Original Article

Effect of liver injury on prognosis and treatment of hospitalized patients with COVID-19 pneumonia

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Background: Liver injury is common in patients with coronavirus disease 2019 (COVID-19), although its effect on patient outcomes has not been well studied. This study aimed to evaluate the effect of liver injury on the prognosis and treatment of patients with COVID-19 pneumonia.

Methods: In this retrospective, single-center study, data on 109 hospitalized patients with COVID-19 pneumonia were extracted and analyzed. The primary composite end-point event was the use of mechanical ventilation or death.

Results: At admission, of the 109 patients enrolled, 56 patients (51.4%) were diagnosed with severe disease, and 39 (35.8%) presented with liver injury, which mainly manifested as elevated levels of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) accompanied simultaneously by an increase in the level of γ-glutamyl transferase. A primary composite end-point event occurred in 21 patients (19.3%). Liver injury was more prevalent in patients with severe disease than in those with non-severe disease (46.4% *vs.* 24.5%, P=0.017). However, there was no significant difference found between severe and non-severe patients in the use of mechanical ventilation, mortality, hospital stay, or use and dosage of glucocorticoids between individuals with and without liver injury (all P>0.05). The degree of disease severity (OR =7.833, 95% CI, 1.834–31.212, P=0.005) and presence of any coexisting illness (OR =4.736, 95% CI, 1.305–17.186, P=0.018) were predictable risk factors for primary composite end-point events, whereas liver injury had no significance in this aspect (OR =0.549, 95% CI, 0.477–5.156, P=0.459).

Conclusions: Liver injury was more common in severe cases of COVID-19 pneumonia than in non-severe cases. However, liver injury had no negative effect on the prognosis and treatment of COVID-19 pneumonia.

Keywords: Coronavirus disease 2019 (COVID-19); pneumonia; liver injury; clinical prognosis; treatment

Submitted Jun 21, 2020. Accepted for publication Sep 29, 2020.
doi: 10.21037/atm-20-4850
View this article at: http://dx.doi.org/10.21037/atm-20-4850

Introduction

In December 2019, pneumonia cases of unknown etiology were reported in the city of Wuhan, Hubei Province, China. The pathogen responsible for the outbreak was identified as a novel enveloped RNA beta coronavirus (1,2). This virus was named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), and the disease it causes has become known as coronavirus disease 2019 (COVID-19) (3,4). SARS-CoV-2 shares approximately 80% of the genetic sequence with severe acute respiratory syndrome coronavirus (SARS-CoV) (5). SARS-CoV-2 is more contagious and has a higher rate of infectivity than SARS-CoV. As the COVID-19 outbreak spread rapidly across the world, the World Health Organization (WHO) declared it a public health emergency of international concern (6). As of September 22, 2020, more than 30,000,000 confirmed COVID-19 cases had been reported globally, and more than 960,000 people had died of the infection (7).

Although SARS-CoV mainly attacked the respiratory system, liver injury was reported in up to 60% of patients with SARS (8). SARS-CoV-2 shares the same viral entry receptor as SARS-CoV, angiotensin-converting enzyme 2 (ACE2), mainly in the respiratory tract mucosa or alveolus (4), and many cases of liver injury have been reported in patients with COVID-19 during disease progression (9,10). In a large cohort study conducted in China, which included 1,099 COVID-19 patients from 552 hospitals in 31 provinces or provincial municipalities, only 2.3% of cases had pre-existing liver illnesses; however, elevated levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were observed in 21.3% and 22.2% of cases, respectively (1).

Therefore, liver injury does not appear to be uncommon in patients with COVID-19. When patients with COVID-19 have liver injury, especially when liver injury becomes more severe during treatment, clinicians need to carefully weigh the benefits and adverse effects of medications used, and even amend the therapeutic strategy and shorten the duration of drug therapy. However, few studies have focused on the effect liver injury has on the prognosis and treatment of COVID-19.

This retrospective study aimed to investigate the prevalence of liver injury in confirmed and hospitalized COVID-19 pneumonia cases, and evaluate its potential impact on the prognosis and treatment of this disease. The following article is presented in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/atm-20-4850).

