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Characteristics of pregnant patients with COVID-19 and liver injury

To the Editor:

The ongoing worldwide COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become a global threat to human health. Qi *et al.*[1] and Cai *et al.*[2] have reported on liver injury in general patients with COVID-19. However, little attention has been paid to pregnant patients with COVID-19 and liver injury.

In this study, we collected the admission data from 37 pregnant patients with COVID-19 from Jan 28 to Feb 28, 2020 at Wuhan Union hospital of Huazhong University of Science and Technology. All the patients had laboratory-confirmed cases and classification of the severity of COVID-19 was based on the New Coronavirus Pneumonia Prevention and Control Program in China.[3] As Qi *et al.* suggested, liver injury was defined as an increase in either of the following parameters: alanine aminotransferase (ALT) >40 U/L, aspartate aminotransferase (AST) >40 U/L and total bilirubin (TBIL) >17.1 μmol/L.[1] Synthetic inflammatory markers were calculated from the full blood count at admission, including neutrophil-lymphocyte ratio, platelet-lymphocyte ratio and systematic immune-inflammation-based prognostic index.[4] These parameters have been reported to be associated with the severity of COVID-19.[5] Continuous variables were expressed as mean ± SD or median (IQR) for normally or abnormally distributed data, followed by unpaired *t* test or Wilcoxon rank sum test. Categorical variables were summarized as counts (percentages) and compared using the Fisher's exact test. p <0.05 was considered statistically significant. This retrospective study was approved by the ethics committee of Union Hospital of Huazhong University of Science and Technology.

A total of 37 pregnant patients were enrolled in this study (Table 1). In detail, 11 (29.7%) patients had laboratory findings consistent with liver injury and 26 (70.3%) patients had normal baseline AST, ALT and TBIL levels. Of the patients with liver injury, the average age was 31.18 years and 2 reported a medical history of gestational hypertension and diabetes, separately. Fever (8 [72.5%]) and dry cough (6 [54.5%]) were the most common initial symptoms. Compared with the pregnant patients without liver injury, those with liver injury had a higher level of procalcitonin, interleukin-6 (IL-6), AST, ALT and lactic dehydrogenase. There were no statistical differences in signs, severity of COVID-19, the interval from onset to hospitalization, hospital stay, radiological findings and obstetric management between pregnant patients with and without liver injury. Four patients with liver injury in the third trimester chose cesarean section voluntarily, 2 had vaginal delivery, and the rest did not reach the delivery time. Finally, 6 livebirths were recorded with no fetal death, neonatal death or neonatal asphyxia observed. Moreover, we did not detect the presence of SARS-CoV-2 by reverse transcription PCR in breastmilk (n = 6), neonatal throat swab (n = 4) or neonatal anal swab (n = 1).

In this study, we reported, for the first time, the clinical, laboratory, and radiological data from pregnant patients with COVID-19, with and without liver injury. We found that the prevalence of liver injury in pregnant COVID-19 patients was 29.7%. In Chen *et al.*'s study, they demonstrated that 23.8%–44.4% of pregnant patients with COVID-19 had liver injury in all the Wuhan laboratory-diagnosed pregnant patients, which was consistent with our finding.[6] However, Qi *et al.* reported that 45.7% of general patients had liver injury, which is a higher frequency than that observed in pregnant patients.[1] Additionally, we found that inflammatory markers including PCT and IL-6 levels were higher in pregnant COVID-19 patients with liver injury. Accumulating evidence has suggested that hyperinflammation plays an essential role in COVID-19-related mortality.[7] SARS-CoV-2-induced inflammatory responses can recruit macrophages, monocytes and T cells to establish a pro-inflammatory feedback loop, causing cytokine storms and aggravations.[8] Besides, we recently showed that elevated inflammatory markers were positively correlated with the severity of COVID-19,[9] suggesting that it is appropriate to monitor liver function in pregnant patients. Interestingly, the elevation of inflammatory markers in pregnant patients was not as marked as in non-pregnant patients. Mor *et al.* demonstrated that the second trimester of pregnancy reflected an anti-

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Table 1. Characteristics of pregnant patients with COVID-19.

