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Pattern of liver function and clinical profile in COVID-19: A cross-sectional study of 91 patients

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ABSTRACT

Background: — COVID-19 caused by SARS-CoV-2 leads to myriad range of organ involvement including liver dysfunction.
Aim: To analyse the liver function in patients with COVID-19 and their association with respect to age, sex, severity of disease and clinical features.
Materials and methods: This study was a cross-sectional study done at Rajendra Institute of Medical Sciences, Ranchi. 91 patients admitted with confirmed SARS-CoV-2 infection were included in this study and divided into asymptomatic, mild, moderate and severe groups. Liver function tests were compared among different severity groups.
Results: Of 91 patients with COVID-19, 70 (76.9%) had abnormal liver function. Aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), total bilirubin levels was 1–2 × ULN in 33(36.3%), 34(37.3%), 12(13.2%), 6(6.6%) cases and >2 × ULN in 20(22%), 18(19.8%), 7(7.7%) and 2 (2.2%) cases respectively. Mean AST and ALP levels among different severity groups of COVID-19 was statistically significant ($p < 0.05$) whereas mean ALT and total bilirubin levels was statistically non-significant ($p > 0.05$). There was no statistical difference between males and females with regard to abnormal liver function. Liver injury was seen in 64.3% cases of hypertension and 73.3% cases of diabetes. Fever, myalgia, headache and breathlessness were found to be correlated significantly with severity of disease.
Conclusion: Liver injury is common in SARS-CoV-2 infection and is more prevalent in the severe disease group. Aspartate transaminase and alkaline phosphatase are better indicators of covid-19 induced liver injury than alanine transaminase and total bilirubin.

1. Introduction

On December 31, 2019, China reported cases of pneumonia of unknown etiology related to Hunan sea food market in Wuhan [1]. A new strain of Coronavirus was later identified as the causative agent. The virus was renamed by WHO as SARS-CoV-2 and the disease as COVID-19 [2]. Since its detection, the disease has spread to 270 countries with 24, 555, 405 cases and 802,762 deaths reported worldwide. India has reported 3,621,245 cases and 64,469 deaths until the time of writing this report [3]. The transmission of SARS-CoV-2 can occur via respiratory secretions directly through droplets from coughing, sneezing or indirectly through contaminated objects or surfaces as well as close contacts [4]. COVID-19 poses a huge risk for the already overloaded and inadequate health infrastructure of India.

The main manifestations of COVID-19 include fever, cough, breathlessness, myalgia, malaise, headache, nausea, vomiting, diarrhea [5]. Cases of seizures, thrombosis-induced-myocardial infarction, neuropathy have also been reported [6–8]. Liver function abnormality has been reported in patients with COVID-19 [9]. Based on clinical severity, COVID-19 has been divided into mild, moderate and severe disease. Mild disease: uncomplicated upper respiratory tract infection with mild symptoms such as fever, cough, sore throat, nasal congestion, malaise, headache with normal SpO2 levels; Moderate disease: pneumonia and no signs of

Abbreviations:: ALT, Alanine transaminase; AST, Aspartate transaminase; ALP, Alkaline phosphatase; ULN, Upper limit of normal; COVID-19, Coronavirus disease-19; SARS-CoV-2, Severe acute respiratory syndrome-coronavirus-2; IQR, interquartile range.

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severe disease, SpO2 90–94% on room air, respiratory rate 24–30/min; Severe disease: severe pneumonia with signs of respiratory distress, respiratory rate >30/min or SpO2 <90% on room air [10]. Studies with the help of single-cell RNA sequencing technique have confirmed ACE-2 receptors to be the entry receptor of SARS-CoV-2 [11]. ACE-2 receptors are present in the bile duct cells 20 times more than that in hepatocytes. SARS-CoV-2 may infect the hepatocytes and bile duct cells and cause liver dysfunction [12]. Studies have shown the presence of pathological changes like moderate micro-vescicular steatosis, lobular and portal activity in a series of liver biopsies, indicating that liver injury may be either due to SARS-CoV-2 induced direct hepatocellular injury or drug induced [13]. Findings from a series of autopsies conducted at Mount Senai, New York reported blood clots in the brain, kidney and liver reflecting endothelial damage, activation of the coagulation cascade and persistently raised elevation of inflammatory markers suggesting the possible additional role of systemic thromboembolism in liver function abnormality among COVID patients [14]. In view of the pathogenicity, infectivity and the high incidence of liver damage, an in-depth study of liver dysfunction in these patients is the need of the hour. In this study, we aimed to analyse the liver function abnormalities in patients with COVID-19 and their association with respect to age, sex, severity of disease and clinical features.

