Liver injury in patients with COVID-19: clinical profiles, CT findings, the correlation of the severity with liver injury

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Abstract

Background and aims Liver injury is found in some of patients with COVID-19. Liver injury of COVID-19 patients based on severity grading and abdominal radiological signs have not been reported until now. The aim of our study is to determine clinical profiles of the patients based on severity grading, describe abdominal radiological signs, and investigate the correlations of the severity with clinical profiles and radiological signs.

Methods This retrospective cohort study included 115 patients with COVID-19 from Jan 2020 to Feb 2020. Medical records of the patients were collected and CT images were reviewed.

Results Common clinical manifestations of patients with COVID-19 were fever (68.70%), cough (56.52%), fatigue (31.30%); some of them had gastrointestinal symptoms (diarrhea, 12.17%; nausea or vomiting 7.83%; inappetence, 7.83%). Abnormal liver function was observed in some of patients with COVID-19. Significant differences in the levels of AST, albumin, CRP were observed among different groups classified by the severity. Common findings of upper abdominal CT scan were liver hypodensity (26.09%) and pericholecystic fat stranding (21.27%); liver hypodensity was more frequently found in critical cases (58.82%). The severity of COVID-19 correlated with semi-quantitative CT score of pulmonary lesions, CT-quantified liver/spleen attenuation ratio in patients with COVID-19.

Conclusions Some of the patients with COVID-19 displayed liver damage revealed by liver functional tests and upper abdominal CT imaging, and the severity of COVID-19 patients correlated with some of liver functional tests and CT signs; thus, it will allow an earlier identification of high-risk patients for early effective intervention.

Keywords COVID-19 · Liver · Clinical profiles · Tomography · X-ray computed

Abbreviations

CT Computed tomography
COVID-19 Coronavirus disease 2019

SARS-CoV-2 The severe acute respiratory syndrome coronavirus 2
2019-nCoV 2019 Novel coronavirus
ARDS Acute respiratory distress syndrome
MOF Multiple organ failure
DILI Drug-induced liver injury
ROI Regions of interest
ICC Intraclass correlation efficient

Ping Lei and Lan Zhang contributed equally to this study.

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RT-PCR	Reverse transcription-polymerase chain reaction
WBC	White blood cells
PLT	Platelet
LY	Lymphocytes
T-BIL	Total bilirubin
ALB	Albumin
PT	Prothrombin time
INR	International normalized ratio
Cr	Creatinine
CRP	C-reactive protein
IQR	Interquartile range
L/S	Liver-to-spleen
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ALP	Alkaline phosphatase
γ -GT	γ -Glutamyl transpeptidase
ULN	Upper limit of normal
LLN	Lower limit of normal
UA	Uric acid
CHOL	Cholesterol
TG	Triglycerides
ACE2	Angiotensin-converting enzyme 2
NAFLD	Non-alcoholic fatty liver disease

Introduction

2019 novel coronavirus disease (COVID-19) is a zoonotic illness caused by a new viral pathogen named as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), previously known as 2019 novel coronavirus(2019-nCoV) [1]. The rapid spread of COVID-19 has created a global health crisis. Lung is considered as a major organ attacked by SARS-CoV-2. Besides the respiratory system, the infection of SARS-CoV-2 leads to various degrees of damage to other organs such as the liver, heart, kidney and gastrointestinal tract [2–5]. The majority of COVID-19 patients only suffered mild symptoms; while some COVID-19 patients progressed rapidly with acute respiratory distress syndrome (ARDS), and eventually resulted in multiple organ failure (MOF) [1, 6].

Previous studies showed that some of patients infected by SARS-CoV-2 had gastrointestinal symptoms, such as diarrhea, abdominal pain, inappetence, nausea and vomiting [7–9]. In addition, liver injury occurred in patients with COVID-19 [8–10]. The abnormality of liver function tests was observed in some of COVID-19 patients at admission [11]. Pathological examination of COVID-19 patient showed hepatocyte degeneration accompanied by focal necrosis, moderate steatosis, infiltration of leukocytes into lobular and portal area, and sinusoidal congestion [12]. Thus, all these indicated liver involvement in patients infected by

SARS-CoV-2. While previous studies collected the data from the whole cohort of patients and some of them probably had chronic liver diseases.

Chest CT, a routine imaging tool for pneumonia diagnosis, plays a central role in the diagnosis and classification of COVID-19 pneumonia [13–15]. Moreover, radiological signs of chest CT varied with the course of diseases, and the change of radiological signs might be associated with the outcomes of diseases [15, 16]. Liver injury in patients infected by SARS-CoV-2 might result in radiological change in liver. However, radiological findings of abdominal CT scan have not been explored so far. Thus, the aim of our study is to determine clinical profiles of the COVID-19 patients based on severity grading, describe abdominal radiological signs, and investigate the correlations of the severity with clinical profiles and radiological signs.

