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Cirrhose réanimatoire et transplantation hépatique

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Résumé

La place de la transplantation hépatique chez les patients cirrhotiques en défaillance multiviscérale fait débat. D'un côté, il s'agit du seul traitement qui peut radicalement améliorer le pronostic vital de ces patients. D'un autre côté, compte tenu d'une survie post-transplantation globalement inférieure à la survie moyenne de la population générale des candidats à une transplantation hépatique, l'accès de ces patients à la greffe doit faire l'objet de précautions particulières pour ne pas péjorer l'utilité globale de l'activité de transplantation hépatique.

Dans un premier temps, trois études identifient différents éléments cliniques pertinents pour aider les praticiens à identifier une fenêtre de transplantabilité optimale chez les patients cirrhotiques en défaillance multiviscérale.

Dans un second temps, nous avons analysé des données épidémiologiques concernant l'accès effectif à la transplantation hépatique de ces patients à travers plusieurs pays européens. Ces analyses soulignent une hétérogénéité des pratiques dans ce domaine qui conduit à une inégalité d'accès au traitement salvateur que constitue la greffe. Une enquête qualitative a également été réalisée auprès de praticiens travaillant dans des centres de transplantation pour identifier des pistes potentielles pour réduire cette inégalité d'accès à la greffe.

Pour finir, les différentes analyses tirées de cette thèse permettent d'une part d'éclaircir la place potentielle que pourraient jouer les algorithmes de répartition d'organes chez ces patients et d'autre part d'ouvrir des perspectives de recherche clinique dans ce domaine clé pour l'avenir de la transplantation hépatique.

Summary

There is considerable debate over the indication of liver transplantation for critically ill patients with cirrhosis. On the one hand, liver transplantation is the only treatment that can radically improve the prognosis of these patients. On the other hand, given current organ shortage and the potentially poor post-transplant prognosis of this subgroup of patients, access to liver transplantation for critically ill patients can only be justified and supported if their post-transplant survival approaches that of the general population of transplant candidates.

This dissertation includes three studies that identify clinical tools that can contribute to identifying the optimal transplantability window of critically ill transplant candidates with cirrhosis.

It also describes and analyses the effective access that this subgroup of patients has to liver transplantation. In particular, this epidemiological approach shows that there is inequity in access to this life-saving treatment across transplant centers in France and in Europe. A qualitative survey among transplant professionals complements these results and identifies obstacles and potential solutions to reducing the inequity of access to liver transplantation for these patients.

Finally, the results of this dissertation shed light on the potential role that organ allocation algorithms could or should play in the context of critically ill patients with cirrhosis. It also offers new research perspectives on this topic that will doubtless play a key part in the future of liver transplantation.

Research and teaching activity related to PhD

PhD-related prize

- 2023: ILTS (international liver transplant society) Vanguard award for clinical research

Multicenter, international studies

- Hernaez R, Karvellas CJ, Liu Y, Sacleux SC, Khemichian S, Stein LL, Shetty K, Lindenmeyer CC, Boike JR, Simonetto DA, Rahimi RS, Jalal PK, Izzy M, Kriss MS, Im GY, Lin MV, Jou JH, Fortune BE, Cholankeril G, Kuo A, Mahmud N, Kanwal F, Saliba F, Sundaram V, Artzner T (joint senior author), Jalan R
  Multi-Organ Dysfunction and Evaluation for Liver Transplantation (MODEL) Consortium, The novel SALT-M score predicts 1-year post-transplant mortality in patients with severe acute-on-chronic liver failure
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- Artzner T, Bernal W, Belli LS, Conti S, Cortesi PA, Sacleux SC, Pageaux GP, Radenne S, Trebicka J, Fernandez J, Perricone G, Piano S, Nadalin S, Morelli MC, Martini S, Polak WG, Zieniewicz K, Toso C, Berenguer M, Iegri C, Invernizzi F, Volpes R, Karam V, Adam R, Faitot F, Rabinowich L, Saliba F, Meunier L, Lesurtel M, Uschner FE, Michard B, Coilly A, Meszaros M, Poinsot D, Besch C, Schnitzbauer A, De Carlis LG, Fumagalli R, Angeli P, Arroyo V, Fondevila C, Duvoux C, Jalan R
  Location and allocation: inequity in access to liver transplantation for patients with severe ACLF
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- Belli LS, Duvoux C, Artzner T (joint first author), Bernal W, Conti S, Cortesi PA, Sacleux SC, Pageaux GP, Radenne S, Trebicka J, Fernandez J, Perricone G, Piano S, Nadalin S, Morelli MC, Martini S, Polak WG, Zieniewicz K, Toso C, Berenguer M, Iegri C, Invernizzi F, Volpes R, Karam V, Adam R, Faitot F, Rabinovich L, Saliba F, Meunier L, Lesurtel M, Uschner FE, Fondevila C, Michard B, Coilly A, Meszaros M, Poinsot D, Schnitzbauer A, De Carlis LG, Fumagalli R, Angeli P, Arroyo V, Jalan R
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  Journal of Hepatology, 2021
- Artzner T, Michard B, Weiss E, Barbier L, Noorah Z, Merle JC, Paugam-Burtz C, Francoz C, Durand F, Soubrane O, Pirani T, Theocharidou E, O'Grady J, Bernal W, Heaton N, Salamé E, Bucur P, Barraud H, Lefebvre F, Serfaty L, Besch C, Bachellier P, Schneider F, Levesque E, Faitot F
  Liver transplantation for critically ill cirrhotic patients: Stratifying utility based on pretransplant factors
  American Journal of Transplantation, 2020

Registry studies

- Artzner T, David S Goldberg D, Sundaram V, Faitot F, Karvellas C, Asrani S,
  Improvement in survival after transplantation for critically ill patients with cirrhosis in the United States
  American Journal of Gastroenterology, 2024
- Artzner T, Legeai C, Antoine C, Jasseron C, Michard B, Faitot F, Schneider F, Bachellier P
  Liver transplantation for critically ill cirrhotic patients: results from the French transplant registry
  Clinics and Research in Hepatology and Gastroenterology, 2021

Single center studies

- Faitot F, Artzner T, Michard B, Besch C, Schenck M, Herbrecht JE, Janssen Langenstein R, Maestraggi Q, Guillot M, Harlay ML, Castelain V, Addeo P, Ellero B, Woehl-Jaegle ML, Serfaty L, Bachellier P, Schneider F
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  Liver Transplantation, 2021
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  Clinical Transplantation, 2017

Reviews/opinions

- Perricone G, Artzner T, De Martin E, Jalan R, Wendon J, Carbone M.
  Intensive care management of acute-on-chronic liver failure
  Intensive Care Medicine, 2023
- Artzner T, Fernandez J, Jalan R
  Liver transplantation for patients with severe acute on chronic liver failure: it is time of change paradigms
  Intensive Care Medicine, 2023
- Michard B, Artzner T
  La transplantation hépatique chez les patients cirrhotiques en réanimation
  Médecine intensive réanimation, 2023
- Artzner T, Besch C, Deridder M, Michard B, Addeo P, Bachellier P, Faitot F
  Entre utilité individuelle et utilité collective : quelle place pour la transplantation hépatique dans la cirrhose réanimatoire en pratique ?
  Courrier de la transplantation, 2022
- Faitot F, Michard B, Artzner T
  Organ allocation in the age of the algorithm: avoiding futile transplantation - utility in allocation
  Current Opinion in Organ Transplantation, 2020
- Michard B, Artzner T, Besch C, Faitot F
  Transplantation hépatique chez le patient cirrhotique en défaillance multiviscérale
  Hépato-Gastro & Oncologie Digestive. 2019
- Artzner T, Michard B, Besch C, Levesque E, Faitot F
  Liver transplantation for critically ill cirrhotic patients: Overview and pragmatic proposals
  World Journal of Gastroenterology, 2018

Letters:

- Artzner T, Belli LS, Faitot F, Jalan R
  Attitudes toward liver transplantation for ACLF-3 determine equity of access
  Journal of Hepatology, 2023 (research letter)
- Artzner T, Belli L, Faitot F, Jalan R
  Causes of variability in listing and access to liver transplantation for critically ill patients with cirrhosis: Acknowledging the elephant in the room
  Liver transplantation, 2023
- Sundaram V, Artzner T
  The costs and health care utilization associated with transplantation for alcoholic hepatitis compared with acute-on-chronic liver failure
  Liver Transplantation, 2022
- Artzner T, Michard B.
  Caring for Cirrhotic patients with multiple organ failure in the ICU: a change of paradigm is underway
  Critical Care Medicine, 2020

Oral presentations at international conferences

- **Société de Réanimation de Langue Française (SRLF), Paris, 2023**

. Quand envisager la transplantation en Réanimation ?

- **American Association for the Study of Liver Diseases (AASLD), Washington D.C., 2022**

. Improvement in post-transplant survival for critically ill patients with cirrhosis, 2005-2020

- **European Association for the Study of the Liver (EASL), London, 2022**

. Effect of recruitement and selection policies on the volume of outcome of patients transplanted with ACLF-3

- **American Association for the Study of Liver Diseases (AASLD), Los Angeles, 2021**

. Location and allocation: inequity of access to liver transplantation for patients with acute-on-chronic liver failure grade 3 (ACLF-3) across Europe **(presidential plenary session)**

. Pre-transplant intensive care unit management and selection of ACLF-3 transplant candidates

- **Société de Réanimation de Langue Française (SRLF), Paris, 2020**

. Liver transplantation for critically ill cirrhotic patients

- **European Association for the Study of the Liver (EASL), Vienna, 2019**

. Liver transplantation in patients with grade 3 acute-on-chronic liver failure: Pre-transplant risk factors of post-transplant mortality **(selected for 'Best of international liver congress' abstracts)**

Poster presentation at internation conferences:

- **European Association for the Study of the Liver (EASL), Vienna, 2023**

. Inequity in access to liver transplantation for critically ill patients with cirrhosis across U.S. transplant centers

- **American Association for the Study of Liver Diseases (AASLD), Washington D.C., 2022**

. Identifying attitudes and barriers to liver transplantation for patients with grade 3 acute-on-chronic liver failure (ACLF-3): an international qualitative study

. Location matters: inequity in access to liver transplantation for critically ill patients with cirrhosis across U.S. transplant centers

- **American Association for the Study of Liver Diseases (AASLD), Los Angeles (online), 2021**

. Liver transplantation for critically ill cirrhotic patients in France: overall results, mortality risk factors and geographic variations

Web presentations

- ILTS Vanguard webinar, Complex liver cases, 2023
- EASL Studio (with Rajiv Jalan, Marina Berenguer and Luca Belli): Liver transplantation for ACLF: Opportunities, challenges and pitfalls, 2022

Other oral presentations

- Padua, Italy, presentation on ACLF at the Hepatologist in a liver transplant program course, 2024
- Zagreb, Croatia, Seminar for intensivists/hepatologists, 2024
- Hospital Clinic Barcelona, Spain, several presentations on ACLF, 2024
- Madrid, Spain, ELITA-ESOT Monothematic Conference on ACLF, Alcohol and Liver Transplantation, 2024
- Paris (service de réanimation médicale, hôpital Saint Louis), France, 2023
- Villejuif (Centre hépato biliaire), France, 2023
- Munich (Hepatology up to date, Leber Centrum), Germany, 2022
- Dallas (Baylor medical center), United States, 2022
- Hospital Clinic Barcelona, Spain, 2022
- Saint Denis (Agence de la Biomédecine), France, 2021

Courses on ACLF

- Villejuif, France, 2022, 2023 : Diplôme universitaire de réanimation hépatique
- Milan (university of Milan-Bicocca), Italy, 2022, 2023, 2004: Master interuniversitario di II livello in Medicina dei Trapianti ed Epatologia Avanzata

Abbreviations

LT: Liver transplantation

ICU: Intensive care unit

ALF: Acute liver failure

ACLF: Acute-on-chronic liver failure

MELD: Model for end-stage liver disease

UNOS: United network for organ sharing

Note

This dissertation is based on 5 original studies (4 of which are already published as original articles and one as a research letter):

- Michard B, Artzner T (joint first author), et al., Pretransplant Intensive Care Unit Management and Selection of Grade 3 Acute-on-Chronic Liver Failure Transplant Candidates., Liver Transpl., 2021
- Artzner T, Goldberg D, et al., Improvement in survival after transplantation for critically ill patients with cirrhosis in the United States, under review (American journal of Gastroenterology)
- Hernaez R, Karvellas K, … , Artzner T (joint senior author), Rajiv J, The novel SALT-M score predicts 1-year post-transplant mortality in patients with severe acute-on-chronic liver failure, J Hepatol., 2023
- Artzner T, Bernal W et al., Location and allocation: inequity in access to liver transplantation for patients with severe ACLF, Liver transplantation, 2022
- Artzner T, Belli LS, Faitot F, Jalan R., Attitudes toward liver transplantation for ACLF-3 determine equity of access, Journal of Hepatology, 2023

These studies include granular single cohort and multicenter international cohort analyses as well as registry analyses and a qualitative survey. The precise methods and statistical analyses vary from one study to the other and are therefore described separately in each study.

Three additional published original articles, 1 short review and 1 opinion letter directly related to the topic of this dissertation are also included as supplementary articles.

- Artzner T, Fernandez J, Jalan R, Liver transplantation for patients with severe acute on chronic liver failure: it is time of change paradigms, Intensive Care Med. 2023
- Artzner T, Belli L, Faitot F, Jalan R, Causes of variability in listing and access to liver transplantation for critically ill patients with cirrhosis: Acknowledging the elephant in the room, Liver transplantation, 2023
- Artzner T, Michard B et al., Liver transplantation for critically ill cirrhotic patients: Stratifying utility based on pretransplant factors, Am J Transplant. 2020
- Belli LS, Duvoux C, Artzner T (joint first author) et al., Liver transplantation for patients with acute-on-chronic liver failure (ACLF) in Europe: Results of the ELITA/EF-CLIF collaborative study (ECLIS), J Hepatol. 2021
- Artzner T, Legeai C et al., Liver transplantation for critically ill cirrhotic patients: results from the French transplant registry, Clin Res Hepatol Gastroenterol. 2021

The introduction of the dissertation is intended to provide a critical (rather than an exhaustive) overview of the topic and highlight how the different studies included interlock.

The outlook of this dissertation is markedly clinical. Discussions concerning liver physiology and the physiopathology of acute-on-chronic liver failure are deliberately left aside. The issue of living donor transplantation for critically ill patients is not discussed either since it constitutes an extremely marginal situation in Europe (it is currently non-existent in France in the context of liver transplantation for critically patients with cirrhosis).

The terms “critically ill patients with cirrhosis”, “patients with severe acute-on-chronic liver failure (ACLF)” and “patients with ACLF-3” are used interchangeably in the introduction even if they sometimes arguably refer to slightly different clinical entities. The definition of ACLF used in this dissertation is the one derived from the European Association for the Study of the Liver (EASL)- European Foundation for the study of Chronic liver failure (EF Clif) CANONIC study (1).

Some of the passages of the introduction are extracts from the publications mentioned above, in particular (but not exclusively) Artzner T, Fernandez J and Jalan R, Liver transplantation for patients with severe acute on chronic liver failure: it is time of change paradigms, Intensive Care Medicine, 2023.

Introduction

1. Foreword

My interest in the topic of this dissertation started on the evening when I intubated a woman in her forties who was vomiting blood.

I was a resident in the ICU where she had been hospitalised for a severe decompensation of primary biliary cholangitis. Her body was swelled up and glowing yellow and she was already hooked up to a dialysis machine and half a dozen infusion pumps. She had been admitted a week earlier for pulmonary infection and jaundice. She was very sick and it was clear that the machines and drugs available in the ICU would not be enough to save her from what seemed like a certain death.

A few days later, a surgeon flew in with a liver she had explanted and carried back from another part of the country. My patient was taken to the operating room and came back to the ICU with her "new" liver. Hepatic function took off rapidly and, over the course of a few days, each extra-hepatic organ function recovered and the machines surrounding her were removed, one after the other. A few weeks later, she was back at home, with her family.

During my clinical training, I had witnessed some of the wonders that medicine could work in the ICU. But I had also seen the limits of what tubes, drugs and machines can achieve when all the organs are failing. The fact that changing a single organ in the body could restore not only the function of the liver but bring life back to a patient in the ICU with multiple organ failure seemed nothing short of a medical miracle. This miracle required a full array of machines, surgeons, peculiar drugs, and complicated decisions. Within the medical landscape, the ICU stands out as a land of plenty, but this standard knows one exception: solid transplantation, which is characterised by scarcity. Thus, the miracle I had witnessed was governed by an algorithm that relied on a combination of principles of justice and empirical evidence, notions that were very foreign to the way intensivists reason and work. Also, I had learned that liver transplantation was classically used to treat fulminant hepatitis and that it too had been described as a miracle in its early days. But transplanting patients with decompensated cirrhosis and multiple organ failure was definitely not in the textbooks I had studied throughout medical school. I decided that I wanted to know more about it.

2. A simple, clinical problem

This dissertation takes a decisively clinical perspective on the issue of liver transplantation (LT) for critically ill patients with cirrhosis. It grapples head-on with a few simple observations that are at the heart of this clinical problem:

- First, patients with decompensated cirrhosis associated with multiple organ failure have an exceedingly high risk of mortality in the ICU[1];
- Second, liver transplantation can constitute a radical life-saving treatment for these patients;
- Third, there is no real alternative to liver transplantation for these patients – e.g. plasma exchange, albumin dialysis or bioartificial livers have not demonstrated radical significant improvement of patient prognosis (2);
- Forth, this subgroup of patients is susceptible to have poorer post-LT survival than the general population of transplant candidates and it is therefore crucial to identify subgroups of patients who have the poorest post-LT prognosis.

These clinical observations give rise to three questions that constitute the core of this dissertation:

- How can we identify patients who are particularly at risk of having poor post-LT survival in order to potentially exclude them from LT?
- Do patients actually have access to LT and, if not, why?
- Should we use formal algorithms to regulate the access of critically ill patients to LT?

These questions have two characteristics that I wish to underline. First, they are clinical, rather than scientific questions and they therefore call for practical answers. Second, they require a multidisciplinary approach since they lie at the crossroads of several clinical specialities (intensive care medicine, anaesthesiology, hepatology, transplant medicine and surgery) as well as epidemiology.

[1] With the exception of specific clinical situations that can usually "easily" be identified and reversed in the ICU, such as certain forms of isolated acute severe hepatic encephalopathy that require short-term mechanical ventilation for airway protection and some cases of gastro-intestinal bleeding that require peri-endoscopic ICU management.

3. Cirrhosis & multiple organ failure: a word of nosology

Cirrhosis is a chronic condition whose natural history can be marked by episodes of decompensation and recompensation that can take various forms. Decompensated chronic liver disease can itself be associated with various extra-hepatic organ and systemic failures (kidney, brain, circulation, lung, coagulation, immune). The natural history of decompensated cirrhosis associated with multiple organ failure is characterised by extremely high short-term mortality. While there are reports in the literature that the survival of critically ill patients admitted in the ICU has slightly improved over time (3–5), the prognosis of these patients remains particularly sombre (6,7). This explains – but hardly justifies – the rule of thumb dogma that is often repeated and taught in medical schools, according to which a patient with cirrhosis and three or more organ failures should not be admitted to the ICU. This also explains that cirrhosis has been a relatively overlooked area of interest among intensivists. The relative lack of interest for issues related to splanchnic hemodynamics (compared to cardio-pulmonary or even renal and neurological hemodynamics) illustrates this fact very clearly.

The development of the concept of acute-on-chronic liver failure (ACLF) in the hepatology community has attracted considerable attention over the past decade. Among the various definitions of ACLF (8), this dissertation uses the one promulgated by the European Association for the Study of the Liver – European Foundation for the study of Chronic liver failure (EASL-EF Clif). This definition is based on the association of three key components: acute decompensation of cirrhosis, organ failure(s) and high short-term mortality (1,9,10). The classification relies on a scoring system that is adapted from the Sequential Organ Failure Assessment (SOFA) score, which allows to stratify clinical situations depending on the number of organ failures (table 1). Several scores have been developed to predict without transplant mortality for these patients (11). Naturally, patients with three or more organ failures (ACLF-3) have the highest short-term mortality (1). These are the patients constitute the focus of this dissertation.

Table 1. ACLF definition and grading - The Chronic Liver Failure-Consortium Organ Failure score (CLIF-C OF score)

Organ system	**Variable**	**Scale**		
		1 point	2 points	3 points
Liver	Bilirubin (mg/dl)	<6.0	≥6.0 to <12.0	≥12
Kidney	Creatinine (mg/dl)	<1.5	≥2.0 to <3.5	≥3.5
		>1.5 to <2.0		or use of RRT
Cerebral	HE grade (West Haven criteria)	0	I - II	III – IV or endotracheal intubation for HE
Coagulation	INR	<2.0	≥2.0 to <2.5	≥2.5
Circulation	MAP (mm Hg)	≥70	<70	Use of vasopressors
Respiration	PaO_2/FiO_2	>300	>200 to ≤300	≤200
	SpO_2/FiO_2	>357	>214 to ≤357	≤214

Adapted from Jalan et al. J Hepatol 2014 (11)

The Chronic Liver Failure Consortium (CLIF-C) Organ Failure (OF) scoring system assigns a score on a scale of 1 to 3 to each of the six organ systems described (kidneys, lungs, liver, coagulation, brain, circulation). The dark and light grey colors indicate the values that are used to define organ system failure and organ dysfunction, respectively. Organ system failures and dysfunction are used to define ACLF.

Diagnostic criteria for ACLF and its Grades

ACLF Grade 1

- Patients with single Kidney failure
- Patients with single Liver, Coagulation, Circulation or Respiratory organ failure and either kidney or brain dysfunction
- Patients with single Brain failure and kidney dysfunction

ACLF Grade 2: Patients with 2 organ failures

ACLF Grade 3: Patients with 3 or more organ failures

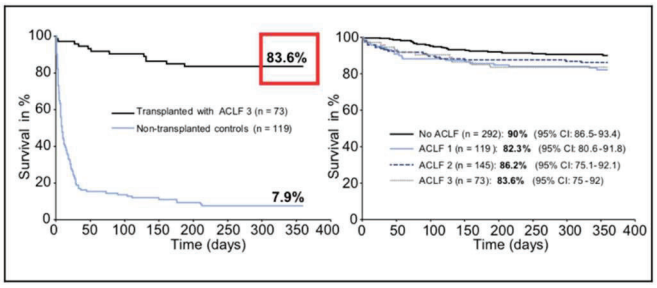
HE: hepatic encephalopathy, MAP: mean arterial pressure, PaO_2 partial pressure of arterial oxygen, FiO_2 fraction of inspired oxygen, and SpO_2 pulse oximetry saturation.

4. The promises and potential pitfalls of liver transplantation in the context of ACLF-3

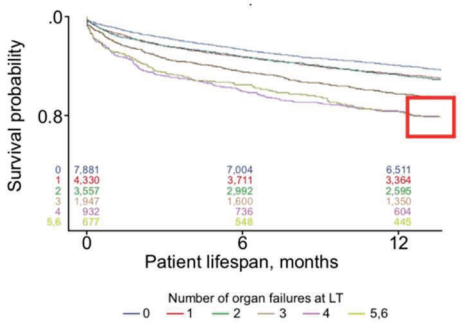
4.1. Promises of LT in the context of ACLF-3

Liver transplantation is the only radical treatment of severe ACLF currently available and it can be associated with extremely high survival. Several studies have reported one-year post-LT survival rates above 80% (12–14, **figure 1**). While there is no control group (and, for ethical reasons, there never will be) to adequately compare transplanted patients with non-transplanted patients, it is pretty clear that the vast majority of the patients who were transplanted in these studies would have died within a few weeks if they had not had access to LT.

Figure 1. Studies reporting high post-LT survival for patients transplanted with ACLF-3



Artru, Journal of Hepatology, 2017



1-year patient survival: no OF 90%, 1 OF 88%, 2 OF 88%, 3 OF 84%, 4 OF 81%, 5-6 OF 81%

Thuluvath, Journal of Hepatology, 2018

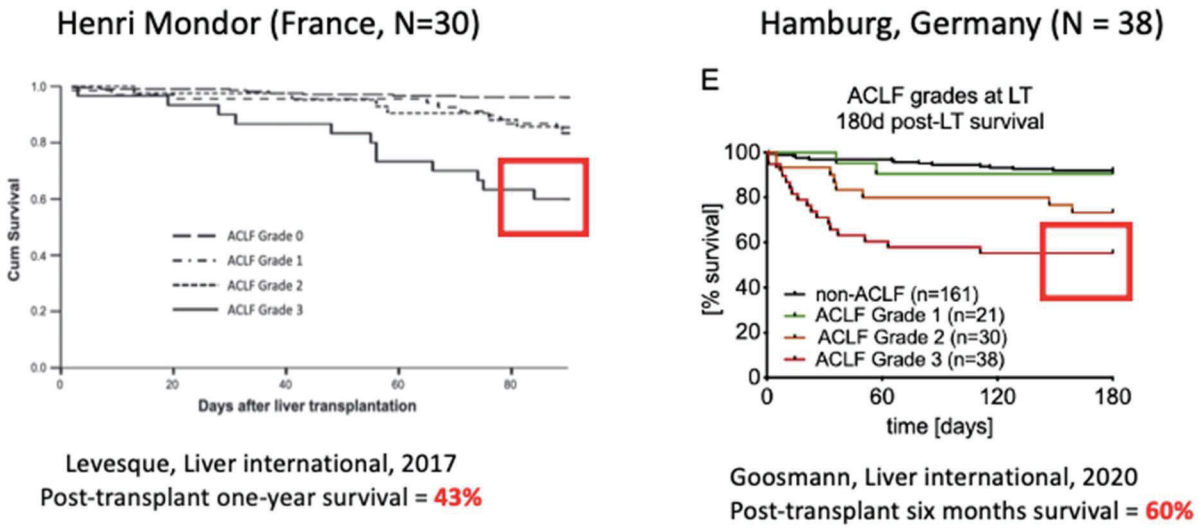
Beyond the issue of post-LT survival, the crucial clinical point to understand both from an ICU and from an organ transplant point of view is that LT reverses non only hepatic failure, but also extra-hepatic organ failures. This is already at the heart of the use of LT for acute liver failure (ALF) in ICUs and LT centers across the world and was described as nothing short of a miracle in its early days. To be sure, the etiology, natural history, prognosis, epidemiology and clinical management of ALF and ACLF are markedly different. ALF typically occurs in patients without preexisting liver disease, it is rarer and most often due to viral infection or acute drug toxicity. Nevertheless, LT delivers a similar promise in both cases: replacing the liver can resolve and reverse multiorgan failure.

4.2. Methodological limits, publication biases and potential ethical pitfalls of LT in the context of ACLF-3

All the studies that have reported post-LT survival of patients with severe ACLF suffer from a key methodological limit: they include patients who were carefully selected by transplant teams. Some of the criteria used to select transplant candidates and accept organ proposals therefore cannot be retrieved retrospectively. In fact, they cannot be properly recorded prospectively either, for they include too many intricated complex factors, many of which are dynamic (e.g.: is the patient's clinical condition "improving" in the ICU), based on clinical experience (e.g.: evaluating frailty in the ICU) or subjective (e.g.: alcohol addiction assessment) (15, **supplementary article 1**).

Several studies have reported low post-LT survival rates in patients transplanted with severe ACLF. In one study, the one-year post-LT survival rate was 43% for patients transplanted with ACLF-3 (16). In another study, six-months survival was only 60% in this subgroup of patients (17) (**figure 2**). While these studies did not meet the editorial success of those that reported higher post-LT survival rates (revealing potential publication bias), they are crucial to our topic. They underline the potential poor post-LT prognosis of these patients and the ethical risk inherent in advocating access to LT for patients with ACLF-3.

Figure 2. Studies reporting "low" post-LT survival for patients transplanted with ACLF-3



Nonetheless, there is clearly an individual benefit for patients with ACLF-3 to be transplanted and, if organs were plentiful (which may perhaps be the case in the future if xenografts take

off), a large part of this dissertation would no doubt be pointless. Yet, today, advocating access to LT for *all* patients with ACLF-3 is unrealistic, irresponsible and unfounded. Indeed, the field of solid organ transplantation is characterized by organ shortage. In 2019 in France, for example, there were 1.9 candidates for each liver allograft and 496 patients who died or were delisted (for a total of 1356 LTs performed in 2019)[2]. That same year, among all the patients listed for LT in 2019, 11% died or were delisted within a year of being listed[2.]. Another illustration of organ shortage in France is that, taking into account the competing risk of LT, the cumulative incidence of death or delisting in the year after being listed was 17% among patients listed between 2017 and 2021[2].

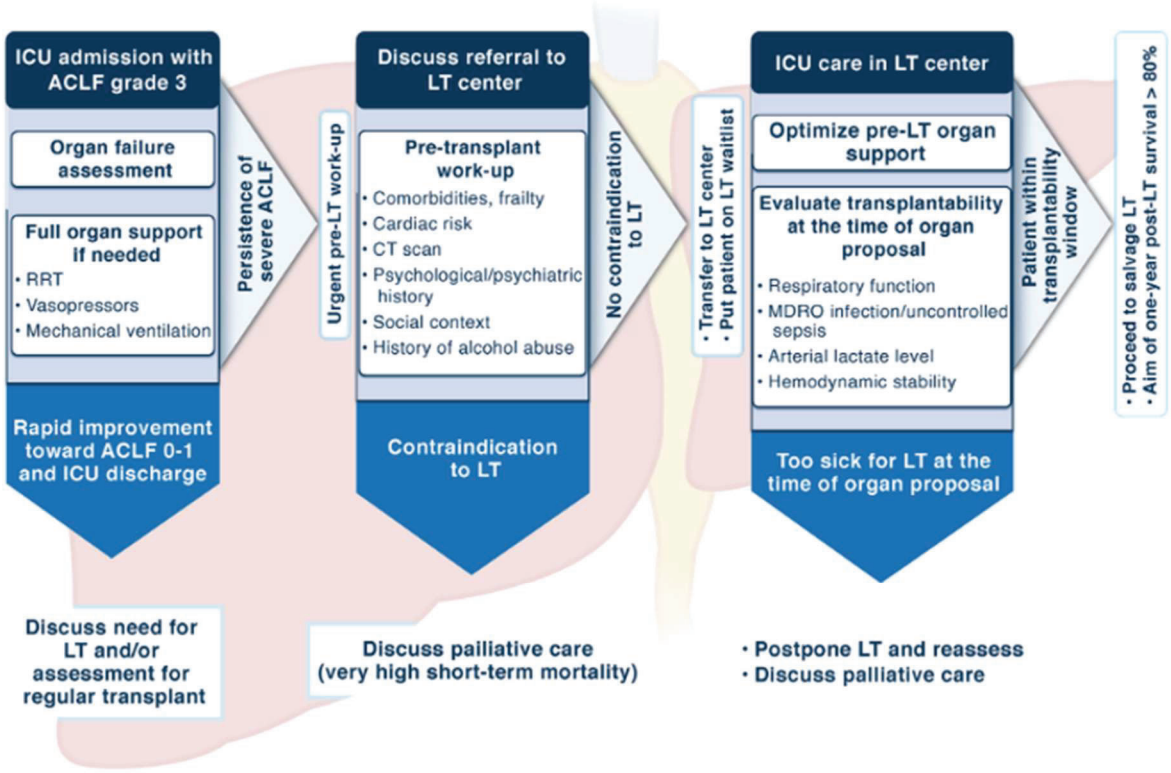
Thus, each and every individual decision to put a patient on an organ waitlist must take into consideration the utility of transplantation for that patient but also the collective utility of transplantation. Current one-year post-LT survival in the general population of transplanted patients is well above 80% (88% one-year survival and 75% five-year survival in France[2]). Advocating access to LT for patients with ACLF-3 can only be justified and acceptable if their post-LT survival approaches the survival rates of the general population of transplant candidates[3].

The aims of a transplantation program for patients with ACLF-3 are therefore twofold. First, to provide access to LT for the largest number of potential LT candidates. Second, to make sure that only the candidates with the highest transplant benefit will actually have access to LT. This requires having lenient ICU admission policies, relying on a network of peripheral ICUs that discuss referrals with transplant centers and, finally, being able to identify patients who are too sick to be transplanted at the time of organ proposal (18, **supplementary article 2, figure 3**)

[2] Agence de la Biomédecine, https://rams.agence-biomedecine.fr/greffe-hepatique-0, accessed January 2024

[3] A more precise formulation of this is that the benefit of transplantation (i.e. the difference in predicted survival of transplant candidates with and without transplant) of transplant candidates should be as close as possible

Figure 3. Schematic proposal for the management of patients with ACLF-3 (supplementary article 2)



Artzner, Intensive Care Medicine, 2023

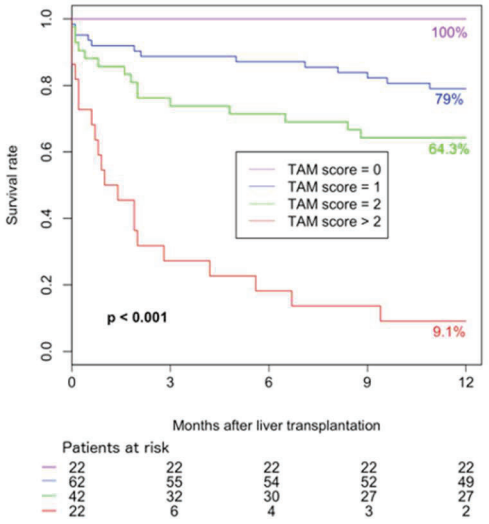
5. Stratifying the risk of post-LT mortality with pre-LT data

5.1. The transplantation for ACLF-3 model (TAM) score (supplementary article 3)

The first step to solve in the ethical et medical puzzle of LT for patients with ACLF-3 is to identify pre-LT factors of post-LT mortality in order to stratify post-LT utility and, ultimately, identify transplant candidates that can be deemed too sick to be transplanted. The TAM score was published in 2020 with precisely this in mind. It is derived from a training cohort (Strasbourg, N=76) and a validation cohort (Hôpital Beaujon in Clichy, Hôpital Henri Mondor in Créteil, Hôpital Trousseau in Tours and King's College Hospital in London, N=76) of patients with ACLF-3 at the time of LT (19). Four independent risk factors of post-LT were identified: high arterial lactate level, respiratory failure (defined by mechanical ventilation AND PaO_2/FiO_2 ratio< 200mmHg), low leukocyte count and recipient age. While patients with a low TAM score (<2) had a one-year post-LT survival >79%, patients with a high TAM score (>2) had unacceptably low post-LT survival (<10%) (**figure 4**).

