Original Article

Clinical Characteristics and Risk Factors of Liver Dysfunction in COVID-19 Patients

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Abstract

Background: COVID-19 outbreak has spread around the world. Liver dysfunction (LD) was related with high mortality in COVID-19. **Methods:** Retrospective, single-center study case series of 425 consecutive hospitalized COVID-19 patients were enrolled. Demographic, clinical, laboratory, and treatment data were collected. **Results:** A total of 425 patients were included in this study, 145 of whom had LD. The overall mortality rate was 8.9%, while 17.9% in the LD group and 4.3% in the nonliver dysfunction (NLD) group. Age, sex, and hypertension were the independent risk factors of LD. LD was an independent risk factor for incidence of severe illness, acute respiratory distress syndrome, and death. The survival rate of patients in LD group was lower than that in NLD group ($P < 0.001$). A similar trend was observed by the multivariate regression analysis (adjusted hazard ratio, 3.52; 95% confidence interval [CI], 1.69–7.33; $P = 0.001$). Angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers had effect to reduce LD (odds ratio of 0.48 [95% CI, 0.232–0.989; $P = 0.045$]). **Conclusions:** LD is one of the main features of hospitalized patients of COVID-19, with a worse prognosis. Patients of COVID-19 with LD on admission should be more cautions.

Keywords: *COVID-19, liver dysfunction, risk factor*

Introduction

In December 2019, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus broke out in Wuhan, China. At present, SARS-CoV-2 has become a global epidemic.[1] The main route of transmission of the virus is respiratory droplets, leading to coronavirus disease-2019 (COVID-19).[2,3] Meanwhile, liver is also one of the organs seriously affected by the virus.[4,5] Previous study showed that liver dysfunction (LD) was one of the major complications in COVID-19 patients[6] and more than one-third of patients admitted to the hospital have abnormal liver function.[7] Patients with severe COVID-19 seem to have higher rates of LD.[8] Liver injury is more prevalent in severe cases than that in mild cases of COVID-19,[9] which suggested that LD was a risk factor of mortality in COVID-19. Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARBs) were exhibited a very important role in COVID-19.[10,11] However, current studies were lack of coverage about the effects of ACEI/ARB on LD. The clinical characteristics and risk factors of COVID-19 patients with LD were still unclear. We aimed to further clarify the clinical characteristics and risk factors of LD in COVID-19 patients.

Methods

Study design and participants

This study was performed at the Wuhan Fourth Hospital, and Zhongnan Hospital of Wuhan University. We retrospectively analyzed 425 patients who were diagnosed according to the World Health Organization's internal

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How to cite this article: Jiang X, Zhang J, Yang C, Xie Q, Xiao G, Wang F, *et al.* Clinical Characteristics and Risk Factors of Liver Dysfunction in COVID-19 Patients. J Transl Crit Care Med 2021;3:7.

Submission: 10-07-2021 **Revision:** 19-08-2021
Accepted: 02-09-2021 **Published:** 28-09-2021

Access this article online

Quick Response Code:

Website: www.tccmjournal.com

DOI: 10.4103/2665-9190.326914

guidelines from December 25 to March 1. All clinical information was collected by a team of qualified clinicians. This study was approved by the institution ethics board of Wuhan Fourth Hospital (202002001) and Zhongnan Hospital of Wuhan University (No. 2020020). Consent was obtained from patients or the patients' next of kin.

Data collection

Data including clinical characteristics, laboratory findings, treatment strategy, complications, and clinical outcomes were obtained from the medical records using a standardized report form designed for this study. The clinical symptoms and laboratory findings were extracted on hospital admission. A continuous history of taking ACEI and ARB was recorded. The complications and clinical outcomes were collected throughout the hospitalization. We define the alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevated group as the LD group, and the ALT and AST normal group as the nonliver dysfunction (NLD) group. Acute respiratory distress syndrome (ARDS) was defined according to the Berlin definition.[12] The severe condition of COVID-19 was defined using the guideline for the diagnosis and treatment of 2019 novel coronavirus-infected pneumonia (standard version).[13] Acute kidney injury was defined according to the Kidney Disease Improving Global Outcomes 2012 guidelines;[14] myocardial injury was defined according to the third universal definition of myocardial infarction.[15] Patients' follow-up times were defined as the time interval from hospitalization to the most recent contact or the time of patient death, whichever came earlier. The latest follow-up date was March 15, 2020.

