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Pattern of liver function test variations in COVID-19 infection & its clinical significance: A study from a dedicated COVID-19 tertiary care centre from India

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***Background & objectives*: Coronavirus disease 2019 (COVID-19) affects respiratory, gastrointestinal, cardiovascular and other systems disease. Studies describing liver involvement and liver function test (LFT) abnormalities are sparse from our population. This study was undertaken to estimate the LFT abnormalities in patients with COVID-19 in a tertiary care set up in India.**

***Methods*: In this retrospective study conducted at a tertiary care centre in Mumbai, India, all consecutive patients with proven COVID-19 by reverse transcriptase–PCR from March 23 to October 31, 2020 were enrolled. Of the 3280 case records profiled, 1474 cases were included in the study. Clinical characteristics, biochemical parameters and outcomes were recorded.**

***Results*: Overall 681 (46%) patient had deranged LFTs. Hepatocellular type of injury was most common (93%). Patients with deranged LFTs had more probability of developing severe disease ($P<0.001$) and mortality ($P<0.001$). Advanced age ($P<0.001$), male gender ($P<0.001$), diabetes mellitus ($P<0.001$), lower oxygen saturation levels at admission ($P<0.001$), higher neutrophil–lymphocyte ratio ($P<0.001$), history of diabetes mellitus and cirrhosiss were associated with deranged LFTs. Acute liver injury was seen in 65 (4.3%) cases on admission and 57 (3.5%) cases during hospital stay. On multivariate analysis for predicting mortality, age >60 yr serum creatinine >2 mg%, PaO_2/FiO_2 ratio ≤200 and raised AST >50 IU/l (OR: 2.34, CI: 1.59-3.48, $P<0.001$) were found to be significant.**

***Interpretation & conclusions*: In COVID-19, LFT abnormalities were common, and derangement increased as severity progressed. The presence of deranged LFT worsens the clinical outcome and predicts in-hospital mortality.**

Key words COVID-19 - hepatitis - liver function tests - mortality - respiratory distress syndrome – SARS-CoV-2

Coronavirus disease 2019 (COVID-19) is a highly infectious respiratory system disease that ranges from mild systemic illness to fulminant acute respiratory distress syndrome (ARDS)[1]. Apart from the respiratory system, COVID-19 affects the gastrointestinal (GI) tract, liver, kidneys and endocrine organs and leads to multisystemic disease[2,3]. In the GI system, it can involve from oral cavity till rectum[4]. In the early pandemic, Guan *et al*[5] described 1099 cases of COVID-19 from Wuhan and showed that 22 per cent had deranged liver function tests (LFTs). Pan *et al*[6] showed 20 per cent occurrence of GI symptoms which significantly increased during hospital stay. A post-mortem analysis of 25 COVID-19 patients showed that liver was found to be commonly involved after cardiorespiratory involvement[7]. Coronavirus (CoV) gains entry in cells by means of angiotensin-converting enzyme-2 (ACE-2) receptor[8]. Bangash *et al*[9] from the United Kingdom observed that LFT derangements were common in non-severe COVID-19 cases but possibly not significant. Rarely, coronaviruses are associated with acute hepatitis or fulminant liver failure-like condition[10]. In a study from southern India, aspartate transaminase (AST) was deranged in 63 per cent and alanine transaminase (ALT) in 47 per cent patients on admission[11]. In a meta-analysis by Kulkarni *et al*[12], the presence of deranged LFTs was associated with three-fold risk of mortality. Thus, the clinical profile and outcomes of patients with COVID-19 having deranged LFTs are sparse from our population. This study was conducted to assess the occurrence of LFT abnormalities, factors associated with it and its relation with overall outcomes such as length of hospital stay and death in patients with COVID-19 in a hospital setup.

Material & Methods

This study was a retrospective analysis of consecutive patients admitted from March 23 to October 31, 2020, with COVID-19 at a single designated COVID-19 tertiary care hospital, at department of Medical Gastroenterology Topiwala National Medical College & BYL Nair Ch. Hospital, Mumbai, Maharashtra, India. COVID-19 was confirmed by nasal or oral throat swab by reverse transcriptase–polymerase chain reaction (RT-PCR) (TaqPath™, Thermo Fisher Scientific, Pleasanton, USA). All patients were screened and categorized according to the classification criteria laid down by the Ministry of Health and Family Welfare, Government of India, into three categories[13,14]: (*i*) mild – patients with uncomplicated upper respiratory tract infection with mild symptoms and no hypoxia; (*ii*) moderate – pneumonia with dyspnoea, fever, tachypnoea (≥24 breaths/min) and hypoxia (SpO_2 between 90 and 93%) on room air; and (*iii*) severe – clinical signs of pneumonia with any one of the following: (a) respiratory rate ≥30/min, and (b) oxygen saturation <90 per cent on room air. Age <18 yr, pregnant patients and cases with missing data were excluded from the study (Fig. 1). Clinical, laboratory and radiological data were obtained retrospectively from hospital records. Patients were screened for GI symptoms and abnormal LFTs (total serum bilirubin >1 mg%, AST >40 IU/l, ALT >40 IU/l, alkaline phosphatase (ALP) >310 IU/l and serum albumin <3.5 g%). Symptoms such as vomiting, diarrhoea, abdominal pain and constipation were noted and classified as GI symptoms. Liver injury was defined as total bilirubin >2 mg% and/or aspartate transaminase (AST)/alanine transaminases (ALT) >3 times upper limit of normal (ULN) and/or international normalized ratio (INR) >1.5[15,16]. On the basis of LFTs, type of liver injury was further categorized into hepatocellular (AST and/or ALT>ULN), cholestatic (ALP>ULN) in the presence of conjugated hyperbilirubinaemia and mixed pattern (AST/ALT and ALP>ULN)[17]. Maximum values of LFTs during the stay were taken as peak LFTs. History of any previous liver disease and comorbidities was recorded. Significant alcohol consumption was defined as an average daily intake of >2 standard drinks (14 g alcohol) per day for >5 yr[18]. Viral hepatitis profile was done in clinically relevant cases. Clinical, biochemical and radiological parameters were compared at baseline on the basis of deranged LFTs at admission. The clinical impact of baseline deranged LFTs on the overall outcome, *i.e*. survival or death, was analyzed. Patients were grouped into non-survivors and survivors. This study was approved by the Institutional Ethics Committee (ECARP/2020/88), and the last patient was enrolled on October 31, 2020.

Chest X-ray involvement was considered present if there were unilateral or bilateral opacities or nodules not fully explained by cardiac failure or fluid overload. It included ground-glass opacity, patchy atelectasis, local patchy shadowing and diffuse alveolar abnormalities[19].