Figure 4. The TAM score

TAM SCORE	Points
Arterial lactate level (mmol/l)	
<4	0
≥4	1
Mechanical ventilation with PaO_2/FiO_2 ratio ≤200mmHg	
No	0
Yes	1
Age (years)	
<53	0
≥53	1
Leukocyte counts (G/l)	
>10	0
≤10	1
TAM score	= Σ



Artzner, American Journal of Transplantation, 2020

The purpose of the TAM score is to be used at the bedside as a rule of thumb to stratify the risk of post-LT mortality and assist clinicians who have to decide whether or not to accept an organ proposal for a particular transplant candidate on the waiting list in the specific circumstances of the intensive care unit.

Importantly, this study also showed that the scores used to predict without transplant mortality in general (the MELD score) and in the context of ALCF-3 (the CLIF-OF and CLIF-C scores) are not useful to assess post-LT survival (note that they are not intended to do so).

5.2. TAM downstaging and the Strasbourg experience (article 1, 20)

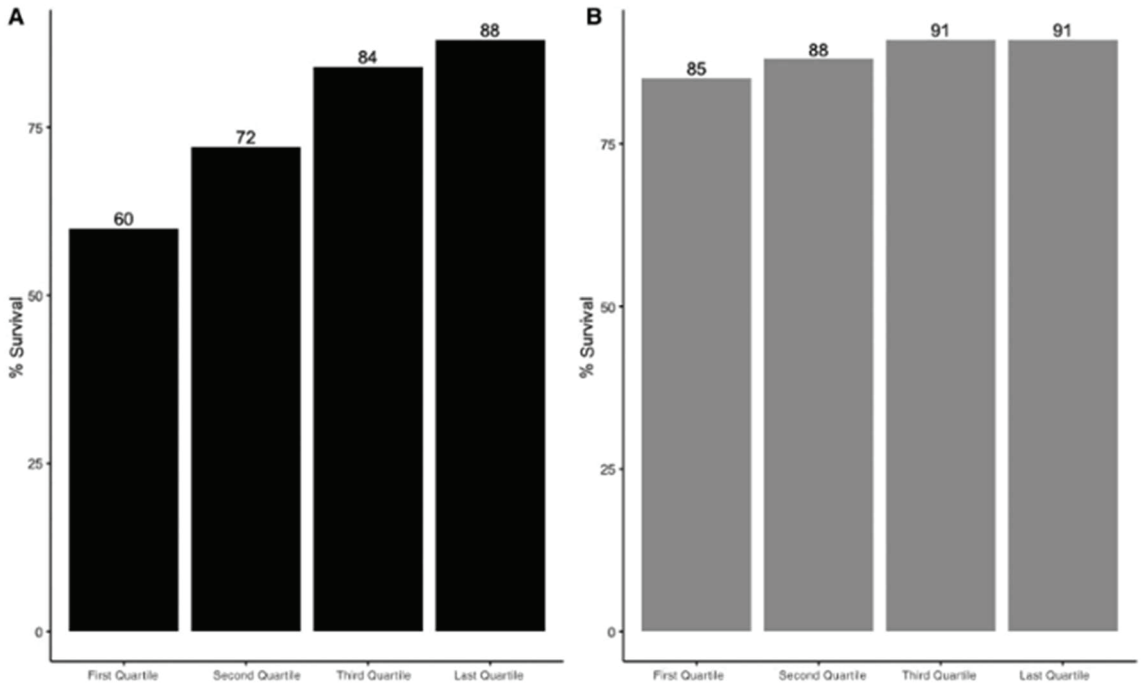
The next step consisted in clarifying the potential use of the TAM score and describing how increasing the number of LTs for patients with ACLF-3 can go hand in hand with increasing their post-LT survival.

The cohort of patients transplanted with ACLF-3 in Strasbourg remains to this day the largest single center granular cohort published in the literature. Over the 2007-2019 period, 102 patients were transplanted with ACLF-3. The analysis of this cohort shows that:

- One-year post-LT survival of ACLF-3 patients significantly improved over time (from 60% for the first quartile of patients to 88% for the last quartile of patients, p=0.02), thus bridging the survival gap between this population of transplant candidates and the general population of patients transplanted in Strasbourg (**figure 5**);
- The average number of LTs for patients with ACLF-3 performed per year increased over the study period (it tripled from the first to the last quartile: from 4.2 to 12.4 patients per year);
- The severity profile of patients was stable over time (both at the time of admission in the ICU and at the time of LT), apart from the proportion of patients transplanted with a TAM score>2, which decreased significantly over time;
- Patients whose clinical condition improved in the ICU (with a TAM score being downstaged between admission and LT) had significantly higher one-year post-LT survival rates compared to those whose TAM score stayed the same or increased: respectively 88% vs. 70% (p=0.04) (**figure 6**);
- The TAM score's predictive accuracy improved over the ICU stay and was highest at the time of LT.

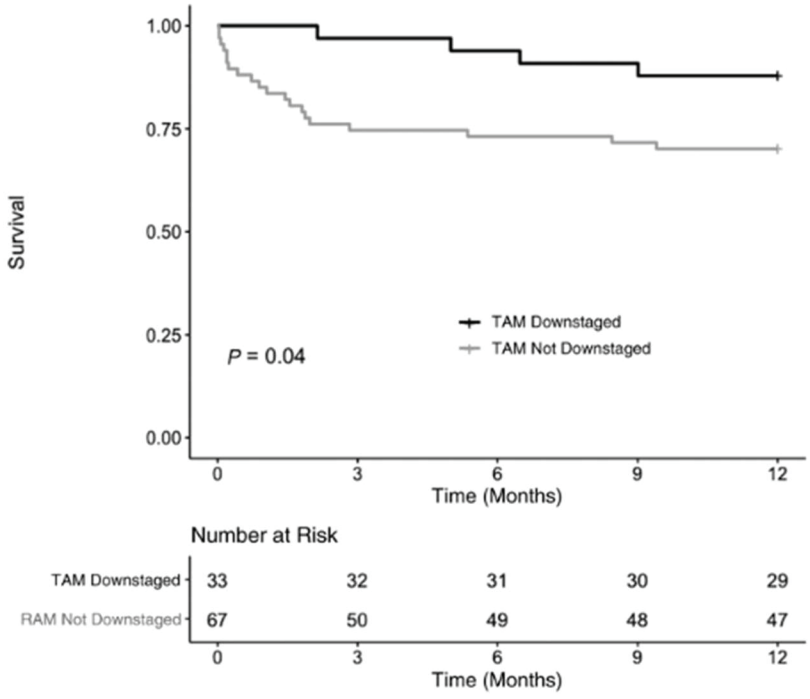
Importantly, these results are consistent with Vinay Sundaram et al.'s registry study that showed that ACLF patients' clinical course prior to LT had an effect on post-LT survival (21).

Figure 5: one-year post-LT survival rate across time for (A) patients with ACLF-3 and (B) patients without ACLF-3 in the Strasbourg cohort



Michard, Liver transplantation, 2022

Figure 6: Post-LT survival of patients whose TAM score decreased prior to LT (in black) compared to patients whose TAM score was stable or increased (in grey)



Michard, Liver transplantation, 2022

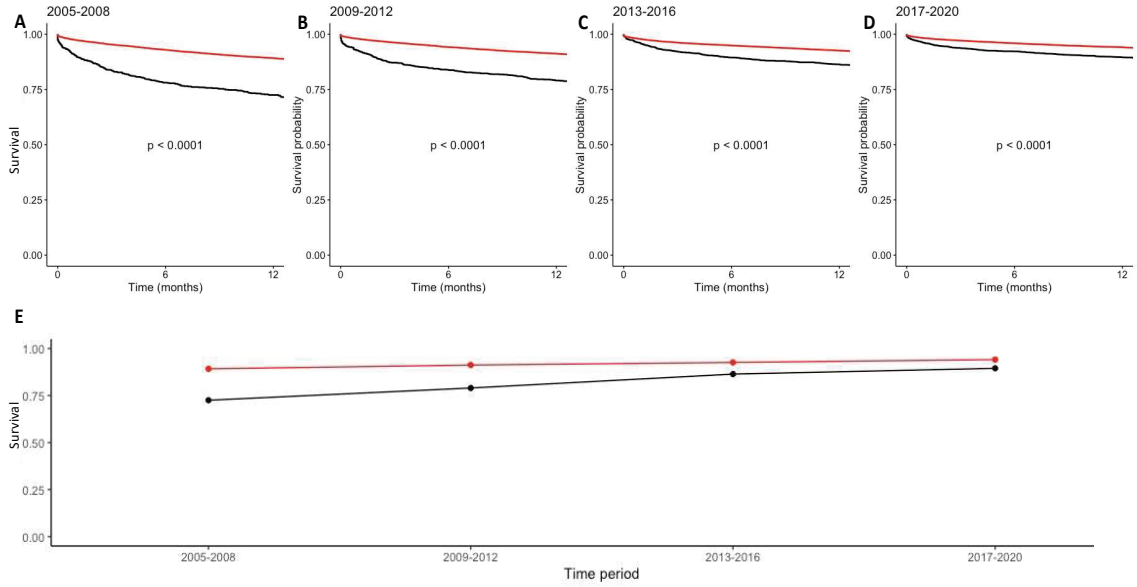
Taken together, these results have practical implications. First, they argue in favour of having lenient ICU admission policies for patients with severe ACLF for two reasons: first, because it is very difficult to predict post-LT survival at the time of ICU admission (rather than at the time of organ proposal); second, because pre-LT ICU management is precisely intended to improve the clinical condition of patients with severe ACLF prior to LT in order to maximise their post-LT survival rates. Second, this single center study describes a learning curve that advocates in favour comprehensive, multidisciplinary programs for LT dedicated to patients with severe ACLF in order to increase the number of LTs performed and improve post-LT survival.

5.3. Increase in the number of LTs performed and improvement of post-LT survival in the U.S. for criticall ill patients with cirrhosis (article 2, 22)

An analysis of the American United Network for Organ Sharing (UNOS) registry dovetails with the results from the Strasbourg single center analysis. Over the 2005-2020 period, the number and proportion of critically ill patients with cirrhosis who were transplanted increased: 819 (4.3%[4]) in 2005-2008 vs. 2,067 (7.9%[4]) in 2017-2020 p<0.001. Over the same period, there was a 17 percentage point increase in one-year post-LT survival: 72.5% in 2005-2008 vs. 89.5% in 2017-2020, p<0.001. The one-year post-LT survival gap between critically ill and non-critically ill patients with cirrhosis narrowed over the study period: 16.7 percentage points in 2005-2008 vs. 4.6 percentage points in 2017-2020 (**figure 7**). This is the first study that shows that the year of LT is independently associated with post-LT survival in the subgroup of critically ill patients with cirrhosis. lt also confirms that portal vein thrombosis (23), diabetes (24), recipient age and intubation (25) are associated with poorer post-LT prognosis in this subgroup of critically ill patients.

[4] This represents the percentage of critically ill patients transplanted over the total number of patients transplanted over the same period

Figure 7. Survival of non-critically ill patients with cirrhosis in red, survival of critically ill patients with cirrhosis in black



Artzner, American Journal of Gastroenterology, 2024

These results uphold the indication of liver transplantation for this subgroup of patients. But it adds a particular note of caution, since it shows that there is a significant gap in terms of survival compared to the general population of transplant candidates and that this gap can be quite large (as was the case in the 2005-2008 period).

5.4. The Sundaram ACLF-LT (SALT) mortality score (article 3, 25)

More recently, a large granular cohort of patients transplanted with ACLF-3 was collided across 15 LT centers in the U.S (N=284) (26). A utility score was derived from it: the SALT score, which was tested on a cohort of French patients transplanted with ACLF-3 (N=120).

This score relies on 5 clinically relevant pre-LT factors to predict post-LT mortality. It confirms that recipient age and respiratory failure[5] are key determinants of post-LT prognosis. It shows that body mass index (BMI) is associated with poorer prognosis in this subgroup of critically ill patients and confirms that diabetes is too (24). Circulatory failure is the fifth pre-LT factor of post-LT mortality.

Other independent risk factors of post-LT mortality have been identified in the literature, in particular infections with multi-drug resistant organisms (MDRO) (**supplementary article 4, 26)** and portal vein thrombosis (23). The overall clinical message that emerges from the TAM and SALT scores and from these two additionnel studies is that post-LT outcome is determined by the interaction between some of the recipient's baseline characteristics (e.g.: age, BMI, diabetes, portal vein thrombosis) and the precise ICU characteristics at the time of organ proposal (e.g.: respiratory and circulatory failure, MDRO infection, possibly leukocyte count). Importantly, hepato-renal characteristics of patients are not predictive of post-LT mortality in the subgroup of critically ill patients with cirrhosis[6].

Additional studies will doubtless identify additional factors associated with post-LT prognosis. Hopefully, some of these factors will be modifiable. In that respect, donor-associated factors, the use of machine perfusion, pre-LT microbial and fungal screening and prophylactic strategies, pre-LT artificial liver support and post-LT immunosuppressive strategies all offer countless perspectives for future studies in the context of LT for patients with ACLF-3 that will help optimize the management of these patients and their post-LT survival. But, before these detailed issues can be elucidated, a far more strategic point needs to be adressed. Namely, the effective access to LT for patients with severe ACLF.

[5] Using the EASL-Clif definition of respiratory failure

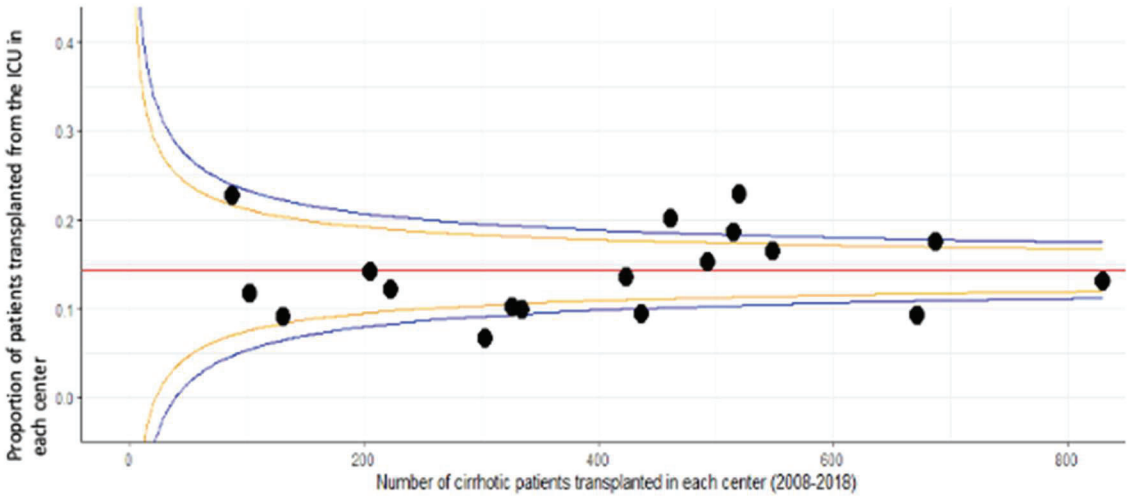
[6] This is not the case in the general population of transplant candidates for whom the MELD score is associated with post-LT mortality (and kidney failure is clearly associated with poorer post-LT prognosis)

6. Epidemiology and the issue of access to LT for patients with ACLF-3 (article 4, 27)

The second part of this dissertation is concerned with the effective access to liver transplantation for critically ill patients with cirrhosis (28).

While there is growing evidence that LT is the most effective treatment for ACLF-3 and growing theoretical consensus in favour of it (29), whether and how this evidence and consensus translate into clinical practice remains unclear. A large study stemming from a collaboration between the European Liver and Intestine Transplant Association (ELITA) and EF Clif was able to collide data from 20 liver transplant centers across 8 European countries over a period of 18 months. Data concerning ICU admissions, listing, transplantation and survival were collected. One of the key results of this study is that the number and proportion of LTs performed for patients with ACLF-3 by centers varied markedly across Europe (from 0 to 29% of patients transplanted with decompensated cirrhosis were transplanted with ACLF-3 across the 20 centers). This confirms the results of a study done in France with a slightly different methodology (using funnel plots and a different definition of critically ill patients with cirrhosis) that also showed that LT activity for critically ill patients with cirrhosis varied significantly across the 20 French LT centers (**figure 8**, **supplementary article 5, 23**).

Figure 8: Funnel plot of the proportion of patients transplanted from the ICU across the 20 French transplant centers



Artzner, Clin Res Hepatol Gastroenterol., 2021

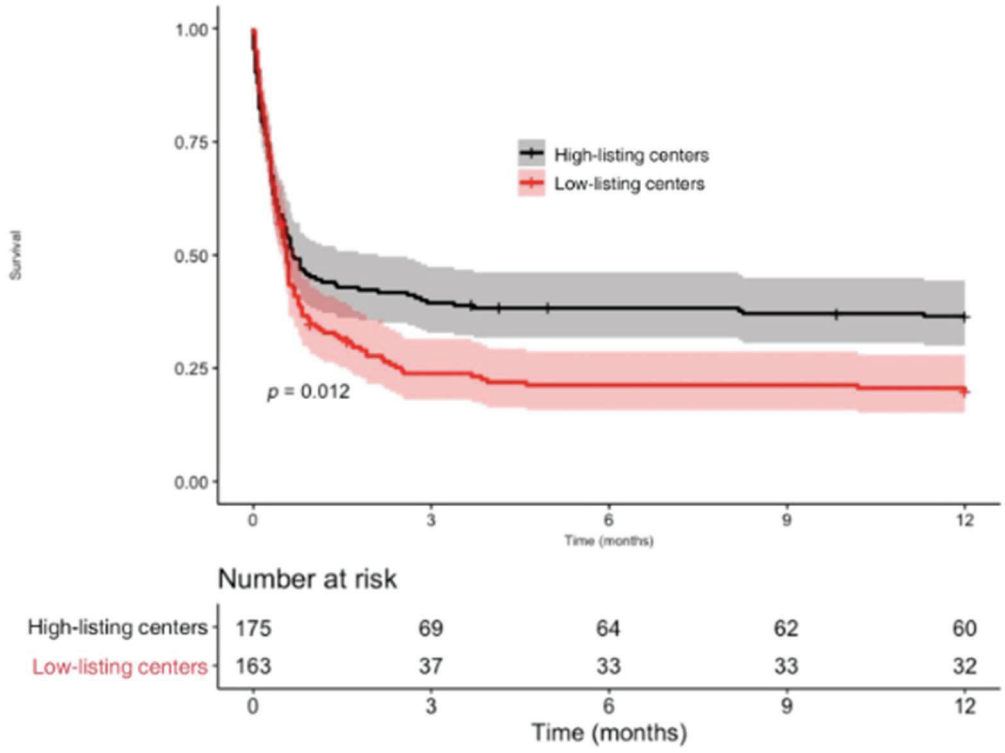
Interestingly, the ELITA-EF Clif European study found no correlation between the number of ICU admissions and LT activity for ACLF-3 patients across centers. By contrast, the correlation between the number of patients listed with ACLF-3 and the number of patients transplanted with ACLF-3 was very strong (correlation coefficient of 0.8, $p<0.001$). In addition, the majority (66%) of patients transplanted with ACLF-3 were also listed with ACLF-3. In other words, from an epidemiological point of view, LT activity for patients with ACLF-3 generally concerns patients *who have not been listed prior to developing ACLF-3* (only 14% of patients transplanted with ACLF-3 had been listed prior to developing ACLF). Finally, among the patients listed with ACLF-3, the vast majority (79%) ended up being transplanted.

Taken together, these observations lead to several non-trivial conclusions with practical implications:

- Lenient admission policies are a necessary but not a sufficient condition for providing access to liver transplantation for patients with ACLF-3;
- In general, transplanting patients with ACLF-3 requires putting them on the waiting list while they have ACLF-3 in the ICU (i.e.: they are not patients who are followed by a transplant center prior to developing ACLF-3);
- The source of inequity in access to LT does not lie in the difficulty to find organs for patients listed with ACLF-3 but in the inclination/ability of transplant centers to put patients on the transplant waiting list in the ICU.

The bottom line of this study is that access to LT varies widely across European centers, leading to inequity of access to a life-saving treatment. Whether a critically ill patient with cirrhosis without formal contraindications to LT will die or not therefore largely depends on the place of residence of the patient and the attitude of the LT center where the patient is taken care of. In fact, this European study shows that the overall survival of patients with ACLF-3 was higher in the 4 centers that had the highest number of patients who were listed/transplanted than in the other centers (respectively 36% vs 20%, $p = 0.012$, **figure 9**).

Figure 9: Survival analysis of ACLF-3 patients depending on the type of center (high listing/transplanting vs. low listing/transplanting)



Artzner, Liver Transplant., 2022

In addition, this study illustrates how the key clinical step that hinders access to LT is the capacity of listing patients while they are in the ICU. This is consistent with the fact that conducting a full pre-LT work-up in the ICU for a previously unlisted patient requires a particular effort and expertise involving a seasoned multidisciplinary team. Indeed, the work-up for these patients is typically more complex than for patients with ALF, who generally have fewer comorbidities and no history of addiction. This study therefore underlines how listing strategies for patients with ACLF-3 influence their access to LT and, ultimately, their survival.

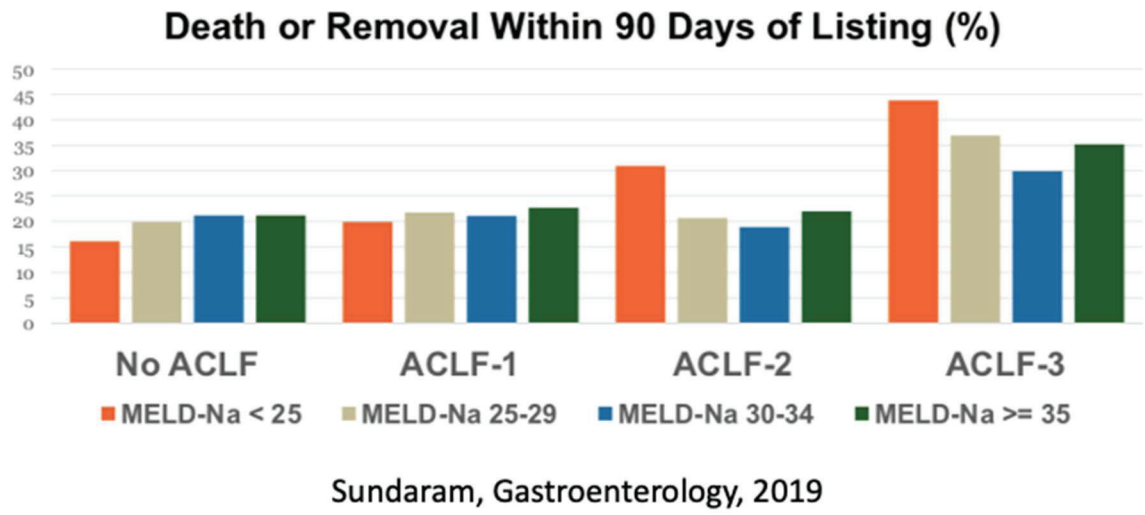
7. Future perspectives: how to improve the survival of critically ill patients with cirrhosis?

7.1. Allocation in the age of the algorithm: should we change our allocations algorithms?

7.1.1. Prioritizing critically ill patients with cirrhosis

The first issue concerns the potential prioritization patients with ACLF-3 beyond the MELD score in order to give them access to LT more rapidly. Such a pilot scheme has recently been implemented in the United Kingdom. A couple of studies based on the United Network for Organ Sharing (UNOS) registry have strongly argued in favor of this idea on the basis that patients with ACLF-3 have a particularly high waitlist mortality (27,28, **figure 10**). These studies highlight the fact that, among patients with identical MELD scores, patients with extra hepato-renal failures have higher mortality rates. Thus, they underline the limits of the MELD score's predictive value in terms of mortality for transplant candidates with ACLF.

Figure 10. Data from the UNOS registry



However, generalizing the prioritization of transplant candidates with ACLF may be problematic for several reasons:

- It could lead to prioritizing patients who are too sick to be transplanted, thus funneling scare resources to patients with the poorest post-LT prognosis and decreasing the overall utility of LT;

- Among patients with low MELD scores and high grades of ACLF (a rare situation in clinical practice), this could lead to selecting potentially unsuited candidates to LT (patients who are “sicker than their liver” – e.g. patients with compensated cirrhosis and severe pulmonary infections);
- One of the key principles guiding allocation algorithms is not only to optimize post-LT survival, but also to minimize pre-LT mortality. In terms of fairness, this can be formulated as the idea that all categories of transplant candidates should have similar access (but also therefore lack of access) to an organ. The ELITA-EF Clif study reports a waitlist mortality of 21% among patients with ALCF-3 (28). This is not necessarily unacceptably high for two reasons. First, because it is (unfortunately) fair that some transplant candidates with ACLF-3 should end up not having access to an organ – just like other transplant candidates with other indications of LT (cf. section 4.2.). Second, because we expect some transplant candidates with ACLF-3 to not have access to an organ because the transplant team ultimately decides that they are too sick to be transplanted (it therefore seems reasonable to assume that the waitlist mortality should be slightly higher for ACLF candidates than for other categories of patients). Aiming for a transplant rate of 100% among transplant candidates with ACLF-3 would therefore be both unfair from an ethical point of view and unsound from a clinical point of view;
- One of the key results of the ELITA-EF Clif study is that difficulties of access to LT are largely driven by difficulties of *access to the waiting list* when patients are in the ICU (28).

Another significant issue is that both the prevalence of severe ACLF and the potential number of transplant candidates with severe ACLF is completely unknown in France and elsewhere. In fact, the exact percetange of patients transplanted with ACLF-3 is not known in general or in any particular country since transplant registry studies only provide proxies for categorizing patients with ACLF-3 (32). In France, among patients transplanted with cirrhosis between 2008 and 2018, 9.4% were transplanted from the ICU, according the French transplant registry (18, **supplementary article 5**). In the U.S., the percentage of patients with cirrhosis transplanted in the ICU with at least one extra hepatic organ failure between 2005 and 2020 was 6.8% according to the UNOS registry (**article 2**). Among the 20 European centers included in the

epidemiological paper of this dissertation, the percetange of patients transplanted with ACLF-3 was 3.7%, but this percentage varied considerably across centers (**article 4,** 27). As a whole, there is both great variability and great uncertainty in the place that severe ACLF currently has in LT and even greater uncertainty in the place that it could have in the future.

In the end, the studies presented in this dissertation are not intended to offer a direct answer to the issue of prioritizing patients with ACLF-3 but they do provide some indirect insight into this complex and hotly debated issue (33–37). More definitive answers will undoubtably require a high degree of nuance. They will have to take into account both the epidemiology of potential LT candidates with ACLF-3 (which is to this day completely unknown) and the epidemiology of potential LT candidates without ACLF-3, but also organ donation rates that vary across regions and countries[7].

7.1.2. Implementing a utility filter in allocation algorithms

Over the past 20 years, solid organ allografts have increasingly been allocated using centralized algorithms that designate a specific ("named") recipient instead of leaving the decision to transplant centers. The driving principle of these algorithms is that the sickest patients should be transplanted first in order to reduce dropout rates due to disease progression or death. They rely on models that predict survival without transplantation (using variations of the MELD score in the case of LT). However, the decision to remove patients from the transplant list and/or to turn down an organ when a patient is deemed too sick to be transplanted is generally left to individual transplant teams. While transplant regulatory agencies are equipped with various benchmarking methods to monitor transplant activity, pre-LT dropout rates and post-LT results, the absence of formal upper limits to how sick an individual transplant candidate can be and still have access to an organ has, understandably, led to serious concern within the transplant community. Indeed, "sickest first" allocation systems can potentially lead to prioritizing patients who are too sick to be transplanted and funnelling scare resources to patients with particularly poor post-transplant prognosis, thus reducing the overall utility of transplant programs.

[7] Organ donation rates for livers vary from less than 5 per million (Romania, Greece) to more than 45 per million (Spain) across Europe (38)

Over the years, a number of utility scores have been developed and implemented within allocation algorithms. They have taken two forms. First, “utility filters”: when the estimated post-transplant survival is below a certain threshold, the transplant candidate becomes ineligible to receive an organ (this is the case, for example, in the heart transplant allocation algorithm in France (39)). Second, benefit scores, which aim at maximising the difference in predicted survival of transplant candidates with and without transplant (this is the case for the transplant benefit score used by the National Health Service in the United Kingdom to allocate liver allografts (40) or in the U.S. to allocate lung allografts (41,42)).

The transplant benefit score used in the UK to allocate livers takes into account 21 recipient-associated parameters and 7 donor-associated parameters. Interestingly, none of the parameters included in the transplant benefit score are ICU-specific risk factors that have been associated with poor post-LT survival for the subgroup of ACLF-3 patients (e.g.: arterial lactate, vasopressors, PaO_2/FiO_2, pre-LT MDRO infection, portal vein thrombosis). In theory, there is probably enough evidence to argue in favour of including some of these factors into allocation algorithms (although their weigth and precise cut-off points should be clarified). In practice, however, there are several foreseeable obstacles to inputing these variables into an allocation algorithm:

- It would require entering parameters several times a day (hemodynamic and respiratory functions can change rapidly and are typically monitored repeatedly in the ICU);
- It would ideally take into account the dynamic evolution of these parameters over time;
- Some of these variables typically vary according to ICU management strategies (e.g.: PaO_2/FiO_2 varies with ventilator settings, fluid management; use of vasopressors depends on fluid management, blood pressure targets and sedation levels).

Hence, while both the TAM score and the SALT score offer insight into some of the risk factors that need to be taken into account when making the decision to accept an organ or not, it does not seem advisable to include these parameters into allocation algorithms. For the time

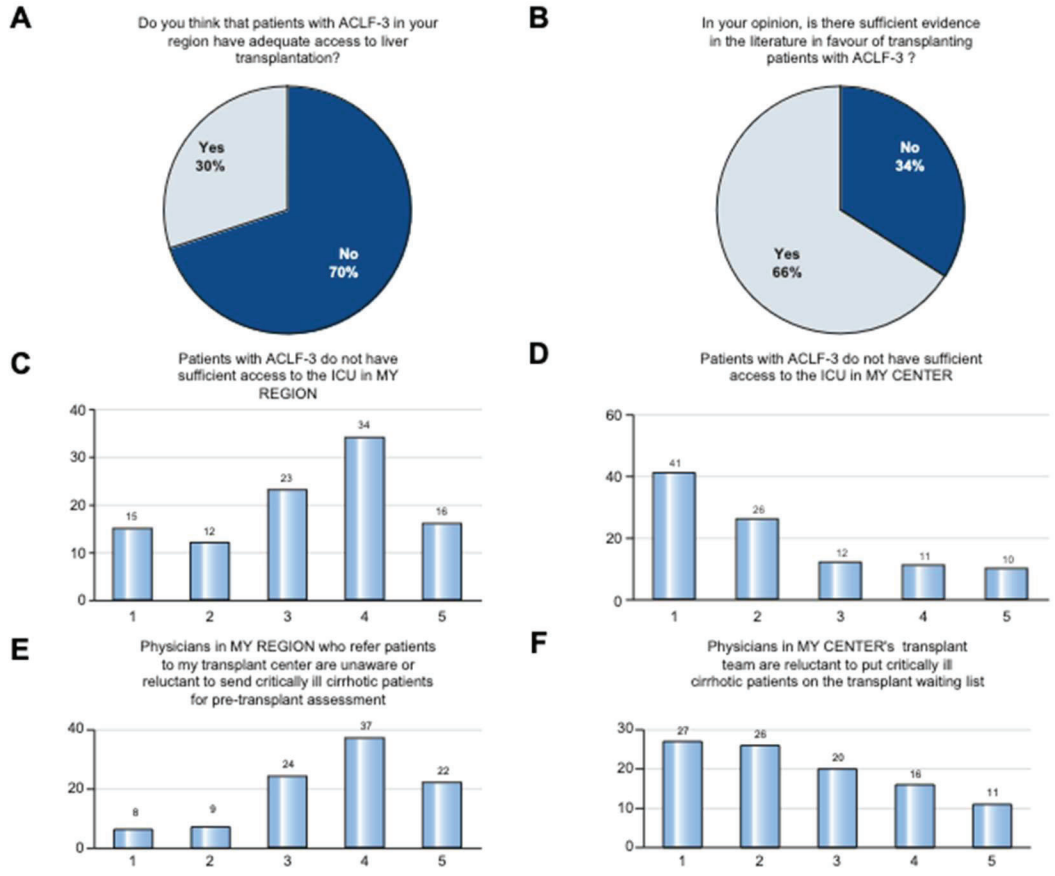
being, the responsibility of declining an organ and abstaining from free-riding the allocation system therefore lies in the hands in individual transplant teams and physicians.

7.2. Going back to the bedside, and beyond (article 5, 36)

This dissertation offers an original perspective on ways to improve the prognosis of critically ill patients with cirrhosis. It shows that, while LT is a life-saving treatment for ACLF-3 patients, actual access to this treatment depends on where patients live. A qualitative survey was organized to further our understanding of the obstacles to LT that these patients face (43). A total of 100 LT clinicians from 26 countries answered the survey.

The majority of respondents (66%) agreed that there was enough evidence in the literature to support transplanting patients with ACLF-3. Yet, 70% declared that patients with ACLF-3 did not have adequate access to LT in their region. Difficulties in access to regional ICUs for critically ill patients with cirrhosis and unawareness or reluctance of physicians in regional centers to consider pre-LT assessment for these patients were considered to be major obstacles to increasing access to LT for critically ill patients with cirrhosis (**figure 11**).

Figure 11: Results from a qualitative survey (scale from 1 "do not agree at all" to 5 "strongly agree")



This simple survey shows that it is fundamental to convince colleagues in transplant centers but also outside transplant centers that critically ill patients with cirrhosis should be considered for ICU admission, referral to a tertiary LT center and pre-transplant work-up for potential listing.

Advocating for access to LT for critically ill patients with cirrhosis is a medical undertaking different in nature and broader in scope from providing greater access to a particular drug, intensive care support technique or surgical procedure. It requires widespread debate, education and the promotion of referral networks for these patients. It also requires putting clinical medicine at the heart of this public health project. Indeed, the final decision to initiate a pre-LT work-up and to move ahead with a life-saving LT often relies on the initial evaluation of the patient's medical history (especially in the context of alcohol-related liver disease). In that respect, the hegemony of biomarkers and the urge to produce (often complex) predictive scores that dominate academic medical research should, in my opinion, be reviewed critically. Academic medical research can all too easily overshadow the importance of careful anamnesis by medical professionals who take care of these patients both at academic and non academic medical centers. Yet, in practice, it is this bedside craft and the decisions that follow from it that will lead to refering patients to the ICU and to transplant centers and, ultimately, to the improvement in the survival of critically ill patients with cirrhosis.

