Original Article

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Biochemistry Section

Impact of COVID-19 on Liver Enzymes: A Retrospective Study

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ABSTRACT

Introduction: The global pandemic of novel Coronavirus Disease-2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) has spread worldwide crippling the healthcare system. Besides the respiratory system, COVID-19 patients show signs of various degrees of liver damage, the mechanism and implication yet undeciphered. Hence, in this study, we aim to find out pattern and trend of derangement in liver functions in COVID-19 patients.

Aim: To depict the pattern and trend of liver enzymes in COVID-19 admitted patients without history of liver disease.

Materials and Methods: The study was conducted as a single centred, retrospective, observational study, from June 2020 till December 2020. It included 1909 admitted COVID-19 positive patients diagnosed via either nasopharyngeal or oropharyngeal swab by Real-Time Reverse Transcription-Polymerase Chain Reaction (RT-PCR). The COVID-19 positive patients were divided into four groups Group I: Age- 15-20 years; 150 patients, Group II: Age 21-40 years; 645 patients, Group III: Age 41-60 years; 560 patients, Group IV: Age >60 years; 554 patients. Abnormality in liver tests was defined as greater than three times of upper limit of normal reference range Alanine Transaminase (ALT) >120 U/L, Aspartate Transaminase (AST) >120 U/L as Hepatocellular injury, greater than two times of upper limit of normal reference range Alkaline Phosphatase (ALP) >250 U/L as Cholestatic Injury (CSI). The statistical analysis was done by the Statistical Package for Social Sciences (SPSS) version 25.0.

Results: It was found that with respect to ALT levels, males in age 21-60 years, whereas females in two extremes of age 15-20 and >60 years age were the most affected. Whereas, females in age group <40 years were more affected with higher AST activity. With respect to abnormal ALP levels female in age group <40 years were most affected but males were most affected in age group >40 years.

Conclusion: Irrespective of age and gender, abnormality in liver enzymes was observed. Liver Function Tests (LFT) are a part of routine investigations carried out at the time of admission; its abnormalities may guide us in devising strategy to prioritise patient management in correlation with inflammatory markers.

Keywords: Alanine transaminase, Alkaline phosphatase, Aspartate transaminase, Coronavirus disease-2019, Severe acute respiratory syndrome coronavirus-2

INTRODUCTION

The novel COVID-19 pandemic caused by SARS-CoV-2 began in Wuhan, China, in December 2019, and has ever since challenged the global health care system [1,2]. On March 11, 2020, the SARS-CoV-2 outbreak was declared as a pandemic by World Health Organisation (WHO) due to the ever-increasing number of cases outside China [3,4].

Despite tedious measures to constrain the disease, the number of cases has spiked around the world, both through increased detection and highly mutating viral spread. Therefore, it is quintessential to develop strategies to protect vulnerable population from SARS-CoV-2 related mortality and morbidity. The Centers for Disease Control and Prevention (CDC) has issued specific guidance for high risk persons, including patients with chronic liver diseases among many others [5].

It has been documented that SARS-CoV-2 shares genome sequence similarity to SARS-CoV (82%) and genome sequence homology (50%) to Middle East Respiratory Syndrome Coronavirus (MERS-CoV)- all three coronaviruses are known to cause severe respiratory symptoms. Liver impairment has been stated in up to 60% of patients with SARS [6,7]. Angiotensin Converting Enzyme-2 (ACE-2) receptor for SARS-CoV-2, has recently been implicated in causing 2019-nCoV infection. Although, the lung is the main target organ of SARS-CoV-2 infection, it can affect multiple organs. Liver being one of the vital organ and its exposure to the viral particles might be an added concern for COVID-19 patients [8,9].

Previous studies have reported substantial proportion of SARS-CoV-2 and COVID-19 patients have been affected by various degrees of liver damage, the mechanism and implication yet undeciphered [10-12]. Further, liver biopsy specimens from patients who died from COVID-19 showed moderate microvesicular steatosis, viral nucleic acid and damage indicating that SARS-CoV-2 may be the aetiological factor [13]. Studies have reported varied clinical features and laboratory test results associated with liver function impairment in patients with COVID-19 infection [14-21]. Hence, it necessitates the importance of studying pattern of liver function derangement which may be considerable risk factors of COVID-19 severity and mortality.

