Original Article

INFECTIOUS Microbes & Diseases

OPEN

Characteristics of Liver Functions in Patients With COVID-19 and Construction of a Prognostic Evaluation Decision Model Based on Liver Functions

Tongtong Pan[1#], Dazhi Chen[2#], Chenwei Pan[3], Yi Kang[4], Junping Liu[4], Feifei Su[5], Liang Hong[6], Huili Li[7], Hui Zhao[8], Zhuo Lin[1], Xiaodong Wang[1], Hongwei Lin[1], Qianjing Du[1], Chao Cai[1], Yongping Chen[1,✉]

Abstract

A number of studies have suggested that coronavirus disease 2019 (COVID-19) can cause liver damage. However, clinical features and outcome of COVID-19 in patients with liver injury remain to be further investigated. In this study, the clinical data of 265 COVID-19 patients admitted to seven tertiary hospitals were collected. Based on a threshold for transaminase or total bilirubin levels at two times the normal upper limit, patients were divided into mild or moderate/severe liver injury groups. Among the 265 patients, 183 patients showed liver injury within 48 hours of admission. Aspartate aminotransferase levels were predominantly elevated in the liver injury group, but albumin levels were reduced. Moreover, fibrinogen and D-dimer were significantly increased. Furthermore, 68% of the patients with moderate/severe liver injury had one or more underlying diseases. Almost half of these patients developed acute respiratory distress syndrome (44%) and secondary infections (46%). These patients showed increased interleukin-6 and interleukin-10 levels and a decrease in PaO_2 and the oxygenation index. In addition, levels of alanine aminotransferase, aspartate aminotransferase, and albumin were correlated with the oxygenation index, D-dimer and lymphocyte counts. Furthermore, a novel prognostic assessment model based on liver function was established, which accuracy reached 88% and was able to accurately assess the prognosis of COVID-19 patients.

Keywords: coronavirus disease 2019; liver injury; prognostic decision model

Introduction

The coronavirus disease 2019 (COVID-19) global pandemic mainly causes lung damage, however, several reports suggest that COVID-19 can affect many organs, including the heart, kidneys, and liver.[1–3] Among these organs, the incidence of liver injury is 15%–76% in COVID-19 patients.[4,5] Except for some patients with extremely high levels of transaminases,[1] most patients show mild to moderate elevation of transaminases with slightly elevated bilirubin levels and reduced protein levels.[2,4–6] Although seven human coronaviruses have been identified so far, three of them have caused epidemic outbreaks. In the previous two coronavirus outbreaks, severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus, liver injury was very common in patients with

Editor: Stijn van der Veen

Author affiliations: [1] Department of Infectious Diseases, The First Affiliated Hospital of Wenzhou Medical University, The Key Laboratory of Diagnosis and Controlment for The Development of Chronic Liver Disease of Zhejiang Province, Wenzhou, Zhejiang, China; [2] Department of Gastroenterology, Peking University First Hospital, Beijing, China; [3] Department of Infectious Diseases, The Second Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, China; [4] Department of Infectious Diseases, Henan provincial people's hospital, Zhengzhou, Henan, China; [5] Department of Infectious Diseases, Wenzhou Central Hospital, Wenzhou, Zhejiang, China; [6] Department of Infectious Diseases, Rui'an People's Hospital, Wenzhou, Zhejiang, China; [7] Department of Infectious Diseases, Cangnan People's Hospital, Wenzhou, Zhejiang, China; [8] Department of Infectious Diseases, Yueqing Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, China.

✉Corresponding author: Yongping Chen, Department of Infectious Diseases, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou 325025, China. E-mail: did@wzhospital.cn

#Tongtong Pan and Dazhi Chen contributed equally to this work.

Author contributions: YC was the study guarantor; TP and DC conceived and designed the study; TP, DC, HZ, ZL, XW, HL, QD and CC analyzed the data; TP, DC, CP, YK, JL, FS, LH and HL interpreted the data; TP and DC drafted the original manuscript; CP, YK, JL, FS, LH and HL edited the manuscript; all authors reviewed and approved the final manuscript.

Funding: This work was supported by the Key Laboratory of Diagnosis and Controlment for The Development of Chronic Liver Disease of Zhejiang Province; and Zhejiang Emergency Project (Grant number: 2020C03123).

Conflicts of Interest: The authors reported no conflict of interest.

Infectious Microbes & Diseases (2020) 2:4

Received: 7 July 2020 / Received in final form: 26 September 2020 / Accepted: 8 October 2020

https://doi.org/10.1097/IM9.0000000000000039

coronavirus infection.[6] Moreover, the degree of liver injury was also related to the severity of the disease. During this current COVID-19 pandemic, there are several reports thus far that indicate COVID-19-related liver injury. However, the cause of liver injury and its contribution to disease progression still remain unclear. This retrospective study evaluated the clinical characteristics of 265 patients diagnosed with COVID-19 and analyzed the liver functions of these patients. In addition, this study also evaluated the weight of liver injury in disease severity and established a prognostic decision model for patients with COVID-19.

Results

General condition and clinical characteristics of COVID-19 patients

Among 265 patients with COVID-19, 138 (52%) patients were determined as non-severe COVID-19 cases, while 127 (48%) patients were severe COVID-19 cases (Figure 1). Moreover, a total of 183 (69%) COVID-19 patients had an abnormal liver function within 48 hours of admission, of which 60 (33%) were non-severe COVID-19 patients and 123 (67%) were severe COVID-19 patients (Figure 1). Among COVID-19 patients with normal liver function, 78 (95%) patients were non-severe and only 4 (5%) patients were in severe cases.

General clinical characteristics of patients with and without abnormal liver function appeared very different. Patients in the abnormal liver function group were older than those in the normal liver function group (Table 1). Moreover, patients with abnormal liver function had one or more underlying diseases (54% vs 39%), suffered more bilateral chest pneumonia (86% vs 57%), had more acute respiratory distress syndrome (32% vs 0%), and had more secondary infections (38% vs 4%). Furthermore, 59% of the patients in the liver injury group had received antiviral treatment before admission. The median of hospitalization days for all patients was 18.0 days (14.0–24.0), and the median of hospitalization days for patients without and with abnormal liver function was 15.0 days [interquartile range (IQR) 10.8–20.0] and 20.0 days (IQR 15.0–28.0), respectively.

General laboratory test results of patients with and without abnormal liver function are shown in Table 1. Lymphocyte counts, PaO_2, and the oxygenation index were significantly decreased in patients with liver injury, while C-reactive protein, interleukin (IL)-6 and IL-10 were significantly increased. For liver function parameters, γ-glutamyl transpeptidase (γ-GT), alkaline phosphatase (ALP), globulin, and activated partial thromboplastin time appeared not to differ between the two groups. All other parameters, such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), fibrinogen (FIB), and D-dimer, were elevated in the liver injury group, while albumin and albumin to globulin ratio were reduced.