Variables	Pregnant patients without liver injury (n = 26)	Pregnant patients with liver injury (n = 11)	*p* value
Age (year)	30.46 ± 4.09	31.18 ± 5.31	0.657
History of disease, n (%)			
Hypertension	0 (0)	1 (9.1)	0.297
Diabetes	0 (0)	1 (9.1)	0.297
Cardiovascular disease	1 (3.8)	0 (0)	1.000
Others*	0 (0)	0 (0)	1.000
Laboratory findings			
WBC ($\times10^9$/L)	7.52 (5.04–10.15)	4.74 (3.81–7.47)	0.111
Neutrophils ($\times10^9$/L)	5.52 (3.60–8.13)	3.20 (2.68–6.84)	0.087
Lymphocytes ($\times10^9$/L)	1.21 (0.91–1.49)	0.95 (0.63–1.62)	0.406
Platelets ($\times10^9$/L)	205.58 ± 51.96	222.45 ± 70.74	0.424
PT (sec)	12.20 (11.78–12.80)	11.90 (11.40–12.30)	0.125
APTT (sec)	35.85 ± 4.35	36.80 ± 4.40	0.549
D-dimer (mg/L)	0.94 (0.63–1.84)	1.04 (0.66–1.64)	0.987
PCT (ng/ml)[#]	0.06 (0.05–0.12)	0.19 (0.08–0.37)	0.008
AST (U/L)	20.0 (16.8–23.3)	44.0 (40.0–55.0)	<0.001
ALT (U/L)	14.0 (10.0–24.0)	47.0 (32.0–87.0)	<0.001
TBIL (μmol/L)	11.12 ± 2.35	11.40 ± 2.31	0.744
Creatinine (μmol/L)	44.48 ± 7.07	49.04 ± 6.43	0.075
BUN (mmol/L)	2.67 ± 0.83	3.06 ± 1.14	0.255
LDH (U/L)	176.5 (149.0–202.0)	232.0 (187.0–281.0)	0.006
CRP (mg/L)	5.72 (1.05–34.17)	22.22 (3.79–30.75)	0.158
IL-6 (pg/ml)[#]	3.25 (2.42–4.90)	6.24 (4.42–10.4)	0.011
NLR, median	5.07 (3.30–6.44)	2.92 (2.57–5.77)	0.158
PLR	165.86 (153.82–208.72)	212.63 (144.44–316.36)	0.327
SII	1,000.32 (649.87–1,321.17)	582.61 (485.05–1,268.40)	0.311

Others* include malignancy, tuberculosis, HBV, HCV and syphilis.
[#]Missing data: PCT, n = 1; IL-6, n = 5.
Continuous variables with normal distribution were expressed as mean ± SD and compared with unpaired *t* test. Continuous data with abnormally distribution were presented as median (IQR) and compared with Wilcoxon rank sum test. Categorical variables were summarized as counts (percentages) and compared using the Fisher's exact test.
ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CRP, C-reactive protein; IL-6, interleukin-6; LDH, lactic dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; PCT, procalcitonin; PLR, platelet-to-lymphocyte ratio; PT, prothrombin time; SII, systemic immune-inflammation index; TBIL, total bilirubin; WBC, white blood cell.

inflammatory phase,[10] indicating that pregnancy might confer some protection against higher inflammation and severe COVID-19. However, only 5 [13.5%] patients were in the second trimester of pregnancy in our study. Previous data showed that younger and female patients had lower rates of severe COVID-19 than older and male patients.[11] Therefore, age and gender effects could mainly account for the low rates of severe COVID-19 in pregnant patients compared with general patients. Considering the low-grade inflammation and non-severe pneumonia in pregnant patients, it seems that pregnant patients are less likely to be treated with the drugs such as lopinavir/ritonavir that are associated with liver injury.[12] To date, though inflammatory cells could be found in the hepatic sinuses from a non-pregnant COVID-19 patient,[2] how and why pregnant patients with liver injury had higher inflammation than those without liver injury still remains to be clarified. Notably, 6 pregnant patients with liver injury gave birth to 6 healthy babies without neonatal death, neonatal asphyxia or SARS-CoV-2 infection. That means that there is currently no evidence that liver injury worsens outcomes of neonates.

In summary, our study demonstrated that pregnant patients with liver injury have worse inflammation than those without liver injury. Liver function should be monitored in pregnant patients. Admittedly, our conclusions are limited by the small sample size, and larger studies are needed to validate these findings.

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

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Authors' contributions
Conception and design: Mingzhu Yin, Xiang Chen, Lijuan Zhang, Hui Chen, Guangtong Deng and Furong Zeng. Acquisition of data: Lijuan Zhang, Hui Chen, Xiang Chen, Mingzhu Yin. Interpretation of data, statistical analysis and manuscript writing: Guangtong Deng and Furong Zeng. Revision of manuscript and administrative, technical, or material support: Guangtong Deng, Furong Zeng, Xiang Chen, Mingzhu Yin, Lijuan Zhang, Hui Chen.

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Supplementary data

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SARS-CoV-2 related liver impairment – perception may not be the reality

To the Editor:

The catastrophic emergence of COVID-19 has led to large volumes of research from epicentres of infection, with some focusing on COVID-19-related liver impairment. In this regard, the study by Wang *et al.* published in the *Journal* intrigued us.[1] The authors associate very minimal elevations in alanine (ALT) and aspartate aminotransferase (AST; ALT >AST) to disease severity and demonstrate 'specific' COVID-19-related cytopathic changes and virus-like particles on post-mortem liver histopathology (n = 2). They found that severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) caused massive apoptosis and binucleation of hepatocytes, resulting in liver enzyme abnormality and synthetic liver dysfunction, the latter in the form of hypoalbuminemia. Their painstaking work is commendable, but their assessment of clinical and investigational events may not reflect the reality. It is recommended that the ideal cut-off for diagnosing acute hepatic injury is 200 U/L and 300 U/L for AST and ALT, respectively.[2] The degree of elevation in AST and ALT in the current study can only be considered an 'altered' liver test, not akin to acute hepatic injury. In hepatic impairment, there must be very clear evidence for metabolic (hypoglycaemia, hyperammonemia), secretory (hyperbilirubinemia) and synthetic (hypoalbuminemia, raised prothrombin time) dysfunction. Except for a mild rise in ALT and hypoalbuminemia, significant liver dysfunction is elusive in the current study. Importantly, hypoalbuminemia, in the absence of other significant liver test abnormalities, virtually rules out the hepatic origin of this abnormality. Acute liver injury

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