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Clinical Features of Patients Infected With Coronavirus Disease 2019 With Elevated Liver Biochemistries: A Multicenter, Retrospective Study

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BACKGROUND AND AIMS: In December 2019, an outbreak of coronavirus disease 2019 (COVID-19) emerged in Wuhan, China. Although it has been reported that some patients with COVID-19 showed elevated liver biochemistries, there are few studies regarding the clinical features and prognosis of these patients.

APPROACH AND RESULTS: In this multicenter, retrospective study, we collected data on laboratory-confirmed patients with COVID-19 from three hospitals in Wuhan, China, who died or were discharged between February 1, 2020, and February 20, 2020. Data on demographics, comorbidities, clinical symptoms, laboratory examinations on admission, complications, treatment, and outcome were collected. A total of 482 patients were enrolled in this study. Of those, 142 (29.5%) patients showed abnormal liver biochemistries on admission, and patients with elevated alanine aminotransferase, aspartate aminotransferase (AST), and total bilirubin (TBIL) accounted for 67.6%, 69.0%, and 16.2%, respectively. Those with abnormal liver biochemistries showed higher percentages of severe cases and comorbidities and were more likely to have dyspnea, chest distress or pain, and increased hemoglobin (Hb) on admission. Higher rates of complications and mortality and worse recovery when discharged were observed in patients with abnormal AST or TBIL. Multivariable regression analysis showed that chest distress or pain (odds ratio [OR], 1.765; P = 0.018), dyspnea (OR, 2.495; P = 0.001), elevated C-reactive protein level (OR, 1.007; P = 0.008), elevated white blood count (OR, 1.139; P = 0.013), and elevated Hb concentration (OR, 1.024; P = 0.001) were independent factors associated with elevated liver biochemistries in patients with COVID-19.

CONCLUSIONS: Elevated liver biochemistries were common in patients with COVID-19. Patients with hypoxia or severe inflammation are more likely to experience increased liver biochemistries on admission. Those with abnormal AST or TBIL on admission are more likely to suffer from severe complications and death. (Hepatology 2021;73:1509-1520).

In December 2019, a coronavirus named "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2) caused an outbreak in Wuhan, China. The World Health Organization named the disease "coronavirus disease 2019" (COVID-19).[1] As of May 8, 2020, the cumulative number of infected people worldwide had risen sharply to more than 3.7 million, with an alarming mortality rate of 6.9%.[2] The main

Abbreviations: ALT, alanine aminotransferase; ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; CI, confidence interval; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; CT, computed tomography; DBIL, direct bilirubin; Hb, hemoglobin; hs-cTnI, high-sensitivity cardiac troponin I; ICU, intensive care unit; IQR, interquartile range; LDH, lactate dehydrogenase; NAFLD, nonalcoholic fatty liver disease; OR, odds ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TBIL, total bilirubin; WBC, white blood count.

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clinical manifestations of COVID-19 include fever, cough, diarrhea, myalgia, and dyspnea. Although most patients show mild symptoms, some progress rapidly to critical conditions and develop acute respiratory distress syndrome (ARDS), acute respiratory failure, coagulopathy, septic shock, and even death.[3]

Retrospective studies have found that liver biochemical abnormalities occurred in some patients infected with COVID-19,[4-6] whereas a large-scale, multicenter study on the detailed manifestations and clinical features of these patients was absent. In this study, we analyzed the clinical characteristics and factors related to abnormal liver biochemistries in patients with COVID-19 to explore the value of these liver biochemical indexes.

Patients and Methods

STUDY DESIGN

In this multicenter, retrospective study, data on patients with laboratory-confirmed COVID-19 were collected from Wuhan Tongji Hospital, Union Hospital main district, and Jin Yin-tan Hospital (Wuhan, China) who died or were discharged between February 1, 2020, and February 20, 2020. Laboratory confirmation was defined as a positive result for the SARS-CoV-2 RNA on real-time RT-PCR assay of pharyngeal swab specimens. All patients enrolled received standard diagnosis and treatment based on the *Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia* (7th interim edition).

The study was approved by the Ethics Commission of Wuhan Tongji Hospital, Union Hospital, and Jin Yin-tan Hospital, and written informed consent was waived. To ensure the accuracy and completeness of the data, all authors reviewed the extracted data and revised errors immediately by checking the original case data after the errors were found.

DATA COLLECTION

From the three hospitals, 484 patients who died or were discharged from February 1, 2020, to February 20, 2020, were included. After exclusion of 2 cases due to the large amount of missing data, a total of 482 cases were finally enrolled into analysis. Data on demographics, comorbidities (cardiovascular disease, chronic pulmonary disease, diabetes, malignancy, chronic liver disease, and chronic kidney disease), clinical symptoms (fever, rigor, cough, chest distress or pain, dyspnea, fatigue, myalgia, anorexia, and diarrhea), laboratory examinations (complete blood count, serum biochemical test, coagulation profile, renal and liver function, C-reactive protein [CRP], and lactate dehydrogenase [LDH]), imaging examination, complications, and treatment (antiviral agents, antibiotics, traditional Chinese medicine, corticosteroids, and mechanical ventilation) were collected from electronic medical records. In this study, "liver biochemical abnormality" was defined as any parameter more than the upper limit of normal value of alanine aminotransferase (ALT; 40 U/L), aspartate aminotransferase (AST; 40 U/L), and total bilirubin (TBIL;

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21 μmol/L). All laboratory findings were the first laboratory test results on admission.

STATISTICAL ANALYSIS

Continuous variables were described as medians and interquartile ranges (IQRs), and categorical variables were expressed as counts and percentages. We adopted the independent *t* test or Mann-Whitney U test to analyze continuous variables based on normally distributed data or nonnormally distributed data. Categorical variables were compared with a χ^2 test or Fisher's exact test. We divided patients into a normal liver biochemistries group and an abnormal liver biochemistries group to compare the differences of baseline characteristics, laboratory findings, and treatment between the two groups. To further analyze liver biochemical abnormality, the cases were divided into an ALT normal group and an ALT elevation group, an AST normal group and an AST elevation group, and a TBIL normal group and a TBIL elevation group. Univariate and multivariate logistic regression methods were used to investigate the factors associated with abnormal liver biochemistries on admission. Odds ratios (ORs) were expressed with their 95% confidence intervals (CIs). All of the data were analyzed in SPSS version 22.0. Statistical tests were two-tailed, and $P < 0.05$ was considered statistically significant.

