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Spectrum of Liver Function Abnormalities and their Association with WHO Severity Grades and Clinical Outcomes in SARS-CoV-2 Infection

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ABSTRACT

Background: The COVID-19 pandemic has been linked to considerable multi-system involvement, including liver dysfunction. Abnormal liver function tests (LFTs) are commonly noted in COVID-19 patients, with indications that they correlate with disease severity and outcomes. This study intends to explore LFT abnormalities in COVID-19 patients and their association with disease severity and mortality.

Methods: An observational study was performed at a tertiary care facility, including 282 confirmed COVID-19 patients. Demographic data, clinical severity, liver function test parameters (bilirubin, ALT, AST), and outcomes were gathered. Statistical analysis was conducted to assess the correlation among liver dysfunction, disease severity, and mortality.

Results: Among 282 patients, 61.7% were male, predominantly within the 21–60 years age range. Liver dysfunction was common, with 21.98% exhibiting elevated bilirubin levels, 56.73% with increased ALT, and 56.38% with elevated AST. Mortality was markedly elevated in patients with abnormal liver function tests, especially in those with increased bilirubin (>2 mg/dL; $p = 0.002021$), ALT (>120 IU/L; $p = 0.082286$), and AST (>120 IU/L; $p = 0.028651$). The severity of disease upon admission was significantly correlated with mortality rates (mild: 1.40%, moderate: 12.98%, severe: 39.68%; $p < 0.00001$). Advanced age emerged as a significant predictor of severity and negative outcomes.

Conclusion: The severity and mortality of COVID-19 are significantly correlated with liver dysfunction. Regular LFT monitoring is essential for risk assessment and prompt intervention in COVID-19 patients. Timely recognition and intervention for hepatic complications may enhance survival rates, especially among high-risk populations.

Keywords: *COVID-19, Liver Dysfunction, SARS-CoV-2.*

INTRODUCTION

The COVID-19 pandemic, resulting from the novel coronavirus SARS-CoV-2, has significantly impacted global healthcare, posing challenges to medical infrastructure and research across the globe. While respiratory involvement is the defining characteristic of the disease, COVID-19 has been recognised as a multi-system condition impacting multiple organs, including the liver. Research indicates that liver dysfunction, characterised by abnormal liver function tests (LFTs), is common among COVID-19 patients and frequently associates with disease severity and negative outcomes. (1, 2) The

mechanisms of liver injury in COVID-19 are multifactorial and not fully understood. Hypotheses encompass direct viral invasion of hepatocytes and cholangiocytes through ACE2 receptors, systemic inflammatory responses, ischemia-reperfusion injury resulting from hypoxia, and drug-induced liver injury (DILI) associated with treatments for the disease. (3, 4) Risk factors including advanced age, male sex, and comorbidities such as diabetes, obesity, and hypertension increase the probability of hepatic complications. (5) Considering the potential impact of liver injury on the prognosis of COVID-19, it is essential to investigate its prevalence, patterns, and clinical implications. This retrospective observational study assesses abnormalities in liver function tests among COVID-19 patients and investigates their correlation with disease severity and mortality. The study correlates hepatic dysfunction with clinical outcomes to offer insights into risk stratification and management strategies for affected patients.

MATERIALS AND METHODS

This observational study was conducted at a tertiary care hospital in northern part of India following approval from the Institutional Ethics Committee. The study evaluated liver function abnormalities in patients hospitalized with COVID-19 and their association with disease severity and mortality. Medical records of adult patients with laboratory-confirmed COVID-19 infection admitted between March 2021 and June 2021 were reviewed.

Patients aged 18 years and above with a positive RT-PCR test for SARS-CoV-2 and complete liver function test (LFT) data available within 24 hours of admission were included in the study. Patients with a known history of chronic liver disease such as cirrhosis, hepatitis B or C, autoimmune hepatitis, or hepatic malignancy were excluded. Records with incomplete clinical or biochemical data were also excluded from the analysis.