Methods

Study design and participants

In this retrospective, single-center study, hospitalized patients with laboratory-confirmed COVID-19 pneumonia were recruited from wards 20 and 22 at the Eastern Branch of People's Hospital of Wuhan University (Wuhan, Hubei, China) between January 31 and February 29, 2020. This hospital was one of the designated hospitals in Wuhan for the treatment of severe adult COVID-19 cases and was supported by a medical assistance team from Zhongshan Hospital of Fudan University, Shanghai, China. All patients with COVID-19 pneumonia enrolled in this study were diagnosed according to the guidelines for the diagnosis and treatment of novel coronavirus (2019-nCoV) infection by the National Health Commission (Trial Version 7) (11). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the Ethics Committee of People's Hospital of Wuhan University (NO. WDRY-2020-K048). Due to the study's retrospective nature, the requirement for individual consent was waived.

Procedures

The following data were obtained from the patients' medical records: epidemiological and demographic information, coexisting illnesses, symptoms, signs, laboratory findings, X-ray or chest computed tomographic (CT) scan images, treatment, and outcome. The final date of follow-up was March 31, 2020. Radiologic and laboratory tests including liver biochemical parameters and nasopharyngeal swab examination were performed within 24 hours after admission. A confirmed case of COVID-19 was defined as a positive result on real-time reverse transcription polymerase chain reaction (RT-PCR) assay of nasopharyngeal swab specimens (10).

According to the guidelines for the diagnosis and treatment of novel coronavirus (2019-nCoV) infection by the National Health Commission (Trial Version 7) (11) and the American Thoracic Society guidelines for community-acquired pneumonia (12), at the time of admission, cases were defined as severe with a respiratory rate >30 breaths/min, blood oxygen saturation (SpO_2) <93% on room air, or oxygenation index (PaO_2/FiO_2) ≤300 mmHg.

Patients who did not meet one of these criteria were classified as non-severe cases.

Liver injury was indicated when the levels of ALT, AST, or γ-glutamyl transferase (GGT) exceeded the upper limit of the normal laboratory reference range.

The primary composite end-point event was the use of mechanical ventilation or death, which has been used to assess the severity of other serious infectious diseases, such as H7N9 infection (1,13).

Statistical analysis

Continuous variables were expressed as median and interquartile range (IQR), and categorical variables were described as counts and percentages. For continuous variables, the medians were compared using independent samples *t* tests when the data were normally distributed, and Mann-Whitney U tests were used if the data were not normally distributed. Proportions for categorical variables were compared using the chi-squared test or Fisher's exact test where appropriate. The degree of association between the parametric variables was measured using Pearson's correlation or Spearman's correlation analysis, and a step-wise logistic regression analysis was conducted to explore the risk factors for the primary composite end-point event. All statistical analyses were performed with the SPSS 26.0 (SPSS Inc., Chicago, IL, USA) software package. A two-tailed P value of <0.05 was considered to be statistically significant.

Results

Clinical characteristics of enrolled patients

Between January 31 and February 29, 2020, 115 patients with COVID-19 pneumonia were admitted. Six of these patients were excluded from this study due to having incomplete medical history or laboratory data. The demographic, clinical and laboratory characteristics of the enrolled patients are shown in *Table 1*. The patients had a median age of 63 years (range, 30–87 years), and 46.8% were male. At admission, the degree of COVID-19 pneumonia was categorized as non-severe in 53 patients (48.6%) and severe in 56 patients (51.4%). Among the admitted patients, 46.8% had at least one coexisting illness (e.g., hypertension or diabetes mellitus). Additionally, one patient (0.9%) had chronic hepatitis B and had been taking entecavir for more than a year; and this patient had normal liver function test at admission. No other cases of chronic liver disease were reported among the enrolled patients.

Thirty-nine (35.8%) patients presented with liver injury, which manifested in 61.5% of these cases as an elevated level of ALT or AST accompanied simultaneously by an increase in the level of GGT. An elevated level of ALT or AST alone was observed in a further 10 patients (25.6%), and mono-elevated levels of GGT were found in 5 patients (12.8%). Only 3 patients (7.7%) had elevated total bilirubin, and the median level was at 10.60 mmol/L (range, 4.50–65.00 mmol/L).

