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Original Article

Elevated Liver Enzymes along with Comorbidity Is a High Risk Factor for COVID-19 Mortality: A South Indian Study on 1,512 Patients

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Abstract

Background and Aims: Liver enzyme abnormalities in coronavirus 2019 (COVID-19) are being addressed in the literature. The predictive risk of elevated liver enzymes has not been established for COVID-19 mortality. In this study, we hypothesized that elevated liver enzymes at admission can predict the outcome of COVID-19 disease with other known indicators, such as comorbidities. ***Methods:*** This retrospective study included all the consecutive hospitalized patients with confirmed COVID-19 disease from March 4th to May 31st, 2020. The study was conducted in Rajiv Gandhi Government General Hospital, Chennai, Tamil Nadu, India. We assessed demography, clinical variables, COVID-19 severity, laboratory parameters, and outcome. ***Results:*** We included 1,512 patients, and median age was 47 years (interquartile range: 34–60) with 36.9% being female. Liver enzyme level (aspartate aminotransferase and/or alanine aminotransferase) was elevated in 450/1,512 (29.76%) patients. Comorbidity was present in 713/1,512 (47.16%) patients. Patients with liver enzymes' elevation and presence of comorbidity were older, more frequently hospitalized in ICU and had more severe symptoms of COVID-19 at the time of admission. Presence of liver enzymes' elevation with comorbidity was a high risk factor for death (OR: 5.314, 95% CI: 2.278–12.393), as compared to patients with presence of comorbidity (OR: 4.096, 95% CI: 1.833–9.157). ***Conclusions:*** Comorbidity combined with liver enzymes' elevation at presentation independently increased the risk of death in COVID-19 by at least 5-fold.

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Keywords: COVID-19; SARS-CoV-2; Liver enzyme; Comorbidity; Aspartate aminotransferase; Alanine aminotransferase.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; CI, confidence interval; CK, creatine kinase; CK-MB, creatine kinase myocardial band; CoV, coronavirus; COVID-19, coronavirus 2019; CRP, C-reactive protein; CT, computed tomography; ICU, intensive care unit; IQR, interquartile range; LDH, lactate dehydrogenase; MERS, middle east respiratory syndrome; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio; PCV, packed cell volume; PR, pulse rate; RBC, red blood cell; RR, respiratory rate; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SpO_2, oxygen saturation; TGL-C, triglyceride cholesterol; WBC, white blood cell.

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Introduction

Coronaviruses (CoVs) are a family of viruses that are known to cause both respiratory and intestinal diseases in various animal species and humans.[1] The viruses are known to cause upper respiratory and lower respiratory tract infections, ranging from mild illnesses such as sore throat to severe pneumonia, leading to acute respiratory distress syndrome (ARDS), respiratory failure and death. To date, seven human coronaviruses have been identified, including the three epidemic viruses of severe acute respiratory syndrome (SARS)-CoV, middle east respiratory syndrome (MERS)-CoV and the newest, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[2] These three epidemic viruses have similar sequence identity, sharing more than 50% of genome sequences.[3] In December 2019, there was an outbreak of pneumonia of unknown origin in the Central city of Wuhan, which rapidly spread to other parts of the world, leading to 44,888,869 cases and 1,178,475 deaths globally as of October 30, 2020.[4] The World Health Organization labelled COVID-19 as a pandemic by March 2020. While most COVID-19 cases have been identified as mild, more extreme manifestations have led to respiratory failure, septic shock, and/or multiple organ dysfunctions.[5]

A number of reports have shown that COVID-19 patients have liver enzyme abnormalities.[6] Our study aimed to determine the liver enzyme abnormality in patients with COVID-19 at the time of hospital admission and to evaluate the outcome of such patients. To our knowledge, this is the first study that analyzes the association of mortality and patients with liver enzyme elevation and comorbidity in Indian COVID-19 subjects.

Methods

The study was designed as a retrospective analysis of data collected from consecutive patients with COVID-19 admitted to the Rajiv Gandhi Government Hospital, Chennai, Tamil Nadu, India. The study period was from 4th March to 31st May 2020. Patients with COVID-19 admitted in the hospital were included in the study. Diagnosis of COVID-19 was confirmed by detection of SARS-CoV-2 RNA from nasopharyngeal/throat swabs using real-time reverse transcription-polymerase chain reaction. The study was approved by the institutional ethics committee of the Madras Medical College, Chennai, India.