General conditions of COVID-19 patients with mild and moderate/severe liver injury

Analyses of general conditions in COVID-19 patients with mild and moderate/severe abnormal liver function revealed that patients over 65 years of age suffered more moderate/severe liver injury (36% vs 21% with mild liver injury) (Table 2), while patients under the age of 18 years had more mild liver injury (4.0% vs 0.0% with moderate/severe liver injury) and age between 19 to 40 years also had more mild liver injury (18% vs 11% with moderate/severe liver injury). Patients with coexisting conditions were more likely to have moderate/severe liver injury (68% vs 43% with mild liver injury), especially with type II diabetes (36% vs 15% with mild liver injury). Moreover, COVID-19 patients with moderate/severe abnormal liver function had more bilateral chest pneumonia (95% vs 79%), acute respiratory distress syndrome (44% vs 23%) and secondary infections (46% vs 32%). Furthermore, COVID-19 patients with a moderate/severe abnormal liver function stayed in the hospital longer than patients with mild abnormal liver function [23.0 days (IQR 20.0–33.5) vs 17.0 days (IQR 14.0–24.0)].

Laboratory characteristics of COVID-19 patients with mild and moderate/severe liver injury

Following the definition for mild and moderate/severe liver injury, COVID-19 patients with a moderate/severe liver injury

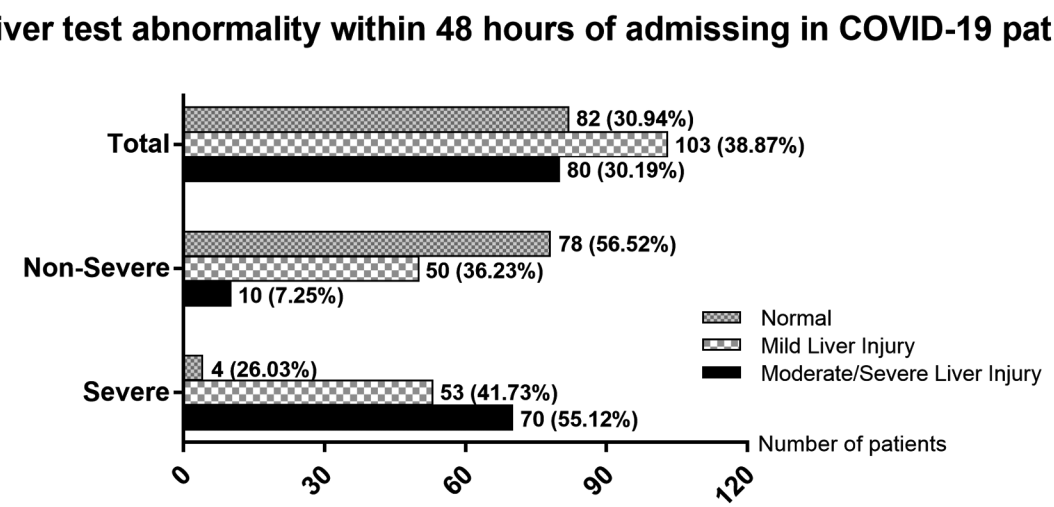

Figure 1. Statistics of COVID-19 patients with an abnormal liver function. COVID-19: coronavirus disease 2019.

Table 1

Personal and clinical characteristics of 265 COVID-19 patients with an abnormal liver function within 48 hours of admission to the hospital