The 109 patients enrolled had a median hospital stay of 30.50 days (range, 6–55 days). During hospitalization, 37 patients (33.9%) were treated with glucocorticoids. Primary composite end-point events occurred in 21 patients (19.3%), including 5 patients (4.6%) who underwent invasive mechanical ventilation, and 5 patients (4.6%) who died. One patient (0.9%) underwent extracorporeal membrane oxygenation, but died after 26 days.

Comparison between patients with non-severe and severe disease

Patients with severe disease were older than those with non-severe disease (P=0.049). Liver injury was more prevalent in patients with severe COVID-19 pneumonia than in those with non-severe disease (46.4% *vs.* 24.5%, P=0.017), with severe cases having higher levels of AST and GGT and a lower level of albumin. However, no significant differences were observed in the levels of ALT, total bilirubin, and prothrombin time or international normalized ratio (INR) between the two groups of patients (all P>0.05). Additionally, inflammatory markers including white blood cell count, the percentage of neutrophil granulocytes, and C-reactive protein levels were all significantly increased in patients with severe disease, whereas the percentage of lymphocytes was significantly decreased (all P<0.05) (*Table 2*).

All of the admitted patients were administered the antiviral drug Abidor. During hospitalization, 23 patients with severe disease and 14 patients with non-severe disease were treated with glucocorticoids (41.1% *vs.* 26.4%, P=0.106); however, the patients with severe disease received far more doses of glucocorticoids than those with non-severe disease (P=0.038). The number of patients who received antibiotic treatment did not differ between the two groups (P=0.195), but more patients with severe disease received intravenous immunoglobulin (58.9% *vs.* 22.6%,

Table 1 Basic characteristics of enrolled patients (N=109)

Clinical and laboratory characteristics	Data
Male sex (N, %)	51 (46.8)
Age, years (median, IQR)	63.00 (50.25–71.75)
Severe disease (N, %)	56 (51.4)
Liver injury (N, %)	39 (35.8)
Smoking history (N, %)	10 (9.2)
Coexisting illness (N, %)	
Any	51 (46.8)
Hypertension	35 (32.1)
Diabetes mellitus	18 (16.5)
Coronary heart disease	10 (9.2)
Chronic obstructive pulmonary disease	2 (1.8)
Cerebrovascular disease	1 (0.9)
Chronic renal disease	3 (2.7)
Chronic liver disease	1 (0.9)
Hospital stay, days (median, IQR)	30.50 (22.25–39.00)
Glucocorticoids treatment (N, %)	37 (33.9)
Dose of glucocorticoids, mg (median, IQR)	0.00 (0.00–206.25)
Antibiotic treatment (N, %)	84 (77.1)
Intravenous immunoglobulin (N, %)	45 (41.3)
Primary composite end-point event (N, %)	
Any	21 (19.3)
Noninvasive mechanical ventilation	20 (18.3)
Invasive mechanical ventilation	5 (4.6)
Death	5 (4.6)
Laboratory findings (reference) (median, IQR)	
White blood cells (3.5–9.5) ($\times 10^9$/L)	5.62 (4.08–7.56)
Percent of neutrophile granulocyte (40–75) (%)	67.25 (53.80–82.03)
Percent of lymphocyte (20–50) (%)	20.60 (11.90–31.85)
Hemoglobin (130–175) (g/L)	123.00 (116.00–136.00)
Platelet count (125–350) ($\times 10^9$/L)	223.00 (171.00–294.00)
C-reactive protein (<5.0) (mg/L)	29.00 (5.00–76.50)
Prothrombin time (9–13) (sec)	12.00 (11.20–12.70)
INR (0.76–1.24)	1.03 (0.95–1.09)
ALT (9–50) (U/L)	23.50 (16.25–42.00)
AST (15–40) (U/L)	24.00 (19.00–41.75)
GGT (10–60) (U/L)	29.50 (17.00–61.00)
Albumin (40–55) (g/L)	37.50 (34.53–40.25)
Globulin (20–40) (g/L)	23.80 (21.10–26.48)
Total bilirubin (0–23) (μmol/L)	10.60 (8.00–15.05)
Urea nitrogen (3.6–9.5) (mmol/L)	4.70 (3.89–6.30)
Creatinine (57–111) (μmol/L)	59.50 (52.00–72.00)
Estimated glomerular filtration rate (>90) (mL/min/1.73 m^2)	95.39 (87.50–103.45)

N, number; IQR, interquartile range; INR, international normalized ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transferase.