Involvement on high-resolution computed tomography (HRCT) of thorax was considered when unilateral or bilateral opacities, ground-glass appearance and lobar or lung collapse were recorded. Scoring of lung involvement was given according to number of lobes involved (0-5). Each lobe was given one point in the final score[19]. Patients were managed

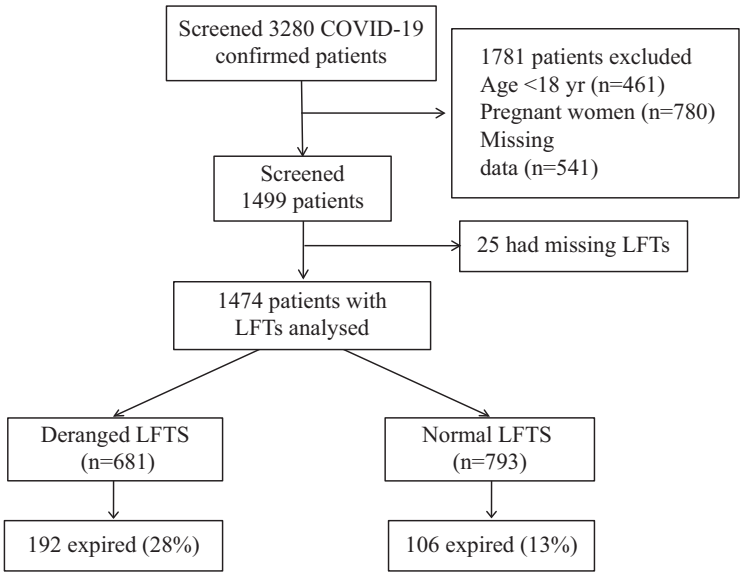

Fig. 1. Flow chart showing Patient selection process. LFT, liver function test

on the basis of protocol laid down by the Indian Council of Medical Research (ICMR)[14]. Severe cases and their ventilation strategy were managed as per ICMR recommendations and acute respiratory distress syndrome (ARDS) protocol[20].

Statistical analysis: Baseline characteristics of the study participants were presented. To understand the normality of data, Shapiro-Wilk test was applied. Continuous data were reported as mean (standard deviation) for normally distributed or median (Interquartile range -25^{th}-75^{th} percentile) for skewed distributions. Continuous data in three groups (mild, moderate, and severe liver injuries) were compared using one-way analysis of variance or Kruskal-Wallis test (for non-parametric distribution) depending on the distribution of data. Categorical variables were reported as counts (percentages). Association between categorical data was assessed by Pearson's Chi-square test/Fisher's exact test (when value in cell of contingency table was <5). Continuous data in survivors and non-survivors were compared using Welch t test or Mann-Whitney U test, depending on the distribution of data.

Model description: To identify the predictors of survival, variables selected were clinically relevant or those previously reported to predict COVID-19 hospitalization-related outcomes. These variables were age, sex, creatinine, AST, ALT, PaO_2/FiO_2 ratio, haemoglobin and neutrophil–lymphocyte ratio. The following variables were dichotomized to categorical variables for ease of interpretation. Age (<60, ≥60 yr), creatinine (<2, ≥2 mg%), haemoglobin (<12, ≥12 g%), neutrophil–lymphocyte ratio (<7.5, ≥7.5), AST (<50, ≥50 IU/l, ALT (<50, ≥50 IU/l and PaO_2/FiO_2 (<200, ≥200). Univariable logistic regression was done to calculate crude odds ratio (OR) for individual variables. Covariates with a P<0.30 for crude OR were selected for multivariable logistic regression. Statistical analyses were performed using R software, version 3.6.2 (R foundation, Vienna, Austria). Missing values in the patients were statistically imputed using a multiple imputation method exploiting correlations between predictor variables and between predictor variables and the survival status[21].

Results

A total of 3280 patients were screened. Seven hundred and eighty pregnant patients were excluded. Missing data were noted in 540 cases and 461 cases were <18 yr of age. Finally, 1499 patients were enrolled, of whom LFT was available in 1474 patients (Fig. 1). Data of 25 patients were adjusted through imputation during analysis. The mean age of the study population was 52.07 ±15.77 yr, of whom 969 (65%) were males. The male:female ratio was 1.91:1. Serum bilirubin levels were available in 1362 patients, serum AST and ALT levels in 1375 cases and serum ALP levels in 584 patients.

Baseline characteristics: In our study, the most common presenting symptoms were fever (75%), cough (68%) and breathlessness (57%). GI symptoms were more

Table I. Comparison of baseline clinical features of patients with COVID-19 on the basis of deranged liver function tests

Parameters	Normal LFT	Deranged LFT	*P*
N	793	681	
Age (yr), median (IQR)†	51.00 (37.00-63.00)	54.00 (44.00-64.00)	<0.001
Sex			
Female, n (%)	316 (39.8)	189 (27.8)	<0.001
Male, n (%)	477 (60.12)	492 (72.5)	<0.001
Duration of hospital stay (days), median (IQR)†	8.00 (6.00-14.00)	8.00 (5.00-15.00)	0.371
SpO_2 % on admission, median (IQR)	96.00 (90.00-98.00)	90.00 (82.00-96.00)	<0.001
COVID-19 symptoms, n (%)			
Fever	574 (74.6)	513 (76.0)	0.592
Cough	488 (63.3)	484 (73.4)	<0.001
Breathlessness	378 (49.8)	433 (65.5)	<0.001
Nasal congestion	82 (11.3)	76 (12.0)	0.724
Anosmia	92 (12.7)	70 (11.1)	0.429
Sore throat	180 (24.6)	132 (20.9)	0.126
Headache	73 (10.0)	49 (7.7)	0.173
Myalgia	94 (12.8)	103 (16.3)	0.080
Altered sensorium	28 (3.9)	37 (5.9)	0.11
Fatigue	137 (18.6)	123 (19.4)	0.783
Anorexia	59 (8.1)	55 (8.7)	0.748
Nausea	58 (8.0)	67 (10.6)	0.113
GI symptoms	204 (27.5)	257 (39.7)	<0.001
Comorbidities, n (%)			
Diabetes mellitus	240 (32.1)	291 (44.8)	<0.001
Hypertension	266 (35.2)	256 (39.2)	0.371
CKD	81 (11.1)	46 (7.3)	0.020
Ischaemic heart disease	67 (9.1)	57 (9.0)	0.656
Hypothyroidism	36 (4.9)	25 (4.0)	0.465
Obstructive airway disease	27 (3.41)	18 (2.6)	0.266
Coexistent pulmonary or pleural TB	19 (2.6)	20 (3.2)	0.082
RVD	8 (1.1)	1 (0.2)	-
Cirrhosis	2 (0.3)	22 (3.2)	-
Compensated cirrhosis††	2 (0.3)	1 (0.2)	-
Decompensated cirrhosis††	0 (0.0)	22 (3.8)	-
Aetiology††, n (%)			-
Alcohol	0 (0.0)	14 (2.0)	
Autoimmune	1 (0.0)	1 (0.2)	
Hepatitis B	0 (0.0)	2 (0.3)	
Hepatitis C	1 (0.1)	2 (0.3)	
NASH	0 (0.0)	2 (0.3)	
Cryptogenic	0 (0.0)	1 (0.2)	
Alcohol	96 (13.2)	138 (20.3)	<0.001
Smoker	93 (12.8)	138 (21.9)	<0.001

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Parameters	Normal LFT	Deranged LFT	*P*
COVID-19 category, n (%)			
Mild	450 (56.7)	200 (29.4)	<0.001
Moderate	158 (19.9)	134 (19.7)	0.231
Severe disease	185 (23.3)	347 (51.0)	<0.001
Ventilation, n (%)			
BMV	107 (13.5)	160 (23.5)	<0.001
MV	45 (5.7)	78 (11.5)	<0.001
NIV	48 (6.1)	101 (14.8)	<0.001
No need of ventilation	444 (56.0)	215 (31.6)	<0.001
Death	106 (11.3)	192 (27.0)	<0.001

GI symptoms include - abdominal pain, diarrhoea, constipation, GI bleeding, vomiting, distension of abdomen, [†]indicates non-parametric test (Mann-Whitney U test), [††]indicates a low sample number to produce significance. It is for descriptive purpose. GI, gastrointestinal; IQR, interquartile range; CKD, chronic kidney disease; BMV, bag and mask ventilation; MV, mechanical ventilation; NIV, non-invasive ventilation; NASH, non-alcoholic steatohepatitis; RVD, retroviral disease; TB, tuberculosis; SD, standard deviation; LFT, liver function test

common in those with deranged LFTs. Patients with deranged LFTs had higher median age (54 yr vs. 51 yr, $P<0.001$) and male gender (72 *vs.* 60%, $P<0.001$) as compared to those with normal LFTs. Patients with deranged LFTs also had significantly lower median oxygen saturation (SpO_2) on admission (90 *vs.* 96%, $P<0.001$). Deranged LFTs were also more commonly noted in those having significant alcohol consumption ($P=0.001$) and in smokers ($P<0.001$; Table I).