2. Materials and methods

Our study was a single centre, cross-sectional study in Rajendra Institute of Medical Sciences, Ranchi, Jharkhand (dedicated COVID hospital of the region). 91 patients with confirmed real-time polymerase chain reaction status for SARS-CoV-2 admitted and treated from 1st to 15th August 2020 were included in this study. The study was approved by the Institutional ethics committee, Rajendra Institute of Medical Sciences, Ranchi, Jharkhand, India. Informed consent was taken from every patient included in the study. Patients were divided into asymptomatic (group I) and clinical severity groups of mild (group II), moderate (group III), severe (group IV) groups based on the National Clinical Management Protocol COVID 19, Revised version 3, dated June 13, 2020 by Ministry of Health and Family Welfare, Government of India [10].

2.1. Inclusion criteria

Patients with confirmed Real-Time Polymerase Chain Reaction for SARS-CoV-2 were included in this study.

2.2. Exclusion criteria

Patients with pre-existing liver disease, alcoholics, Hepatitis B, Hepatitis C, those on drugs known to be hepatotoxic were excluded from the study.

Detailed clinical history, clinical examination, laboratory investigations such as complete blood counts, liver function tests including AST (Normal; 13–38 U/L), ALT (Normal; 9–41 U/L), ALP (Normal; 35–135 U/L), total bilirubin (Normal; 0.1–1.1 mg/dL), renal function tests etc were done using standard methods. AST, ALT, ALP and total bilirubin were grouped into normal (<ULN), 1–2 ULN and >2 ULN and their frequencies in various severity groups were studied. Abnormal liver function test was defined as elevation of any of the liver enzymes and/or total bilirubin more than upper limit of normal value.

2.3. Statistical analysis

Categorical data were expressed as percentages and groups were compared using the chi-square (*X2*) test.

Student's *t*-test was applied to compare continuous data of two groups. One-way analysis of variance (ANOVA) was used to compare continuous data of more than two groups. The level of statistical significance was $p < 0.05$. All hypothesis tests were 2-tailed. SPSS software version 21.0 was used to perform the analysis.

3. Results

The clinical characteristics and liver function tests of the subjects on admission was tabulated (Table- 1). The proportion of subjects in group I was 4.4% (4/91), group II 53.8% (49/91), group III 13.2% (12/91) and group IV 28.6% (26/91). The patients in this study had clinical manifestations of fever (58.9%), myalgia (37.9%), malaise (24.2%) headache (10.5%), cough (25.2%), anosmia (5.2%), diarrhea (4.2%), pain abdomen (1.05%), anorexia (3.1%), breathlessness (17.9%) and chest pain in 3.1% cases.(Table- 1).

The median age was 44 years (IQR: 29, 58; Range: 15–82) in the present study. Median age among Group I, II, III, IV was 41 ± 5.67 (n = 4), 41.35 ± 18.38 (n = 49), 49.42 ± 10.41 (n = 12) and 49.46 ± 17.96 (n = 26) respectively (p = 0.186). The male-female ratio in the entire study was 2:1. Male-female ratio among group I was 1:1 vs 2.5:1 in group II vs 3:1 in group III vs 1.3:1 in group IV (p = 0.508). The proportion of males and females with abnormal liver function was 77% and 76.6% respectively (p = 1.00).