Table 2 Comparison of clinical and laboratory characteristics between patients with non-severe disease and those with severe disease

	Patients with non-severe disease (N=53)	Patients with severe disease (N=56)	P value
Male sex (N, %)	26 (49.1)	25 (44.6)	0.644
Age, years (median, IQR)	61.00 (48.00–69.00)	66.00 (51.75–75.00)	0.049
Liver injury (N, %)	13 (24.5)	26 (46.4)	0.017
Coexisting illness (N, %)			
Any	23 (43.4)	28 (50.0)	0.490
Hypertension	15 (28.3)	20 (35.7)	0.407
Diabetes mellitus	9 (17.0)	9 (16.1)	0.898
Coronary heart disease	4 (7.5)	6 (10.7)	0.567
Chronic obstructive pulmonary disease	0	2 (3.6)	NA
Cerebrovascular disease	0	1 (1.8)	NA
Chronic renal disease	1 (1.9)	2 (3.6)	1.000
Chronic liver disease	1 (1.9)	0	NA
Hospital stay, days (median, IQR)	28.50 (19.00–34.00)	34.00 (24.00–43.00)	0.043
Glucocorticoids treatment (N, %)	14 (26.4)	23 (41.1)	0.106
Dose of glucocorticoids, mg (median, IQR)	0.00 (0.00–100.00)	0.00 (0.00–416.25)	0.038
Antibiotic treatment (N, %)	38 (71.7)	46 (82.1)	0.195
Intravenous immunoglobulin (N, %)	12 (22.6)	33 (58.9)	<0.001
Primary composite end-point event (N, %)	3 (5.7)	18 (32.1)	<0.001
Laboratory findings (median, IQR)			
White blood cells ($\times 10^9$/L)	4.84 (3.60-6.41)	6.57 (5.19-8.08)	<0.001
Percent of neutrophile granulocyte (%)	59.85 (50.75–71.03)	79.10 (65.38–85.53)	<0.001
Percent of lymphocyte (%)	28.20 (19.05–35.35)	13.25 (8.50–24.36)	<0.001
Hemoglobin (g/L)	124.00 (116.50–134.50)	121.00 (114.50–136.00)	0.718
Platelet count ($\times 10^9$/L)	226.00 (165.00–286.00)	217.00 (179.00–298.75)	0.658
C-reactive protein (mg/L)	19.00 (5.00–61.00)	44.50 (7.25–94.50)	0.007
Prothrombin time (sec)	11.95 (11.10–12.60)	12.00 (11.30–12.95)	0.233
INR	1.02 (0.95–1.08)	1.03 (0.96–1.12)	0.250
ALT (U/L)	19.50 (16.00–39.75)	27.00 (18.00–47.50)	0.182
AST (U/L)	21.50 (17.00–32.75)	31.00 (20.25–46.75)	0.019
GGT (U/L)	23.00 (16.25–40.50)	36.00 (20.00–65.25)	0.048
Albumin (g/L)	38.70 (36.73–40.85)	36.70 (33.10–39.18)	0.004
Globulin (g/L)	23.10 (21.03–25.25)	24.40 (22.03–27.15)	0.023
Total bilirubin (μmol/L)	11.00 (8.13–12.78)	10.20 (7.63–15.73)	0.778
Urea nitrogen (mmol/L)	4.35 (3.62–5.79)	5.25 (4.11–7.43)	0.005
Creatinine (μmol/L)	59.00 (53.00–71.75)	61.00 (51.25–72.00)	0.947
Estimated glomerular filtration rate (mL/min/1.73 m^2)	95.39 (89.02–106.31)	95.53 (82.16–103.13)	0.258

N, number; IQR, interquartile range; INR, international normalized ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transferase.

