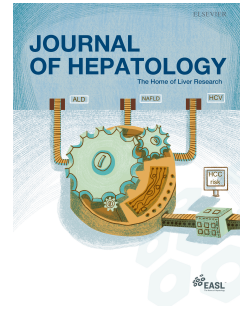


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Thierry Artzner, Luca S. Belli, François Faitot, Rajiv Jalan

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## **Attitudes toward liver transplantation for ACLF-3 patients determine equity of access**

### **Authors**

Thierry Artzner<sup>1</sup>, Luca S Belli<sup>2</sup>, François Faitot<sup>1</sup>, Rajiv Jalan<sup>3,4</sup>

<sup>1</sup> Service de Chirurgie Hépato-Biliaire et Transplantation Hépatique, Hôpital de Hautepierre, Strasbourg, France.

<sup>2</sup> Hepatology and Gastroenterology Unit, ASST GOM Niguarda, Milan, Italy

<sup>3</sup> Liver Failure Group, Institute for Liver and Digestive Health, University College London, Royal Free Campus, London, United Kingdom

<sup>4</sup> European Foundation for the Study of Chronic Liver Failure (EF Clif)

### **Corresponding author**

Thierry Artzner

Hôpitaux Universitaires de Strasbourg

1 avenue Molière

67000 Strasbourg, France

### **Conflicts of interest**

Rajiv Jalan is the inventor of OPA, which has been patented by UCL and licensed to Mallinckrodt Pharma. He is also the founder of Yaqrit Discovery, a spin out company from University College London, Hepyx Limited and Cyberliver. He had research collaborations with Yaqrit Discovery.

The other authors have no conflicts of interest to declare.

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Liver transplantation (LT) is currently the most effective treatment available for critically ill patients with cirrhosis and multiple organ failure, provided they are carefully selected (1). While support for LT for patients with grade 3 acute-on-chronic liver failure (ACLF-3) is increasing through the transplant community in theory, in practice, utilization of LT for these patients remains debated and problematic. For example, studies of the French transplant registry (2) and of a European cohort (3,4) of critically ill patients with cirrhosis have shown that access to LT varies significantly across countries and across individual transplant centers, leading to inequities in access to this life-saving treatment. We are therefore still far from equity and justice in this area of transplant medicine. Several potential obstacles may hinder access to LT for patients with ACLF-3: admission to the ICU, referral to a tertiary center, inclusion in the waiting list, timely organ allocation and, most importantly, an agreement between the members of the transplant team on the value of LT in this indication. Access to LT and optimal care for this specific group of potential transplant candidates requires a comprehensive, multidisciplinary approach. Transplant hepatologists, surgeons, anesthesiologists and intensivists, both within transplant centers but also in primary and secondary centers, need to be aware and convinced that LT is a potential treatment for a critically ill patient with cirrhosis.

This survey was designed through discussion between experts of EFClif and ELITA and an online questionnaire was sent to the participants of the CHANCE trial (5). Multiple choice questions were targeted at describing LT practices, identifying obstacles to LT for patients with ACLF-3 and determining potential solutions to overcome these obstacles. Questionnaires were sent to 1,031 transplant doctors and the first 100 responses were analyzed. All data were collected anonymously.

The 100 participants who completed the survey came from 26 different countries. Of these, 76 identified themselves as hepatologists, 13 as intensivists and/or anesthesiologists and 11 as surgeons. Most respondents (58%) came from transplant centers that performed more than 50 LTs yearly. While fewer than 5 patients with ACLF-3 were transplanted annually in the majority of the respondents' centers (65%), most respondents (70%) claimed that their centers could transplant more than 5 every year.

The majority (66%) agreed that there was enough evidence in the literature to support transplanting patients with ACLF-3. Despite such evidence, 70% declared that patients with ACLF-3 did not have adequate access to LT in their region (Figure 1A and 1B). When asked whether patients with ACLF-3 did not have sufficient access to the ICU in their region, on a scale of 1 ("do not agree at all") to 5 ("strongly agree"), 50 responses were between 4 and 5. When asked the same question, but this time in their own center, only 21 responses were between 4 and 5 (Figure 1C and 1D).

While 27 respondents noted that colleagues in their own transplant centers were reluctant to put critically ill patients with cirrhosis on the transplant waiting list, this was reported more frequently (59 respondents) concerning physicians who referred patients to LT centers but did not directly work in them (Figure 1E and 1F). When respondents were asked to identify the group(s) of physicians that was/were most unwilling to consider LT for patients with ACLF-3 in their center, anesthesiologists came first (40 respondents), followed by intensivists (38 respondents), surgeons (32 respondents) and hepatologists (21 respondents). There was a significant split over the issue of prioritizing access to LT for patients with ACLF-3, with 48 respondents declaring that the average waiting time for patients with ACLF-3 was too long in

their center. When asked whether the allocation system in their region/country did not prioritize patients with ACLF-3 sufficiently, 53 respondents agreed. Finally, 82 respondents were in favor of adding mechanisms to organ allocation algorithms in order to exclude critically ill cirrhotic patients if they are too sick at the time of organ proposal.

In summary, this survey reveals a discrepancy between clinical evidence and actual practice concerning access to LT for patients with ACLF-3. It illustrates the growing view that the use of LT should be expanded for patients with ACLF-3, while highlighting some of the key obstacles that need to be overcome to achieve this aim. From an institutional perspective, organ allocation algorithms need to be tailored according to regional and national determinants to enable adequate prioritization of patients with ACLF-3, while ensuring that patients who are too sick to be transplanted can be identified. From a clinical perspective, it is fundamental to convince colleagues in transplant centers but also outside transplant centers that patients with ACLF-3 should be considered for ICU admission, referral to a tertiary LT center and pre-transplant work-up for potential listing.

Spreading LT for patients with ACLF-3 is a medical undertaking different in nature and broader in scope from providing greater access to a particular drug, intensive care support or surgical technique. It requires widespread discussion, education and further research, which will change the paradigm in the way the medical community thinks about critically ill patients with cirrhosis.

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**Figure 1. Selected responses to the ACLF Liver Transplant Questionnaire.**