Materials and methods

Study population

Our retrospective study was performed at Cancer Center of Union Hospital and main campus of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology from Jan 24, 2020 to Feb 17, 2020. 178 consecutive patients with COVID19 pneumonia were enrolled. The diagnosis of COVID19 patients are: (1) fever and/or respiratory symptoms; (2) positive nucleic acid of the virus (RT-PCR analysis of throat swab specimens). A severity-grading system for patients with COVID19 was issued by National Health Commission of the People's Republic of China and National Administration of Traditional Chinese Medicine of the People's Republic of China. The severity of COVID19 patients is classified into four grades: mild, ordinary, severe and critical [13]. Mild cases: symptomatic infection includes fever, cough, sore throat, fatigue, headache or myalgia, but there were no pneumonia signs on chest imaging. Ordinary cases: symptomatic infection includes fever, cough, sore throat, fatigue, headache or myalgia, and pneumonia signs showed on chest imaging, meanwhile, these patients do not have any of the severe or critical symptoms and complications described below. Severe cases: the disease progresses to meet any of the following conditions: ① significantly increased respiration rate: $RR \geq 30/\text{min}$; ② $SpO_2 \leq 93\%$ from a finger oximeter; ③ $PaO_2/FiO_2 \leq 300$ mmHg; ④ patients with $> 50\%$ lesions progression within 24–48 h in pulmonary imaging. Critical cases: with any of the following conditions: ① respiratory failure which requires mechanical ventilation; ② shock; ③ accompanied by other organ failure that needs ICU monitoring and treatment. Inclusion criteria were as follows: ① confirmed cases with COVID-19; ② pneumonia manifestation on chest CT scan; ③ CT scan

and laboratory examinations were performed within 2 days after admission. Exclusion criteria included: ① patients who received antiviral treatment for more than 3 days before admission, such as interferon, chloroquine phosphate, arbidol, lopinavir/ritonavir, which may result in the alleviation of COVID-19 and side effects including GI symptoms and drug-induced liver injury, etc., ($n=30$); ② CT images of upper abdomen were not obtained ($n=19$); ③ patients with hematological malignancy who were receiving chemotherapy ($n=6$); ④ patients with severe underlying pulmonary diseases ($n=4$); ⑤ patients with chronic liver diseases and liver cancer ($n=4$) (Fig. 1).

Data collection

The pertinent data of the patients were collected from medical records and tabulated in a database. The pertinent data of the patients included demographic data; presenting symptoms and signs; medical history; laboratory tests; imaging findings; therapeutic process.

Imaging technique and imaging analysis

All CT examinations were performed with one of the following three scanners: 64-detector spiral CT scanner (Somatom Definition AS, Siemens, Germany), gemstone spectral CT scanner (Discovery CT750 HD, GE, USA), 16-detector spiral CT scanner (Activion 16, Toshiba, Japan). Images were reconstructed into lung window and soft tissue mediastinal window with a slice thickness of 1.5 mm, 2 mm or 5 mm

and an interval of 1.5 mm, 2 mm or 5 mm, respectively. The radiological evaluation included pulmonary involvement and abnormal signs of upper abdomen. All CT images were independently reviewed and the findings were recorded by two experienced radiologists who were unaware of clinical data. For semi-quantitative and qualitative imaging evaluation, discrepant evaluation was jointly re-evaluated to reach a final consensus [17–19]; whereas, intraclass correlation coefficient (ICC) was introduced to assess interobserver consistency for quantitative imaging evaluation. The severity of pneumonia was evaluated by a semi-quantitative scoring system, i.e., each of the 5 lung lobes was visually scored from 0 to 5 as: 0, no involvement; 1, <5% involvement; 2, 5–25% involvement; 3, 26–49% involvement; 4, 50–75% involvement; 5, >75% involvement. The total CT score was the sum of individual lobar scores and ranged from 0 (no involvement) to 25 (maximum involvement) [20, 21]. Radiologic signs reviewed in upper abdominal CT scan include: hepatomegaly, the density of liver, periportal edema, pericholecystic fat stranding, portal lymphadenopathy, biliary ductal dilatation, ascites. Liver hypodensity was defined when the density of liver is homogeneous or heterogeneous lower than or nearly equal to that of spleen. CT-quantified hepatic density was measured by liver-to-spleen (L/S) attenuation ratio. Hepatic and splenic CT attenuation values were measured using regions of interest (ROI) > 100 mm² in area [22] on the PACS (CARESTRAM 3.1.S12.1, Canada). Two ROIs were in the right liver lobe, one ROI in the left liver lobe and three ROIs in the spleen. ROI should include a greater area of the liver and spleen whenever possible,

Fig. 1 Flowchart of the patients' selection, inclusion, and exclusion

meanwhile ROI selection should exclude regions of hepatic vessels and bile ducts (Fig. S1). Then L/S ratio was calculated by taking mean HU measurement of liver lobe ROIs and dividing it by the mean splenic HU measurement of its ROIs (Fig.S1).