Data collection

Demographics, clinical characteristics, laboratory findings, and radiography findings were collected from the medical records of the Community Medicine Department, Internal Medicine Department, pathology laboratory, biochemical laboratory, and Radiology Department by the Multidisciplinary Research Unit, Madras Medical College. The patient outcomes (discharge or death) were also collected for this analysis. Any uncertain or missing records were clarified and obtained by direct communication with patients and their families.

Biochemical and hematological parameters studied were complete blood count with differential count, white blood cell (WBC), red blood cell (RBC), hemoglobin, neutrophil-to-lymphocyte ratio (NLR), blood glucose, liver function test, and kidney function test. Markers of acute phase reaction proteins, such as lactate dehydrogenase (LDH), ferritin and C-reactive protein (CRP), were also collected. Creatine kinase (CK) and creatine kinase myocardial band (CK-MB) were also studied from the time of admission.

Clinical severity definitions

The clinical classification of COVID-19 was based on the Indian Ministry of Health and Family Welfare.[7] Mild type was defined as without evidence of breathlessness or hypoxia (normal saturation). Moderate type was defined as a patient with pneumonia, without signs of severe disease and presence of clinical features of dyspnea and or hypoxia, fever, cough, including peripheral oxygen saturation (SpO_2) <94% (range: 90–94%) on room air, respiratory rate (RR) more or equal to 24 per minute; fast breathing (in breaths/m) < 2 months was ≥60, for 2–11 months was ≥50 and for 1–5 years was ≥40. Severe type was defined as patients with clinical signs of pneumonia plus one of the following: respiratory rate >30 breaths/m, severe respiratory distress, or SpO_2 <90% on room air. We graded severity of pneumonia based on computed tomography (CT) scan imaging of chest as percentage of total lung volume involved, with <25 as Grade 1, 25–50% as Grade 2, 51–75% as Grade 3, and >75% as Grade 4.

Inclusion criteria

All patients with COVID-19 diagnosed with swab test irrespective of age, and gender.

Patients were followed from the time of hospital admission till their death or discharge.

Exclusion criteria

Patients were excluded if they had preexisting liver diseases or liver enzyme abnormalities.

Definitions

Abnormal/elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) was defined by taking the reference upper limit of normal as defined in male (ALT: 37 IU/L, AST: 41 IU/L) and in female (ALT: 37 IU/L, AST: 35 IU/L).[8] Other test abnormalities were defined as the following reference: WBCs <3,800 or >11,000 cells/mm^3; RBCs in male <4.2 or >5.6 (×10^6/μL) and in female <3.8 or >5.1 (×10^6/μL); hemoglobin in male <14 or >18 g/dL and in female <11 or >16 g/dL; packed cell volume (PCV) in male <40 or >52% and in female <35 or >47%; platelets <1.40 or <4.5 (×10^6/μL); neutrophils <50 or >81%; lymphocytes <14 or >44%; NLR <1 or >3; glucose (Random Blood Sugar) >140 mg/dL; urea <15 or >40 mg/dL; creatinine <0.5 or >1.3 mg/dL; sodium <136 or >146 m.eq/L; potassium <3.5 or >5.0 m.eq/L; triglyceride cholesterol (TGL-C) <40 or >170 mg/dL; CK <20 or >200 IU/L; CK MB <5 or >25 IU/L; LDH <125 or >220 IU/L; ferritin >400 ng/mL; CRP >10 mg/L; total bilirubin <0.3 or >1.3 mg/dL; direct bilirubin <0.0 or >0.4 mg/dL; total protein <6.5 or >8 g/dL; albumin <3.5 or >5.0 g/dL; alkaline phosphatase <32 or >110 U/L; pulse rate (PR) <60 or >100 beats/min; respiratory rate (RR) <14 or > 24 breaths per minute; saturation (SpO_2) <94%. We graded severity of pneumonia based on computed tomography (CT) scan imaging of chest as percentage of total lung volume involved <25 as Grade 1, 25–50% as Grade 2, 51–75% as Grade 3, and >75% as Grade 4.