The present study was designed to assess pattern of liver enzymes in COVID-19 patients without any previous history of liver disease.

MATERIALS AND METHODS

A retrospective observational single centered study was conducted where the authors evaluated and analysed the liver function test results along with the medical history obtained from 1909 adult patients of both genders with confirmed COVID-19 from June 2020 to December 2020 admitted in ESIC MCH (Employee State Insurance Medical College and Hospital, Faridabad, Haryana, India. The present study is approved by Institutional Ethics Committee of ESIC Medical College and Hospital, Faridabad with reference number 134X/11/13/2021-IEC/16 dated 19.06.2021.

Inclusion and Exclusion criteria: All COVID-19 positive patients admitted in wards were included in the study. Patients suffering from chronic liver diseases, alcoholism, hepatitis, pregnant women were excluded from the study.

Study Procedures

The COVID-19 positive status was confirmed by RT-PCR analysis of oropharyngeal/nasal swab samples in the Department of

Microbiology, ESICMCH, Faridabad, Haryana, India, as per instructions given by Indian Council of Medical Research (ICMR), New Delhi, India.

Following standard operating procedures, the blood samples were handled by a designated technician with proper Personal Protective Equipment (PPE). The sample tubes were decontaminated by wiping and spraying with 0.1% hypochlorite solution. The samples were centrifuged for 10 minutes at 3500 Revolutions Per Minute (RPM) with the lid of the centrifuge closed for the next 15 minutes for the aerosols to settle down. The serum samples for liver function tests were analysed after maintaining proper quality control (VITROS XT 7600 Dry chemistry fully automated autoanalyser). All tests were performed according to standard protocols and procedures provided by VITROS XT 7600, Ortho Clinical Diagnostics company.

Liver function tests parameters and inflammatory markers: The normal values of liver function enzymes were considered as 10-40 IU/L for ALT and AST and between 30-125 IU/L for ALP. Abnormality in liver tests was defined as: ALT>40 U/L, AST>40 U/L, ALP>125 U/L at any given time point during the hospitalisation.

The COVID-19 is a new, evolving infectious disease where the liver injury classifications have not been visibly defined. Liver function impairment was classified as hepatocellular, cholestatic or mixed type. Hepatocellular impairment was defined in patients who had increased liver enzymes ALT and/or AST more than three times the upper limit unit of normal (ULN); CSI in patients with raised ALP more than two times the upper limit ULN [14].

STATISTICAL ANALYSIS

The statistical analysis was conducted by the SPSS version 25.0. All continuous variables were described as both mean and standard deviation as well as median and interquartile range depending upon distribution of data.

RESULTS

Recruited patients for study fulfilling the inclusion criteria were analysed for their liver function enzyme levels (ALT, AST, and ALP). Total 1909 patients were selected after fulfilment of criteria. Further, to elaborate the pattern of LFT parameters, COVID-19 positive patients were divided according into four groups- group I: 15-20 years age group; 150 participants, group II: 21-40 years age group; 645 participants, group III: 41-60 years age group, 560 participants, group IV: >60 years age group; 554 participants. The gender and age distribution for different liver enzymes are shown in [Table/Fig-1].

Age (yrs)	Total no. of patients	Mean age (years)	ALT (median value, IU/L)		AST (median value, IU/L)		ALP (median value, IU/L)	
			Males	Females	Males	Females	Males	Females
15-20	150.0	17±2.2	84.5	88.6	83.5	85.8	107.0	257.3
21-40	645.0	30±5.43	79.3	88.6	93.8	88.8	218.6	200.8
41-60	560.0	51.0±5.5	96.8	77.0	93.6	80.6	153.7	152.0
>60	554.0	69.7±6.8	92.3	88.3	94.5	120.0	162.1	189.5

[Table/Fig-1]: Showing demographic status of the patients with median values of AST, ALT and ALP.

