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LETTER TO THE EDITOR

Clinical characteristics and outcomes of COVID-19 patients with hypoxic hepatitis



Liver injury is a common extrapulmonary manifestation of coronavirus disease 2019 (COVID-19) with an incidence of 37%–53% [1–3]. Liver injury can be manifested as mild to moderate elevation of transaminases levels, and even fulminant liver failure [4]. Major causes of COVID-19-associated liver injury probably include viral infection itself, systemic inflammatory response, hypoxic injury, drug-induced liver injury, and exacerbation of pre-existing liver disease. Hypoxic hepatitis is a life-threatening type of liver injury with a short-term mortality of 45%–72% [5]. Until now, the information regarding hypoxic hepatitis in COVID-19 patients has been scarcely reported [1,2].

All researchers work at the General Hospital of Northern Theater Command in Shenyang, and a majority of them volunteered to participate in the clinical management of COVID-19 patients at the Huoshenshan hospital in Wuhan from February 2020 to April 2020. Diagnosis and severity of COVID-19 were in accordance with the Chinese practice guidelines [6]. A confirmed case of COVID-19 was defined as a positive result on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) nucleic acid in samples of sputum, nasopharynx swab, and secretions of lower respiratory tract tested by real-time reverse-transcriptase-polymerase-chain reaction (rRT-PCR) assay. Severe case was defined as: 1) shortness of breath, respiration rate ≥ 30 times/minute; 2) oxygen saturation $\leq 93\%$ in the resting state; or 3) partial pressure of oxygen/fraction of inspired oxygen ≤ 300 mmHg. Critical case was defined as: 1) respiratory failure requiring mechanic ventilation; 2) other organ failure requiring intensive care unit (ICU) management; or 3) shock.

In the present study, we retrospectively reviewed the medical records of 3041 COVID-19 patients who were consecutively admitted to the Huoshenshan hospital, and then identified 8 COVID-19 patients with a high suspicion of hypoxic hepatitis, but without previous history of hepatobiliary diseases. Hypoxic hepatitis should meet the following criteria [7]: 1) underlying diseases, such as cardiac failure, respiratory failure, or shock; 2) a rapid increase of serum aminotransferase by more than 20 times the upper limit of normal (ULN); and 3) exclusion of other causes of liver

injury. Based on the electronic medical records, we collected the information regarding demographic data (i.e., age and gender), comorbidities (i.e., diabetes, coronary heart disease, and hypertension), clinical presentations, severity of COVID-19 at admission, laboratory tests [i.e., alanine aminotransferase (ALT) and aspartate aminotransferase (AST)], and in-hospital outcome. This study followed the Declaration of Helsinki and obtained the ethical approved of the Medical Ethical Committee of the General Hospital of Northern Theater Command (Y [2021] 001).

Continuous and categorical variables were expressed as median (range) and frequency (percentage), respectively. Line charts were drawn to show the changes in AST and ALT levels over time. Statistical analyses were performed with IBM SPSS 20.0 software (SPSS Inc., Armonk, New York, USA) and Microsoft Office Excel 2019 software (Microsoft Corp, Redmond, WA, USA).

The median age of the 8 COVID-19 patients was 68 (range: 65–81) years old, and 4 (50%) of them were male. Three patients had diabetes, 4 hypertension, 2 cardiovascular disease, and 1 chronic respiratory disease. At admission, 6 and 4 patients presented with cough and fever, respectively; 2 and 6 patients had moderate and severe/critical COVID-19, respectively. During hospitalizations, all patients developed major complications, including shock (7 [87.5%]), followed by respiratory failure (6 [75%]), acute cardiac injury (6 [75%]), acute kidney injury (5 [62.5%]), acute respiratory distress syndrome (3 [37.5%]), and cardiac failure (1 [12.5%]). Seven patients underwent mechanical ventilation. All patients were admitted/transferred to ICU with a median ICU duration of 20.5 (range: 3–29) days. Only 1 (12.5%) patient was discharged, and 7 (87.5%) died.

At admission, 3 (37.5%) patients had mildly increased serum aminotransferase levels, of whom 1 had an increased AST level of 57.8 IU/L, and 3 had an increased ALT level of 42.4–65.6 IU/L; and the remaining 5 patients had normal AST level of 22.5–38.7 IU/L and ALT level of 20.8–26.2 IU/L. During hospitalizations, serum aminotransferase levels were sharply increased beyond 20 times the ULN within a median duration of 1.5 (range: 1–7) days after respiratory failure, cardiac failure, and/or shock (Fig. 1). Five patients died at the same time of peak ALT/AST level (cases 1, 4, 5, 6 and 7), 2 died within 6 days after AST and ALT levels became nearly