Results

Among 1,512 COVID-19 patients, 450 (29.76%) had elevated liver enzyme and 1,062 (70.24%) had normal range. The clinical characteristics of the patients were grouped based on discharged or death and presented in Table 1. Clinical characteristics and outcomes of COVID-19 stratified by elevated liver enzyme and comorbidity are presented in Table 2. To further understand the pattern of liver enzyme elevation, we classified these biomarkers into three distinct subtypes, such as AST elevation, ALT elevation, and both AST and ALT elevation, which showed a significant difference among survivors and non-survivors (Table 3).

Age group

In the study population, of 1,512 cases, the median age was 47 years (IQR: 34–60 years) and 63.1% cases were male. Compared to survivors, non-survivors were significantly older (44 years [IQR: 33-49] vs. median age 56 years [IQR: 52-73], $p<0.001$) and were more likely to have underlying comorbid illness with elevated liver enzyme. A majority of non-survivors (66/73) were in the more than 40 years of age group (Table 1). In the study population, patients with age >40 years were more likely to have elevated liver enzyme (127/992), comorbidity (398/992), and elevated liver enzyme with comorbidity (208/992), as compared to the younger age population (<40 years) ($p>0.0001$), as shown in the Table 2. It was also observed that, AST or ALT elevation was more common in the age group >40 years ($p>0.0001$), as shown in the Table 3.

Gender distribution

More than half of non-survivors were male (64.4%). However, mortality was not significantly different between genders ($p>0.815$). Males with elevated liver enzyme num-

Table 1. Characteristics of 1,512 patients with COVID-19 at admission grouped by survival

Characteristics		Total, *n* (%)	Discharged, *n* (%)	Death, *n* (%)	*p* value[a]
Age in years	<18	47 (3.1)	47 (3.3)	0 (0)	0.0001
	18–29	229 (15.1)	227 (15.8)	2 (2.7)	
	30–39	244 (16.1)	239 (16.6)	5 (6.8)	
	40–49	298 (19.7)	288 (20)	10 (13.7)	
	50–59	300 (19.8)	284 (19.7)	16 (21.9)	
	>60	394 (26.1)	354 (24.6)	40 (54.8)	
Gender	Male	954 (63.1)	907 (63)	47 (64.4)	0.815
	Female	558 (36.9)	532 (37)	26 (35.6)	
Chest CT	Normal	664 (43.9)	647 (45)	17 (23.3)	0.0001
	Abnormal	848 (56.1)	792 (55)	56 (76.7)	
Chest CT grade	Grade 1	465 (30.8)	450 (31.3)	15 (20.5)	0.0001
	Grade 2	248 (16.4)	234 (16.3)	14 (19.2)	
	Grade 3	105 (6.9)	89 (6.2)	16 (21.9)	
	Grade 4	30 (2)	19 (1.3)	11 (15.1)	
	Normal	664 (43.9)	647 (45)	17 (23.3)	
Symptoms	Absent	681 (45)	668 (46.4)	13 (17.8)	0.0001
	Present	831 (55)	771 (53.6)	60 (82.2)	
Disease severity	Asymptomatic/Mild	729 (48.2)	723 (50.2)	6 (8.2)	0.0001
	Moderate	373 (24.7)	358 (24.7)	15 (20.5)	
	Severe	410 (27.1)	358 (27.1)	52 (71.2)	
ICU	Not admitted	1,029 (68.1)	1,015 (70.5)	14 (19.2)	0.0001
	Admitted	483 (31.9)	424 (29.5)	59 (80.8)	
WBCs	Normal	1,186 (78.4)	1,154 (80.2)	32 (43.8)	0.0001
	Abnormal	326 (21.6)	285 (19.8)	41 (56.2)	
RBCs	Normal	1,154 (76.3)	1,106 (76.9)	48 (65.8)	0.029
	Abnormal	358 (23.7)	333 (23.1)	25 (34.2)	
Hemoglobin	Normal	887 (58.7)	853 (59.3)	34 (46.6)	0.032
	Abnormal	625 (41.3)	586 (40.7)	39 (53.4)	
PCV	Normal	929 (61.4)	894 (62.1)	35 (47.9)	0.015
	Abnormal	583 (38.6)	545 (37.9)	38 (52.1)	
Platelets	Normal	1,303 (86.2)	1,242 (86.3)	61 (83.6)	0.507
	Abnormal	209 (13.8)	197 (13.7)	12 (16.4)	
Neutrophils	Normal	1,072 (70.9)	1,026 (71.3)	46 (63)	0.128
	Abnormal	440 (29.1)	413 (28.7)	27 (37)	
Lymphocytes	Normal	1,133 (74.9)	1,094 (76)	39 (53.4)	0.0001
	Abnormal	379 (25.1)	345 (24)	34 (46.6)	
NLR	Normal	907 (60)	879 (61.1)	28 (38.4)	0.0001
	Abnormal	605 (40)	560 (38.9)	45 (61.6)	
Glucose	Normal	567 (37.5)	545 (37.9)	22 (30.1)	0.183
	Abnormal	945 (62.5)	894 (62.1)	51 (69.9)	
Urea	Normal	971 (64.2)	937 (65.1)	34 (46.6)	0.001
	Abnormal	541 (35.8)	502 (34.9)	39 (53.4)	