Data were extracted from the hospital information system using a structured proforma. Information collected included demographic characteristics (age and sex), comorbid conditions (such as diabetes mellitus, hypertension, and obesity), and clinical classification of COVID-19 severity based on World Health Organization (WHO) guidelines (mild, moderate, or severe). Laboratory parameters analyzed comprised liver function tests, including serum bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and serum albumin levels. Where available, other inflammatory markers such as C-reactive protein (CRP), ferritin, and D-dimer were also recorded.

Liver dysfunction was defined as serum total bilirubin greater than 1.0 mg/dL, ALT levels exceeding 40 IU/L, or AST levels above 40 IU/L. The primary outcome of interest was the association of abnormal LFTs with disease severity, while the secondary outcome was the relationship between LFT abnormalities and in-hospital mortality.

Statistical Analysis: -

Descriptive statistics summarised demographic and clinical data. The chi-square test was applied to assess the relationship between liver dysfunction and disease severity or mortality. A P-value less than 0.05 was considered statistically significant.

RESULTS AND INTERPRETATION

Demographic Distribution and Disease Severity

This study included 282 COVID-19 patients, with a majority being male (61.7%). The ages of the patients varied from 18 to 100 years, predominantly within the 21–60 years age range. Patients aged 0–20 years primarily presented with mild disease (86.67%), with no instances of mortality recorded. In contrast, middle-aged (41–60 years) and elderly (61–80 years) patients demonstrated greater disease severity and higher mortality rates. The 41–60 years age group exhibited the highest mortality rate at 54.05% (Table 1). The findings indicate that age is a significant predictor of disease severity and negative outcomes.

Admission Severity and Mortality Rates

The severity of COVID-19 at the time of admission had a significant impact on survival outcomes. Mild cases represented 50.35% of admissions, exhibiting a mortality rate of 1.40%. Mortality rates increased in moderate cases (12.98%) and reached their peak in severe cases (39.68%). The relationship between disease severity at admission and mortality was statistically significant ($p < 0.00001$, Table 2). This highlights the significance of early risk stratification according to disease severity to enhance management strategies.

Liver Function Abnormalities and Mortality

A significant proportion of patients exhibited abnormal liver function tests (LFTs), especially among those with severe disease. In a cohort of patients, elevated serum bilirubin levels (>1.0 mg/dL) were observed in 21.98%, correlating with a markedly increased mortality rate of 48.64%, in contrast to a mortality rate of 17.95% in patients with normal bilirubin levels ($p = 0.000027$, Table 3). Increased levels of ALT (>40 IU/L) and AST (>40 IU/L) were observed in 56.73% and 56.38% of patients, respectively, with both showing a significant correlation with elevated mortality ($p = 0.004365$ for ALT, $p = 0.003798$ for AST, Table 3).

The findings indicate a strong association between liver dysfunction, as evidenced by abnormal liver function tests, and adverse outcomes in patients with COVID-19. Monitoring liver function tests is essential for identifying patients at risk of adverse outcomes.

Association of Liver Dysfunction with Severity and Mortality

Liver dysfunction exhibited a significant correlation with disease severity and mortality. Elevated bilirubin levels (>2 mg/dL) correlated with the highest mortality rate (18.91%, p = 0.002021). Elevated AST and ALT levels (>120 IU/L) were associated with greater severity and increased mortality rates (p = 0.00191 for AST and p = 0.034844 for ALT concerning severity; p = 0.028651 for AST and p = 0.082286 for ALT concerning mortality, Table 4).

The data indicate that severe liver dysfunction, as evidenced by significantly elevated bilirubin, AST, and ALT levels, serves as a robust predictor of adverse outcomes in COVID-19 patients. The association between liver dysfunction and disease outcomes underscores the complex influence of COVID-19 on liver function, possibly mediated by systemic inflammation, direct viral effects, and drug-induced liver injury.