Statistical analysis

The continuous variables were summarized as medians and interquartile ranges and compared by the Mann–Whitney–Wilcoxon test. Logistic regression analysis was used to identify the effects of variables on hospital mortality. The survival curves of COVID-19 patients were drawn by Kaplan–Meier plots and assessed with the log-rank test. The Cox proportional hazards regression model was used to determine the hazard ratios (HRs) of treatments on death. A HR or an odds ratio (OR) was reported along with a 95% confidence interval (CI). All statistical analyses were performed using Statistical Package for the Social Sciences version 13.0 software (SPSS Inc., IBM, Chicago, IL, USA). The statistical significance level was set at a two-sided $P < 0.05$.

Results

General features

A total of 425 patients were included in this study, 145 of them developed LD on admission. The median age was 55 and 62 years in LD group and NLD group, respectively. More comorbidities including hypertension, cardiovascular disease, and chronic obstructive pulmonary disease existed in LD group compared to the NLD group ($P < 0.05$). However, there was no significant difference about the proportions of other comorbidities, such as diabetes, cerebrovascular disease, chronic kidney disease, chronic liver disease, and malignant tumor between the two groups. Three hundred and eight-five (90.6%) of the patients had fever, 35%–50% had cough and expectoration, 68.6% had fatigue, 28.6% had myalgia, and about 10% had digestive tract symptoms. The incidence of dyspnea in the LD group was higher than that in the NLD group. Of the 425 patients included in this study, 387 were discharged from the hospital and 38 died. The overall mortality rate was 8.9%, while 17.9% in the LD group, and 4.3% in the NLD group. The other characteristics of patients are summarized in Table 1.

Laboratory findings

The oxygenation index of patients in the LD group was lower than that in the NLD group ($P < 0.05$), and there was no difference in arterial partial pressure of CO_2. The white blood cell count, neutrophil count, creatine kinase, D-dimer, urea, C-reactive protein, and lactate dehydrogenase of the LD group were higher than those of the NLD group, and the lymphocyte count and albumin were lower ($P < 0.05$). Indicators of coagulation function of prothrombin time (PT), activated partial thromboplastin time (APTT) creatinine, and fibrinogen showed no significant difference between the two groups [Table 2].

Risk factors of liver dysfunction

Multifactor regression analysis showed that age, sex, and hypertension were the independent risk factors of LD [Table 3].

Effects of drugs

There were 54 (12.7%) patients using ACEI/ARBs, 34 (12.1%) in LD group, and 20 (13.8%) in NLD group. After adjusting confounders by age, sex, and comorbidities, the using of ACEI/ARBs significantly reduce the incidence of LD (OR 0.48 [95% CI, 0.232–0.989]; $P = 0.047$). In addition, the effect of antiviral drugs (oseltamivir, lopinavir–ritonavir tablets, Arbidol, and Lianhua Qingwen Capsule) on liver function was not significant.

Outcome

LD was an independent risk factor of incidence of ARDS (OR 2.789, 95% CI 1.7–4.5), severe illness (OR 2.094, 95% CI 1.3–3.3), and mortality (OR 2.754, 95% CI 1.2–6.1) after multivariate analysis. The Kaplan–Meier survival curve showed that the survival rate of patients in the LD group was lower than that in NLD [$P < 0.001$,