Characteristics	All patients (n = 265)	Liver tests		P value
		Normal (n = 82)	Liver injury (n = 183)	
Median (interquartile) age (years)	52.00 (42.00–62.00)	47.00 (32.50–52.00)	56.00 (43.75–66.00)	0.000†
Sex (No (%)):				0.351
Male	146 (55.09)	42 (51.22)	104 (56.83)	
Female	119 (44.91)	40 (48.78)	79 (43.17)	
Coexisting conditions	130 (49.06)	32 (39.02)	98 (53.55)	0.023*
Pneumonia	241 (90.94)	71 (86.59)	170 (92.90)	0.098
Bilateral involvement on chest radiographs	203 (76.60)	46 (56.98)	157 (85.79)	0.000†
Acute respiratory distress syndrome	59 (22.26)	0 (0.00)	59 (32.24)	0.000†
Secondary infection	73 (27.55)	3 (3.66)	70 (38.25)	0.000†
Antiviral	110 (41.51)	2 (2.44)	108 (59.02)	0.000†
Length of stay	18.00 (14.00–24.00)	15.00 (10.75–20.00)	20.00 (15.00–28.00)	0.023*
Laboratory changes:				
White blood cell count ($\times 10^9$/L)	6.10 (4.67–8.66)	4.99 (3.64–5.88)	6.50 (4.89–10.15)	N
Neutrophil count ($\times 10^9$/L)	4.03 (2.59–6.17)	2.99 (3.64–5.88)	4.48 (2.93–8.74)	N
Lymphocyte count ($\times 10^9$/L)	1.08 (0.75–1.37)	1.37 (1.08–1.67)	1.00 (0.69–1.30)	0.002†
Erythrocyte count ($\times 10^9$/L)	4.23 (3.84–4.63)	4.26 (3.98–4.64)	4.17 (3.81–4.62)	N
Haemoglobin (g/L)	126.50 (115.00–138.25)	132.00 (122.25–140.00)	124.00 (112.75–138.25)	N
Platelet count ($\times 10^9$/L)	217.00 (172.50–280.00)	262.50 (175.00–321.25)	213.00 (168.50–264.50)	N
Potassium (mmol/L)	3.82 (3.45–4.18)	3.99 (3.49–4.57)	3.81 (3.40–4.14)	N
Sodium (mmol/L)	138.00 (135.00–140.05)	137.10 (134.93–139.00)	138.00 (135.00–140.45)	N
Urea nitrogen (mmoL/L)	4.40 (3.45–5.96)	3.63 (2.84–4.48)	4.68 (3.50–6.50)	N
Creatinine (U/L)	58.00 (49.40–74.50)	53.20 (41.78–66.50)	59.00 (50.00–75.00)	N
Creatine kinase (U/L)	71.00 (42.50–133.00)	68.50 (37.25–115.5)	72.00 (44.00–158.00)	N
Lactate dehydrogenase (U/L)	288.50 (198.00–418.00)	243.00 (158.00–380.00)	307.00 (201.00–431.00)	0.085
Myohemoglobin (ng/mL)	40.75 (24.25–74.75)	25.25 (18.00–39.25)	45.95 (29.60–96.85)	N
Type B brain natriuretic peptide (pg/mL)	37.50 (11.00–134.80)	13.00 (9.00–61.00)	42.00 (11.55–145.50)	N
C-reactive protein (CRP) (mg/L)	25.40 (8.92–62.20)	10.39 (4.455–37.00)	36.17 (12.63–81.14)	0.000†
Interleukin-2 (IL-2) (pg/mL)	0.80 (0.53–1.02)	0.61 (0.30–1.02)	0.80 (0.53–1.04)	N
Interleukin-4 (IL-4) (pg/mL)	0.82 (0.45–1.39)	0.48 (0.10–0.64)	0.65 (0.43–1.13)	N
Interleukin-6 (IL-6) (pg/mL)	5.32 (2.01–27.98)	1.73 (0.87–6.17)	6.19 (2.46–44.89)	0.019*
Interleukin-10 (IL-10) (pg/mL)	3.50 (1.76–8.35)	2.06 (1.03–3.04)	4.13 (2.03–9.30)	0.000†
Interferon-γ (INF-γ) (pg/mL)	1.47 (0.27–3.40)	0.22 (0.02–0.31)	1.61 (0.36–3.71)	N
Tumor necrosis factor-α (TNF-α) (pg/mL)	0.46 (0.10–1.21)	0.59 (0.13–1.15)	0.42 (0.10–1.21)	N
Blood PH	7.42 (7.39–7.44)	7.43 (7.39–7.44)	7.41 (7.38–7.44)	N
PaO_2 (mm Hg)	91.75 (75.48–112.40)	111.00 (98.10–138.30)	88.40 (74.60–108.60)	0.002†
Oxygenation index (mm Hg)	360.78 (206.67–466.49)	519.05 (380.57–623.57)	353.64 (199.76–451.43)	0.001†
Liver biochemistry examination:				
Alanine aminotransferase (U/L)	33.50 (22.00–59.50)	24.00 (19.75–30.25)	38.00 (24.00–63.00)	N
Aspartate aminotransferase (U/L)	32.00 (24.00–48.63)	20.65 (16.90–25.00)	36.00 (25.00–51.10)	0.000†
Alkaline phosphatase (U/L)	65.00 (47.20–86.00)	49.00 (42.95–62.75)	67.00 (50.00–86.00)	N
γ-Glutamyltransferase (U/L)	45.00 (23.80–83.95)	16.65 (11.00–30.50)	50.00 (26.50–94.50)	N
Total protein (g/L)	67.00 (62.40–70.40)	72.90 (67.95–76.40)	66.10 (61.15–69.28)	N
Albumin (g/L)	33.80 (29.30–38.80)	41.80 (40.5–43.40)	32.50 (28.00–36.75)	0.000†
Globulin (g/L)	30.90 (27.60–34.30)	29.80 (26.60–32.75)	31.00 (27.95–34.65)	N
Albumin/Globulin ratio	1.10 (1.00–1.30)	1.30 (1.30–1.50)	1.10 (0.90–1.30)	0.002†
Total bilirubin (umoL/L)	11.25 (8.00–16.95)	9.00 (5.95–14.05)	12.00 (9.00–17.90)	N
Prothrombin time (PT) (s)	13.10 (11.65–13.70)	13.00 (11.00–13.50)	13.10 (12.08–13.73)	N
International normalized ratio (INR)	1.04 (0.96–1.08)	1.03 (0.95–1.06)	1.04 (0.97–1.10)	N
Fibrinogen (FIB) (g/L)	4.96 (3.68–6.34)	4.40 (3.63–5.08)	5.37 (3.92–6.80)	0.005†
Activated partial thromboplastin time (APTT) (s)	37.65 (32.38–44.08)	36.20 (28.75–44.05)	38.00 (34.10–44.70)	N
Thrombin time (s)	16.40 (15.35–18.90)	15.00 (14.53–15.80)	17.00 (15.75–19.45)	N
D-dimer (mg/L)	0.69 (0.32–1.80)	0.44 (0.24–0.87)	0.83 (0.36–1.86)	0.020*

Data are N (%) or median with 95% CI (IQR).

N indicates that parameters of both groups are in the normal range.

* $P < 0.05$.

† $P < 0.01$ versus No liver injury group.

had higher ALT levels [63.00 U/L (27.95–111.95) vs 30.00 U/L (21.50–42.95)] and AST levels [49.00 U/L (29.50–76.50) vs 28.10 U/L (24.00–40.50)]. Compared to patients with mild liver injury, patients with moderate/severe liver injury also showed a significant elevation of γ-GT, FIB, D-dimer, IL-6, and IL-10 levels and significant reduction of total protein and albumin levels, albumin to globulin ratio, PaO_2, and the oxygenation index (Table 3).

Table 2

Personal and clinical characteristics of 183 COVID-19 patients with an abnormal liver function

Characteristics	All patients (n = 183)	Liver tests		
		Mild liver injury (n = 103)	Moderate/severe liver injury (n = 80)	*P* value
Median (interquartile) age (years) (No (%))	56.00 (43.75–66.00)	53.00 (41.00–62.50)	57.00 (48.00–70.00)	0.044*
Age groups (years) (No (%)):	No. (%)	No. (%)	No. (%)	
≤18	5 (2.75)	5 (4.85)	0 (0.00)	
19–40	28 (15.30)	19 (18.45)	9 (11.25)	
41–65	99 (54.10)	57 (55.34)	42 (52.50)	
≥66	51 (27.87)	22 (21.36)	29 (36.25)	
Sex (No (%)):				0.644
Male	104 (56.83)	57 (55.34)	47 (58.75)	
Female	79 (43.17)	46 (44.66)	33 (41.25)	
Coexisting conditions (No (%)):				
Any	98 (53.55)	44 (42.72)	54 (67.50)	0.001†
Hypertension	51 (27.87)	24 (23.30)	27 (33.75)	
Diabetes	44 (24.04)	15 (14.56)	29 (36.25)	
Chronic lung disease	8 (4.37)	2 (1.94)	6 (7.50)	
Heart disease	17 (9.29)	6 (5.83)	11 (13.75)	
Renal disease	3 (1.64)	0 (0.00)	3 (3.75)	
Cancer	2 (1.09)	0 (0.00)	2 (2.50)	
Pneumonia (No (%))	170 (92.90)	92 (89.32)	78 (97.50)	0.033*
Bilateral involvement on chest radiographs (No (%))	157 (85.79)	81 (78.64)	76 (95.00)	0.002†
Acute respiratory distress syndrome (No (%))	59 (32.24)	24 (23.30)	35 (43.75)	0.003†
Secondary infection (No (%))	70 (38.25)	33 (32.04)	37 (46.25)	0.050*
Antiviral	108 (59.02)	46 (44.66)	62 (77.50)	0.000†
Length of stay	20.00 (15.00–28.00)	17.00 (14.00–24.00)	23.00 (20.00–33.50)	0.001†

Data are N (%) or median with 95% CI (IQR).
* $P < 0.05$,
† $P < 0.01$ versus mild liver injury cases.