Table 1: Age-wise Distribution of COVID-19 Patients and Correlation with Disease Severity and Survival

Age Group (Years)	Total (n = 282)	Mild (n = 142)	Moderate (n = 77)	Severe (n = 63)	p-value (Severity)	Expired (n = 37)	p-value (Mortality)
0–20	15	13 (9.15%)	0	2 (3.17%)	0.000034	0	0.111509
21–40	106	69 (48.59%)	23 (29.87%)	14 (22.22%)		8 (21.62%)	
41–60	107	44 (30.98%)	36 (46.75%)	27 (42.85%)		20 (54.05%)	
61–80	51	16 (11.26%)	17 (22.07%)	18 (28.57%)		9 (24.32%)	
81–100	3	0	1 (1.29%)	2 (3.17%)		0	

Table 2: Severity of COVID-19 at Admission and Correlation with Mortality

Severity at Admission	Total (n = 282)	Survived (n = 245)	Expired (n = 37)	Mortality (%)	p-value
Mild	142	140	2	1.40%	< 0.00001
Moderate	77	67	10	12.98%	
Severe	63	38	25	39.68%	

Table 3: Liver Function Test Abnormalities in COVID-19 Patients and Correlation with Mortality

Parameter	Total (n = 282)	Survived (n = 245)	Expired (n = 37)	p-value
Serum Bilirubin > 1.0 mg/dL	**62 (21.98%)**	**44 (17.95%)**	**18 (48.64%)**	**0.000027**
ALT > 40 IU/L	**160 (56.73%)**	**131 (53.46%)**	**29 (78.37%)**	**0.004365**
AST > 40 IU/L	**159 (56.38%)**	**130 (53.06%)**	**29 (78.37%)**	**0.003798**

Table 4: Correlation of Liver Dysfunction with COVID-19 Severity and Mortality

Parameter	Category	Total (n = 282)	Mild (n = 142)	Moderate (n = 77)	Severe (n = 63)	p-value (Severity)	Expired (n = 37)	p-value (Mortality)
Serum Bilirubin	≤ 1 mg/dL	220	114 (80.28%)	60 (77.92%)	46 (73.01%)	0.162185	19 (51.35%)	0.002021
	1.1–2		14	11	14		11	

	mg/dL	39	(9.85%)	(14.28%)	(22.22%)		(29.72%)	
	> 2 mg/dL	23	14 (9.85%)	6 (7.79%)	3 (4.76%)		7 (18.91%)	
AST (IU/L)	≤ 40	123	78 (54.92%)	29 (37.66%)	16 (25.39%)	0.00191	8 (21.62%)	0.028651
	41–80	75	35 (24.64%)	22 (28.57%)	18 (28.57%)		10 (27.02%)	
	80–120	47	18 (12.67%)	13 (16.88%)	16 (25.39%)		12 (32.43%)	
	> 120	37	11 (7.74%)	13 (16.88%)	13 (20.63%)		7 (18.91%)	
ALT (IU/L)	≤ 40	122	72 (50.70%)	33 (42.85%)	17 (26.98%)	0.034844	8 (21.62%)	0.082286
	41–80	89	44 (30.98%)	21 (27.27%)	24 (38.09%)		15 (40.54%)	
	80–120	34	14 (9.85%)	11 (14.28%)	9 (14.28%)		6 (16.21%)	
	> 120	37	12 (8.45%)	12 (15.58%)	13 (20.63%)		8 (21.62%)	

DISCUSSION

This study's findings provide significant insights into the relationship among liver dysfunction, disease severity, and outcomes in patients with COVID-19. The findings align with current literature, underscoring the necessity of monitoring liver function in COVID-19 management.

Liver Dysfunction and Mechanisms in COVID-19

Liver dysfunction in COVID-19 patients is extensively documented, involving multiple mechanisms that contribute to hepatic injury. SARS-CoV-2 binds to ACE2 receptors present in hepatocytes and cholangiocytes, resulting in direct viral-induced damage. (6, 7) Systemic inflammatory responses, hypoxia, ischemia-reperfusion injury, and drug-induced hepatotoxicity significantly contribute to liver injury. (8, 9). The findings indicate a significant prevalence of abnormal liver function tests (LFTs) in severe cases, supporting the proposed mechanisms.