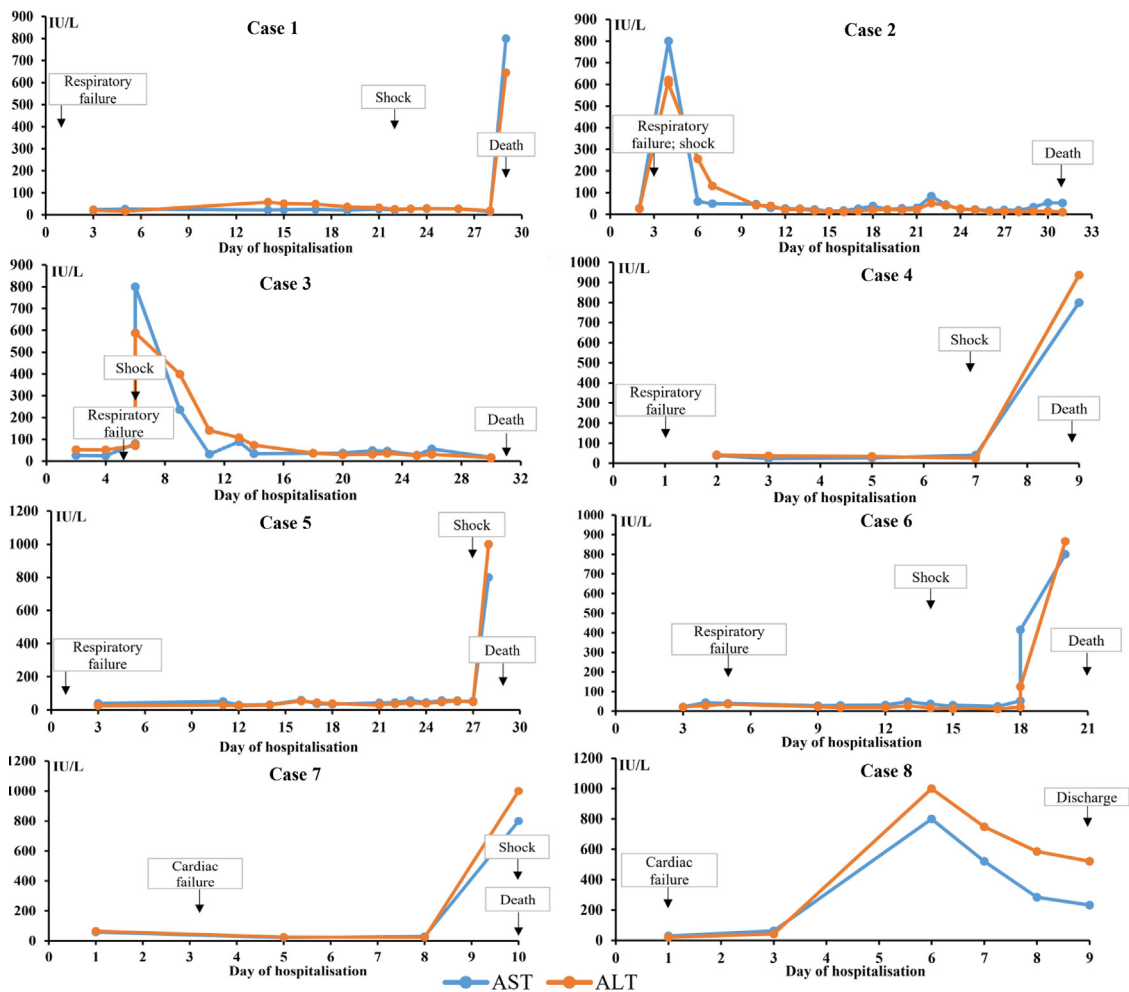


Figure 1 Evolution of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels during hospitalizations.

normal (cases 2 and 3), and 1 discharged within 3 days after AST and ALT levels obviously decreased (case 8).

Hypoxia may be one of the most important contributors for liver injury in COVID-19 patients. The severity of hypoxemia is often in parallel with the elevation of serum transaminase level [8], and hypoxemia is also an independent risk factor for hypoxic hepatitis and its related death [9]. Severe/critical COVID-19 is not only complicated with severe hypoxemia, but also with circulatory disorders, even requirement of extracorporeal membrane oxygenation, further aggravating ischemia and hypoxia and increasing the risk of hypoxic hepatitis [10]. The present study shows that hypoxic hepatitis is rare, but extremely lethal in COVID-19 patients. Therefore, a probability of developing hypoxic hepatitis should be sufficiently recognized and rigorously concerned, once COVID-19 patients develop respiratory and circulatory failure and/or shock. Certainly, the use of multiple drugs in severe/critical COVID-19 patients as a contributor of severe liver injury should not be neglected.

Conflict of interest

The authors declare that there is no conflict of interest in this study.

Availability of data and material

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Yanyan Wu: Methodology, Software, Validation, Formal analysis, Investigation, Data curation, Writing - original draft, Writing - review & editing, Visualization. **Zhuang Ma:** Validation, Writing - review & editing, Visualization, Project administration. **Xiaozhong Guo:** Writing - review & editing, Visualization. **Hongyu Li:** Methodology, Formal analysis, Data curation, Writing - review & editing. **Yufu Tang:** Writing - review & editing, Visualization. **Hao Meng:** Writing - review & editing, Visualization. **Hao Yu:** Writing - review & editing, Visualization. **Chengfei Peng:** Writing - review & editing, Visualization. **Guiyang Chu:** Data curation, Writing - review & editing, Visualization. **Xinwei Wang:** Writing - review & editing, Visualization. **Yue Teng:** Writing - review & editing, Visualization. **Quanyu Zhang:** Writing - review & editing. **Tianyi Zhu:** Writing - review & editing. **Bing Wang:** Writing - review & editing. **Zhenhua Tong:**

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