Results

CLINICAL FEATURES

A total of 482 laboratory-confirmed patients with COVID-19 were enrolled in this study (Table 1). The median age was 56.5 years (IQR, 39.0-67.3; range, 14-91 years), and 243 (50.4%) cases were male. Relevant laboratory results on admission are shown in Table 2. Of these patients, 142 (29.5%) had abnormal liver biochemistries on admission, and most of them were male (55.6%; $P = 0.139$) and older (median, 57.0; IQR, 42.8-67.0; $P = 0.413$). The proportion of severe cases in the abnormal liver biochemistries group was significantly higher than in the normal liver biochemistries group (52.8% versus 33.2%; $P < 0.001$). The proportion of severe cases in the TBIL elevation group was the highest (69.6%; $P = 0.002$), followed by the AST elevation group (58.2%; $P < 0.001$), whereas the ALT elevation group was the lowest (47.9%; $P = 0.045$) (Table 3). The common comorbidities were hypertension (25.3%), chronic liver disease (19.9%), diabetes (14.9%), cardiovascular disease (7.7%), chronic obstructive pulmonary disease (COPD) (3.7%), malignancy (2.9%), and chronic kidney disease (1.2%). The proportion of patients with diabetes (22.5%; $P = 0.002$) and chronic liver disease (26.1%; $P = 0.029$) was higher in the abnormal liver biochemistries group. Chronic liver disease (96; 19.9%) included viral hepatitis (91; 18.9%) and nonalcoholic fatty liver disease (NAFLD) (5; 1%). Compared with the normal liver biochemistries group, the proportion of patients with viral hepatitis in the abnormal liver biochemistries group was significantly higher (24.6% versus 16.5%; $P = 0.037$), and the proportion of patients with NAFLD was not significantly different between groups (2.1% versus 0.6%; $P = 0.311$). Common symptoms included fever (88.0%), cough (60.0%), anorexia (40.0%), fatigue (33.0%), chest distress or pain (30.1%), and dyspnea (17.0%). Compared with the normal liver biochemistries group, the incidence of chest distress or pain (39.4%; $P = 0.004$) and dyspnea (28.9%; $P < 0.001$) was higher in the abnormal liver biochemistries group. The proportion of ARDS and acute cardiac injury in the AST elevation group and the TBIL elevation group was significantly higher than in the normal liver biochemistries group (Table 3). In the abnormal liver biochemistries group, there were more patients who had received corticosteroid therapy (7.7%; $P = 0.010$) before admission, whereas the proportion of patients who had undergone antiviral therapy (55.6%; $P = 0.021$) was relatively smaller (Table 1). After admission, the proportion of patients who had received corticosteroid therapy was also higher in the abnormal liver biochemistries group (47.2% versus 32.9%; $P = 0.003$) (Table 1).

Compared with normal liver biochemistries, patients with abnormal liver biochemistries had poor prognosis with a significantly higher proportion of death (29.6% versus 6.5%; $P < 0.001$), especially in the AST elevation group (33.7% versus 8.1%; $P < 0.001$) and the TBIL elevation group (60.9% versus 10.9%; $P < 0.001$) (Table 3). Among patients with abnormal liver biochemistries, the percentages of patients who had achieved chest computed tomography (CT) improvement (57.7% versus 72.9%; $P = 0.001$), normal CRP (28.9% versus 42.9%; $P = 0.004$), and normal lymphocyte count (59.9% versus 74.4%; $P = 0.001$) were lower than in the normal group when discharged (Table 1).

TABLE 1. Clinical Features, Treatment, and Prognosis of Patients With COVID-19 on Admission

Indicators	Total (482)	Liver Biochemistries		*P*
		Normal (340, 70.5%)	Abnormal (142, 29.5%)	
Age, median (IQR), years	56.5 (39.0-67.3)	55.5 (38.0-68.0)	57.0 (42.8-67.0)	0.413
Sex				
Male	243 (50.4%)	164 (48.2%)	79 (55.6%)	0.139
Female	239 (49.6%)	176 (51.8%)	63 (44.4%)	
Severity				
Nonsevere	294 (61%)	227 (66.8%)	67 (47.2%)	<0.001
Severe	188 (39%)	113 (33.2%)	75 (52.8%)	
Comorbidities				
Hypertension	122 (25.3%)	80 (23.5%)	42 (29.6%)	0.164
Diabetes	72 (14.9%)	40 (11.8%)	32 (22.5%)	0.002
Cardiovascular disease	37 (7.7%)	23 (6.8%)	14 (9.9%)	0.245
COPD	18 (3.7%)	10 (2.9%)	8 (5.6%)	0.155
Malignancy	14 (2.9%)	9 (2.6%)	5 (3.5%)	0.823
Chronic liver disease	96 (19.9%)	59 (17.4%)	37 (26.1%)	0.029
Chronic kidney disease	6 (1.2%)	6 (1.8%)	0 (0%)	0.253
Signs and symptoms				
Fever	424 (88%)	293 (86.2%)	131 (92.3%)	0.062
Rigor	58 (12%)	42 (12.4%)	16 (11.3%)	0.738
Cough	289 (60%)	203 (59.7%)	86 (60.6%)	0.861
Chest distress or pain	145 (30.1%)	89 (26.2%)	56 (39.4%)	0.004
Dyspnea	82 (17%)	41 (12.1%)	41 (28.9%)	<0.001
Fatigue	159 (33%)	107 (31.5%)	52 (36.6%)	0.273
Myalgia	74 (15.4%)	53 (15.6%)	21 (14.8%)	0.824
Anorexia	193 (40%)	130 (38.2%)	63 (44.4%)	0.210
Diarrhea	129 (26.8%)	92 (27.1%)	37 (26.1%)	0.821
Complications				
ARDS	44 (9.1%)	13 (3.8%)	31 (21.8%)	<0.001
Acute kidney injury	47 (9.8%)	29 (8.5%)	18 (12.7%)	0.162
DIC	1 (0.2%)	1 (0.3%)	0 (0%)	1.000
Acute cardiac injury	7 (1.5%)	0 (0%)	7 (4.9%)	<0.001
Treatment before admission				
Antiviral	306 (63.5%)	227 (66.8%)	79 (55.6%)	0.021
Antibiotic	303 (62.9%)	220 (64.7%)	83 (58.5%)	0.195
Corticosteroid	20 (4.1%)	9 (2.6%)	11 (7.7%)	0.010
Traditional Chinese medicine	136 (28.2%)	97 (28.5%)	39 (27.5%)	0.813
Other	101 (21%)	71 (20.9%)	30 (21.1%)	0.952
Treatment after admission				
Antiviral	472 (97.9%)	338 (99.4%)	134 (94.4%)	0.001
Antibiotic	436 (90.5%)	306 (90%)	130 (91.5%)	0.598
Traditional Chinese medicine	254 (52.7%)	189 (55.6%)	65 (45.8%)	0.049
Corticosteroid	179 (37.1%)	112 (32.9%)	67 (47.2%)	0.003
Mechanical ventilation	66 (13.7%)	42 (12.4%)	24 (16.9%)	0.185
Clinical outcome				
Discharged	418 (86.7%)	318 (93.5%)	100 (70.4%)	<0.001
Died	64 (13.3%)	22 (6.5%)	42 (29.6%)	
Discharge status				
Chest CT improvement	330 (68.5%)	248 (72.9%)	82 (57.7%)	0.001