Table 3 Correlation between liver injury and other variables at admission

Variables	Sex	Age	Severity of disease	Any coexisting illness	White blood cells count	Percent of neutrophile granulocyte	Percent of lymphocyte	C-reactive protein
r	0.221	0.063	0.228	0.067	0.208	0.361	–0.358	0.409
P value	0.021	0.515	0.017	0.487	0.030	<0.001	<0.001	<0.001

P<0.001). Primary composite end-point events occurred more in patients with severe disease than in those with non-severe disease (32.1 *vs.* 5.7%, P<0.001).

Associated risk factors of liver injury at admission

The correlations between liver injury and other variables at admission were further analyzed. The occurrence of liver injury was positively correlated with the severity of COVID-19 infection and inflammatory markers including white blood cell count, the percentage of neutrophil granulocytes, and C-reactive protein levels, but negatively correlated with the percentage of lymphocyte count. No correlation was found between liver injury and age or any coexisting illness (*Table 3*).

Effects of liver injury on the prognosis and treatment of COVID-19 pneumonia

As shown in *Table 4*, in patients with non-severe disease, liver injury was more common in males than females (84.6% *vs.* 37.5%, P=0.003). Individuals with liver injury presented with higher levels of ALT, AST, and GGT than those without liver injury, regardless of the severity of their disease (all P<0.05). However, no difference in the level of total bilirubin was recorded (P>0.05).

During hospitalization, in the non-severe patient group, glucocorticoids were used to treat 5 individuals with liver injury and 9 individuals without liver injury (38.5% *vs.* 22.5%, P=0.292). No significant difference was found between non-severe patients with and without liver injury in terms of glucocorticoid dosage (P=0.913) or hospital stay (P=0.977). Additionally, 2 individuals with liver injury and 1 individual without liver injury underwent noninvasive ventilation (15.4% *vs.* 2.5%, P=0.145). None of the non-severe patients underwent invasive ventilation, and there were no deaths in patients with and without liver injury.

Among patients with severe disease, no significant difference was observed in the use or dosage of glucocorticoids, hospital stay, or the incidence of primary composite end-point events between those who presented with and without liver injury (all P>0.05). Two individuals with liver injury and 3 individuals without liver injury died of the infection (7.7% *vs.* 10.0%, P=0.763).

A logistic regression analysis was carried out to assess the possible risk factors for primary composite end-point events (*Table 5*). The degree of disease severity at admission (OR =7.833, 95% CI, 1.834–31.212, P=0.005) and the presence of any coexisting illness (OR =4.736, 95% CI, 1.305–17.186, P=0.018) were found to be predictable risk factors for primary composite end-point events, whereas liver injury was not (OR =0.549, 95% CI, 0.477–5.156, P=0.459).

Discussion

In the present study, at admission, 35.8% of patients with COVID-19 pneumonia presented with liver injury, which was more common in patients with severe COVID-19 pneumonia than in those with non-severe disease. However, among patients with severe disease and non-severe disease, no difference was found in the use of mechanical ventilation, mortality, hospital stay, or the use or dosage of glucocorticoids between individuals who presented with and without liver injury. Moreover, liver injury at admission did not show an independent correlation with the occurrence of primary composite end-point events.

Liver injury was reported to be a common clinical manifestation in patients with SARS-CoV infection (14,15), and pathological examinations confirmed the presence of the virus in liver tissue of patients with SARS (8). SARS-CoV-2 has been found to share about 80% of its genetic sequence with SARS-CoV and has the same virus entry receptor, and similar to SARS, liver injury is also common in patients with COVID-19 infection (1,9). More than a third of patients with COVID-19 pneumonia in this investigation presented with liver injury at admission, which manifested mainly as an elevated ALT or AST levels accompanied simultaneously by an increase in GGT levels. Liver injury was found to be more common in patients with severe disease, who had higher levels of AST and

Table 4 Comparison of the prognosis and treatment of patients with and without liver injury

