± 0.15, 167.5 ± 84.13*, 143.3 ± 47.81* and 220.37 ± 119.73** Concentration of cytokine IL-6 9.24±1.20, 14.14±1.50*, 15.34±1.40* and 36.76±11.56** acute phase protein CRP 0.90±1.10 1.96±0.50*, 1.99±0.54* and 2.18±0.90 was significantly elevated in Group II, III, IV as compared to Group I.
Conclusion: Results of the present study indicate that the levels of ALT, AST, Total Bilirubin, CRP and IL-6 increased in parallel with the progression of COVID-19 positive patients which indicates COVID-19 might end with hepatic injury.

Keywords: Novel coronavirus termed, hepatic response, COVID-19, vomiting and diarrhoea

Introduction
The coronavirus disease (COVID-19) has been declared a pandemic by the World Health Organization (WHO) prompted a large number of passings and hospitalizations globally. COVID-19 alters the current lifestyle, restrained the interactive activities and furthermore, we significantly indeed, need to follow health protocols, to anticipate contamination by COVID-19. Coronavirus cannot be viewed as the common cold virus, since this virus may have more serious consequences, especially in persons who have underlying medical conditions. The infection is received by means of inhaling droplets containing the virus or via fomites, having the option to survive on surfaces for quite a long term. Viral debris has been identified within the feces, allowing for fecal-oral transmission conceivable. The incubation duration varies from 7 to 14 days [1].
In India, comorbidities diseases are the driving cause of death for COVID-19 patients. A standout amongst those comorbidities diseases that irritate the health issues of patients of COVID-19 is liver ailment. For this reason, further investigations are required regarding the extent of liver disorder that can magnify COVID-19. An amount of claiming reports have demonstrated that more than a large portion of patients with COVID-19 indicate varied levels of liver disease [2]. New research shows that the SARS-CoV-2 virus may bind to angiotensin-converting enzyme 2 (ACE2) on cholangiocytes, prompting to bile duct cell

dysfunction and causing a general inflammatory response driving to liver damage [3]. However, little information exists that has extensively dissected other liver enzymes and clinical characteristics of liver disappointment among patients with COVID-19.

Hence, the aim of this study was to report the liver test parameters in patients with COVID-19 admitted to our Medical College with better information of pathogenesis, more focused treatments and holistic care models could be created, which may offer assistance to avoid serious liver injury or failure in patients with COVID-19.

Clinical signs change, from asymptomatic to respiratory failure. The most prevalent manifestations are fever and cough. The severity of the infection is related to the increase in inflammatory cytokines, such as IL1, IL6, IL8, and TNF-alpha. Headache, nausea, vomiting, and diarrhoea have also been reported [1].

The levels of liver enzymes and bilirubin are abnormal in severe infections, with challenges in the management of patients with liver disease, especially those with autoimmune hepatitis or cirrhosis using immunosuppressants [4, 5, 6].

The meaning of liver injury by COVID-19 is not standardized in the established researcher community, some scholars consider any change in liver function parameters as injury, and others require the need to raise the hepatogram's standard limit by three times [4, 6]. Another research revealed that 48.4% of the patients with normal liver function developed liver injury during hospitalisation, suggesting that a high percentage of patients with COVID-19 have liver injury [7]. SARS-CoV-2-mediated liver injury might be a key factor in liver damage [8]. The goal should be to reduce the risk of liver failure for patients with COVID-19 by monitoring liver function closely and analysing risk factors for liver failure. Previous researches have shown that liver injury could influence the prognosis of patients with COVID-19, and the mortality rate was significantly increased in patients with severe liver injury [9, 10]. Liver injury is a comorbidities disease that is categorized as severe, because this disease can worsen COVID-19 [11]. Acute liver injury have been reported and are associated with higher mortality. Involvement of liver disease in COVID-19 is associated with the direct cytopathic effect of the virus, an uncontrolled immune reaction, sepsis or drug induced liver injury [12]. Patients who have liver disease should receive special care because this group has a high risk of being infected with COVID-19 [13]. Hence, when examining hepatic indicators in COVID-19 patients, it is essential to do so by studying the mechanism by which the liver is injured, the devices for recognizing the injury quickly, as well as the management of patients with previous liver damage. High sensitive C-reactive protein (CRP) is one of the major acute phase proteins produced by the liver in many inflammatory conditions and is a marker of systemic inflammation. Oxidative stress has been implicated in the pathogenesis of COVID-19 positive patients. One of the most frequently used biomarkers providing an indication of the overall lipid peroxidation level is malondialdehyde (MDA). There are a number of antioxidants present in the body derived from the diet. Main non-enzymatic cellular antioxidant is reduced glutathione (GSH). Significantly raised Serum Alanine Transaminase, Aspartate Transaminase and Total Bilirubin levels in COVID-19 positive patients have been reported by several workers.