Table 1: Demographics and clinical characteristics of patients with COVID-19

Characteristic	Total (*n*=425)	NLD group (*n*=280)	LD group (*n*=145)	*P*
Age (IQR)	56 (44-67)	55 (41-64)	62 (51-70)	<0.001
Gender, *n* (%)				
Male	211 (49.6)	115 (41.1)	96 (66.2)	<0.001
Female	214 (50.4)	165 (58.9)	49 (33.8)	<0.001
BMI (IQR)	23.88 (21.93-25.95)	23.84 (21.85-25.58)	24.22 (21.93-27.04)	0.496
Smoking history	32 (11.0)	18 (9.4)	14 (13.9)	0.248
Comorbidities, *n* (%)				
Hypertension	164 (38.6)	91 (32.5)	73 (50.3)	<0.001
Diabetes	66 (15.5)	41 (14.6)	25 (17.2)	0.483
Cardiovascular disease	60 (14.1)	32 (11.4)	28 (19.3)	0.027
Cerebrovascular disease	25 (5.9)	16 (5.7)	9 (6.2)	0.838
COPD	8 (1.9)	1 (0.4)	7 (4.8)	0.001
Chronic kidney Disease	13 (3.1)	9 (3.2)	4 (2.8)	0.796
Malignancy	30 (7.1)	19 (6.8)	11 (7.6)	0.760
Chronic liver disease	9 (2.1)	4 (1.4)	5 (3.4)	0.170
Signs and symptoms, *n* (%)				
Fever	385 (90.6)	256 (91.4)	129 (89.0)	0.410
Cough	217 (54.7)	140 (53.6)	77 (56.6)	0.572
Expectoration	128 (34.7)	80 (32.0)	48 (40.3)	0.116
Chest distress	77 (37.6)	49 (34.0)	28 (45.9)	0.109
Dyspnea	106 (24.9)	59 (21.1)	47 (32.4)	0.010
Diarrhea	39 (9.6)	27 (9.8)	12 (9.3)	0.879
Nausea	30 (7.4)	23 (8.3)	7 (5.4)	0.298
Vomiting	16 (4.1)	14 (5.3)	2 (1.6)	0.081
Abdominal pain	11 (2.7)	8 (2.9)	3 (2.3)	0.741
Headache	50 (12.9)	34 (13.0)	16 (12.7)	0.939
Fatigue	277 (68.6)	187 (68.0)	90 (69.8)	0.721
Myalgia	111 (28.6)	79 (30.2)	32 (25.4)	0.332
Temperature (IQR)	36.8 (36.5-37.8)	36.9 (36.5-37.8)	36.8 (36.5-37.9)	0.499
Hear rate (IQR)	85 (78-94)	84 (79-92)	85 (78-97)	0.382
Respiratory rate (IQR)	20 (18-21)	20 (18-21)	20 (19-22)	0.113
Therapy, *n* (%)				
Glucocorticoid	170 (42.0)	106 (38.4)	64 (49.6)	0.033
Mechanical ventilation	26 (6.1)	11 (3.9)	15 (10.3)	0.009
Renal replacement therapy	1 (0.2)	1 (0.4)	0 (0)	0.471
Extracorporeal membrane oxygenation	4 (0.9)	1 (0.4)	3 (2.1)	0.083
ACEI/ARB	54 (12.7)	34 (12.1)	20 (13.8)	0.628
Oseltamivir	199 (49.3)	171 (49.9)	28 (45.9)	0.569
Lopinavir–ritonavir tablets	106 (44.2)	87 (43.5)	19 (47.5)	0.642
Arbidol	81 (36.2)	70 (36.6)	11 (33.3)	0.714
Lianhua Qingwen capsule	105 (46.9)	87 (45.5)	18 (54.5)	0.339
Complication, *n* (%)				
Acute kidney injury	77 (18.1)	41 (14.6)	36 (24.8)	0.010
ARDS	147 (34.6)	73 (26.1)	74 (51.0)	<0.001
Acute myocarditis	28 (6.9)	7 (2.6)	21 (14.8)	<0.001
Shock	18 (5.0)	9 (3.8)	9 (7.1)	0.168
Outcome, *n* (%)				
Severe case	166 (40.0)	89 (32.1)	77 (55.8)	<0.001
Death	38 (8.9)	12 (4.3)	26 (17.9)	<0.001
Hospital duration (IQR)	13 (10-17)	13 (10-17)	14 (10-19)	0.171

LD: Liver dysfunction, NLD: Non-LD, COPD: Chronic obstructive pulmonary disease, IQR: Interquartile range, BMI: Body mass index, ACEI: Angiotensin-converting enzyme inhibitors, ARB: Angiotensin II receptor blocker, ARDS: Acute respiratory distress syndrome