7.3. Conclusion

The issue of liver transplantation for critically ill patients with cirrhosis is a fascinating medical and ethical puzzle. While it concerns a relatively small proportion of transplant candidates (and an even smaller proportion of ICU patients), its potential benefit for individual patients is tremendous. It also constitutes a particular medical challenge. Indeed, a radically effective treatment exists. What lies ahead of the transplant and the ICU community is building more effective referral networks, persuading colleagues that LT is the best treatment for these patients, educating young clinicians to recognize potential candidates for liver transplantation in the ICU and promoting collaborations and debate between medical specialities that are all too often fragmented.

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ARTICLE 1

Pretransplant Intensive Care Unit Management and Selection of Grade 3 Acute-on-Chronic Liver Failure Transplant Candidates

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The aim of this study is to report on the liver transplantation (LT) activity and posttransplant outcome, over time, of patients with grade 3 acute-on-chronic liver failure (ACLF-3) in a single transplant center performing a large number of LTs for patients with ACLF-3. It aims at showing how pre-LT intensive care unit (ICU) management impacts post-LT outcomes, in particular through monitoring the transplantation for ACLF-3 model (TAM) score. A total of 100 patients who had ACLF-3 at the time of LT between 2007 and 2019 were included retrospectively. The cohort was divided in 2 periods, with 50 patients in each period. There was an increase in the number of patients with ACLF-3 who received an LT during the course of the study period and significantly higher 1-year post-LT survival rates in the second period compared with the first period (86% versus 66%, respectively; $P = 0.02$). Interestingly, patients during both periods had similar severity profiles and scores apart from a significantly lower number of patients with TAM scores >2 at the time of LT in the second period compared with the first period (1 [2%] versus 11 [22%], respectively; $P \leq 0.01$). In addition, patients whose clinical condition improved in the ICU (with a TAM score downstaged between admission and LT) had significantly higher post-LT survival rates than those whose TAM score stayed the same or increased: 88% versus 70%, respectively ($P = 0.04$). This study shows a learning curve in LT for patients with ACLF-3, with optimized ICU management and patient selection leading to increased numbers of LTs for patients with ACLF-3 and improved post-LT outcomes. It also delineates how the TAM score can be used to identify the optimal transplantability window for patients with ACLF-3.

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Patients with grade 3 acute-on-chronic liver failure (ACLF-3) constitute a frontier in liver transplantation (LT). Optimizing post-LT outcomes for patients who are critically ill with cirrhosis relies on a multidisciplinary approach involving specialized intensivists, transplant surgeons, and hepatologists as well as anesthesiologists. A number of studies have shown that LT is the only truly effective treatment for patients with cirrhosis and multiple organ failures, and it is clear that it is nearly always in their individual interest to have access to LT.[1-8] In contrast, identifying patients with ACLF-3 who are too sick to receive an LT (in the light of collective utility) and finding the optimal window of transplantability remains a challenge for clinicians.[9]

The aim of this study is to describe the experience and results of a single transplant center with high-volume ACLF-3 transplant activity during a 13-year time period. It also aims at delineating the way in

Abbreviations: ACLF, acute-on-chronic liver failure; ACLF-3, grade 3 acute-on-chronic liver failure; BMI, body mass index; CLIF-C, Chronic Liver Failure Consortium; CLIF-OF, Chronic Liver Failure–Organ Failure; HCV, hepatitis C virus; ICU, intensive care unit; IQR, interquartile range; LT, liver transplantation; NASH, nonalcoholic steatohepatitis; SOFA, Sequential Organ Failure Assessment; TAM, transplantation for ACLF-3 model; UNOS, United Network for Organ Sharing.

which the transplantation for ACLF-3 model (TAM) score can be used to identify the transplantability window of patients who are critically ill with cirrhosis and how the pre-LT clinical course of patients in the ICU affects post-LT outcomes. This dynamic approach to the issue of LT for patients who are critically ill with cirrhosis can be assessed by the evolution of the TAM score during hospitalization. This article studies how TAM score downstaging can affect post-LT outcomes.

The TAM score, which was recently published,[10,11] was specifically designed to identify patients with ACLF-3 with particularly poor post-LT prognosis to help clinicians decide whether a patient who is critically ill with cirrhosis is too sick to receive a transplant at the time of organ proposal. The TAM score was derived from the analysis of the largest multicenter granular cohort of patients with ACLF-3 who received a transplant published so far. This simple score is based on the following 4 categorical pretransplant variables (1 or 0 points): age ≥53 years, arterial lactate ≥4 mmol/L, mechanical ventilation with partial pressure of arterial oxygen/fraction of inspired oxygen (PaO_2/FiO_2) ≤200 mm Hg, and white blood cell count of ≤10 G/L (Supporting Fig. 1). A calculator is available online (http://www.chru-strasbourg.fr/Transplantation-ACLF-3-patients-Model-TAM-score).

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Baptiste Michard, Thierry Artzner, and François Faitot participated in the study concept and design; acquisition of data, analysis, and interpretation of data; manuscript drafting; and statistical analysis. Baptiste Michard, Thierry Artzner, Mathilde Deridder, Camille Besch, Pietro Addeo, Vincent Castelain, Max Guillot, Marie-Line Harlay, Jean-Etienne Herbrecht, Ralf Janssen Langenstein, Maleka Schenck, Philippe Bachellier, Francis Schneider, and François Faitot participated in manuscript revision and approval of the final version of the article.

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Potential conflict of interest: Nothing to report.

Patients and Methods

STUDY POPULATION

Consecutive adult patients from the Strasbourg (France) LT center with ACLF-3 at the time of LT between January 1, 2007, and December 31, 2019, were retrospectively included, thus extending the initial cohort published recently.[10] The criteria used to define ACLF-3 were based on the European Association for the Study of the Liver–Chronic Liver Failure Consortium (CLIF-C) definition.[12]

Exclusion criteria were as follows: 1 multivisceral transplantation, 2 retransplantations, and 3 LTs for acute liver failure. Patients with missing variables to compute the TAM score were also excluded.

Prognostic scores (SOFA, CLIF-C-SOFA, CLIF-C-OF and CLIF-C-ACLF) were calculated according to the published formula, and organ failures (liver, kidney, coagulation, brain, respiratory, and circulatory) were defined according to the CLIF-C–OF system.[12,13]

The various clinical and biological constituents of the CLIF-C–OF system as well as additional laboratory data were recorded at the following 4 points in time: on ICU admission, immediately prior to LT, 2 days after ICU admission, and 2 days prior to LT (for patients who received LT less than 4 days after being admitted to the ICU, intermediary time points closer to ICU admission and LT were used). The primary outcome was 1-year post-LT survival.

Data were collected in accordance with the General Data Protection Regulation and the European Union legislation. All procedures were followed in accordance with the guidelines established in Strengthening the Reporting of Observational Studies in Epidemiology.

STATISTICAL ANALYSIS

Continuous variables are presented as mean ± standard deviation and were compared using the Student *t* test or presented as median with interquartile range (IQR) and were compared with the Mann-Whitney U test as appropriate. Qualitative variables are presented as numbers and percentages and were compared using the χ^2 test or Fisher's exact test as appropriate. Survival probabilities were computed using the Kaplan-Meier curve method and compared with the log-rank test. All analyses were

performed using the R statistical software version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

NUMBER OF PATIENTS INCLUDED AND POST-LT SURVIVAL DURING THE STUDY PERIOD

There were 924 single-organ LTs performed for the first time during the study period; 102 of the patients had ACLF-3 at the time of transplant. A total of 2 patients with ACLF-3 were excluded from the analysis because data were not available to compute their TAM scores. There were no missing data for the 1-year follow-up.

In this section of the study, the cohort was divided into 4 consecutive periods with the same number of patients in each period (25 patients with ACLF-3 in each quarter) to study the evolution over time of the number and the outcome of patients with ACLF-3 who received a transplant. The number of patients with ACLF-3 who received LTs increased during the study period. Indeed, the average number of LTs for ACLF-3 per year from the first quarter to the last tripled during the study period: 4.2 (January 1, 2007, to December 10, 2012), 9.6 (December 11, 2012, to July 17, 2015), 10.2 (July 18, 2015, to December 28, 2017), and 12.4 (December 29, 2017, to December 31, 2019).

The 1-year post-LT survival rate also increased steadily from the first quarter to the last: 60%, 72%, 84%, and 88% (Fig. 1A). These results therefore show both a significant and important increase in the number and survival rate of patients who had access to LT with ACLF-3 at the time of LT in our center.

In contrast, the activity of the center for patients without ACLF-3 was more stable across all quarters (note that the quarter time limits were defined by ACLF-3 LT activity) both in terms of transplant activity (average numbers of LTs for patients without ACLF-3 per year from the first quarter to the last: 61.9, 63.5, 64.0, 65.6) and in terms of posttransplant outcomes (1-year survival rates from the first quarter to the last: 85%, 88%, 91%, 91%; Fig. 1B).

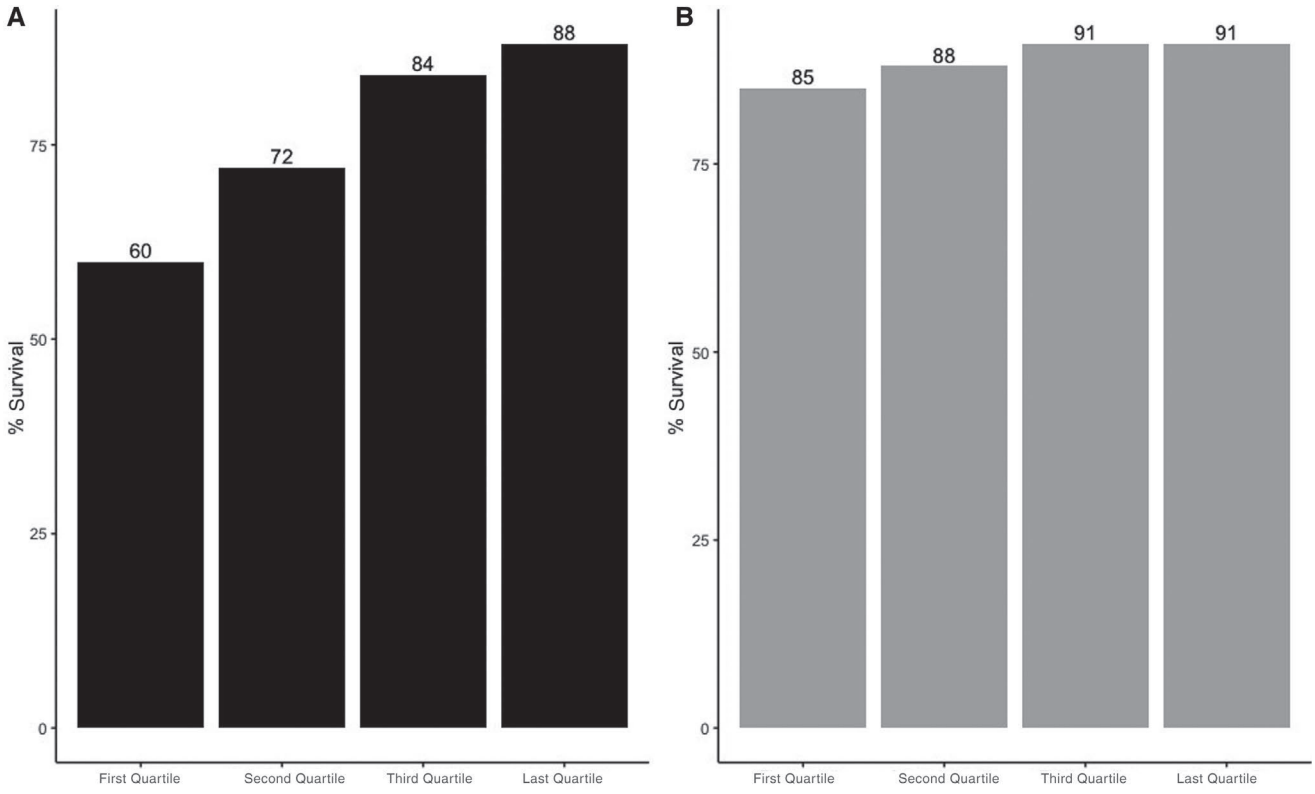

FIG. 1. The 1-year posttransplant survival rate across time for (A) patients with ACLF-3 and (B) patients without ACLF-3.

POPULATION CHARACTERISTICS ACROSS TIME

In this section of the study, the cohort was divided into 2 consecutive periods with the same number of patients in each period (50 patients with ACLF-3 in each half) to compare the patients' characteristics over time (Table 1). The first period extends from January 1, 2007, to July 17, 2015, and the second period extends from July 18, 2015, to December 31, 2019. The number of 1-year post-LT survivors was significantly higher in the second period than in the first period: 43 (86%) versus 33 (66%), respectively ($P = 0.02$). The baseline characteristics of the patients between the 2 periods were very similar in terms of age, sex, and etiology of cirrhosis. The CLIF-C–acute-on-chronic liver failure (ACLF) score on admission was higher in the second period than in the first (68 [IQR, 60-73] versus 62 [IQR, 56-68], respectively; $P = 0.03$). At the time of LT, the number of patients treated with vasopressors was lower in the second period than in the first (32 [64%] versus 43 [86%], respectively; $P = 0.01$), the median arterial lactate level was also lower (1.80 [IQR, 1.30-2.60] versus 2.85 [IQR, 2.0-4.42], respectively; $P < 0.01$), and there was a large and significant difference in the number of patients with an unfavorable TAM score (>2) between the second period and the first period: 1 (2%) versus 11 (22%), respectively ($P < 0.01$). Other markers of critical illness (mechanical ventilation, dialysis, norepinephrine dose, and the SOFA and the CLIF-C scores) were not significantly different between the 2 periods.

In the first period, the proportion of patients listed with ACLF-3 was 5%, and in the second period it was 8%. The proportion of patients with ACLF-3 who received an LT was 9% in the first period and 17% in the second period. It is noteworthy that the increase in the proportion of patients listed (and who received a transplant) with ACLF-3 during the study period did not have an impact on the mortality/dropout rate on the center's waiting list: during the first period, 75 patients (10%) died while on the waiting list or were delisted, and during the second period, 45 patients (9%) died while on the waiting list or were delisted.

USING THE TAM SCORE TO SELECT PATIENTS AT LT

The post-LT survival rate decreased significantly as the TAM score at the time of LT increased, from 100% and 90% survival for patients with TAM scores of 0 (n = 15) and 1 (n = 42), respectively, to 10% and 0% for patients with TAM scores of 3 (n = 10) and 4 (n = 2), respectively (Fig. 2). Patients with a TAM score of 2 had an intermediate 1-year post-LT survival rate of 71%.

POST-LT SURVIVAL DEPENDS ON PATIENTS' CHARACTERISTICS AT THE TIME OF LT

The predictive power of the TAM score increased as patients who were critically ill with cirrhosis were closer to the time of LT (Fig. 3). In particular, the TAM score at the time of admission in the ICU did not discriminate post-LT survivors from post-LT nonsurvivors (1-year post-LT survival rate for patients with TAM scores 0-2 at the time of ICU admission versus TAM scores >2 at the time of ICU admission: 76% versus 75%, respectively; $P = 0.99$). The TAM score applied 2 days after ICU admission was not discriminatory either. It reached significance 2 days prior to LT and was most predictive immediately prior to LT (at the time of organ proposal), with significantly higher survival rates for patients with TAM scores 0 to 2 versus TAM scores >2: 85% versus 8%, respectively ($P < 0.01$).

EFFECT OF TAM SCORE DOWNSTAGING ON POST-LT SURVIVAL

The TAM scores of 33 patients decreased between ICU admission and the time of LT (ie, TAM downstaged), whereas the TAM scores of 67 patients either stayed the same or increased (ie, TAM not downstaged). The patients whose TAM scores were downstaged had significantly higher survival rates than the patients whose TAM scores were not downstaged: 88% versus 70%, respectively ($P = 0.04$; Fig. 4).

In the specific population (n = 31) of patients with a TAM score of 2 at LT (who had a post-LT survival of 71%), the patients whose TAM scores were downstaged (n = 9) had a tendency of having higher post-LT survival rates than the patients whose TAM scores were not downstaged (n = 22): 89% versus 64%, respectively ($P = 0.16$; Fig. 5).

Discussion

The transplant community has shown great interest in extending the indication of LT to patients with

TABLE 1. Comparison of Patients With ACLF-3 Who Received LTs in the First and Second Periods

Patients' Characteristics	First Period, n = 50*	Second Period, n = 50†	*P* Value
Demographics			
Age, years	54 (49-60)	56 (51-63)	0.31
Female sex	15 (30)	15 (30)	1
BMI (kg/m^2)	25 (23-31)	26 (22-30)	0.75
Etiology of cirrhosis‡			
Alcohol-related cirrhosis	30 (60)	35 (70)	0.29
Hepatitis B virus	3 (6)	1 (2)	0.62
Hepatitis C virus	9 (18)	3 (6)	0.12
NASH	2 (4)	10 (20)	0.03
Autoimmune hepatitis	4 (8)	1 (2)	0.36
Biliary	4 (8)	2 (4)	0.68
Other	3 (6)	6 (12)	0.49
Precipitant factor of ACLF			
Sepsis	24 (48)	25 (50)	0.84
Sepsis with positive bacterial blood cultures	12 (24)	10 (20)	0.63
Gastrointestinal bleeding	20 (40)	19 (38)	0.84
Nongastrointestinal bleeding	5 (10)	9 (18)	0.25
Alcoholic hepatitis	6 (12)	8 (16)	0.56
Hepatocellular carcinoma	0 (0)	3 (6.0)	0.24
Data on admission in ICU			
Mechanical ventilation	32 (64)	30 (60)	0.68
Dialysis	37 (74)	42 (84)	0.22
Vasopressors	37 (74)	36 (72)	0.82
Norepinephrine dose, μg/kg/minute	0.15 (0.01-0.34)	0.12 (0.00-0.38)	1
Arterial lactate, mmol/L	2.70 (1.92-3.70)	2.60 (1.92-4.00)	1
Number of organ failures >4	12 (24)	17 (34)	0.27
SOFA score	14 (13-16)	16 (12-19)	0.19
CLIF-C–SOFA score	16 (15-19)	18 (15-20)	0.08
CLIF-C–OF score	14 (13-16)	15 (13-17)	0.15
CLIF-C–ACLF score	62 (56-68)	68 (60-73)	0.03
TAM score >2	8 (16)	12 (24)	0.32
Data at the time of transplant			
Mechanical ventilation	42 (84)	39 (78)	0.44
Dialysis	43 (86)	45 (90)	0.54
Vasopressors	43 (86)	32 (64)	0.01
Norepinephrine dose, μg/kg/minute	0.20 (0.07-0.46)	0.16 (0.00-0.46)	0.26
Arterial lactate, mmol/L	2.85 (2.00-4.42)	1.80 (1.30-2.60)	<0.01
Number of organ failures >4	22 (44)	23 (46)	0.84
SOFA score	18 (14-20)	17 (13-19)	0.28
CLIF-C–SOFA score	19 (16-22)	18 (16-20)	0.13
CLIF-C–OF score	16 (14-18)	16 (14-17)	0.31
CLIF-C–ACLF score	70 (62-74)	66 (62-74)	0.31
TAM score >2	11 (22)	1 (2)	<0.01
TAM downstaged	14 (28)	19 (38)	0.29
Extended criteria donor§	33 (66)	21 (42)	0.02
Time between admission and LT, days	8 (4-13)	8 (5-12)	0.72
Post-LT survival at 1 year	33 (66)	43 (86)	0.02

NOTE: Binary variables are displayed as number (%), and continuous variables are displayed as median (IQR).
*From January 1, 2007, to July 17, 2015.
†From July 18, 2015, to December 31, 2019.
‡Some patients had more than 1 etiology.
§Eurotransplant criteria.

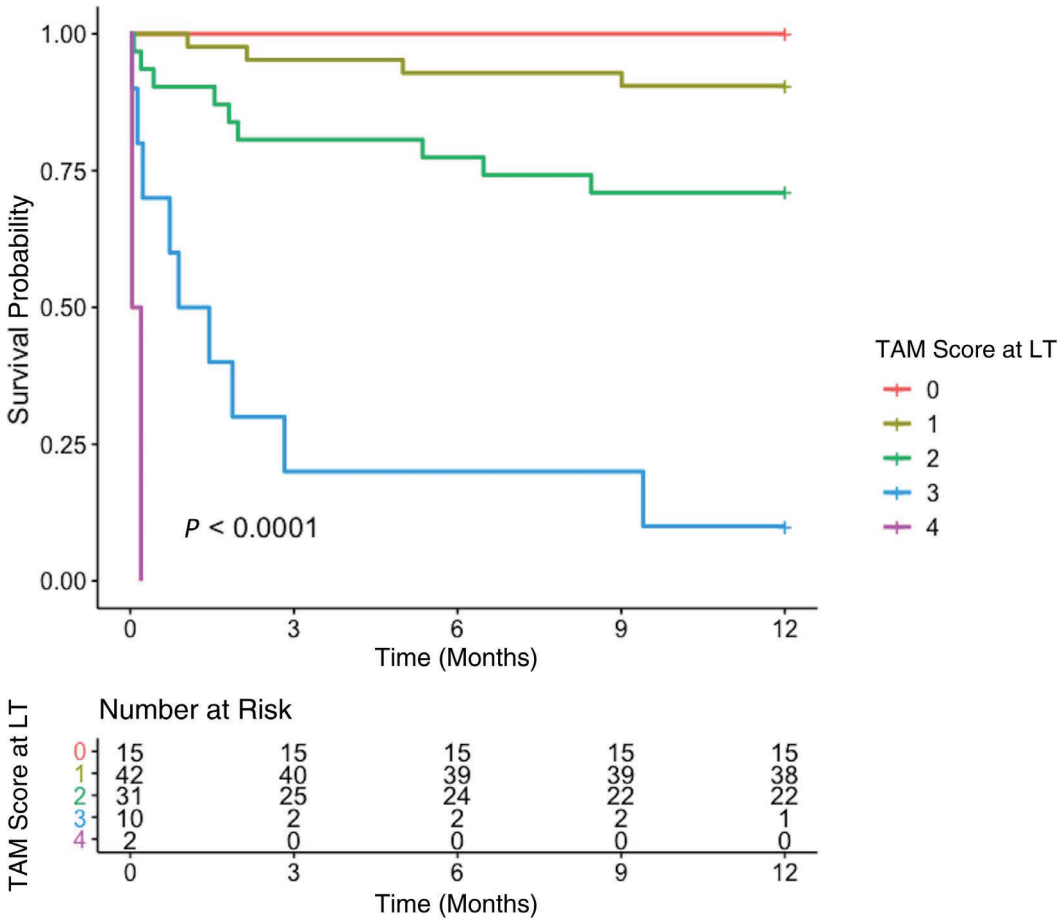

FIG. 2. Posttransplant survival rates according to TAM score at LT.

ACLF-3. In practice, however, there is significant variability among countries and centers in terms of transplant activity for this subgroup of patients, with some centers and countries performing few (if any) LTs for critically ill patients with cirrhosis.[14] The results presented in this study are derived from the center with 1 of the highest volumes of patients in Europe with ACLF-3 who received transplants and constitutes by far the largest single-center cohort of patients with ACLF-3 at the time of LT in the literature. The TAM score was recently developed to help assess the transplantability of critically ill patients with cirrhosis at the time of LT and in particular reject organ proposals (on the basis of collective utility) for patients with TAM scores >2 given their poor 1-year post-LT prognosis (<10%). Building on this experience, this study adds 3 additional pragmatic clinical messages. First, starting a program aimed at providing access to LT for patients who are critically ill entails a learning curve. Second, the degree of severity of a patient who is critically ill with cirrhosis at the time of ICU admission is not predictive of his or her post-LT survival. Third, the clinical course of patients with ACLF-3 in the ICU prior to LT affects post-LT survival and can be monitored by the TAM score.

Large studies derived from the United Network for Organ Sharing (UNOS) registry have noticeably contributed to showing that post-LT survival rates for patients with ACLF-3 who received an LT weigh in favor of giving them greater access to LT.[5,6] Although we share this view in general, the high degree of granularity of our study adds a particular note of caution to it. The first message derived from this study is that, although post-LT survival for patients with ACLF-3 is high in general, there can be large variations of outcomes depending on the experience of centers in

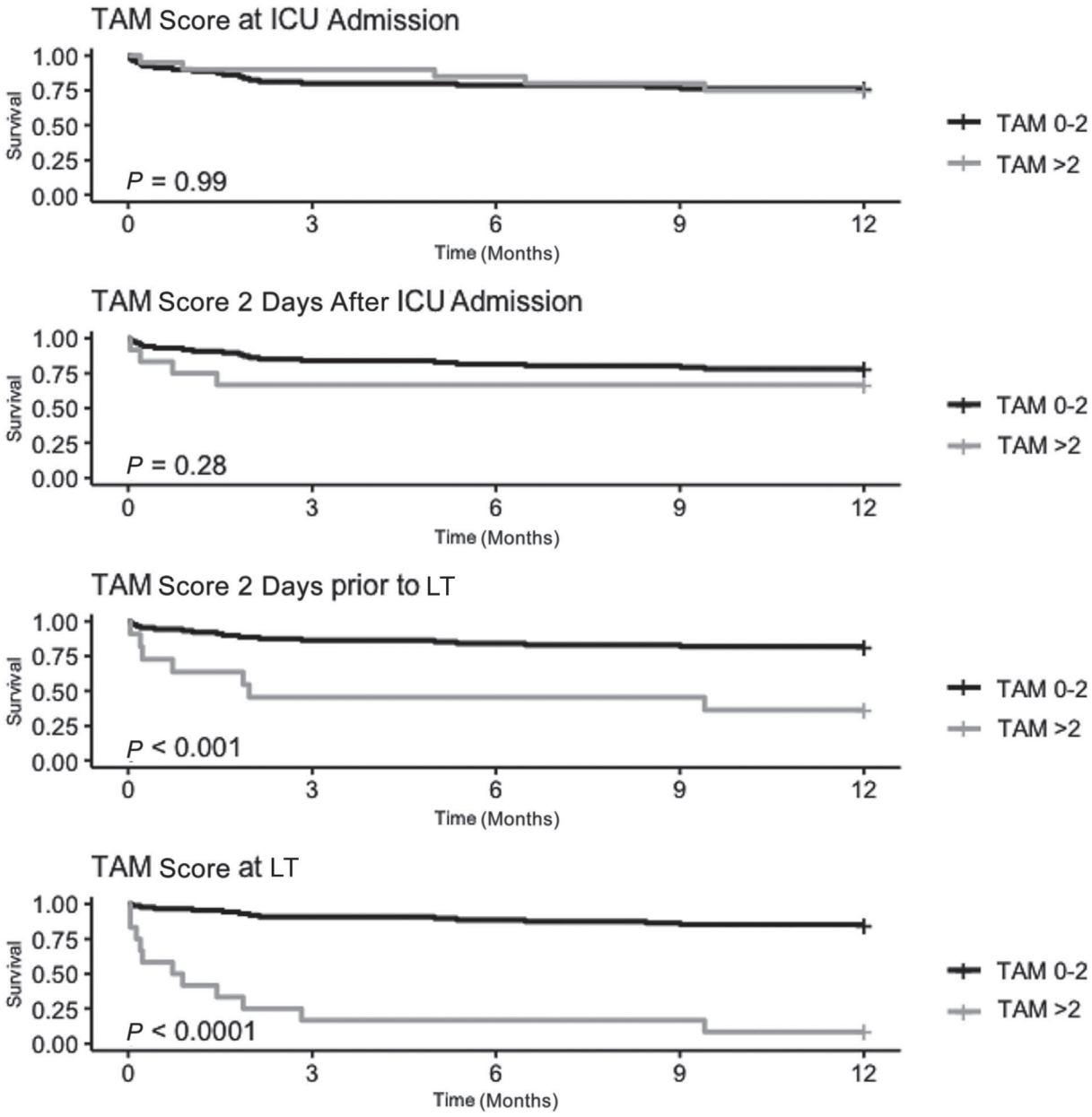

FIG. 3. Performance of the TAM score depending on time.

managing and selecting transplant candidates who are critically ill with cirrhosis. In our cohort, the first 25 patients studied had a post-LT survival rate of 60%, which is much lower than the survival rate of the last 25 patients studied (88%), but also much lower than the survival rate of the patients who received transplants in our center during the same period of time without ACLF-3 (85%). Improved ICU care (both in general and more specifically for LT patients) certainly accounts for part of the improvement of post-LT outcomes of patients with ACLF-3, but it cannot account for the steepness of the learning curve in our cohort. Neither can new treatments for hepatitis C virus (HCV) account for it (none of the 12 patients positive for HCV included in this study died or had to receive retransplantations because of HCV recurrence during the study period). Time, experience, and deepening ties between the ICU and the transplant team

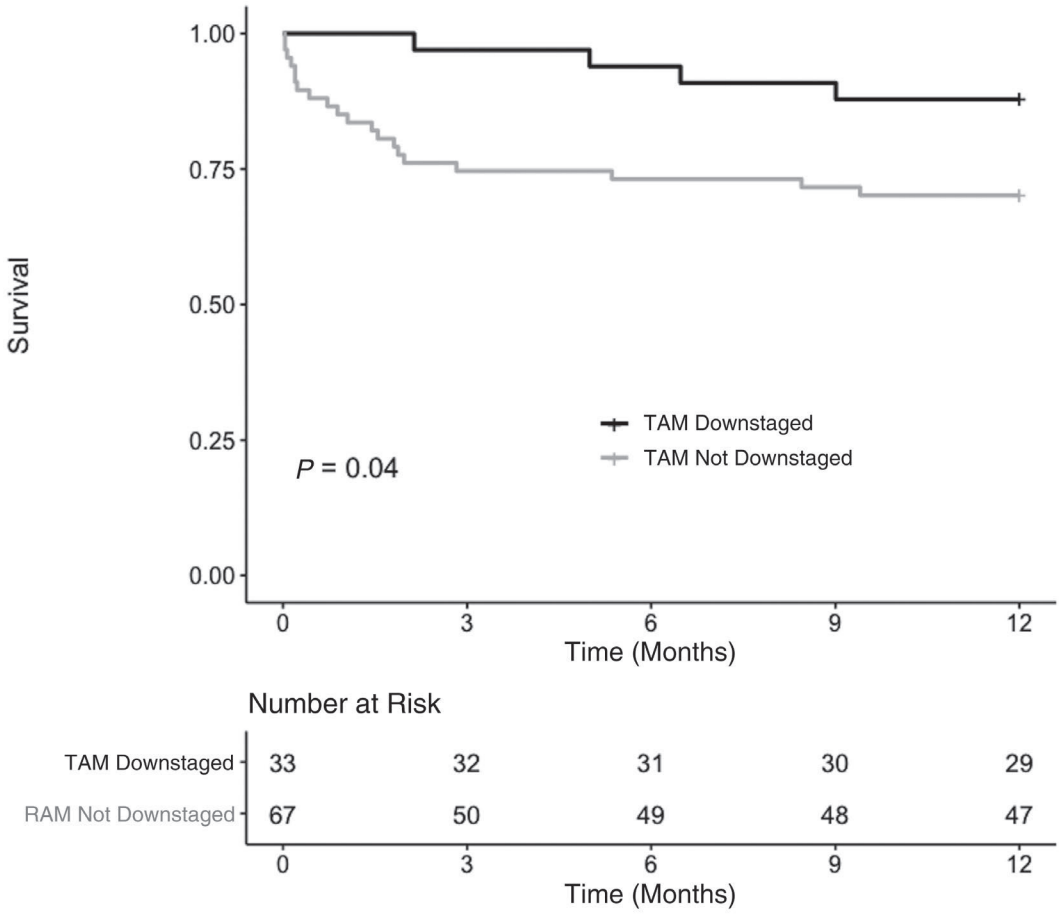

FIG. 4. Survival depending on TAM downstaging.

have contributed to an optimization of the selection and management of ACLF-3 LT candidates, increasing both the number of patients with ACLF-3 having access to LT and their post-LT survival rates. By the last quarter of the study period, the gap between 1-year post-LT survival for patients with ACLF-3 and patients without ACLF-3 (88% versus 91%) was almost entirely bridged.

The second message derived from this study is that the severity and number of organ failures at the time of ICU admission do not predict post-LT outcomes. This is made clear, on one hand, by the fact that patients in the second period had better post-LT survival than in the first period, despite having similar (if not more severe) organ failures, and, on the other hand, by the fact that the TAM score, which takes into account 2 crucial markers of ICU severity (respiratory failure and arterial lactate level), is not predictive of post-LT survival when applied to patients within the first 48 hours of ICU admission. This in turn has important clinical implications. Because the transplantability of patients who are critically ill with cirrhosis should not be judged too quickly after ICU admission, the admission criteria for critically ill LT candidates with cirrhosis should be lenient so as to avoid prematurely turning them down for the only life-saving therapy available to them. Hindsight is essential to correctly predicting both transplant-free survival of patients with ACLF[1] and post-LT outcomes. The ACLF scores are designed for the first goal[13] and the TAM score for the second.[10]

The third message derived from this study is that the clinical course of patients, assessed in particular by the evolution of their TAM score between ICU admission and LT, can contribute to stratifying post-LT outcomes. Patients whose TAM scores were downstaged had significantly higher survival rates than those whose TAM scores were stable or increased: 88% versus 70%, respectively ($P = 0.04$). This was particularly useful

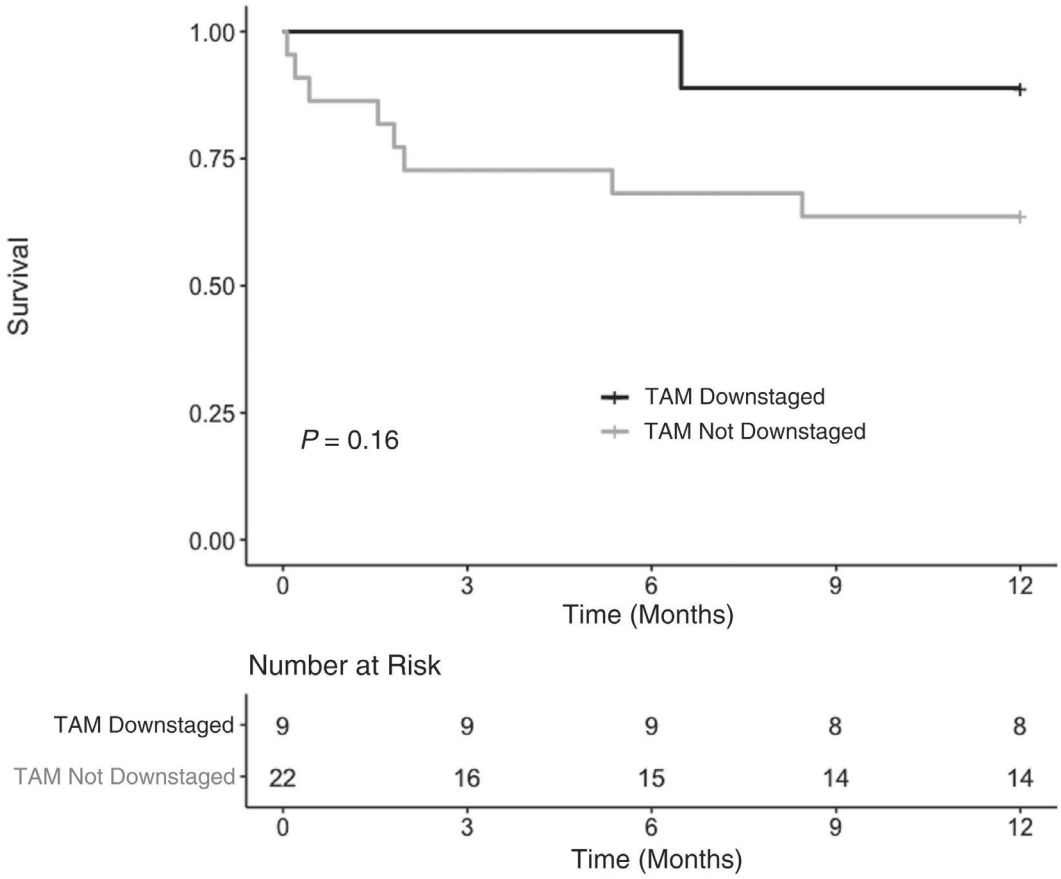

FIG. 5. Survival depending on TAM downstaging for patients with TAM scores of 2 at LT.

for the subgroup of patients with TAM scores of 2 at the time of organ proposal who had an intermediary 1-year post-LT survival rate of 71% and who tended to have much better post-LT results if their TAM score decreased than if it was stable or increased: 89% versus 64%, respectively ($P = 0.16$). Recent results from the UNOS registry have also shown that patients who improved during the course of their ICU stay had better post-LT results than others.[15] In the case of patients with ACLF-3, our data show that pretransplant ICU optimization (in particular the improvement of respiratory function and hemodynamics) has a major impact on posttransplant outcomes and that a dynamic assessment of patients improves our ability to correctly predict post-LT outcomes.