TABLE 1. *Continued*

Indicators	Total (482)	Liver Biochemistries		*P*
		Normal (340, 70.5%)	Abnormal (142, 29.5%)	
Chest CT normal or fibrosis	49 (10.2%)	39 (11.5%)	10 (7%)	0.142
CRP normal	187 (38.8%)	146 (42.9%)	41 (28.9%)	0.004
Lymphocyte count normal	338 (70.1%)	253 (74.4%)	85 (59.9%)	0.001
Hospital stays, median (IQR), days	13 (10-17)	13 (10-18)	12 (9-16)	0.005

Data are presented as numbers (percentages) unless otherwise indicated.
Other treatments before admission include anti-inflammatory drugs, hypoglycemic drugs, and antihypertensive drugs.
Abbreviation: DIC, diffuse intravascular coagulation.

TABLE 2. Laboratory Findings of Patients With COVID-19 on Admission

Indicators	Total (482)	Liver Biochemistries		*P*
		Normal (340, 70.5%)	Abnormal (142, 29.5%)	
Blood routine				
WBC (×10⁹/L)	5.2 (3.9-6.8)	4.9 (3.8-6.3)	6.1 (4.6-8.4)	<0.001
<4	130/481 (27%)	101/339 (29.8%)	29/142 (20.4%)	<0.001
>10	37/481 (7.7%)	12/339 (3.5%)	25/142 (17.6%)	
Lymphocyte count (×10⁹/L)	1.1 (0.7-1.5)	1.2 (0.8-1.5)	0.9 (0.6-1.4)	<0.001
<1.0	202/481 (42%)	124/339 (36.6%)	78/142 (54.9%)	<0.001
Eosinophil count (×10⁹/L)	0.02 (0.00-0.07)	0.03 (0.00-0.07)	0.01 (0.00-0.05)	0.001
<0.02	226/481 (47%)	143/339 (42.2%)	83/142 (58.5%)	0.001
Platelet count (×10⁹/L)	202.0 (149.0-265.0)	205.0 (152.0-259.0)	194.5 (140.5-287.3)	0.509
Hb (g/L)	129.0 (118.0-138.0)	127.0 (117.0-136.0)	132.5 (122.0-143.0)	<0.001
Infection-related biomarkers				
CRP (mg/L)	16.1 (3.4-51.5)	10.8 (1.7-39.8)	42.7 (10.1-96.8)	<0.001
>10	268/462 (58%)	165/326 (50.6%)	103/136 (75.7%)	<0.001
Blood biochemistry				
Albumin (g/L)	36.4 (32.0-39.8)	37.2 (33.1-40.4)	33.8 (30.7-37.7)	<0.001
<35	199/482 (41.3%)	112/340 (32.9%)	87/142 (61.3%)	<0.001
Globulin (g/L)	31.0 (27.7-34.5)	30.3 (26.8-34.0)	32.7 (29.1-36.2)	<0.001
Alkaline phosphatase (U/L)	64.0 (53.0-78.3)	61.0 (50.0-73.0)	74.0 (61.0-98.3)	<0.001
γ-Glutamate transpeptidase (U/L)	26.0 (16.0-48.0)	21.0 (14.0-37.8)	54.0 (30.8-99.3)	<0.001
LDH (U/L)	244.0 (193.0-331.0)	224.0 (183.5-280.0)	358.0 (260.5-503.0)	<0.001
>245	223/450 (49.6%)	120/321 (37.4%)	103/129 (79.8%)	<0.001
Creatinine (μmol/L)	68.0 (56.9-83.1)	65.3 (54.5-80.6)	73.5 (61.8-88.3)	<0.001
>133	14/480 (2.9%)	7/338 (2.1%)	7/142 (4.9%)	0.161
hs-cTnI (pg/mL)	4.2 (1.9-11.3)	3.6 (1.1-7.6)	7.0 (2.2-20.2)	<0.001
Coagulation function				
Prothrombin time (seconds)	13.4 (12.7-14.1)	13.4 (12.7-14.0)	13.6 (12.4-14.5)	0.152
≥ 16	24/458 (5.2%)	9/322 (2.8%)	15/136 (11%)	<0.001
D-dimer (μg/mL)	0.6 (0.3-1.3)	0.5 (0.3-1.0)	0.9 (0.5-2.3)	<0.001
≥ 0.5	245/446 (54.9%)	143/313 (45.7%)	102/133 (76.7%)	<0.001

Data are number out of total number (percentage) and median (IQR).

LABORATORY INSPECTION

Compared with the normal liver biochemistries group, patients with abnormal liver biochemistries had higher levels of CRP, leukocytes, creatinine, LDH, D-dimer, hemoglobin (Hb), high-sensitivity cardiac troponin I (hs-cTnI), and globulin and lower levels of lymphocytes, eosinophils, and albumin (Table 2).

TABLE 3. Clinical Features, Treatment, and Prognosis of Patients With COVID-19 on Admission

