

Futility of Care in Patients With Acute-on-Chronic Liver Failure

TO THE EDITOR:

In their article on the clinical course of acute-on-chronic liver failure (ACLF), Gustot et al.⁽¹⁾ proposed that organ support in the intensive care unit (ICU) should be discontinued for patients with four or more organ failures or Chronic Liver Failure Consortium (CLIF-C) ACLF score >64 at days 3-7 postinclusion, in the absence of liver transplantation, due to futility.

In our ICU, 50 consecutive patients with ACLF were admitted between April 2013 and March 2016; 40 (80%) were male, and median (interquartile range) age was 59 (50-63) years. The precipitant event of ACLF was infection in 32 (64%) patients. Median (interquartile range) Model for End-Stage Liver Disease score at ICU admission was 29 (22-32).

ACLF grade 3 was present in 23 (46%) patients at days 3-7 post-ICU admission, with a median (interquartile range) CLIF-C ACLF score of 55 (48-68). All-cause death occurred in 29 (58%) and 32 (64%) patients at days 28 and 90 post-ICU admission, respectively (Fig. 1). Liver transplantation was performed in 13 (26%) patients during follow-up (3 of these patients died within 90 days post-ICU admission).

The number of organ failures at days 3-7 post ICU admission was associated with 28-day mortality with an odds ratio of 2.7 (95% confidence interval 1.5-4.8, $P = 0.001$). Among 11 patients with four or more organ failures at days 3-7 post-ICU admission, without liver transplantation, 1 (9%) was alive at day 90 post-ICU admission (0% in Gustot et al.⁽¹⁾) (Table 1).

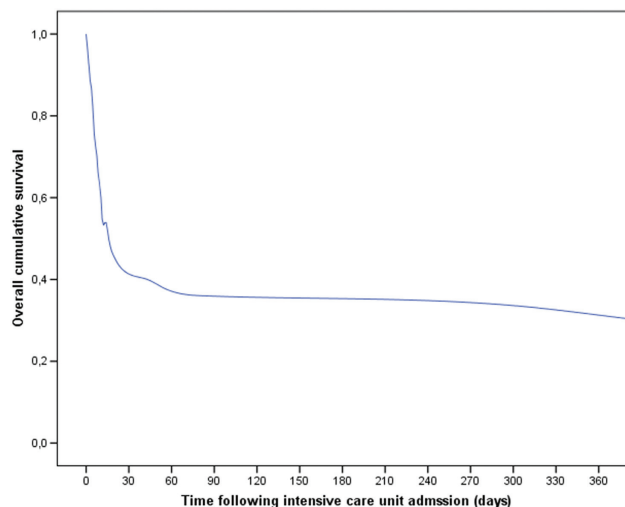


FIG. 1. Overall cumulative survival following intensive care unit admission for patients with acute-on-chronic liver failure at Curry Cabral Hospital, Lisbon, Portugal (April 2013-March 2016).

Nevertheless, all 7 patients with five or more organ failures at days 3-7 post-ICU admission were dead at day 28 post-ICU admission.

Median CLIF-C ACLF score at days 3-7 post-ICU admission was greater among nonsurvivors at day 28 post-ICU admission (62 versus 46, $P < 0.001$). CLIF-C ACLF score at days 3-7 post-ICU admission predicted 28-day mortality with an area under the curve of 0.79 (95% confidence interval 0.66-0.92). Among 14 patients with a CLIF-C ACLF score >64 at days 3-7 post-ICU admission, without liver

TABLE 1. Patients' Characteristics Stratified by Gustot et al.⁽¹⁾ Futility-of-Care Criteria at Days 3-7 Post-ICU Admission for Patients With ACLF Without Liver Transplantation at Curry Cabral Hospital, Lisbon, Portugal (April 2013-March 2016)