Statistical analysis

Continuous variables were expressed as mean and standard deviation for normal distribution data and median (25th–75th percentiles) if the distribution was skewed. Categorical variables were presented as count (percentage). The interobserver agreement for measurement of CT-quantified hepatic density was determined using the intraclass correlation coefficient (ICC). The level of agreement was generally recognized as follows: poor, $ICC < 0.20$; fair, $0.2 < ICC \leq 0.40$; moderate, $0.4 < ICC \leq 0.60$; good, $0.6 < ICC \leq 0.80$; and very good, $0.8 < ICC \leq 1.0$. The differences of categorical variables among groups were analyzed by Chi-square test (the Fisher exact test was used when the data were limited) and continuous variables by Kruskal–Wallis H test. The correlation of categorical variables was analyzed by Spearman correlation test and continuous variables by Pearson correlation test. All statistical tests were two-sided. *p* value less than 0.05 was considered to indicate statistical significance. Statistical analyses were performed using SPSS version 22.0 (SPSS Inc., Chicago, Illinois, USA).

Results

Clinical presentation

115 patients with COVID-19 pneumonia were consecutively enrolled in our study. The patients were classified into mild group, ordinary group, severe group and critical group according to the severity [13]. Mild cases without pneumonia manifestation did not receive inpatient hospital care in Wuhan, China, so mild cases were not included in our study. Thus, the enrolled patients included ordinary cases (50 patients), severe cases (48 patients) and critical cases (17 patients) (Fig. 1). The median age of enrolled patients were 66 years (IQR: 60–70), there was 58 males and 57 females, with a male-to-female ratio of 1.02:1 (Supplementary Table 1). Significant difference in patients' age existed among different groups, which revealed that older patients were at higher risk for severe illness. Then, the clinical manifestations of the patients were analyzed, and the results showed fever in 68.70% (79/115) of the patients, cough in 56.52% (65/115), fatigue in 31.30% (36/115), and shortness of breath in 13.91% (16/115) of the patients (Supplementary Table 1). Thirdly, gastrointestinal symptoms were determined in the patients, and we found that 12.17%

(14/115) of the cases had diarrhea, 7.83% (9/115) of the cases with nausea or vomiting, 7.83% (9/115) of the cases with inappetence (Supplementary Table 1). In addition, no significant differences in clinical manifestations were evident among different groups.

Laboratory tests (peripheral blood routine examination and clinical biochemistry)

Laboratory results of the patients containing peripheral blood routine examination and clinical biochemistry were summarized in Table 1 at the time of baseline evaluation. Firstly, blood routine examination of the patients was determined. Generally, the values of erythrocyte, leukocyte and platelet were within normal limit in most of COVID-19 patients (Table 1). Lymphocytopenia was observed in 54.78% of the COVID-19 patients and lymphocytopenia occurred in 100% of critical cases. T cell subsets were also analyzed and the results showed that CD3+, CD4+ and CD8+ T lymphocyte subsets were decreased in some of the COVID-19 patients. Compared with the ordinary group and the severe group, the proportion of CD3+, CD4+ and CD8+ T cells decreased significantly in the critical group (Table 1). Secondly, the parameters of liver functional tests were analyzed. Most of the patients had normal levels of AST, ALT, ALP, γ GT and total bilirubin. Significant difference in AST level was observed among different groups. Liver synthetic function was also assessed by the detection of albumin and PT, and we found that 60.00% (69/115) of the cases had hypoalbuminemia, 3.88% of the cases had increased prothrombin time. Thirdly, biomarkers of renal function indicated by serum urea and creatinine showed that most of the patients had normal renal function (Table 1). Fourthly, some biomarkers of metabolic syndrome were collected and the results showed that no significant differences in the levels of cholesterol (CHOL) and triglyceride (TG) were observed among different groups. Most of the patients had normal uric acid level; surprisingly, critical cases with the lowest level of uric acid (Table 1). Finally, abnormal CRP level was detected in 64.42% of the patients. Elevated AST level, hypoalbuminemia and increased CRP level were frequently found in critical cases.