		ALT			AST			TBIL		
Indicators	Total (482)	ALT ≤ 40 (386, 80.1%)	ALT >40 (96, 19.9%)	*P*	AST ≤ 40 (384, 79.7%)	AST > 40 (98, 20.3%)	*P*	TBIL ≤ 21 (459, 95.2%)	TBIL > 21 (23, 4.8%)	*P* Value
Age, median (IQR), years	56.5 (39.0-67.3)	56.0 (39.0-68.0)	57.0 (40.3-66.8)	0.906	55.5 (38.0-68.0)	57.0 (47.8-67.0)	0.208	57.0 (39.0-68.0)	54.0 (44.0-63.0)	0.690
Sex										
Male	243 (50.4%)	190 (49.2%)	53 (55.2%)	0.294	187 (48.7%)	56 (57.1%)	0.136	231 (50.3%)	12 (52.2%)	0.863
Female	239 (49.6%)	196 (50.8%)	43 (44.8%)		197 (51.3%)	42 (42.9%)		228 (49.7%)	11 (47.8%)	
Severity										
Nonsevere	294 (61%)	244 (63.2%)	50 (52.1%)	0.045	253 (65.9%)	41 (41.8%)	<0.001	287 (62.5%)	7 (30.4%)	0.002
Severe	188 (39%)	142 (36.8%)	46 (47.9%)		131 (34.1%)	57 (58.2%)		172 (37.5%)	16 (69.6%)	
Comorbidities										
Hypertension	122 (25.3%)	101 (26.2%)	21 (21.9%)	0.387	92 (24%)	30 (30.6%)	0.176	114 (24.8%)	8 (34.8%)	0.284
Diabetes	72 (14.9%)	49 (12.7%)	23 (24%)	0.006	50 (13%)	22 (22.4%)	0.019	68 (14.8%)	4 (17.4%)	0.969
Cardiovascular disease	37 (7.7%)	29 (7.5%)	8 (8.3%)	0.787	28 (7.3%)	9 (9.2%)	0.530	35 (7.6%)	2 (8.7%)	1.000
COPD	18 (3.7%)	13 (3.4%)	5 (5.2%)	0.582	14 (3.6%)	4 (4.1%)	1.000	16 (3.5%)	2 (8.7%)	0.470
Malignancy	14 (2.9%)	11 (2.8%)	3 (3.1%)	1.000	10 (2.6%)	4 (4.1%)	0.660	14 (3.1%)	0 (0%)	1.000
Chronic liver disease	96 (19.9%)	69 (17.9%)	27 (28.1%)	0.024	69 (18%)	27 (27.6%)	0.034	92 (20%)	4 (17.4%)	0.965
Chronic kidney disease	6 (1.2%)	6 (1.6%)	0 (0%)	0.475	6 (1.6%)	0 (0%)	0.462	6 (1.3%)	0 (0%)	1.000
Signs and symptoms										
Fever	424 (88%)	336 (87%)	88 (91.7%)	0.213	331 (86.2%)	93 (94.9%)	0.018	405 (88.2%)	19 (82.6%)	0.631
Rigor	58 (12%)	46 (11.9%)	12 (12.5%)	0.875	49 (12.8%)	9 (9.2%)	0.331	55 (12%)	3 (13%)	1.000
Cough	289 (60%)	225 (58.3%)	64 (66.7%)	0.134	230 (59.9%)	59 (60.2%)	0.956	274 (59.7%)	15 (65.2%)	0.757
Chest distress or pain	145 (30.1%)	105 (27.2%)	40 (41.7%)	0.006	108 (28.1%)	37 (37.8%)	0.064	136 (29.6%)	9 (39.1%)	0.332
Dyspnea	82 (17%)	53 (13.7%)	29 (30.2%)	<0.001	53 (13.8%)	29 (29.6%)	<0.001	75 (16.3%)	7 (30.4%)	0.141
Fatigue	159 (33%)	119 (30.8%)	40 (41.7%)	0.043	122 (31.8%)	37 (37.8%)	0.261	156 (34%)	3 (13%)	0.037
Myalgia	74 (15.4%)	58 (15%)	16 (16.7%)	0.690	61 (15.9%)	13 (13.3%)	0.521	71 (15.5%)	3 (13%)	0.985
Anorexia	193 (40%)	151 (39.1%)	42 (43.8%)	0.407	148 (38.5%)	45 (45.9%)	0.183	187 (40.7%)	6 (26.1%)	0.162
Diarrhea	129 (26.8%)	101 (26.2%)	28 (29.2%)	0.552	103 (26.8%)	26 (26.5%)	0.953	126 (27.5%)	3 (13%)	0.128
Complications										
ARDS	44 (9.1%)	33 (8.5%)	11 (11.5%)	0.376	19 (4.9%)	25 (25.5%)	<0.001	34 (7.4%)	10 (43.5%)	<0.001
Acute kidney injury	47 (9.8%)	36 (9.3%)	11 (11.5%)	0.529	36 (9.4%)	11 (11.2%)	0.582	45 (9.8%)	2 (8.7%)	1.000
DIC	1 (0.2%)	1 (0.3%)	0 (0%)	1.000	1 (0.3%)	0 (0%)	1.000	1 (0.2%)	0 (0%)	1.000
Acute cardiac injury	7 (1.5%)	4 (1%)	3 (3.1%)	0.292	2 (0.5%)	5 (5.1%)	0.004	5 (1.1%)	2 (8.7%)	0.037
Treatment after admission										
Antiviral	472 (97.9%)	380 (98.4%)	92 (95.8%)	0.227	379 (98.7%)	93 (94.9%)	0.050	453 (98.7%)	19 (82.6%)	<0.001
Antibiotic	436 (90.5%)	346 (89.6%)	90 (93.8%)	0.220	345 (89.8%)	91 (92.9%)	0.365	416 (90.6%)	20 (87%)	0.824

TABLE 3. *Continued*

Indicators	Total (482)	ALT		*P*	AST		*P*	TBIL		*P* Value
		ALT ≤ 40 (386, 80.1%)	ALT >40 (96, 19.9%)		AST ≤ 40 (384, 79.7%)	AST > 40 (98, 20.3%)		TBIL ≤ 21 (459, 95.2%)	TBIL > 21 (23, 4.8%)	
Traditional Chinese medicine	254 (52.7%)	204 (52.8%)	50 (52.1%)	0.893	214 (55.7%)	40 (40.8%)	0.008	247 (53.8%)	7 (30.4%)	0.028
Corticosteroid	179 (37.1%)	137 (35.5%)	42 (43.8%)	0.134	127 (33.1%)	52 (53.1%)	<0.001	167 (36.4%)	12 (52.2%)	0.126
Mechanical ventilation	66 (13.7%)	50 (13%)	16 (16.7%)	0.344	49 (12.8%)	17 (17.3%)	0.238	60 (13.1%)	6 (26.1%)	0.144
Clinical outcome										
Discharged	418 (86.7%)	339 (87.8%)	79 (82.3%)	0.153	353 (91.9%)	65 (66.3%)	<0.001	409 (89.1%)	9 (39.1%)	<0.001
Died	64 (13.3%)	47 (12.2%)	17 (17.7%)		31 (8.1%)	33 (33.7%)		50 (10.9%)	14 (60.9%)	
Discharge status										
Chest CT improvement	330 (68.5%)	265 (68.7%)	65 (67.7%)	0.859	276 (71.9%)	54 (55.1%)	0.001	323 (70.4%)	7 (30.4%)	<0.001
Chest CT normal or fibrosis	49 (10.2%)	42 (10.9%)	7 (7.3%)	0.298	43 (11.2%)	6 (6.1%)	0.138	48 (10.5%)	1 (4.3%)	0.553
CRP normal	187 (38.8%)	156 (40.4%)	31 (32.3%)	0.144	165 (43%)	22 (22.4%)	<0.001	181 (39.4%)	6 (26.1%)	0.200
Lymphocyte count normal	338 (70.1%)	272 (70.5%)	66 (68.8%)	0.742	282 (73.4%)	56 (57.1%)	0.002	332 (72.3%)	6 (26.1%)	<0.001
Hospital stays, median (IQR%), days	13 (10-17)	13 (10-18)	13 (11-16)	0.368	13 (10-18)	13 (9-16)	0.095	13 (10-17)	9 (4-13)	<0.001

Data are presented as numbers (percentages) unless otherwise indicated.
Abbreviation: DIC, diffuse intravascular coagulation.

