

**Supplementary data**

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jhep.2021.04.006>.

- [3] Sundaram V, Jalan R, Ahn JC, Charlton MR, Goldberg DS, Karvellas CJ, et al. Class III obesity is a risk factor for the development of acute-on-chronic liver failure in patients with decompensated cirrhosis. *J Hepatol* 2018;69(3):617–625.

**References**

Author names in bold designate shared co-first authorship

- [1] **Wong F, Piano S**, Singh V, Bartoletti M, Maiwall R, Alessandria C, et al. Clinical features and evolution of bacterial infection-related acute-on-chronic liver failure. *J Hepatol* 2021;74(2):330–339.
- [2] **Sundaram V, Jalan R**, Shah P, Singal AK, Patel AA, Wu T, et al. Acute on chronic liver failure from nonalcoholic fatty liver disease: a growing and aging cohort with rising mortality. *Hepatology* 2020;73(5):1932–1944.

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## Bacterial infection-related acute-on-chronic liver failure: The standpoint matters!

To the Editor:

We read with great interest the article by Wong and Piano *et al.*<sup>1</sup> regarding the differences among the geographic areas in the development and outcomes of bacterial infection triggered acute-on-chronic liver failure (ACLF). The study highlighted a higher rate and severity of bacterial infection-triggered ACLF in the Indian subcontinent than in Europe and America. The authors also demonstrated a higher incidence of multidrug-resistant (MDR) bacterial infection-related ACLF, leading to a worse outcome in the Asian population. Given the increased mortality associated with ACLF, it is crucial to know the local epidemiology of bacterial infections. Although it is a global study, centers in Eastern Europe were not represented.

We recently performed a prospective observational study (data not published), including 76 patients (70% men, 70% alcohol-induced liver disease) admitted to the intensive care unit (ICU) in a Romanian tertiary hospital for acutely decompensated cirrhosis. Patients were admitted directly to ICU (60%) or transferred to ICU after a mean stay of 14±9.5 days in a regular ward. The main reason for admission to ICU was the need for mechanical ventilation, either for respiratory failure (n = 5), for respiratory failure and airway protection in overt hepatic encephalopathy (n = 15), or airway protection in severe hepatic encephalopathy (n = 24).

A complete infectious evaluation was performed at admission to ICU. Infection diagnosis was established according to conventional criteria.<sup>2,3</sup> The diagnosis and grading of ACLF were made according to the CANONIC study criteria.<sup>4</sup>

Patients had a mean Child-Pugh score of 12±2 and a mean model for end-stage liver disease score of 28±8. The clinical decompensation events were ascites (n = 67/76, 88%), hepatic

encephalopathy (n = 47/76, 61.8%), variceal bleeding (n = 24/76, 31.65%) and jaundice (n = 43/76, 56.5%), respectively.

Fifty-one patients (67%) had bacterial infections at admission, and among them, 18 (35%) had a nosocomial infection. Nineteen patients had multiple infections. Pneumonia (44%) was the most frequent type, followed by urinary tract infection (18%) and spontaneous bacterial peritonitis (15%).

Most of the bacterial infections were of Gram-negative etiology. There were 18 infections with multidrug-resistant germs (30%); 80% were nosocomial, and carbapenemase-producing Enterobacteriaceae and *Acinetobacter baumannii* were the most frequent (55%).

The majority (36 cases, 70%) of the infected patients had a quick sequential organ failure assessment score ≥2, and among them, almost all (97%) met the criteria for sepsis. In patients with a bacterial infection, 43 (74%) had ACLF: 34.9% ACLF grade 2 and 62.8% ACLF grade 3. Only 1 patient had ACLF grade 1. Respiratory (30/43) and cerebral failure (31/43) with the need for mechanical ventilation were the most frequent organ failures in our study, being present in almost 70% of cases, followed by coagulation (21/43), renal (21/43), circulation (19/43) and liver (12/43) failure, respectively.