Imaging findings of chest and upper abdominal CT in COVID-19 patients

Pneumonia in COVID-19 patients was commonly manifested as ground-glass opacity, smooth or irregular interlobular septal thickening, consolidation with air bronchogram, crazy-paving pattern, and pleura effusion (Figs. 2 and 3). Most of the patients suffered pneumonia in multiple lobes. The severity of pneumonia was evaluated by a semi-quantitative scoring system and the median score

Table 1 Laboratory tests of patients with COVID-19 on admission

	All patients	Ordinary	Severe	Critical	<i>p</i> Value*
Peripheral blood routine examination					
Erythrocytes, $10^{12}/L$	3.84 (3.52–4.24)	3.94 (3.74–4.38)	3.72 (3.36–4.14)	3.92 (3.36–4.18)	0.459
RBC < $1 \times LLN$, % (<i>n/N</i>)	79.13% (91/115)	74.00% (37/50)	83.33% (40/48)	82.35% (14/17)	
Leukocyte, $10^9/L$	5.20 (4.06–6.77)	5.21 (3.92–6.38)	4.66 (3.87–6.63)	7.23 (5.04–9.56)	0.138
WBC > $1 \times ULN$, % (<i>n/N</i>)	5.22% (6/115)	0	2.08% (1/48)	29.41% (5/17)	
WBC < $1 \times LLN$, % (<i>n/N</i>)	13.04% (15/115)	14.00% (7/50)	14.58% (7/48)	5.88% (1/17)	
Platelet, $10^9/L$	229.00 (178.00–305.00)	252.50 (207.50–310.25)	213.00 (167.50–290.50)	169.00 (123.00–284.50)	0.455
PLT < $1 \times LLN$, % (<i>n/N</i>)	7.83% (9/115)	2.00% (1/50)	8.33% (4/48)	23.53% (4/17)	
Lymphocytes, $10^9/L$	1.04 (0.80–1.41)	1.23 (0.90–1.65)	1.04 (0.81–1.41)	0.61 (0.45–0.87)	<0.001
LY < $1 \times LLN$, % (<i>n/N</i>)	54.78% (63/115)	38.00% (19/50)	56.25% (27/50)	100% (17/17)	
CD3+ T cells, $10^9/L$	0.74 (0.54–1.03)	0.87 (0.63–1.20)	0.74 (0.60–1.05)	0.35 (0.29–0.52)	<0.001
< $1 \times LLN$, % (<i>n/N</i>)	71.43% (80/112)	90.47% (33/49)	65.96% (31/47)	100% (16/16)	
CD4+ T cells, $10^9/L$	0.32 (0.22–0.48)	0.35 (0.26–0.53)	0.34 (0.24–0.49)	0.14 (0.10–0.22)	<0.001
< $1 \times LLN$, % (<i>n/N</i>)	81.25% (91/112)	77.55% (38/49)	78.72% (37/47)	100% (16/16)	
CD8+ T cells, $10^9/L$	0.17 (0.10–0.25)	0.18 (0.12–0.28)	0.18 (0.13–0.28)	0.07 (0.04–0.09)	<0.001
< $1 \times LLN$, % (<i>n/N</i>)	81.25% (91/112)	79.59% (39/49)	76.60% (36/47)	100% (16/16)	
Biochemistry					
ALT, U/L	27.00 (19.00–45.00)	27.00 (16.75–50.50)	27.00 (20.00–41.00)	26.00 (18.00–55.00)	0.938
ALT > $1 \times ULN$, % (<i>n/N</i>)	27.83% (32/115)	30.00% (15/50)	25.00% (12/48)	29.41% (5/17)	
AST, U/L	28.00 (20.00–40.00)	23.50 (16.00–34.50)	30.00 (21.25–40.75)	37.00 (27.00–46.00)	0.014
AST > $1 \times ULN$, % (<i>n/N</i>)	22.61% (26/115)	14.00% (7/50)	25.00% (12/48)	41.18% (7/17)	
ALP, U/L	65.00 (52.00–80.00)	65.50 (50.75–84.25)	63.00 (54.25–77.75)	65.00 (53.00–91.00)	0.796
ALP > $1 \times ULN$, % (<i>n/N</i>)	5.22% (6/115)	4.00% (2/50)	4.17% (2/48)	11.76% (2/17)	
γ GT, U/L	27.00 (17.00–49.00)	26.00 (15.00–49.00)	26.50 (18.00–36.50)	42.00 (21.50–100)	0.188
γ GT > $1 \times ULN$, % (<i>n/N</i>)	27.83% (32/115)	32.00% (16/50)	16.67% (8/48)	47.06% (8/17)	
T-BIL, μ mol/L	11.20 (8.70–14.40)	10.80 (7.78–14.40)	12.15 (9.83–14.38)	11.10 (8.95–22.50)	0.288
T-BIL > $1 \times ULN$, % (<i>n/N</i>)	13.04% (15/115)	12.00% (6/50)	8.33% (4/48)	29.41% (5/17)	
ALB, g/L	34.10 (31.60–37.30)	35.20 (32.88–38.30)	33.50 (30.83–37.03)	32.20 (28.15–34.65)	0.003
ALB < $1 \times LLN$, % (<i>n/N</i>)	60.00% (69/115)	46.00% (23/50)	64.58% (31/48)	88.24% (15/17)	
PT, s	13.40 (12.90–14.20)	13.30 (12.90–13.85)	13.65 (13.03–14.20)	13.70 (12.95–15.35)	0.290
PT > $1 \times ULN$, % (<i>n/N</i>)	3.88% (4/103)	0 (0/41)	2.17% (1/46)	18.75% (3/16)	
INR	1.04 (0.99–1.12)	1.03 (0.99–1.09)	1.07 (1.00–1.12)	1.07 (1.00–1.24)	0.294
INR > $1 \times ULN$, % (<i>n/N</i>)	3.88% (4/103)	0 (0/41)	2.17% (1/46)	18.75% (3/16)	
Urea, μ mol/L	3.92 (3.10–5.05)	3.66 (2.76–4.53)	4.00 (3.23–5.32)	3.95 (3.45–5.87)	0.138
Urea > $1 \times ULN$, % (<i>n/N</i>)	26.09% (30/115)	28.00% (14/50)	25.00% (12/48)	23.53% (4/17)	
Cr, μ mol/L	68.10 (56.90–77.80)	62.35 (54.73–73.13)	71.40 (63.50–83.98)	63.90 (54.30–80.50)	0.011
Cr > $1 \times ULN$, % (<i>n/N</i>)	5.22% (6/115)	4.00% (2/50)	6.25% (3/48)	5.88% (1/17)	
Uric acid, μ mol/L	228.00 (184.20–295.60)	238.20 (188.25–295.15)	235.60 (189.83–329.98)	211.70 (133.35–233.90)	0.017
UA > $1 \times ULN$, % (<i>n/N</i>)	3.48% (4/115)	0	8.33% (4/48)	0	
CRP, mg/L	22.10 (3.28–67.15)	10.20 (3.14–29.5)	15.30 (3.39–69.50)	81.00 (62.20–156.00)	<0.001
CRP > $1 \times ULN$, % (<i>n/N</i>)	64.42% (67/104)	55.32% (26/47)	60.00% (24/40)	100% (17/17)	
CHOL, mmol/L	3.92 (3.42–4.39)	3.93 (3.38–4.81)	3.96 (3.44–4.32)	3.76 (3.51–4.73)	0.993
CHOL > $1 \times ULN$, % (<i>n/N</i>)	15.38% (16/104)	20.00% (9/45)	11.36% (5/44)	13.33% (2/15)	
TG, mmol/L	1.18 (0.91–1.53)	1.24 (0.96–1.60)	1.15 (0.84–1.56)	1.27 (0.85–1.51)	0.618
TG > $1 \times ULN$, % (<i>n/N</i>)	14.56% (15/103)	20.00% (9/45)	11.36% (5/44)	7.14% (1/14)	