A score is a tool, nothing more. It is not intended to replace clinical experience but, rather, to enhance it. LT for critically ill patients with cirrhosis is an ethical and clinical puzzle too complex to be encapsulated in formulaic algorithms. The clinical course of LT candidates who are critically ill with cirrhosis can change dramatically in a matter of hours. Bleeding, sepsis, or respiratory failure, for example, can suddenly render a patient too sick to receive a transplant. Registry studies can only convey a "big picture" approach to this complex medical issue, and granular data will also always remain limited compared with the clinical experience of a multidisciplinary team. In addition, this study does not address 3 crucial aspects of LT for patients with ACLF-3. First, it does not address the issue of the selection of critically ill patients with cirrhosis according to their medical background and their addiction assessment, which is not captured by ICU scores or the TAM score. Preselection biases remain a clear limit to all the literature published so far concerning LT for patients with ACLF-3. Second, the importance of donor–recipient matching is not at the center of this study but clearly deserves more attention from multidisciplinary teams that perform LT for patients with ACLF-3. In this respect, it is noteworthy

that the number of extended criteria donors was significantly higher in the first period than in the second period (33 [66%] versus 21 [42%]; $P = 0.02$). Finally, post-LT management for patients with ACLF-3 is a complex clinical puzzle that remains an untrodden field of research. Optimizing immunosuppression strategies for these patients who are critically ill to balance the risk of sepsis, kidney failure, and graft rejection will require collective scientific efforts in the years to come.

Conclusion

LT in transplant candidates who are critically ill with cirrhosis can yield excellent results, but it requires experience in managing patients with multiple organ failure before LT, selecting candidates carefully, and identifying the optimal transplantability window. Potential LT candidates should not be excluded from ICU admission prematurely on the basis of their clinical severity because their clinical condition at the time of LT as well as their evolution during the course of their ICU stay are better predictors of post-LT survival than their clinical condition when they are admitted to the ICU.

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ARTICLE 2

Improvement in Survival After Transplantation for Critically Ill Patients With Cirrhosis in the United States

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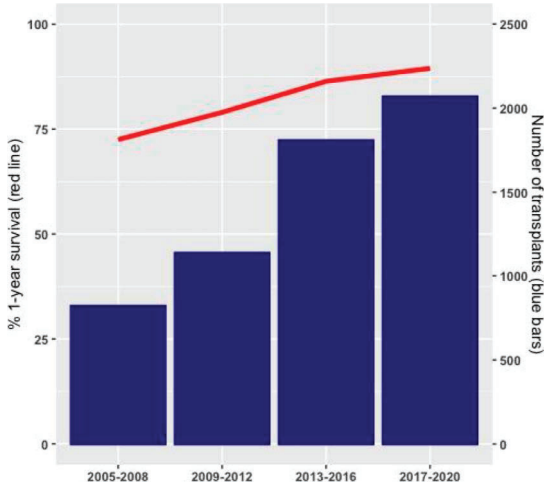
INTRODUCTION: **There is considerable debate over the indication of liver transplantation (LT) for critically ill patients with cirrhosis, in part due to their potentially poor post-LT prognosis. We analyzed the epidemiology and outcome of LT for critically ill patients with cirrhosis over 4 time periods of 4 years.**

METHODS: **We included adult patients who underwent liver transplant alone between 2005 and 2020 using the United Network for Organ Sharing registry database. We defined critically ill patients with cirrhosis as being in the intensive care unit with 1 or more of the following characteristics at the time of LT: (i) grade III/IV hepatic encephalopathy, (ii) mechanical ventilation, (iii) dialysis, and (iv) vasopressors.**

RESULTS: **A total of 85,594 LT recipients were included, 5,827 (6.8%) of whom were classified as being critically ill with cirrhosis at the time of LT. The number and percentage of critically ill LT recipients with cirrhosis increased over the study period: 819 (4.3%) in 2005–2008 vs 2,067 (7.9%) in 2017–2020, $P < 0.001$. There was a 17% absolute increase in 1-year survival after LT: 72.5% in 2005–2008 vs 89.5% in 2017–2020, $P < 0.001$. The 1-year post-LT survival gap between critically ill and noncritically ill patients with cirrhosis narrowed over the study period: 16.7 percentage points in 2005–2008 vs 4.6 percentage points in 2017–2020. The year of LT was independently associated with lower 1-year post-LT mortality (hazard ratio 0.92, 95% confidence interval 0.91–0.93, $P < 0.001$).**



Between 2005 and 2020:

- The number of critically ill patients with cirrhosis who were transplanted in the United States increased (blue bars)
- Their one-year post-transplant survival increased by 17 percentage points (red line)
- This has led to a decrease in the post-transplant survival gap between critically ill patients and non critically ill patients with cirrhosis
- These results are in favor of advocating access to liver transplantation for carefully selected critically ill patients with cirrhosis

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DISCUSSION: **The absolute number and relative percentage of LT recipients who were critically ill increased over time, as did 1-year post-LT survival. Meanwhile, the gap in survival between this group of patients and noncritically ill patients with cirrhosis decreased but persisted. Cautious access to selected LT candidates who are critically ill may be warranted, provided the gap in survival with noncritically ill patients remains as small as possible.**

KEYWORDS: ACLF; acute on chronique liver failure; liver transplantion; ICU

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/D332

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INTRODUCTION

Liver transplantation (LT) for patients with cirrhosis who are critically ill is a challenging medical, ethical, and public health issue. There is growing interest in this topic, especially since the development of the acute-on-chronic liver failure (ACLF) classification (1–3) and reports that LT may be the only radical treatment for patients with the most severe forms of ACLF (4–8). However, there are still limited data concerning the epidemiology of LT for critically ill patients with cirrhosis and the evolution of post-LT survival over time of this subgroup of LT recipients. Thus, there is still considerable controversy over the role that LT should play for these patients and the limits of patient suitability for LT. This is illustrated by (among others) (i) variations in responses to clinical scenarios in a survey of US-based transplant providers (9), (ii) heated debates over the soundness of prioritizing patients with ACLF beyond the model for end-stage liver disease (MELD) score (10–14), (iii) regional variations in actual access to LT for critically ill patients (15,16), and (vi) variations in clinical practice guidelines (17,18).

This study focuses on 2 aspects of LT for critically ill patients with cirrhosis over a 16-year period of time (2005–2020) in the United States through the United Network for Organ Sharing (UNOS) standard transplant analysis and research file. First, it considers the issue from an epidemiological point of view: did the number and the proportion of critically ill patients who were transplanted change over this period of time? Second, it focuses on the post-LT outcome of these patients: what was their survival compared with other populations of patients transplanted over the same period? How did this survival evolve over the study period? Was the effect of time an independent, significant factor affecting post-LT outcome?

One particular focal point of this study is the gap in survival between critically ill patients with cirrhosis and noncritically ill patients with cirrhosis who were transplanted over the study period and how this gap changed over the study period. Indeed, this survival gap is one of the key practical points that needs to be taken into consideration when deliberating on access to LT for critically ill patients (19). This article therefore reports the evolution of this gap in survival across study period.

METHODS

Study cohort

Adult patients older than 18 years who received a primary single liver transplant from a deceased donor between 2005 and 2020 were included using the UNOS registry database. Patients who received an organ from a living donor were excluded. Multiorgan transplants (in particular simultaneous liver-kidney transplants) were excluded.

Five categories of patients were distinguished (note that categories 2, 3, and 5 are not mutually exclusive).

1. Critically ill patients with cirrhosis were defined as having a diagnosis of cirrhosis and being in the intensive care unit (ICU) at the time of LT with 1 or more of the following characteristics at the time of LT: (i) grade III/IV hepatic encephalopathy, (ii) mechanical ventilation, (iii) dialysis, and (iv) vasopressors. Patients transplanted/listed with Status1a were excluded from this category of patients;
2. Patients with a diagnosis of cirrhosis who were not critically ill and who were not transplanted/listed with Status1a;
3. Patients who had a MELD score $\geq$35 at the time of LT who were not critically ill and who were not transplanted/listed with Status1a;
4. Patients who were transplanted/listed with Status1a, but who were not in the category of critically ill patients with cirrhosis;
5. Patients transplanted with a diagnosis of hepatocellular carcinoma (HCC) who were not critically ill and who were not transplanted/listed with Status1a.

Ethical and regulatory approval

This project was deemed to be exempt from IRB approval as UNOS data are publicly available within the standard transplant analysis and research file.

Primary and secondary outcomes and statistical methods

The study period was divided into 4 equal intervals of 4 years for greater clarity (2005–2008, 2009–2012, 2013–2016, and 2017–2020).

The baseline characteristics of critically ill patients with cirrhosis who were transplanted at different intervals were compared using the Kruskal-Wallis for continuous variables and the χ^2 tests for categorical variables.

The primary outcome was 1-year post-LT survival over the different intervals of the study period for critically ill patients with cirrhosis.

The first secondary outcome was the identification of predictors associated with 1-year post-LT mortality in the subgroup of critically ill patients with cirrhosis. Survival analysis was performed using a Cox proportional hazards model. Independent variables were selected a priori, based on hypothesized clinical significance. Variables associated with post-LT mortality at $P < 0.1$ in the univariable analysis were included in the multivariable analysis. The variables of the final, multivariable model were selected by means of a backward stepwise procedure. All tests were 2-sided, and $P < 0.05$ was considered statistically significant.

The number of patients transplanted in each categories outlined above, along with their 1-year post-LT survival were also computed.

Post-LT survival curves (at 1-year, 3-year, and 5-year post-LT) were computed using the Kaplan-Meier method and compared with the log-rank test.

Finally, the number and percentage of patients who received a rescue kidney transplant (i.e., within 365 days of receiving a liver transplant) was also computed over the study period.

All statistical analyses and plots were done using R version 4.0.2 (R Core Team, 2020), in particular the survival, the survminer, and the ggplot2 packages.

RESULTS

Study population (entire population)

A total of 85,594 patients were included in the study, 5,827 (6.8%) of whom had a diagnosis of cirrhosis and were critically ill at the time of LT, 68,903 (80.5%) patients had a diagnosis of cirrhosis but were not critically ill at the time of LT, 7,931 patients (9.3%) were transplanted with a MELD score ≥35, 28,851 (33.7%) patients had HCC at the time of LT, and 2,613 (3.1%) patients were transplanted/listed with Status1a.

A flowchart (see Supplementary Figure 1, Supplementary Digital Content 1, http://links.lww.com/AJG/D332) illustrates these results.

Study population (critically ill patients with cirrhosis) over time

Table 1 presents the characteristics of critically ill patients with cirrhosis who were transplanted over the study period and during each 4-year interval. The number of patients transplanted during each 4-year interval increased over time (from 819 patients in the 2005–2008 interval to 2,067 in the 2017–2020 interval), as did its percentage compared with the total number of patients included in the study (from 4.3% to 7.8%, with a peak at 8.5% in the 2013–2016 interval, $P < 0.001$) (see Supplementary Table 1, Supplementary Digital Content 1, http://links.lww.com/AJG/D332).

Table 1. Recipient and donor characteristics of critically ill patients with cirrhosis at the time of LT, categorized by the period of LT

	Total (N = 5,827)	2005–2008 (N = 819)	2009–2012 (N = 1,135)	2013–2016 (N = 1,806)	2017–2020 (N = 2,067)	*P* value
Age, yr, median (IQR)	55 (48–61)	54 (48–59)	56 (50–61)	56 (49–62)	54 (46–62)	<0.001
Female, n (%)	2,365 (41)	301 (37)	439 (39)	736 (41)	889 (43)	0.008
BMI, kg/m^2, median (IQR)	28 (24–33)	28 (24–32)	28 (24–33)	29 (24–33)	29 (24–34)	<0.001
Race, n (%)						0.055
Asian	229 (3.9)	40 (4.9)	38 (3.3)	77 (4.3)	74 (3.6)	
African American	387 (6.6)	54 (6.6)	83 (7.3)	131 (7.3)	119 (5.8)	
Hispanic	1,286 (22)	166 (20)	225 (20)	415 (23)	480 (23)	
White	3,833 (66)	548 (67)	777 (68)	1,155 (64)	1,353 (65)	
Other	92 (1.6)	11 (1.3)	12 (1.1)	28 (1.6)	41 (2.0)	
Etiology, n (%)						
HBV	182 (3.1)	47 (5.7)	29 (2.6)	60 (3.3)	46 (2.2)	<0.001
HCV	1,643 (28)	402 (49)	498 (44)	560 (31)	183 (8.9)	<0.001
NASH	1,093 (19)	53 (6.5)	141 (12)	372 (21)	527 (25)	<0.001
ALD	2,714 (47)	298 (36)	410 (36)	782 (43)	1,224 (59)	<0.001
HCC	698 (12)	71 (8.7)	139 (12)	248 (14)	240 (12)	0.003
Diabetes	1,407 (24)	181 (23)	265 (24)	482 (27)	479 (23)	0.034
Characteristics at the time of LT						
MELD score, median (IQR)	38 (34–42)	36 (31–41)	38 (32–42)	39 (35–42)	39 (35–42)	<0.001
Bilirubin, mg/dL, median (IQR)	18 (8–31)	18 (8–32)	22 (9–34)	18 (9–30)	16 (8–29)	<0.001
INR, median (IQR)	2.30 (1.90–2.94)	2.20 (1.80–2.80)	2.21 (1.80–2.82)	2.40 (2.00–3.00)	2.30 (1.90–2.99)	<0.001
Dialysis, n (%)	4,334 (74)	414 (51)	794 (70)	1,402 (78)	1,724 (83)	<0.001
Vasopressors, n (%)	538 (9.2)	40 (4.9)	74 (6.5)	196 (11)	228 (11)	<0.001
Mechanical ventilation, n (%)	2,234 (38)	433 (53)	518 (46)	684 (38)	599 (29)	<0.001
Grade III/IV HE, n (%)	2,586 (44)	441 (54)	531 (47)	767 (42)	847 (41)	<0.001
Portal vein thrombosis, n (%)	708 (12)	59 (7.4)	136 (12)	246 (14)	267 (13)	<0.001
Cold ischemia time, hr, median (IQR)	6.25 (5.00–7.86)	6.97 (5.00–8.75)	6.50 (5.00–8.00)	6.40 (5.05–8.00)	5.97 (4.93–7.32)	<0.001
Donor age, median (IQR)	38 (26–51)	41 (25–54)	40 (26–52)	37 (26–51)	36 (26–49)	<0.001
No. of days on waiting list, median (IQR)	12 (4–84)	16 (5–155)	22 (6–164)	14 (5–108)	8 (3–36)	<0.001

ALD, alcoholic liver disease; BMI, body mass index; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HE, hepatic encephalopathy; INR, international normalized ratio; IQR, interquartile range; LT, liver transplantation; MELD, model for end-stage liver disease; NASH, nonalcoholic steatohepatitis.

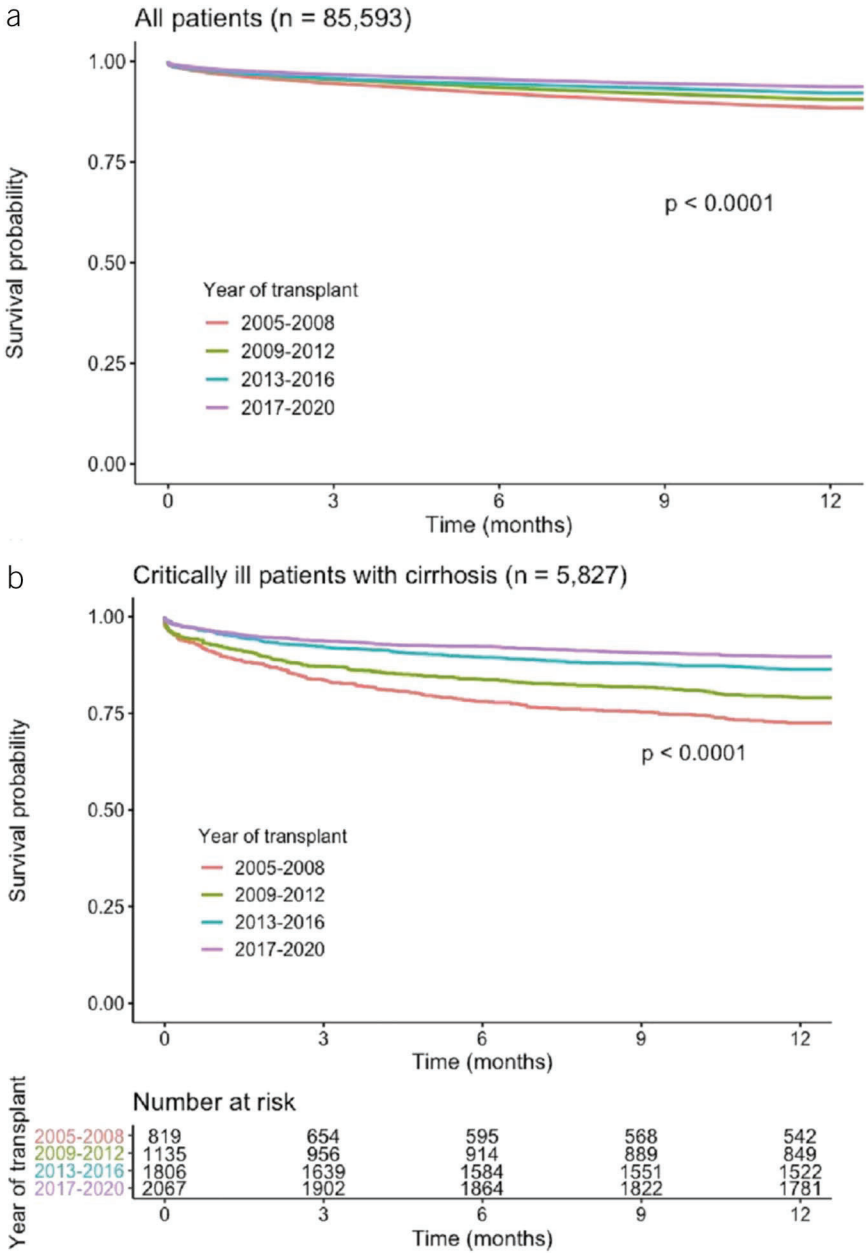

Figure 1. Post-LT survival of all patients (**a**) included in the study and of critically ill patients with cirrhosis (**b**) depending on the period of LT. LT, liver transplantation.

The percentage of female patients transplanted increased over the study period (37%–43%, $P = 0.008$). The percentage of patients transplanted with hepatitis C virus decreased over the study period (from 28% to 8.9%, $P < 0.001$), while the percentage of patients transplanted with nonalcoholic steatohepatitis and alcohol-related liver disease increased (from 6.5% to 25% and from 36% to 59%, respectively, both $P < 0.001$).

The percentage of patients transplanted with dialysis and with vasopressors increased over the study period (from 51% to 83% and from 4.9% to 11%, respectively, both $P < 0.001$), while the percentage of patients transplanted with mechanical ventilation at the time of LT decreased (from 53% to 29%, $P < 0.001$).

The median MELD score of the population of patients who were critically ill patients with cirrhosis was 38 (interquartile range [IQR] 34–42). By contrast, the median MELD score of the population of patients who were not critically ill patients with cirrhosis was 20 (IQR 13–28).

Cold ischemia time decreased (from a median of 6.97 hours [IQR 5.0–8.0] to 5.97 hours [IQR 4.93–7.32], $P < 0.001$), as did donor age (41 years [IQR 25–54] to 36 years [IQR 26–49], $P < 0.001$). The number of days on the waitlist for these patients decreased over the study period (from 16 days [IQR 5–155] to 8 days [IQR 3–36], $P < 0.001$).

Number of patients transplanted and evolution of post-LT survival over the study period

The total number of patients transplanted over the study period gradually increased from 19,192 in 2005–2008 to 26,008 in

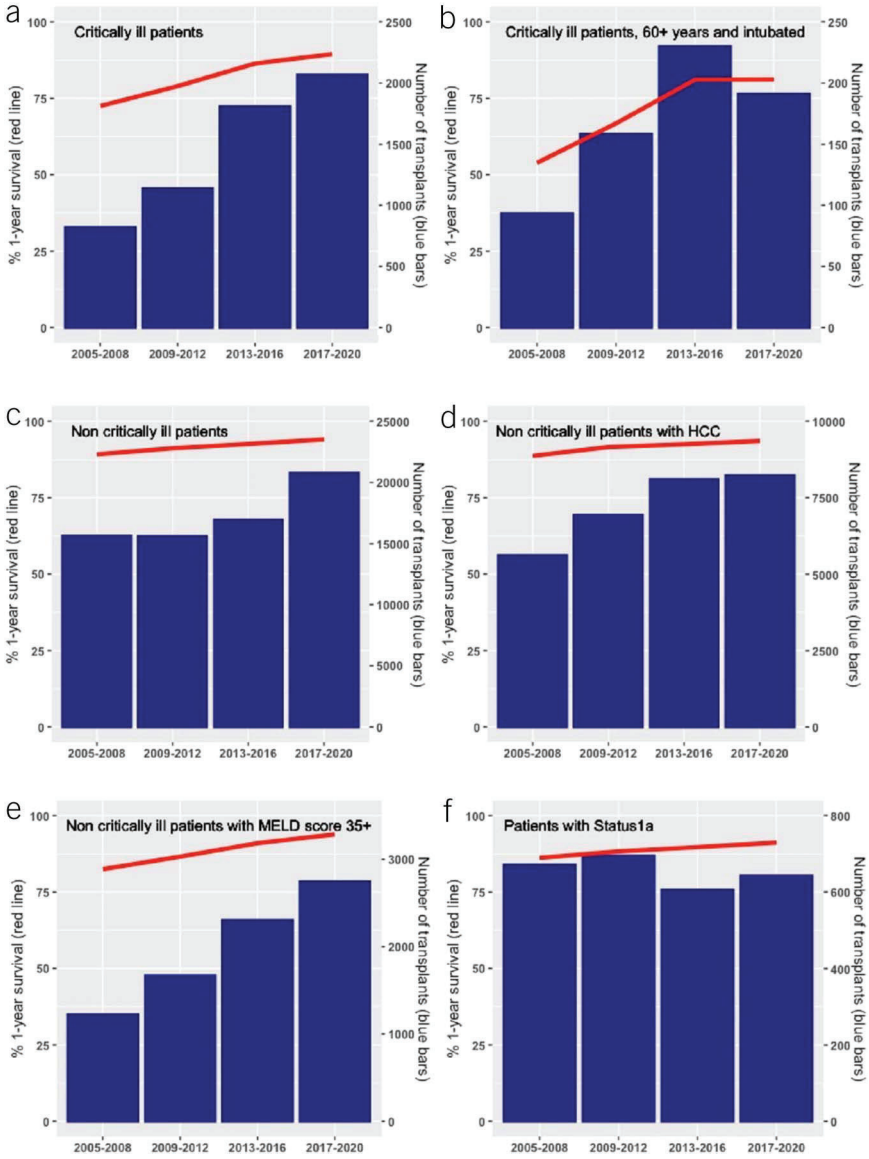

Figure 2. One-year post-LT survival (red lines) and number of patients transplanted across time (blue bars), categorized LT indication. LT, liver transplantation.

2017–2020 (+35.6%). One-year post-LT survival also gradually increased from 88.4% to 93.7% (+5.3 percentage points, Figure 1a).

The increase in the total number of critically ill patients with cirrhosis and in their 1-year post-LT survival was more important. The number of patients went from 819 in 2005–2006 to 2,067 patients in 2017–2020 (+152.4%) with 1-year post-LT survival increasing from 72.5% to 89.5% (+17 percentage points, Figures 1b and 2a).

It is noteworthy that dialysis was not the driving force behind the increased post-LT survival among critically ill patients with cirrhosis (see Supplementary Table 2, Supplementary Digital Content 1, http://links.lww.com/AJG/D332). Indeed, (i) for critically ill patients with only dialysis (N = 1,875), survival increased from 82.1% in 2005–2008 to 93.2% in 2017–2020 (+11.1 percentage points) and (ii) for critically ill patients, excluding patients with only dialysis at the time of LT, survival increased from 70.5% in 2005–2008 to 87.2% in 2017–2020 (+16.7 percentage points).

The number of LTs and post-LT survival also increased in other indications but to a lesser extent. One-year post-LT survival increased from 89.2% to 94.1% (+4.9 percentage points) for noncritically ill patients with cirrhosis (Figure 2c), from 88.7% to 93.6% (+4.9 percentage points) for patients with HCC (Figure 2d), from 82.5% to 93.9% (+11.4 percentage points) for noncritically ill patients with MELD scores ≥35 (Figure 2e), and from 86.2% to 91.2% (+5 percentage points) for patients transplanted with Status1a (Figure 2f).

In the subgroup of patients who were critically ill at the time of LT, aged 60 years or older, and with mechanical ventilation, 1-year post-LT survival increased from 53.9% to 81.2% (+27.3 percentage points) (Figure 2b).

The gap in survival between critically ill and noncritically ill patients with cirrhosis was significant throughout the study

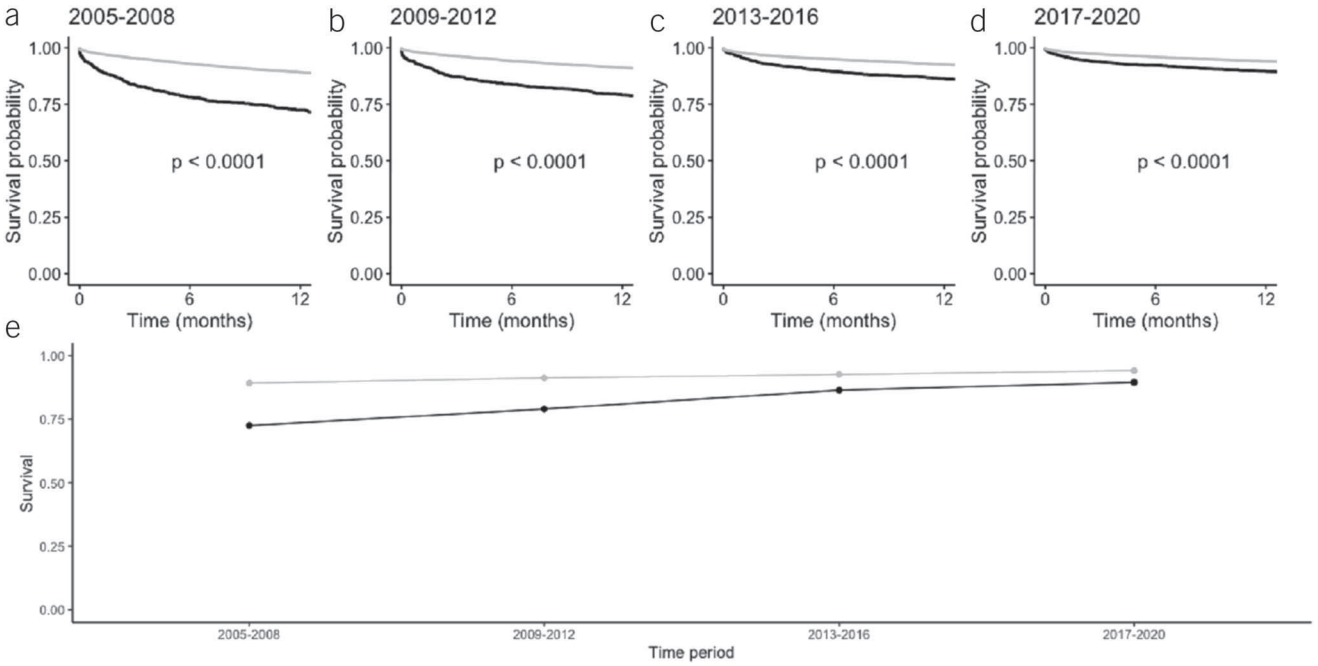

Figure 3. Post-transplant survival of critically ill patients with cirrhosis (gray line) compared with noncritically ill patients with cirrhosis (black line) (**a**–**d**) and 1-year post-transplant survival (**e**), categorized by the period of LT. LT, liver transplantation.

period, but it decreased steadily over time (Figure 3e): 16.7 percentage points (72.5% vs 89.2%, $P < 0.0001$) in 2005–2008 (Figure 3a), 12.2 percentage points (79% vs 91.2%, $P < 0.0001$) in 2009–2012 (Figure 3b), 6.2 percentage points (86.4% vs 92.6%, $P < 0.0001$) in 2013–2016 (Figure 3c), and 4.6 percentage points (89.5% vs 94.1%, $P < 0.0001$) in 2017–2020 (Figure 3d).

Finally, the increase in post-LT survival over the study period was also observed over a 3-year and 5-year period both among the general population of LT recipients and among critically ill patients with cirrhosis at the time of LT (see Supplementary Figure 2 and Supplementary Table 3, Supplementary Digital Content 1, http://links.lww.com/AJG/D332).

Analysis of risk factors of post-LT mortality in the cohort of critically ill patients with cirrhosis

After performing a univariable analysis (see Supplementary Table 4, Supplementary Digital Content 1, http://links.lww.com/AJG/D332), a multivariable analysis identified 7 factors that were independently associated with 1-year post-LT outcome for critically ill patients with cirrhosis (Table 2). Five of these were recipient-associated independent risk factors: recipient age hazard ratio (HR) 1.02, 95% confidence interval (CI) 1.02–1.03, $P < 0.001$; diabetes HR 1.28, 95% CI 1.10–1.48, $P = 0.001$; grade III-IV hepatic encephalopathy HR 1.19, 95% CI 1.05–1.36, $P = 0.008$; pre-LT mechanical ventilation HR 1.66, 95% CI 1.45–1.90, $P < 0.001$; and portal thrombosis HR 1.44, 95% CI 1.20–1.73, $P < 0.001$. Donor age was also associated with poorer post-LT survival: HR 1.01, 95% CI 1.01–1.01, $P < 0.001$. Time, measured as each year after 2005, was an independent protective factor: HR 0.92, 95% CI 0.91–0.93, $P < 0.001$.

Table 2. Independent factors of post-LT mortality for critically ill patients with cirrhosis (cox analysis)

	HR (95% CI)	*P* value
Recipient age, yr	1.02 (1.02–1.03)	<0.001
Diabetes	1.28 (1.10–1.48)	0.001
Grade III/IV hepatic encephalopathy	1.19 (1.05–1.36)	0.008
Mechanical ventilation	1.66 (1.45–1.90)	<0.001
Portal vein thrombosis	1.44 (1.20–1.73)	<0.001
Donor age, yr	1.01 (1.01–1.01)	<0.001
Year of LT	0.92 (0.91–0.93)	<0.001

CI, confidence interval; HR, hazard ratio; LT, liver transplantation.

Rescue kidney transplant

The proportion of patients who received rescue kidney transplant (i.e., within 1 year of LT) was higher in the population of critically ill patients with cirrhosis compared with the general population of transplant recipients (1.7% vs 0.5% over the entire study period, cf. Supplementary Tables 5 and 6, Supplementary Digital Content 1, http://links.lww.com/AJG/D332). The number of rescue kidney transplants remained relatively small (100 over the study period for the population of critically ill patients with cirrhosis), but this number and the proportion of LT recipients who had access to a rescue kidney transplant increased in 2017–2020, probably due to the implementation of the safety net policy in August 2017.

DISCUSSION

This study shows that the epidemiology and outcome of LT for critically ill patients with cirrhosis has changed dramatically over time. In particular, it shows that the number of patients with cirrhosis who were transplanted increased (+152.4%) over the study period, as did their 1-year post-LT survival (+17 percentage points). An increase in the number of patients transplanted

and in their post-LT survival was observed for other subgroups of transplant recipients (HCC, Status1a, MELD score ≥35, noncritically ill patients with cirrhosis) but to a lesser degree.

Taken together, these findings carry both a call for prudence and a message of hope. First, patients with cirrhosis who are transplanted while they are critically ill have significantly poorer post-LT outcomes than other groups of transplant candidates. In some subgroups of patients, post-LT survival can be unacceptably low (e.g., critically ill patients with cirrhosis aged 60 years or older and with mechanical ventilation at the time of transplant in the 2005–2008 interval had a 1-year post-LT survival of 53.9%). This is consistent both with registry studies outside the United States (15) and with several granular studies that have found significantly lower post-LT survival in subgroups of patients with ACLF-3 (20–23). Nevertheless, this study shows that the survival gap between critically ill and noncritically ill patients with cirrhosis has consistently narrowed over the course of time (from 16.7 percentage points in 2005–2008 to 4.6 percentage points in 2017–2020), in parallel with an increase in the number of patients transplanted while they were critically ill. This result is consistent with results from a single center granular study carried out in France on a cohort of patients transplanted with ACLF-3 (24).

