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COVID-19 AND HEPATIC DYSFUNCTION- A PROSPECTIVE STUDY ON THE SEVERITY OF THE DISEASE

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Abstract

Background

A patient who died due to respiratory failure suffering from COVID-19 revealed severe liver injuries in the postmortem. This indicated that the virus starts affecting other organs of the body simultaneously with the respiratory system. Around 23% of the patients who suffered due to COVID-19 had liver injuries. This study has been conducted to determine the relationship between liver injuries with COVID-19 and also to determine the severity of COVID-19 when liver injuries are reported.

Method

This was a cross-sectional study conducted prospectively to determine the correlation between liver dysfunction and the severity of COVID-19. The study was carried out for 6 months at IGIMS, Patna in Bihar, India. 150 patients above the age of 18 years suffering from COVID-19 were considered for this study. Liver function tests and tests for inflammatory markers were carried out and the patients were monitored thoroughly during hospitalization and one month later.

Results

95 patients among the 150 had severe COVID and the remaining 55 had moderate COVID-19. The patients who had moderate COVID-19 infection had around 80% survival rate whereas the patients with severe COVID-19 infection had a 30% survival rate. The non-survivors and those with severe COVID-19 had a higher occurrence of liver dysfunction. Also, it was found that liver enzymes had a substantial association with the presence of inflammatory markers.

Conclusion

This study reported higher levels of liver enzymes in the patients infected with COVID-19 indicating its association. Overall liver dysfunction was prominent among the non-survivors and those who had severe COVID-19. Also, a significant relationship was derived between inflammatory markers and the occurrence of liver dysfunction.

Recommendation

Doctors should monitor inflammatory markers and liver function as well to check the prognosis of the disease in elderly individuals suffering from COVID-19.

Keywords: *COVID-19, liver dysfunction, Association, severity.*
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Introduction

COVID-19 emerged as a pandemic in 2019 it spread rapidly worldwide causing severe crisis and death. There were more than 7 million people infected with COVID-19. The causative organism of this disease was SARS-CoV 2, the primary target of this virus was the respiratory system. It involved various symptoms related to the respiratory system which included severe cough, chest congestion, fever, chest pain, trouble breathing, and headache. Essentially SARS-CoV 2 weakened the immunity of the patients which affected every organ system in the body.

The rapid spread of the pandemic led to a steep increase in the number of patients admitted with COVID-19. It was observed that patients had compromised immunity due to preexisting comorbidities such as hypertension and diabetes mellitus. Gradually the virus would surpass the respiratory system and start infecting various organs due to weakened immunity. Such cases increased mortality rates of COVID-19. In most of the patients apart from respiratory failure multiple organs are infected leading to failure of various systems and collapse of the overall body.

Statistics indicated that various organ failure and liver dysfunction were quite prevalent [1, 2]. The causative organism SARS-CoV 2 binds specifically to ACE-2 in the

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liver which triggers a systemic inflammatory cycle and causes inflammation to spread damaging other organs. A peculiar indication of such an occurrence is a rise in particular liver enzymes such as aspartate aminotransferase and alanine aminotransferase. This has been reported in various instances [3-5].

Nevertheless, patients who died due to respiratory failure revealed severe liver injuries in the postmortem. This indicates that the virus starts affecting other organs of the body simultaneously with the respiratory system. Around 23% of the patients who suffered due to COVID-19 had liver injuries [6]. Along with that, there was up to 50% rise in the liver enzymes mentioned above [7]. This study has been conducted to determine the relationship between liver injuries with COVID-19 and also to determine the severity of COVID-19 when liver injuries are reported.

Method

Study design

This was a cross-sectional study conducted prospectively to determine the correlation between liver dysfunction and the severity of COVID-19. The study was carried out for a period of 6 months.

Study setting

The study was conducted in Indira Gandhi Institute of Medical Sciences in Patna, Bihar, India.

Participants

150 patients above the age of 18 years suffering from COVID-19 were considered for this study. Patients having pathological conditions related to the liver such as fatty liver due to alcohol, hepatitis, liver injury, and malignancy were not included in this study.

Data Collection

The demographic details and the details regarding liver function were collected by conducting a test for the presence of liver enzymes, this test included aspartate aminotransferase and alanine aminotransferase. The test to check the presence of inflammatory markers such as reactive C protein, D-dimer, and lactate dehydrogenase was carried out. The patients were getting treatment as per the standard national protocol for the treatment of COVID-19 patients. They were regularly followed up in this study, until their discharge and after that, they were followed up for a month.