Table 2: Laboratory founding in nonliver dysfunction and liver dysfunction group

Laboratory data	Total (*n*=425)	NLD group (*n*=280)	LD group (*n*=145)	*P*
Oxygenation index (IQR)	275.0 (208.3-374.3)	288.5 (223.3-423.3)	252.5 (167.0-336.8)	0.014
$PaCO_2$ (IQR)	34.9 (29.6-39.1)	35.5 (31.0-40.2)	33.5 (28.7-38.6)	0.078
White blood cell count, $\times10^9$/L (IQR)	4.75 (3.49-6.18)	4.35 (3.35-5.45)	5.66 (4.28-7.76)	<0.001
Neutrophil count, $\times10^9$/L (IQR)	3.12 (2.15-4.73)	2.82 (1.93-3.96)	4.11 (2.80-6.44)	<0.001
Lymphocyte count, $\times10^9$/L (IQR)	0.90 (0.62-1.25)	0.96 (0.66-1.29)	0.79 (0.56-1.13)	0.001
Platelet count, $\times10^9$/L (IQR)	175.0 (131.0-223.3)	175.0 (137.0-220.0)	174.0 (125.0-236.0)	0.617
Hemoglobin concentration (IQR)	128.5 (118.0-141.0)	128.0 (118.0-140.0)	130.0 (118.0-142.0)	0.302
PT (IQR)	11.40 (11.00-12.00)	11.45 (11.00-12.03)	11.40 (11.20-12.00)	0.968
APTT (IQR)	27.00 (25.20-30.70)	26.90 (25.40-31.20)	27.7 (23.45-30.55)	0.597
Fibrinogen (IQR)	3.69 (2.97-4.27)	3.61 (2.78-4.17)	3.80 (3.16-4.36)	0.267
Creatine kinase, U/L (IQR)	85.0 (49.0-136.0)	76.5 (47.0-116.5)	98.0 (54.0-241.0)	0.002
Lactate dehydrogenase, U/L (IQR)	241.5 (178.0-324.0)	221.0 (172.0-281.0)	297.0 (239.5-427.5)	<0.001
ALT, U/L (IQR)	25.0 (16.0-40.5)	19.0 (13.5-26.0)	49.0 (33.0-70.0)	<0.001
AST, U/L (IQR)	30.0 (22.0-45.0)	25.0 (20.0-30.0)	54.0 (44.0-78.0)	<0.001
Albumin (IQR)	35.5 (31.8-39.3)	36.5 (32.9-39.4)	33.8 (30.5-38.5)	0.006
Creatinine, μ mol/L (IQR)	69.6 (57.0-84.9)	65.5 (54.3-82.3)	76.4 (64.8-88.4)	<0.001
Urea, mmol/L (IQR)	4.58 (3.62-6.28)	4.29 (3.40-5.85)	5.00 (3.96-6.85)	<0.001
C-reactive protein (IQR)	33.4 (11.4-66.1)	24.6 (7.9-54.9)	55.1 (24.8-83.8)	<0.001
D-dimer, mg/L (IQR)	0.435 (0.243-1.035)	0.420 (0.220-0.895)	0.645 (0.320-1.655)	0.047

LD: Liver dysfunction, NLD: Non-LD, PT: Prothrombin time, APTT: Activated partial thromboplastin time, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, $PaCO_2$: Partial pressure of CO_2, IQR: Interquartile range

Table 3: Multivariate analysis of risk factors of liver dysfunction

Factor	Adjust OR (95% CI)	*P*
Age	1.023 (1.008-1.038)	0.003
Sex (male)	2.873 (1.868-4.419)	<0.001
Hypertension	1.596 (1.014-2.512)	0.043

Adjusted by sex, age, and comorbidities. OR: Odds ratio, CI: Confidence interval

Figure 1]. A similar trend was observed by the multivariate regression analysis (adjusted HR, 3.52; 95% CI, 1.69–7.33; $P = 0.001$) [Table 4].

Discussion

In our study, of 34.1% patients developed LD on admission. Gender, age, hypertension, chronic heart disease, and chronic pulmonary disease were shown to be associated with LD. LD on admission has a significant impact on the prognosis of patients with COVID-19 with a higher mortality, together with more severity and more complications.