The causes of the increase in the number and in the survival of patients transplanted while they were critically ill are foreseeably complex, multiple, and difficult to grasp through a retrospective transplant registry. They are likely to be due to progress in pre-LT and post-LT intensive care management, per operative anesthesiologic and surgical techniques. In addition, improvements in donor-recipient matching and candidate selection have probably contributed to the improvement of post-LT survival. Quantifying the impact of these different factors would require large-scale granular studies that, to this date, have not yet been performed. Interestingly, this study shows that the increase in post-LT survival was particularly sharp among a subgroup of patients that combined multiple mortality risk factors: 1-year post-LT survival for critically ill patients aged 60 years or older with cirrhosis and with mechanical ventilation at the time of transplant increased by 27.3 percentage points over the study period.

Widening access to LT while increasing post-LT outcomes is the cornerstone of the medical and ethical predicament of LT for critically ill patients (25). In that respect, identifying pre-LT risk factors of post-LT mortality is crucial (19,26). This study identifies several factors that are consistent with earlier registry and granular studies on critically ill/ACLF-3 transplant candidates. In particular, it confirms that recipient age (20,21), diabetes (15,21), pre-LT mechanical ventilation (5,20,21,27), and portal vein thrombosis (28) are simple clinical factors that should be taken into account when assessing the transplantability of critically ill patients with cirrhosis.

This study has several limitations. Apart from being retrospective, it is based on transplant registry data. This implies that some of the key variables that are clinically relevant to the management of critically ill patients but also to their retrospective identification are absent from the database (in particular sepsis-related data, PaO_2/FiO_2, lactate levels, vasopressors doses), thus leading to potential exclusion of some critically ill patients from the study. It also implies that the European Association for the Study of the Liver and the North American Consortium for the Study of End-Stage Liver Disease ACLF classifications cannot be applied straightforwardly to patients in the UNOS registry, due to a risk of misclassification (10,29). This is the reason why the notion of critically ill patients with cirrhosis was used instead of the ACLF classification, in particular through the identification of patients who were in the ICU at the time of LT (variable MED_COND_TRR in the UNOS registry database). While, from a scientific perspective, the meaning of the term critically ill is fuzzier than the ACLF classification, there is less risk of misclassification. In addition, from a medical perspective, this notion is clearly relevant for day-to-day clinical practice. In addition, we can assume that there is significant overlap between our notion of critically ill patients with cirrhosis and patients with ACLF as defined by the North American Consortium for the Study of End-Stage Liver Disease (3,30) or European Association for the Study of the Liver classifications. Finally, the size and the exhaustive nature of the UNOS registry make it a unique and indispensable tool for exploratory and epidemiological studies in the field of LT for critically ill patients with cirrhosis.

Another limitation of this study is that we did not study patients who were not transplanted. Unfortunately, the MED_COND variable from the UNOS database (which determines if a patient was at home, in the hospital or in the ICU) only concerns patients at the time of LT. Indeed, this variable has ceased to be recorded in the UNOS registry at the time of listing since 2015. Using different definitions of critically ill patients at the time of listing and at the time of LT would have introduced biases that we preferred avoiding in this study. More generally, the denominator of critically ill patients (i.e., all the potential LT candidates, including those that did not end up being transplanted or listed) is not available when analyzing the UNOS registry. This issue, which is crucial from an epidemiological point of view, requires alternative methods and databases and has been addressed in other, prospective studies (30).

This study leaves open the issue of what lies ahead. Will the number and proportion of critically ill patients continue to rise? Is there still scope for the survival gap between critically ill and noncritically ill patients with cirrhosis to further narrow? The answers to these crucial questions will help to shape the overall future of LT in the coming years.

LT for critically ill patients with cirrhosis is feasible and their post-LT survival has dramatically improved over time, gradually bridging the gap in survival between this subgroup of patients and patients with cirrhosis in general.

ACKNOWLEDGEMENTS

The authors wish to honor the memory of Vinay Sundaram who contributed to the design of this study and to the abstract that was presented at the meeting of the American Association for the Study of Liver Disease in November 2022.

CONFLICTS OF INTEREST

Guarantor of the article: Thierry Artzner, MD.

Specific author contributions: T.A., D.S.G., V.S., F.F., C.J.K., and S.K.A.: contributed to the study design and interpretation of data. T.A.: performed the statistical analysis and drafted the initial manuscript that was revised and approved by the authors. V.S.: passed away after the initial abstract was approved for presentation at AASLD meeting.

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Potential competing interests: None.

Study Highlights

WHAT IS KNOWN

✓ There is considerable debate over the indication of liver transplantation (LT) for critically ill patients with cirrhosis, in part due to their potentially poor post-LT prognosis.

WHAT IS NEW HERE

✓ While the absolute number and relative percentage of LT recipients who were critically ill increased over time, one-year post-LT survival also increased. Meanwhile, the gap in survival between this group of patients and non-critically ill patients with cirrhosis decreased, but persisted. These results support advocating cautiously in favor of access to LT for critically ill transplant candidates with cirrhosis.

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Supplementary table 1. Total number and number of critically ill patients with cirrhosis transplanted, categorized by the period of LT						
	Total period	2005-2008	2009-2012	2013-2016	2017-2020	p-value
Total number of patients transplanted[1]	85,594	19,192	19,174	21,219	26,009	
Number of critically ill patients with cirrhosis, (and as a percentage of the total number of transplants)	5,827 (6.8%)	819 (4.3%)	1,135 (5.9%)	1,806 (8.5%)	2,067 (7.9%)	<0.001
[1]Adult patients who received a primary single liver transplant. Living donor excluded.						

Supplementary table 2. One-year post-LT survival of critically ill patients with cirrhosis, categorized according to pre-LT dialysis				
	2005-2008	2009-2012	2013-2026	2017-2020
Critically ill patients with "only" dialysis at the time of LT (N = 1,875)	82.1%	85.4%	89.9%	93.2%
Critically ill patients with cirrhosis, excluding patients with "only" dialysis at the time of LT (N = 3,952)	70.5%	76.7%	84.5%	87.2%
Abbreviations: LT: liver transplantation				

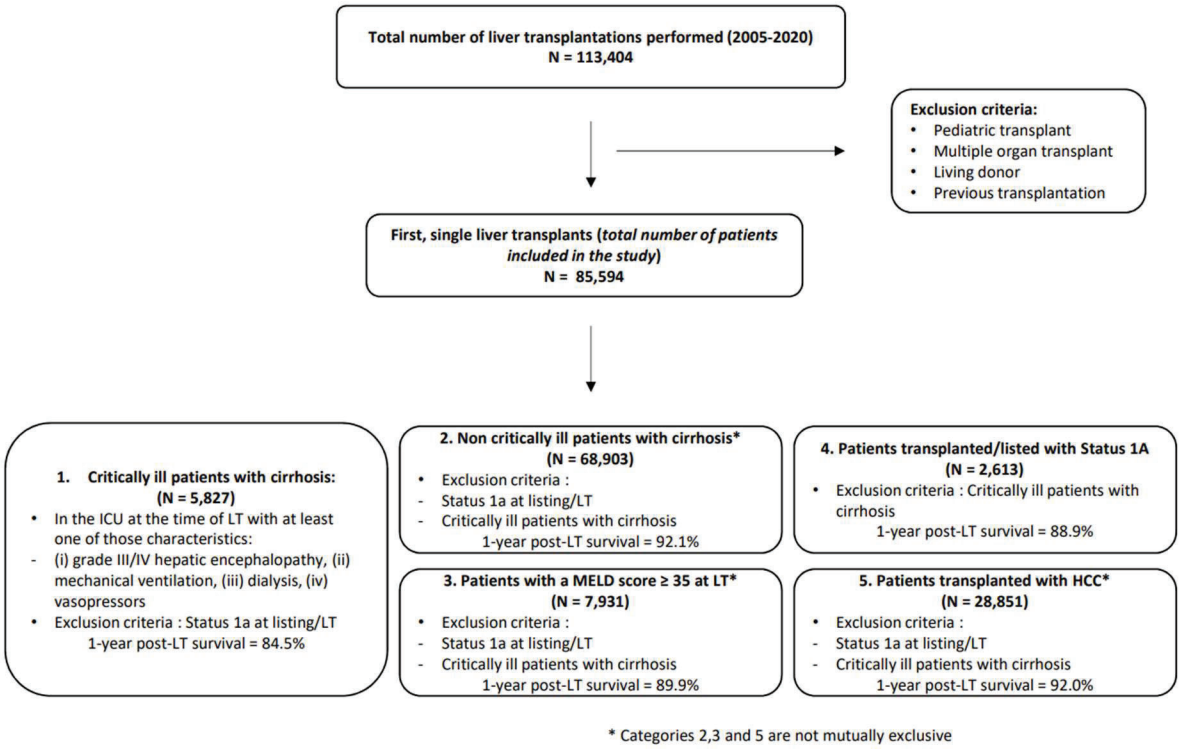
Supplementary table 3. 1-, 3- and 5-year post-LT survival for the entire cohort and the subgroup of critically ill patients with cirrhosis.				
	2005-2008	2009-2012	2013-2016	2017-2020
Entire cohort (N=85,593)				
1-year survival (%)	88.4	90.5	92.1	93.7
3-year survival (%)	79.9	82.5	86.2	87.2
5-year survival (%)	73.6	76.6	81.2	NA*
Critically ill patients with cirrhosis (N=5,827)				
1-year survival (%)	72.5	79.0	86.4	89.6
3-year survival (%)	63.8	70.9	78.8	83.0
5-year survival (%)	58.0	65.2	74.2	NA*
* Non applicable due to the high number of censored data				

Supplementary table 4. Univariable Cox analysis of factors potentially associated with post-LT mortality for critically ill patients with cirrhosis (factors independently associated with post-LT mortality are in bold – cf. table 2 in the main text).		
	HR (95% CI)	p-value
Recipient age (years)	**1.03 (1.02-1.04)**	**<0.001**
Gender (male)	1.11 (0.97-1.28)	0.13
BMI (kg/m^2)	0.99 (0.99-1.01)	0.96
HCC, n (%)	1.17 (0.87-1.42)	0.11
Diabetes	**1.39 (1.21-1.61)**	**<0.001**
MELD score	0.99 (0.98-0.99)	0.005
Bilirubin mg/dl	1.00 (0.99-1.01)	0.11
INR	0.96 (0.91-1.02)	0.19
Dialysis	0.69 (0.60-0.79)	<0.001
Vasopressors	1.06 (0.85-1.32)	0.62
Mechanical ventilation	**1.86 (1.63-2.12)**	**<0.001**
Grade III/IV HE	**1.29 (1.14-1.48)**	**<0.001**
Portal vein thrombosis	**1.45 (1.22-1.73)**	**<0.001**
Cold ischemia time (hours)	1.04 (1.01-1.06)	0.003
Donor age (years)	**1.01 (1.01-1.02)**	**<0.001**
Number of days on waiting list	1.00 (1.00-1.00)	0.003
Year of LT	**0.91 (0.89-0.92)**	**<0.001**
Abbreviations: BMI: body mass index; HCC: hepatocellular carcinoma; MELD: model for end-stage liver disease; INR: international normalized ratio; HE: hepatic encephalopathy; LT : liver transplantation ; HR : hazard ratio		

Supplementary table 5. Number and percentage of liver transplant recipients who underwent kidney transplantation within one year of liver transplantation (critically ill patients with cirrhosis)					
	Total	2005-2008	2009-2012	2013-2016	2017-2020
Critically ill patients with cirrhosis LT recipients	5,827	819	1,135	1,806	2,067
Kidney transplants within one year of LT (n, %)	100 (1.7)	6 (0.7)	10 (0.9)	8 (0.4)	75 (3.6)

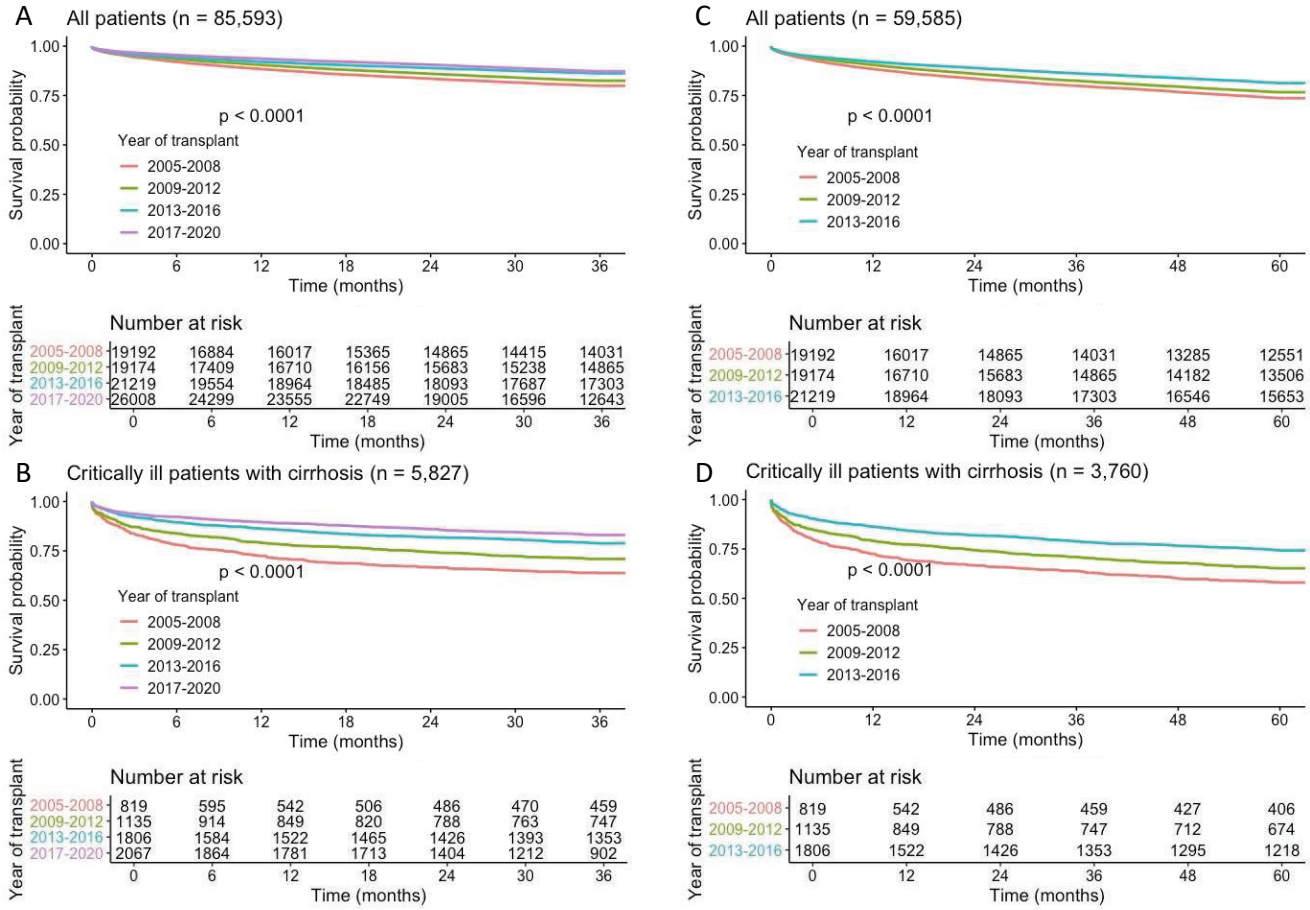
Supplementary table 6. Number and percentage of liver transplant recipients who underwent kidney transplantation within one year of liver transplantation (all patients included in the study)					
	Total	2005-2008	2009-2012	2013-2016	2017-2020
Total number of LT recipients	85,594	19,192	19,174	21,219	26,008
Kidney transplants within one year of LT (n, %)	437 (0.5)	53 (0.3)	54 (0.3)	42 (0.2)	288 (1.1)

Supplementary figure 1. Study flowchart and one-year post-LT survival



* Categories 2,3 and 5 are not mutually exclusive

Supplementary figure 2. 3- and 5-year post-LT survival of all patients (A and C) included in the study and of critically ill patients with cirrhosis (B and D) depending on the period of LT (note: patients transplanted in the 2017-2020 were excluded from the 5-year survival analysis due to the number of censored data)



ARTICLE 3

Research Article
Liver Transplantation

JOURNAL
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The novel SALT-M score predicts 1-year post-transplant mortality in patients with severe acute-on-chronic liver failure

Authors

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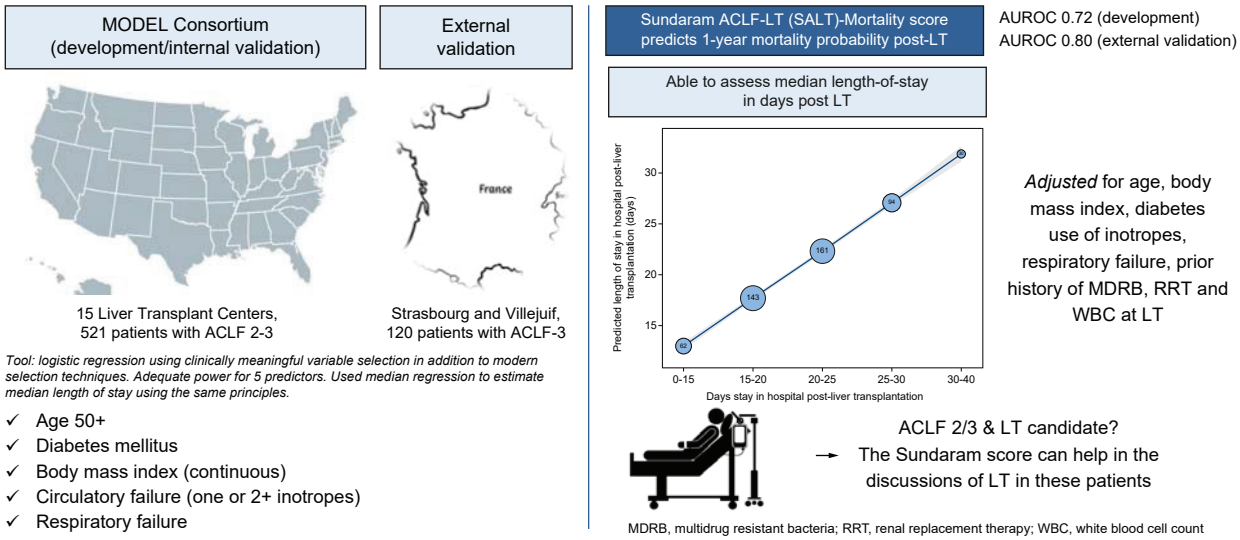
Graphical abstract



Highlights

- We derived and externally validated a model to predict 1-year mortality after LT in patients with ACLF-grade 2 or 3.
- Age, BMI, and the presence of diabetes, respiratory failure, and/or circulatory failure predicted death ≤1 year with reasonable accuracy.
- In addition, the prior presence of infection, use of renal replacement therapy, and leukocyte count at LT also influenced the median length of stay.
- Our scores can help in discussions with patients and care teams when patients are considered “too sick” for LT.

Impact and implications

Liver transplantation (LT) may be the only life-saving procedure available to patients with acute-on-chronic liver failure (ACLF), but clinically instability can augment the perceived risk of post-transplant mortality at 1 year. We developed a parsimonious score with clinically and readily available parameters to objectively assess 1-year post-LT survival and predict median length of stay after LT. We developed and externally validated a clinical model called the Sundaram ACLF-LT-Mortality score in 521 US patients with ACLF with 2 or ≥3 organ failure(s) and 120 French patients with ACLF grade 3. The c-statistic was 0.72 in the development cohort and 0.80 in the validation cohort. We also provided an estimation of the median length of stay after LT in these patients. Our models can be used in discussions on the risks/benefits of LT in patients listed with severe ACLF. Nevertheless, the score is far from perfect and other factors, such as patient’s preference and center-specific factors, need to be considered when using these tools.

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Research Article
Liver Transplantation

JOURNAL
OF HEPATOLOGY

The novel SALT-M score predicts 1-year post-transplant mortality in patients with severe acute-on-chronic liver failure

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Journal of Hepatology **2023**. vol. 79 | 717–727

Background & Aims: Twenty-eight-day mortality ranges from 30-90% in patients with acute-on-chronic liver failure grades 2/3 (severe ACLF). Though liver transplantation (LT) has demonstrated a survival benefit, the scarcity of donor organs and uncertainty regarding post-LT mortality among patients with severe ACLF may cause hesitancy. We developed and externally validated a model to predict 1-year post-LT mortality in severe ACLF, called the Sundaram ACLF-LT-Mortality (SALT-M) score, and estimated the median length of stay (LoS) after LT (ACLF-LT-LoS).

Methods: In 15 LT centers in the US, we retrospectively identified a cohort of patients with severe ACLF transplanted between 2014-2019, followed up to Jan'2022. Candidate predictors included demographics, clinical and laboratory values, and organ failures. We selected predictors in the final model using clinical criteria and externally validated them in two French cohorts. We provided measures of overall performance, discrimination, and calibration. We used multivariable median regression to estimate LoS after adjusting for clinically relevant factors.

Results: We included 735 patients, of whom 521 (70.8%) had severe ACLF (120 ACLF-3, external cohort). The median age was 55 years, and 104 with severe ACLF (19.9%) died within 1-year post-LT. Our final model included age >50 years, use of 1/≥2 inotropes, presence of respiratory failure, diabetes mellitus, and BMI (continuous). The c-statistic was 0.72 (derivation) and 0.80 (validation), indicating adequate discrimination and calibration based on the observed/expected probability plots. Age, respiratory failure, BMI, and presence of infection independently predicted median LoS.

Conclusions: The SALT-M score predicts mortality within 1-year after LT in patients with ACLF. The ACLF-LT-LoS score predicted median post-LT stay. Future studies using these scores could assist in determining transplant benefits.

Introduction

The natural history of a patient with cirrhosis changes when they develop a liver-related complication such as variceal bleeding, ascites, hepatic encephalopathy, or bacterial infection. This transition to decompensated cirrhosis is associated with a decrease in life expectancy to a median of 3-5 years.[1] In some cases, acute decompensation is associated with extrahepatic organ failure(s) (OFs), further increasing short-term mortality. This entity is defined as acute-on-chronic liver failure (ACLF)[2] and is prevalent across the globe.[3] Consistently, patients with two or more OFs have very high 28-day mortality (36% ACLF-2 [95% CI 31-40%]; 68% ACLF-3 [95% CI 63-74]).[3] As there is no approved treatment for ACLF, liver transplantation (LT) remains the only life-saving treatment option.

However, LT in these critically ill patients is challenging due to the risk of post-transplant mortality, which is a consequence of circulatory failure requiring vasopressors, mechanical ventilation, or an infectious trigger as the culprit of ACLF development.[4] Furthermore, given limited organ availability, the care team may hesitate to pursue liver transplantation[5] despite excellent reported outcomes.[6] Thus, there is a lack of equity of access for patients with severe ACLF across centers.[5,6] Accurately predicting post-LT outcomes in patients with severe ACLF remains an unmet need. More granularity toward understanding transplant risk and benefits would be clinically

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relevant to select patients more likely to do well.[7] Therefore, we internally developed and externally validated a risk score that determines the probability of 1-year mortality after LT in severe ACLF (patients with two or more OFs), and named it the Sundaram ACLF-LT-Mortality (SALT-M) probability score to honor the memory of the Consortium's founder.[8] As a secondary aim, we explored clinically important variables that impacted the length of stay (LoS) and created a second prediction model called ACLF-LT LoS.

Patients and methods

According to the TRIPOD (transparent reporting of a multivariable prediction model for individual prognosis or diagnosis) statement for risk score reporting,[9] prediction model studies can be broadly categorized as model development, model validation (with or without updating), or a combination of both. We conducted a type 3 model development study with validation using external data,[9] and we followed the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) report[10] for the initial data collection in the Multi-Organ Dysfunction and Evaluation for Liver Transplantation (MODEL) Consortium. The following describes the derivation cohort with model-building and validation strategies.

Derivation cohort: the MODEL Consortium

We retrospectively collected data from 15 transplant centers in the United States as part of the MODEL Consortium. The institutional review board approved the study protocol at Cedars-Sinai Medical Center and obtained subsequent approval from the other participating institutions' respective institutional review boards, including the Baylor College of Medicine (data analysis center). At inception, we conducted training sessions about data entry with each site investigator and relevant study staff to increase the accuracy of entered data. After data extraction from the central database, an additional query was sent to institutions in the event of erroneous or missing data, followed by a second round of data entry as needed.

We included patients 18 years or older who were transplanted from January 2014 through December 2019. We required a minimum of 2 days in the intensive care unit (ICU) at some point before LT surgery during their transplant hospitalization since most prior studies addressing futility were based on patients with ACLF in the ICU.[11] We further excluded patients listed as status-1a, re-transplanted, or who underwent multi-organ transplantation (except simultaneous liver and kidney transplantation). We collected data regarding recipient characteristics at the time of hospital admission, the time of transfer to the ICU, and the time of transplantation.

ACLF was defined according to the EASL-CLIF definition

Patients meeting the criteria for severe ACLF (grade 2 or 3) at the time of LT based on the European Association for the Study of the Liver-Chronic Liver Failure (EASL-CLIF) criteria were included.[3] We defined renal failure as creatinine ≥2.0 mg/dl and/or the use of any renal replacement therapy (RRT), such as intermittent hemodialysis or continuous renal replacement therapy, at any point during their hospitalization. We did not consider a patient to have *renal failure* if the review of records indicated a need for dialysis due to chronic kidney disease or if their creatinine at LT was less than 1.5 times their baseline creatinine. We considered patients to have *respiratory failure* when they had a PaO_2/FiO_2 ratio <200 mmHg and/or required mechanical ventilation specifically for respiratory support. We did not include elective mechanical ventilation in the definition of respiratory failure. We defined circulatory failure at LT as the requirement for vasopressor support at the time of transplantation to maintain either a mean arterial pressure <70 mmHg or for an indication of hypotension; we also recorded how many were used (none, 1 or ≥2).[7,12] We defined the presence of multidrug-resistant bacteria (MDRB) and/or fungal infection by positive blood culture data at any point during pre-transplant hospitalization.

Study outcomes: mortality within 1 year after LT and LoS

The *primary outcome* was overall mortality within 1 year after the LT because this is a common benchmark used by government agencies to assess centers' LT performance.[13] As a *secondary outcome*, we examined the predictors associated with the median LoS following LT in patients transplanted for ACLF. We defined LoS as the time from LT to the *first* hospital discharge following LT.

Statistical analysis

Selection of predictor variables

A priori, we chose clinically relevant variables associated with post-transplant outcomes in previous studies: age, BMI, LoS, presence of diabetes mellitus, chronic kidney disease, use of inotropes, or presence of respiratory failure. For key variables, data were missing in 0 to 4% of cases. Assuming data were missing at random, we imputed missing data using the MICE (Multivariate Imputation by Chained Equations) procedure in R and created five imputed datasets with 50 iterations.[14] We included all candidate predictors and the outcome in the imputation model.

SALT-M score development

Considering our small sample, we followed the TRIPOD recommendations and initially conducted validation with internal resampling (study type 1b).[9] We did not use split-sample validation techniques because this small size could produce instability in performance estimates and lead to overestimation of the AUROC.[15] For the internal resampling, we built multivariable binary logistic regressions in each imputed dataset with the multiple imputation-bootstrapping methods[16] using 100 bootstrap samples from each imputed dataset. Subsequently, we analyzed the pooled model on each set of bootstrap training data and tested it on the original imputed data. We pooled regression coefficient estimates and standard errors according to Rubin's rules.[17] The model performance was estimated in the five imputed datasets and combined.[16,18] All the candidate predictors were entered into the model and then removed from the pooled model using the pooled sampling variance method (a pooling of the total covariance matrix)[19] and backward selection with p value at <0.157.[16,20] Because increasing age is clinically important as a surrogate of cumulative exposures and frailty, we included age in all the models. We studied linearity and non-linearity in the continuous

candidate predictors and presented in the final model the best variable coding that showed the highest performance.

Internal validation, calibration, and performance measures
We internally validated our prediction model with 100 bootstrapping across imputed datasets. We used backward selection in each bootstrap sample. We examined the pooled model performance using AUROC, Nagelkerke's R^2, scaled Brier score, and calibration plots. We calculated Nagelkerke's R^2 and AUROC to assess its discriminative performance. We demonstrated calibration by the calibration slope, plot, and Hosmer–Lemeshow test. We constructed the calibration plots across multiple imputed datasets, and the Hosmer–Lemeshow test with a p value >0.05 was considered evidence of good calibration.[17] A perfect calibration has a calibration slope of 1 and an intercept of 0.

Comparison of discriminatory prediction with selected scoring models
We compared the SALT-M score with other models with available information, including the model for end-stage liver disease-sodium (MELD-Na),[21] the change in MELD from ICU to transplantation over time (Delta-MELD),[22] donor MELD-Na,[23] the Chronic Liver Failure-Consortium (CLIF-C) ACLF[24] and BAR (balance of risk) scores.[25]

External validation cohorts: Strasbourg and Paul-Brousse data

We included data from two large transplant centers in France: Strasbourg and Paul-Brousse. For our validation effort, we required that participants should have been transplanted for severe ACLF (either grade 2 and/or 3), and with the completeness of the following variables: age, BMI, the use of inotropes or mechanical ventilation, and diabetes mellitus status.

Sensitivity analysis with other variables
After selecting our final model, we conducted several sensitivity analyses to assess the change in discriminative accuracy (AUROC) to predict 1-year post-LT mortality. In these analyses, we assessed factors the clinician could consider prognostic for mortality post-LT. For example, we included the cause of underlying chronic liver disease, triggers of ACLF, prior abdominal surgery, portal vein thrombosis, white blood cell count (WBC) at LT, MDRB and/or fungal infection during hospitalization, RRT, and MELD-Na at LT. We further examined the performance of the SALT-M score to predict 90-day mortality, as well as 6- and 9-month mortality, since it may be considered as a future benchmark in the US.[26] We also studied the discrimination of our model when stratifying patients by ACLF grade 2 *vs.* 3, owing to their different mortality risks at baseline, and examined center-specific mortality rates using a fixed effect model to account for these differences. While we used logistic modeling to build our score due to its methodological robustness, we also performed a time-to-event analysis using a Cox proportional hazards model. In such a strategy, there was evidence of proportional hazards violation with BMI, thus, we presented Cox modeling as a secondary analysis.

Sample size for SALT-M score development
We could target a mean absolute prediction error of 0.04 between the observed and the actual mortality rate, considering a fixed sample size of 521 participants, a mortality rate within 1 year of 20% and up to eight candidate predictor parameters.[27] We performed all analyses using SAS version 9.4 and R version 4.2.1 (R Core Team, 2022, https://www.R-project.org) with the package MICE for the imputation and pooling procedures and *psfmi* for model estimation and validation.[16] We considered statistical significance when the two-sided p value is less than 0.05.

Estimation of median LoS and development of the ACLF-LT-LoS score
We considered the same clinically important variables to predict these patients' median LoS after LT. Because the observed distribution of LoS post-LT was positively skewed, we used quantile regression (SAS QUANTREG) wherein one can predict any percentile of the distribution (labeled a "quantile") instead of the mean as in traditional linear regression. In our quantile regressions, we determined the point estimates for the predictor slopes by minimizing the weighted function of the absolute value of the model residuals (in which the weights reflect the chosen percentile). We further evaluated the significance of the model predictors in predicting the median LoS by assessing the residual denominator degrees of freedom. We then added the additional predictors one at a time. We also studied the linearity and non-linearity of continuous variables and modeled the variable to optimize the Akaike's information criterion. Most of the deaths post-LT occurred within the first 90 days, so we included death within 3 months as a variable in the model and other clinically essential variables associated with prolonged LoS. We chose the final model based on variables that providers consider important prognostic factors in LoS.

Bedside tool to assess mortality risk
We provide an online calculator to estimate the probability of 1-year mortality post-LT and median LoS, which is available at: https://vocal.shinyapps.io/MODEL/.

Results

The Multi-Organ Dysfunction and Evaluation for Liver Transplantation (MODEL) Consortium

Of 735 patients in the MODEL Consortium, 521 had severe ACLF at the time of LT Table S1. The 214 participants excluded from this analysis were older (aged 50+: 72.4% *vs.* 64.7%), more often male (59.4% *vs.* 55.3%), had a higher prevalence of diabetes (33.2 *vs.* 22.5%), had lower mean MELD-Na score (31.4 *vs.* 37.0), and shorter mean LoS (25.7 *vs.* 29.6 days). In contrast, BMI and 1-year survival were similar between the participants included in this analysis (n = 521) *vs.* not (n = 214) (Table S2). The analytical cohort was followed up for a median of 3.1 (1.6-5) years. The median survival time of these patients was 1,143 days (Q1-Q3, 579-1,827), and 104 (19.9%) died within 1 year of LT (range 6.3%-47.7%, median 16.7%, mean 16.3%). The median age of our population was 55 years (46-61), 45% were females, and 61% were white. The median BMI was 29.8 kg/m^2 (25.0-35.3), and 22.5% had diabetes. Alcohol was the most common underlying chronic liver disease (~40%). Due to the severity of ACLF, the median MELD-Na at

transplantation was 40 (36-40), 284 patients (54.5%) had ACLF-3 at the time of transplantation. More than half (52%) of the patients required inotropes at LT, 58.2% continuous renal replacement therapy, 25.3% had respiratory failure, and 18.2% had grade III-IV hepatic encephalopathy.

Natural history and baseline predictors of death within 1 year

The majority of post-transplant deaths occurred within the first 3 months post-transplant: 63 (60.6%) within 3 months, 10 between 3 and 6 months (9.6%), 18 (17.3%) between 6 and 9 months, and 13 (12.5%) between 9 to 12 months. Of the known causes of death, the most common were infectious, including septic shock, with 21 deaths (20.2%), followed by multi-organ failure (including other forms of shock) (11.5%), cardiac (*e.g.*, cardiac arrest, myocardial infarction, 9.6%) and cancer (for example, one patient died from a recurrence of hepatocellular carcinoma, two of colorectal cancer, and two of cholangiocarcinoma) (8.7%) (Fig. 1). Compared to patients who survived, patients with severe ACLF who died after LT had a higher median BMI (31.3 *vs.* 29.6 kg/m^2), were more likely to have non-alcoholic steatohepatitis (19.2 *vs.* 14.4%) or HCV (22.1 *vs.* 13%), and had a higher likelihood of respiratory, cardiac, renal and brain failure (Table 1).