Ethical consideration

The investigators adhered to the principles of the declaration of Helinski while conducting this study. Ethical approval was obtained from the respective ethical committee of the institute. The patients participating in this study were informed regarding the conduction of the study and consent was taken from them before recording the data for this study.

Statistical analysis

Data obtained from the patients if they were descriptive were arranged category-wise, and the frequency and the percentage values were determined for each category. If the data was continuously obtained for each patient, then it was calculated as average values and standard deviation. The data was arranged then the chi-square method was used to determine the significance of correlation which was obtained if the p-value was less than 0.05.

Result

The nasal swab was taken and the RTPCR reports were obtained to determine the level of infection in an individual. The majority of the patients participating were above the age of 40 years and male. The average age of the patients participating in this study was 45 years. 95 patients among the 150 had severe COVID and the remaining 55 had moderate COVID-19.

The data regarding the inflammatory markers including the C-reactive protein, lactate dehydrogenase, D dimer, and ferritin levels were obtained. The average was calculated from the data of each patient. Table no. 1 gives the average values of inflammatory markers.

Table no. 1: Average values of inflammatory markers

Sr no.	Inflammatory markers	Average values (± SD)
1	C- reactive protein	31.25 ± 15 mg/L
2	Lactate dehydrogenase	334.35 ± 80 U/L
3	D dimer	4.34 ± 2.5 microgram/mL
4	Ferritin	420.33 ± 60 nanogram/mL

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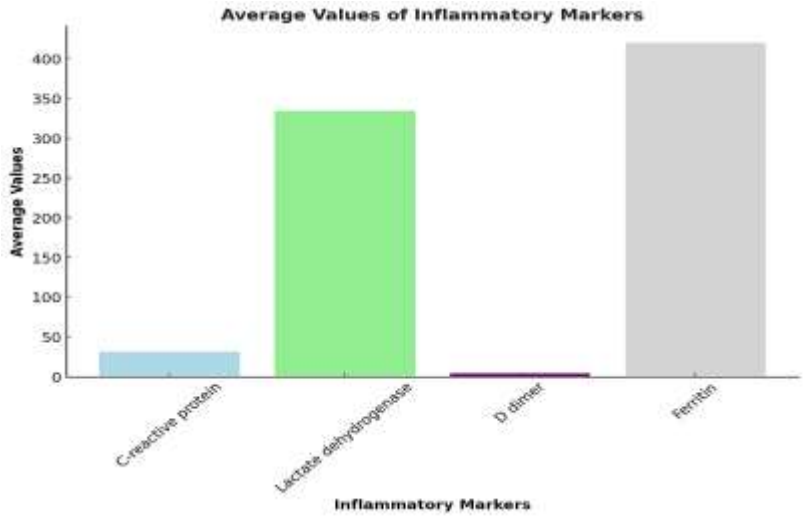

Figure 1: Average values of inflammatory markers

The liver dysfunction was determined with the test results obtained of serum bilirubin level, direct bilirubin level, Aspartate aminotransferase level, Alanine aminotransferase level, alkaline phosphate level, serum albumin level, and prothrombin time normalized ratio. From the literature available there were levels specified for each of the tests stated above which indicated liver dysfunction. Serum bilirubin level of more than 1mg/dL, direct bilirubin more than 0.2 mg/dL, Aspartate aminotransferase more than 40 U/L, Alanine aminotransferase more than 45 U/L, alkaline phosphate more than 120 U/L, SGPT more than 56 U/L, SGOT more than 50 U/L prothrombin time normalized ration more than 1.5 and decrease in serum albumin level less than 3.5 g/dL. Table no.2 illustrates the details regarding the number of patients with liver dysfunction.

Table no. 2: Liver function tests among the patients

Sr no.	Liver function test	Frequency of patients	p-value
1.	Serum bilirubin level more than 1mg/dL	147	0.01
2.	Direct bilirubin more than 0.2 mg/dL	134	0.02
3.	Aspartate aminotransferase of more than 40 U/L	150	<0.001
4.	Alanine aminotransferase of more than 45 U/L	150	<0.001
5.	Alanine aminotransferase of more than 56 U/L	57	0.05
6.	Aspartate aminotransferase of more than 50 U/L	63	0.04
7.	A prothrombin time normalized ratio of more than 1.5	150	0.03
8.	Serum albumin less than 3.5 g	135	0.01