Diabetes mellitus (38%), hypertension (35%) and chronic kidney disease (8.6%) were the most common comorbidities. Patients with diabetes mellitus (44.8 *vs.* 32.1%, $P<0.001$) were more likely to develop deranged LFTs. Overall, 24 patients had a history of cirrhosis. These patients had deranged LFTs, but they did not suffer from severe disease significantly (Table I).

Deranged liver function tests: Overall, 681 (46.2%) cases had abnormal LFTs during the course of stay and 556 (37.68%) cases developed severe COVID-19 disease. At the time of admission, total bilirubin, AST and ALT levels were significantly higher and serum albumin was significantly lower in the deranged LFT group ($P<0.001$). However, acute liver injury was seen in only 7.93 per cent (n=118)) of total patients. Most of these patients, *i.e.* 65 (4.33%), presented with severe disease on admission, and 57 (3.5%) progressed to severe disease during hospitalization. Isolated increase in total bilirubin (>2 mg%) was the least common abnormality, noted only in 25 patients of this group. More number of patients with severe disease had deranged LFTs than with mild disease (51 *vs*. 29%, $P<0.001$; Table II). Male sex, advanced age, low SpO_2 levels on admission, presence of cough, breathlessness, previous history of diabetes mellitus, chronic kidney disease (CKD), cirrhosis, history of significant alcohol consumption and smoking, high neutrophil–lymphocyte (NL) ratio, clinically severe disease and presence of chest X-ray findings were associated with deranged LFTs (Table II).

Hepatocellular type of injury was commonly seen in 93.09 per cent patients (n=1372). The most common form of liver injury seen was a change in levels 1-2 times of ULN in 60.6 per cent patients. Medical cholestatic liver disease was not seen in our study.

LFTs in different categories of COVID-19: On admission, as the severity of COVID-19 increased, liver injury also became more marked, $P<0.001$ (Table II). On admission, patients with severe disease showed significant changes in four of six (higher bilirubin levels, AST, ALT and lower serum albumin) LFT parameters as compared to mild disease ($P<0.001$). ALP was not significantly altered (Table II). The highest level of AST (5190U/l) and ALT (3020U/l) was noted in a case of ischaemic hepatitis. On assessing peak values, liver enzymes, INR, total protein and low serum albumin levels were significantly deranged in the severe category. Furthermore, hepatocellular type of injury was more significant in severe category than in mild disease (58.5 *vs*. 28.5%, $P<0.001$). More patients with liver injury on admission had clinically severe disease

Table II. Clinical, laboratory and imaging characteristics of patients with various grades of severity in COVID-19

Parameters	Mild	Moderate	Severe	*P*
N	650	293	556	
Age (yr)[#ǂ]	50.00 (36.00-60.00)	52.00 (42.00-61.00)	58.00 (46.00-66.00)	<0.001
Sex				
Female, n (%)	249 (38.3)	88 (30.0)	175 (31.5)	0.020
Male, n (%)	401 (61.5)	205 (70.0)	381 (68.3)	
Duration of hospital[#ǂ]	8.00 (6.00-12.00)	11.00 (6.00-18.00)	8.00 (4.00-15.00)	<0.001
SpO_2 at admission[#ǂ]	98.00 (96.00-99.00)	92.00 (90.00-94.00)	83.00 (75.00-88.00)	<0.001
Fever, n (%)	467 (73.7)	218 (77.0)	422 (76.4)	0.414
Cough, n (%)	389 (62.8)	195 (67.9)	405 (74.2)	<0.001
Breathlessness, n (%)	182 (30.0)	209 (73.6)	441 (79.6)	<0.001
Nasal congestion, n (%)	55 (9.4)	39 (14.6)	66 (12.5)	0.060
Anosmia, n (%)	55 (9.4)	36 (13.5)	74 (14.0)	0.043
GI symptoms, n (%)	174 (28.9)	93 (33.8)	200 (37.4)	0.009
Comorbidities, n (%)				
Diabetes mellitus	151 (25.1)	118 (42.6)	271 (50.0)	<0.001
Hypertension	165 (27.3)	135 (47.9)	220 (40.5)	<0.001
CKD	50 (8.5)	31 (11.6)	47 (8.8)	0.332
IHD	44 (7.5)	31 (11.5)	51 (9.5)	0.089
Hypothyroidism	24 (4.1)	16 (5.9)	21 (4.0)	0.404
OAD	23 (0.0)	11 (0.7)	12 (0.2)	0.019
TB[ǂ]	0 (0.0)	0 (0.0)	10 (1.9)	-
Alcohol intake	66 (11.3)	47 (17.6)	117 (22.1)	<0.001
Smoker	59 (10.1)	56 (21.0)	120 (22.6)	<0.001
Haemoglobin (g%)[#ǂ]	11.50 (10.00-13.07)	11.60 (10.50-13.20)	11.20 (9.90-12.80)	0.081
Platelet count ($\times 10^5$/µl)[#ǂ]	2.11 (1.64-2.56)	2.12 (1.46-2.45)	1.90 (1.39-2.51)	0.009
WBC (/µl)[#ǂ]	7290.00 (5600.00-9600.00)	8600.00 (6500.00-11000.00)	9600.00 (6700.00-12172.50)	<0.001
Neutrophils (%)[#ǂ]	74.00 (65.00-80.00)	76.70 (66.00-84.00)	78.00 (67.00-86.45)	<0.001
Lymphocytes (%)[#ǂ]	18.00 (12.00-28.00)	15.00 (10.00-24.00)	14.00 (9.00-22.00)	<0.001
NL ratio on admission[#ǂ]	4.12 (2.38-6.21)	5.13 (2.67-8.60)	5.69 (3.05-8.80)	<0.001
NL ratio >3.5 on admission	349 (60.5)	181 (64.6)	375 (70.6)	0.002
CRP[#ǂ]	70.00 (48.00-89.00)	90.00 (60.00-112.00)	101.00 (85.00-114.00)	<0.001
D dimer (mg/ml)[#ǂ]	1.30 (0.50-3.40)	4.90 (1.80-11.80)	9.16 (4.50-14.40)	<0.001
IL-6 (pg/ml)[#ǂ]	662.00 (230.00-1612.00)	1450.00 (960.00-2340.00)	1500.00 (882.50-2310.00)	<0.001
Serum creatinine (mg%)[#ǂ]	0.90 (0.60-1.10)	1.00 (0.80-1.20)	1.10 (0.80-1.60)	<0.001
BUN[#ǂ]	12.00 (10.00-15.00)	14.00 (11.00-21.00)	20.00 (12.00-31.00)	<0.001
At admission				
Total bilirubin (mg%)[#ǂ]	0.30 (0.30-0.50)	0.40 (0.30-0.60)	0.40 (0.30-0.70)	<0.001
AST (IU/l)[#ǂ]	24.00 (18.00-39.00)	32.50 (22.00-53.25)	44.00 (27.00-65.00)	<0.001
ALT (IU/l)[#ǂ]	24.00 (18.00-38.00)	32.00 (20.00-51.75)	41.00 (22.00-60.00)	<0.001
ALP (IU/l)[#ǂ]	156.00 (124.00-188.50)	145.00 (114.00-188.00)	145.00 (117.00-189.00)	0.201