(continued)

Table 1. *(continued)*

Characteristics		Total, *n* (%)	Discharged, *n* (%)	Death, *n* (%)	*p* value[a]
Creatinine	Normal	1,348 (89.2)	1,286 (89.4)	62 (84.9)	0.234
	Abnormal	164 (10.8)	153 (10.6)	11 (15.1)	
Sodium	Normal	911 (70.5)	872 (70.7)	39 (66.1)	0.453
	Abnormal	382 (29.5)	362 (29.3)	20 (33.9)	
Potassium	Normal	838 (65.3)	802 (65.4)	36 (62.1)	0.601
	Abnormal	446 (34.7)	424 (34.6)	22 (37.9)	
TGL-C	Normal	1,156 (76.5)	1,093 (76)	63 (86.3)	0.042
	Abnormal	356 (23.5)	346 (24)	10 (13.7)	
CK	Normal	663 (67.4)	640 (68)	23 (53.5)	0.047
	Abnormal	321 (32.6)	301 (32)	20 (46.5)	
CK-MB	Normal	1,145 (75.7)	1,097 (76.2)	48 (65.8)	0.042
	Abnormal	367 (24.3)	342 (23.8)	25 (34.2)	
LDH	Normal	390 (33.2)	386 (34.5)	4 (7.3)	0.0001
	Abnormal	783 (66.8)	732 (65.5)	51 (92.7)	
Ferritin	Normal	774 (65)	749 (66)	25 (45.5)	0.002
	Abnormal	416 (35)	386 (34)	30 (54.5)	
CRP	Normal	558 (46.7)	550 (48.3)	8 (14.3)	0.0001
	Abnormal	637 (53.3)	589 (51.7)	48 (85.7)	
Total bilirubin	Normal	1,437 (95)	1,368 (95.1)	69 (94.5)	0.834
	Abnormal	75 (5)	71 (4.9)	4 (5.5)	
Direct bilirubin	Normal	1,370 (90.6)	1,307 (90.8)	63 (86.3)	0.196
	Abnormal	142 (9.4)	132 (9.2)	10 (13.7)	
Total protein	Normal	1,037 (97.6)	993 (97.6)	44 (97.8)	0.952
	Abnormal	25 (2.4)	24 (2.4)	1 (2.2)	
Albumin	Normal	1,223 (80.9)	1,173 (81.5)	50 (68.5)	0.006
	Abnormal	289 (19.1)	266 (18.5)	23 (31.5)	
AST	Normal	1,198 (79.2)	1,153 (80.1)	45 (61.6)	0.0001
	Abnormal	314 (20.8)	286 (19.9)	28 (38.4)	
ALT	Normal	1,166 (77.1)	1,112 (77.3)	54 (74)	0.512
	Abnormal	346 (22.9)	327 (22.7)	19 (26)	
ALP	Normal	763 (80.9)	736 (81.6)	27 (65.9)	0.012
	Abnormal	180 (19.1)	166 (18.4)	14 (34.1)	
PR	Normal	1,385 (91.6)	1,331 (92.5)	54 (74)	0.0001
	Abnormal	127 (8.4)	108 (7.5)	19 (26)	
RR	Normal	972 (64.3)	940 (65.3)	32 (43.8)	0.0001
	Abnormal	540 (35.7)	499 (34.7)	41 (56.2)	
SpO_2	Normal	1,389 (91.9)	1,348 (93.7)	41 (56.2)	0.0001
	Abnormal	123 (8.1)	91 (6.3)	32 (43.8)	

