Editorial

Acute-on-chronic liver failure—old concepts made clearer

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Provenance: This is a Guest Editorial commissioned by Editor-in-Chief Jia-Fu Ji, MD, FACS (Department of Gastrointestinal Surgery, Peking University School of Oncology & Beijing Cancer Hospital, Beijing, China).

Comment on: Hernaez R, Solà E, Moreau R, *et al*. Acute-on-chronic liver failure: an update. Gut 2017;66:541-53.

Received: 22 November 2017; Accepted: 24 November 2017; Published: 18 December 2017.

doi: 10.21037/tgh.2017.11.17

View this article at: http://dx.doi.org/10.21037/tgh.2017.11.17

Acute-on-chronic liver failure (ACLF) is not a new disease. Instead, it refers to extremely severe forms of acute decompensation of chronic liver diseases, which lead to high short-term mortality. What changed in the past few years is that the old concepts regarding ACLF have been made clearer through the proposition of objective definitions for this condition. With clear definitions of ACLF, medical knowledge concerning it is rapidly growing, so that now we can begin to understand its epidemiology, its pathophysiology, its natural course and prognosis, as well as we can start working on treatments for it. Recently, Hernaez *et al*. have published a very interesting update on ACLF (1). Nevertheless, as this is one of the most promising areas of research in hepatology, new information is already available, and we intend to discuss it.

Hernaez *et al*. presented four definitions for ACLF (1), among which we understand the one proposed by the European Association for the Study of the Liver-Chronic Liver Failure Consortium (CLIF-C) is the most interesting. It was based on well-defined premises (patients should present with an acute decompensation of cirrhosis, have at least one organ failure and a 28-day mortality above 15%) and on data from a large prospective cohort of patients, the CANONIC study (2). Moreover, when it was compared to the definition of ACLF proposed by the Asian Pacific Association for the Study of the Liver (APASL), the CLIF-C definition proved to be more sensitive for the diagnosis of ACLF and also to have a better prognostic performance (3). Despite there is no head-to-head comparison between the CLIF-C definition and the definition proposed by the North American Consortium for the Study of End-Stage Liver Disease (NACSELD) (4), we understand that the latter uses excessively restrictive criteria to define organ failures, aside from being based on a study which included only infected patients. Finally, the definition suggested by the World Gastroenterology Organization is not based on a prospective cohort study and still needs validation.

According to the CLIF-C definition, patients should be diagnosed with ACLF when they present with an acute decompensation of cirrhosis and single organ failure associated with renal or brain dysfunction, or single brain failure associated with renal dysfunction, or single renal failure (ACLF grade 1); two organ failures (ACLF grade 2); three or more organ failures (ACLF grade 3) (2). Organ failures are defined by the CLIF-Sequential Organ Failure Assessment (CLIF-SOFA) score (2) or by its simplification, the CLIF-C Organ Failure (CLIF-C OF) score (5). Using this definition, a quite recent study demonstrated an incidence of ACLF of 25% when 466 cirrhotic patients from an outpatient clinic were followed-up for 45 months. Moreover, authors verified that baseline mean arterial pressure, ascites, baseline model for end-stage liver disease (MELD) and baseline hemoglobin were independently associated to the development of ACLF (6).

Regarding the prognosis of ACLF, an interesting study demonstrated that 49.2% of patients resolved or improved it, 30.4% had a steady or fluctuating course, and 20.4% worsened its grade during hospitalization. It is noteworthy that the ACLF grade between the third and the seventh day of diagnosis predicted the final ACLF

grade in 81% of patients and correlated better with mortality than ACLF grade at the time of diagnosis (7). Still concerning prognosis, a study that used the definition of ACLF proposed by NACSELD demonstrated that hepatic encephalopathy severity was associated to mortality independently of other extrahepatic organ failures (8), and a study that used the definition proposed by APASL verified that patients with ACLF who were infected had higher mortality rates than those who were not (9).

With the objective of predicting mortality in patients with the diagnosis of ACLF, the CLIF-C ACLF score was proposed. It performed better than MELD, MELD-Sodium and Child-Pugh scores in the prediction of 28-day and 90-day mortalities both in a sample of patients from the CANONIC study and in another European external validation cohort (5). Understanding the importance of verifying the performance of CLIF-C ACLF outside Europe, we have recently published its validation in a cohort of Brazilian patients, in which it performed better than MELD, MELD-Sodium, CLIF-C OF and Child-Pugh scores in the prediction of 28-day mortality (10).

Concerning management of ACLF, specific treatments are still under study. A recent retrospective cohort study, evaluating patients with ACLF diagnosed according to the CLIF-C criteria, demonstrated that molecular adsorbent recirculating system (MARS) was effective in decreasing 14-day mortality, a benefit which was related specifically to its effects on patients with ACLF grades 2 or 3 (11). Even more interestingly, a randomized controlled trial conducted on hepatitis B virus-related ACLF demonstrated that allogeneic bone marrow-derived mesenchymal stromal cells infusions significantly increased 24-week survival compared to standard medical therapy. This result was attributed to an improvement of liver function and to a reduction of severe infections, associated to possible anti-inflammatory, immunoregulatory, cell-repairing and antifibrosis effects (12).

Currently, however, it is of the utmost importance to provide patients with close observation, organ support, and treatment of associated complications and management of the precipitating factors when identifiable. Therefore, patients should be thoroughly evaluated regarding indication for an early intensive care unit admission and for liver transplantation (1). We understand that, at this point, it is premature to make general recommendations on patterns of futility of care, since evidences are scarce and related to small numbers of patients. Despite the fear that ACLF patients could have poor outcomes after liver transplantation, a recent study demonstrated that they had a 12-month survival rate of 70%, which in fact is inferior to the rate of 91.4% of patients without ACLF, but is far from unacceptable. In that study, survival rate was significantly lower in ACLF grade 3 patients when compared to ACLF grades 1 or 2 patients (13). Nevertheless, in an even more recent paper, there was no significant difference concerning 12-month survival when authors compared patients transplanted with ACLF grade 3, ACLF grade 2, and ACLF grade 1 or without ACLF. Moreover, 12-month survival of transplanted ACLF grade 3 patients was over 10 times greater than that of their non-transplanted counterparts, and none of the studied futility scores was associated to 12-month mortality, all of them having a poor capacity to distinguish between patients who would survive or die. Such good results were attributed mainly to a short period of time between intensive care unit admission and transplantation (median of 9 days) (14).

In conclusion, we understand that classifying cirrhotic patients as having ACLF or not already has important prognostic and therapeutic implications (these patients will need closer observation in order to reach the expected outcomes). This should be sufficient to stress the relevance of ACLF, even if it is not a new disease, but rather the extreme presentation of the spectrum of cirrhosis. Hopefully, in a near future, this classification will bear even higher importance as specific treatments become available.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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doi: 10.21037/tgh.2017.11.17
Cite this article as: de Mattos ÂZ, de Mattos AA. Acute-on-chronic liver failure—old concepts made clearer. Transl Gastroenterol Hepatol 2017;2:111.