The Hb of the abnormal liver biochemistries group (median, 132.5 g/L; IQR, 122.0-143.0) was higher than in the normal group (median, 127.0 g/L; IQR, 117.0-136.0) ($P < 0.001$), and the differences were statistically significant when grouped by ALT elevation ($P = 0.001$), AST elevation ($P = 0.001$), or TBIL elevation ($P = 0.006$). The levels of CRP and leukocytes in the liver biochemistries elevation groups were higher than in the normal groups ($P < 0.001$). The absolute values of lymphocytes in patients with elevated AST ($P < 0.001$) and TBIL ($P = 0.003$) were lower, and the TBIL elevation group had a minimum lymphocyte count of 0.7×10^9/L (IQR, 0.4-1.1; $P = 0.003$) (Table 4). The levels of hs-cTnI were significantly higher in patients with elevated AST (10.7 versus 3.6 pg/mL; $P < 0.001$) or TBIL (15.0 versus 4.0 pg/mL; $P = 0.002$) than those with normal levels (Table 4).

FACTORS ASSOCIATED WITH ELEVATED LIVER BIOCHEMISTRIES

Multivariate logistic regression was performed to analyze the factors associated with elevated liver biochemistries (Table 5). It was found that chest distress or pain (OR, 1.765; 95% CI, 1.104-2.820; $P = 0.018$) , dyspnea (OR, 2.495; 95% CI, 1.434-4.341; $P = 0.001$), elevated CRP (OR, 1.007; 95% CI, 1.002-1.012; $P = 0.008$), increased white blood count (WBC) (OR, 1.139; 95% CI, 1.028-1.263; $P = 0.013$), and increased Hb (OR, 1.024; 95% CI, 1.009-1.039; $P = 0.001$) were independent factors associated with elevated liver biochemistries.

Discussion

In this multicenter, retrospective study, we found that elevated liver biochemistries were common in patients with COVID-19. Approximately one third of the subjects presented with elevated liver biochemistries on admission, which was similar to a previous report.[7] However, most of the patients just showed mildly elevated liver biochemistries at the preliminary stage of infection,[8] which was consistent with what was found in our study, that most patients only had slight elevation of ALT, AST, and TBIL on admission. The mechanism of abnormal liver biochemistries caused by SARS-COV-2 is still unclear. In our study, 19.9% of patients with COVID-19 had coexisting chronic liver diseases (viral hepatitis and NAFLD). Viral hepatitis co-comorbidity accounted for a higher proportion in patients with elevated liver biochemistries ($P = 0.037$). However, it is hard to say whether NAFLD co-comorbidity contributes to elevated liver biochemistries because we only had 5 patients with NAFLD. Although patients with previous liver diseases more easily developed abnormal liver biochemistries, it was possible that they had abnormal biochemistries before being infected by SARS-CoV-2. Of the patients, 4.8% presented with elevated TBIL, especially direct bilirubin (DBIL); and median DBIL/TBIL was 0.42 (0.34-0.48). As reported by a recent study, angiotensin-converting enzyme 2 was highly expressed in type 2 alveolar epithelial cells as well as in bile duct cells and had an important role in mediating SARS-CoV-2 infection.[9] These findings indicated that elevated TBIL may be associated with SARS-CoV-2-induced bile duct cell injury rather than direct hepatic cell injury caused by the virus.[10,11]

We demonstrated that CRP and leukocyte count were associated with abnormal liver biochemistries, which was consistent with a previous study.[12] CRP, an acute-phase protein, is an indicator for active inflammation. An increased number of leukocytes is a response to bacterial infection. Both are important clinical inflammatory indicators. It has been reported that the levels of CRP and WBC were significantly higher in severe cases,[13] and abnormal liver biochemistries were more commonly seen in critical patients.[6] In a previous COVID-19 study, patients who had been admitted to the intensive care unit (ICU) had higher levels of ALT and AST relative to non-ICU patients, and the proportion of patients with elevated AST was also higher in ICU patients (62% versus 37%).[14] According to another study, 39.4% of severe patients showed elevated AST, whereas 28.1% had elevated ALT, the proportions of both being higher than in nonsevere cases.[15] Thus, patients with severe disease were more likely to have elevated liver biochemistries, which may be related to cytokine storm.[6] Cytokine storm is an overactive inflammatory response caused by pathogens, leading to a persistent activation of lymphocytes and macrophages that can secrete an abundance of inflammatory cytokines, followed by ARDS and multiorgan failure. Previous studies have shown that cytokine storm was associated with poor