In each group, parameters were divided according to normal and abnormal range of parameters. Mean along with median of all biochemical parameters in the four groups are also described in [Table/Fig-1-4].

Based on group I Age (15-20 Years), 150 patients of which 61 (40.7%), 25 (16.7%) and 73 (48.7%) patients had raised levels of AST, ALT and ALP, respectively during their hospitalisation. In these patients, the median values of AST, ALT, ALP were found to be 57.5 U/L, 60 U/L and 159.5 U/L, respectively, as compared to 30 U/L, 17.9 IU/L and 78.5 U/L, respectively, in patients with normal liver enzymes. Out of these 16 (10.7%), 10 (6.6%) of patients had abnormal liver enzyme levels higher than two times the ULN (AST, ALT) with median value of 173.5 U/L, 179 U/L, respectively and 25 (16.6%) had abnormal liver ALP (median value 308 U/L) enzyme levels higher than three times the ULN [Table/Fig-2].

In Group II (age 21-40 years, 645 patients) there were 232 (35.97%), 206 (31.9%) and 166 (25.74%) patients raised levels of AST, ALT and ALP respectively at any time point during their hospitalisation. In these patients, the median values of AST, ALT, ALP were found to be 57 U/L, 60 U/L and 165 U/L, respectively, as compared to 30 U/L, 20 U/L and 72 U/L, respectively, in patients with normal liver enzymes [Table/Fig-3]. It was also observed that 42 (6.5%), 63 (9.8%) of patients had abnormal liver enzyme levels greater than twice the ULN (AST, ALT) with median value of 168.6 U/L and,196 U/L respectively and 71 (11%) had abnormal liver ALP (median value 327 U/L) enzyme levels greater than three times the ULN [Table/Fig-3].

In group III (age 41-60 years, 560 patients) of which 266 (47.5%), 219 (39.1%) and 128 (22.9%) patients had raised levels of AST, ALT and ALP respectively at any time point during their hospitalisation. In these patients, the median values of AST, ALT, ALP were found to be 55 U/L, 59 U/L and 154 U/L respectively, as compared to 31 U/L, 24 U/L and 75 U/L, respectively, in patients with normal liver enzymes. A 35 (6.2%), 61 (10.9%) of patients had abnormal liver enzyme levels greater than twice the ULN (AST, ALT) with median value of 172,166U/L, respectively and 22 (3.9%) had abnormal liver ALP (median value 301 U/L) enzyme levels greater than three times the ULN [Table/Fig-4].

In group IV (age >60 years, 554 patients) of which 262 (47.2%), 184 (33.2%) and 121 (21.8%) patients had raised levels of AST, ALT and ALP, respectively, at any time point during their hospitalisation. In these patients, the median values of AST, ALT, ALP were found to be 57 U/L, 61U/L and 149 U/L respectively, as compared to 29U/L, 23 U/L and 78.0 U/L, respectively, in patients with normal liver enzymes. Out of these 48 (8.7%), 49 (8.8%) of patients had abnormal liver enzyme levels exceeding twice the ULN (AST, ALT) with median value of 177.5, 231.5 U/L, respectively and 15 (2.7%) had abnormal liver ALP (median value 420 U/L) enzyme levels greater than three times the ULN [Table/Fig-5]. An increasing trend in ALT, AST and ALP was seen with age with highest value median in group IV median values being 231.5 IU/L, 177.5 IU/L, 420 IU/L, respectively) compared to other groups.

