RESEARCH ARTICLE

Probing liver function test patterns in COVID-19 pneumonia: Implications for disease severity assessment

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Abstract

Objective: To explore the incidence of liver function test derangement, the precise patterns of derangement, and their relationship with coronavirus disease-2019 pneumonia severity.

Method: The retrospective study was conducted at the Dow University Hospital and the Ojha Institute of Chest Diseases, Karachi, and comprised consecutive data from December 16, 2020, to March 16, 2021, of adults of either gender who had nasal swabs positive for coronavirus disease-2019 on real-time reverse transcriptase-polymerase chain reaction. Data regarding patients' demographics, co-morbidities, addictions, laboratory results, and standard information was retrieved from electronic and manual records. The severity of the disease was determined based on World Health Organisation protocols. Data was analysed using SPSS 23.

Results: Of the 344 patients, 235(68.3%) were males and 109(31.7%) were females. The overall mean age was 54.58±14.75 years, 187(54.4%) had severe coronavirus disease-2019 pneumonia and 157(45.6%) had non-severe disease at the time of admission. There was a significant prevalence of both mixed and cholestatic patterns of liver function test abnormality among the cases (p=0.046). The presence of a mixed pattern was linked to the disease severity (p<0.05). Advanced age and hypertension were significant risk factors for the development of severe coronavirus disease-2019 pneumonia (p<0.001 and p=0.002).

Conclusion: Liver function test abnormality and coronavirus disease-2019 pneumonia severity were fund to have a significant relationship.

Keywords: SARS CoV-2, COVID-19-pneumonia, Liver function test, Pattern of LFT abnormality, Severe COVID pneumonia. (JPMA 74: 1423; 2024) **DOI: https://doi.org/10.47391/JPMA.10178**

Introduction

In February 2020, the World Health Organisation (WHO) designated the instances of severe pneumonia resulting from the Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) virus originating in China in late 2019, as coronavirus disease-2019 (COVID-19). Subsequently, it was officially declared a pandemic.[1] Emerging data has highlighted COVID-19 as a comprehensive systemic ailment that impacts various organ systems, encompassing the lungs, liver, heart, kidneys and the coagulation system.[2,3]

It is widely held that COVID-19 gains entry into cells by utilising angiotensin-converting enzyme II (ACE-II), which is abundantly present in the epithelial layers of the gastrointestinal tract (GIT), including the gastric, duodenal and rectal epithelial layers. Additionally, ACE-II is also displayed on hepatocytes and cholangiocytes.[3-5] Notably, a substantial number of studies have revealed abnormal liver function tests (LFTs) in COVID-19 patients, ranging from 14% to 75%.[1,3]

Numerous researches have consistently revealed that people with severe COVID-19 infections had increased values of alanine aminotransferases (ALT), aspartate aminotransferases (AST) and total bilirubin (T-Bili). Additionally, deranged prothrombin values have also been witnessed in such cases.[6,7] These deranged LFT results have been identified as an independent risk factor associated with higher morbidity and death rates.[8]

The majority of studies[9] examining the link between deranged LFTs and COVID-19 were conducted retrospectively, displaying significant variability in the prevalence of LFT abnormalities. Moreover, limited research had been conducted[9,10] to elucidate the specific patterns and correlations of LFT abnormality with COVID-19 pneumonia severity. The current study was planned to fill the gap in literature by investigating the incidence and patterns of LFT abnormalities in conjunction with COVID-19 pneumonia severity.