All MDR bacterial infections were associated with ACLF and half of them with ACLF grade 3. Patients had a mean ICU stay of 9.8±11.9 days. During follow-up 63 patients worsened (defined as the occurrence of a new organ failure or the diagnosis of a second infection). In most cases (47/63), circulatory failure was the new organ failure. Moreover, 30 patients presented a second infection. Thus, during admission to ICU, we registered 3 more cases of bacterial infection-related ACLF, and at the time of worsening, the majority of patients reached grade 3 ACLF (90%).

MDR bacteria were responsible for the etiology of 60% of the bacterial infections when worsening. We registered 4 extensively drug-resistant (XDR) bacterial infections too.

The overall mortality at 28 days was 68%. When we considered only the infected patients, the registered mortality at 28 days was higher: 76%. The increased mortality rate observed in

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our study could be explained by the high percentage of patients with grade 3 ACLF, also by the high percentage of mechanically ventilated patients, which has been associated with a worse outcome in previous studies.<sup>5</sup>

Our data showed a higher rate of bacterial infection-triggered ACLF in patients with decompensated cirrhosis than that described by Wong *et al.* The explanation lies in the exclusive inclusion of patients needing ICU admission. Moreover, the predominance of respiratory and cerebral failure and the high rate of respiratory infections in our study group explain the need for mechanical ventilation, while the other organ failures frequently are managed in high-dependency or regular wards.

On the other hand, it is essential to know that the incidence of bacterial infection-triggered ACLF seems higher in patients admitted to ICU. Given the extremely high mortality observed in this kind of patient, several measures should be adopted to reduce this syndrome's incidence. These preventive measures could be the prompt diagnosis of bacterial infections in patients with decompensated cirrhosis, the use of broad-spectrum antibiotics for severe infections, and the subsequent de-escalation of the treatment as early as possible, as well as avoiding the emergence of bacterial resistance through judicious use of antibiotics.

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### Conflict of interest

The authors declare they have no conflict of interest regarding the content of this manuscript. Please refer to the accompanying ICMJE disclosure forms for further details.

### Authors' contributions

Study concept: Petra Fischer, Bogdan Procopet, Daniela Ionescu. Data collection: Petra Fischer, Raluca Hategan. Study design: Petra Fischer, Bogdan Procopet, Daniela Ionescu. Analysis and interpretation of data: Petra Fischer, Bogdan Procopet. Drafting of the manuscript: Petra Fischer, Bogdan Procopet. Critical revision for important intellectual content: Bogdan Procopet, Horia Stefanescu, Raluca Hategan, Daniela Ionescu

### Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jhep.2021.04.046>.

### References

*Author names in bold designate shared co-first authorship*

- [1] **Wong F, Piano S**, Singh V, Bartoletti M, Maiwall R, Alessandria C, et al., International Club of Ascites Global Study Group. Clinical features and evolution of bacterial infection-related acute-on-chronic liver failure. *J Hepatol* 2021;74:330–339.
- [2] European Association for the Study of the Liver. EASL clinical practice guidelines for the management of patients with decompensated cirrhosis. *J Hepatol* 2018;69:406–460.
- [3] Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *Am J Infect Control* 2008;36:309–332.
- [4] Moreau R, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J, et al. CANONIC Study Investigators of the EASL-CLIF Consortium. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. *Gastroenterology* 2013;144:1426–1437.
- [5] Levesque E, Saliba F, Ichaï P, Samuel D. Outcome of patients with cirrhosis requiring mechanical ventilation in ICU. *J Hepatol* 2014;60:570–578.

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## Reply to: Correspondence on “Clinical features and evolution of bacterial infection-related acute-on-chronic liver failure”

*To the Editors:*

Firstly, the authors would like to thank Dr. Sundaram<sup>1</sup> and Dr. Fischer *et al.*<sup>2</sup> for their interest in our paper.<sup>3</sup> We also want to thank Dr. Fischer for providing some local data on a subgroup of patients with cirrhosis who were admitted to the intensive

care unit (ICU). Comparing their patients to the entire group of patients in the global study, Dr. Fischer's patients were a lot sicker, by virtue of the fact that they required ICU care. Many of them had multiple complications of cirrhosis, multiple infection sites, many more nosocomial infections (which are usually associated with a worse outcome),<sup>4</sup> had a higher qSOFA score or sepsis. Therefore, it is not surprising that many more of them had higher grades of acute-on-chronic liver failure

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