Continuous variables are presented as median (25th–75th percentiles), and categorical variables are presented as count (percentage)

*The *p* values refer to Kruskal–Wallis *H* test among different groups. Normal ranges: erythrocytes (RBC): $4.3\text{--}5.8 \times 10^{12}/L$; leukocyte (WBC): $3.5\text{--}9.5 \times 10^9/L$; platelet (PLT): $125\text{--}350 \times 10^9/L$; lymphocytes (LY): $1.1\text{--}3.2 \times 10^9/L$; CD3+ T cells: $\geq 0.995 \times 10^9/L$; CD4+ T cells: $\geq 0.550 \times 10^9/L$; CD8+ T cells: $\geq 0.320 \times 10^9/L$; alanine aminotransferase (ALT): 5–40 U/L; aspartate aminotransferase (AST): 8–40 U/L; alkaline phosphatase (ALP): 40–150 U/L; γ -glutamyl transpeptidase (γ -GT): 11–50 U/L; total bilirubin (T-BIL): 5.1–19.0 μ mol/L; albumin (ALB): 35–55 g/L; prothrombin time (PT): 11.0–16.0 s; international normalized ratio (INR): 0.80–1.31; urea: 2.9–8.2 mmol/L; creatinine (Cr): 44.0–106.0 μ mol/L; C-reactive protein (CRP): < 8 mg/L; uric acid (UA): 208–428 μ mol/L; cholesterol (CHOL): < 5.2 mmol/L; triglycerides (TG): < 1.7 mmol/L

Fig. 2 CT findings in an 80-year-old male patient with severe COVID-19. **a** and **b** Transverse thin-section chest CT scan showed ground-glass opacities in both sides, partial consolidation and small

amount of pleural effusion in right side, semi-quantitative score of pulmonary lesions was 10; **c** transverse thin-section CT scan revealed homogeneous liver hypodensity, the L/S attenuation ratio is 0.99