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Materials and Methods

The retrospective study was conducted at the Dow University Hospital (DUH) and the Ojha Institute of Chest Diseases (OICD), Karachi, and comprised consecutive data from December 16, 2020, to March 16, 2021, of adults of either gender who had nasal swabs positive for COVID-19 on real-time reverse transcriptase-polymerase chain reaction (rRT-PCR). Data was retrieved from electronic and manual records after approval from the DUH ethics review board, which waived the need for informed consent. Patients with pre-existing liver diseases or incomplete/ missing LFT data were excluded. Data retrieved included age, gender, addictions, vitals, pulse oxygen saturations, fraction of inspired oxygen (FiO_2) levels, comorbidities, such as chronic respiratory disease, chronic kidney disease (CKD), cerebrovascular disease (CVD), hypertension (HTN), type 2 diabetes mellitus (T2DM) and cardiovascular disease. Laboratory data included lactate dehydrogenase (LDH), C-reactive protein (CRP), ferritin, white blood cell (WBC) count, neutrophil and lymphocyte counts, alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), T-Bili and direct bilirubin (D-Bili) levels, alanine transaminase (ALT) and aspartate transaminase (AST). Available D-dimer (D-D) and procalcitonin (PCT) biochemical values were also incuded in the analysis. Abnormal liver function was defined as T-Bili, ALT, ALP, GGT and AST levels exceeding 1.2 mg/dL, 45 U/L, 128 U/L and 35 U/L, respectively. The pattern of LFT derangement was classified based on the R factor: hepatocellular if the R factor was >5, mixed if the R factor ranged 2-5 and cholestatic if the R factor was <2. The R factor was calculated using the formula (patient's ALT/upper limit of normal ALT) / (patient's ALP/upper limit of normal ALP).[11] The abnormality cut-off points were set as >10 mg/L, 220 U/L, >0.5 ng/mL, >0.5mg/L, and 250ng/mL for CRP, LDH, PCT, D-D and ferritin, respectively.

COVID-19 pneumonia severity was classified as per the WHO provisional assistance,[12] where severe pneumonia was defined as saturation of peripheral oxygen (SpO_2) less than or equal to 90% in a symptomatic individual on room air, and non-severe pneumonia as SpO_2>90% in a symptomatic patient on ambient air.

Data was analysed using SPSS 23. Data was expressed as mean±standard deviation or as percentages and frequencies, as appropriate. Inflammatory markers, COVID-19 severity and LFTs were analysed using chi-square test. Clinical and laboratory characteristics of severe and non-severe COVID-19 pneumonia were compared using independent-samples *t*-test. The relationship between laboratory variables and LFT pattern was investigated using one-way analysis of variance (ANOVA). Games-Howell and Hochberg's GT2 tests and post-hoc tests were conducted as part of ANOVA analysis. A 95% confidence interval (CI) was generated, and $p<0.05$ was considered statistically significant.

Results

Of the 344 patients, 235(68.3%) were males and 109(31.7%) were females. The overall mean age was 54.58±14.75 years, 187(54.4%) had severe COVID-19 pneumonia and 157(45.6%) had non-severe disease at the time of admission. Baseline characteristics of all the subjects were noted in detail (Table 1).

The most common LFT patterns were cholestatic 121(35.2%) and mixed 121(35.2%), followed by hepatocellular 45(13.1%). There were 57(16.6%) patients without any LFT abnormality. T2DM 157(45.6%) and HTN 151(43.9%) were the most prevalent comorbidities (Table 2).

Table-1: Baseline characteristics (n=344).

Characteristics	Mean±SD
Age (years)	54.58±14.75
Systolic BP (mmHg)	127.36±18.75
Diastolic BP (mmHg)	76.69±11.26
Pulse (beats / minute)	96.40±16.80
Temperature	98.44±4.90
Respiratory Rate (breaths/min)	22.60±4.11
SpO_2	90.55±17.75
FiO_2	39.15±22.53
Hb	12.35±2.16
Hct (%)	37.39±6.42
MCV	83.56±7.54
WBC	11.85±12.90
Neutrophil count	77.79±12.69
Lymphocyte Count	15.45±10.55
Platelet Counts	267.61±129.18
Ferritin Levels	724.21±893.91
D-Dimer Levels	2.3078±2.55
PCT Levels	2.53±7.99
CRP Levels	87.18±82.06
LDH Levels	543.87±280.37
PT	12.05±2.74
INR	1.12±0.27
T- Bili	0.90±2.22
D-Bili	0.48±1.22
I-Bili	0.42±1.32
ALT	66.52±69.82
ALP	125.38±162.51
GGT	119.38±163.20
AST	71.04±88.67

Hb: Haemoglobin; Hct: Haematocrit; MCV: Mean corpuscular volume; WBC: White blood cells; PCT: Procalcitonin; CRP: C-reactive protein; LDH: Lactate dehydrogenase; PT: Prothrombin time; INR: International normalised ratio; T-Bili: Total bilirubin; D-Bili: Direct bilirubin; I-Bili: Indirect bilirubin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; GGT: Gama glutamyl transpeptidase.