Correlation between the levels of liver injury and severity of COVID-19 disease

To study whether the severity of liver injury could predict the outcome of COVID-19, several parameters of liver function were correlated with severity of COVID-19 disease. As shown in Figure 2, the levels of ALT and AST correlated well with the severity of COVID-19 disease, however, the levels of albumin showed a negative correlation with severity of COVID-19 disease. In addition, since the oxygenation index, D-dimer, and lymphocyte counts are commonly used in the clinic to evaluate severity of COVID-19 disease, a correlation analysis of these parameters with liver function parameters such as ALT, AST and albumin is shown in Figure 3. ALT and AST were negatively correlated with the oxygenation index and positively correlated with D-dimer. Moreover, albumin was positively correlated with the oxygenation index and lymphocyte counts but negatively correlated with D-dimer (both $P < 0.05$). Furthermore, the correlation coefficient (r) of albumin with the oxygenation index, D-dimer, and lymphocyte counts all exceeded 0.5, which indicates that albumin may be a good monitor for severity of COVID-19 (Figure 3).

Establishment of a COVID-19 prognostic evaluation decision model

A decision tree is a flowchart-like tree structure that maps the structure between the stages of the decision process into an arrow diagram to help categorize and predict. Due to the complexity of clinical factors, many clinical decisions are uncertain. At this time, a decision tree can help clinicians choose the best decision or course of action. By employing the GridsearchCV algorithm that could find hyper-parameters strongly correlated with the severity of COVID-19, a COVID-19 prognostic evaluation decision model was constructed. The first model (model 1) was constructed by employing the oxygenation index, age, D-dimer, and FIB as shown in Figure 4A. The second model (model 2) was established by employing albumin, the oxygenation index, age, D-dimer, and PaO_2 as shown in Figure 5A. In model 2, albumin was the most important indicator, although the gap between the two models during the training phase was not large [Area Under The Curve (AUC) model 1: 0.9828 vs AUC model 2: 0.9987 (Figure 4B and 5B)]. However, by using 50 random verification data to validate these models, the prediction accuracy of Model 2 was 88% while the prediction accuracy of Model 1 was 80% (Figure 4C and 5C), suggesting a better prediction using model 2.

According to the decision tree of model 2, three main decision paths for COVID-19 severity (severe/critical cases) can be made:

Path 1: When albumin is <35.0 g/L and the patient's age is over 39.5 years old, and if PaO_2 is not low, the patient deflects to mild; while if PaO_2 is low, the patient deflects to severe.
Path 2: When albumin is <35.0 g/L, if the patient is over 39.5 years old and the oxygenation index is ≤353.467 mm Hg, the patient is more likely to be severe; if the patient is over 51.5 years old and the oxygenation index is >353.467 mm Hg, the patient still deflects to severe.
Path 3: When albumin is ≥35.0 g/L, if the oxygenation index is ≤296.67 mm Hg, the patient is more likely to be severe; if the oxygenation index is >296.67 mm Hg, but the D-dimer is elevated and the patient's age is over 54.5 years old, there is still a small probability of deflecting to severe.

Discussion

Although there are few reports of COVID-19 combined with liver injury, it has been a severe concern among clinicians. Our

Table 3

Laboratory examination of COVID-19 patients with an abnormal liver function within 48 hours of admission to the hospital

Variables	All patients (n = 183)	Liver test		
		Mild liver injury (n = 103)	Moderate/severe liver injury (n = 80)	*P* value
Liver injury:				
Alanine aminotransferase (U/L)	38.00 (24.00–63.00)	30.00 (21.50–42.95)	63.00 (27.95–111.95)	0.000†
Aspartate aminotransferase (U/L)	36.00 (25.00–51.10)	28.10 (24.00–40.50)	49.00 (29.50–76.50)	0.000†
Alkaline phosphatase (U/L)	67.00 (50.00–86.00)	64.00 (48.00–71.00)	82.50 (550.75–127.25)	N
γ-Glutamyl transferase (U/L)	50.00 (26.50–94.50)	34.00 (24.00–52.60)	79.75 (44.25–157.25)	0.000†
Total protein (g/L)	66.10 (61.15–69.28)	66.70 (62.28–69.55)	63.60 (58.83–68.98)	0.614
Albumin (g/L)	32.50 (28.00–36.75)	34.90 (30.00–38.75)	31.20 (28.40–34.00)	0.001†
Albumin (g/L) (No (%)):				
≤35.0	126 (68.85)	52 (50.49)	74 (92.50)	
35.0–40.0	42 (22.95)	37 (35.92)	5 (6.25)	
≥40.0	15 (8.20)	13 (12.61)	2 (2.50)	
Globulin (g/L)	31.00 (27.95–34.65)	30.90 (27.40–33.78)	31.70 (29.20–37.20)	N
Albumin/Globulin ratio	1.10 (0.90–1.30)	1.20 (1.00–1.31)	1.00 (0.90–1.10)	0.004†
Total bilirubin (umoL/L)	12.00 (9.00–17.90)	11.30 (8.20–11.90)	15.00 (11.00–20.25)	N
Liver ischemia and hypoxia:				
Prothrombin time (PT) (s)	13.10 (12.08–13.73)	13.10 (12.30–13.70)	13.10 (11.40–13.95)	N
International normalized ratio (INR)	1.04 (0.97–1.10)	1.03 (0.96–1.07)	1.05 (0.95–1.13)	N
Fibrinogen (FIB) (g/L)	5.37 (3.92–6.80)	4.96 (3.38–6.04)	6.64 (4.58–8.07)	0.027*
Activated partial thromboplastin time (APTT) (s)	38.00 (34.10–44.70)	37.65 (33.05–43.48)	39.60 (35.50–46.30)	N
Thrombin time (s)	17.00 (15.75–19.45)	16.00 (15.25–17.10)	19.15 (16.73–25.03)	N
D-dimer (mg/L)	0.83 (0.36–1.86)	0.51 (0.26–1.29)	1.40 (0.80–4.52)	0.000†
PaO_2 (mm Hg)	88.40 (74.60–108.60)	92.00 (81.50–110.50)	79.80 (68.13–106.30)	0.045*
Oxygenation index (mm Hg)	353.64 (199.76–451.43)	404.76 (233.09–467.14)	278.98 (152.83–383.21)	0.045*
Systemic abnormal immune and inflammatory response:				
White blood cell count ($\times 10^9$/L)	6.50 (4.89–10.15)	6.10 (4.57–8.30)	7.50 (5.48–11.13)	N
White blood cell count ($\times 10^9$/L) (No (%)):				
<4	19 (10.38)	12 (11.65)	7 (8.75)	
4–10	53 (28.86)	34 (33.01)	19 (23.75)	
>10	111 (60.66)	57 (55.34)	54 (67.50)	
Neutrophil count ($\times 10^9$/L)	4.48 (2.93–8.74)	4.04 (2.36–5.93)	5.33 (3.53–9.06)	N
Lymphocyte count ($\times 10^9$/L)	1.00 (0.69–1.30)	1.10 (0.79–1.34)	0.91 (0.56–1.20)	0.095
C-reactive protein (CRP) (mg/L)	36.17 (12.63–81.14)	25.40 (8.00–71.20)	46.40 (17.85–90.50)	0.068
Interleukin-2 (IL-2) (pg/mL)	0.80 (0.53–1.04)	0.67 (0.52–1.07)	0.86 (0.60–1.01)	N
Interleukin-4 (IL-4) (pg/mL)	0.65 (0.43–1.13)	0.57 (0.31–1.15)	0.80 (0.52–1.13)	N
Interleukin-6 (IL-6) (pg/mL)	6.19 (2.46–44.89)	4.25 (2.06–22.91)	12.00 (4.98–57.97)	0.004†
Interleukin-10 (IL-10) (pg/mL)	4.13 (2.03–9.30)	3.50 (1.59–6.96)	5.00 (3.15–12.88)	0.028*
Interferon-γ (INF-γ) (pg/mL)	1.61 (0.36–3.71)	0.93 (0.17–2.89)	2.06 (0.84–4.13)	N
Tumor necrosis factor-α (TNF-α) (pg/mL)	0.42 (0.10–1.21)	0.29 (0.10–0.93)	0.52 (0.10–1.55)	N
Other lab examinations:				
Erythrocyte count ($\times 10^9$ /L)	4.17 (3.81–4.62)	4.16 (3.84–4.80)	4.18 (3.60–4.42)	N
Hemoglobin (g/L)	124.00 (112.75–138.25)	127.00 (119.50–142.00)	119.00 (104.50–134.50)	N
Platelet count ($\times 10^9$ /L)	213.00 (168.50–264.50)	234.00 (164.00–323.00)	200.00 (175.50–263.50)	N
Urea nitrogen (mmoL/L)	4.68 (3.50–6.50)	4.14 (3.50–6.00)	5.16 (3.60–7.53)	N
Creatinine (U/L)	59.00 (50.00–75.00)	60.70 (51.05–74.75)	56.00 (48.00–78.50)	N
Creatine kinase (U/L)	72.00 (44.00–158.00)	72.00 (46.75–140.25)	65.00 (41.00–221.00)	N
Lactate dehydrogenase (U/L)	307.00 (201.00–431.00)	289.50 (204.25–378.00)	343.00 (201.00–460.00)	0.639
Myohemoglobin (ng/mL)	45.95 (29.60–96.85)	37.40 (24.00–54.40)	70.00 (42.50–111.80)	N
Type B brain natriuretic peptide (pg/mL)	42.00 (11.55–145.50)	28.50 (9.00–64.50)	91.50 (16.75–209.00)	N
Blood PH	7.41 (7.38–7.44)	7.41 (7.38–7.44)	7.42 (7.39–7.45)	N
Potassium (mmol/L)	3.81 (3.40–4.14)	3.84 (3.47–4.15)	3.71 (3.29–4.12)	N
Sodium (mmol/L)	138.00 (135.00–140.45)	138.80 (136.00–140.25)	138.00 (135.00–141.08)	N