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Parameters	Mild	Moderate	Severe	*P*
Total protein (g%)[#†]	6.60 (6.20-6.80)	6.65 (6.05-7.10)	6.45 (6.00-7.00)	0.195
Serum albumin (g%)[#†]	3.80 (3.42-4.18)	3.60 (3.40-3.90)	3.40 (2.80-3.70)	<0.001
INR[#†]	1.10 (0.98-1.18)	1.10 (1.00-1.20)	1.10 (1.00-1.20)	0.052
Liver injury at admission, n (%)	14 (2.2)	9 (3.1)	42 (7.6)	<0.001
Peak levels				
Total bilirubin (mg%)[#†]	0.40 (0.30-0.80)	0.40 (0.30-0.60)	0.50 (0.30-0.80)	0.076
AST (IU/l)[#†]	42.00 (24.00-62.75)	39.00 (28.00-58.00)	61.00 (42.00-132.00)	<0.001
ALT (IU/l)[#†]	29.00 (21.00-52.50)	50.00 (43.00-71.50)	67.00 (44.00-132.00)	<0.001
ALP (IU/l)[#†]	144.00 (122.00-212.00)	114.00 (51.00-128.00)	167.00 (140.00-200.00)	0.002
Total protein (g%)[#†]	6.70 (6.45-6.73)	4.30 (4.15-6.02)	6.00 (4.60-6.03)	<0.001
Serum albumin (g%)[#†]	3.85 (3.42-4.23)	4.10 (4.10-4.10)	3.05 (2.80-3.50)	0.005
INR[#†]	1.24 (1.18-2.11)	1.00 (1.00-1.10)	1.02 (1.00-1.16)	0.113
Liver injury during hospitalization, n (%)	8 (1.2)	4 (1.4)	40 (7.2)	-
Total bilirubin (mg%)[††], n (%)				
<2	582 (97.7)	258 (99.2)	483 (95.5)	-
>2-<5	9 (1.5)	0 (0.0)	12 (2.4)	-
>5	5 (0.8)	2 (0.8)	11 (2.2)	-
AST (U/l), n (%)				
5-40 (ULN)	453 (75.5)	157 (59.9)	223 (43.5)	<0.001
1-2 times ULN	121 (20.2)	77 (29.4)	214 (41.7)	
2-3 times ULN	19 (3.2)	14 (5.3)	45 (8.8)	
>3 times ULN	7 (1.2)	14 (5.3)	31 (6.0)	
ALT (U/l), n (%)				
0-40 (ULN)	455 (75.8)	166 (63.4)	248 (48.3)	<0.001
1-2 times ULN	115 (19.2)	71 (27.1)	184 (35.9)	
2-3 times ULN	25 (4.2)	19 (7.3)	55 (10.7)	
>3 times ULN	5 (0.8)	6 (2.3)	26 (5.1)	
ALP (U/l)[††], n (%)				
0-310 (ULN)	178 (95.2)	129 (92.8)	237 (91.9)	-
1-2 times ULN	8 (4.3)	10 (7.2)	17 (6.6)	-
>2 times ULN	1 (0.5)	0 (0.0)	4 (1.6)	-
Hepatocellular pattern of liver injury	185 (28.5)	124 (42.3)	325 (58.5)	<0.001
Cirrhosis[††]	9 (1.4)	4 (1.4)	11 (2.0)	-
PaO_2/FiO_2 ratio[#]	354.37 (78.34)	235.07 (71.67)	164.79 (71.36)	<0.001
X-ray involvement	75 (15.9)	201 (85.2)	478 (93.5)	<0.001
Lung involvement on HRCT (score 0-5), mean (SD)	0.43 (0.71)	1.73 (0.81)	2.65 (0.79)	<0.001
Modes of ventilation, n (%)				
BMV	4 (0.6)	69 (23.5)	199 (35.8)	-
MV	0 (0.0)	6 (2.0)	132 (23.7)	-
NIV	0 (0.0)	10 (3.4)	143 (25.7)	-
Number of ICU days, mean (SD)	0.08 (0.02)	1.99 (3.83)	3.62 (4.66)	<0.001

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Parameters	Mild	Moderate	Severe	*P*
Mortality	0 (0.0)	18 (6.1)	280 (50.4)	-

[#]Data presented as median (IQR). GI symptoms include - abdominal pain, diarrhoea, constipation, GI bleeding, vomiting, distension of abdomen, [ŧ]indicates non-normal distribution and non-parametric Kruskal-Wallis test, [ŧŧ]indicates low sample number in a shell to produce significance. Data are for descriptive purpose. CKD, chronic kidney disease; IHD, ischaemic heart disease; WBC, white blood count; NL ratio, neutrophil-lymphocyte ratio; AST, aspartate transaminase; ALT, alanine transaminase; ALP, alkaline phosphatase; INR, international normalized ratio; BMV, bag and mask ventilation; MV, mechanical ventilation; NIV, non-invasive ventilation; ICU, intensive care units; HRCT, high-resolution computed tomography; ULN, upper limit of normal; BUN, blood urea nitrogen; IL-6, interleukin-6; CRP, C-reactive peptide; TB, tuberculosis; OAD, obstructive airway disease; GI, gastrointestinal; IQR, interquartile range

(7.6 *vs*. 2.2%, *P*<0.001). A similar finding was noted in patients developing liver injury during hospital stay (7.2 *vs*. 1.2%, *P*<0.001) (Table III).

Deranged LFTs and clinical outcomes: Patients with clinically severe disease were found to have higher scores of lung involvement on chest X-ray (93 *vs*. 16%, *P*<0.001) and on HRCT (2.6 *vs*. 0.4%, *P*<0.001) as compared to the mild category. However, deranged LFTs were more significantly correlated with positive chest X-ray findings (73.4 *vs*. 48.9%, *P*<0.001) only. Patients with deranged LFTs had higher need of non-invasive ventilation (14.8 *vs*. 6.1%, *P*<0.001) and mechanical ventilation (11.5 *vs*. 5.7%, *P*<0.001). Mortality was also significantly higher (27 *vs*. 11.1%, *P*<0.001) in those with deranged LFTs (Table I).

On univariate analysis, comparing survivors and non-survivors, deranged LFTs were found significant (67 *vs.* 42%, *P*<0.001). Other clinical parameters found significant were advanced age, male gender, low SpO_2 levels on admission, history of diabetes mellitus, cirrhosis and tuberculosis (Table III). However, on multivariate analysis on non-survivors versus survivors, raised AST (>50 IU/l), higher age (>60 yr), serum creatinine >2 mg% and low PaO_2/FiO_2 (≤200) were found to be significant (Table IV). On receiver operating curve analysis (ROC) for predicting mortality, SpO_2 on admission was found to be most significant (SpO_2<89%, AUROC: 0.868, CI: 0.848-0.886, Sn: 83%, Sp: 78%) (Table V and Figs 2 and 3). Among LFTs, AST had AUROC 0.65 in predicting mortality (Figs. 2 and 3).

Role of drugs on deranged LFTs: After admission, deranged LFTs were also associated with drugs used in the treatment such as hydroxychloroquine (*P*<0.001), low-molecular-weight heparin (*P*<0.001) and ivermectin (*P*<0.001). Methylprednisolone (*P*<0.001), tocilizumab (*P*<0.001), antivirals like remdesivir (*P*<0.001), favipiravir (*P*<0.001) and lopinavir-ritonavir (Lpv/r) (*P*<0.001) combination were also associated with deranged LFTs (Table VI).

