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Supplementary data

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Non-alcoholic fatty liver diseases in patients with COVID-19: A retrospective study

To the Editor:

Liver injury has been observed in patients with COVID-19, at an incidence ranging from 14–53%.^{1–3} We examined the liver injury patterns and implication of non-alcoholic fatty liver diseases (NAFLD) on clinical outcomes in Chinese patients with COVID-19.

Methods

From January 20 through February 17, 2020, consecutive patients admitted to 2 designated COVID-19 Hospitals in China with confirmed COVID-19 and information on NAFLD status were studied. The diagnosis and clinical management of patients with COVID-19 were conducted in accordance with the practice guidelines issued by The Chinese National Health Commission.⁴ COVID-

19 was confirmed by the detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) sequences in the throat swab by reverse transcription PCR. Liver injury was defined as hepatocellular if the alanine aminotransferase (ALT) level was >30 IU/L for males and >19 IU/L for females⁵; ductular if alkaline phosphatase (ALP) was >the upper limit of normal (ULN) accompanied by gamma-glutamyltransferase (GGT) >ULN; mixed if both hepatocellular and ductular enzymes were raised >ULN. NAFLD was identified as hepatic steatosis index (HSI = 8 × [ALT/AST] + BMI [+ 2 if type 2 diabetes yes, + 2 if female]) >36 points and/or by abdominal ultrasound examination.⁶ The ALT/AST value used for HSI was taken either at complete recovery on discharge or from records of the patients before and within 12 months of the diagnosis of COVID-19. The patients were followed till discharged with recovery or disease progression. The study was approved by

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the Ethics Committees of FYSPPH (20200303006) and the Fifth Medical Center of PLAGH (2020005D).

The significance of clinical characteristics on admission were assessed by univariate and multivariate logistic regression analysis to investigate the independent risk factors of disease progression. *p* values <0.05 were considered significant.

Results

Two hundred and two consecutive patients with confirmed COVID-19 and information relating to NAFLD status were studied. Liver injury was observed in 101 (50%) and 152 (75.2%) patients on admission and during hospitalization, respectively. Almost all liver injury was mild with hepatocellular pattern, only 2.6% (4/152) had ductular or mixed pattern. Sixty-seven (33.2%) patients had persistent abnormal liver function from admission to last follow-up. Thirty-nine (19.3%) and 163 (80.7%) had progressive and stable disease, respectively. Patients with progressive disease were older, had higher BMI, and a higher percentage of comorbidity and NAFLD (Table 1). Univariate and multivariate logistic regression analysis showed that male sex (odds ratio [OR] 3.1; 95% CI 1.1–9.4), age >60 years (OR 4.8; 95% CI 1.5–16.2), higher BMI (OR 1.3; 95% CI 1.0–1.8), underlying comorbidity (OR 6.3; 95% CI 2.3–18.8) and NAFLD (OR 6.4; 95% CI 1.5–31.2), were associated with COVID-19 progression.

Patients with NAFLD had a higher risk of disease progression (6.6% [5/126] vs. 44.7% [34/76] *p* <0.0001), higher likelihood of abnormal

liver function from admission to discharge (70% [53/76] vs. 11.1% [14/126]; *p* <0.0001) and longer viral shedding time (17.5 ± 5.2 days vs. 12.1 ± 4.4 days *p* <0.0001) compared to patients without NAFLD.

Discussion

Similar to other reports, our study showed that liver injury in patients with COVID-19 was frequent but mild in nature.^{1–3} The pattern of liver injury was mostly hepatocellular rather than cholestatic. This is of interest as it had been shown that biliary cells have high expression of angiotensin-converting enzyme (ACE2) receptor with a high affinity for the spike protein of SARS-CoV-2.⁷ In other respiratory viral infection, hepatitis has been related to the collateral damage mediated by virus-specific effector cells generated in response to the pulmonary infection.⁸ The postmortem liver biopsy in one of our patients showed only microvesicular steatosis, accompanied by overactivation of T cells, suggesting that liver injury in COVID-19 is likely immune mediated rather than being the result of direct cytopathic damage, as described for other viral respiratory diseases.⁹ The majority of patients in our series with persistent liver injury had NAFLD and high BMI. Patients with NAFLD also had a higher risk of progression to severe COVID-19 and longer viral shedding time. With increasing global prevalence of NAFLD, this may suggest a large proportion of our population could be at risk of severe COVID-19.

Table 1. Baseline characteristics of patients with COVID-19 on admission.