	Patients with non-severe disease			Patients with severe disease		
	Without liver injury (N=40)	With liver injury (N=13)	P value	Without liver injury (N=30)	With liver injury (N=26)	P value
Male sex (N, %)	15 (37.5)	11 (84.6)	0.003	12 (40.0)	13 (50.0)	0.453
Age, years (median, IQR)	61.50 (48.00-69.00)	58.00 (48.00-63.50)	0.306	63.50 (51.00-75.00)	68.00 (58.25-75.00)	0.296
Hospital stay, days (median, IQR)	29.50 (17.50-34.00)	27.00 (22.00-34.00)	0.893	30.00 (22.50-40.50)	36.00 (28.25-48.25)	0.148
Glucocorticoids treatment (N, %)	9 (22.5)	5 (38.5)	0.292	10 (33.3)	13 (50.0)	0.206
Dose of glucocorticoids, mg (median, IQR)	0.00 (0.00-0.00)	0.00 (0.00-150.00)	0.394	0.00 (0.00-316.25)	52.50 (0.00-620.00)	0.338
Primary composite end-point event (N, %)	1 (2.5)	2 (15.4)	0.145	8 (26.7)	10 (38.5)	0.346
Laboratory findings (median, IQR)						
Prothrombin time (sec)	11.90 (11.10–12.60)	12.20 (11.40–12.60)	0.223	11.90 (11.20–12.55)	12.40 (11.63–13.25)	0.071
INR	1.02 (0.95–1.08)	1.05 (0.97–1.08)	0.227	1.02 (0.95–1.08)	1.06 (0.99–1.15)	0.068
ALT (U/L)	18.00 (11.50–26.75)	60.00 (48.00–117.00)	<0.001	18.50 (16.00–24.50)	51.50 (29.75–76.00)	<0.001
AST (U/L)	19.50 (17.00–24.00)	49.00 (32.50–67.00)	<0.001	22.00 (16.75–30.25)	46.50 (38.50–53.25)	<0.001
GGT (U/L)	20.00 (14.00–31.75)	79.00 (67.00–100.50)	<0.001	22.50 (16.00–35.50)	70.00 (40.75–120.25)	<0.001
Albumin (g/L)	38.60 (35.80–40.85)	38.60 (33.50–40.95)	0.577	37.35 (34.90–40.23)	34.40 (32.38–37.83)	0.025
Globulin (g/L)	22.95 (20.85–25.05)	24.10 (20.75–25.70)	0.457	24.55 (21.00–27.05)	24.60 (23.40–27.28)	0.402
Total bilirubin (μmol/L)	10.45 (7.83–12.65)	12.00 (9.90–15.85)	0.057	9.15 (6.93–14.98)	11.10 (8.23–18.48)	0.129

N, number; IQR, interquartile range; INR, international normalized ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transferase.

Table 5 Risk factors for primary composite end-point event by multivariate analysis

	OR	95% CI	P value
Severity of disease	8.203	1.858–36.213	0.005
Liver injury	1.652	0.495–5.513	0.414
Coexisting illness	4.736	1.305–17.186	0.018

GGT. However, there was no significant difference in the levels of total bilirubin or prothrombin time, both of which are considered to be indicators of liver function, between patients with severe and non-severe disease. Serum albumin level, which is an indicator of liver function, was observed to be significantly decreased in patients with severe disease compared to those with non-severe disease. To some extent, serum albumin levels reflect liver synthetic function; however, they may be affected by the nutritional status of the patient. Patients with severe COVID-19 have been reported to be more likely to suffer from malnutrition (1,16). Therefore, in patients with COVID-19 infection, liver injury does not seem to give rise to liver dysfunction. Our results were consistent with the liver pathological findings in patients with COVID-19 infection reported previously (16-18). An autopsy performed on a patient with COVID-19 identified no definite change in the macroscopic appearance of the liver (17). Also, in the liver biopsy specimens of two patients died of COVID-19 pneumonia, moderate microvesicular steatosis, and mild lobular and portal inflammation were observed in the liver tissue of one patient, and mild sinusoidal dilatation and

minimal lymphocytic infiltration were observed in the liver tissue of another (16,18). These results indicate that liver injury in patients with COVID-19 is mild, and often does not cause extensive hepatocellular damage, nor does it cause liver dysfunction.