[a]Chi square test.

bered 291/450 (64.7%) and females numbered 159/450 (35.3%). Gender-wise distribution of AST/ALT elevation also had not significantly differed ($p>0.725$). The analysis of gender-wise distribution of liver enzyme elevation and comorbidity was statistically significant. It was observed that males had high liver enzyme elevation (63.8%) and comorbidity (56.5%), and males also had both elevated liver enzyme and comorbidity (65.4%).

Table 2. Characteristics of 1,512 patients with COVID-19 at admission grouped by comorbidity and liver function test

Characteristics		Absence of comorbidity and normal level of liver enzyme (*n*=586)	Elevated liver enzyme (*n*=213)	Presence of comorbidity (*n*=476)	Elevated liver enzyme with presence of comorbidity (*n*=237)	*p* value[a]
Age in years	<40 (*n*=520)	327 (55.8)	86 (40.4)	78 (16.4)	29 (12.2)	0.0001
	>40 (*n*=992)	259 (44.2)	127 (59.6)	398 (83.6)	208 (87.8)	
Gender	Male	394 (67.2)	136 (63.8)	269 (56.5)	155 (65.4)	0.003
	Female	192 (32.8)	77 (36.2)	207 (43.5)	82 (34.6)	
Chest CT	Normal	362 (61.8)	80 (37.6)	151 (31.7)	71 (30)	0.0001
	Abnormal	224 (38.2)	133 (62.4)	325 (68.3)	166 (70)	
Symptoms	Absent	324 (55.3)	103 (48.4)	174 (36.6)	80 (33.8)	0.0001
	Present	262 (44.7)	110 (51.6)	302 (63.4)	157 (66.2)	
Disease severity	Asymptomatic/Mild	408 (69.6)	110 (51.6)	146 (30.7)	65 (27.4)	0.0001
	Moderate	104 (17.7)	51 (23.9)	149 (31.3)	69 (29.1)	
	Severe	74 (12.6)	52 (24.4)	181 (38)	103 (43.5)	
ICU	Not Admitted	480 (81.9)	135 (63.4)	302 (63.4)	112 (47.3)	0.0001
	Admitted	106 (18.1)	78 (36.6)	174 (36.6)	125 (52.7)	
Outcome	Discharged	578 (98.6)	206 (96.7)	441 (92.6)	214 (90.3)	0.0001
	Death	8 (1.4)	7 (3.3)	35 (7.4)	23 (9.7)	

[a]Chi-square test.

Comorbidity

The occurrence of comorbidities was: cardiovascular diseases including hypertension (180/713, 25.2%); diabetes (171/713, 24%); diabetes with hypertension (133/713, 18.7%); chronic kidney diseases (80/713, 11.2%); cancer (44/713, 6.2%); respiratory disease (34/713, 4.8%); and others (71/713, 10%). In the study population, mortality of patients with pre-existing comorbid illness with elevated liver enzyme was high at 23/73 (9.7%) when compared to patients with comorbidity alone (7.4%), patients with liver enzyme elevation alone (3.3%) or patients without liver enzyme elevation and comorbidity (1.4%). Patients with comorbidity and liver enzyme

Table 3. Elevated liver enzyme and its association with characteristics of patients with COVID-19