Clinical characteristics on admission	Overall	Stable	Progressive ^a	<i>p</i> values
	<i>n</i> = 202	<i>n</i> = 163	<i>n</i> = 39	
Male sex (n, %)	113 (55.9)	86 (52.8)	27 (69.2)	0.093
Age (years)	44.5 (34.8–54.1)	42.9 (32.6–51.8)	55.1 (43.7–71.8)	<0.001
Age >60 years (n, %)	31 (15.3)	14 (8.6)	17 (43.6)	<0.001
BMI (kg/m ²)	24.0 ± 2.8	23.4 ± 2.5	26.6 ± 2.2	<0.001
Smoke (n, %)	19 (9.4)	15 (9.2)	4 (10.3)	1.000
Drink (n, %)	6 (3.0)	5 (3.1)	1 (2.6)	1.000
Comorbidity (n, %)	47 (23.3)	23 (14.1)	24 (61.5)	<0.001
NAFLD (n, %)	76 (37.6)	42 (25.8)	34 (87.2)	<0.001
HBsAg positive (n, %)	7 (3.5)	5 (3.1)	2 (5.1)	0.885
Epidemiology (n, %)				0.866
No contact history	46 (22.8)	36 (22.1)	10 (25.6)	
Travel to Wuhan	100 (49.5)	82 (50.3)	18 (46.2)	
Close contact	56 (27.7)	45 (27.6)	11 (28.2)	
Severity (n, %)				<0.001
Mild	5 (2.5)	4 (2.5)	1 (2.6)	
Moderate	168 (83.2)	146 (89.6)	22 (56.4)	
Severe	28 (13.9)	12 (7.4)	16 (41.0)	
Critical	1 (0.5)	1 (0.6)	0 (0.0)	
Elevated ALT (n, %)	101 (50.0)	82 (50.3)	19 (48.7)	0.859
Elevated ALP (n, %)	5 (2.5)	5 (3.1)	0 (0)	0.585
Elevated AST (n, %)	34 (16.8)	24 (14.7)	10 (25.6)	0.102
Elevated GGT (n, %)	46 (22.8)	31 (19.0)	15 (38.5)	0.009
Elevated TBIL (n, %)	17 (8.4)	13 (8.0)	4 (10.3)	0.747
Elevated GGT plus ALP ^b (n, %)	1 (0.5)	1 (0.6)	0 (0)	1.000
Viral shedding days ^b	13.0 (10.0–17.0)	12.0 (10.0–16.0)	17.0 (16.0–19.5)	<0.001
Hospitalization days ^c	16.0 (12.0–22.0)	15.0 (12.0–20.0)	21.0 (16.5–27.0)	0.001

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; GGT, gamma-glutamyltransferase; NAFLD, non-alcoholic fatty liver disease; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TBIL, total bilirubin.

^aThe continuous variables were expressed as median (IQR), and compared using the Mann-Whitney *U* test, categorical variables were presented as numbers (percentage) and compared by the chi-square test or Fisher's exact test.

[†] Comorbidity included hypertension, diabetes, cardiovascular disease, chronic lung disease and HIV infections. One patient had elevated ALP and GGT on admission. Another 3 developed during hospitalization.

^aProgression of illness was defined as development of at least one of the following: respiratory rate ≥30 breaths/min, resting oxygen saturation ≤93% and PaO₂/FiO₂ ≤300 mmHg or worsening of lung CT findings, during the hospitalization period.

^bViral shedding period was defined as the time to undetectable SARS-CoV-2 from admission.

^cThe criteria of discharge include all the following conditions: body temperatures remain normal over 3 days, significant improvement of respiratory symptoms, resolution of pulmonary imaging of inflammation, and repeated tests at least 24 hours apart confirms SARS-CoV-2 clearance.

The underlying mechanism is unknown but might be related to impaired innate immunity to the virus. In particular, there are abundant ACE2 receptors in the small intestine and clinically, patients complain of abdominal pain and diarrhea. Circulation of the virus via the hepatic reticular system is expected, given the rich supply of blood to the liver from the small bowel. The liver contains the largest number of macrophages (Kupffer cells) in the body and is a potent cytokine producer. Impaired hepatic innate immune status might play a critical role in COVID-19 outcome. We postulate that in patients with NAFLD, the polarization status of hepatic macrophages might be skewed from inflammation-promoting M1 macrophages to inflammation-suppressing M2 macrophages, leading to progression of COVID-19.¹⁰ However, a better understanding of the role of NAFLD in COVID-19 may have therapeutic implications.

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Conflicts of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

DJ, DZ, JX, and EQ treated the patients. DJ, GC, YW and GL processed statistical data and drafted the manuscript. DJ and GL had the idea for and designed the study.

Supplementary data

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Management of patients with autoimmune liver disease during COVID-19 pandemic

To the Editor:

Although coronavirus disease 2019 (COVID-19) is mainly characterised by respiratory symptoms that can progress to acute respiratory distress syndrome (ARDS),^{1,2} abnormalities in liver enzymes

have been reported during severe infections.³ Many liver centres worldwide have faced the challenge of managing patients with liver diseases during this pandemic³ and particular concerns have been raised about immunocompromised patients. This is mainly based on previous data on the higher risk of severe respiratory viral infections in patients treated with immunosuppressive medications.^{4,5} However, preliminary experience from Bergamo, Lombardy, suggests that immunosuppressed patients are not at

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