Correlation between Liver Dysfunction and Disease Severity

The study demonstrated a significant association between abnormal liver function tests and the severity of the disease. Severe cases exhibited elevated serum bilirubin levels (>1.0 mg/dL), ALT (>40 IU/L), and AST (>40 IU/L), with the highest mortality rates noted in patients presenting with increased bilirubin and AST levels. A meta-analysis by Kulkarni et al. indicates that elevated bilirubin and transaminase levels correlate with severe disease and increased mortality rates. (9) Fan et al. conducted another study that reported similar findings, indicating that abnormal liver function tests may act as early prognostic indicators in

COVID-19 patients. (6)

Age as a Predictor of Severity and Mortality

Advanced age was identified as a significant predictor of disease severity and mortality in our study, with the highest mortality rates recorded in the 41–60 years and 61–80 years age groups. This is consistent with previous research highlighting advanced age as a significant risk factor for severe outcomes, attributed to diminished immunity and an increased prevalence of comorbidities. (10, 11)

Impact of Severity at Admission on Outcomes

The severity of COVID-19 at the time of admission was an important element influencing survival in this study. Mild cases demonstrated a low mortality rate of 1.40%, whereas severe cases exhibited a markedly elevated mortality rate of 39.68%. This finding aligns with the observations of Wang et al., who indicated that patients with severe disease have a higher

likelihood of developing multi-organ dysfunction, including hepatic injury, which results in poorer outcomes. (12) The data underscore the significance of early identification and proactive management of severe cases.

Clinical Implications of Liver Dysfunction

The study emphasises the prognostic significance of liver function test abnormalities in patients with COVID-19. Elevated transaminase levels exceeding 120 IU/L and hyperbilirubinemia greater than 2 mg/dL were significantly correlated with mortality. The systematic review conducted by Wong et al. supports these findings, indicating that liver enzyme abnormalities serve as predictors for ICU admission, extended hospitalisation, and mortality. (10)

Comparison with Existing Studies

Multiple studies have confirmed that liver dysfunction serves as an indicator of disease severity in COVID-19. Cai et al. found that increased ALT and AST levels correlated with ICU admission and the need for mechanical ventilation. (13)A study by Zhang et al. indicated that hypoalbuminemia, frequently linked to liver dysfunction, serves as a marker of systemic inflammation and poor prognosis in COVID-19. The findings of this study align with previous research, highlighting the multifactorial effects of COVID-19 on liver function and the necessity for targeted interventions. (7)

Strengths and Limitations

The study demonstrates significant strength through its thorough analysis of LFT abnormalities and their association with disease outcomes in a large cohort. Limitations include the retrospective design, potential selection bias, and the inability to establish causality between liver dysfunction and mortality. Further prospective studies are required to confirm these findings and investigate the underlying mechanisms.

Another limitation of our study is the inability to evaluate the impact of metabolic risk factors such as obesity, diabetes mellitus, and hypertension on liver dysfunction in COVID-19 patients. These comorbidities are recognized contributors to metabolic dysfunction-associated steatotic liver disease (MASLD/MAFLD) and may confound the interpretation of transaminitis observed. Due to the retrospective design and limited availability of detailed metabolic data in patient records, these factors were not systematically assessed in our cohort.

Clinical Recommendations

The results indicate that regular monitoring of LFTs ought to be incorporated into the management protocols for COVID-19 patients. Timely identification of hepatic dysfunction aids in risk stratification and personalised interventions, especially for elderly patients and those presenting with severe disease upon admission.

Future prospective studies incorporating comprehensive metabolic profiling are warranted to delineate the independent and combined effects of metabolic comorbidities and SARS-CoV-2 infection on liver injury and clinical outcomes.

CONCLUSION

This research highlights the considerable influence of liver dysfunction on the severity and outcomes associated with COVID-19. Elevated bilirubin, ALT, and AST levels in liver function tests were significantly correlated with heightened disease severity and mortality. Advanced age and the severity of disease at the time of admission were significant predictors of negative outcomes.

The findings highlight the necessity for regular assessment of liver function in COVID-19 patients, particularly in those exhibiting severe symptoms and comorbid conditions. Timely identification and intervention in hepatic dysfunction may enhance clinical outcomes and decrease mortality rates. Additional prospective studies are necessary to investigate the underlying mechanisms and improve therapeutic strategies.

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