Derivation of the SALT-M score using clinically meaningful variables

In the design of the prediction score, we *a priori* focused our attention on clinically important variables based on prior knowledge. The final model included age (≥50 years), BMI (continuous), use of inotropes (none, 1, or ≥2), presence of respiratory failure, and diabetes. The following formula provides the probability of death within 1 year following LT, adjusting for the shrinkage factor:

P(death within 1 year after LT)= 1/[1 + exp(-(-3.412 + 0.366*(Age>50) + 0.032*BMI + 0.414*one pressor + 1.192*two or more pressors + 0.599*respiratory failure + 0.417*diabetes mellitus))]*100%

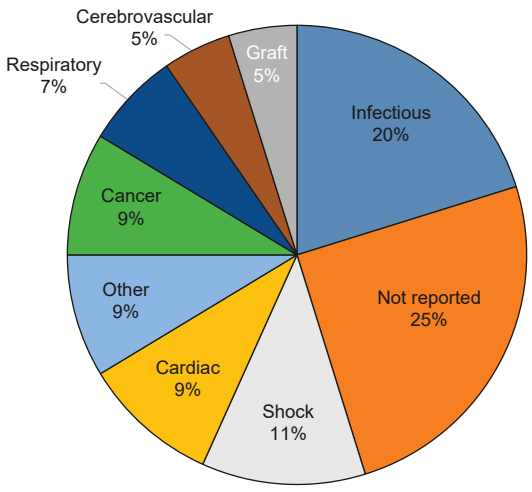

Fig. 1. Proportion of causes of deaths in the MODEL Consortium (n = 521). (This figure appears in color on the web.)

The SALT-M score predicts post-LT mortality well, with good calibration and improvement over other scores

Our development model showed acceptable discriminative ability (AUROC of 0.72, 95% CI 69-0.76) with some miscalibration (calibration slope coefficient 0.93; 95% CI 0.73-1.13, with 1 being a perfectly calibrated model). Also, considering the 20% event rate, a model with a Brier score of less than 0.16 is informative,[28] and our model achieved a score of 0.09 (Table 2, Figs S1 and S2). Next, we compared the model with readily available scores. Overall, our development model had superior discriminative ability compared to other scores frequently used in patients listed for LT (Table S3 and Fig. 2).

The SALT-M score was robust despite the addition of other clinical variables or analyses

We conducted sensitivity analyses to assess whether the AUROC changed significantly by adding other clinically relevant variables (Table S4). The presence of MDRB infections, fungal infections, or both were not independently associated with 1-year post-LT mortality. Considering the severe inflammatory response in patients with ACLF, measured by WBC, we found no independent association between WBC and post-LT mortality within 1 year. The discriminatory ability to predict 3-, 6- or, 9-month post-LT survival remained the same, with AUROCs between 0.71 and 0.74 (Table S5). The Cox proportional hazard model using the same variables as the SALT-M score showed an AUROC of 0.69 (95% CI 0.58-0.77), however, there was evidence of proportional hazards violation with BMI (Table S6). The discriminatory performance of our model to assess 1-year post-LT mortality in ACLF-2 and -3 is reflected by AUROCs of 68% and 76%, respectively (Table S7). We used a fixed effect model to account for the differences in the center-specific mortality thresholds and found that the SALT-M score had similar discriminatory ability, independent of different center-specific mortality rates (Table S8) (AUROC 0.73; 95% CI 0.68-0.69; SALT-M model adjusted by center, fixed effect model).

The SALT-M score consistently performed well in the external validation sample

There were 120 participants with complete data to validate our model. All of these participants had ACLF-3, with inotrope use recorded as yes/no, rather than our original ordinal 0, 1 or ≥2. A higher proportion of the French participants used inotropes (77% *vs.* 64%), more had respiratory failure (48% *vs.* 36%), and the French cohort had a lower median BMI (26 *vs.* 30 kg/m^2) compared to the MODEL Consortium (Table S9). Using the French cohorts, the AUROC of the SALT-M score was 0.80 (95% CI 0.69-0.87) (Table 3), with a moderate underestimation (intercept 0.36, slope 1.38, Fig. S3).

Median LoS in transplanted patients

Using the same principle of selecting impactful clinical variables, we built on our ACLF-LT-LoS score in an exploratory analysis, assessing independent covariates associated with the median LoS after LT. For example, we added the presence of MDRB and/or fungal infection, the use of any form of RRT, higher WBC count at LT, or prior history of abdominal surgery (hypothetically leading to longer surgery time) to our model.

Table 1. Baseline characteristics by status at 1 year from LT in severe ACLF.

Variables	All included patients (n = 521)		Alive (n = 417)		Dead within 1-year post-LT (n = 104)		*p* value
	Median (P25-P75)	Missing (%)	Median (P25-P75)	Missing (%)	Median (P25-P75)	Missing (%)	
Age, years	55.0 (46.0-61.0)	0.0%	54.0 (45.0-61.0)	0.0%	57.0 (49.5-60.5)	0.0%	0.201
≤50 years old	184 (35.3)		155 (37.2)		29 (27.9)		
Female, n (%)	222 (42.6)		170 (40.8)		52 (50.0)		0.136
Race, n (%)							0.057
White	318 (61.0		246 (59.0)		72 (69.2)		
Black	60 (11.5)		46 (11.0)		14 (13.5)		
Hispanic	98 (18.8)		87 (20.9)		11 (10.6)		
Other	43 (8.3)		37 (8.9)		6 (5.8)		
Etiology, n (%)							**0.037**
HCV	77 (14.8)		54 (13.0)		23 (22.1)		
Alcohol	207 (39.7)		171 (41.0)		36 (34.6)		
NASH	80 (15.4)		60 (14.4)		20 (19.2)		
Other	157 (30.1)		132 (31.7)		25 (24.0)		
Hepatocellular carcinoma, n (%)	58 (11.1)		45 (10.8)		13 (12.5)		0.626
Triggers							0.737
Hepatic	31 (6.0)		26 (6.2)		5 (4.8)		
Extrahepatic	239 (45.9)		186 (44.6)		53 (51.0)		
Others (*e.g.*, incarcerated hernia, anemia, hyperkalemia)	28 (5.4)		23 (5.5)		5 (4.8)		
Unknown	223 (42.8)		182 (43.7)		41 (39.4)		
Presence of diabetes, n (%)	117 (22.5)		83 (19.9)		34 (32.7)		**0.005**
Presence of CKD, n (%)	158 (30.3)		110 (26.4)		48 (46.2)		**<0.0001**
BMI, kg/m^2	29.8 (25.0-35.3)	3.8% (*)	29.6 (24.7-34.6)	5.8%	31.3 (26.3-36.5)	1.4%	**0.013**
BMI group, n (%)							0.198
<25 kg/m^2	123 (23.6)		120 (28.8)		23 (22.1)		
25–<30 kg/m^2	130 (25.9)		106 (25.4)		24 (23.1)		
30–<35 kg/m^2	118 (22.7)		95 (22.8)		23 (22.1)		
≥35 kg/m^2	130 (25.0)		96 (23.0)		34 (32.7)		
White blood cell, count/mm^3	8.4 (5.4-12.3)	1.9%	8.4 (5.4-12.3)	3.8%	7.90 (5.4-12.3)	1.0%	0.300
Albumin, mg/dl	3.1 (2.7-3.5)	0.6%	3.10 (2.7-3.6)	1.0%	3.00 (2.6-3.4)	0.2%	0.175
MELD-Na	39.5 (35.6-42.8)	0.8%	39.7 (36.1-43.0)	1.0%	38.9 (33.8-41.9)	0.2%	0.133
Glucose, mg/dl	115 (96-155)	0.8%	115 (97-152)	1.0%	115 (90-167)	0.2%	0.223
Bilirubin, mg/dl	17.4 (9.3-27.8)	0.8%	17.4 (9.2-28.6)	1.0%	17.4 (9.8-26.9)	0.2%	0.634
Creatinine, mg/dl	1.5 (0.96-2.3)	0.4%	1.5 (1.0-2.2)	1.0%	1.53 (0.9-2.3)	0.2%	0.817
INR	2.5 (1.9-3.0)	0.4%	2.5 (1.9-3.1)	1.0%	2.3 (1.7-2.9)	0.2%	0.636
ACLF category, at ICU admission, n (%)					0.435		
Non-ACLF	73 (14.0)		54 (13.0)		19 (18.3)		
ACLF-1	80 (15.4)		63 (15.1)		17 (16.4)		
ACLF-2	171 (32.8)		142 (34.1)		29 (27.9)		
ACLF-3	197 (37.8)		158 (37.9)		39 (37.5)		
ACLF category at LT, n (%)							0.0233
Non-ACLF	—		—		—		
ACLF-1	—		—		—		
ACLF-2	237 (45.5)		200 (48.0)		37 (35.6)		
ACLF-3	284 (54.5)		217(52.0)		67 (64.4)		
Vasopressor medication use, n (%)							<0.0001
None	250 (48.0)		220 (52.8)		30 (28.9)		
One pressor	146 (28.0)		120 (28.8)		26 (25.0)		
Two or more pressors+	125 (24.0)		77 (18.5)		48 (46.2)		
Renal replacement therapy at transplant, n (%)			0.011				
Unknown/missing	1 (0.19)		1 (0.2)				
None	85 (16.3)		70 (16.8)		15 (14.4)		
HD	129 (24.8)		115 (26.4)		14 (13.5)		
CRRT	306 (58.7)		231 (55.2)		75 (72.1)		
Brain failure at transplant, n (%)	95 (18.2)		66 (15.8)		29 (27.9)		0.004
Ventilator use at transplant, n (%)	252 (48.4)		184 (44.1)		68 (65.4)		<0.0001
Respiratory failure, at transplant, n (%)	132 (25.3)		88 (21.1)		44 (42.3)		<0.0001
MELD-Na, median (IQR) - capped at 40	40.00 (36.0-40.0)		40.0 (36.0-40.0)		39.0 (34.0-40.0)		0.087
Fungal infection							
Presence of fungal infection (**, n [%])	88 (16.89)		69 (16.55)		19 (18.27)		0.675
Presence of MDRB**, n (%)	208 (39.92)		164 (39.33)		44 (42.31)		0.579
Presence of fungal or MDRB**, n (%)	266 (51.06)		211 (50.60)		55 (52.88)		0.677
Donation after cardiac death	73 (14.0)		57 (13.67)		16 (15.38)		0.119
Donor age, years	36.0 (26.0-50.0)	4.0%	36.0 (27.0-50.0)	1.9%	37.0 (26.0-49.0)	0.5%	0.685
Length of stay in ICU before transplant (days)	7.0 (4.0-13.0)	0.0%	7.0 (4.0-13.0)	0.0%	7.0 (4.0-13.0)	0.0%	0.093

(*continued on next page*)

Table 1. (*continued*)

Variables	All included patients (n = 521)		Alive (n = 417)		Dead within 1-year post-LT (n = 104)		
	Median (P25-P75)	Missing (%)	Median (P25-P75)	Missing (%)	Median (P25-P75)	Missing (%)	*p* value
Length of stay after liver transplant (days)	20.0 (13.0-33.0)	1.3%	20.0 (13.0-32.0)	1.0 %	18.0 (12.0-34.0)	0.7 %	0.924
Days from waitlisting to liver transplantation, days	7.0 (3.0-36.0)		7.0 (3.0-36.0)		7.0 (3.00-36.0)		
Survival post-LT (days)	1,143 (579-1,827)	0.0%	1,351 (947-1,933)	0.0%	60.5 (18.5-203.5)	0.0%	**<0.0001**

*Represents missingness.
**During hospitalization.

Overall, the median (IQR) LoS in this cohort after LT was 20.0 (13.0-33.0) days, including those who died within 1 year. Given that 60.6% of deaths occurred within 3 months, we added mortality within 90 days as an independent variable to other variables of the ACLF-LT-LoS score. We removed the only two deaths that occurred during the post-LT hospital stay, since all other deaths occurred after the first post-LT discharge. BMI showed a U-shape association with LoS and was thus transformed into a quadratic component (Table 4). We found that older age, respiratory failure at LT, BMI, and MDRB/fungal infection were independently associated with median LoS. Other factors such as circulatory failure, WBC at LT, and the use of RRT, while not associated with median LoS, were still included within the ACLF-LT-LoS score because of their clinical relevance, with the score demonstrating adequate calibration (Fig. 3).

Clinical applicability

In Fig. 4 we show two different patient clinical scenarios using our two scores, which can be incorporated into the discussion of these patients. In these two patients with severe ACLF, the 1-year mortality probability is 53% with a median LoS of 31 days for a 60-year-old patient, compared to 19% mortality with a median post-LT LoS of 20 days for a 40-year-old patient. The tool can also be used in the following free online calculator https://vocal.shinyapps.io/MODEL/

Discussion

Severe ACLF is common in hospitalized patients admitted with decompensated cirrhosis,[3] and those who are transplanted have good outcomes. However, access to LT for patients with severe ACLF remains poor and there is a need to accurately identify patients who are more likely to benefit. Hereby, our work provides three major findings that can guide decision-making for this clinical conundrum. *First*, older age, factors associated with metabolic syndrome (BMI and diabetes), and respiratory and circulatory failures were independent prognostic factors associated with 1-year mortality after LT. In contrast, prior MDRB or fungal infections, the presence of abdominal surgery or portal vein thrombosis, among others, were not independent predictors of 1-year mortality. *Second*, following strict methodological guidelines and ensuring an adequate sample size, we developed and externally validated a new prognostic model, the SALT-M score, with acceptable calibration and diagnostic accuracy, to predict the probability of death within 1 year after LT using objective and readily available clinical variables. *Finally*, we provided another score to understand factors associated with median LoS after LT, and showed that age, respiratory failure, BMI, and presence of infection were independent covariates associated with the median LoS.

How will the score be used? These patients were transplanted, so their transplant teams considered them good LT candidates. Despite this, the 1-year post-LT mortality was about 20% higher than in patients transplanted without ACLF. In this study, we found a way to identify patients who are at a high risk of suboptimal outcomes after 1 year (highest risk group), the use of which may allow for more careful monitoring of this group post-LT and perhaps enable targeting of modifiable risk factors such as weaning from inotropes or mechanical ventilation, that could offer a way to impact survival. In the clinical vignette (Fig. 4), we show clinicians how to incorporate this model into clinical practice. ACLF is a dynamic disease, and patients at extremely high risk at assessment may improve during their hospital course. Likewise, those who are lower risk may deteriorate after listing and may have a very high model score by the time a donor organ becomes available. So, ideally, the SALT-M score should be applied sequentially. Nevertheless, due to the high mortality risk of patients with severe ACLF, it is a clinical dilemma whether to accept a marginal quality donor organ to allow for earlier LT or wait for either an optimal organ offer or improvement in the number of OFs to increase post-LT survival. Using a Markov decision process model, we showed that LT yielded significantly greater overall survival probability *vs.* remaining on the waiting list for even 1 additional day (p <0.001), regardless of organ quality. Further, the probability of improvement from ACLF-3 to ACLF-2 should not change the recommendations to proceed with LT because the likelihood of organ recovery appears to be less than 10%.[29]

Compared with other scores, the SALT-M score was powered for its development and had the largest sample size to date, with granular patient data overcoming the limitation of transplant registry analyses.[30] The SALT-M score combines transplant candidates' baseline characteristics with patients' precise ICU parameters at the time of LT. The SALT-M score confirms the impact of age on the post-LT mortality outcomes for patients with ACLF-3[31] and shows that diabetes and BMI are also cardinal comorbidities to consider. Concerning ICU characteristics, it confirms that respiratory status significantly impacts the post-LT outcome. Registry studies derived from the UNOS (United Network for Organ Sharing) database have shown that intubation is associated with poorer post-LT outcomes.[32,33] Still, these studies lacked the granularity to assess respiratory status precisely (regarding the indication of intubation and PaO_2/FiO_2 levels). Previous data have shown that the combination of intubation and PaO_2/FiO_2 ratio <200 mmHg was significantly associated with poorer post-LT outcomes.[31]

Table 2. Regression coefficients of logistic regression of the apparent and internally validated.

	Model development			Internal validation
Predictors	**ß-coefficient (SE)**	**Odds (95% CI)**	***p* value**	**ß-coefficient***
Intercept	-3.57 (0.57)		<0.001	-3.41
Variable selection				
Age group				
Age ≤50	Reference			
Age>50	0.39 (0.26)	1.48 (0.89-2.46)	0.13	0.37
Body mass index (continuous)	0.03 (0.02)	1.03 (1.00-1.06)	0.03	0.03
Inotrope use				
None	Reference			
One	0.44 (0.30)	1.56 (0.87-2.79)	0.14	0.41
Two or more	1.28 (0.28)	3.59 (2.06-6.26)	0.00	1.19
Respiratory failure (EASL-CLIF criteria)	0.64 (0.25)	1.91 (1.16-3.13)	0.01	0.60
Diabetes mellitus	0.45 (0.26)	1.56 (0.93-2.61)	0.09	0.42
Performance, discrimination and calibration				
Performance	**Apparent performance (95% CI)**			**Optimism-corrected** (95%CI)**
Nagelkerke's R^2	0.16 (0.10-0.22)			0.13 (0.11-0.16)
Brier score	0.11 (0.06-0.16)			0.09 (0.07-0.11)
AUROC (95% CI)	0.72 (0.69-0.76)			0.71 (0.69-0.72)
Calibration slope	0.99 (0.79-1.19)			0.93 (0.73-1.13)

EASL-CLIF, European Association for the Study of the Liver-Chronic Liver Failure.
*Regression coefficients after adjustment for overfitting by shrinkage (shrinkage factor 0.85).
**Optimism-corrected performance = apparent performance–optimism.

However, we did not consistently collect the PaO_2/FiO_2 ratio or the *arterial* lactate before LT, so we could not reliably replicate the TAM (Transplantation for ACLF-3 Model) score, which has been described to predict mortality 1-year post-LT in recipients with ACLF-3.[31] Finally, the SALT-M score has circulatory failure as a key component. This confirms the importance of assessing the hemodynamic status of LT candidates in the ICU immediately before LT.

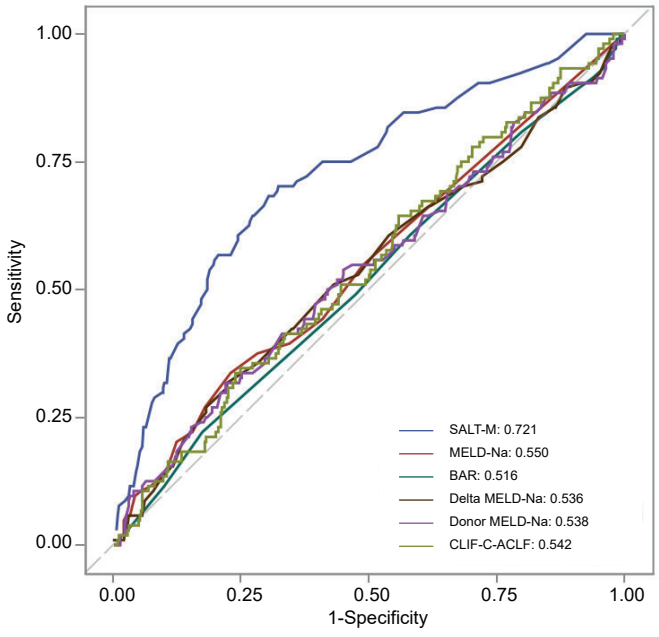

Fig. 2. Discriminatory prediction of different models used in liver transplant candidates to predict 1-year post-liver transplantation. Discriminative ability of the SALT-M score compared to the MELD-Na score,[21] the change in MELD from ICU to transplantation over time (Delta-MELD),[22] donor MELD-Na,[23] the CLIF-C ACLF score[24] and BAR score.[25] BAR, balance of risk; CLIF-C ACLF, Chronic Liver Failure-Consortium acute-on-chronic liver failure; ICU, intensive care unit; MELD(-Na), model for end-stage liver disease-(sodium); SALT-M, Sundaram-ACLF-LT-Mortality. (This figure appears in color on the web.)

The SALT-M score is an important step towards reducing the traditional drop-out rate of 20% in listed patients,[6] since the drop-out cases certainly include some patients who are "too sick for liver transplant". With our model, transplant teams can gain insights about transplant benefits in individual patients. One-year outcomes after LT are a common benchmark used to assess centers' LT performance (13). However, as we move towards 90-day and 365-day grafts in the US, center-specific surgical organ acceptance practices (Summer of 2023), and medical death on waitlist metrics (Summer of 2024),[26] it is expected that listing and transplant behaviors in individual centers will be adapted to these newly measured outcomes over the next 5-10 years. While we are waiting for the implementation of these metrics, our ancillary analyses showed that center-specific mortality rates vary but our model's discriminatory ability is still robust. This study underscores the importance of understanding which patients with ACLF should remain listed and which should be offered a transplant, including of a marginal donor organ.

ACLF care is a burden for all stakeholders. We showed that it increases healthcare costs and that we can estimate the median LoS in these specific populations. Further, an important proportion of these patients have an unmet need for a specialty palliative care consultation at any point during their hospital stay.[34,35] Gustot, Fernandez *et al.* proposed that having a CLIF-C ACLF score of 64 or more (or four OFs) suggested futility and recommended withdrawal of care if patients were not LT candidates.[11] Plotting the SALT-M score value to the predicted probability of post-LT mortality, it would not be unreasonable to consider whether patients with a score of more than 35 should undergo an LT in the setting of ACLF (Fig. 4). The SALT-M estimates need to be considered with caution because, in 28% of cases, the prediction may be incorrect based on the AUROC. Although our example shows a 21% post-LT mortality in the sample patient, it still could be considered a dismal outcome for

Table 3. Discrimination and calibration analysis comparing the SALT-M score and the external validation cohorts from Strasbourg and Hôpital Paul-Brousse, France, in patients transplanted in the setting of ACLF-3 (n = 120).

	Derivation and internally validated data MODEL Consortium		External data (Strasbourg and Paul-Brousse)	
Parameters	**Coefficient**	***p* value**	**Coefficient**	***p* value**
Intercept	-4.38	<0.0001	-8.39	<0.0001
Age 50+	0.63	0.061	2.68	0.002
BMI, continuous	0.04	0.020	0.12	0.003
Inotropes use (yes/no)	1.25	0.001	1.13	0.085
Presence of respiratory failure	0.59	0.055	1.28	0.013
Presence of diabetes mellitus	0.90	0.008	0.68	0.243
Performance	**Internally validated model performance**		**Externally validated model performance**	
Nagelkerke's R^2	0.17 (0.13-0.20)		0.23 (0.22-0.23)	
Brier score	0.11 (0.07-0.14)		0.15 (0.01-0.02)	
AUROC (95% CI)	0.73 (0.70-0.75)		0.80 (0.69-0.87)	
Calibration intercept	-0.15 (-0.34-0.03)		0.36 (0.33-0.40)	
Calibration slope	0.84 (0.62-1.06)		1.38 (1.37-1.39)	

ACLF, acute-on-chronic liver failure; SALT-M, Sundaram-ACLF-LT-Mortality.
Using multivariate logistic regression.

Table 4. Predictors of length of stay (days), calculated using median regression (*).

	Full Model		Selected model (ACLF-LT-LoS)		Baseline model (variables included in the SALT-M)	
	Coeff (SE)	***p* value**	**Coeff (SE)**	***p* value**	**Coeff (SE)**	***p* value**
Intercept	42.51 (11.81)	0.000	45.65 (11.02)	<0.0001	44.43 (12.63)	0.001
Age >50	4.08 (1.52)	0.007	3.83 (1.35)	0.005	2.98 (1.54)	0.053
One inotrope (*vs.* none)	1.92 (2.22)	0.387	2.43 (1.83)	0.185	2.11 (1.87)	0.261
≥2 inotropes (*vs.* none)	0.58 (1.88)	0.757	1.49 (1.69)	0.380	-0.94 (1.88)	0.620
Presence of Diabetes mellitus	1.72 (1.55)	0.268	1.05 (1.69)	0.534	-0.73 (1.94)	0.706
Presence of respiratory failure at LT	6.26 (2.35)	0.008	5.95 (2.45)	0.016	6.84 (2.51)	0.007
BMI, continuous	-1.82 (0.73)	0.013	-1.99 (0.70)	0.005	-1.56 (0.79)	0.050
BMI*BMI	0.02 (0.01)	0.029	0.03 (0.01)	0.013	0.02 (0.01)	0.088
Dead within 90 days	-4.61 (2.15)	0.033	-4.20 (1.77)	0.018	-4.06 (1.89)	0.032
MDRB or fungal infection[b]	4.76 (1.53)	0.002	4.56 (1.58)	0.004		
WBC at LT	0.25 (0.11)	0.022	0.18 (0.11)	0.117		
Renal replacement therapy	-0.04 (1.46)	0.978	0.55 (1.49)	0.713		
Abdominal surgery	1.82 (1.52)	0.230				
Model fit						
ADJUSTED R^2	11.0%		11.1%		9.2%	
Akaike's information criterion (lower better)	2,029.3		2,028.4		2,050.7	

LT, liver transplantation; MDRB, multidrug-resistant bacteria; SALT-M, Sundaram-ACLF-LT-Mortality; WBC, white blood cell count.
*Excluded two patients that died after the LT and before their first discharge and using quantile regression.
[b]during hospitalization

that particular center if it were highly conservative in terms of survival outcomes (*e.g.*, >90%). Future studies in ACLF may need to expand the survival time frame; rather than 1 year, we should look at 5 years (not available in our database): a national colloquium in the UK in 1998 concluded that patients should be offered LT only if the expected odds of 5-year survival are >50%.[36]

Further, we examined independent covariates associated with the median LoS to inform patients/caregivers and providers about the potential burden of prolonged hospitalization. This information can help when discussing prognosis and health equity in these patients with advanced liver disease.[34,37] Hereby, we also provided an online calculator incorporating the probability of within 1-year mortality after LT and estimated median LoS to guide the discussion further when assessing the risks/benefits of LT in patients with severe ACLF.

Our study has some limitations that deserve attention. First, we did not capture the change in the clinical setting (change from or to the ICU to stepdown/ward), but we feel that our results are still robust since we have considered OF(s) at the time of LT. Despite the exclusion of elective intubations, respiratory failure still did not capture those with lung parenchymal disease – a contraindication to orthotopic LT for most transplant centers until there is resolution on imaging and improved oxygen requirements. These should be fixed with prospectively collected data. On the other hand, the dedicated curation of our database creation with rigorous methodology using modern estimation techniques and appropriate sample sizes allowed us to generate, with confidence, the clinically applicable SALT-M score. Second, the study's retrospective nature inherently creates biases, which we tried to minimize by collecting detailed and consecutive data from each clinical site. Also, limiting the data collection to a relatively recent period ensured the availability of granular data with less than 4% missing data. Third, given the retrospective nature of our study, it fails to consider the role of frailty and sarcopenia, which are important

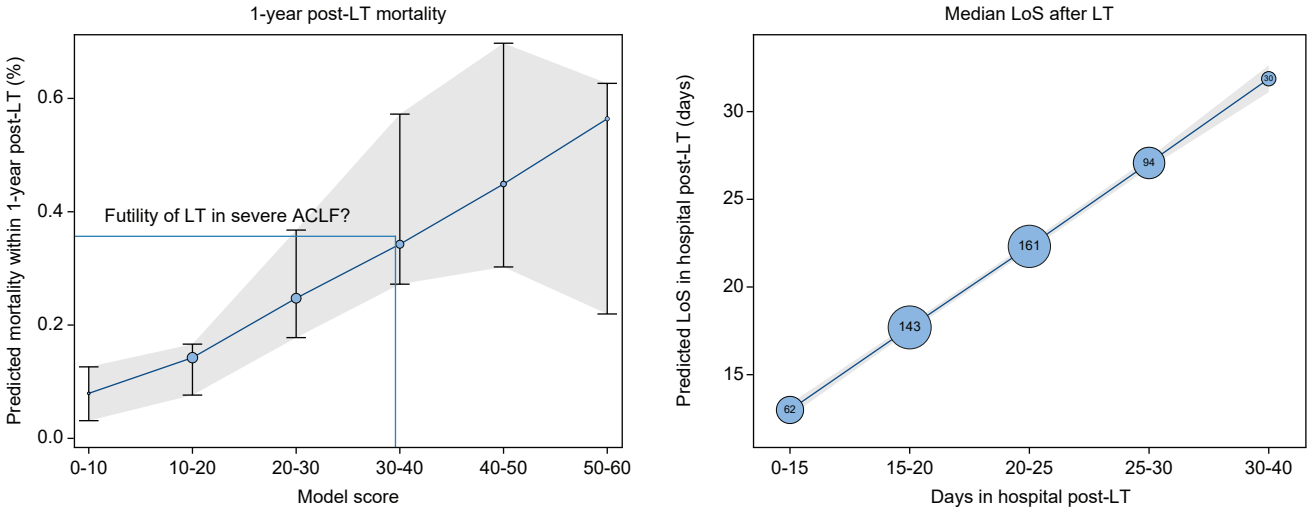

Fig. 3. Calibration plots showing observed *vs.* predicted probability 1-year mortality and median length of stay between LT and first hospital discharge. ACLF, acute-on-chronic liver failure; LoS, length of stay; LT, liver transplantation.

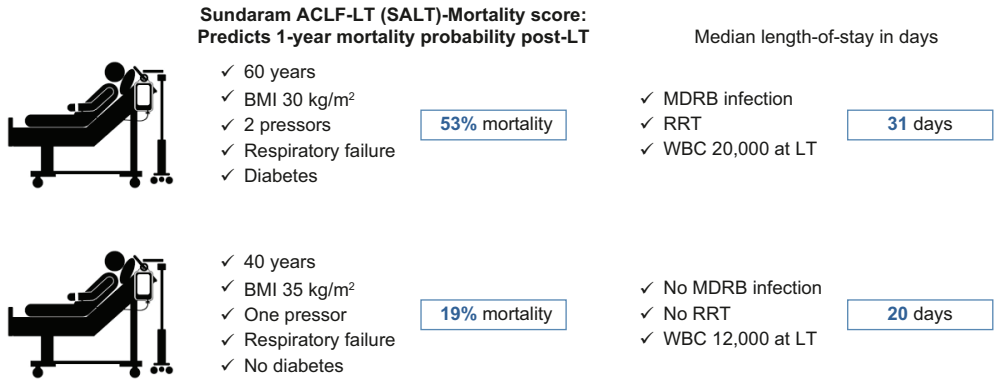

Fig. 4. Example to illustrate how to use the SALT-M and ACLF-LT-LoS scores clinically. LT, liver transplantation; MDRB, multi-drug resistant bacteria; RRT, renal replacement therapy; WBC, white blood cell count.

determinants of post-transplant mortality. Growing evidence indicates that sarcopenia in transplant candidates is an independent predictor of post-transplant survival and LoS.[38,39] We used BMI, but this is an imperfect measure of sarcopenia. Therefore, we believe that future studies in the field of ACLF and LT should address the use of non-invasive tools to assess the prognostic value of sarcopenia.[40,41] Finally, our ACLF-LT-LoS score is still considered an exploratory analysis but can give patients and providers a sense of the burden of hospitalization when transplanting patients with severe ACLF. Future directions of the SALT-M score will include its application to prospective cohort studies (*e.g.* CHANCE study[6]), whether it can be expanded to ACLF 1, and whether additional pre-transplant characteristics ACLF influences our predictive ability (*e.g.*, arterial lactate at LT, PaO_2/FiO_2). In fact, arterial lactate at LT could be superior to the use of inotropes as a surrogate of circulatory failure in patients with ACLF-3, and therefore, it could improve further the performance of the SALT-M score.[5,31]

Additionally, given some deaths were attributable to occult malignancy and cardiac failure in this context of rapid evaluation in unstable and/or critically ill patients, teams should, where possible, perform appropriate investigations, particularly in high-risk groups. Unfortunately, causes of death were not available for 25% of deaths in this study. Future studies addressing mortality outcomes after LT should standardize cause of death data, with a focus on five major categories: cardiovascular, cerebrovascular, cancer, infectious, and graft-related.

In conclusion, we have developed a novel and important clinical decision-making tool that provides essential and relevant information to decide whether the benefits of LT in patients with severe ACLF balance the risk of mortality and LoS.

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Abbreviations

ACLF, acute-on-chronic liver failure; EASL-CLIF, European Association for the Study of the Liver-Chronic Liver Failure; LoS, length of stay; LT, liver transplantation; MDRB, multi-drug resistant bacteria; MODEL, Multi-Organ Dysfunction and Evaluation for Liver Transplantation; OF(s), organ failure(s); RRT, renal replacement therapy; SALT-M, Sundaram ACLF-LT-Mortality.

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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. All other authors declare no conflict of interests.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

All the authors listed above participated in the study concept and design; acquisition of data; interpretation of data; critical revision of the manuscript for important intellectual content; obtained funding; and administrative, technical, or material support; study supervision).

Ruben Hernaez, Yan Liu performed the statistical analysis. Ruben Hernaez, Constatine Karvellas and Rajiv Jalan drafted the initial manuscript. The Consortium authors listed at the end of this manuscript, acquired the data, performed a critical revision of the manuscript, and agreed with the current manuscript.

Data availability statement

The de-identified data are only internally available for the MODEL Consortium researchers after approval of the Ancillary Studies Steering Committee.