In view of this, the present study was undertaken to ascertain the role of cytokines in deranging liver profile, increased oxidative stress, including direct damage by radical species and the inflammatory response which further leads to hepatic risk in some COVID-19 positive patients.

Materials and Methods

The present study was carried out in Govt. Medical College, Jalaun at Department of Biochemistry. The diagnosis of COVID-19 was made by at least one positive SARS-CoV-2 (RdRP) or Beta CoV (E-gene) or COVID-19 (E-gene/Orf1A) TrueNat test performed on nasopharyngeal swab samples.

10 ml of fasting venous blood was collected from the antecubital vein in a plain, fluoride and EDTA vacutainers. The blood sample was centrifuged and stored at 4 °C for biochemical and immunological investigations. The study group consisted of four groups Normal (Group I) n=50 and COVID-19 positive patients (Total) (Group II) in two groups, Stable Patients (Group III) n=25 and Unstable patients (Group IV) are critically ill patients requiring ICU admission or intensive support of either sex aged between 40-65 years. The diagnosis of Liver disease was done by ultrasonographic examination of the liver. Serum levels of ALT, AST, Total Bilirubin, Cytokine (IL-6), malondialdehyde (MDA), reduced glutathione (GSH) and acute phase protein (CRP) were estimated.

A detailed history of all the normal individuals and COVID-19 positive patients was taken. All the subjects were clinically examined before the start of the study to assess liver functions.

During the course of the study, 22/50 COVID-19 positive patients showed changes in their ultrasonographic examination of the liver. This prompted us to classify the total COVID-19 patients (n=50) into stable patients (n=25) and Unstable patients (n=25) so as to assess the impending liver risk in apparently healthy COVID-19 Positive patients.

Venous blood samples were collected after overnight fasting. Serum CRP (Immunoturbidimetry), MDA (Thiobarbituric acid reactive substance TARBS), GSH (Ellman's method). Routine LFT was analyzed by standard Clinical Chemistry procedures on multi-channel Auto Analyzer (Selectra-E Clinical System) using kits from Merck Ltd. Quality control samples from Merck Ltd. were run time-to-time on analyzer to check the accuracy and precision of these tests.

Statistical analysis

The statistical analysis was performed using SPSS. The results are shown as mean ± SD (Standard Deviation) and median (range). The data were analyzed using the student's t-test. The p-value of <0.05 was denoted as statistically significant.

Results and Discussions

The levels of CRP, MDA and GSH in various groups have been presented in (Table 1). Serum Alanine Transaminase, Serum Aspartate Transaminase, and Total Bilirubin various groups have been presented in (Table 2).

CRP levels were significantly elevated across the all groups (Table 1) CRP was significantly elevated in all the group of

stable and unstable COVID-19 positive patients, when compared to controls. Moreover, CRP elevation in unstable patients was significant when compared to stable COVID-19 positive patients.

These findings suggest that the increase in CRP levels was more pronounced in unstable patients when compared to stable COVID-19 positive patients and controls. (Table 1)

Moreover, significantly elevated MDA was observed in unstable patients when compared to stable COVID-19 positive patients. (Table 1)

GSH was significantly lower in both the groups of stable and unstable COVID-19 positive patients when compared to controls. (Table 1). COVID-19 positive as a risk factor for Hepatic injury is closely associated with increased oxidative stress, and the CRP plays an important role in increasing the level of oxidative damage and reducing antioxidant defense [14].

There was also evidence that drug-induced liver toxicity occurred, probably because of antipyretics, antibiotics, or antiviral drugs [15]. Moreover, severely ill COVID-19 patients presented with inflammatory responses, which may further contribute to liver injury. When macrophages and lymphocytes are activated by an inflammatory cytokine storm, they may secrete large quantities of inflammatory cytokines, which would be necessary during infection to keep an overactive innate response under control.