Further liver enzymes were studied individually to see its pattern and distribution from the available data of ALT levels. ALT/Serum Glutamate Pyruvate Transaminase (SGPT): Irrespective of age groups, hepatocellular injury described by ALT >3 URL (>120 IU/L) was observed in groups I, II, III, and IV as 10 (6.6%), 63 (9.8%), 61 (10.9%), 49 (8.8%), respectively [Table/Fig-6]. It was more pronounced in males {39 (6.05%), 54 (9.64%)} compared to females {24 (3.72%), 7 (1.25%)} in group II and III. Whereas, more number of females were affected in extreme age groups, where group I had 6 (3.9%) affected females as compared to 4 (3.3%) affected males and group IV had 41 (7.4%) affected females as compared to 8 (1.4%) affected males [Table/Fig-7]. In a snapshot, males were the most affected between the age of 21-60 years, whereas in the two extremes of ages 15-20 and >60 years females were more affected than males. Moreover, according to age an increasing trend in ALT was seen with highest value median in group IV, 200 (150-362.5) IU/L in males and 276 (204.8-365.8) IU/L in females [Table/Fig-8].

The AST/Serum Glutamate Oxaloacetate Transaminase (SGOT): irrespective of age groups, hyepatocellular injury described by AST> 3URL (>120 IU/L) was observed in group I, II, III, IV as 16 (10.7%), 42 (6.5%), 35 (6.3%), 48 (8.7%), respectively [Table/Fig-9]. In age between 0-40 years the abnormality was more pronounced in females (22.7, 29.6% in I and II) compared to males (18%, 6.4%) whereas, it was more in males {194 (34.6%), 192 (34.7%) in III, IV

Parameters	Mean	SD	SEM	Median	Minimum	Maximum	Total no. of patients (N)	Patients (%)
AST normal	30.68	5.97	0.70	30.00	20.00	40.00	73	48.67
AST abnormal	62.25	17.50	2.12	57.50	41.00	114.00	61	40.67
AST HCI	184.56	70.99	17.75	173.50	124.00	401.00	16	10.67
ALT normal	20.73	8.69	0.79	17.92	6.00	40.00	115	76.6
ALT abnormal	62.19	16.07	3.21	60.00	42.00	97.00	25	16.6
ALT HCI	212.20	114.18	36.11	179.00	124.00	526.00	10	6.6
Alkaline phosphatase normal	78.13	24.30	3.25	78.50	15.10	120.00	52	34.67
Alkaline phosphatase abnormal	165.37	30.88	3.54	159.50	121.00	249.00	73	48.67
Alkaline phosphatase CSI	338.07	99.45	18.47	308.00	251.00	690.00	25	16.67

[Table/Fig-2]: Liver enzymes in group I (15-20 years; 150 patients).
ALT: Alanine transaminase; AST: Aspartate transaminase; ALT Normal (10-40 IU/L), ALT Abnormal (40-120 IU/L), ALT Hepatocellular injury (HCI) >120 IU/L, AST Normal (10-40 IU/L); AS Abnormal (40-120 IU/L); AST Hepatocellular injury (HCI) >125 IU/L; Alkaline phosphatase normal (30-125IU/L), Alkaline phosphatase abnormal (126-250IU/L), Alkaline phosphatase CSI (>250 IU/L); M: Male, F: Female; N: Total no. of patients; n: No of patients

Parameters	Mean	SD	SEM	Median	Minimum	Maximum	Total no. of patients (N)	Patients (%)
AST normal	29.19	6.11	0.32	30.00	6.00	40.00	371	57.52
AST abnormal	63.86	20.87	1.37	57.00	41.00	120.00	232	35.97
AST HCI	224.89	154.39	23.82	168.50	123.29	927.00	42	6.51
ALT normal	21.57	8.39	0.43	20.00	6.00	40.00	376	58.29
ALT abnormal	66.12	21.38	1.49	60.00	41.00	120.00	206	31.94
ALT HCI	241.55	144.69	18.23	196.00	121.00	714.00	63	9.77
Alkaline phosphatase normal	73.62	21.98	1.09	72.00	15.10	120.00	408	63.26
Alkaline phosphatase abnormal	172.02	36.58	2.84	165.00	121.00	250.00	166	25.74
Alkaline phosphatase CSI	364.74	115.71	13.93	327.00	254.00	816.00	71	11

[Table/Fig-3]: Liver enzymes in group II (21-40 years; 645 patients).