Fig. 3 CT findings in a 51-year-old male patient with critical COVID-19 who had type I respiratory failure and received mechanical ventilation. **a** and **b** transverse thin-section chest CT scan showed ground-glass opacities, consolidation with air bronchogram and pleural effusion in both sides, semi-quantitative score of lung lesions was 22; **c** transverse thin-section CT scan showed heterogeneous liver hypodensity, the L/S attenuation ratio was 1.04; **d** enlarged view of the gallbladder showed pericholecystic fat stranding (arrows)

of lung involvement was 11 (IQR: 8–15) (Table 2). More importantly, significant difference in semi-quantitative scores of lung involvement was observed among different groups (Table 2). Then, imaging features of abdominal CT were determined. Common CT findings in upper abdominal CT scan were liver hypodensity and pericholecystic fat stranding (Table 2). Hepatomegaly, splenomegaly, periportal edema, edema of the gallbladder walls, periportal lymphadenopathy, biliary dilatation and ascites were not observed. Homogeneous or heterogeneous hepatic hypodensity was the most common CT finding (Figs. 2 and 3). Liver hypodensity was observed in 26.09% (30/115) of the patients and statistical analysis revealed significant difference among

different groups (Table 2). Moreover, the liver-to-spleen (L/S) attenuation ratio was measured and the interobserver agreement for assessment of L/S attenuation ratios was very good (ICC = 0.98). A decrease in the L/S attenuation ratio (< 1) was detected in 16.52% of the whole cohort, up to 47.06% of critical cases. Meanwhile, significant difference in the L/S attenuation ratio was observed among different groups (Table 2). Finally, pericholecystic fat stranding was evaluated. Unfortunately, 21 cases were excluded due to the patients with cholecystolithiasis or cholecystectomy. Pericholecystic fat stranding was observed in 21.27% (21/94) of the patients (Fig. 3), but no significant difference was evident among different groups.

Table 2 Baseline radiologic findings of patients with COVID-19

	All Patients	Ordinary	Severe	Critical	<i>p</i> Value
Radiologic features of upper abdominal CT					
Liver hypodensity, % (<i>n/N</i>)	26.09% (30/115)	14.00% (7/50)	27.08% (13/48)	58.8% (10/17)	0.002 [#]
Pericholecystic fat stranding	21.27% (20/94)	20.00% (8/40)	22.50% (9/40)	21.43% (3/14)	1 [#]
Quantitative analysis of liver hypodensity					
L/S attenuation ratio	1.21 (1.06–1.30)	1.24 (1.15–1.34)	1.21 (1.06–1.32)	1.01 (0.90–1.11)	<0.001*
L/S attenuation ratio, % (<i>n/N</i>) ^a	16.52% (19/115)	6.00% (3/50)	16.67% (8/48)	47.06% (8/17)	0.001 [#]
Radiologic features of chest CT					
CT scores of pulmonary involvements	11 (8–15)	9.5 (7–13)	11 (9–15)	20 (14–24)	<0.001*
Pleural effusion	27.83% (32/115)	12.00% (6/50)	39.58 (19/48)	41.18% (7/17)	0.003 [#]

Continuous variables are presented as median (25th–75th percentiles), and categorical variables are presented as count (percentage)

L/S liver-to-spleen

*The *p* values refer to Kruskal–Wallis *H* test among different groups

[#]The *p* values refer to Fisher exact test among different groups

^aL/S attenuation ratio < 1

Correlation of severity grading with clinical manifestations, radiologic features and liver function tests

To evaluate the value of radiological features and liver function tests, the correlations of severity grading with clinical manifestations, CT features and liver function tests were determined. Firstly, the correlations of clinical manifestation with a panel of liver function tests and severity grading were investigated in patients with COVID-19 and the results showed no correlation of clinical manifestations with pulmonary lesions, severity grading and liver functional tests (Table S2); secondly, the correlations of semi-quantitative scoring of pulmonary lesions with a panel of liver function tests and severity grading were investigated in patients with COVID-19, and the correlation tests demonstrated that the score of pulmonary lesions was associated with liver function tests, severity grading and CRP (Table 3). Thirdly, the correlations of severity grading with a panel of liver function tests, CRP and pulmonary lesions were determined. The results demonstrated the severity correlated with AST, albumin, CRP, semi-quantitative CT-scoring of pulmonary lesions and CT-quantified liver/spleen attenuation ratio (Table 3).

Discussion

COVID-19 has turned into a global pandemic disease. Previous studies demonstrated coronavirus COVID-19 (SARS-CoV-2) resulted in liver injury in the whole cohort [8–10], we described clinical profiles and abdominal radiological features of COVID-19 patients according to severity grading, and then determined the correlation of radiological

features with clinical profiles. Abnormal liver function tests were observed in some of COVID-19 patients, radiological signs of liver in non-contrast CT scan included liver hypodensity and pericholecystic fat stranding. The correlation tests demonstrated that disease severity correlated with AST, albumin, CRP, the score of pulmonary lesions, the L/S attenuation ratio. Thus, it will allow an earlier identification of high-risk patients for immediate effective intervention in future.