SARS-CoV-2 uses the ACE2 receptor for entry into target cells.[16] ACE2 is predominantly expressed by epithelial cells of the lung, intestine, kidney, heart, liver, and blood vessels.[17] SARS-COV-2 and SARS-COV share 79.6% of the same genome sequence,[18] the early study reported that SARS-COV was detected high expression in the liver.[19] Existing studies have shown that hospitalizations with ACEI/ARB use are associated with a lower risk of gastrointestinal system involvement and a significantly reduced risk of LD compared with patients without

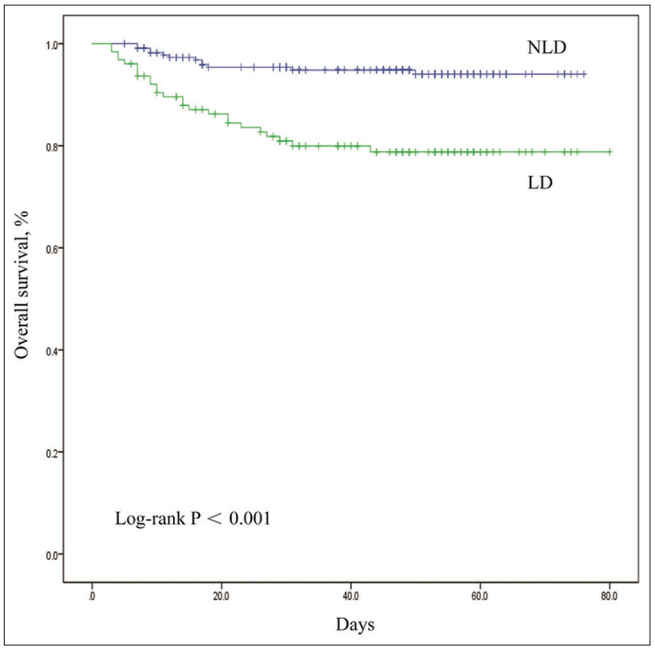

Figure 1: Kaplan–Meier survival curves of liver dysfunction on overall survival in patients with COVID-19

ACEI/ARB use.[20] In addition, serum angiotensin II levels were significantly elevated in COVID-19 patients, and were positively correlated with viral load and abnormal liver function.[21] Our results showed that using ACEI/ARB could reduce the incidence of LD. It has been described that the liver presents a local renin–angiotensin system,[22] and that the major effector peptide of the system, Ang II, can be secreted by activated hepatic stellate cells and plays an important role in amplifying oxidative stress in

Table 4: Multivariate analysis of Liver dysfunction

Factor	Death		ARDS		Critically ill	
	Adjust OR (95% CI)	*P*	Adjust OR (95% CI)	*P*	Adjust OR (95% CI)	*P*
Liver dysfunction	2.754 (1.245-6.093)	0.012	2.789 (1.716-4.533)	<0.001	2.094 (1.328-3.302)	0.001

ARDS: Acute respiratory distress syndrome, OR: Odds ratio, CI: Confidence interval

the organ.[23] Hence, we speculate that this may be the reason for the liver benefit of ACEI/ARB use However, previous study reported that liver histopathologic features from COVID-19 patients also did not show any significant damage in hepatocytes cells,[4] which suggested that LD is more likely due to secondary liver damage caused by inflammatory response and hypoxia. Drug-induced liver injury, particularly secondary to investigational agents such as remdesivir and tocilizumab, may also have impact.[24,25] Hypoxia can lead to necrotic hepatocyte death[26] and contribute to the development of LD. It can drive tissue dysfunction and disease development through immune cell dysregulation.[27] The dysregulation of immune cells in the liver was critical in the pathogenesis of almost all types of liver diseases.[28] High level of inflammatory biomarkers (C-reactive protein and neutrophil counts) from laboratory data and a symptom of dyspnea (manifestation of hypoxia) may indicate such a hypothesis.

Coagulopathy, marked by elevated D-dimer, PT, APTT, and fibrinogen levels, is associated with disease severity in COVID-19.[29] Our results showed that there was a significant difference of D-dimer in LD and NLD group, with no difference of PT, APTT, and fibrinogen. Patients with elevated AST or ALT (LD group) may have coagulopathy in early stage. The early laboratory abnormalities of high D-dimer levels are likely to reflect excess inflammation, rather than overt disseminated intravascular coagulation, which is commonly seen only in later stages of the illness.[30] In LD group, patients presented with low serum albumin, which was also described as a marker of disease severity on hospital admission.[31] Lymphopenia, a marker of impaired cellular immunity, is a cardinal laboratory finding in COVID-19 patients with prognostic association.[32] A lower lymphocyte count was found in our study of LD patients which also indicated a worse prognosis.