Parameters	Mean	SD	SEM	Median	Minimum	Maximum	Total no of patients (N)	Patients (%)
AST normal	30.21	6.27	0.39	31.00	13.00	40.00	259	46.25
AST abnormal	62.88	19.59	1.20	55.00	41.00	120.00	266	47.50
AST HCI	291.03	35.14	74.63	172.00	121.00	2636.00	35	6.25
ALT normal	24.08	8.34	0.50	24.00	6.00	40.00	280	50.00
ALT abnormal	65.42	19.91	1.35	59.00	41.00	115.00	219	39.11
ALT HCI	245.72	160.99	20.61	166.00	121.00	845.00	61	10.89
Alkaline phosphatase normal	75.70	22.50	1.11	75.00	18.15	120.00	410	73.21
Alkaline phosphatase abnormal	160.88	31.07	2.74	154.00	121.00	250.00	128	22.86
Alkaline Phosphatase CSI	375.64	189.91	40.49	301.50	251.00	1097.00	22	3.93

[Table/Fig-4]: Liver enzymes in age group III (41-60 years; 560 patients).

Parameters	Mean	SD	SEM	Median	Minimum	Maximum	Total no. of patients (N)	Patients (%)
AST Normal	29.68	5.96	0.38	29.00	12.00	40.00	244	44.04
AST Abnormal	62.75	19.77	1.22	57.00	41.00	120.00	262	47.2
AST HCI	224.33	117.22	16.92	177.50	122.00	650.00	48	8.66
ALT Normal	23.76	8.12	0.45	23.00	6.00	40.00	321	57.94
ALT Abnormal	66.81	20.94	1.54	61.00	41.00	116.00	184	33.21
ALT HCI	281.98	169.07	24.40	231.50	124.00	826.00	49	8.84
Alkaline phosphatase normal	77.63	22.72	1.11	78.00	20.00	120.00	418	75.45
Alkaline phosphatase abnormal	158.96	30.06	2.73	149.00	121.00	250.00	121	21.84
Alkaline phosphatase CSI	441.07	143.99	37.18	420.00	270.00	720.00	15	2.71

[Table/Fig-5]: Liver enzymes in group IV (>60 years; 554 patients).

Age (yrs)	No. of patients n (%)			Total no. of patients
	ALT Normal	ALT Abnormal	ALT Hepatocellular injury	
15-20	115 (76.7)	25 (16.7)	10 (6.6)	150
21-40	376 (58.3)	206 (31.9)	63 (9.8)	645
41-60	280 (50)	219 (39.1)	61 (10.9)	560
>60	321 (57.9)	184 (33.2)	49 (8.8)	554

[Table/Fig-6]: No. of COVID-19 patients in different age groups with normal, abnormal and hepatocellular injury based on ALT enzyme activity.

respectively} compared to females {72 (12.9%), 70 (12.6%) in III, IV respectively} in age >40 years [Table/Fig-10]. Overall, it was seen that females of age <40 years had higher median values of 177 (127.5-237) in group I and 180 (136-285) IU/L in group II females, whereas, they were 165 (133.8-194.8) in group I, and, 151 (130-224) IU/L in group II males) It was vice versa in males of age >40 years where the AST values for group I males were higher {184.5 (141-313.3) IU/L in group III and 187 (139.5-298.8) IU/L in group IV} when compared with AST values of females {152 (121.8-201) IU/L in group III and 181 (133.8-222.5) IU/L in group IV} [Table/Fig-11]. It

Age (yrs)	No. of patients male/female n (%)						M	F	Total
	ALT Normal M	ALT Normal F	ALT Abnormal M	ALT Abnormal F	ALT HCI M	ALT HCI F			
15-20	36 (24)	79 (52.67)	10 (6.67)	15 (10)	4 (2.7)	6 (4)	50	100	150
21-40	116 (17.98)	260 (40.31)	161 (24.96)	45 (6.98)	39 (6.05)	24 (3.7)	316	329	645
41-60	167 (29.82)	113 (20.18)	148 (26.43)	171 (30.5)	54 (9.64)	7 (1.25)	369	191	560
>60	112 (20.18)	209 (37.76)	44 (7.94)	140 (25.27)	8 (1.4)	41 (7.4)	164	390	554

[Table/Fig-7]: No of COVID-19 patients in different age groups and gender with normal, abnormal and hepatocellular injury based on ALT enzyme activity.