	≥4 Organ Failures	<4 Organ Failures	P^*	CLIF-C ACLF >64	CLIF-C ACLF ≤64	P^*
Age (years)	55 (49-63)	61 (53-65)	0.16	61 (50-66)	59 (51-63)	0.65
Sex (male)	9/11 (82%)	21/26 (81%)	1.00	10/14 (71%)	20/23 (87%)	0.39
MELD	39 (32-46)	24 (15-26)	<0.001	35 (23-43)	25 (15-26)	0.008
Organ failures	NA	NA	NA	4 (3-5)	2 (1-3)	<0.001
CLIF-C ACLF	73 (67-76)	54 (49-62)	<0.001	NA	NA	NA
28-day death [†]	10/11 (91%)	16/26 (62%)	0.12	12/14 (86%)	14/23 (61%)	0.15
90-day death [†]	10/11 (91%)	19/26 (73%)	0.39	12/14 (86%)	17/23 (74%)	0.68

*Mann-Whitney or chi-squared test.

[†]Transplant-free death (overall n of 50 - 13 = 37).

Abbreviations: MELD, Model for End-Stage Liver Disease score; NA, not applicable.

transplantation, 2 (14%) were alive at day 90 post-ICU admission (0% in Gustot et al.⁽¹⁾) (Table 1).

Taking into account our results and those of McPhail et al.,⁽²⁾ Gustot et al.'s⁽¹⁾ futility-of-care algorithm may be oversimplified and difficult to generalize. For patients with cirrhosis and organ failures, futility of care may be more complex to define than using a single cutoff of overall number of organ failures or the CLIF-C ACLF score. Furthermore, indications and limitations of liver transplantation in this context remain controversial.

The study of futility of care for patients with ACLF could benefit by adding qualitative measures (e.g., comorbidities, performance status, local ICU practice, and transplantation criteria). Finally, each individual's, family's, and community's perceptions of goals of care and life need to be respected.

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REPLY:

We thank Cardoso et al. for their comments about our paper.⁽¹⁾ The concept of futility of care is always a complex and controversial issue. Thanks to the collection of objective data, we are moving from an era in which intensivists were reluctant to admit patients with cirrhosis to an intensive care unit (ICU) to one in

which clinicians have access to robust criteria that help them to decide to maintain or withdraw/withhold organ support in patients who have cirrhosis and multiple organ failure (OF). Because of the limitation of resources, we need to address the issue of futility of care by collecting externally validated prospective data. Like others, Cardoso et al. challenge our suggested criteria for futility of care.⁽²⁾ In their single-center experience of 50 patients with acute-on-chronic liver failure (ACLF), patients with four or more OFs or a Chronic Liver Failure Consortium ACLF score (CLIF-C ACLFs) > 64 at 3-7 days after ICU admission had 90-day transplant-free survival rates of 9% and 14%, respectively, in contrast to 0% in our observation.

Several factors could explain this discrepancy. In our multicenter European CANONIC study, analysis was performed in patients with ACLF grade 3 (ACLF-3) at enrollment or at any time of the 28-day follow-up, in contrast to the data presented by Cardoso et al., where all ACLF patients (46% with ACLF-3) admitted to an ICU were assessed. On diagnosis of ACLF-3, there was also no critical cutoff number of OFs or level of CLIF-C ACLFs over which the mortality rate reached 100% but, at day 3-7, patients with four or more OFs (n = 25) or CLIF-C ACLF score > 64 (n = 24) had a 90-day mortality of 100%.

Moreover, ICU admission of ACLF patients included in the CANONIC study was not systematic (10% in patients with ACLF-1, 32% in ACLF-2 and 67% in ACLF-3) in comparison with the Cardoso et al. study, where all patients were managed in an ICU at baseline.

Finally, type of OF and organ support at day 3-7 could also differ between both series. In CANONIC, 11 out of the 25 patients with four or more organ failures (44%) were under mechanical ventilation, renal replacement therapy, and vasopressors at day 3-7 and 10 (40%) under vasopressors and mechanical ventilation or renal replacement therapy (n = 5, each).

In conclusion, we believe that it is essential to collect high-quality prospective externally validated data to try to define inappropriate, ineffective, or futile treatment in critical ill patients with cirrhosis. Our study presents—for the first time—potential criteria for defining futility of care in patients with ACLF. Obviously, these criteria must be always questioned with improvement of care and the introduction of new therapeutic strategies.

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