Our results also showed that sex, age, and hypertension were independent risk factors of LD. Previous study showed that those factors were also associated with mortality,[33] which suggested that LD was related to mortality. Indeed, our results showed that LD was a risk factor of mortality after adjusting confounders. The laboratory data showed that patients with LD also had a worse kidney function though it was difficult to ascertain causal association. Previous studies also reported that LD could increase the incidence of acute kidney injury in COVID-19.[34] Kidney injury could be secondary to the overall higher severity of disease. As the result showed that LD was associated with severe illness and more complications, physicians should take precautions against multi-organ failure.

Our study has several limitations. First, as a retrospective study, we did not collect more relevant indicators for the evaluation of liver injury, such as liver ultrasound and blood inflammatory factors. Second, we collected information on prior chronic disease based on patients' self-reports, and patients may have had LD prior to sarS-CoV-2 infection, but the patients were unaware of it, which could have affected our results. Third, due to insufficient follow-up time, we were unable to assess whether patients developed chronic liver insufficiency due to COVID-19. Long-term follow-up studies are needed to assess the incidence and prognosis of chronic liver failure.

Conclusions

Our study found that male, age, and hypertension were the risk of LD which lead to a worse outcome in COVID-19. Patients of COVID-19 with LD on admission should be more cautions by physicians.

Ethics Approval and Consent to Participate

This study was approved by the institution ethics board of Wuhan Fourth Hospital (202002001) and Zhongnan Hospital of Wuhan University (No. 2020020). Consent was obtained from patients or the patients' next of kin.

Acknowledgments

We would like to thank the staff of the Department of Critical Care Medicine of Zhongnan Hospital of Wuhan University and Wuhan Fourth Hospital, who contributed to this study by collecting the required data in the hospital data system.

Financial support and sponsorship

This work was supported by the National Natural Science Foundation (Grant No. 81772046 and 81971816 to Dr. Peng) and the Special Project for Significant New Drug Research and Development in the Major National Science and Technology Projects of China (Grant No. 2020ZX09201007 to Dr. Peng).

Conflicts of interest

Zhiyong Peng is the Executive Editor-in-Chief of the journal. The article was subject to the journal's standard procedures, with peer review handled independently of these members and their research groups.