Data are N (%) or median with 95% CI (IQR).

N indicates that parameters of both groups are in the normal range.

* $P < 0.05$.

† $P < 0.01$ versus mild liver injury cases.

data shows that 69% of the COVID-19 patients had varying degrees of liver injury within 48 hours of admission. We also found that in the liver injury group, levels of ALT, AST, FIB, and D-dimer were elevated, while albumin levels were reduced. However, the underlying reason for liver injury in COVID-19 patients is still unclear. Since the target receptor for SARS-COV-2 is the angiotensin-converting enzyme 2 receptor, which mainly expresses in bile duct epithelial cells rather than hepatocytes, hepatocyte injury is likely due to other mechanisms.[7] Moreover, recent studies have found that SARS-CoV-2 can greatly weaken the barrier and bile acid transport function in angiotensin-converting enzyme 2 receptor positive liver bile duct organoids.[8]

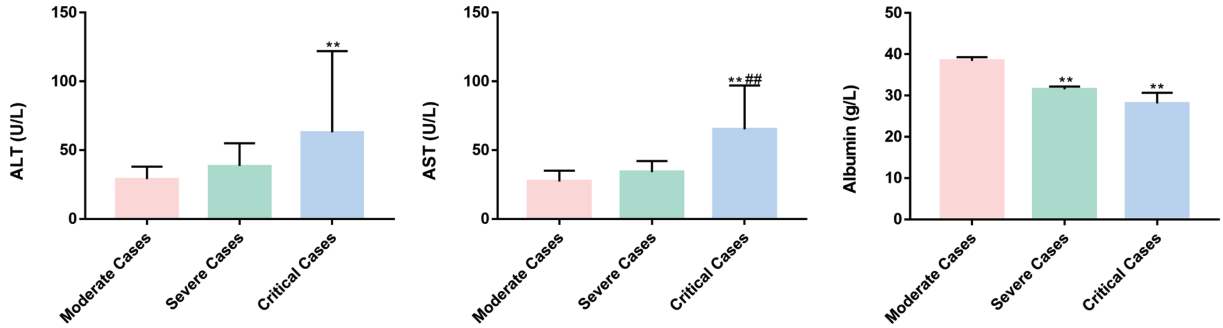

Figure 2. Levels of ALT, AST and albumin in COVID-19 patients. The data is described using median (interquartile range IQR) values. $^{*}P<0.05$, $^{**}P<0.01$ versus moderate cases; $^{\#}P<0.05$, $^{\#\#}P<0.01$ versus severe cases. ALT: alanine aminotransferase; AST: aspartate aminotransferase.