TABLE 4. Laboratory Findings of Patients With COVID-19 on Admission

		ALT			AST			TBIL		
Indicators	Total (482)	ALT ≤ 40 (386, 80.1%)	ALT > 40 (96, 19.9%)	*P*	AST ≤ 40 (384, 79.7%)	AST > 40 (98, 20.3%)	*P*	TBIL ≤ 21 (459, 95.2%)	TBIL > 21 (23, 4.8%)	*P* Value
Blood routine										
WBC (×10⁹/L)	5.2 (3.9-6.8)	5.0 (3.8-6.6)	6.1 (4.8-7.4)	<0.001	5.0 (3.8-6.5)	6.2 (4.5-8.1)	<0.001	5.1 (3.9-6.7)	10.6 (5.6-15.3)	<0.001
<4	130/481 (27%)	113/385 (29.4%)	17/96 (17.7%)	0.020	109/383 (28.5%)	21/98 (21.4%)	<0.001	126/458 (27.5%)	4/23 (17.4%)	<0.001
>10	37/481 (7.7%)	25/385 (6.5%)	12/96 (12.5%)		20/383 (5.2%)	17/98 (17.3%)		25/458 (5.5%)	12/23 (52.2%)	
Lymphocyte count (×10⁹/L)	1.1 (0.7-1.5)	1.1 (0.7-1.5)	1.0 (0.7-1.5)	0.247	1.2 (0.8-1.5)	0.9 (0.6-1.2)	<0.001	1.1 (0.8-1.5)	0.7 (0.4-1.1)	0.003
<1.0	202/481 (42%)	155/385 (40.3%)	47/96 (49%)	0.122	142/383 (37.1%)	60/98 (61.2%)	<0.001	185/458 (40.4%)	17/23 (73.9%)	0.001
Eosinophil count (×10⁹/L)	0.02 (0.00-0.07)	0.02 (0.00-0.07)	0.02 (0.00-0.07)	0.788	0.03 (0.00-0.07)	0.00 (0.00-0.04)	<0.001	0.02 (0.00-0.07)	0.01 (0.00-0.02)	0.008
<0.02	226/481 (47%)	182/385 (47.3%)	44/96 (45.8%)	0.800	162/383 (42.3%)	64/98 (65.3%)	<0.001	209/458 (45.6%)	17/23 (73.9%)	0.008
Platelet count (×10⁹/L)	202 (149-265)	197.0 (148.5-256.0)	217.0 (152.5-313.8)	0.056	206 (152-265)	176.5 (132.3-269.5)	0.064	205 (152-268)	147 (87-202)	<0.001
Hb (g/L)	129 (118-138)	128 (117-136)	133.0 (123.5-143.0)	0.001	128 (117-136)	133 (122-144)	0.001	128 (118-137)	140 (125-144)	0.006
Infection-related biomarkers										
CRP (mg/L)	16.1 (3.4-51.5)	13.0 (2.4-45.8)	36.8 (7.1-81.5)	<0.001	10.2 (1.9-40.5)	57.1 (29.0-114.4)	<0.001	14.6 (3.0-47.6)	62.7 (24.8-137.7)	<0.001
>10	268/462 (58%)	203/371 (54.7%)	65/91 (71.4%)	0.004	185/367 (50.4%)	83/95 (87.4%)	<0.001	250/440 (56.8%)	18/22 (81.8%)	0.020
Blood biochemistry										
Albumin (g/L)	36.4 (32.0-39.8)	37.0 (33.0-40.2)	33.5 (30.5-37.8)	<0.001	37.2 (33.1-40.3)	33.0 (30.6-36.2)	<0.001	36.5 (32.1-39.9)	34.0 (30.1-38.9)	0.094
<35	199/482 (41.3%)	141/386 (36.5%)	58/96 (60.4%)	<0.001	129/384 (33.6%)	70/98 (71.4%)	<0.001	186/459 (40.5%)	13/23 (56.5%)	0.128
Globulin (g/L)	31.0 (27.7-34.5)	30.7 (27.1-34.4)	32.0 (28.6-35.6)	0.031	30.3 (26.9-34.0)	33.8 (29.8-36.7)	<0.001	30.6 (27.5-34.4)	34.4 (31.9-36.4)	0.004
ALT (U/L)	21.5 (15.0-35.3)	19.0 (14.0-26.0)	66.5 (51.0-88.5)	<0.001	NA	NA	NA	21.0 (15.0-34.0)	25.0 (18.0-57.0)	0.305
>40	96/482 (19.9%)	NA	NA	NA	NA	NA	NA	88/459 (19.2%)	8/23 (34.8%)	0.118
AST (U/L)	26 (19-37)	NA	NA	NA	23 (18-30)	59.0 (46.8-76.5)	<0.001	19 (26-36)	40 (24-87)	0.013
>40	98/482 (20.3%)	NA	NA	NA	NA	NA	NA	87/459 (19%)	11/23 (47.8%)	0.002
Alkaline phosphatase (U/L)	64.0 (53.0-78.3)	61 (51-74)	77.5 (63.3-104.0)	<0.001	62 (51-76)	72.5 (60.0-96.3)	<0.001	63 (52-77)	87 (70-156)	<0.001
γ-Glutamate transpeptidase (U/L)	26 (16-48)	22.0 (15.0-35.3)	66.0 (38.3-122.5)	<0.001	22 (15-37)	56.0 (32.8-106.0)	<0.001	26 (16-45)	57 (22-123)	0.005
LDH (U/L)	244 (193-331)	231.5 (186.0-303.3)	335.0 (256.8-454.0)	<0.001	229 (184-287)	405 (314-523)	<0.001	241.0 (192.5-319.5)	558.0 (231.5-829.5)	<0.001
>245	223/450 (49.6%)	152/362 (42%)	71/88 (80.7%)	<0.001	141/359 (39.3%)	82/91 (90.1%)	<0.001	208/429 (48.5%)	15/21 (71.4%)	0.040
TBIL (μmol/L)	9.1 (6.7-12.5)	8.8 (6.4-11.8)	10.7 (8.0-14.5)	<0.001	8.7 (6.4-11.6)	11.4 (8.0-14.9)	<0.001	8.9 (6.6-11.8)	22.9 (21.8-29.8)	<0.001
DBIL (μmol/L)	3.6 (2.6-5.0)	3.5 (2.5-4.7)	4.4 (3.2-5.8)	<0.001	3.5 (2.5-4.5)	4.9 (3.4-7.0)	<0.001	NA	NA	NA
DBIL/TBIL	0.42 (0.34-0.48)	0.41 (0.34-0.48)	0.44 (0.35-0.50)	0.063	0.40 (0.34-0.46)	0.48 (0.39-0.54)	<0.001	NA	NA	NA
Creatinine (μmol/L)	68.0 (56.9-83.1)	67.0 (56.0-83.1)	70.1 (60.0-83.2)	0.349	66 (55-80)	78.9 (64.0-95.0)	<0.001	68.0 (56.1-82.9)	80 (64-100)	0.040
>133	14/480 (2.9%)	12/384 (3.1%)	2/96 (2.1%)	0.839	7/382 (1.8%)	7/98 (7.1%)	0.014	13/457 (2.8%)	1/23 (4.3%)	0.502
hs-cTnI (pg/mL)	4.2 (1.9-11.3)	4.0 (1.8-10.3)	4.5 (1.9-15.5)	0.351	3.6 (1.2-7.9)	10.7 (2.9-21.8)	<0.001	4.0 (1.8-9.8)	15.0 (2.1-229.5)	0.002
Coagulation function										
Prothrombin time (seconds)	13.4 (12.7-14.1)	13.5 (12.8-14.1)	13.3 (11.9-14.2)	0.493	13.3 (12.7-14.1)	13.8 (12.8-14.5)	0.036	13.4 (12.7-14.1)	14.7 (13.6-17.3)	<0.001
≥ 16	24/458 (5.2%)	16/366 (4.4%)	8/92 (8.7%)	0.161	14/363 (3.9%)	10/95 (10.5%)	0.019	18/436 (4.1%)	6/22 (27.3%)	<0.001
D-dimer (μg/mL)	0.6 (0.3-1.3)	0.5 (0.3-1.2)	0.9 (0.5-1.7)	<0.001	0.5 (0.3-1.1)	1.0 (0.6-2.2)	<0.001	0.6 (0.3-1.2)	10.8 (1.1-38.6)	<0.001
≥ 0.5	245/446 (54.9%)	180/356 (50.6%)	65/90 (72.2%)	<0.001	168/353 (47.6%)	77/93 (82.8%)	0.001	228/425 (53.6%)	17/21 (81%)	0.014

Data are number out of total number (percentage) and median (IQR).
Abbreviation: NA, not available.