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Supplementary data

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Supplemental information

The novel SALT-M score predicts 1-year post-transplant mortality in patients with severe acute-on-chronic liver failure

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Fig. S1. Calibration plot in the Sundaram ACLF-LT (SALT)-M score

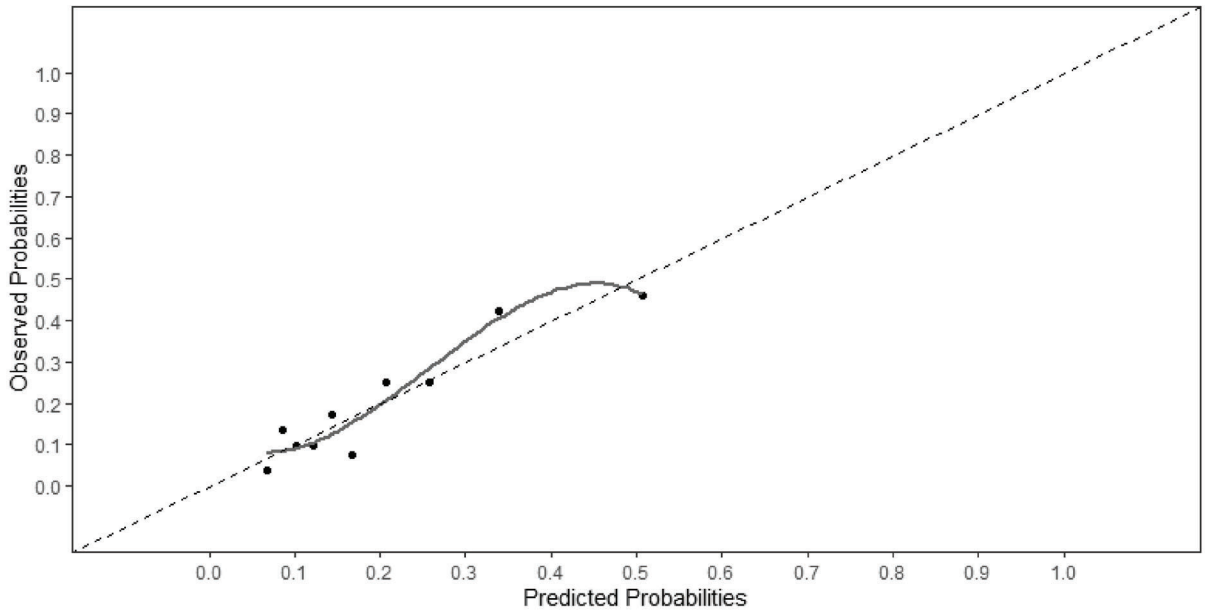

Fig. S2. Calibration plot showing observed vs. expected probabilities using Sundaram ACLF-LT (SALT)-M score

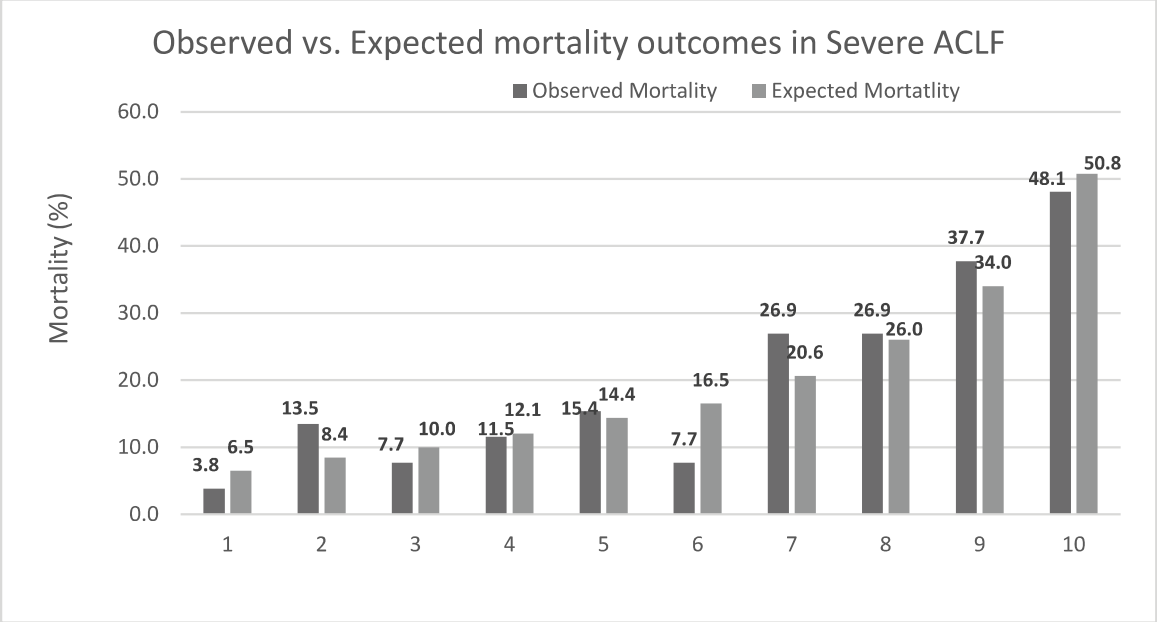

Fig. S3. Calibration plot of the external validation from Strasbourg and Hôpital Paul-Brousse, France in patients transplanted in the setting of ACLF-3 (n=120)

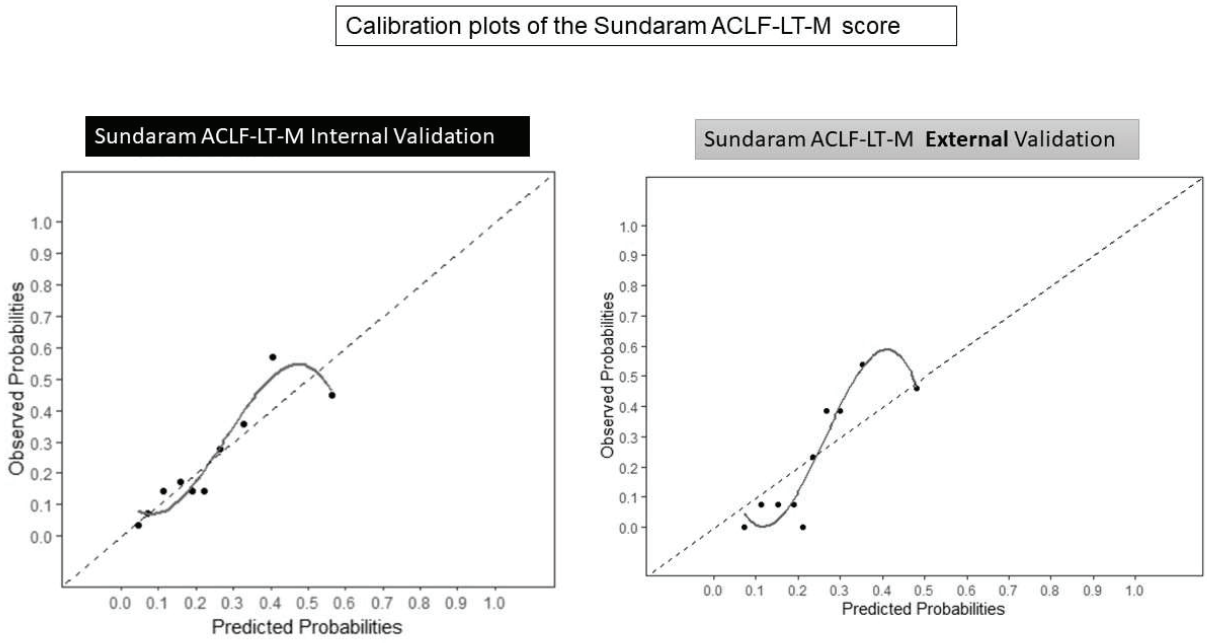

Table S1. Centers from the MODEL Consortium providing patients for this study ranked by contribution to the analytical sample size.

	Original Sample size (n=732)		Analytical sample size (N=521)	
Center	N	%	N	%
Cedars Sinai Medical Center, LA	155	21.1	97	18.6
Piedmont Transplant Institute	98	13.3	88	16.9
University of Maryland, Baltimore	94	12.8	84	16.1
University of Southern California	104	14.2	74	14.2
Cleveland Clinic Foundation,	45	6.1	24	4.6
Mayo Clinic, Rochester	33	4.5	24	4.6
Northwestern University, Chicago	42	5.7	20	3.8
Baylor Scott and White, Dallas	28	3.8	18	3.5
Lahey Clinic Medical Center	18	2.5	17	3.3
Baylor College of Medicine, Houston	30	4.1	16	3.1
Mt. Sinai School of Medicine	19	2.6	16	3.1
University of Colorado	20	2.7	14	2.7
Vanderbilt University Medical Center, Nashville	25	3.4	12	2.3
Oregon Health and Science University	17	2.3	12	2.3
Weill Cornell, NYC	7	1	5	1

Table S2. Comparison between patients included in the analytical cohort vs. those excluded from the analysis

	Overall	Analytical cohort	Excluded from the analysis	P-value
N	**735**	**521**	**214**	
Age +50 years, n(%)	492 (66.9)	337 (64.7)	155 (72.4)	0.043
>50				
Male Sex, n(%)	415 (56.5)	288 (55.3)	127 (59.4)	0.031
Race, n(%)				0.066
White	434 (59.0)	318 (61.0)	116 (54.2)	
Black	87 (11.8)	60 (11.5)	27 (12.6)	
Hispanic	157 (21.4)	98 (18.8)	59 (27.6)	
Other	54 (7.3)	43 (8.3)	11 (5.1)	
Unknown	3 (0.4)	2 (0.4)	1 (0.5)	
BMI (kg/m^2)	30.5 (7.4)	30.6 (7.5)	30.2 (7.4)	0.545
Presence DM, n(%)	188 (25.6)	117 (22.5)	71 (33.2)	0.003
MELD-Na , mean (SD)	35.4 (6.28)	37.0 (4.8)	31.4 (7.6)	<.0001
Dead within 1 year post-LT, n(%)	137 (18.6)	104 (20.0)	33 (15.4)	0.151
LoS-postLT,mean(SD)	27.3 (28.6)	28.7 (29.6)	23.9 (25.7)	0.038

For descriptive statistics, mean with standard deviations or median with range were calculated for continuous data, while proportions (%) were used for categorical data. Comparisons between different events/groups, we used independent Student's t -test or the Wilcoxon's rank-sum test if the distribution was not symmetric for continuous variables. The Mann-Whitney U $\chi 2$ test was used for categorical variables.

Abbreviations: BMI, body mass index; DM: diabetes mellitus: LoS: length of stay; LT: liver transplantation; MELD-Na: model of end-stage liver disease with sodium correction

Table S3. Discriminatory prediction of the Sundaram ACLF-LT (SALT)-M score compared to others

Score	**AUROC (95% CI)**	p-value (vs. Sundaram score)
Sundaram ACLF-LT-M	0.72* (0.69-0.76)	--
MELD-Na [21]	0.55 (0.48-0.61)	<.0001
BAR score [25]	0.52 (0.45-0.58)	<.0001
Delta-MELD [22]	0.54 (0.48-0.60)	<.0001
D_MELD [23]	0.54 (0.47-0.60)	<.0001
CLIF-C-ACLF [24]	0.54 (0.48-0.60)	<.0001

Abbreviations: ACLF-LT-M: acute-on-chronic liver failure liver transplant mortality; MELD-Na: model for end-stage liver disease with sodium correction; BAR: balance of risk; D_MELD: donor_MELD; CLIF-C-ACLF: Chronic Liver Failure-C- acute-on-chronic liver failure score. AUROC: Area under the receiver operating curve
*Model Development

Number in brackets represent the references in the main manuscript, e.g., [21] Biggins S W, Kim WR, Terrault NA, Saab S, Balan V, Schiano T et al. Evidence-based incorporation of serum sodium concentration into MELD. Gastroenterology 2006; 130:1652-1660.

Table S4: Sensitivity analysis showing the robustness of our Sundaram ACLF-LT (SALT)-M score by the addition of candidate variables

Variables	AUROC	Δ AUROC (AUROC new – AUROC model)	AIC	Δ AIC(AICnew-AICmodel)
Sundaram ACFL-LT-M score (Development model)	0.72	---	483.3	----
Brain failure	0.73	0.009	477.6	-5.7
Etiology	0.74	0.021	480.8	-2.5
Dialysis at LT	0.74	0.015	480.8	-2.5
Prior abdominal surgery	0.72	0.000	484.4	1.1
Presence of PVT	0.72	-0.003	484.5	1.2
HCC	0.72	-0.002	484.8	1.5
White blood cell count at LT	0.72	-0.001	484.3	1.0
MELD-Na	0.72	-0.001	484.8	1.5
MDRB	0.72	-0.001	483.7	0.4
Fungal infection	0.72	-0.001	483.7	0.4
MDRB or fungal infection	0.72	-0.001	483.4	0.1
Triggers	0.72	0.002	487.4	4.1
Donation after cardiac death (ref. Donation after Brain Death)	0.726	0.006	483.4	0.1
Main PV or SMV thrombosis	0.723	0.003	484.0	1.3

Abbreviations: AUROC: area under the receiver operating characteristics curve, AIC: Akaike's information Criterion, LT: liver transplantation; MELD-Na: model of end-stage liver disease with sodium correction, MDRB: multidrug resistant bacteria; HCC: hepatocellular carcinoma; PV: portal venous vein; SMV: superior mesenteric vein

Table S5. Discriminatory performance of Sundaram ACLF-LT (SALT)-M score with three additional post-liver transplantation mortality cut-offs

	Within 1 year		Within 3 months		Within 6 months		Within 9 months	
Parameters	**Coeff***	**p-value**	**Coeff**	**p-value**	**Coeff**	**p-value**	**Coeff**	**p-value**
Intercept	-3.57	<.0001	-3.03	<.0001	-3.42	<.0001	-3.53	<.0001
Age 50+	0.39	0.131	0.22	0.408	0.41	0.150	0.37	0.164
BMI (continuous)	0.03	0.03	0.01	0.457	0.02	0.210	0.03	0.054
One inotrope	0.44	0.135	0.06	0.859	0.04	0.898	0.33	0.293
2+ inotropes	1.28	<.0001	1.09	0.000	1.30	0.000	1.38	0.000
Presence of respiratory failure	0.64	0.011	0.30	0.250	0.46	0.089	0.55	0.030
Presence of diabetes mellitus	0.45	0.088	0.36	0.170	0.42	0.130	0.47	0.072
AUROC	0.721		0.712		0.741		0.737	

*using the development model

Abbreviations: DM: diabetes; BMI: body mass index: AUROC: area under the receiver operating characteristics curve

Table S6. Cox proportional hazards regression for the base model (Sundaram ACLF-LT-M) and proportional hazards assumptions check.

Parameter	HR	Proportional Hazards Assumption
Age>50	0.63	0.717
Body mass index	1.41	***0.034***
One inotrope	1.30	0.131
2+ inotropes	1.22	0.217
Presence of respiratory failure at liver transplantation	1.30	0.080
Presence of diabetes mellitus	0.82	0.443

The AUROC for the Cox Proportional hazards model was 0.69 (95% CI: 0.58-0.77). Grey shows violation of proportional hazards assumption.

Table S7. ACLF post-LT one-year mortality stratified by ACLF grade

	Overall (n=521)*		ACLF-2 (n=237)		ACLF-3 (n=284)	
Parameters						
Intercept	-3.57	<.0001	-2.743	0.001	-4.13	<.0001
Age 50+	0.39	0.131	0.146	0.727	0.54	0.098
Body mass index (continuous)	0.03	0.023	-0.083	0.360	0.04	0.025
One inotrope	0.44	0.135	1.089	0.864	0.88	0.032
2+ inotropes	1.28	0.000	-0.036	0.020	1.50	0.000
Presence of respiratory failure (EASL CLIF)	0.64	0.011	0.921	0.053	0.46	0.138
Presence of diabetes mellitus	0.45	0.088	0.02	0.933	0.84	0.012
AUROC (95% CI)	**0.72**		**0.68**		**0.76**	
	(0.67-0.78)		**(0.58-0.77)**		**(0.69-0.82)**	
Calibration data						
Intercept	-0.03		-0.55		0.04	
	(-0.42- 0.35)		(-1.30- 0.19)		(-0.53-0.60)	
Slope	0.93		0.65		1.00	
	(0.73-1.13)		(0.31-1.00)		(0.59-1.41)	

*Using the development model, multivariate logistic regression modeling.

Abbreviations: ACLF: acute-on-chronic liver failure; AUROC: area under the receiver operating characteristics curve. EASL-CLIF: European Association for the Study of the Liver- Chronic Liver Failure

Table S8. Sundaram ACLF Liver Transplantation (SALT)-M score results comparing model performance comparing the original vs. adjustment by center using logistic regression and fixed effect model (center-specfic mortality)

	Final model (Original submission)			**Final model (Adjusted by center, fixed effect)**		
Predictors	**ß-coefficient (se)**	**Odds Ratio (95% CI)**	**p-value**	**ß-coefficient (se)**	**Odds Ratio (95% CI)**	**p-value**
Intercept	-3.49 (0.56)			-3.88 (0.60)		
Age group						
Age ≤50						
Age>50	0.39 (0.26)	1.48 (0.89-2.46)	0.13	0.40 (0.26)	1.49 (0.90-2.49)	0.12
Body mass index	0.03 (0.02)	1.03 (1.00-1.06)	0.03	0.03 (0.01)	1.03 (1.00-1.06)	0.03
Inotropes						
None (reference)						
One	0.44 (0.30)	1.56 (0.87-2.79)	0.14	0.36 (0.30)	1.44 (0.79-2.60)	0.23
Two or more	1.28 (0.28)	3.59 (2.06-6.26)	<0.01	1.07 (0.31)	2.91 (1.59-5.32)	0.001
Respiration failure	0.64 (0.25)	1.91 (1.16-3.13)	0.01	0.62 (0.25)	1.86 (1.13-3.06)	0.08
Diabetes mellitus	0.45 (0.26)	1.56 (0.93-2.61)	0.09	0.47 (0.26)	1.60 (0.95-2.67)	0.01
Center	--	--	--	0.05 (0.03)	**1.05 (0.99-1.11)**	0.1
Performance						
Nagelkerke's R^2	0.17 (0.10-0.24)			0.73 (0.68-0.78)		
Brier score	0.12 (0.06-0.18)			0.16 (0.10-0.23)		
AUROC (95% CI)	0.73 (0.68-0.78)			0.73 (0.68-0.79)		
Calibration intercept	-0.14 (-0.44-0.16)			-0.04 (-0.48-0.40)		
Calibration slope	0.97 (0.74-1.19)			0.92 (0.69-1.15)		

Table S9. Comparison of baseline characteristics between the MODEL Consortium and the external validation from Strasbourg and Hôpital Paul-Brousse, France, in patients transplanted in the setting of ACLF-3 (n=120)

	MODEL Consortium	**French Cohorts**	**P-value**
N	284	120	
Died post LT within 1y (%)	23.6	23.3	0.955
Age 50+,(%)	181 (63.7)	85 (70.8)	0.169
BMI (continuous)			<.0001
Mean (SD)	31.2 (7.7)	27.09 (7.0)	
Median (p25-p75)	30.0 (25.3-36.4)	26.1 (22.6-30.2)	
Inotrope use (yes/no) ,(%)	181 (63.7)	92 (76.7)	0.011
Presence of respiratory failure [EASL-CLIF criteria], yes/no,(%)	103 (36.3)	57 (47.5)	0.035
Presence of Diabetes mellitus,(%)	57 (20.1)	22 (18.3)	0.688

Abbreviations: EASL-CLIF: European Association for the Study of the Liver- Chronic Liver Failure; SD: standard deviation; LT: liver transplantaiton

For descriptive statistics, mean with standard deviations or median with range were calculated for continuous data, while proportions (%) were used for categorical data. Comparisons between different events/groups, we used independent Student's t -test or the Wilcoxon's rank-sum test if the distribution was not symmetric for continuous variables. The Mann-Whitney U $\chi 2$ test was used for categorical variables.

ARTICLE 4

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ORIGINAL ARTICLE

Location and allocation: Inequity of access to liver transplantation for patients with severe acute-on-chronic liver failure in Europe

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Abbreviations: ACLF, acute-on-chronic liver failure; CH, Switzerland; CI, confidence interval; CT, computed tomography; DC, decompensated cirrhosis; DE, Germany; EF-CLIF, European Foundation for the Study of Chronic Liver Failure; ELITA, European Liver and Intestine Transplant Association; ELTR, European Liver Transplant Registry; ES, Spain; FR, France; HCC, hepatocellular carcinoma; ICU, intensive care unit; IT, Italy; LT, liver transplantation; MDR, multidrug resistance; MELD, Model for End-Stage Liver Disease; NL, the Netherlands; PL, Poland; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; UK, United Kingdom; UNOS, United Network for Organ Sharing.

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Abstract

There is growing evidence that liver transplantation (LT) is the most effective treatment for acute-on-chronic liver failure grade-3 (ACLF-3). This study examines whether and how this evidence translates into practice by analyzing the variability in intensive care unit (ICU) admissions, listing strategies, and LT activity for patients with ACLF-3 across transplantation centers in Europe. Consecutive patients who were admitted to the ICU with ACLF-3, whether or not they were listed and/or transplanted with ACLF-3, between 2018 and 2019 were included across 20 transplantation centers. A total of 351 patients with ACLF-3 were included: 33 had been listed prior to developing ACLF-3 and 318 had not been listed at the time of admission to the ICU. There was no correlation between the number of unlisted patients with ACLF-3 admitted to the ICU and the number listed or transplanted while in ACLF-3 across centers. By contrast, there was a correlation between the number of patients listed and the number transplanted while in ACLF-3. About 21% of patients who were listed while in ACLF-3 died on the waiting list or were delisted. The percentage of LT for patients with ACLF-3 varied from 0% to 29% for those transplanted with decompensated cirrhosis across centers (average = 8%), with an I^2 index of 68% (95% confidence interval, 49%–80%), showing substantial heterogeneity among centers. The 1-year survival for all patients with ACLF-3 was significantly higher in centers that listed and transplanted more patients with ACLF-3 (>10 patients) than in centers that listed and transplanted fewer: 36% versus 20%, respectively (p = 0.012). Patients with ACLF-3 face inequity of access to LT across Europe. Waitlisting strategies for patients with ACLF-3 influence their access to LT and, ultimately, their survival.

INTRODUCTION

Liver transplantation (LT) is currently the most effective treatment available for selected critically ill patients with cirrhosis and multiple organ failure. In the absence of LT, the 3-month mortality rate of patients with acute-on-chronic liver failure grade 3 (ACLF-3) has been reported to be as high as 80%.[1]

Several studies have now shown that access to LT may hugely improve the survival of these patients.[2,3] While support for LT increases through the transplantation community, in practice, utilization of LT for patients with ACLF-3 remains a frontier in transplantation, and continues to raise specific ethical and clinical questions.[4]

Extending LT for patients with ACLF-3 potentially requires fundamental changes to intensive care unit (ICU) admission practices, listing strategies, surgical and anesthesiologic techniques, and post-LT management. It also requires carefully balancing the individual benefit of LT for patients with ACLF-3 against the collective utility of LT for the broader community of transplantation candidates.

While previous registry or multicenter studies on LT for patients with ACLF-3 have predominantly focused on post-LT *outcomes* among groups of transplantation centers, this report focuses on variations of *practices* among individual transplantation centers, offering an analytic panorama of the access to LT for patients with ACLF-3 across Europe.

In particular, this study aims to describe variation in the access to three key steps of LT for patients with ACLF-3: ICU admission, listing, and transplantation. First, we investigate the issue of ICU access for patients with ACLF-3 and analyze the reasons for which some patients were admitted to the ICU but were not listed for LT. Second, we assess the relationship between listing strategies and LT activity. In particular, we determine the percentage of patients listed with ACLF-3 who actually went on to receive LT. Third, we assess the variability in LT activity for ACLF-3 across centers. Finally, we conduct a survival analysis of all patients with ACLF-3 according to the inclination of centers to list patients with ACLF-3 for LT.

PATIENTS AND METHODS

Study cohort

This study is a collaboration among the European Liver and Intestine Transplant Association (ELITA), the European Liver Transplant Registry (ELTR), and the European Foundation for the Study of Chronic Liver Failure (EF-CLIF). A total of 20 centers from 8 European countries participated in the study. Consecutive patients between January 1, 2018, and June 30, 2019, were retrospectively included if (i) they were admitted to the ICU with ACLF-3 or developed ACLF-3 3–7 days after admission to the ICU and/or if (ii) they were transplanted with ACLF-3. In parallel, total LT activity, LT activity for hepatocellular carcinoma (HCC), and DC during the same period were recorded in each center.

Diagnostic criteria of ACLF and data collection

Diagnostic criteria of ACLF and its grades and data collection details have been described previously.[5] The definition and grades of the CLIF-Consortium were strictly followed.

Ethical and regulatory approval

Data were collected in accordance with the General Data Protection Regulation, the European Union legislation, and the ELTR privacy declaration. All procedures were followed in accordance with STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines.[6]

Statistical analysis

We assessed the correlation between the total number of patients transplanted in each center and the number of patients transplanted for HCC, DC, and ACLF-3 by analyzing the Kendall tau correlation. The variability of ACLF-3 LT activity was represented through a forest plot, reporting center-specific estimates of proportion of LTs for ACLF-3 among LTs for DC in each center. Confidence intervals (CIs) at a 95% level for the proportions were computed using the Clopper–Pearson method. The pooled estimate of the total proportion was obtained from a fixed-effects meta-analysis, based on a generalized linear mixed-effects model. I^2, with its 95% CI, and χ^2, with correlated p value, were reported as measures of heterogeneity among centers.

The relationship between the number of patients listed with ACLF-3 and the number of patients transplanted with ACLF-3 was also explored using the Kendall tau correlation coefficient, as was the relationship between the number of patients admitted to the ICU and the number of patients listed/transplanted with ACLF-3.

The overall 1-year survival analysis from the time of ACLF-3 diagnosis was stratified according to the number of patients listed for LT with ACLF-3 over the study period in each center. Survival curves were computed using the Kaplan–Meier method and compared with the log-rank test.

Centers were stratified into high- and low-listing centers according to the number of patients that were listed over the study period. The cutoff was determined to minimize the difference in the number of patients in each group. When stratifying by high- and low-listing centers, distribution of categorical variables was compared using χ^2 or Fisher's exact tests. All tests were two-sided and used a significance level of 0.05.

All statistical analyses were conducted using R version 4.0.2 (R Core Team, Vienna, Austria) with the

specific packages ggplot2, survival, survminer, metafor, ggpubr, and cowplot.

RESULTS

Study population

A total of 351 patients with ACLF-3 were included (Figure 1): 318 were not listed at the time of admission in the ICU and 33 had already been listed prior to developing ACLF-3.

Over the study period, a total of 2683 LTs were performed across the 20 centers (Table 1). As many as 1226 LTs were performed for DC, 897 for HCC, and 560 for other indications.

The four centers (FR1, FR2, FR3, and FR4) that transplanted the highest number of patients with ACLF-3 (>10 over the study period) were also the centers that listed the most patients with ACLF-3: they were identified as "high-listing/transplanting centers", as opposed to "low-listing/transplanting centers" (UK1, UK2, ES1, NL1, DE1, IT1, IT2, IT3, IT4, IT5, and PL1). The five centers that did not provide data on the total number of patients admitted to the ICU with ACLF-3 were not included in the analyses comparing high- and low-listing/transplanting centers (ES2, DE2, IT6, IT7, CH1). The full list of participating centers is provided in Table S1.

ICU admissions and access to the transplantation list for patients with ACLF-3 in Europe

The number of unlisted patients admitted to the ICU ranged from 5 to 62 across the cohort (Table 1 and Figure 2A). The number of patients listed with ACLF-3 ranged from 0 to 16 across centers. The ratio of patients listed to patients admitted to the ICU ranging from 0% to 80% (Figure 2A).

There was no significant correlation between the number of patients admitted to the ICU and the number of patients listed with ACLF-3 (Figure 2B) or those transplanted with ACLF-3 (Figure S1).

Among the 227 patients who were admitted to the ICU with ACLF-3 but not listed, the most frequent reason for not listing was illness severity (88 patients, 39%; Table 2). Addiction issues (62 patients, 28%), comorbidities (30 patients, 13%) and uncontrolled bacterial infection (21 patients, 9%) were the other important causes (Table 2).

When comparing high- and low-listing/transplanting centers, a significant difference was only observed for the illness severity criteria (31% vs. 46%; $p = 0.042$).

There were individual differences in the balance of the main reasons for not listing patients among centers (Figure S1), with no clear pattern emerging.

In addition, the percentage of female patients not listed was not significantly different between the high- and low-listing/transplanting centers (27% vs. 29%; $p = 0.79$), as was the mean age of patients not listed (55 vs. 53 years; $p = 0.14$).

Relationship between listing and transplanting patients with ACLF-3

Among the 91 patients who were *listed* while in ACLF-3 (Figure 3A), the majority (65 patients, 71%) were transplanted with ACLF-3 and 19 patients (21%) died or were delisted before LT (none of these 19 patients were alive 1 year after listing).

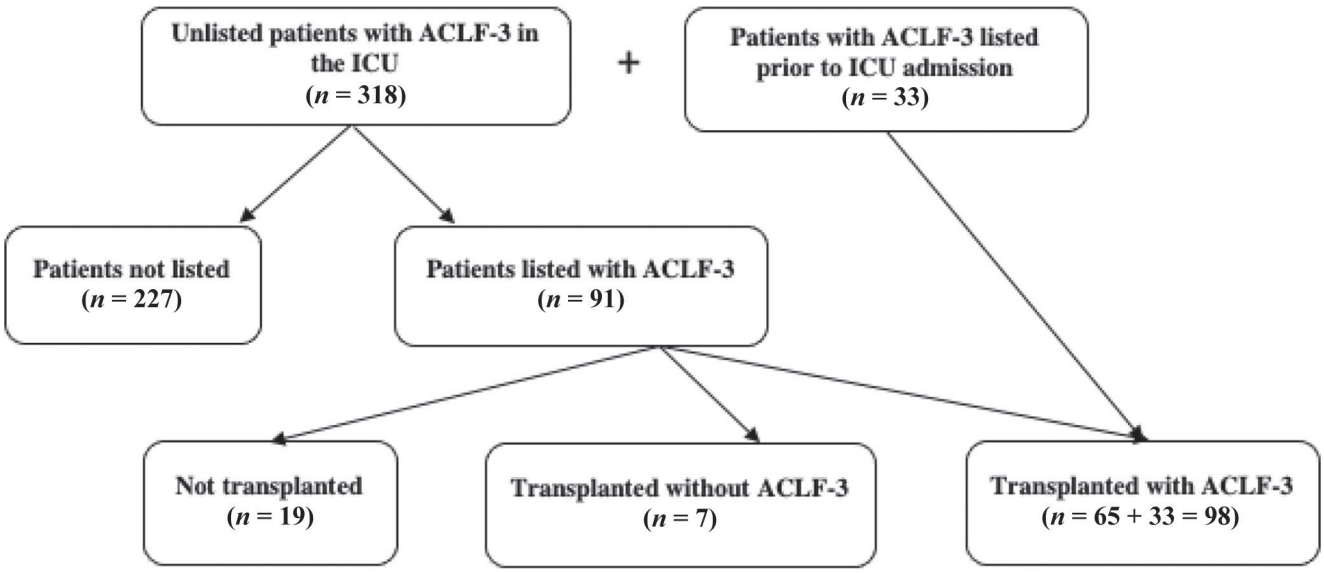

FIGURE 1 Study flowchart.

TABLE 1 Transplantation activity, ICU admission of ACLF-3 patients, and listing of patients with ACLF-3 across centers

Center	Total number of LTs	LT for DC	LT for HCC	LT for other indications	LT for ACLF-3	Unlisted patients admitted to the ICU with ACLF-3 (patients subsequently listed with ACLF-3, %)
FR1	250	100	76	75	12	62 (16, 26)
FR2	120	69	39	12	20	47 (16, 34)
FR3	107	55	28	24	12	24 (9, 38)
FR4	136	92	36	8	16	23 (16, 70)
UK1	310	160	70	70	6	42 (6, 14)
UK2	185	115	33	37	0	16 (0, 0)
ES1	112	51	32	29	1	28 (1, 4)
ES2	117	50	54	13	0	NA[a] (0)
NL1	114	59	40	24	3	14 (3, 21)
DE1	16	14	2	0	3	12 (1, 8)
DE2	69	27	19	23	4	NA[a] (3)
IT1	121	33	68	20	6	9 (3, 33)
IT2	76	38	34	4	2	7 (3, 43)
IT3	142	56	65	21	0	7 (0, 0)
IT4	164	68	84	12	2	6 (1, 17)
IT5	81	36	30	15	3	5 (4, 80)
IT6	114	53	34	27	2	NA[a] (2)
IT7	199	79	98	22	3	NA[a] (2)
PL1	184	45	22	117	1	6 (2, 33)
CH1	66	26	33	7	2	NA[a]
Total	2683	1226	897	560	98	318 (91)

Abbreviations: ACLF, acute-on-chronic liver failure; CH, Switzerland; DC, decompensated cirrhosis; DE, Germany; ES, Spain; FR, France; HCC, hepatocellular carcinoma; ICU, intensive care unit; IT, Italy; LT, liver transplantation; NL, the Netherlands; PL, Poland; UK, United Kingdom.
[a]Five centers could not provide data on patients admitted to the ICU and not listed/transplanted.

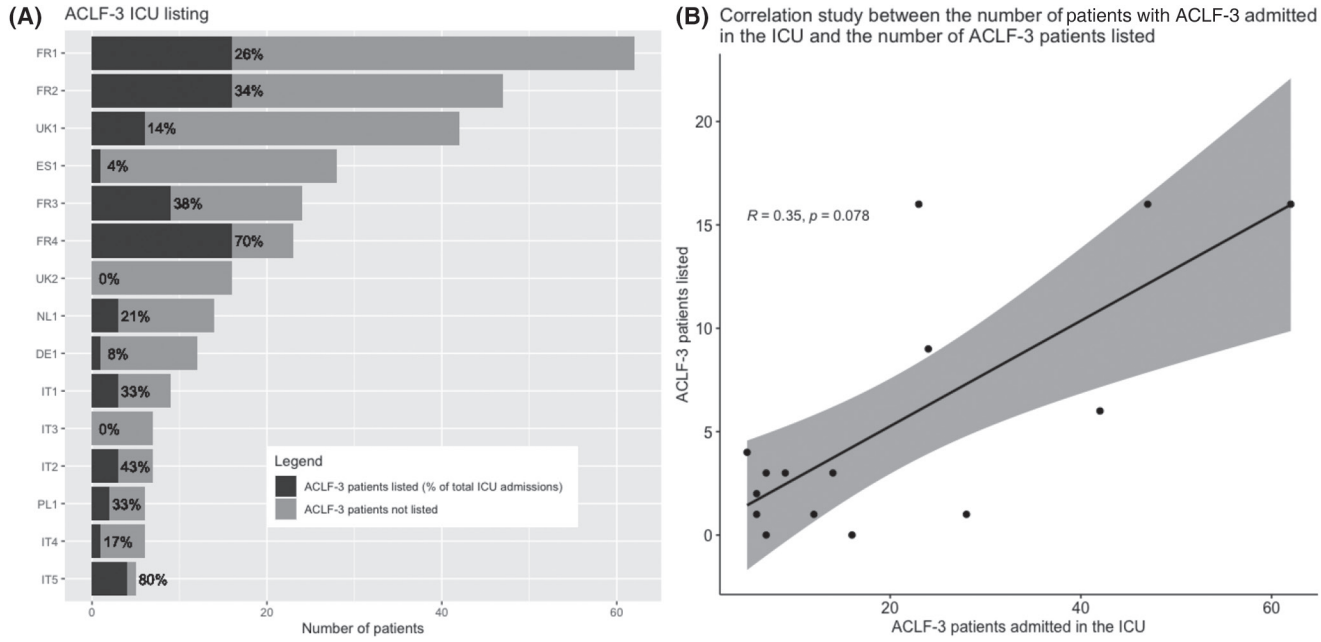

FIGURE 2 Barplot (A) and correlation study (B) of ICU admission and listing strategies for patients with ACLF-3[a]. [a]Five centers did not provide data on patients admitted to the ICU and not listed/transplanted.

TABLE 2 Main reason for not listing patients with ACLF-3 in the ICU

Main reason for not listing	Total[a] (*N* = 227)	High-listing/transplanting centers[b] (*N* = 99)	Low-listing/transplanting centers[c] (*N* = 128)	*p* value
Illness severity	88 (39)	31 (31)	57 (46)	0.04
Addiction	62 (28)	32 (32)	30 (24)	0.14
Comorbidities	30 (13)	16 (16)	14 (11)	0.25
Uncontrolled bacterial infection	21 (9)	8 (8)	13 (10)	0.59
Other	23 (10)	12 (12)	11 (8.8)	0.38

Note: Data are presented as *n* (%).