Currently, there are no specific medications available to treat COVID-19 infection, and comprehensive treatments including antiviral treatment, the use of antibiotics, and nutritional support, are recommended (3,11). In China, traditional Chinese medicine is also used to treat COVID-19 infection (11). However, these medications may also cause liver damage, and can exacerbate existing liver injury and even induce liver failure. Therefore, different treatment strategies may be recommended for patients with and without liver injury. Inevitably, the effect of such treatment strategy modifications on the therapeutic efficacy in patients with COVID-19 infection is a concern. Nevertheless, in this study, the incidence of primary composite end-point events, which included the use of mechanical ventilation and mortality during hospitalization, was not higher in individuals with liver injury than in those without liver injury. Additionally, the hospital stay for individuals with liver injury was the same as that for patients without liver injury. All of our results indicate that liver injury at admission does not have a negative impact on the prognosis and treatment of patients with COVID-19 pneumonia with different degrees of severity.

Although the guidelines recommend low doses of glucocorticoids for COVID-19 patients with rapid disease progression (11), glucocorticoid use has been controversial in the treatment of COVID-19 (19). Theoretically, glucocorticoid therapy may play a role in the treatment of COVID-19, as it suppresses lung inflammation. Additionally, Chen *et al.* reported that patients admitted to the intensive care unit (ICU) were unable to defervesce without glucocorticoid therapy (20). In this study, low-dose glucocorticoid therapy was initiated when a patient's symptoms became significantly worse or rapid progression of lung lesions was indicated by follow-up chest CT examination. No significant difference was observed in the use or dosage of glucocorticoids between individuals with and without liver injury, regardless of disease severity. Our results also indicate that liver injury at admission does not play a significant role in the deterioration of COVID-19 pneumonia during hospitalization. Furthermore, glucocorticoid therapy itself may suppress liver inflammation, which might explain why liver dysfunction was not observed prior to death in the five patients who died this study (data not shown).

A preliminary study found that cholangiocytes are the major cell type expressing ACE2 in the liver, which indicates that SARS-CoV-2 might mainly act on ACE2-positive cholangiocytes, rather than hepatocytes (21). Most importantly, viral inclusions were not observed in the pathological assessment of liver tissue from a patient who died from COVID-19 infection (18). Therefore, the direct attack on hepatocytes by SARS-CoV-2 was not considered to be the main cause of liver injury. Because all patients in this study were confirmed with COVID-19 infection and were hospitalized in isolation wards to avoid cross infection as much as possible, it was impractical for them to undergo abdominal ultrasonography to determine whether fatty liver or chronic liver disease was present or not, or to undergo liver biopsy to confirm the cause of liver injury at admission. However, only one patient in this study was reported to have chronic hepatitis B. More importantly, liver injury was more common in patients with severe disease and was found to be significantly correlated with the severity of COVID-19 and inflammatory markers at admission. Thus, we speculated that hypoxia and systemic inflammatory response might be two major causes of liver injury at admission in patients with COVID-19. Additionally, because fever is the most common symptom during onset of COVID-19 pneumonia, and patients may have taken antipyretics, such as acetaminophen, to relieve symptoms before admission, drug-induced liver injury should also be considered (1,20).

In conclusion, in this study, more than a third of patients with COVID-19 pneumonia presented with liver injury at admission, and this was more common in individuals with severe disease. However, liver injury was mild in most of the patients and had no negative impact on the prognosis and treatment of COVID-19 pneumonia during hospitalization.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist (available at http://dx.doi.org/10.21037/atm-20-4850).

Data Sharing Statement: Available at http://dx.doi.org/10.21037/atm-20-4850

Peer Review File: Available at http://dx.doi.org/10.21037/atm-20-4850

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-20-4850). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of People's Hospital of Wuhan University (NO. WDRY-2020-K048) and individual consent for this retrospective analysis was waived.

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Cite this article as: Ma GG, Shen YX, Wu L, Luo Z, Zhu CW, Chen SY, Yu KH, Li F. Effect of liver injury on prognosis and treatment of hospitalized patients with COVID-19 pneumonia. Ann Transl Med 2021;9(1):10. doi: 10.21037/atm-20-4850