Characteristics		COVID-19 patients with elevated liver enzyme			Total	P value[a]
		AST (*n*=103, 22.9%)	ALT (*n*=135, 30.0%)	AST and ALT (*n*=212, 47.1%)	*n*=450	
Age in years	<40	21 (20.4%)	53 (39.3%)	41 (19.3%)	115 (25.6%)	0.0001
	>40	82 (79.6%)	82 (60.7%)	171 (80.7%)	335 (74.4%)	
Gender	Male	65 (63.1%)	91(67.4%)	135 (63.7%)	291 (64.7%)	0.725
	Female	38 (36.9%)	44 (32.6%)	77 (36.3%)	159 (35.3%)	
Chest CT	Normal	29 (28.2%)	64 (47.4%)	58 (27.4%)	151 (33.6%)	0.0001
	Abnormal	74 (71.8%)	71(52.76%)	154 (72.6%)	299 (66.4%)	
Symptoms	Absent	37(35.9)	58 (43)	76 (35.8)	171 (38)	0.365
	Present	66 (64.1)	77 (57)	136 (64.2)	279 (62)	
Disease severity	Asymptomatic/Mild	35 (34.0%)	67 (49.6%)	73 (34.4%)	175 (38.9%)	0.030
	Moderate	28 (27.2%)	34 (25.2%)	58 (27.4%)	120 (26.7%)	
	Severe	40 (38.8%)	34 (25.2%)	81 (38.2%)	155 (34.4%)	
ICU	Not admitted	53 (51.5%)	97 (71.9%)	97 (45.8%)	247 (54.9%)	0.0001
	Admitted	50 (48.5%)	38 (28.1%)	115 (54.2%)	203 (45.1%)	
Outcome	Death	11 (10.7%)	2 (1.5%)	17 (8%)	30 (6.7%)	0.001
	Discharged	92 (89.3%)	133 (98.5%)	195 (92%)	420 (93.3%)	

[a]Chi-square test.

Table 4. Multivariate analysis of elevated liver enzyme and comorbidity with COVID-19 mortality (age, gender adjusted)

Characteristics	OR	95% CI for EXP(B)		*p* value
Normal level of liver enzyme and absence of comorbidity			*R*	
Liver enzyme elevated	2.125	0.756	5.974	0.153
Presence of comorbidity	4.096	1.833	9.157	0.001
Liver enzyme elevated with presence of comorbidity	5.314	2.278	12.393	0.0001

elevation had higher mortality than patients without.

Symptoms

Non-survivors were more likely to have symptoms than survivors ($p<0.0001$). Among symptomatic patients, the most common symptom is respiratory distress (33.6%), followed by fever with cough (9.6%), fever (6.9%), cough (4.7%), and other symptoms (2.7%). Symptomatic patients were more likely to have comorbidity with elevated liver enzyme (66.2%), with comorbid illness (63.4%), and with elevated liver enzyme (51.6%), as compared to patients without liver enzyme elevation or comorbidity (44.7%) ($p<0.0001$). Subgroup analysis of liver enzyme elevation did not find any statistically significant difference between the three groups.

Laboratory and clinical parameters

Various laboratory parameters and clinical parameters were assessed to study the association with outcome (discharge/death). Non-survivors had significantly higher median levels of AST (42.5 [31.25–70.25]) and ALT (32.5 [27.75–48.25]) than AST (26 [19–40]) and ALT (21 [14–34]) of survivors. The laboratory parameters such as WBC and RBC counts, hemoglobin, TGL-C, NLR, blood urea, CK-myoglobin fraction, ferritin, LDH, CRP and ALP were elevated in the poorer outcome group. Patients with lower serum albumin and lymphocyte count also had higher mortality. As shown in the Table 1, abnormal clinical parameters such as pulse rate (<60 or >100 beats/m), respiratory rate (<14 or >24 breaths per m) and low saturation (<94%) at the time of admission correlated with mortality.

Chest CT

On admission, lung involvement was more common in non-survivors than survivors (76.7% vs. 55%, $p=0.001$) (Table 1). The total severity CT grade was significantly higher in the non-survivor group than the survivor group ($p<0.0001$). By further characterizing the patients based on severity of lung involvement in non-survivors, Grade 1 was in 15/73 (20.5%), Grade 2 in 14/73 (19.2%), Grade 3 in 16/73 (21.9%) and Grade 4 in 11/73 (15.1%), suggesting severe lung involvement was common among non-survivors. A high frequency of patients [166/237 (70%)] had both elevated liver enzyme and comorbidity with abnormal chest CT than did patients with comorbidity 325/476 (68.3%) or liver enzyme elevation 133/213 (62.4%). Patients with abnormal chest CT had both AST and ALT elevated [154/212 (72.6%)] or AST elevated [74/103 (71.8%)] numbered more than patients with ALT elevated [71/135 (52.76%)].

