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.[5]

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.

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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[1] and Dr. Fischer *et al.*[2] for their interest in our paper.[3] 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),[4] 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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Table 1. Characteristics of patients with NASH-related cirrhosis according to the presence of acute-on-chronic liver failure during their hospital admission.

	No ACLF (n = 72)	ACLF (n = 62)	*p* value
Type of infection, n (%)			0.531
Spontaneous bacterial peritonitis	20 (28)	21 (34)	
Urinary tract infections	17 (24)	16 (26)	
Pneumonia	9 (13)	10 (16)	
Spontaneous bacteremia	3 (4)	2 (3)	
Skin and soft tissues infection	7 (10)	7 (11)	
Other	16 (22)	7 (11)	
Site of acquisition of infection, n (%)			0.374
Community acquired	33 (46)	32 (52)	
Health care acquired	23 (32)	22 (36)	
Nosocomial	16 (22)	8 (13)	
Type of bacteria, n (%)[#]			0.124
Gram negative[◦]	20/40 (50)	19/28 (68)	
Gram positive[§]	20/40 (50)	8/28 (29)	
Fungi	0/40 (0)	1/28 (4)	
MDR bacterial infection, n (%)[#]	14/40 (35)	13/28 (46)	0.343
XDR bacterial infection, n (%)[#]	1/40 (3)	1/28 (4)	0.797
Organ failures, n (%)			
Liver failure	1 (1)	26 (42)	<0.001
Coagulation failure	1 (1)	27 (44)	<0.001
Kidney failure	0 (0)	46 (74)	<0.001
Cerebral failure	1 (1)	12 (19)	0.001
Circulatory failure	1 (1)	29 (47)	<0.001
Lung failure	0 (0)	22 (36)	<0.001
Infection resolution, n (%)	67 (93)	40 (64)	<0.001
In-hospital mortality, n (%)	2 (3)	25 (40)	<0.001
28-day mortality, n (%)	3 (4)	22 (36)	<0.001

Denominators have been pointed out when lower than the whole population. ACLF, acute-on-chronic liver failure; MDR, multidrug resistant; NASH, non-alcoholic steatohepatitis; XDR, extensively drug resistant. Comparison made with Chi square test and Fisher's exact test.
[#]Only patients with positive cultures (n = 68) were considered in this analysis.
[◦]The most common Gram-negative bacteria were Enterobacteriaceae in both groups (n = 19 in patients without ACLF and n = 17 in patients with ACLF).
[§]The most common Gram-positive bacteria were *Staphylococci* (n = 5 in patients without ACLF and n = 3 in those with ACLF) and *Enterococci* (n = 4 in patients without ACLF and n = 5 in those with ACLF).

Table 2. Comparison of baseline clinical characteristics of patients with NASH-related cirrhosis who developed *vs.* those who did not develop ACLF after infection diagnosis during hospitalization.[*]

	No ACLF (n = 72)	ACLF (n = 23)	*p* value
Type of infection, n (%)			0.889
Spontaneous bacterial peritonitis	20 (28)	6 (26)	
Urinary tract infections	17 (24)	6 (26)	
Pneumonia	9 (13)	4 (17)	
Spontaneous bacteremia	3 (4)	0 (0)	
Skin and soft tissues infection	7 (10)	3 (13)	
Other	16 (22)	4 (17)	
Site of acquisition of infection, n (%)			0.451
Community acquired	33 (46)	8 (35)	
Health care acquired	23 (32)	7 (30)	
Nosocomial	16 (22)	8 (35)	
Type of bacteria, n (%)[#]			0.097
Gram negative[◦]	20/40 (50)	10/13 (77)	
Gram positive[§]	20/40 (50)	3/13 (23)	
Fungi	0/40 (0)	0/13 (0)	
MDR bacterial infection, n (%)[#]	14/40 (35)	6/13 (46)	0.343
XDR bacterial infection, n (%)[#]	1/40 (3)	0/13 (0)	1.000
Organ failures, n (%)			
Liver failure	1 (1)	12 (52)	<0.001
Coagulation failure	1 (1)	12 (52)	<0.001
Kidney failure	0 (0)	13 (57)	<0.001
Cerebral failure	1 (1)	3 (13)	0.043
Circulatory failure	1 (1)	13 (57)	<0.001
Lung failure	0 (0)	10 (44)	<0.001
Infection resolution, n (%)	67 (93)	17 (57)	<0.001
In-hospital mortality, n (%)	2 (3)	12 (52)	<0.001
28-day mortality, n (%)	3 (4)	9 (39)	<0.001

Denominators have been pointed out when lower than the whole population. ACLF, acute-on-chronic liver failure; MDR, multidrug resistant; NASH, non-alcoholic steatohepatitis; XDR, extensively drug resistant. Comparison made with Chi square test and Fisher's exact test.
[*]Only patients without baseline ACLF were included in this analysis.
[#]Only patients with positive cultures (n = 53) were considered in this analysis.
[◦]The most common Gram-negative bacteria were Enterobacteriaceae in both groups (n = 19 in patients without ACLF and n = 10 in patients with ACLF).
[§]The most common Gram-positive bacteria were *Staphylococci* (n = 5 in patients without ACLF and n = 1 in those with ACLF) and *Enterococci* (n = 4 in patients without ACLF and n = 1 in those with ACLF).

(ACLF), associated with significantly higher 28-day mortality of 68% compared to 37% in the GLOBAL study. Therefore, Dr. Fischer and colleagues are entirely correct that depending on their standpoint, the results are totally different. Study results can also depend on local epidemiology and clinical practice, as indicated by a subgroup of patients from the Indian sub-continent who had a higher rate and severity of bacterial infection-triggered ACLF than in Europe and America. We apologize for not having included many centres from Eastern Europe. Dr. Fischer's information has now provided a glimpse of what infection triggered ACLF is like amongst ICU patients. Hopefully sometime in the future, we will be able to see some data from non-ICU patients from Eastern Europe.

With respect to Dr. Sundaram's request, it is indeed true that we did not have too many patients from North America, and therefore the patients with non-alcoholic steatohepatitis (NASH) are under-represented. We have now included 2 tables providing data on patients with NASH as the etiology of cirrhosis. Table 1 compares patients with NASH who had ACLF irrespective of whether it was evident on admission or acquired during hospitalization to those with NASH who did not have ACLF throughout their entire hospital stay, whereas Table 2 compares NASH non-ACLF patients to those who developed ACLF after hospital admission. Table 1 tells us that essentially those patients with NASH-related ACLF were similar to those with ACLF related to other aetiologies of cirrhosis.[3] The same outcomes were observed irrespective of whether the patients already had ACLF on admission or developed ACLF after acquiring infection during hospitalization. As NASH becomes more of a global problem, we will probably see a higher prevalence of NASH-related cirrhosis together with their many co-morbid conditions, such as diabetes and chronic kidney failure, making these patients more prone to the development of organ failure, ACLF and failure to respond to treatment.[5]

Therefore, careful antibiotic stewardship is ever more important in our daily care of these patients.

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