Age (yrs)	ALT Normal median (Q1-Q3) IU/L		ALT Abnormal median (Q1-Q3) IU/L		ALT HCI median (Q1-Q3) IU/L	
	M	F	M	F	M	F
15-20	18 (13-29)	17 (13-27)	54 (44.4-67)	61.5 (51.2-81.7)	178.5 (134-221.5)	179 (162.5-286)
21-40	23.5 (18-30)	18 (14-26)	61 (48-77.5)	59 (49-79)	197 (155-297)	189.5 (131-261.5)
41-60	26 (19-32)	21 (16-28)	60 (49-81)	56 (47.2-73.5)	195 (141-336)	165 (132-346)
>60	24 (17.7-30.2)	22 (17-28)	59.5 (47-75.5)	62 (50-82)	200 (150-362.5)	276 (204.8-365.8)

[Table/Fig-8]: ALT enzyme activity (IU/l) of COVID-19 patients in different age groups and gender.

Age (yrs)	No. of patients n (%)			Total no. of patients
	AST normal	AST abnormal	AST hepatocellular injury	
15-20	73 (48.6)	61 (40.7)	16 (10.7)	150
21-40	371 (57.5)	232 (36)	42 (6.5)	645
41-60	259 (46.2)	266 (47.5)	35 (6.3)	560
>60	244 (44)	262 (47.3)	48 (8.7)	554

[Table/Fig-9]: No. of COVID-19 patients (%) in different age groups with normal, abnormal and hepatocellular injury based on AST enzyme activity.

may be inferred that females of age <40 years were more affected with higher AST activity as compared to males and reverse was observed in age >40 years with more male predilection. According to age distribution, highest AST enzyme activity was similarly found in group IV {187 (139.5-298.8) IU/L, 181 (133.8-222.5) in both male and female, respectively} [Table/Fig-11].

Age (yrs)	No of patients M/F n (%)						Total
	ASTN M	ASTN F	AST abnormal M	AST abnormal F	AST HCI M	AST HCI F	
15-20	30 (20)	43 (28.7)	27 (18)	34 (22.7)	10 (6.7)	6 (4)	150
21-40	139 (21.6)	232 (36)	41 (6.4)	190 (29.6)	19 (3)	23 (3.6)	645
41-60	173 (30.9)	85 (15.2)	194 (34.6)	72 (12.9)	26 (4.6)	8 (1.4)	560
>60	158 (28.6)	85 (15.3)	192 (34.7)	70 (12.6)	36 (6.5)	12 (2.2)	554

[Table/Fig-10]: No of COVID-19 patients in different age groups and gender with normal, abnormal and hepatocellular injury based on AST enzyme activity (IU/L).

Age (yrs)	AST N median (Q1-Q3) IU/L		AST Ab median (Q1-Q3) IU/L		AST HCI median (Q1-Q3) IU/L	
	M	F	M	F	M	F
15-20	33 (27.7-36.2)	29 (24-35)	55.7 (49.2-72.5)	60 (48.2-71.7)	165 (133.8-194.8)	177 (127.5-237)
21-40	31 (27-36)	28 (23-33)	56 (46-74)	58 (48-78)	151 (130-224)	180 (136-285)
41-60	48 (27-36)	28 (23-34)	58 (48-80)	51 (44.5-65.2)	184.5 (141-313.3)	152 (121.8-201)
>60	30 (26-35)	29 (25-33.5)	60 (48-77)	55 (44-63.5)	187 (139.5-298.8)	181 (133.8-222.5)

[Table/Fig-11]: AST enzyme activity (IU/l) in COVID-19 patients of different age groups and gender.