TABLE 5. Univariate and Multivariate Analyses of Patients With COVID-19 and Abnormal Liver Biochemistries

	Univariate Analysis		Multivariate Analysis	
Indicators	OR (95% CI)	*P*	OR (95% CI)	*P*
Baseline characteristics				
Age (years)	1.019 (1.006-1.032)	0.003	1.002 (0.986-1.019)	0.810
Sex (male)	1.346 (0.908-1.995)	0.139	NA	NA
Severity				
Severe	2.249 (1.508-3.352)	<0.001	1.003 (0.595-1.691)	0.990
Comorbidities				
Hypertension	1.365 (0.880-2.117)	0.165	NA	NA
Diabetes	2.182 (1.305-3.647)	0.003	1.322 (0.717-2.441)	0.371
Cardiovascular disease	1.507 (0.752-3.022)	0.247	NA	NA
COPD	1.970 (0.761-5.100)	0.162	NA	NA
Malignancy	1.342 (0.442-4.078)	0.604	NA	NA
Chronic liver disease	1.678 (1.051-2.680)	0.030	1.478 (0.859-2.543)	0.158
Signs and symptoms				
Fever	1.910 (0.960-3.801)	0.065	NA	NA
Rigor	0.901 (0.488-1.662)	0.739	NA	NA
Cough	1.036 (0.695-1.547)	0.861	NA	NA
Chest distress or pain	1.836 (1.213-2.779)	0.004	1.765 (1.104-2.820)	0.018
Dyspnea	2.960 (1.817-4.823)	<0.001	2.495 (1.434-4.341)	0.001
Fatigue	1.258 (0.834-1.898)	0.274	NA	NA
Myalgia	0.940 (0.543-1.626)	0.824	NA	NA
Anorexia	1.288 (0.866-1.916)	0.211	NA	NA
Diarrhea	0.950 (0.609-1.482)	0.821	NA	NA
Treatment before admission				
Antiviral	0.624 (0.418-0.932)	0.021	0.685 (0.432-1.087)	0.108
Antibiotic	0.767 (0.514-1.146)	0.196	NA	NA
Corticosteroid	3.088 (1.251-7.625)	0.014	2.095 (0.724-6.062)	0.172
Traditional Chinese medicine	0.949 (0.613-1.469)	0.813	NA	NA
Other	1.015 (0.628-1.641)	0.952	NA	NA
Laboratory findings				
CRP (mg/L)	1.013 (1.008-1.017)	<0.001	1.007 (1.002-1.012)	0.008
WBC (×10⁹/L)	1.248 (1.159-1.344)	<0.001	1.139 (1.028-1.263)	0.013
Platelet count (×10⁹/L)	1.000 (0.998-1.002)	0.782	NA	NA
Lymphocyte count (×10⁹/L)	0.546 (0.372-0.803)	0.002	0.937 (0.576-1.526)	0.795
Eosinophil count (×10⁹/L)	0.083 (0.003-2.064)	0.129	NA	NA
Creatinine (μmol/L)	1.004 (0.999-1.010)	0.100	NA	NA
Prothrombin time (seconds)	1.018 (0.979-1.058)	0.364	NA	NA
D-dimer (μg/mL)	1.050 (1.025-1.077)	<0.001	0.999 (0.964-1.035)	0.949
Hb (g/L)	1.022 (1.009-1.035)	0.001	1.024 (1.009-1.039)	0.001
Globulin (g/L)	1.102 (1.058-1.147)	<0.001	1.028 (0.979-1.079)	0.272
hs-cTnI (pg/mL)	1.000 (1.000-1.000)	0.173	NA	NA

Other treatments before admission include anti-inflammatory drugs, hypoglycemic drugs, and antihypertensive drugs.
Abbreviation: NA, not available.

outcomes in SARS-CoV and Middle East respiratory syndrome coronavirus infection.[16,17] As reported, inflammatory cytokines reached a peak a few days after hospitalization, indicating that some cytokines might be involved in the early stage of abnormal liver biochemistries.[18] It was also demonstrated in a study

that more than half of the patients with COVID-19 had elevated liver enzymes, which may be associated with drug effects or overreaction of the immune system [19]

In our study, 20 cases received glucocorticoid treatment before admission, including 17 severe patients. Based on the *Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia*, glucocorticoids can be used in severe cases if necessary. The higher proportion of glucocorticoid therapy in patients with elevated liver biochemistries was possibly owing to the disease severity. Among the patients in this study, 63.5% received antiviral therapies before admission. Although more patients received antiviral treatments before admission in the normal liver biochemistries group, a report has demonstrated that the percentage of patients receiving lopinavir or ritonavir treatment after admission was markedly higher in patients with liver injury.[8] Accordingly, prospective studies are needed to investigate the exact association between various antiviral agents and liver function. In addition, in a previous study, the liver biopsy specimens showed moderate microvesicular steatosis and mild lobular and portal necrosis, which could be related to either SARS-CoV-2 infection or drug-induced liver injury.[20] Concrete evidence is still needed to confirm the cause of abnormal liver biochemistries.

In our study, increased Hb, chest distress or pain, and dyspnea were found to be associated with abnormal liver biochemistries. Hb is a functional protein in red blood cells that can deliver oxygen from the lungs to the far reaches of the body, and increased Hb level is an indicator of chronic hypoxia. Chest distress and dyspnea indicate that oxygenation of the lungs may be significantly damaged. Hypoxia can cause liver damage through a decrease in membrane potential, reducing the level of adenosine triphosphate, damaging sodium pump activity, and increasing membrane permeability.[21] Liver congestion or ischemia can also cause secondary liver function damage in clinic. These results illustrated that hypoxia probably was a cause of abnormal liver biochemistries in patients with COVID-19.

In patients with elevated AST or TBIL, the proportions of severe and deceased cases and patients with ARDS and acute cardiac injury were higher compared with those in ALT-elevated patients, whereas the lymphocyte count was relatively lower. Our results showed that hs-cTnI was much higher in patients with elevated AST or TBIL, indicating that those patients may have cardiac injury. One study found that 7.2% of patients with COVID-19 had elevated hs-cTnI.[22] Another study showed that hs-cTnI was elevated in the early stage of COVID-19 and sharply increased with the deterioration of the disease.[5] Elevation of hs-cTnI was more common in severe cases, and more than half of the deceased patients showed elevated hs-cTnI during hospitalization. Several studies have demonstrated that cardiac injury was associated with poor prognosis.[6,15,23] Thus, our results suggested that elevated AST and TBIL may be indicators for cardiac injury and were associated with poor prognosis. In addition, as shown in the results, patients with elevated AST or TBIL had worse chest CT images and lower rates for normalization of CRP and lymphocyte count. Lymphocyte count is an important predictor for disease severity, prognosis, and therapeutic response.[14,24] Therefore, patients with elevated AST or TBIL were more severe and had worse prognosis or recovery conditions, reminding us to pay close attention to these patients.

One study demonstrated that LDH is an independent risk factor for poor outcomes (transfer to the ICU or in-hospital death) in SARS patients.[25] Owing to the poor specificity, LDH cannot represent a specific indicator for liver injury.[26] In our study, LDH level was higher in patients with elevated liver biochemistries. Whether a combination of LDH, AST, and TBIL can more accurately predict the outcomes of patients with COVID-19 needs further investigation.