Table-2: Clinical features.

Clinical characteristics	n (%)
Gender	
Male	235 (68.3)
Female	109 (31.7)
COVID-19 Severity	
Non-severe	157 (45.6)
Severe	187 (54.4)
HTN	151 (43.9)
Cardiovascular Disorder	35 (10.2)
Chronic Lung Disease	21 (6.1)
T2DM	57 (45.6)
Cerebrovascular Disease	15 (4.4)
CKD	22 (6.4)
Addictions	
Smoking	23 (6.7)
Chewing tobacco	8 (2.3)
Alcohol	3 (0.9)
Pattern of Liver Function Tests	
Hepatocellular	45 (13.1)
Cholestatic	121 (35.2)
Mixed	121 (35.2)
Normal	57 (16.6)

HTN: Hypertension, T2DM: Type 2 diabetes mellitus, CKD: Chronic kidney disease.

Table-3: Comparison of clinical characteristics between non-severe and severe coronavirus disease-2019 (COVID-19) cases.

	COVID-19 Severity		x^2	*p*-value
	Non-severe	Severe		
	n (%)	n (%)		
Gender			0.003	0.95
Male	107 (45.5)	128 (54.5)		
Female	50 (45.9)	59 (54.1)		
HTN	55 (35.0)	96 (51.3)	9.21	0.002*
Cardiac Disease	15 (9.6)	20 (10.7)	0.12	0.73
Chronic Lung Disease	12 (7.6)	9 (4.8)	1.19	0.27
T2DM	65 (41.4)	92 (49.2)	2.09	0.15
Cerebrovascular Disease	5 (3.2)	10 (5.3)	0.96	0.33
CKD	10 (6.4)	12 (6.4)	<0.001	0.99
Smoking	14 (8.9)	9 (4.8)	2.30	0.13
Alcohol	3 (1.9)	0 (0)	3.60	0.06
Chewing tobacco	3 (1.9)	5 (2.7)	0.22	0.64

HTN: Hypertension; T2DM: Type 2 diabetes mellitus; CKD: Chronic kidney disease; *p-values lower than 0.05 will be regarded as significant; X^2: Chi square.

COVID-19 pneumonia severity was significantly linked only with HTN (Table 3).

There were significant disparities in the outcomes between severe and non-severe cases in terms of age (p<0.001), WBC count (p=0.04), neutrophil count (p<0.001), lymphocyte count (p<0.001), international normalised ratio (INR) level (p=0.01), T-Bili (p=0.02), and AST level (p<0.001).

There were no significant variations between the two clusters in terms of gender, haemoglobin (Hb), haematocrit (Hct), mean corpuscular volume (MCV), GGT, ALP, ALT levels and platelet count (p>0.05).

There were significant disparities in the four LFT groups in terms of age (p=0.007), Hb level (p<0.001), Hct level (p=0.001), neutrophil count (p=0.031), lymphocyte count (p=0.047), and platelet count (p=0.031).

Patients with hepatocellular pattern were significantly older than patients with normal pattern (p=0.02). Patients with cholestatic (p=0.003) and normal (p=0.001) patterns had significantly lower Hb levels than those with hepatocellular pattern. The cases with mixed pattern had significantly lower Hb levels than those with normal pattern (p=0.013). Patients with cholestatic (p=0.033) and normal (p=0.009) patterns had significantly lower Hct levels than the cases with hepatocellular pattern. The cases with mixed pattern had lesser Hct levels than those with normal pattern (p=0.013). The cases with mixed pattern had significantly higher neutrophil count than patients with normal pattern (p=0.024). Patients with mixed pattern had significantly lower lymphocyte counts than individuals with normal pattern (p=0.045). Patients with hepatocellular pattern had lower platelet count than cases with cholestatic pattern (p=0.050). There were no significant variations among the four LFT patterns concerning prothrombin time and INR level (p>0.05).