Therefore, most researchers believe that SARS-CoV-2 infection in the liver may damage bile duct cells directly and cause hepatocyte damage consequently.[9] However, ultrastructural and histological evidence from a recent study showed that hepatocytes in patients with COVID-19 combined with liver injury had typical viral infection lesions, implying that SARS-COV-2 can also directly damage hepatocytes.[10] In addition, histopathological features of COVID-19 patients' liver did not show any obvious specific damage to hepatocytes or bile duct cells.[11] This is consistent with our results showing that in patients with COVID-19, there were moderate increases in ALT and AST levels. Only one critically ill patient showed extremely high levels of ALT and AST at 662.20 U/L and 863.70 U/L, respectively. Moreover, the indicators of bile duct injury, ALP, and γ-GT, did not increase significantly in the liver injury group. Even in the moderate/severe liver injury group, there was only a slight increase in γ-GT levels. Furthermore, a recent study showed that COVID-19 patients exhibited either hepatocyte type or hepatobiliary mixed type injuries with severe pneumonia.[6] Therefore, liver injury may be secondary due to a variety of factors, such as the patients' basic physical conditions, systemic inflammatory responses, ischemia-hypoxia-reperfusion injuries, and medication.[12]

Although 108 out of 183 COVID-19 patients with liver injury received antiviral therapy before admission, there were still 75 patients (41%) who had liver injury before admission, suggesting that COVID-19-related liver damage is not just caused by antiviral drugs. Moreover, many COVID-19 patients may also have received other medications before admission, such as antipyretics, antibiotics and steroids, which may cause liver function disorder.[2] The current study revealed that patients with liver injury usually had a poor basic condition with a median age of 56.0 years and one or more underlying diseases (54%). C-reactive protein and inflammatory factors such as IL-6 and IL-10 were elevated at baseline in COVID-19 patients with liver injury. Furthermore, more than 40% of the COVID-19 patients required oxygen therapy.[13] It is conceivable that PaO_2 and the oxygenation index of patients with liver injury decreased significantly. Hypoxia in the liver may cause liver cell death and inflammatory cell infiltration can aggravate liver injury.[14] Our study also revealed abnormal coagulation functions in patients with liver injury due to elevated FIB and D-dimer. Activation of the blood coagulation function may enhance immune responses and provide important defenses against viral infections and sepsis.[15] Therefore, abnormal coagulation could further deteriorate liver function and D-dimer and fibrin degradation products could be important to predict COVID-19 disease progression.[16]

Although liver injury is a prominent manifestation of COVID-19, can liver function parameters be used to monitor and predict progression of COVID-19 patients? Previous studies have shown that the incidence of liver damage in severe COVID-19 cases was significantly higher than that in non-severe cases, and the incidence of liver injury in fatal cases was as high as 58%–78%.[17,18] There are also reports that liver injury is an independent risk factor for COVID-19 illness.[19] Our observation also found that as the condition of COVID-19 patients worsened, patients' transaminase levels and total bilirubin levels increased, while albumin levels decreased. Moreover, the levels of ALT and AST as well as albumin were correlated with the oxygenation index and D-dimer as well as lymphocyte counts. The correlation coefficient (r) between albumin and these parameters was higher than 0.5, indicating a good correlation. In addition, the degree of reduction in albumin levels can also predict severity of Middle

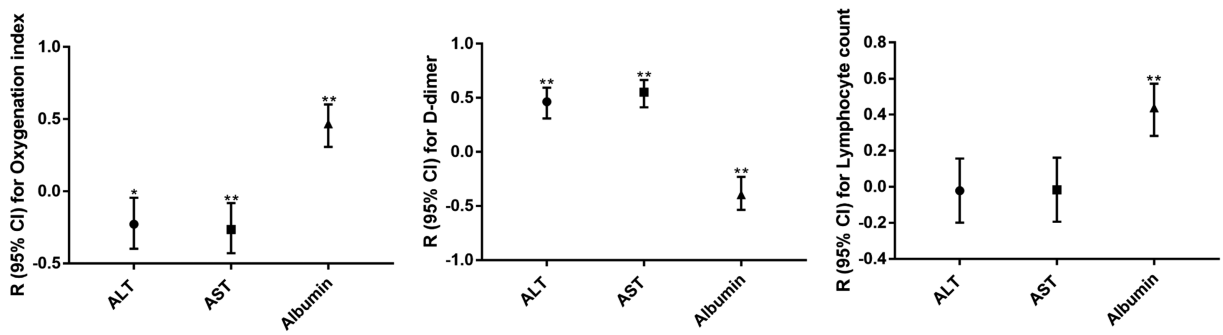

Figure 3. Correlation analysis of liver function indices showing the oxygenation index, D-dimer and lymphocyte counts. The data is described using the median (interquartile range IQR) value. R, Pearson correlation coefficient, $^{*}P<0.05$, $^{**}P<0.01$.