Outcomes in cirrhosis: Patients with cirrhosis had more deranged LFTs, irrespective of aetiology. Alcohol-related chronic liver disease was most common (14 patients). Overall, the frequency of decompensating events was more than the number of patients with cirrhosis. Ascites was the most common decompensating event. Patients with cirrhosis were more likely to suffer in-hospital mortality (3.7 *vs.* 1.1%) (Table III).

Discussion

Median serum AST levels were more than ALT levels on admission in our patients. The most commonly deranged parameter was AST (37%) than ALT (34%); ALP was less commonly deranged (2.7%). In a meta-analysis by Kumar *et al*[22], a lesser number of patients had elevated transaminases, but the AST levels were more than ALT levels on admission. This was consistent across all COVID-19 severity classes. It is in consonance with studies from Beijing and from the West[23-25]. However, this relationship changed when patients developed liver injury during hospital stay (ALT>AST). Similar findings have been previously reported[24,25]. Very few cases had ALP >2 times of normal (6 cases) and isolated hyperbilirubinaemia. Similar findings have been reported by Cai *et al*[15].

In the severe category, our patients had significantly elevated levels of total bilirubin, AST, ALT, INR and low serum albumin. Furthermore, liver injury on admission was found to be significantly more in this group. These parameters were also found significant in the non-survivors. This validates the findings of Hundt *et al*[25] who showed that peak levels of AST were at increased odds for mortality. Thus, as the severity of

Table III. Comparison of clinical, laboratory and radiological variables between survivors and non-survivors

Variables	Survivors, n (%)	Non-survivors, n (%)	*P*
Total cases	1201	298	
Age (yr)[#ǂ]	52.00 (39.00-62.00)	59.00 (46.00-67.75)	<0.001
Sex			
Female	419 (34.9)	95 (31.2)	0.020
Male	782 (64.9)	205 (68.2)	
Duration of hospital stay[#ǂ]	9.00 (6.00-15.00)	5.50 (3.00-8.00)	<0.001
SpO_2 at admission[#ǂ]	96.00 (90.00-98.00)	80.50 (70.00-88.00)	<0.001
Fever	899 (76.8)	208 (69.8)	0.016
Cough	776 (67.1)	213 (72.2)	0.105
Breathlessness	576 (50.2)	256 (85.9)	<0.001
Nasal congestion	121 (11.2)	39 (13.1)	0.414
Anosmia	117 (10.8)	48 (16.1)	0.016
Sore throat	239 (21.9)	85 (28.5)	0.021
Headache	95 (8.7)	31 (10.4)	0.430
Myalgia	160 (14.6)	42 (14.1)	0.890
Altered sensorium	39 (3.6)	31 (10.4)	0.001
Fatigue	197 (18.0)	70 (23.5)	0.001
Anorexia	85 (7.8)	32 (10.7)	0.134
Nausea	88 (8.1)	37 (12.4)	0.029
GI symptoms	351 (31.5)	116 (38.9)	0.018
Comorbidities			
Diabetes mellitus	394 (35.1)	146 (49.0)	<0.001
Hypertension	401 (35.5)	122 (39.6)	0.093
CKD	94 (8.6)	34 (11.4)	0.174
IHD	104 (9.5)	22 (7.4)	0.459
Hypothyroidism	51 (4.7)	10 (3.4)	0.403
Obstructive airway disease	40 (3.5)	6 (2.1)	0.313
Cancer	23 (2.1)	12 (4.0)	0.102
RVD[ǂǂ]	7 (0.6)	2 (0.7)	-
TB	28 (2.3)	11 (3.7)	0.001
Cirrhosis	13 (1.1)	11 (3.7)	-
Aetiology[ǂǂ]			
Alcoholic liver disease	8 (0.8)	6 (2.0)	
Autoimmune hepatitis	1 (0.1)	1 (0.3)	
Hepatitis C	2 (0.1)	1 (0.3)	
Hepatitis B	2 (0.2)	0 (0.0)	
NASH	0 (0.0)	2 (0.7)	
Cryptogenic	0 (0.0)	1 (0.0)	
Alcohol	158 (13.1)	76 (24.5)	<0.001
Smoker	149 (13.9)	82 (27.5)	<0.001
On admission			
Haemoglobin (g%)[#ǂ]	11.60 (10.10-13.10)	11.20 (9.80-12.80)	0.029

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Variables	Survivors, n (%)	Non-survivors, n (%)	*P*
Platelet count ($\times10^5$/µl)[#ǂ]	2.11 (1.58-2.60)	1.77 (1.28-2.34)	<0.001
White blood cell count (/µl)[#ǂ]	8200.00 (6000.00-10500.00)	8900.00 (6700.00-12500.00)	<0.001
NL ratio[#ǂ]	4.53 (2.62-7.25)	5.47 (2.91-8.70)	0.008
NL ratio >3.5 ADM	700 (64.1)	205 (69.3)	0.114
Creatinine (mg%)[#ǂ]	0.90 (0.60-1.20)	1.20 (0.80-1.82)	<0.001
BUN[#ǂ]	13.00 (10.00-20.00)	23.00 (12.00-36.00)	<0.001
Total bilirubin (mg%)[#ǂ]	0.40 (0.30-0.60)	0.40 (0.30-0.70)	<0.001
AST (IU/l)[#ǂ]	29.00 (21.00-47.00)	46.00 (29.25-65.00)	<0.001
ALT (IU/l)[#ǂ]	28.00 (18.00-49.00)	38.00 (23.00-56.00)	<0.001
ALP (IU/l)[#ǂ]	150.00 (118.25-189.00)	137.50 (115.00-188.00)	0.182
Total protein (g%)[#ǂ]	6.60 (6.10-7.00)	6.50 (6.05-7.00)	0.435
Serum albumin (g%)[#ǂ]	3.70 (3.40-4.10)	3.10 (2.65-3.60)	<0.001
INR[#ǂ]	1.10 (1.00-1.16)	1.10 (1.10-1.40)	<0.001
Liver injury at admission	40 (3.3)	25 (8.4)	<0.001
Peak LFT's			
Total bilirubin (mg%)[#ǂ]	0.40 (0.30-0.70)	1.00 (0.50-1.60)	<0.001
AST (IU/l)[#ǂ]	45.00 (29.00-70.00)	86.00 (49.00-150.00)	<0.001
ALT (IU/l)[#ǂ]	50.00 (28.00-88.00)	54.00 (44.00-120.00)	0.039
ALP (IU/l)[#ǂ]	128.00 (110.00-178.00)	182.50 (160.25-212.25)	0.025
Total protein (g%)[#ǂ]	6.10 (4.60-6.65)	6.00 (6.00-6.35)	0.793
Serum albumin (g%)[#ǂ]	3.50 (3.13-4.12)	2.30 (2.15-3.28)	0.063
INR[#ǂ]	1.02 (1.00-1.16)	2.40 (2.40-2.40)	0.029
Liver injury during hospitalization	38 (3.2)	14 (4.7)	0.263
Deranged LFT	497 (41.4)	184 (67.2)	<0.001
LFT 1-2 times ULN	271 (22.6)	108 (36.2)	<0.001
LFT 2-3 times ULN	106 (8.8)	40 (13.4)	0.022
LFT >3 times ULN	69 (5.8)	23 (7.7)	0.259
Cholestatic pattern	16 (1.3)	2 (0.7)	-
Hepatocytic pattern	462 (38.5)	172 (57.7)	<0.001
Cirrhosis	13 (1.1)	11 (3.7)	-
ESR (mm/h)[#ǂ]	82.00 (61.00-108.00)	108.00 (89.00-123.50)	<0.001
CRP (mg%)[#ǂ]	84.50 (57.25-108.00)	108.00 (87.00-118.00)	<0.001
Serum LDH (mg%)[#ǂ]	677.00 (549.25-890.00)	749.00 (632.75-900.00)	0.033
IL-6 (pg/ml)[#ǂ]	1200.00 (569.00-2300.00)	1340.00 (847.00-1890.00)	0.758
Serum ferritin (mg%)[#ǂ]	875.00 (586.25-1254.50)	890.00 (657.00-1350.00)	0.278
D-dimer (ng/ml)[#ǂ]	3.50 (1.20-9.80)	9.80 (5.60-14.50)	<0.001
CPK total (mg%)[#ǂ]	110.00 (78.00-146.50)	124.00 (109.00-160.50)	<0.001
PaO_2:FiO_2 ratio[#ǂ]	280.00 (188.00-365.00)	164.00 (126.00-188.00)	<0.001
Lung involvement scores on HRCT[#ǂ]	2.00 (0.00-2.00)	3.00 (2.00-3.00)	<0.001
COVID-19 category			
Mild	650 (54.1)	0 (0.0)	-
Moderate	275 (22.9)	18 (6.0)	-
Severe	276 (23.0)	280 (94.0)	-