Disease severity

Symptomatic patients with severe illness at the time of hospital admission had higher mortality ($p<0.0001$). A higher percentage of severe-symptom patients [103 (43.5%)] had elevated liver enzyme and presence of comorbidity than patients with comorbidity alone [181 (38%)] or liver enzyme elevation alone [52 (24.4%)]. Among patients with mild disease, 34% had elevated AST, 49.6% had elevated ALT, and 34.4% had both enzymes elevated. Among patients with moderate disease, 27.2% had elevated AST, 25.2% had elevated ALT, and 27.4% had both enzymes elevated. Whereas, among patients with severe disease, 38.8% had elevated AST, 25.2% had ALT elevation, and 38.2% had both enzymes elevated. Patients with severe disease had higher prevalence of both AST and ALT elevated or AST alone elevated than did those with ALT alone elevated ($p<0.030$).

Intensive care unit (ICU) admission

Most non-survivors were admitted to the ICU (80.8%). Patients with liver enzyme elevation and comorbidity were more frequently admitted to ICU (52.7%), while 47.3% of patients were managed in wards without ICU admission (54.9%). On further analysis, among patients who required ICU admission, 54.2% had both AST/ALT elevated and 48.5% had AST elevated.

Clinical outcome

AST/ALT subgroups showed a statistically significant difference between the groups for mortality. Patients with AST elevation [11/30 (10.7%)] or both AST and ALT [17/30 (8%)] elevation had higher mortality than those with only ALT elevation [2/30 (1.5%)]. Multiple variable logistic regression was assessed for poorer outcome (death). Compared with COVID-19 patients with presence of comorbidity (OR: 4.096; 95% CI: 1.833–9.157), patients with liver enzyme elevations and presence of comorbidity had higher observed death risk (OR: 5.314; 95% CI: 2.278–12.393) (Table 4).

Discussion

In this study, clinical and laboratory parameters of 1,512 patients with COVID-19 were analyzed. We found that over 95% of the COVID-19 patients in the study population survived. Non-survivors with confirmed COVID-19 were older than 40 years of age and more likely to have elevated liver enzyme with comorbidity, compared to liver enzyme elevation or comorbidity alone. Consistent with findings reported by other authors, increased age was associated with mortality.[9] It is postulated that the SARS-CoV-2 takes advantage of the natural decline in immunity in individuals with increasing age to cause severe and fatal infection. However, our study showed that age >40 years is associated with increased risk ($p<0.0001$). This warrants aggressive protective strategies for all persons >40 years of age to limit exposure, as active infection in such patients carries a very

poor prognosis, at least for now, until a safe vaccine is developed and fully available. In this study, more than 67% (484/713) of patients had diabetes and/cardiovascular diseases as a common underlying comorbid illness. Meanwhile, a greater number of non-survivors had higher WBC count, neutrophils, NLR, and lower lymphocyte and platelet levels. This is consistent with previous findings that indicated severe patients with COVID-19 display higher neutrophil count and NLR, and lower lymphocyte count during the period of diseases.[10–12] Elevated ALP is rare and has less commonly been observed among the COVID-19 liver injury patients.[13] However, interestingly, our analysis found elevated ALP levels to be associated with mortality. The elevated clinical parameters such as PR, RR and decreased saturation at the time of admission were significantly associated with increased mortality. In this study, we observed that severely ill patients were more likely to die compared with the non-severe patients and that more than 71% (52/73) non-survivors were severely ill at the time of admission.