Gastrointestinal symptoms of patients with COVID-19 were analyzed, and common GI symptoms included diarrhea, nausea, vomiting, and inappetence. The proportion of COVID-19 patients with GI symptoms in our study was similar to that of previous research [7]. GI symptoms in patients with COVID-19 may result from the infection of COVID-19 in intestinal tissues [7]. In addition, the interaction between brain and gut might cause discomfort to the gastrointestinal tract. The results of peripheral routine blood examination showed the values of erythrocyte, leukocyte and platelet were within normal limit in most of the patients. Some of the patients had lymphocytopenia, especially CD3+ T cells. CD3+ T cells are mainly composed of CD4+ T and CD8+ T cells, CD4+ T and CD8+ T cells are critical for mediating clearance following many acute viral infections in the lung, which leads to a decrease in CD4+ T and CD8+ T cells [23, 24]. A panel of liver functional tests was determined, and the result showed that some of the patients had abnormal liver function, and clinically significant liver injury was uncommon even in critical cases. The mechanism underlying liver damage has not been explored until now. Liver damage in the COVID-19 patients might be caused by viral infection of liver cells, adverse drug reactions, systemic inflammation, underlying liver diseases, hypoxic hepatitis, etc. [3–5]. Xu et al. reported the drugs used for COVID-19

Table 3 The correlation of severity grading with clinical profiles and radiologic features in patients with COVID-19

Variable	Liver functional test							CRP	CT-quantified L/S attenuation ratio	Semi-quantitative CT scoring of pulmonary lesions
	ALT	AST	ALP	γ GT	T-BIL	ALB	PT			
	<i>n</i> = 115	<i>n</i> = 115	<i>n</i> = 115	<i>n</i> = 115	<i>n</i> = 115	<i>n</i> = 115	<i>n</i> = 103	<i>n</i> = 104	<i>n</i> = 115	<i>n</i> = 115
Semi-quantitative CT scoring of pulmonary lesions ^a	0.173	0.279	0.281	0.373	0.260	– 0.397	0.315	0.495	– 0.389	/
<i>p</i> value	0.064	0.002	0.002	< 0.001	0.005	< 0.001	0.001	< 0.001	< 0.001	/
Severity of COVID-19 ^b	0.033	0.273	0.012	0.111	0.145	– 0.317	0.155	0.468	– 0.354	0.493
<i>p</i> value	0.723	0.003	0.898	0.238	0.122	0.001	0.117	< 0.001	< 0.001	< 0.001

L/S liver-to-spleen

^aPearson correlation test^bSpearman correlation test

patients probably induced liver damage, such as antibiotics, antiviral agents, etc.[5]. Thus, to exclude drug-induced liver injury (DILI), liver functional tests were collected within 2 days after admission. In addition, liver dysfunction occurred in patients with chronic liver diseases, so the patients with chronic liver diseases were excluded in our study. Thus, we speculate liver injury in COVID-19 patients might result from viral infection of liver cells, inflammatory responses, and hypoxic hepatitis in our study. Preliminary studies showed that angiotensin-converting enzyme 2 (ACE2) receptor expression is enriched in cholangiocytes [25] and SARS-CoV-2 enters the target cell through ACE2 receptor [25], which results in abnormality of serum γ GT, a diagnostic biomarker for cholangiocyte injury. Abnormal PT and hypoalbuminemia were found in some of COVID-19 patients. Severe COVID-19 frequently induces hypercoagulability with both microangiopathy and local thrombus formation; abnormality in prothrombin time is relatively uncommon in initial presentations [26, 27]. Abnormal PT might result from liver injury or coagulopathy. Hypoalbuminemia is caused by liver dysfunction, heart failure, kidney damage, protein-losing enteropathy, and malnutrition. In our study, heart failure, kidney damage, protein-losing enteropathy were not observed in our study. Thus, hypoalbuminemia would be caused by malnutrition or liver dysfunction. Interestingly, hypoalbuminemia and increased AST level were frequently found in critical cases, and correlation analysis revealed the correlations of albumin and AST level with severity grading. Thus, biomarkers of liver function containing AST and albumin should be detected in patients with COVID-19.