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Variables	Survivors, n (%)	Non-survivors, n (%)	*P*
Plasma therapy	48 (4.1)	40 (13.4)	<0.001
Modes of ventilation			
BMV	195 (16.2)	77 (25.8)	<0.001
MV[ff]	0 (0.0)	138 (46.3)	-
NIV	70 (5.8)	83 (27.9)	<0.001
Number of days in ICU[#f]	0.00 (0.00-0.00)	2.00 (0.00-4.00)	<0.001

[#]Data presented as median (IQR). GI symptoms include - abdominal pain, diarrhoea, constipation, GI bleeding, vomiting, distension of abdomen, [f]indicates non-normal data and Mann-Whitney test, [ff]indicates low sample number to produce significance. Data are for descriptive purpose. GI, gastrointestinal; IQR, interquartile range; CKD, chronic kidney disease; NASH, Non-alcoholic steatohepatitis; RVD, retroviral disease; IHD, ischaemic heart disease; NL ratio, neutrophil-lymphocyte ratio, AST, aspartate transaminase; ALT, alanine transaminase; ALP, alkaline phosphatase; INR, international normalized ratio; BUN, blood urea nitrogen; BMV, bag and mask ventilation; MV, mechanical ventilation; NIV, non-invasive ventilation; ICU, intensive care units; TB, tuberculosis; LFT, liver function test; ULN, upper limit of normal; HRCT, high-resolution computed tomography; LDH, lactate dehydrogenase; IL-6, interleukin-6; CPK, creatine phosphokinase; CRP, C-reactive peptide; ESR, erythrocyte sedimentation rate

Table IV. Comparison of significant variables in fatal and non-fatal cases with COVID-19

Variable	Cut-off	Survivor, n (%)	Dead, n (%)	OR (unadjusted)	*P*	OR (adjusted)	*P*
Age (yr)	<60 (reference category)	837 (84.6)	152 (15.4)	-		-	
	≥60 (study category)	364 (71.4)	146 (28.6)	2.21 (1.71-2.86)	<0.001	1.76 (1.27-2.44)	0.001
Sex	Female (reference category)	421 (81.6)	95 (18.4)	-		-	
	Male (study category)	780 (79.3)	203 (20.7)	1.15 (0.88-1.52)	0.302	1.08 (0.76-1.55)	0.664
PAO_2/FiO_2 ratio	>200 (reference category)	703 (93.1)	52 (6.9)	-		-	
	≥200 (study category)	285 (53.7)	246 (46.3)	11.67 (8.46-16.36)	<0.001	11.70 (8.16-17.11)	<0.001
Creatinine (mg%)	<2 (reference category)	949 (80.9)	224 (19.1)	-		-	
	≥2 (study category)	114 (64.8)	62 (35.2)	2.30 (1.63-3.23)	<0.001	2.04 (1.31-3.18)	0.002
Haemoglobin (g%)	>12 (reference category)	461 (81.6)	104 (18.4)	-		-	
	≤12 (study category)	635 (77.0)	190 (23.0)	1.33 (1.02-1.74)	0.039	1.28 (0.90-1.83)	0.172
NLR	>7.5 (study category)	830 (79.7)	212 (20.3)	1.26 (0.94-1.68)	0.114	0.74 (0.52-1.07)	0.110
	≤7.5 (reference category)	264 (75.6)	85 (24.4)	-		-	
AST (IU/l)	<50 (reference category)	840 (85.5)	142 (14.5)	-		-	
	≥50 (study category)	261 (66.4)	132 (33.6)	2.99 (2.27-3.94)	<0.001	2.34 (1.59-3.48)	<0.001
ALT (IU/l)	<50 (reference category)	832 (82.5)	177 (17.5)	-		-	
	≥50 (study category)	269 (73.5)	97 (26.5)	1.69 (1.27-2.25)	<0.001	0.82 (0.55-1.22)	0.336

OR, odds ratio; NLR, neutrophil-lymphocyte ratio; AST, aspartate transaminase; ALT, alanine transaminase

COVID-19 progressed, derangement of LFTs occurred and there was an increase in mortality.

Another explanation for deranged LFTs could be the use of drugs. In our study, multiple drugs were associated with deranged LFTs. as have already been reported[25]. In a study from China, Lpv/r fixed-dose combination was associated with deranged LFTs. Severe COVID-19 could be a confounding factor, which can explain the use of a large number of drugs found significantly associated with deranged LFTs. Moreover, severe COVID-19 patients frequently suffer from hypoxia and altered haemodynamic responses, which can lead to ischaemic changes in the liver that may lead to deranged LFTs. In a meta-analysis by Kulkarni *et al*[12], pooled incidence of drug-induced liver injury was 25 per cent, mainly to Lpv/r combination (37%) and with remdesivir (15.2%). Bilirubin levels increase with Lpv/r combination, while remdesivir causes an increase in transaminases. Hence, the role of

Table V. Comparisons of various variables with confidence intervals in predicting inhospital mortality using area under receiver operating curve

Variable	AUC	SE	95% CI	Optimal cut-offs	Sensitivity (%)	Specificity (%)
Age	0.630	0.018	0.603-0.656	>55 yr	59.73	63.26
Creatinine	0.661	0.018	0.635-0.687	>1.1 mg%	58.04	71.5
SpO_2 on admission	0.868	0.011	0.848-0.886	<89%	82.89	77.47
Total bilirubin	0.568	0.019	0.541-0.595	>0.4 mg%	49.45	63.45
AST	0.650	0.018	0.623-0.676	>39 IU/l	62.04	66.21
ALT	0.578	0.019	0.550-0.605	>31 U/l	63.50	53.68

AUC, area under curve; SE, standard error; SpO_2, oxygen saturation; CI, confidence interval; AST, aspartate transaminase; ALT, alanine transaminase