This study has some limitations. First, it was a retrospective study, and some cases had incomplete medical history, such as the detailed treatment before hospitalization. Liver function of those patients with coexisting chronic liver diseases before infection cannot be evaluated. Second, cases that ended in death may affect the evaluation of some indices, such as the length of hospital stay; and asymptomatic or mild patients were isolated at home, so we were unable to enroll these patients. Third, direct evidence of abnormal liver biochemistries caused by SARS-COV-2 is still uncovered, and the underlying mechanism needs to be further studied.

In conclusion, our study demonstrated that although abnormal liver biochemistries were common in patients with COVID-19, most of them just showed mild elevation, which may result from chronic hypoxia and excessive inflammation. Patients with elevated AST or TBIL on admission may have

cardiac injury simultaneously and need more attention because they had worse prognosis.

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REFERENCES

1) Xia J, Tong J, Liu M, Shen Y, Guo D. Evaluation of coronavirus in tears and conjunctival secretions of patients with SARS-CoV-2 infection. J Med Virol 2020;92:589-594. https://doi.org/10.1002/jmv.25725.
2) World Health Organization. Coronavirus disease (COVID-19) situation report: 109. Geneva, Switzerland: World Health Organization. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200508covid-19-sitrep-109.pdf?sfvrsn=68f2c6326. Published May 8, 2020. Accessed May 14, 2020.
3) Jin J-M, Bai P, He W, Wu F, Liu X-F, De-Min H, et al. Gender differences in patients with COVID- 19: focus on severity and mortality. Front Public Health 2020;8:152. https://doi.org/10.3389/fpubh.2020.00152.
4) **Chen N**, **Zhou M**, **Dong X**, **Qu J**, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395:507-513.
5) **Zhou F**, **Yu T**, **Du R**, **Fan G**, **Liu Y**, **Liu Z**, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054-1062.
6) **Wang D**, **Hu B**, Hu C, Zhu G, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020;323:1061-1069.
7) **Yang X**, **Yu Y**, **Xu J**, **Shu H**, **Xia J**, **Liu H**, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020;8:475-481.
8) **Fan Z**, **Chen L**, Li J, Cheng X, Yang J, Tian C, et al. Clinical features of COVID-19-related liver functional abnormality. Clin Gastroenterol Hepatol 2020;18:1561-1566. https://doi.org/10.1016/j.cgh.2020.04.002.
9) **Chai X**, **Hu L**, **Zhang Y**, **Han W**, Lu Z, Ke A, et al. Specific ACE2 expression in cholangiocytes may cause liver damage after 2019-nCoV infection. bioRxiv 2020. https://doi.org/10.1101/2020.02.03.931766. [Epub ahead of print]
10) **Zhao Y**, **Zhao Z**, **Wang Y**, Zhou Y, Ma Y, Zuo W. Single-cell RNA expression profiling of ACE2, the receptor of SARS-CoV-2. bioRxiv 2020. https://doi.org/10.1101/2020.01.26.919985. [Epub ahead of print]
11) **Zhang H**, **Kang Z**, **Gong H**, **Xu D**, Wang J, Li Z, et al. The digestive system is a potential route of 2019-nCov infection: a bioinformatics analysis based on single-cell transcriptomes. bioRxiv 2020. https://doi.org/10.1101/2020.01.30.927806. [Epub ahead of print]
12) **Diao B**, **Wang C**, **Tan Y**, Chen X, Liu Y, Ning L, et al. Reduction and functional exhaustion of T cells in patients with coronavirus disease 2019 (COVID-19). Front Immunol 2020;11:827. https://doi.org/10.3389/fimmu.2020.00827.
13) **Feng Y**, **Ling Y**, **Bai T**, **Xie Y**, Huang J, Li J, et al. COVID-19 with different severity: a multi-center study of clinical features. Am J Respir Crit Care Med 2020. https://doi.org/10.1164/rccm.202002-0445OC. [Epub ahead of print]
14) **Huang C**, **Wang Y**, **Li X**, **Ren L**, **Zhao J**, **Hu Y**, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506.
15) **Guan WJ**, **Ni ZY**, **Hu Y**, **Liang WH**, **Ou CQ**, **He JX**, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382:1708-1720.
16) Chien JY, Hsueh PR, Cheng WC, Yu CJ, Yang PC. Temporal changes in cytokine/chemokine profiles and pulmonary involvement in severe acute respiratory syndrome. Respirology 2006;11:715-722.
17) **Zhou J**, **Chu H**, Li C, Wong BHY, Cheng ZS, Poon VKM, et al. Active replication of Middle East respiratory syndrome coronavirus and aberrant induction of inflammatory cytokines and chemokines in human macrophages: implications for pathogenesis. J Infect Dis 2014;209:1331-1342.
18) **Li L**, **Li S**, Xu M, Yu P, Zheng S, Duan Z, et al. Risk factors related to hepatic injury in patients with corona virus disease 2019. medRxiv 2020. https://doi.org/10.1101/2020.02.28.20028514. [Epub ahead of print]
19) Wadman M, Couzin-Frankel J, Kaiser J, Matacic C. How does coronavirus kill? Clinicians trace a ferocious rampage through the body, from brain to toes. Science 2020 Apr 17. https://doi.org/10.1126/science.abc3208. [Epub ahead of print]
20) **Xu Z**, **Shi L**, **Wang Y**, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med 2020;8:420-422.
21) Lambotte L. Effect of anoxia and ATP depletion on the membrane potential and permeability of dog liver. J Physiol 1977;269:53-76.
22) Clerkin KJ, Fried JA, Raikhelkar J, Sayer G, Griffin JM, Masoumi A, et al. COVID-19 and cardiovascular disease. Circulation 2020;141:1648-1655.
23) **Guo T**, **Fan Y**, Chen M, Wu X, Zhang L, He T, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). JAMA Cardiol 2020 Mar 27. https://doi.org/10.1001/jamacardio.2020.1017. [Epub ahead of print]
24) **Tan L**, **Wang Q**, Zhang D, Ding J, Huang Q, Tang Y-Q, et al. Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. Signal Transduct Target Ther 2020;5:33. https://doi.org/10.1038/s41392-020-0148-4.
25) Lee N, Hui D, Wu A, Chan P, Cameron P, Joynt GM, et al. A major outbreak of severe acute respiratory syndrome in Hong Kong. N Engl J Med 2003;348:1986-1994.
26) Kraft J, Aastrup H, Schroder P. Diagnostic value for acute myocardial infarction of creatine kinase and lactate dehydrogenase isoenzymes compared with total enzymes. Creatine kinase isoenzyme specificity for myocardial damage. Acta Med Scand 1978;203:167-174.

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