Common findings of upper abdominal CT scan in the patients with COVID-19 were mainly manifested as homogeneous or heterogeneous liver hypodensity and pericholecystic fat stranding. Further study revealed the L/S attenuation ratio and pulmonary lesions correlated positively with the severity of the disease. These indicated that the infection of SARS-CoV-2 may result in multiple organ dysfunction syndrome (MODS) containing liver injury. Pathological examination of liver showed moderate steatosis and mild lobular and portal activity in a patient with COVID-19 [12]. Liver hypodensity was a common sign of liver steatosis or acute hepatitis, while other imaging signs of acute hepatitis, such as hepatomegaly, periportal edema, edema of the gallbladder wall, and periportal lymphadenopathy were not observed in patients with COVID-19. Thus, liver hypodensity and a decrease in the L/S attenuation ratio might be attributed to liver steatosis. Obviously, transient elastography (FibroScan) with controlled attenuation parameter (CAP) has demonstrated good accuracy in quantifying the levels of liver steatosis; however, most of the patients did not receive Fibroscan due to mild liver injury and uncovered medical procedures. The etiologies of hepatic steatosis

include NAFLD, alcoholism, hepatitis C infection, some drugs, autoimmune disease, malnutrition, etc. Liver steatosis resulting from NAFLD should be excluded. Some of clinical profiles in the COVID-19 patients were different from those of NAFLD patients. Firstly, the enrolled patients had normal value for ALT and AST before hospital admission. Thus, liver damage was not caused by chronic liver diseases, such as NAFLD. Secondly, elevated levels of liver enzymes are often seen in NAFLD, hypoalbuminemia is often observed in COVID-19 patients. Thirdly, liver hypodensity on CT scans was improved within a short time in some COVID-19 patients (Fig. S2); however, the improvement of CT sign needs a long period of time in NAFLD. Fourthly, no significant differences in plasma lipid levels were observed among different groups of the COVID-19 patients divided by the severity. Thus, the hypothesis is supported by indirect evidences and it should be confirmed by a large sample of pathological examinations in future. More importantly, the mechanism underlying liver steatosis should be explored in the patients infected with SARS-CoV-2. In addition, pericholecystic fat stranding, a common sign of abdominal CT scan, might be associated with inflammation. Interestingly, enlargement of hilar lymph nodes and spleen were not found.

The correlations of clinical profiles and radiological signs with severity grading were investigated, and the results showed severity grading correlated with AST, albumin, CRP, semi-quantitative scoring of pulmonary lesions, the liver-to-spleen (L/S) attenuation ratio. These indicated elevated AST level, hypoalbuminemia, a high CRP, a low L/S attenuation ratio, a high score of pulmonary lesions might be indicators of severe or critical cases. Our study demonstrated the severity of SARS-CoV-2 infection correlated with CRP and pulmonary lesions, which was similar to previous studies. Interestingly, the severity correlates with AST, CT-quantified liver/spleen attenuation ratio in patients with COVID-19. Elevated AST can be caused by liver injury, cardiovascular disease, kidney diseases, muscle disorders, etc. Elevated AST might result from multiple organ dysfunction, which is associated with the severity of SARS-CoV-2 infection. CT-quantified liver/spleen attenuation ratio revealed the severity of liver damage, which was related to multiple organ dysfunction syndrome.

Obviously, our study had several limitations. Firstly, it was a single-center retrospective study. Selection bias occurred in retrospective cohort studies, the patients with mild system and normal lung manifestation were excluded in our study. In addition, most of the enrolled patients were middle-aged and aged people. Secondly, the patients did not receive contrast-enhanced CT scan. Thirdly, limited number of the cases in our cohort might have resulted in the bias of the results. Finally, follow-up data of the patients were not provided. At the end of the 2-month follow-up, 106 patients survived, nine patients died. We analyzed the prognosis of

COVID-19 patients; unfortunately, we did not get useful data due to small sample size and relatively few deaths. In conclusion: COVID-19 patients display abdominal and pulmonary CT imaging abnormalities and some of the patients have abnormal liver function. Furthermore, some of CT signs and CRP are positively correlated with severity grading; thus, it will allow an earlier identification of high-risk patients. Further studies should be performed to confirm our conclusion and develop suitable therapeutic strategies, and investigate the prognosis in future.

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Author contributions XL and YS designed the study; PL, LZ, XL, QT collected data; PL, LZ, XL, FY reviewed CT imaging; XL, YS, PH, CZ, YH interpreted the data; LZ, HS performed statistical analysis; PL, LZ, XL, YS analyzed the data, reviewed the chart, interpreted the data, and wrote the paper.

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Compliance with ethical standards

Conflict of interest Ping Lei, Lan Zhang, Ping Han, Chuansheng Zheng, Qiaoxia Tong, Haitao Shang, Fan Yang, Yu Hu, Xin Li, Yuhu Song disclose no conflicts.

Ethical approval This study was conducted in accordance with the Declaration of Helsinki. Our study was approved by Ethics Committee of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology (No2020-0312).

Informed consent Informed consent was waived because of the retrospective nature of the study and the usage of anonymous clinical data.

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