The statistical analysis of liver function tests has been presented in Table 1. On analysis of ALT levels, 52 of 91 (57.1%) subjects had elevated ALT levels, out of which 18 had levels > 2 ULN (34.6%) and 34 had levels between 1 and 2 ULN (65.4%) and 39 had normal ALT levels (42.9%). Significant difference in the distribution of ALT at different levels among groups I, II, III and IV was noted (p = 0.004) (Table- 1). Mean ALT in group I was 37.50 ± 16.31 U/L, in group II was 44.83 ± 26.91 U/L, in group III 79.88 ± 82.99 U/L, in group IV 141.68 ± 190.96 U/L (p = 0.07). Mean values of ALT (U/L) among different groups was found to be statistically non-significant (Table 2). The highest level of ALT was 926 U/L, in a subject of group IV.

On analysis of AST levels 53 of 91 (58.2%) subjects had elevated, out of which 20 had levels > 2 ULN (37.7%) and 33 had levels between 1 and 2 ULN (62.3%) and 39 had normal AST values (41.9%). Significant difference in the distribution of AST at different levels among groups I, II, III and IV was noted (p < 0.001) (Table- 1). Mean AST in group I was 31.25 ± 8.65 U/L, group II was 38.34 ± 19.32 U/L, group III 73.98 ± 72.54 U/L, in group IV was 113.34 ± 154.98 U/L (p = 0.038). Mean values of AST (U/L) among different groups was statistically significant (Table- 2). The highest level of AST was 764 U/L, in a subject of group IV.

On analysis of ALP levels, 19 of 91 (20.8%) subjects had elevated ALP levels, out of which 7 had levels > 2 ULN (36.8%) and 12 had levels between 1 and 2 ULN (63.2%) and 72 had normal ALP levels (79.2%). Significant difference in distribution of ALP at different levels among groups I, II, III and IV was noted (p < 0.001) (Table- 1). Mean ALP in group I was 88 ± 22.89 U/L, in group II was 95.24 ± 49.175 U/L, in group III 178 ± 223.10 U/L, in group IV 161.15 ± 89.25 U/L (p = 0.016). Mean ALP (U/L) among different groups was found statistically significant (Table- 2). The highest level of ALP was 434 U/L, in a subject of group III.

On analysis of total bilirubin levels, 8 of 91 (8.8%) subjects had elevated total bilirubin levels. No significant difference was observed in distribution of total bilirubin at different levels among groups I, II, III and IV (p = 0.301) (Table- 1). Mean total bilirubin in group I was 1 ± 0.0 mg/dL, in group II was 1.04 ± 0.19 mg/dL, in group III 1.08 ± 0.28 mg/dL, in group IV 1.26 ± 0.60 mg/dL (p = 0.082). Mean values of total bilirubin (mg/dL) among different groups was statistically non-significant (Table- 2). The highest level

Table-1
Clinical profile and liver function characteristics of patients on admission.