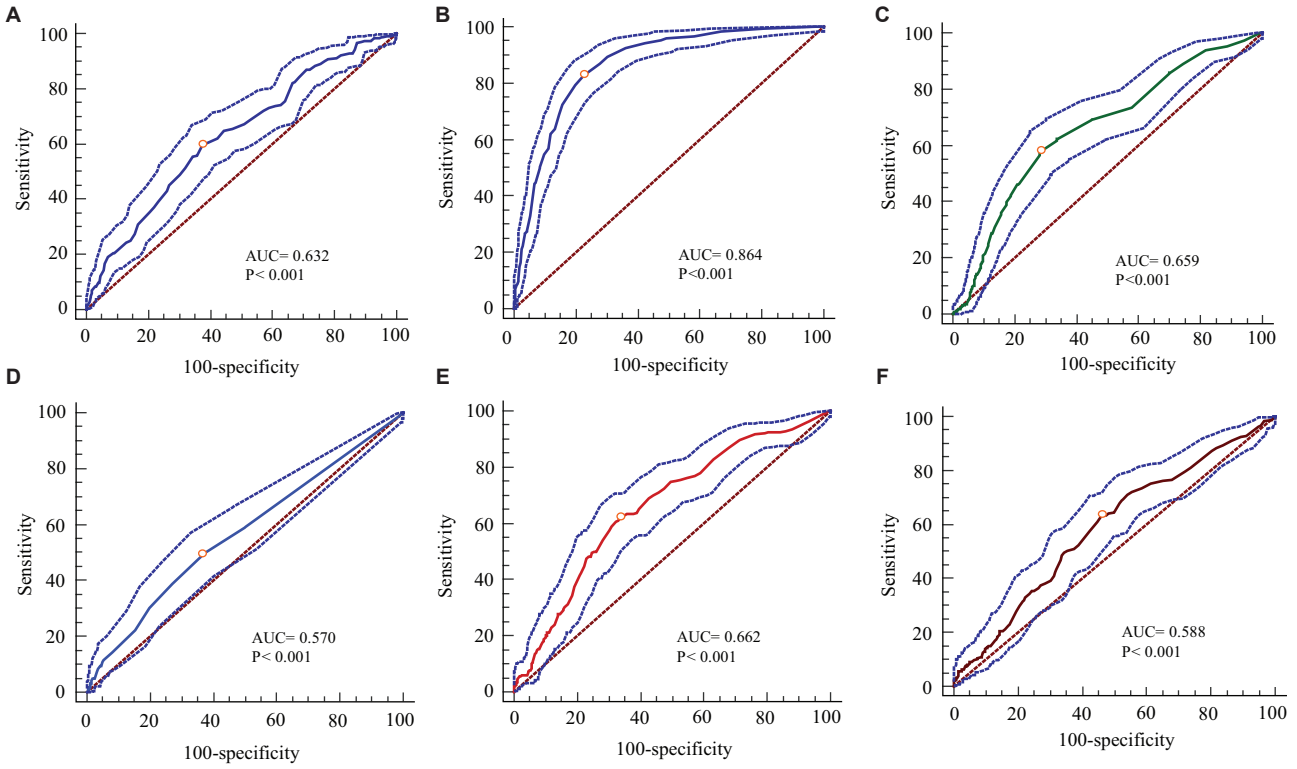

Fig. 2. Graphs showing area under receiver operating characteristic (AUROC) of different variables in predicting mortality. (**A**) age, (**B**) SpO2 on admission, **(C)** creatinine, **(D)** total bilirubin on admission, **(E)** AST on admission, **(F)** ALT on admission. AST, aspartate transaminase; ALT, alanine transaminase; SpO_2, oxygen saturation.

drugs in causing liver toxicity needs to be evaluated in a well-designed prospective study applying causality scores.

Most elevations in transaminase levels in our patients were <2 times the ULN (60%). Further, 25 per cent had elevated liver enzymes up to 2-3 times the ULN. This suggests that 85 per cent of patients had only mild derangement, as shown in studies from California and Wuhan[24,26]. Our study showed a progressive increase in LFT derangement (total bilirubin, AST, ALT and serum albumin) with an increase in severity. Maximum levels were seen in ischaemic hepatitis determined by the degree of shock or hypoxaemia. Acute liver failure due to COVID-19 was not seen in our study.

It was observed that patients with deranged LFT had significantly higher age than those with normal LFTs. On multivariate analysis, age was found to be significant in predicting mortality. Similar findings have been reported by others[23,27,28]. More males than

Table VI. Comparison of laboratory, radiological findings and drugs in cases with and without deranged liver function tests

Variables	Normal LFT, n (%)	Deranged LFT, n (%)	*P*
Haemoglobin (g%)[#ǂ]	11.20 (9.83-12.90)	11.80 (10.40-13.20)	0.001
Platelet count ($\times 10^5$/µl)[#ǂ]	2.11 (1.65-2.68)	1.98 (1.43-2.46)	0.809
WBC (/µl)[#ǂ]	8000.00 (6075.00-10225.00)	8700.00 (6125.00-11500.00)	0.332
NL ratio[#ǂ]	4.49 (2.84-7.18)	5.00 (2.66-8.50)	0.482
Serum creatinine[#ǂ]	0.90 (0.60-1.30)	1.00 (0.80-1.30)	0.035
BUN[#ǂ]	13.00 (10.00-21.00)	14.00 (11.00-24.00)	0.016
On admission			
Total bilirubin (mg%)[#ǂ]	0.30 (0.30-0.50)	0.50 (0.30-0.80)	<0.001
AST (IU/l)[#ǂ]	22.00 (16.00-27.00)	54.00 (42.00-68.25)	<0.001
ALT (IU/l)[#ǂ]	20.00 (15.00-26.00)	51.00 (36.75-67.00)	<0.001
ALP (IU/l)[#ǂ]	145.00 (116.00-186.25)	148.00 (121.00-189.75)	0.084
Total protein (g%)[#ǂ]	6.65 (6.30-7.00)	6.45 (6.00-6.90)	0.003
Serum albumin (g%)[#ǂ]	3.80 (3.40-4.00)	3.50 (3.00-3.90)	0.001
INR[#ǂ]	1.10 (1.00-1.20)	1.10 (1.00-1.20)	0.199
Peak levels			
Total bilirubin (mg%)[#ǂ]	0.30 (0.30-0.43)	0.50 (0.30-0.90)	<0.001
AST (IU/l)[#ǂ]	25.50 (21.00-29.00)	58.00 (41.00-88.00)	<0.001
ALT (IU/l)[#ǂ]	24.00 (14.75-27.00)	59.00 (45.00-103.00)	<0.001
ALP (IU/l)[#ǂ]	116.00 (114.50-137.00)	167.00 (113.00-198.00)	0.142
Total protein (g%)[#ǂ]	5.65 (4.60-6.73)	6.00 (5.85-6.60)	0.599
Serum albumin (g%)[#ǂ]	3.50 (2.80-4.23)	3.50 (2.97-3.58)	0.613
INR[#ǂ]	1.02 (1.02-1.14)	1.14 (1.00-1.19)	0.642
CRP (mg/dl)[#ǂ]	78.00 (56.00-104.25)	94.00 (76.00-116.00)	<0.001
LDH (U/l)[#ǂ]	666.00 (522.50-859.50)	760.00 (643.00-923.00)	<0.001
IL-6 (pg/ml)[#ǂ]	1200.00 (521.50-1890.00)	1450.00 (789.75-2300.00)	0.082
D-dimer (ng/ml)[#ǂ]	4.10 (1.20-10.50)	6.70 (1.87-13.00)	0.003
PaO_2/FiO_2 ratio[#ǂ]	288.00 (186.00-367.00)	200.00 (150.00-290.00)	<0.001
Chest X-ray findings[†]	296 (48.9)	433 (73.4)	<0.001
Lung involvement on HRCT mean score (0-5)[†]	1.49 (1.23)	2.04 (1.14)	0.670
Azithromycin	625 (78.8)	539 (79.1)	0.926
Doxycycline	78 (26.8)	73 (34.3)	0.087
Amoxicillin-clavulanic acid	272 (34.3)	226 (33.2)	0.693
Ceftriaxone	157 (19.8)	116 (17.0)	0.195
Rifaximin	41 (5.2)	59 (8.7)	0.011
Diuretics	82 (10.3)	78 (11.5)	0.911
Antiplatelets	87 (11.0)	75 (11.0)	0.014
LMWH	387 (48.8)	433 (63.6)	<0.001
HCQS	420 (53.0)	405 (59.5)	0.001
Methylprednisolone	319 (40.2)	405 (59.5)	<0.001
Remdesivir	64 (8.1)	93 (13.7)	<0.001
Tocilizumab	65 (8.2)	128 (18.8)	<0.001