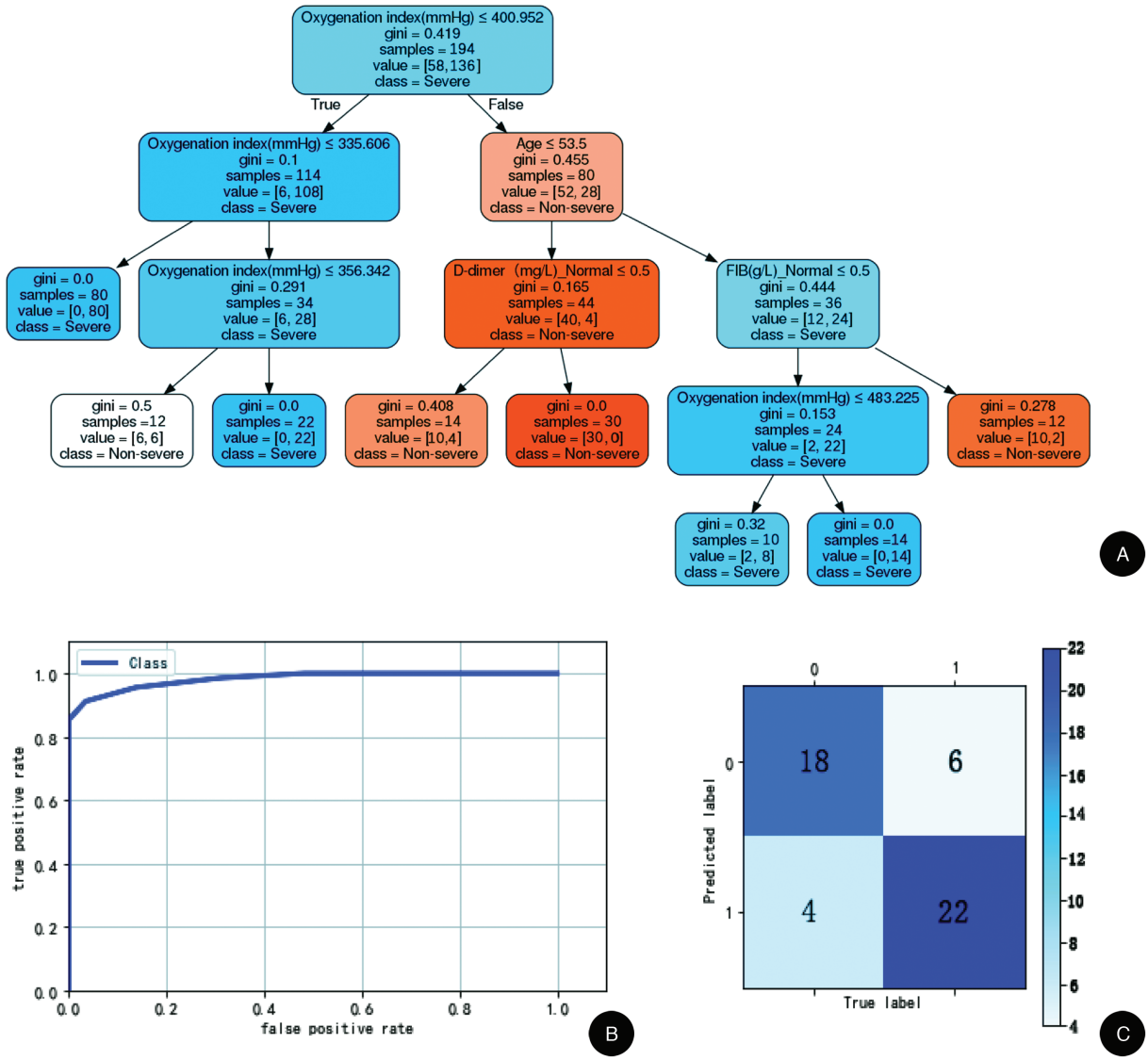

Figure 4. Decision model and decision path without liver function. A. Decision tree and decision path without liver function (Model 1), B. Model 1 receiver operating characteristic curve, C. Model 1 validation sample confusion matrix.

East respiratory syndrome disease.[20] Therefore, liver injury parameters, especially albumin, could monitor severity of disease in patients with COVID-19.

Since there are no reports about COVID-19 prognostic assessment models based on liver injury indicators, establishment and comparison of the COVID-19 prognostic evaluation decision model with and without liver function parameters could be useful for physician to make clinical decision. For the two models established in this study, AUCs exceeded 0.98 during training, but accuracy of the model with liver function verification was 88%, which higher than the model without liver function verification (80%). Using the model with liver function verification, three quick and reliable decision paths for severe and critical COVID-19 cases were proposed. To our knowledge, this is the first COVID-19 prognostic assessment decision model that includes liver injury parameters. Compared with other complicated COVID-19 assessment methods, this model is also concise and simple to operate. Therefore, it allows physicians to quickly identify severe COVID-19 patients and to achieve early diagnosis and treatment for these patients. It is also of great significance to save medical and health resources and reduce the death rate of COVID-19 patients.

Our study has some limitations. First, this study was retrospective, and patients were not followed up for a long time to study the dynamic change of liver function in COVID-19 patients and its impact on long-term prognosis. Second, practical application of the prognostic evaluation decision model still needs to be evaluated with large multi-center clinical trials.

Conclusions

With 265 confirmed COVID-19 patients, clinical characteristics and liver function were analyzed and liver injury was observed in 69% of the patients. Moreover, moderate and severe liver injuries were closely correlated with severity of COVID-19. Furthermore, a prognostic evaluation decision model with liver function parameters was proposed, which could be helpful for physicians to quickly assess conditions and prognosis of COVID-19 patients.

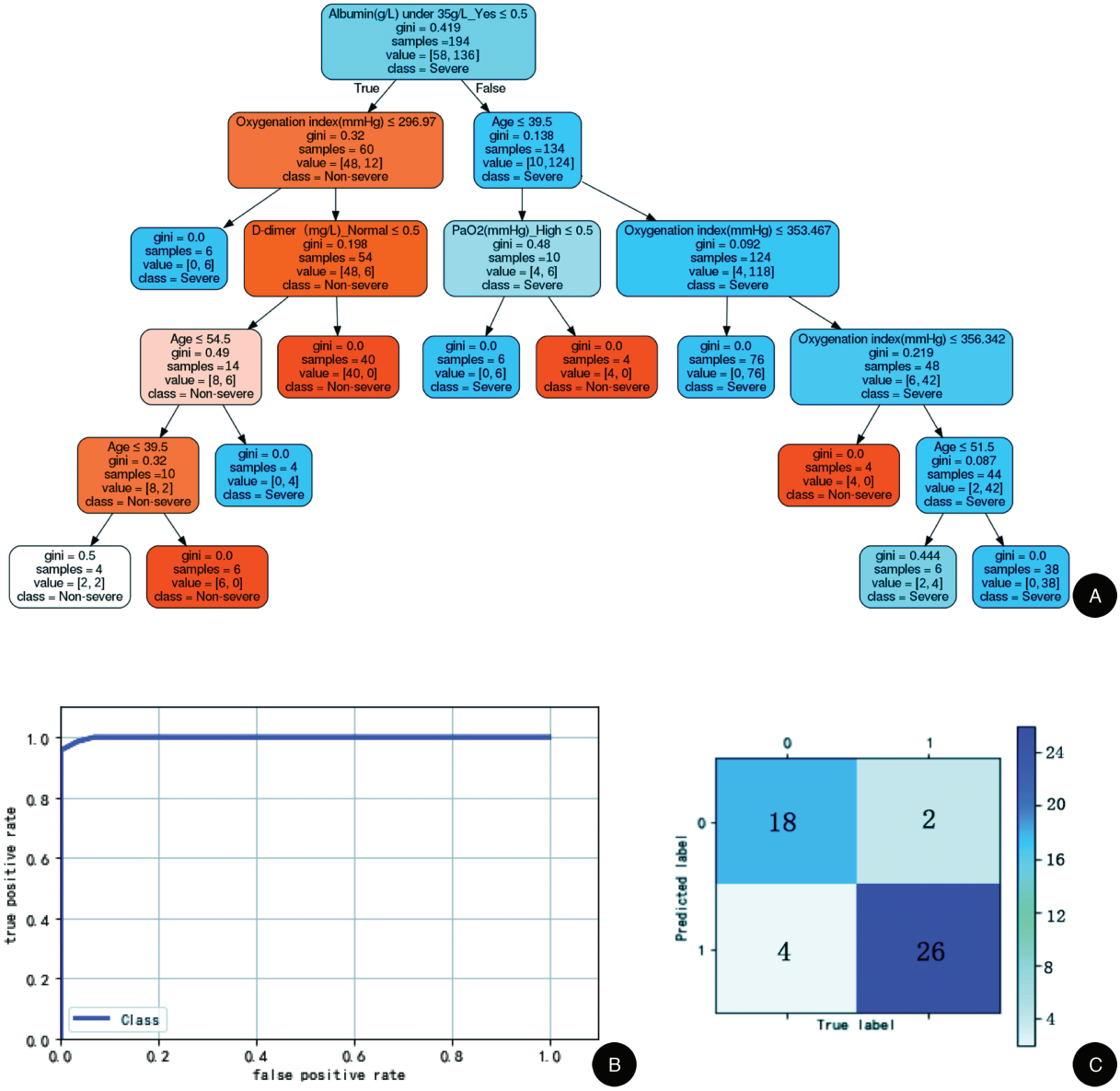

Figure 5. Decision model and decision path with liver function. A: Decision tree and decision path with liver function (Model 2), B: Model 2 receiver operating characteristic curve, C: Model 2 validation sample confusion matrix.