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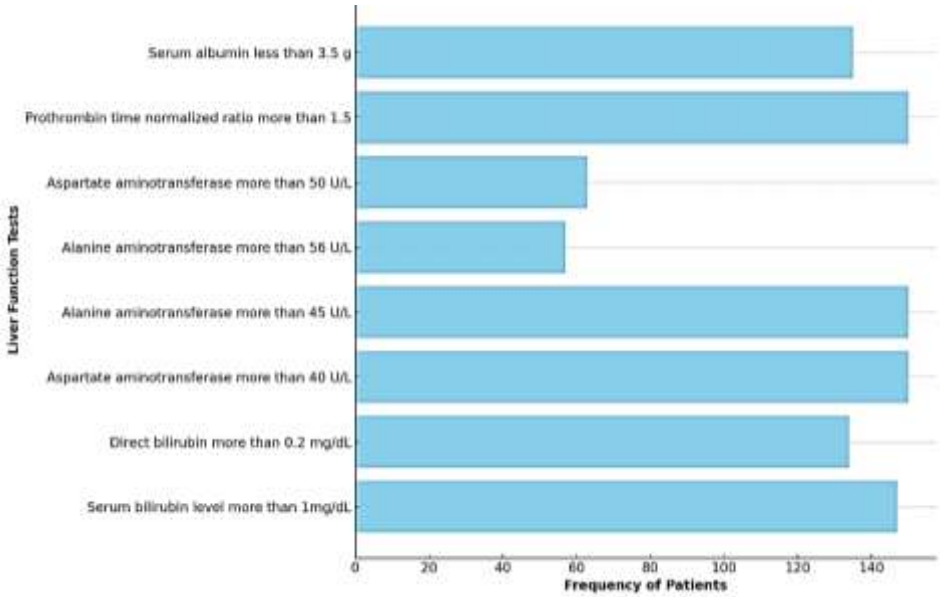

Figure 2: Liver function tests among the patients

The patients who had moderate COVID-19 infection had around 80% survival rate whereas the patients with severe COVID-19 infection had a 30% survival rate. During the study, it was observed that serum bilirubin level, direct bilirubin level, Aspartate aminotransferase level, Alanine aminotransferase level, alkaline phosphate level, and prothrombin time normalized ratio were substantially higher in those with severe COVID-19 compared to the patients who had moderate COVID-19. The levels of serum protein were substantially lower amongst the patients who had severe COVID-19.

Similarly, it was reported that the patients who did not survive had higher levels of liver enzymes and lower levels of serum protein compared to the patients who survived. The correlation of liver function test with inflammatory markers was determined statistically and it was found that liver enzymes under study had significant correlation with inflammatory markers such as C-reactive protein, ferritin, and Lactate dehydrogenase enzyme.

Table no. 3 illustrates the correlation and the significance of the correlation between liver function tests and inflammatory markers. Elevated liver enzymes, such as Aspartate Aminotransferase and Alanine Aminotransferase, were notably higher in patients with severe COVID-19 and non-survivors. Concurrently, inflammatory markers like C-reactive protein (CRP), lactate dehydrogenase (LDH), D-dimer, and ferritin were also elevated. The statistical analysis showed significant correlations, with bilirubin levels correlating with CRP (0.56), ferritin (0.44), and LDH (0.37). This correlation suggests that systemic inflammation caused by COVID-19 triggers liver injury, as evidenced by the elevated enzyme levels. These findings indicate that monitoring liver function tests and inflammatory markers can serve as valuable prognostic tools, helping to identify patients at higher risk of severe disease and mortality, thereby aiding in early intervention and improved clinical management.

Table no. 3: Correlation between liver function test and inflammatory markers

Sr no.	Liver function test	C- reactive protein	Ferritin	Lactate dehydrogenase	D-dimer
1.	Bilirubin	0.56	0.44	0.37	0.008
2.	Direct bilirubin	0.42	0.38	0.47	0.17
3.	Aspartate amino transferase	0.308	0.24	0.17	0.048
4.	Alanine aminotransferase	0.49	0.22	0.11	-0.0321
5.	Prothrombin normalized ratio	0.32	0.36	0.24	0.158
6.	Alkaline phosphate	0.23	0.052	-0.08	-0.25
7.	Total protein	-0.23	-0. 35	-0.13	0.05
8.	Serum albumin	-0.031	-0.15	0.24	0.1