		GRADE OF COVID-19					LIVER FUNCTION		
	All	Asymptomatic	Mild	Moderate	Severe	p- value	Abnormal	Normal	p-value
AGE (median ± S.D))	44 (15–82)	41 ± 5.67	41.35 ± 18.38	49.42 ± 10.41	49.46 ± 17.96	0.186	45 (15–82)	42 (20–77)	0.411
SEX (n, %)									
MALE	61 (67%)	2 (3.3%)	35 (57.3%)	9 (14.7%)	15 (24.5%)	0.508	47 (77%)	14 (23%)	1.00
FEMALE	30 (23%)	2 (6.7%)	14 (46.6%)	3 (10%)	11 (36.6%)		23 (76.6%)	7 (23.4%)	
FEVER (n, %)	56 (61.5%)	–	34 (60.7%)	8 (14.3%)	14 (25%)	**0.037**	43 (76.7%)	13 (23.3%)	0.969
MYALGIA (n, %)	36 (39.5%)	–	24 (66.7%)	6 (16.7%)	6 (16.7%)	**0.047**	24 (66.6%)	12 (33.3%)	0.061
MALAISE (n, %)	23 (25.2%)	–	15 (65.2%)	5 (21.7%)	3 (13%)	0.094	17 (73.9%)	6 (26.1%)	0.696
HEADACHE (n, %)	10 (10.9%)	–	10 (100%)	0	0	**0.022**	5 (50%)	5 (50%)	0.109
COUGH (n, %)	24 (26.3%)	–	11 (45.8%)	6 (25%)	7 (29.2%)	0.153	19 (79.1%)	5 (20.9%)	0.764
ANOSMIA (n, %)	5 (5.5%)	–	5 (100%)	0	0	0.209	3 (60%)	2 (40%)	0.361
DIARRHEA (n, %)	4 (4.4%)		0	1 (25%)	3 (75%)		3 (75%)	1 (25%)	0.927
PAIN ABDOMEN (n, %)	1 (1.09%)		1 (100%)	0	0	0.833	1 (100%)	0	0.587
ANOREXIA (n, %)	3 (3.2%)		2 (66.7%)	0	1 (33.3%)	0.881	3 (100%)	0	0.083
BREATHLESSNESS (n, %)	17 (18.6%)		0	1 (5.9%)	16 (94.1%)	**<0.001**	15 (88.2%)	2 (11.8%)	0.154
CHEST PAIN (n, %)	3 (3.2%)		0	1 (33.3%)	2 (66.7% (66.6%)	0.227	3 (100%)	0	0.083
AST (n, %)									
<1 ULN	38 (41.7)	2 (5.3)	27 (71.1)	5 (13.2)	4 (10.5)	**<0.001**			
1-2 ULN	33 (36.3)	2 (6.1)	19 (57.6)	4 (12.1)	8 (24.2)				
>2 ULN	20 (22)	0	3 (15)	3 (15)	14 (70)				
ALT (n, %)									
<1 ULN	39 (42.9)	2 (5.1)	26 (66.7)	5 (12.8)	6 (15.4)	**0.004**			
1-2 ULN	34 (37.3)	2 (5.9)	20 (58.8)	4 (11.8)	8 (23.5)				
>2 ULN	18 (19.8)	0	3 (16.7)	3 (16.7)	12 (66.7)				
ALP (n, %)									
<1 ULN	72 (79.1)	4 (5.6)	46 (63.9)	9 (12.5)	13 (18.1)	**<0.001**			
1-2 ULN	12 (13.2)	0	1 (8.3)	1 (8.3)	10 (83.3)				
>2 ULN	7 (7.7)	0	2 (28.6)	2 (28.6)	3 (42.9)				
T BIL (n, %)									
<1 ULN	83 (91.2)	4 (4.8)	47 (56.6)	11 (13.3)	21 (25.3)	0.301			
1-2 ULN	6 (6.6)	0	2 (33.3)	1 (16.7)	3 (50)				
>2 ULN	2 (2.2)	0	0	0	2 (100)				

Data were expressed as median ± SD or as percentages. P values were calculated from independent samples t tests or x2 tests for categorical data. Bold data indicated $p < 0.05$. ALT- Alanine transaminase, AST – Aspartate transaminase, T BIL – total bilirubin, ULN – Upper limit of normal, COVID- coronavirus disease.

Table 2
Comparison of mean aspartate transaminase, alanine transaminase, alkaline phosphatase, total bilirubin values among clinical severity groups.

		MEAN ± S.D			
Grade of COVID	Numbers	AST (U/L)	ALT (U/L)	ALP (U/L)	T BILIRUBIN (mg/dL)
ASYMPTOMATIC (group I)	4	31.25 ± 8.65	37.50 ± 16.34	88 ± 22.89	1 ± 0.0
MILD (group II)	49	38.34 ± 19.32	44.83 ± 26.91	95.24 ± 49.175	1.04 ± 0.19
MODERATE (group III)	12	73.98 ± 72.54	79.88 ± 82.99	178 ± 223.10	1.08 ± 0.28
SEVERE (group IV)	26	113.34 ± 154.98	141.68 ± 190.96	161.15 ± 89.25	1.26 ± 0.60
SIGNIFICANCE p-value		**0.038**	0.07	**0.016**	0.082
F		4.368	4.70	3.94	2.30

Data were expressed as means ± SD. p values were calculated from independent samples t tests. Bold data indicated $p < 0.05$. ALT- Alanine transaminase, AST – Aspartate transaminase, T BIL – total bilirubin.