Discussion

The current study was planned to determine the frequency of liver function abnormalities in individuals diagnosed with COVID-19 pneumonia, to categorize the abnormalities depending on the severity of COVID-19 pneumonia, and to identify any discernible patterns associated with the severity of the disease.

The cohort's average age was 54.58±14.75 years, and male patients were in majority (68.3%). There was a significant association between older age and COVID-19 pneumonia severity, which was compatible with previous studies.[13-19] In contrast, the current study found no significant relationship between gender and the severity of COVID-19 pneumonia. The findings implied that age could serve as a crucial risk factor in determining the severity of COVID-19, while gender may not have a substantial influence. HTN and T2DM were the most common prevailing comorbidities among the patients, but only HTN was associated with COVID-19 pneumonia severity. The finding was in line with other studies.[16,18] Other comorbidities did not show significant association with COVID-19 severity, but their assessment remains important for comprehensive patient care, and should not be overlooked.

The current study excluded patients with a history of liver disease, and found that 16.6% of the patients had normal

LFT on admission. Previous studies suggested hepatocellular derangement as the prevailing pattern of LFT abnormalities in COVID-19 pneumonia[4,8,13,20] but in the current study, majority of patients had cholestatic (35.2%) and mixed (35.2%) patterns. Additionally, the current study demonstrated a positive association between advancing age and the presence of hepatocellular pattern of liver injury. In patients with severe COVID-19 pneumonia, inflammatory markers were found to be raised, including WBC and neutrophil counts, which have also been correlated with LFT derangement.[4,8] Among the LFT elements assessed, only AST level exhibited a significant association with the severity of COVID-19 pneumonia, aligning with earlier reports.[3,16,21]

The precise mechanism underlying liver damage in individuals with COVID-19 is not completely understood. Numerous possible explanations have been proposed, such as direct viral invasion of hepatocytes and cholangiocytes via ACE-II receptors[4,5,20,22] the virus interacting with mitochondrial proteins, resulting in a mainly AST pattern of liver damage,[4,23] cytokine storm induced by viral infection,[4] drug-induced hepatotoxicity[24] and cardiovascular dysfunction causing congestive liver damage.[4]

Based on its findings, the current study found that older patients with HTN, elevated WBC and lymphopaenia were at a greater risk of developing severe COVID-19 pneumonia. It is important for emergency department staff to closely monitor these individuals for any signs of deterioration, as they may need to be transferred to an intensive care unit (ICU) promptly. Additionally, the current findings indicated that cholestatic and mixed patterns of LFT derangement were more frequently observed. Notably, the mixed pattern was linked to severe illness and high inflammatory indicators, such WBC count, neutrophil count and lymphopaenia.

AST levels were significantly linked with COVID-19 severity in the current study, making it a potential marker for ICU monitoring. Age and certain LFT characteristics identified as possible indicators for COVID-19 pneumonia severity in individuals with liver illnesses might help healthcare providers with risk assessment, prompt interventions, and individualised treatment modalities. The findings emphasised the importance of considering liver function and associated derangement patterns when managing COVID-19 cases.

The current study had limitations, such as missing data or potential confounding factors due to its retrospective design. Generalisability of the findings may be limited by the fact that it was a single-centre study. The cross-sectional design restricted the study from exploring the causal relationship.

Despite the limitations, however, the findings highlighted the potential role of age and specific LFT parameters as indicators of COVID-19 pneumonia severity in the patient population. Incorporating these factors into clinical assessments could improve risk stratification and guide appropriate management strategies for individuals with liver diseases affected by COVID-19 pneumonia.

Conclusion

Older individuals with a previous history of medical conditions, especially HTN, had a greater risk of developing severe COVID-19 pneumonia. With respect to LFT derangement, the mixed pattern demonstrated a significant link with COVID-19 severity, and was also associated with elevated levels of inflammatory markers, including WBC and neutrophil counts. AST was associated with increased levels of inflammatory markers and greater disease severity.

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Author Contribution:

AKK: Concept, data acquisition and analysis, drafting, revision, final approval and agreed to be accountable for all aspects of work.

HS: Concept, revision, final approval and agreed to be accountable for all aspects of work.

MK: Data acquisition, revision, final approval and agreed to be accountable for all aspects of work.