References

1. Zhang J, Lin G, Zeng J, Lin J, Tian J, Li G. Challenges of SARS-CoV-2 and lessons learnt from SARS in Guangdong Province, China. J Clin Virol 2020;126:104341.
2. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, *et al.* Genomic characterisation and epidemiology of 2019 novel coronavirus: Implications for virus origins and receptor binding. Lancet 2020;395:565-74.
3. Wang Y, Kang H, Liu X, Tong Z. Combination of RT-qPCR testing and clinical features for diagnosis of COVID-19 facilitates management of SARS-CoV-2 outbreak. J Med Virol 2020;92:538-9.
4. 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;8:420-2.
5. Sun J, Aghemo A, Forner A, Valenti L. COVID-19 and liver disease. Liver Int 2020;40:1278-81.
6. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, *et al.* Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020;323:1061-9.
7. Fan Z, Chen L, Li J, Cheng X, Jingmao Y, Tian C, *et al.* Clinical features of COVID-19-related liver damage. Clin Gastroenterol Hepatol 2020;18:1561-6.
8. 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.
9. Zhang C, Shi L, Wang FS. Liver injury in COVID-19: Management and challenges. Lancet Gastroenterol Hepatol 2020;5:428-30.
10. Zhang P, Zhu L, Cai J, Lei F, Qin JJ, Xie J, *et al.* Association of inpatient use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers with mortality among patients with hypertension hospitalized with COVID-19. Circ Res 2020;126:1671-81.
11. Vaduganathan M, Vardeny O, Michel T, McMurray JJ, Pfeffer MA, Solomon SD. Renin-angiotensin-aldosterone system inhibitors in patients with Covid-19. N Engl J Med 2020;382:1653-9.
12. Ferguson ND, Fan E, Camporota L, Antonelli M, Anzueto A, Beale R, *et al.* The berlin definition of ARDS: An expanded rationale, justification, and supplementary material. Intensive Care Med 2012;38:1573-82.
13. Jin YH, Cai L, Cheng ZS, Cheng H, Deng T, Fan YP, *et al.* A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). Mil Med Res 2020;7:4.
14. Stevens PE, Levin A; Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group Members. Evaluation and management of chronic kidney disease: Synopsis of the kidney disease: Improving global outcomes 2012 clinical practice guideline. Ann Intern Med 2013;158:825-30.
15. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, *et al.* Third universal definition of myocardial infarction. Eur Heart J 2012;33:2551-67.
16. Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. Cell 2020;181:281-92.e6.
17. Cheng H, Wang Y, Wang GQ. Organ-protective effect of angiotensin-converting enzyme 2 and its effect on the prognosis of COVID-19. J Med Virol 2020;92:726-30.
18. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, *et al.* A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020;579:270-3.
19. Adamzik M, Broll J, Steinmann J, Westendorf AM, Rehfeld I, Kreissig C, *et al.* An increased alveolar CD4 + CD25 + Foxp3 + T-regulatory cell ratio in acute respiratory distress syndrome is associated with increased 30-day mortality. Intensive care Med 2013;39:1743-51.
20. Tan ND, Qiu Y, Xing XB, Ghosh S, Chen MH, Mao R. Associations between angiotensin-converting enzyme inhibitors and angiotensin II receptor blocker use, gastrointestinal symptoms, and mortality among patients with COVID-19. Gastroenterology 2020;159:1170-2.e1.
21. Liu Y, Yang Y, Zhang C, Huang F, Wang F, Yuan J, *et al.* Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. Sci China Life Sci 2020;63:364-74.
22. Leung PS. The physiology of a local renin-angiotensin system in the pancreas. J Physiol 2007;580:31-7.
23. Bataller R, Sancho-Bru P, Ginès P, Lora JM, Al-Garawi A, Solé M, *et al.* Activated human hepatic stellate cells express the renin-angiotensin system and synthesize angiotensin II. Gastroenterology 2003;125:117-25.
24. Bangash MN, Patel J, Parekh D. COVID-19 and the liver: Little cause for concern. Lancet Gastroenterol Hepatol 2020;5:529-30.
25. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, *et al.* A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. N Engl J Med 2020;382:1787-99.
26. Smith MK, Mooney DJ. Hypoxia leads to necrotic hepatocyte death. J Biomed Mater Res A 2007;80:520-9.
27. Taylor CT, Colgan SP. Regulation of immunity and inflammation by hypoxia in immunological niches. Nat Rev Immunol 2017;17:774-85.
28. Feng D, Mukhopadhyay P, Qiu J, Wang H. Inflammation in liver diseases. Mediators Inflamm 2018;2018:3927134.
29. Wan S, Xiang Y, Fang W, Zheng Y, Li B, Hu Y, *et al.* Clinical features and treatment of COVID-19 patients in northeast Chongqing. J Med Virol 2020;92:797-806.
30. Klok FA, Kruip M, van der Meer NJ, Arbous MS, Gommers D, Kant KM, *et al.* Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res 2020;191:145-7.
31. Xu L, Liu J, Lu M, Yang D, Zheng X. Liver injury during highly pathogenic human coronavirus infections. Liver Int 2020;40:998-1004.
32. Terpos E, Ntanasis-Stathopoulos I, Elalamy I, Kastritis E, Sergentanis TN, Politou M, *et al.* Hematological findings and complications of COVID-19. Am J Hematol 2020;95:834-47.
33. Madjid M, Safavi-Naeini P, Solomon SD, Vardeny O. Potential effects of coronaviruses on the cardiovascular system: A review. JAMA Cardiol 2020;5:831-40.
34. Rismanbaf A, Zarei S. Liver and kidney injuries in COVID-19 and their effects on drug therapy; a letter to editor. Arch Acad Emerg Med 2020;8:e17.