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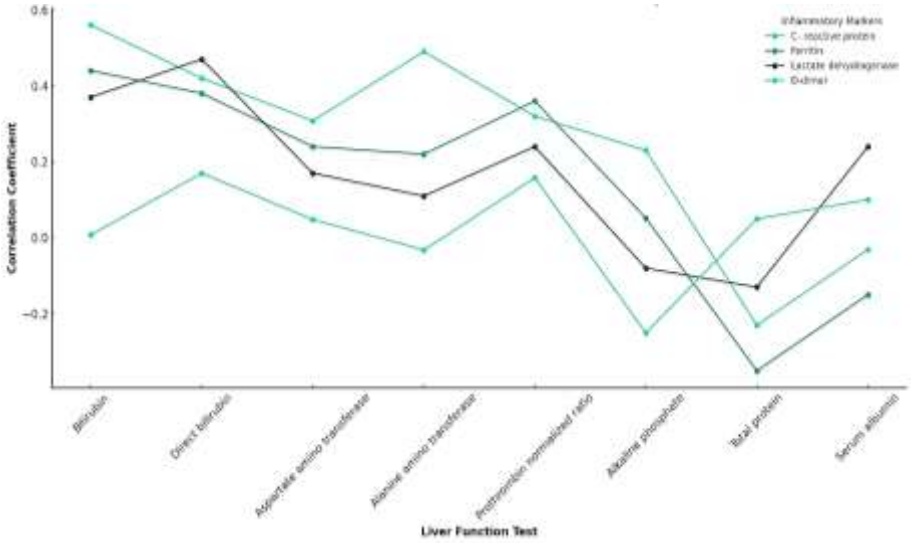

Figure 3: Correlation between liver function test and inflammatory markers

Discussion

The liver abnormalities were reported in the patients with severe COVID-19. Literature states that such abnormalities could be due to inflammation in the body because of the infection, direct action of the virus on the liver, drugs could initiate certain responses that could damage the liver, and due to aggravated pre-existing liver pathology. In this study, the majority of the participants were males above 40 years of age suffering from severe COVID-19. Similarly, another study to determine the association of liver dysfunction with the severity of COVID-19 had a demographically larger number of males above 60 years of age [8].

Liver dysfunction was reported among the patients who had severe COVID-19 and especially the non-survivors had higher serum bilirubin levels, direct bilirubin levels, Aspartate aminotransferase levels, Alanine aminotransferase levels, alkaline phosphate levels, and prothrombin time normalized ratio. They also had lower levels of serum protein. A study reported similar findings they had more than 60% of the patients who had liver dysfunction indicated by the level of liver function test [9]. A study also included the levels of gamma glutyl transferase to check the liver function and it was higher in patients suffering from severe COVID-19 [10].

The liver dysfunction triggered an immune response which caused an increase in the inflammatory markers. From this study, it was found that inflammatory markers had a significant association with liver enzymes. Studies conducted with similar objectives found D-dimer and ferritin to increase significantly with the occurrence of liver dysfunction [11, 12]. In our study, C-reactive protein, lactate dehydrogenase, D-dimer, and ferritin each of them had a significant association with the occurrence of liver dysfunction.

Retrospective and cumulative analysis conducted to determine the correlation between liver dysfunction and the severity of COVID-19 stated that the overall occurrence of liver dysfunction was 23% among the infected individuals [13, 14]. However individual studies reported a higher proportion of liver dysfunction as found in this study [8, 9, 15].

Conclusion

This study reported higher levels of liver enzymes in the patients infected with COVID-19 indicating its association. Overall liver dysfunction was prominent among the non-survivors and those who had severe COVID-19. Also, a significant relationship was derived between inflammatory markers and the occurrence of liver dysfunction. Both inflammatory markers and liver function tests can indicate the severity of the infection.

Limitation

The findings of this study cannot be generalized as the participants mostly belonged to higher age group. Also, the relationship between severe COVID-19 and liver dysfunction was determined studies are required for mild and moderate cases.

Recommendation

Doctors should monitor inflammatory markers and liver function as well to check the prognosis of the disease in elderly individuals suffering from COVID-19.

Acknowledgment
We are grateful to the hospital's staff and patients involved in the study for their cooperation during the study.

List of abbreviation
SARS COV-2 Severe Acute Respiratory Syndrome Coronavirus 2
RTPCR- Reverse transcriptase polymerase chain reaction
ACE-2- Angiotensin-converting enzyme 2
COVID-19- Coronavirus disease 2019

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Conflict of interest
The authors declare no conflicts of interest.

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