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Variables	Normal LFT	Deranged LFT	*P*
Favipiravir	62 (7.8)	123 (18.1)	<0.001
Oseltamivir	227 (28.6)	268 (39.4)	0.428
Ivermectin	224 (51.7)	225 (55.1)	<0.001
Lpv/r combination	51 (6.5)	88 (13.0)	<0.001
Plasma therapy	36 (4.5)	52 (7.7)	0.070

[#]Data presented as median (IQR). [†]indicates non-normal data and Mann-Whitney U tests. WBC, white blood count; NL ratio, neutrophil-lymphocyte ratio; AST, aspartate transaminase; ALT, alanine transaminase; ALP, alkaline phosphatase; INR, international normalized ratio; CRP, C reactive protein; LDH, lactate dehydrogenase; IL-6, Interleukin-6; HCQS, hydroxychloroquine; LMWH, low-molecular-weight heparin; HRCT, high-resolution computed tomography; BUN, blood urea nitrogen; IQR, interquartile range; LFT, liver function test; Lpv/r, lopinavir-ritonavir

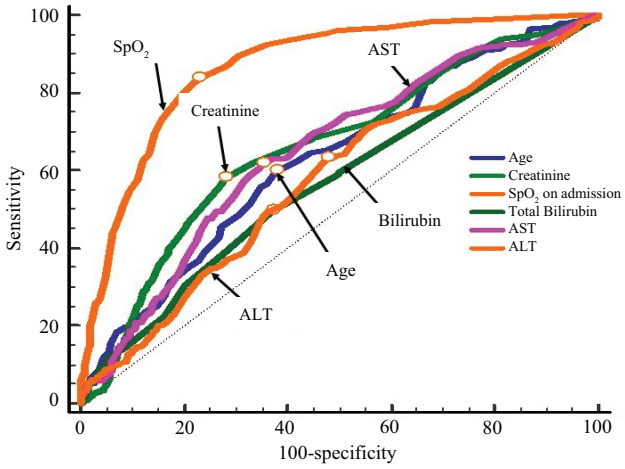

Fig. 3. Comparison of different variables and their area under receiver operating characteristic (AUROC) curve in predicting mortality.

females had deranged LFTs. However, the male gender was not significant in predicting death on multivariate analysis. A similar observation has been reported from China and the West[15,24,27,28]. Hundt *et al*[25] observed that male sex was associated with mortality. Lian *et al*[29] also reported that female sex was protective on multivariate analysis in predicting mortality. In a French study by Chaibi *et al*[30], age and gender both were not significant in predicting mortality.

Cirrhosis was present in around 1.6 per cent of our patients, similar to a multicentre study from the USA (1.8%)[31]. Alcohol was the most common underlying cause. On univariate analysis, cirrhosis was associated with increased mortality. This was similar to the earlier findings which showed significantly poor outcomes among patients with cirrhosis[16,17,32].

Diabetes mellitus followed by hypertension were the most common other comorbidities in our patients. Diabetes mellitus was found to be significantly associated with deranged LFTs. This was in contrast to studies, where it was not found to be significant[17,24,27,31]. On comparing different groups of severity, diabetes mellitus, hypertension, obstructive airway disease (OAD) and history of pulmonary or pleural tuberculosis (in past or active) were associated with more severe disease. A meta-analysis by Wang *et al*[33] also showed that the presence of comorbidities such as OAD, diabetes, hypertension, ischaemic heart disease and cerebrovascular accidents was associated with increased risk.

On multivariate analysis comparing non-survivors and survivors, AST >50 IU/l, along with age >60 yr, low PaO_2/FiO_2 (≤200 IU/l) and serum creatinine >2 mg% levels were found to be significant. Raised AST (>50 IU/l) was found significant in both univariate and multivariate analyses. This observation was similar to that of Zhang *et al*[27] and Hundt *et al*[25].

The causes of deranged LFTs could be multi-factorial. Various aetiologies proposed are direct cytotropic effects of COVID-19, drugs, other coexisting viruses, consumption of complementary and alternative medications, pre-existing diagnosed or undiagnosed liver disease, ischaemic hepatitis, cytokine storm and probably other unknown causes. In our study, 46 per cent had deranged LFTs, while liver injury was noted in only 7.9 per cent. Similar findings have been reported from northern India, Wuhan and Shenzhen[15,23,34]. Liver involvement based on LFTs from 19-36 per cent has been reported in a meta-analysis[35]. However, in a study from Yale on 1827 cases, there were a larger number of cases with deranged LFTs, including ALP. Serum AST and total bilirubin abnormalities were seen in 83 and 23 per cent of cases during hospitalization, respectively. This study proposed a higher proportion of hospitalized patients having severe hepatitis than studies from China[36]. It could be due to higher average

BMI, obesity and diabetes mellitus in these patients[25]. The primary cause of mortality in COVID-19 has been respiratory failure and cardiovascular events. Despite widespread organ involvement by the virus, liver failure as a primary pathology leading to mortality has not been recorded. However, as severity increases, derangement in LFTs increase, and are also associated with mortality.

The strength of our study was that it was carried out at a dedicated COVID-19 tertiary care hospital. The study had a large sample size, and almost all patients had LFTs on admission. Comprehensive analysis was available. However, our study had some limitations. It was a single-centre retrospective study. Hence, the presence of bias cannot be excluded. The retrospective nature of the study provided limited data on the classification of patients according to severity, admission criteria and exact treatment received. At a dedicated tertiary care referral centre for COVID-19 patients, selection bias of including more severe diseases was not ruled out. Propensity score matching was not done between groups. Organ failures were not taken into consideration. BMI was not recorded. Data on the effects of antihypertensive drugs such as angiotensin converting enzyme (ACE) inhibitors and complimentary and alternative medications were not included. Due to a lack of evidence on treatment, different classes of drugs were given, which had no clinical evidence from trials. Certain investigations such as gamma-glutamyl transpeptidase, abdominal sonography, liver fibroelastography or liver biopsy were not done. Bleeding and thrombosis events were not recorded. Only a few cases had a pre-existing liver disease, and therefore, it was difficult to evaluate the influence of liver-related comorbidities.

Our study showed that deranged LFTs were common in patients with COVID-19. It was multifactorial in origin, more common with advanced age, male gender and the presence of comorbidities such as diabetes mellitus, CKD and cirrhosis. Mild hepatocellular derangement pattern (up to 2 times ULN) was most common. Deranged ASTs, followed by ALT, were the most common abnormalities. As the level of severity increased, LFT derangement also increased. Deranged LFTs (AST >50 IU/l) are associated with in hospital mortality. More studies with short-term follow up with detailed investigations and drug profiles are required to determine the exact aetiology and outcome.

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