Alkaline Phosphatase (ALP): The CSI defined by ALP activity >250 IU/L was observed in all age groups 25 (16.67%), 71 (11%), 22 (3.9%), 15 (2.7%) in group I, II, III, IV respectively [Table/Fig-12]. Abnormality in ALP as well as CSI was more in females compared to males in group I and II and more in males in group III and IV [Table/Fig-13]. Similarly, the median concentration of ALP was higher in females compared to males of age group <40 years, whereas, in the age group of >40 years it was more in males. In short, females in age group <40 years were most affected with CSI [Table/Fig-14]. However, males >40 years had to bear the brunt of CSI.

Age (yrs)	No. of patients M/F n (%)			Total no. of patients
	ALP normal n (%)	ALP abnormal n (%)	ALP CSI n (%)	
15-20	52 (34.6)	73 (48.6)	25 (16.67)	150
21-40	408 (63.3)	166 (25.8)	71 (11)	645
41-60	410 (73.2)	128 (22.9)	22 (3.9)	560
>60	418 (75.5)	121 (21.8)	15 (2.7)	554

[Table/Fig-12]: No of COVID-19 patients (%) in different age groups with normal, abnormal and Cholestatic Injury (CSI) based on ALP enzyme activity.

Age (yrs)	No. of patients M/F, n (%)						Total
	ALP Normal M	ALP Normal F	ALP Abnormal M	ALP Abnormal F	ALP CSI M	ALPCSI F	
15-20	18 (12)	34 (22.7)	28 (18.63)	45 (30)	12 (8)	13 (8.7)	150
21-40	281 (43.5)	127 (19.7)	35 (5.5)	130 (20.3)	14 (2.2)	58 (9)	645
41-60	293 (52.4)	121 (21.6)	112 (20)	12 (21.4)	16 (2.9)	6 (1.08)	560
>60	296 (53.3)	122 (22.1)	111 (20.1)	10 (1.8)	9 (1.7)	6 (1.07)	554

[Table/Fig-13]: No of COVID-19 patients in different age groups and gender with normal, abnormal, and Cholestatic Injury (CSI) based on ALP enzyme activity.

Age (yrs)	ALP N median (Q1-Q3), IU/L		ALP Ab median (Q1-Q3) IU/L		ALP CSI median (Q1-Q3) IU/L	
	M	F	M	F	M	F
15-20	81 (66.7-99.5)	156 (136.5-167)	74 (60.2-103.30	308 (271.8-380)	166 (147-191)	308 (287.1-347.5)
21-40	76 (61-95)	81 (63-100.5)	154 (135.5-191.5)	148 (135.9-169.5)	426 (289.5-589.5)	373.5 (370-377)
41-60	61 (28-76)	54 (18.1-72.5)	134.3 (121-154)	138 (126-156)	266 (251-318)	264 (251-274)
>60	61 (20-76)	63 (22-81)	135.9 (123-148)	135.5 (121-154)	289.5 (270-426)	370 (370-373.5)

[Table/Fig-14]: ALP enzyme activity (IU/L) of COVID-19 patients in different age groups and gender.

DISCUSSION

The present study was retrospectively carried out in COVID-19 positive patients admitted to ESIC MCH, Faridabad, Haryana, India. Irrespective of age and gender it affects all with great diversity. Patients included in the study were divided into four groups based on age 15-20, 21-40, 41-60, >60 years and a significant proportion of patients in all age groups had abnormal liver functions.

This suggests the presence of liver damage in patients with coronavirus infection irrespective of age. Earlier studies have reported similar findings, suggesting liver damage may be directly caused by the viral infection [22]. Studies have indicated that ACE-2

is the key receptor for the entry of SARS-CoV-2 into the cells and the direct binding of SARS-CoV-2 to ACE2 receptors in cholangiocytes might result in the liver damage [23].