During the course of COVID-19 infection, lymphopenia can cause an increase in cytokines, such as IL-6 and gamma-interferon, resulting in an overactive inflammatory response that damages the lungs and extrapulmonary sites as well. According to a study, C-reactive protein levels and lymphopenia have an independent relationship with liver injury risk factors.

The most primitive phase in hepatic injury is the passage of the virus into the liver parenchyma cells. In fact, this is followed by a phasic immune response of the host cell and ultimate infiltration of the infected host cell by potentially activated leucocytes. In the present study, Table 2 shows a comparison between the patient and controls for the routine tests of liver function.

COVID-19 positive patients have higher ALT levels in Group II, III and IV than COVID-19 negative patients with similar clinical presentations. There is a possibility that some patients with severe COVID-19 had probably experienced liver insults, including ischemia, congestion, and drug-induced liver injury. Furthermore, Mean value of AST and T. Bilirubin was significantly elevated in Group II, III and IV as compared to Group I. We also assumed that this scenario is likely to involve extrahepatic sources of AST, including a breakdown of the heart and skeletal muscle; therefore, we looked more closely at ALT and T. Bilirubin levels in our analysis. Nevertheless, the correlation between ALT levels and markers of inflammation appears to be strong and is more common among cytokine-releasing syndrome patients [16]. This is supported by the significantly higher peak values of all inflammatory markers in those with severe ALT elevation, including CRP and IL-6. It has been suggested that severe COVID-19 related diseases have been associated with IL-6 levels [17]. Significant associations were also found between higher ALT values with overall disease severity and worse clinical outcome.

Conclusions

A global pandemic of COVID-19 is being experienced at the present time. In most cases, the virus causes a lung infection additionally, cardiac and liver complications that can cause serious health problems, as well as death. The patients with COVID-19 presenting with severe disease were more likely to be suffering from acute liver damage, which led to a greater mortality rate. Further analysis with long-term follow-ups are needed to assess the extent and cause of liver injury and its clinical implications. COVID-19-associated liver injury is likely the result of immune-mediated inflammation. Patients with abnormal LFTs had higher risks of becoming severely ill as a result of liver injury. Other potential risk factors for liver injury include IL-6 and CRP. In severely/critically ill patients, liver function should be monitored periodically during COVID-19. We can use the data provided here to enhance our understanding of the disease, allowing us to take immediate action in the event of an early diagnosis. COVID-19 patients are likely to have reduced liver injury after receiving the appropriate intervention and reasonable supportive care. Lastly, advanced studies are required to better understand how the coronavirus injures the liver, a problem that's not fully understood yet.

Table 1: CRP, MDA, GSH & IL-6 levels in normal, total COVID-19 positive, stable and unstable patients

Individuals	CRP (mg/L)	MDA (μmol/L)	GSH (mg/dl)	IL-6 (pg/ml)
I Normal n=50	0.90±1.10	2.32±0.98	7.10±0.58	9.24±1.20
II Total n= 50 COVID- 19 +Ve	1.96±0.50*	8.68±2.50	6.90±0.70	14.14±1.50*
III Stable Patients n=25	1.99±0.54*	8.98±2.70	5.98±0.76	15.34±1.40*
IV Unstable Patients n=25	2.18±0.90*	9.80±2.72**	5.60±0.80*	36.76±11.56**

The data were expressed as mean ± SD. The data were analyzed using the student's t-test.* indicates $p<0.05$ and statistically significant

Table 2: Serum ALT, AST & total bilirubin level in normal, total COVID-19 positive, stable and unstable patients

Individuals	ALT (IU/L)	AST (IU/L)	Total Bilirubin (mg/dl)
I Normal n=50	20.10 ± 5.60	28.50 ± 7.50	0.80 ± 0.15
II Total n= 50 COVID- 19 +Ve	110.34 ± 48.02*	104.20± 38.55*	167.5 ± 84.13*
III Stable Patients n=25	158.6 ± 51.24*	144.35 ± 46.60*	143.3 ± 47.81*
IV Unstable Patients n=25	200.61 ± 58.35*	193.15 ± 52.43*	220.37± 119.73*

The data were expressed as mean ± SD. The data were analyzed using the student's t-test. * indicates $p<0.05$ and statistically significant

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