Liver enzyme abnormality is common in patients with COVID-19 at the time of hospital admission. We found that 450/1,512 (29.76%) had elevated liver enzyme. Our study showed that both AST and ALT represented the most frequently elevated pattern [212 (47.1%) of 450 patients], followed by ALT alone [135 (30%) of 450 patients] and AST alone [103 (22.9%) of 450 patients]. AST and ALT (both together) were elevated in 212/1,512 (14%) of patients at the time of hospital admission, as compared to the findings of many studies in which AST was found to be more frequently elevated than ALT.[14–16] Additionally, symptomatic patients were more likely to have elevated liver enzyme (62%) at the time of hospital admission. The most common symptoms were respiratory distress, followed by cough and fever. In the present study, patients with lung involvement were more likely to have elevated liver enzyme at the time of presentation (66.4%, 299/450). Information regarding potential risks of severe conditions in COVID-19 associated with each type of liver enzyme elevation were calculated. Elevation of AST alone or ALT and AST (both together) was much more common in patients with severe disease than in patients with mild or moderate infection ($p<0.030$). Previous studies by Zhang *et al*.[17] and Huang *et al*.[18] also showed that liver enzyme abnormality was more common in patients with severe disease. A recently published meta-analysis reported pooled risk of AST elevation (OR: 3.4, 95% CI: 2.3–5.1) and risk of ALT elevation (OR: 2.8, 95% CI: 1.8–4.3) of severe COVID-19 patients.[19] The findings reported may be explained by the fact that, apart from direct effects of SARS-CoV2 on liver, liver itself may also be involved in the development of Systemic Inflammatory Response Syndrome (SIRS) due to COVID-19. Further analysis showed that higher percentage of patients with AST and ALT (both together) elevated (115/212, 54.2%) needed ICU admission, suggesting that these enzyme elevation correlates with need for ICU admission, which may be revealed that hepatic dysfunction, being significantly higher in critically ill patients and associated with a poor outcome. Another study yielded similar results, showing elevated AST in 8/13 (62%) of patients in the ICU compared to 7/28 (25%) in the non-ICU setting.[18] Patients with both AST and ALT elevation had a relatively higher death rate (17/30, 56.7%) and patients with AST elevated had the second-highest death rate (11/30, 36.7%), which was similar to the findings of a systematic review and meta-analysis study that found the presence of elevated liver enzyme also had statistical correlation with worse outcome (death).[20]

Most of the COVID-19 management protocols follow that patients with comorbidities should be closely monitored;[21,22] however, specific recommendations for patients with elevated liver enzyme are sparse. The risk of comorbidities with elevated liver enzyme in COVID-19 patients had not been considered in most of the previous studies. In this large-sample-sized study, patients were categorized into four groups (patients with normal liver enzymes, liver enzyme elevation, comorbidity and liver enzyme elevation with comorbidity) and the mortality rates were 1.36%, 3.28%, 7.35%, and 9.7%, respectively. Multivariate logistic regression analysis of our study showed that liver enzyme elevation and comorbidity had the highest risk for death (OR: 5.314, 95% CI: 2.278–12.393) as compared to comorbidity alone (OR: 4.096, 95% CI: 1.833–9.157). In general, patients with liver enzyme elevated with comorbidity deteriorated more rapidly than those without liver damage and comorbidity, in which utility of liver enzyme elevation among the comorbid patients at the onset of the COVID-19 will be beneficial for stratification for aggressive early management of the disease. However, the mechanisms for increased risk for specified patients in COVID-19 should be thoroughly studied or explained in future.

Conclusions

From the present data analysis, we first conclude that comorbid illness with elevated liver enzyme at the early stage, associates with disease severity and worse clinical features. Second, we found that patients of age more than 40 years are at increased risk for severe disease, ICU admission, and mortality. Finally, logistic regression analysis suggested that elevated liver enzyme and presence of comorbidity could impart a 5-fold increase in risk for fatal outcomes of COVID-19.

Limitations

There were certain limitations in our study. First, serial liver enzyme levels during the course of hospitalization were not analyzed; as a result of which, a probability of drug-induced liver injury could not be ruled out with certainty. However, our major objective was to study patients with liver enzyme elevation at the time of hospital admission and its association with outcome. Second, patients were not followed prospectively with respect to their biochemical abnormality during their course of hospital admission; it is difficult to ascertain whether subsequent liver injury (due to sepsis, drug-induced liver injury, COVID-19 per se) affected the disease outcome and future studies should be undertaken to address this problem. Since, Covid-19 is a relatively new disease and we have limited knowledge, the full disease spectrum of the virus may unfold in the future.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Overall study supervision (NK), conception of the study design, data analysis, drafting of the article, and statistical analysis (KR), assistance in drafting of the article (PB), and assistance in acquisition of data (AR, PP, MR).

Data sharing statement

All data are available upon request.

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