In short, with respect to ALT levels, males were the most affected in age group 21-60 years, whereas in two extremes of age 15-20 and >60, females were more affected than males. Overall, it was observed that females of age <40 years were more affected with higher AST activity compared to males and reverse was observed in age >40 years with more male predilection. When compared to abnormal ALP levels, female in age group <40 years were most affected with CSI. However, males >40 years had to bear the brunt of CSI.

A different trend was observed in different age groups and gender and there were noticeably elevated AST, ALT and ALP enzyme activity. This differential predisposition in different age and gender could be attributed to the differential expression of ACE-2 receptors [24,25]. An increasing trend in liver enzymes was observed with increasing age, which was consistent with a previous report [26].

Similarly, in a study conducted in Chandigarh on 170 patients, 41.5% had normal liver enzymes, while with raised increased levels of any of the liver enzymes were 89 (52.3%), out of which 43 (48.31%) had liver injury [27]. Elevated levels of ALT and AST were noted in admitted COVID-19 cases but rise was less than two times the upper level of normal in Kolkata based study [28]. Kaushik A et al., in their study in Uttar Pradesh, India showed that 59.04% of admitted COVID-19 patients had abnormal LFT with elevated AST in 45.71% and elevated ALT in 25.71% [29]. A similar study from Pakistan by Asghar MS et al., found deranged values of LFT enzymes [30]. The prevalence of ALT elevations among patients with COVID-19 ranged averaged 19% in Chinese cohorts to 39% in New York city area [31,32]. The prevalence of AST elevations ranged average: 21% to 58% in the US cohort [33]. However, ALT, AST elevations were less than five times the upper reference limit. Elevated ALP was reported in 2-5% of patients [34,35].

Liver function tests are a part of routine array of tests carried at the time of admission, test abnormalities could, therefore play integral role in predicting the severity of the disease in correlation with inflammatory markers. Elevated ALT and AST levels were reported in patients irrespective of age and gender. Despite liver dysfunction being mild, transient, not clinically significant, patients with abnormal liver test of hepatocellular/cholestatic type or mixed type may predispose to higher risk of progressing to severe disease in absence of proper intervention.

Liver injury leading to abnormality in liver enzymes may be explained by different theories. The SARS-CoV-2 virus uses the ACE-2 as a means for cell entry ACE2 receptors are present mainly in cholangiocytes which could act as route of direct viral entry leading to derangement. The cause of the liver injury is yet undeciphered, but probably it could be a synergism of cytokine storm, immune dysregulation, hypoxia, hypotension, endothelitis, microtrombitis drugs, direct viral effect, and other hospital acquired infections. Further various other factors still unknown may also play a role in causing injury of hepatocytes and cholangiocytes leading to different patterns of liver injury in different age and genders in diverse population [35].

The COVID-19 is having a major impact on clinical practice and patient care worldwide. Therefore, it is eminent to focus on the care of patients with abnormal liver enzymes if not may lead to adverse scenario. Further research should be planned to delineate the exact mechanism leading to liver injury in COVID-19 affected patients to minimise liver injury. It is affected by different factors in different regions, states, countries and between continents. Collection of information from all diversities is crucial to understand aetiology and pathogenesis of this heterogenous infection.

Limitation(s)

Firstly, it was a retrospective study carried out from retrieved data obtained from laboratory record. Secondly, first-hand information directly from patient of history of any medications was not available. Thirdly, in present study it was planned to determine the association between COVID-19 and abnormal liver function but did not involve the follow-up of the patient and correlation with inflammatory markers. Therefore, further studies are need of the hour to decipher the pathogenesis of liver injury caused due to COVID-19 disease and its association with other inflammatory markers.

CONCLUSION(S)

Liver enzymes levels tested as a part of routine investigations are altered in COVID-19 patients. Although, the altered liver enzyme levels may not lead to an emergency, the findings of this study suggests monitoring liver functions in order to avoid liver injury at later stages. Therefore, further large scale future, prospective studies from different population cohort should be conducted to study the heterogeneity of COVID-19 to study the impact of liver impairment in patients of different age, gender, and ethnicity to explore the causal association.

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