Materials and methods

Study design and participants

Patients' data in this retrospective study were collected from seven designated hospitals for COVID-19 in Zhejiang and Henan provinces from January 30, 2020 to April 20, 2020. Inclusion criteria were: 1) patients diagnosed as COVID-19 with laboratory evidence according to WHO's Country and Technical Guidance on COVID-19 (https://www.who.int/emergencies/diseases/novel-coronavirus-2019); 2) patients with complete clinical data. Patients with any other known liver diseases, such as viral hepatitis, fatty liver disease, and liver malignancies, were excluded from this study. On the basis of the *New Coronavirus Pneumonia Diagnosis and Treatment Program (Trial Version 7)* (covid19.alliancebrh.com | Updated: 2020-03-27), patients were divided into non-severe group (moderate cases) and severe group (severe/critical cases). Since there is no unified definition of COVID-19-related liver injury, mild liver injury was defined as more than one time the upper limit of normal of any of the following liver function parameters: ALT, AST, γ-GT, ALP, and total bilirubin. When these liver function parameters exceeded two times upper limit of normal, it was defined as moderate/severe liver injury.

Data collection and proofing

The data of the epidemiological situation, symptoms, laboratory findings, radiological features, comorbidity, treatments, and clinical outcomes were collected from January 30, 2020 to April 20, 2020 in a unified form. All data were proofed by two physicians. If records were missing or clarification was needed, we directly communicated with the attending physicians.

Ethics permission and practices

The study was approved by the First Affiliated Hospital of Wenzhou Medical University Ethics Committee (KY-2020-

06.01). All patients signed the informed consent. The privacy rights of human subjects were observed. The procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975 with revision in 2000 (http://www.wma.net/e/policy/17-c_e.html).

Construction of the prognostic evaluation decision model based on liver injury

The decision tree was used to establish the COVID-19 disease assessment model. Python 3.6.7 was used as a tool and the main third-party tool libraries included: pandas/numpy/matplotlib/skearn/seaborn/statsmodel/scipy. The text code ran on ubuntu 18.04. The lTS operating system and the core computing hardware were AMD Ryzen3 2200G with 16G DDR4 memory. The CART algorithm was used to generate a decision tree, and the GridsearchCV algorithm was used to measure the importance of each feature and to find hyper-parameters based on gini impurity. A COVID-19 prognostic decision model was established with or without liver function by random selection of 194 cases with complete clinical data as training sets and 50 cases as verification of data.

Statistical analysis

Categorical variables were described as percentages, and continuous variables were described using median with 95% confidence interval (interquartile range) values. Continuous variables were compared using independent group t tests when the data were normally distributed; otherwise, the Mann-Whitney test was used. Categorical variables were compared using the χ^2 test; Fisher exact test was used when the data were limited. All statistical analyses were performed using SPSS 23.0. The significance was recognized at $P < 0.05$.

References

[1] Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020;395(10223):507–513.

[2] Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;395(10223):497–506.

[3] Evans PC, Ed Rainger G, Mason JC, et al. Endothelial dysfunction in COVID-19: a position paper of the ESC Working Group for Atherosclerosis and Vascular Biology, and the ESC Council of Basic Cardiovascular Science. *Cardiovasc Res* 2020;116(14):2177–2184.

[4] Fan Z, Chen L, Li J, et al. Clinical features of COVID-19-related liver functional abnormality. *Clin Gastroenterol Hepatol* 2020;18(7):1561–1566.

[5] Cai Q, Huang D, Yu H, et al. COVID-19: abnormal liver function tests. *J Hepatol* 2020;73(3):566–574.

[6] Kukla M, Skonieczna-Żydecka K, Kotfis K, et al. COVID-19, MERS and SARS with concomitant liver injury-systematic review of the existing literature. *J Clin Med* 2020;9(5):1420.

[7] Parohan M, Yaghoubi S, Seraj A. Liver injury is associated with severe Coronavirus disease 2019 (COVID-19) infection: a systematic review and meta-analysis of retrospective studies. *Hepatol Res* 2020;50(8):924–935.

[8] Zhao B, Ni C, Gao R, et al. Recapitulation of SARS-CoV-2 infection and cholangiocyte damage with human liver ductal organoids. *Protein Cell* 2020;11(10):771–775.

[9] Bangash MN, Patel J, Parekh D. COVID-19 and the liver: little cause for concern. *Lancet Gastroenterol Hepatol* 2020;5(6):529–530.

[10] Wang Y, Liu S, Liu H, et al. SARS-CoV-2 infection of the liver directly contributes to hepatic impairment in patients with COVID-19. *J Hepatol* 2020;73(4):807–816.

[11] Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med* 2020;8(4):420–422.

[12] Zhang C, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. *Lancet Gastroenterol Hepatol* 2020;5(5):428–430.

[13] Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020;382(18):1708–1720.

[14] Yang L, Wang W, Wang X, et al. Creg in hepatocytes ameliorates liver ischemia/reperfusion injury in a TAK1-dependent manner in mice. *Hepatology* 2019;69(1):294–313.

[15] Minasyan H, Flachsbart F. Blood coagulation: a powerful bactericidal mechanism of human innate immunity. *Int Rev Immunol* 2019;38(1):3–17.

[16] Han H, Yang L, Liu R, et al. Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. *Clin Chem Lab Med* 2020;58(7):1116–1120.

[17] Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020;395(10229):1054–1062.

[18] Hoffmann M, Kleine-Weber H, Krüger N, Müller M, Drosten C, Pöhlmann S. The novel coronavirus 2019 (2019-nCoV) uses the SARS-coronavirus receptor ACE2 and the cellular protease TMPRSS2 for entry into target cells. Preprint. Posted online January 31, 2020. bioRxiv.

[19] Hao SR, Zhang SY, Lian JS, et al. Liver enzyme elevation in coronavirus disease 2019: a multicenter, retrospective, cross-sectional study. *Am J Gastroenterol* 2020;115(7):1075–1083.

[20] Saad M, Omrani AS, Baig K, et al. Clinical aspects and outcomes of 70 patients with Middle East respiratory syndrome coronavirus infection: a single-center experience in Saudi Arabia. *Int J Infect Dis* 2014;29:301–306.

How to cite this article: Pan T, Chen D, Pan C, Kang Y, Liu J, Su F, Hong L, Li H, Zhao H, Lin Z, Wang X, Lin H, Du Q, Cai C, Chen Y. Characteristics of liver functions in patients with COVID-19 and construction of a prognostic evaluation decision model based on liver functions. *Infect Microb Dis* 2020;2(4):151–159. doi: 10.1097/IM9.0000000000000039