Table 3
Comparison of Diabetes and hypertension among various severity groups and association with liver injury.

	GRADE OF COVID-19						LIVER FUNCTION		
	All	Asymptomatic	Mild	Moderate	Severe	p- value	Abnormal	Normal	p-value
Diabetes mellitus (n, %)	15 (16.5%)	0	5 (33.3%)	2 (13.3%)	8 (53.3%)	0.109	11 (73.3%)	4 (26.7%)	0.718
Hypertension (n, %)	14 (15.4%)	0	4 (28.6%)	2 (14.3%)	8 (57.1%)	0.059	9 (64.5%)	5 (35.7%)	0.222

Data were expressed as frequency and percentages. P values were calculated from Chi square (x^2) tests.

of total bilirubin was 6 mg/dL, in a subject of group IV. In our study, mortality rate was 2 (2.1%). Both patients had severe COVID-19 disease with ARDS.

Diabetes and hypertension were present in 16.5% (15/91) and 15.4% (14/91) cases respectively. Liver injury was seen in 64.3% cases of hypertension and 73.3% cases of diabetes (Table 3).

4. Discussion

The median age in our study was 44 years (IQR: 29, 58; Range: 15–82) and 61 of 91 patients were male (67%). This is consistent with a previous report [15]. A recent Indian study reported median age of 33 years [16]. SARS-CoV-2 infection was more common in males (67%) than females (23%) as consistent with other studies [17–20]. Patients with liver dysfunction in our study were more likely to be males (67.1%) than females (22.9%). However, among

each sex group, liver dysfunction was similar i.e. 77% in males and 76.6% in females which is different from other studies showing males with more prevalence of liver dysfunction [16,21].

Abnormal LFTs were observed in 73.6% patients which is similar to other studies [16,18,20]. AST and ALT was elevated in 58.2% and 57.1% cases respectively which is similar to previous studies [16,21,22]. In our study, the levels of AST and ALP between different groups of disease severity was highly significant which is consistent with a previous report [15]. However, mean values of ALT and total bilirubin between different groups was statistically non-significant. This suggests AST and ALP values are indicative of severity of the disease and increase progressively with increasing severity. Highest AST and ALT observed in our study was 764 and 926 U/L respectively. AST and ALT of 1445 U/L and 7590 U/L respectively was reported in a Chinese retrospective study [20]. ALP was elevated in 37.9% cases in our study while ALP was elevated in 20% cases in a similar study [16]. 16.5% cases were diabetic and 15.4% cases were hypertensive in our study compared to 5.7% cases of diabetes and 14.3% cases of hypertension in a previous report [15].. Liver injury was seen in 64.3% cases of hypertension and 73.3% cases of diabetes in our study. In our centre, patients were mainly administered with antibiotics (Ceftriaxone, Azithromycin), antivirals (Favipiravir, Remdesivir), Low molecular weight heparin, steroids, symptomatic management with anti-pyretic (paracetamol) and oxygen support via oxygen mask, high flow nasal cannula and mechanical ventilatory support. Fan et al. suggested the use of Lopinavir-Ritonavir in covid-19 patients following admission as a possible cause for liver dysfunction [18] which was not the case in our study. At present, there is no standardised definition or criteria for covid-19 related liver injury. In-depth study and further studies are warranted to define covid-19-induced liver injury to guide proper care and management.

Our study has some limitations. Firstly, it is a single centre, cross-sectional study. The levels of biochemical parameters were recorded at the time of admission. Serial measurements can help to draw better conclusions. Secondly, GGT and albumin levels were not investigated in our study. Thirdly, the association of other co-morbidities like diabetes, hypertension, coronary artery disease on the severity and prognosis of liver injury was not investigated.

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