Abbreviations: ACLF, acute-on-chronic liver failure; ICU, intensive care unit.

[a]The main reason for not listing was not provided for three patients in the low-listing group.

[b]"High-listing/transplanting centers": Four centers that listed the most patients (and that were also the centers which transplanted >10 patients with ACLF-3 over the study period).

[c]"Low-listing/transplanting centers": The 11 other centers. (The four remaining centers that did not provide data on patients in the ICU with ACLF-3 who were not listed were not included in this analysis.)

Among the 98 patients who were *transplanted* with ACLF-3 over the study period, 65 (66%) were also *listed* while in ACLF-3 (Figure 3B). The makeup of the population of patients transplanted with ACLF-3 was similar across centers. In particular, among the centers that transplanted patients with ACLF-3, none of them restricted the access to LT for patients who had been listed prior to developing ACLF.

There was a significant correlation between listing and transplanting patients with ACLF-3 (correlation coefficient: 0.8; $p<0.0001$; Figure 3D). In particular, the 4 centers that transplanted the highest number of patients with ACLF-3 were also the centers that listed the highest number of patients with ACLF-3 (red box in Figure 3A–C).

Variability of LT activity for patients with ACLF-3 across the cohort

On average, LT for ACLF-3 accounted for 8% of patients transplanted for decompensated cirrhosis (DC) in the study cohort. However, the number of LTs for patients with ACLF-3 ranged from 0 (in three centers) to 20 patients across transplantation centers, with percentages ranging from 0% to 29% (Figure 4). The forest plot of LT activity for ACLF-3 shows consistent variation of such percentage among centers, with an I^2 of 67.7% (95% CI 48.6%-79.7%) showing substantial heterogeneity, confirmed by the χ^2 test ($p<0.01$).

There was a significant correlation between the transplantation volume of the LT center over the study period and both the number of LTs performed for HCC (correlation coefficient: 0.55; $p = 0.00082$) and for DC (correlation coefficient: 0.66; $p<0.0001$; Figure S1A,B).

By contrast, there was no significant correlation between LT center transplantation volume and the number of LTs performed for ACLF-3 (Figure S1C) or between the number of LTs for DC and the number for ACLF-3 (Figure S1D).

Analysis of overall survival depending on the type of center (high listing/transplanting vs. low)

One-year survival of the whole cohort (including patients admitted to the ICU but not listed, and all those listed and transplanted with ACLF-3) from the time of ACLF-3 diagnosis was significantly higher in the four centers that listed/transplanted the most patients in ACLF-3 when compared with the 11 other centers (36% vs. 20%, respectively; $p = 0.012$; Figure 5).

On intention to transplantation analysis for patients listed while in ACLF-3, the overall 1-year survival was 64%, with no significant difference between high-listing and low-listing centers (71% vs. 60%, respectively; $p = 0.25$; none of the patients listed while in ACLF-3 who were not transplanted survived 1 year).

Finally, the 1-year survival of patients transplanted while in ACLF-3 was 79% with no significant difference between high-listing and low-listing centers (76% vs. 80%, respectively, $p = 0.71$).

DISCUSSION

The results of this study reveal a substantial variability of LT activity for patients with ACLF-3 across European transplantation centers. This is despite the observation that the overall 1-year survival of patients with ACLF-3 from the time of ACLF-3 diagnosis was significantly higher in centers that listed and transplanted more patients with ACLF-3 than in centers that listed and transplanted fewer. It is important to note that there was no correlation between the number of patients transplanted with ACLF-3 and the volume of LTs performed by individual centers. In addition, the number of patients with ACLF-3 admitted in the ICU and the number of patients who were listed for LT with ACLF-3 was unrelated. The main reason for not waitlisting patients with ACLF-3 differed between the

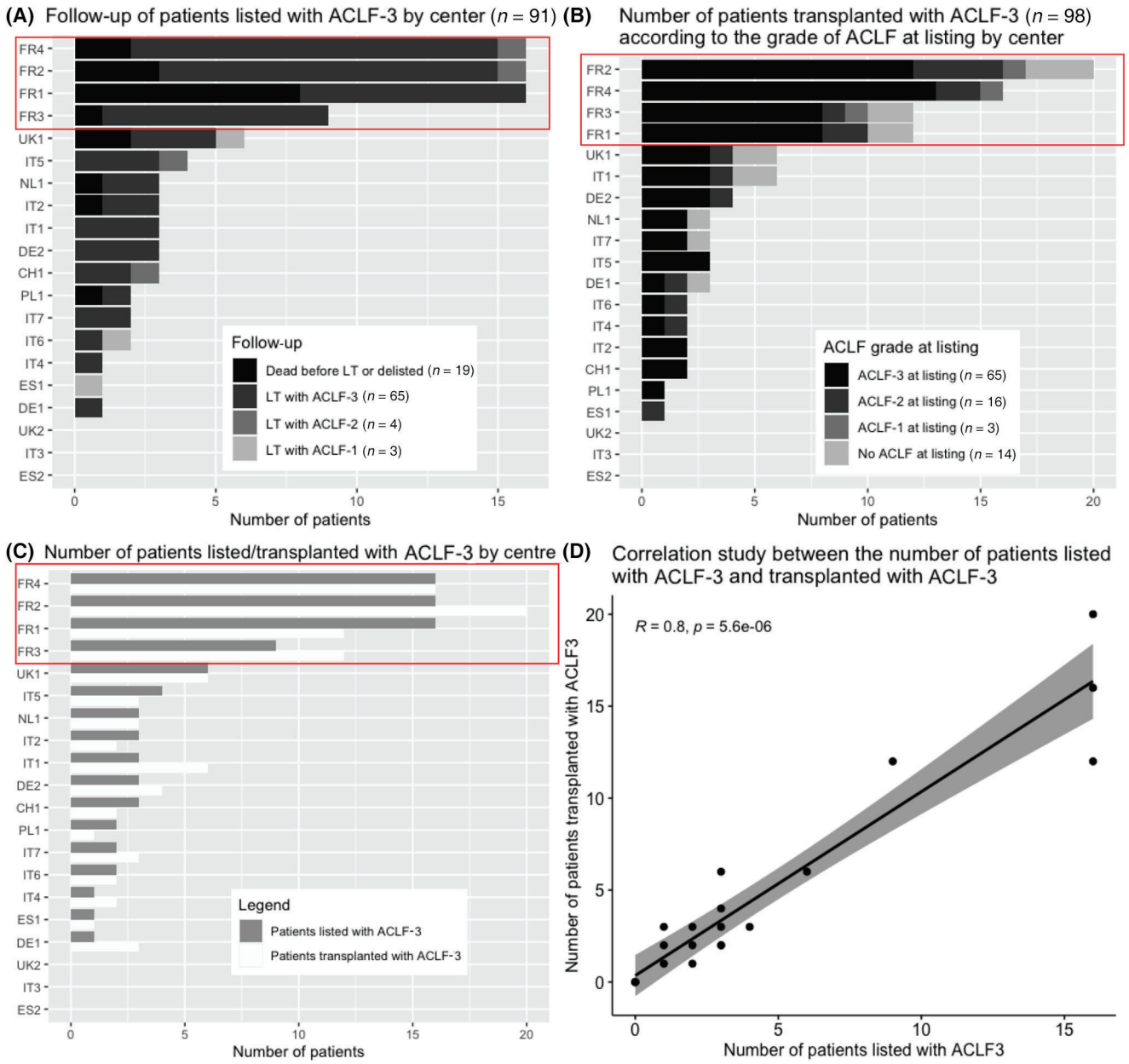

FIGURE 3 Barplots (A–C) and correlation study (D) of listing and transplanting strategies for patients with ACLF-3.

two groups of "higher" and "lower" listing centers, with the low-listing group more commonly citing illness severity as a reason for not listing patients with ACLF-3.

Taken together, the results of this study help clarify three key steps in the clinical management of patients with ACLF-3.

First, it shows that ICU admission practices of patients with ACLF-3 vary across centers but this does not correlate with their waitlisting strategies for LT. In particular, admitting higher numbers of unlisted patients with ACLF-3 to the ICU did not translate into more waitlisting and greater access to LT for these patients.

Second, the attitude of the center toward waitlisting patients with ACLF-3 was a key element that defined the variability of transplantation activity for these patients across centers. In practice, this implies that a transplantation program for patients with ACLF-3 may require listing patients who are too ill to be transplanted at the time of listing, optimizing their care in the ICU, and potentially transplanting them later, when a degree of improvement has occurred. It was therefore striking that the criterion that distinguished high- and low-listing centers as the principal reason for not listing patients with ACLF-3 in the ICU was illness severity, rather than comorbidities or addiction issues. There was a strong and significant correlation between waitlisting and LT while patients had ACLF-3. The majority (66%) of patients who were transplanted with ACLF-3 had been listed while they had ACLF-3 and only 14% of patients transplanted with ACLF-3 had been listed

Center	Liver transplants for ACLF-3	Liver transplants for DC	% Liver transplants for ACLF-3 (95% CI)
UK1	6	160	3.8 [1.4–8.0]
UK2	0	115	0.0 [0.0–3.2]
FR1	12	100	12.0 [6.4–20.0]
FR4	16	92	17.4 [10.3–26.7]
IT7	3	79	3.8 [0.8–10.7]
FR2	20	69	29.0 [18.7–41.2]
IT4	2	68	2.9 [0.4–10.2]
NL1	3	59	5.1 [1.1–14.1]
IT3	0	56	0.0 [0.0–6.4]
FR3	12	55	21.8 [11.8–35.0]
IT6	2	53	3.8 [0.5–13.0]
ES1	1	51	2.0 [0.0–10.4]
ES2	0	50	0.0 [0.0–7.1]
PL1	1	45	2.2 [0.1–11.8]
IT2	2	38	5.3 [0.6–17.7]
IT5	3	36	8.3 [1.8–22.5]
IT1	6	33	18.2 [7.0–35.5]
DE2	4	27	14.8 [4.2–33.7]
CH1	2	26	7.7 [0.9–25.1]
DE1	3	14	21.4 [4.7–50.8]
Total	**98**	**1226**	**8.0 [6.6–9.6]**

Heterogeneity: I^2 = 67.7% [48.6%–79.7%], χ^2_{19} = 58.9 (p < 0.01)

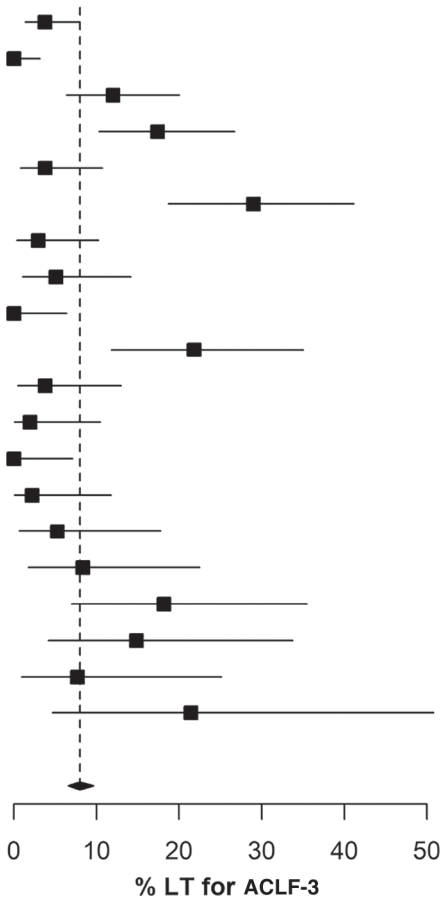

FIGURE 4 Forest plot of the percentage of LT for ACLF-3 over LT for decompensated cirrhosis (DC) across European centers.

prior to developing ACLF (30% had been listed with ACLF-1 or ACLF-2). This finding implies that transplanting critically ill patients requires being able to fast-track the pre-LT assessment of patients who have often not been previously considered as LT candidates by the transplantation team. It is a clinical challenge that requires obtaining medical and psychosocial background information about the patient and organizing multidisciplinary decision-making meetings with different team members rapidly on the basis of what may be limited or fragmentary information (when the patient is intubated, for example).

Third, the percentage of patients who were listed with ACLF-3 but died on the waiting list or were delisted was much lower (21%) than that reported in the literature, in particular in the United Network for Organ Sharing (UNOS) database.[7] The data suggest that this may be due to many patients with ACLF-3 not being listed at all because they are thought to be too sick. In addition, it may suggest that in Europe, patients listed with ACLF-3 are less likely to need prioritization beyond the Model for End-Stage Liver Disease (MELD) score to have access to LT (the median time from listing to transplantation was 5 days for patients listed with ACLF-3). In other words, variations in listing strategies for patients with ACLF-3 seem to be the main obstacle for their access to LT. Interestingly, the four centers that listed and transplanted most patients came from France, where there is no extra prioritization for patients with ACLF beyond the MELD score (this is also the case in the other countries included in this study) and where it has been shown that there are also important variations in access to LT for critically ill patients with cirrhosis despite a single, centralized allocation algorithm.[8] However, whether lack of prioritization prevents patients with ACLF-3 from being listed is beyond the scope of this study.

The observation that the main difference between the low- and the high-volume centers was that the patients were thought to be too ill to undergo LT in the low-volume centers suggests a lack of consensus defining which patients with ACLF-3 should not be transplanted. It is therefore crucial to distinguish criteria that should be used to decide that a patient is too sick to be *listed* for LT (based chiefly on comorbidities) from criteria to decide that a patient is too sick to be *transplanted* at

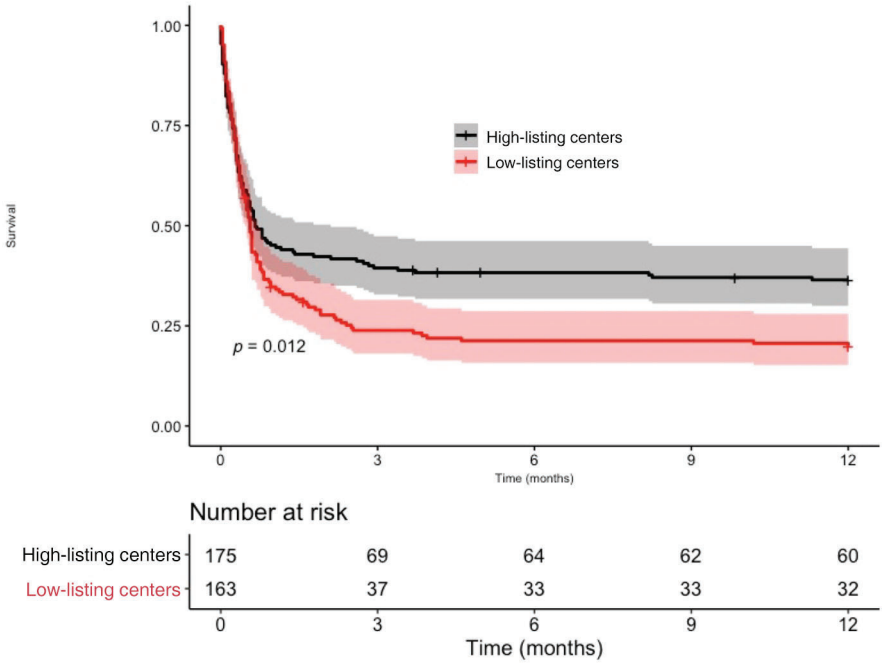

FIGURE 5 Survival analysis depending on the type of center (high-listing/transplanting vs. low).

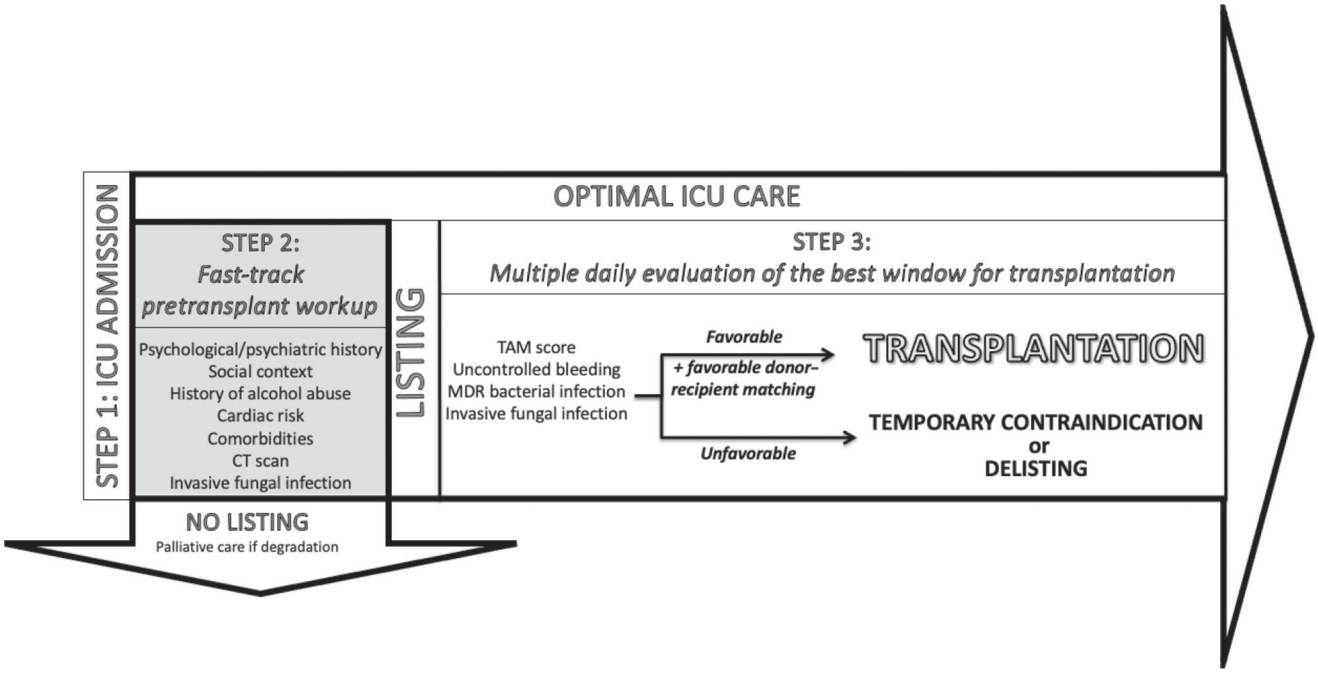

FIGURE 6 Management algorithm for patients with ACLF-3.

the time when an organ becomes available (Figure 6). Granular studies have shown that respiratory failure, arterial lactate level, age, the transplantation for ACLF-3 model score, multidrug resistant organism and fungal infections are useful criteria to judge whether a patient is too sick to be transplanted at the time of organ availability, based on poor post-LT survival.[5,9–11] Without this appreciation and consensus, we risk transplanting too few patients with ACLF-3 or too many with poor outcomes, thereby funneling scarce resources to patients with potentially unacceptably low post-LT survival rates.

The variability of LT activity for patients with ACLF-3 among European transplantation centers described in this study highlights the inequity of access to LT for patients with ACLF-3. This variability among centers also reflects a lack of consensus among European

transplantation teams on this specific indication of LT. Such a lack of consensus is possibly due to the relative scarcity of prospectively collected data. While studies from the UNOS registry report >80% 1-year post-LT survival rates for patients with ACLF-3,[12] smaller case series studies report contrasting findings. Some, including the results from the current series, report similar post-LT survival,[5,13] while others report significantly poorer results.[10,14] To date, only one registry study has reported on longer-term survival.[15] In addition to this relative scarcity of data, the variability of LT activity probably also relates to diverging views concerning the overall utilization of LT and its application to patients with DC. There are justifiable concerns that more widespread use of LT for patients with ACLF-3 could disadvantage candidates with cirrhosis who were listed without ACLF with a "traditional" elective pre-LT assessment and more certainty of optimal outcomes.

The scope of this study is limited by its retrospective nature and by the limited number of patients included over selected centers in Europe. However, it uses granular data and reports exhaustively on all patients treated. The other major limitation is that we did not did not report on patients with ACLF-3 who did not have access to the ICU. To date, no study has been able to provide a consistent picture of this subgroup of critically ill patients with cirrhosis who are denied access to the ICU and whose epidemiology remains hard to assess.

CONCLUSION

The results of this study highlight the inequity of access to LT that patients with ACLF-3 experience across European transplantation centers. It underlines how listing strategies for patients with ACLF-3 influence their access to LT and, ultimately, their survival. Finally, this study demonstrates the lack of practical consensus among European transplantation teams on this specific indication of LT, highlighting the need for more prospective data defining the role of LT in ACLF-3.

AUTHOR CONTRIBUTIONS

Luca S. Belli, Christophe Duvoux, Thierry Artzner, William Bernal, and Rajiv Jalan were responsible for study concept and design. Luca S. Belli, Thierry Artzner, William Bernal, Sophie-Caroline Sacleux, George-Philippe Pageaux, Sylvie Radenne, Jonel Trebicka, Javier Fernandez, Giovanni Perricone, Salvatore Piano, Silvio Nadalin, Maria C. Morelli, Silvia Martini, Wojciech G. Polak, Krzysztof Zieniewicz, Christian Toso, Marina Berenguer, Claudia Iegri, Federica Invernizzi, Riccardo Volpes, François Faitot, Liane Rabinowich, Faouzi Saliba, Lucy Meunier, Mickael Lesurtel, Frank E. Uschner, Constantino Fondevila, Baptiste Michard, Audrey Coilly, Magdalena Meszaros, and Domitille Poinsot performed data collection. Sara Conti, Paolo A. Cortesi, Luca S. Belli, George-Philippe Pageaux, Christophe Duvoux, Thierry Artzner, William Bernal, and Rajiv Jalan performed analysis and interpretation of data. Thierry Artzner, Luca S. Belli, William Bernal, and Rajiv Jalan wrote the paper. Luca S. Belli, Thierry Artzner, William Bernal, Sara Conti, Paolo A. Cortesi, Sophie-Caroline Sacleux, George-Philippe Pageaux, Sylvie Radenne, Jonel Trebicka, Javier Fernandez, Giovanni Perricone, Salvatore Piano, Silvio Nadalin, Maria C. Morelli, Silvia Martini, Wojciech G. Polak, Krzysztof Zieniewicz, Christian Toso, Marina Berenguer, Claudia Iegri, Federica Invernizzi, Riccardo Volpes, François Faitot, Liane Rabinowich, Faouzi Saliba, Lucy Meunier, Mickael Lesurtel, Frank E. Uschner, Constantino Fondevila, Baptiste Michard, Audrey Coilly, Magdalena Meszaros, Domitille Poinsot, Paolo Angeli, Vincent Karam, René Adam, Vincente Arroyo, and Rajiv Jalan were responsible for the revision of this paper for important intellectual content and the final approval of the version to be published.

CONFLICT OF INTEREST

Paolo Angeli advises, is on the speakers' bureau for, and received grants from BioVie; advises and is on the speakers' bureau for Grifols; is on the speakers' bureau for and received grants from Gilead Italy; on the speakers' bureau for Roche and Pfizer; and advises CSL Behring. Marina Berenguer consults for Intercept, AbbVie, and Orphalan and has received grants from Gilead. Costantino Fondevila received grants from Guangdong Shunde Innovative Design Institute. Rajiv Jalan owns stock and intellectual property rights in, is employed by, consults for, advises, and received grants from Yaqrit Ltd. and consults for, advises, and received grants from Grifols. Vincente Arroyo advises Grifols.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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ARTICLE 5

JOURNAL
OF HEPATOLOGY

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

To the Editor:

Liver transplantation (LT) is currently the most effective treatment available for critically ill individuals with cirrhosis and multiple organ failure, provided they are carefully selected.[1] While support for LT for those with grade 3 acute-on-chronic liver failure (ACLF-3) is theoretically increasing within the transplant community, 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 individuals 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 intensive care unit (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

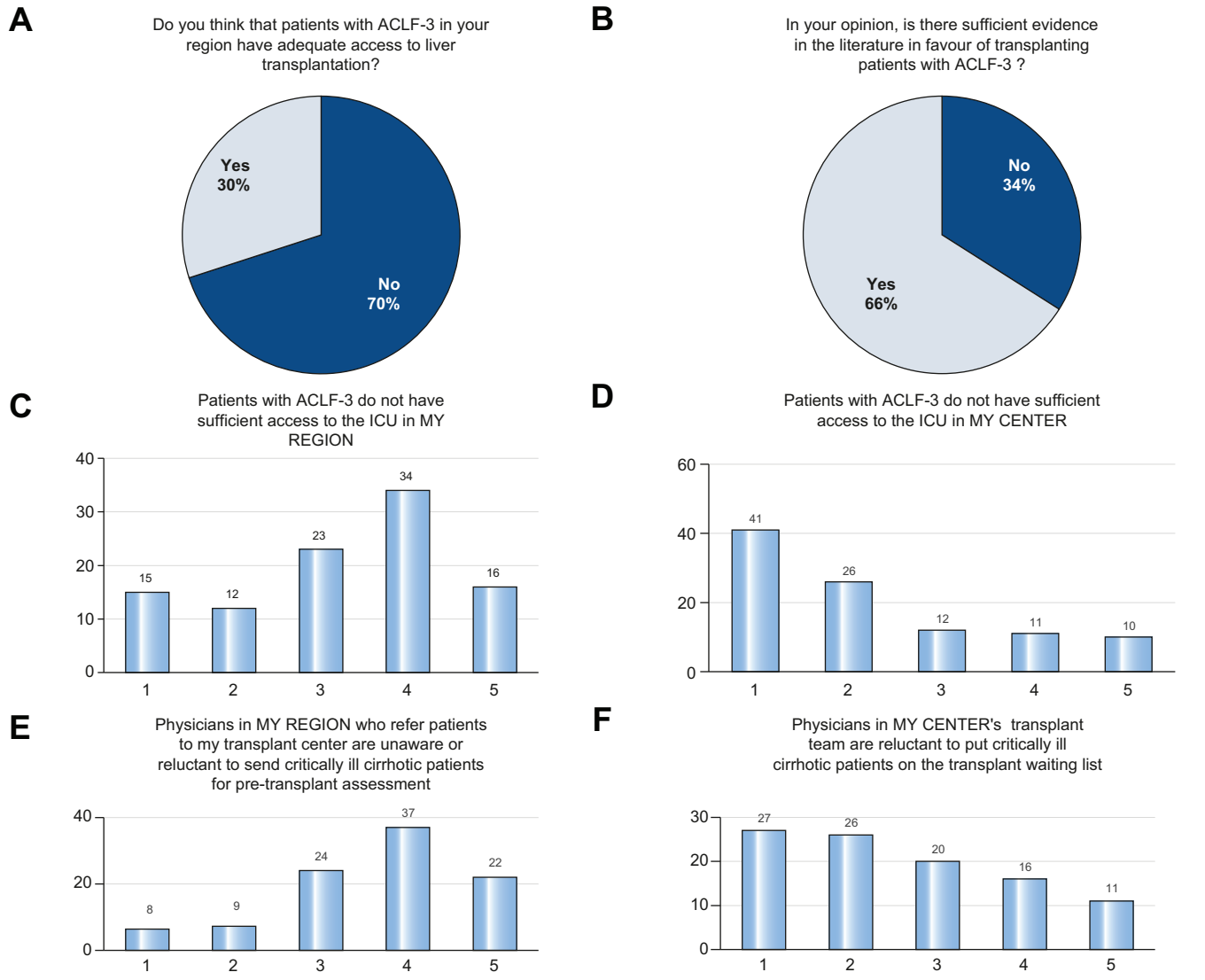

Fig. 1. Selected responses to the ACLF liver transplant questionnaire. ACLF, acute-on-chronic liver failure; ICU, intensive care unit.

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 individual with cirrhosis.

This survey was designed through discussion between experts of EF-CLIF 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 individuals 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 individuals 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 those with ACLF-3. Despite such evidence, 70% declared that individuals with ACLF-3 did not have adequate access to LT in their region (Fig. 1A,B). 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 (Fig. 1C,D).

While 27 respondents noted that colleagues in their own transplant centers were reluctant to put critically ill individuals with cirrhosis on the transplant waiting list, this was reported more frequently (59 respondents) by physicians who referred patients to LT centers but did not directly work in them (Fig. 1E,F). When respondents were asked to identify the group(s) of physicians that was/were most unwilling to consider LT for individuals 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 individuals with ACLF-3, with 48 respondents declaring that the average waiting time for those with ACLF-3 was too long in their center. When asked whether the allocation system in their region/country did not prioritize those 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 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 individuals with ACLF-3. It illustrates the growing view that the use of LT should be expanded for individuals 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 those 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 those with ACLF-3 should be considered for ICU admission, referral to a tertiary LT center and pre-transplant work-up for potential listing.

Expanding the use of LT for those with ACLF-3 is a medical undertaking different in nature and broader in scope than increasing access to a particular drug, intensive care support or surgical technique. It requires widespread discussion, education and further research, which will change the way the medical community thinks about managing critically ill individuals with cirrhosis.

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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.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

All authors contributed equally to this work. Concept: TA, LB, FF, RJ. Writing: TA, LB, FF, RJ. Revision for important intellectual content and final approval of the version to be published: TA, LB, FF, RJ.

Supplementary data

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Unmasking a hepatitis C genotype 3a/1b dual infection in an individual treated with elbasvir/grazoprevir

To the Editor:

Pan-genotypic direct-acting antivirals (DAAs) for the treatment of HCV infections remain expensive. To reduce costs, genotype-specific regimens can be considered, according to the EASL guidelines.[1] The presence of mixed genotype HCV infections has been reported, and detection rates have been found to be method dependent.[2] The identification of a second infection with a different genotype could be of importance when considering genotype-specific DAAs.

A 33-year-old male presented to our outpatient clinic with a newly diagnosed HIV-1/HCV co-infection with a CD4 count of 470/ml, CDC-classification B2. He had recently migrated from the Ukraine to the Netherlands and was not treated previously for HIV or HCV. As a potential source of infection, he reported the use of unsterilized needles during a hospital visit 10 years prior. He reported no intravenous drug use nor sex with men. HCV-RNA viral load was 1,500,000 IU/ml and a genotype 1b infection was reported.[3] FibroScan showed no signs of fibrosis (6.5 kPa; Metavir F0–F1). Treatment with bictegravir/emtricitabine/tenofoviralafenamide was initiated for the HIV infection and 18 weeks thereafter the patient started a 12-week course of elbasvir/grazoprevir according to Dutch HCV treatment guidelines.

Six weeks after HCV treatment initiation the HCV-RNA load was 1,100,000 IU/ml. He reported no issues with adherence and HIV-1 RNA was undetectable in the same sample. A reinfection or baseline mixed infection was suspected, and genotyping showed the presence of a genotype 3a infection at this time point. Sequence analysis using Sanger sequencing showed an A156G RAS (resistance-associated substitution) in the NS3 gene, which is associated with a 1,654-fold reduced susceptibility to glecaprevir.[4] In addition, we detected N244T as a potential RAS in the NS5B gene, of which the clinical significance is unknown. No RASs in the NS5A gene were detected.

Reanalysing the raw Sanger sequencing data of the sample prior to initiation of DAAs, by specifically investigating the presence of minor or ambiguous peaks, suggested the presence of a minority genotype 3a co-infection, without mutations in NS3, but with the previously described N244T mutation in the NS5B gene. Elbasvir/grazoprevir was stopped and 6 weeks after cessation the genotype 1b infection was no longer detected using the same technique. We started a 12-week course of the pan-genotypic treatment with sofosbuvir/velpatasvir/voxilaprevir (Vosevi), which resulted in a sustained virological response.

This case demonstrates that in individuals in whom genotype-specific DAAs fail, genotyping and resistance analysis should be considered prior to retreatment. Alternatively, pan-genotypic regimens could be considered as a treatment option.

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SUPPLEMENTARY ARTICLE 1

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LETTER TO THE EDITOR

Causes of variability in listing and access to liver transplantation for critically ill patients with cirrhosis: Acknowledging the elephant in the room

To the editor,

We appreciate the interest of Yehuda and Ramona in our study.[1] They raise two important points.

First, they note that a "fast-track pre-transplant assessment is impractical in many ICU-admitted unlisted ACLF-3 patients since essential pre-transplant cardiac workup is frequently unobtainable in critically ill candidates." We beg to differ. First, transthoracic echocardiogram is easily available in intensive care units (ICUs). Second, though patients cannot undergo cardiac stress tests, coronary angiography can be performed, even if it sometimes requires transferring the patients to another hospital temporarily. Finally, further explorations of right heart function and pressure can be directly performed in the ICU when required with pulmonary artery catheterization. While cardiac evaluation raises technical issues that can be overcome, the authors underline another obstacle to fast-track assessment: social and psychiatric assessment of alcohol addiction. True, the ICU is not an appropriate setting to undergo such an evaluation. But there is no way around this predicament and evaluating critically ill patients with alcohol-related liver disease for transplantation candidacy will always remain an ethical puzzle and rely on some degree of subjectivity on the part of individual clinicians and transplantation teams. Listing patients while they are in the ICU is therefore both a technical and an ethical challenge, and we hope that our article constitutes a springboard to debate the role of liver transplantation for critically ill patients with cirrhosis and the importance of collaborations between intensivists and transplantation teams.

The second point that Yehuda and Ramona raise relates to the underlying causes of variability in listing and transplanting practices. While we agree in theory that epidemiological factors and illness severity may conceivably drive some of the variability, our study shows variation in access to transplantation to a degree (from 0% to 29% of patients transplanted with decompensated cirrhosis across centers) that cannot be explained solely by these factors.

Concerning epidemiological factors, useful clinical granular data concerning critically ill cirrhotic patients in Europe simply do not exist to assess the epidemiology of acute-on-chronic liver failure grade 3 (ACLF-3) across Europe meaningfully. Besides, dramatic variations in transplantation practices are observed across French transplantation centers, despite this country's single-organ allocation algorithm and presumably smaller epidemiological variations than those potentially at play at the level of Europe.[2]

Concerning illness severity, the study period was 18 months long, which left enough time for patients with various degrees of illness severity to be admitted in each center. Besides, we believe that there is no straightforward way of assessing illness severity for a critically ill transplantation candidate with cirrhosis throughout their stay in the ICU. The Model for End-Stage Liver Disease (MELD), Sequential Organ Failure Assessment (SOFA), and CLIF scores predict transplantation-free mortality[3] but not posttransplantation outcomes for patients in the ICU.[4] An additional pitfall of clinical scores is that they fail to capture the dynamic dimension of illness severity during the ICU stay, which can change dramatically within hours. At the bedside, subjective clinical judgment, which apprehends organ failures dynamically and with greater detail (taking into account the dose of norepinephrine and its variation through time, for example), which takes into account specific ICU biomarkers (such as arterial lactate level), and which captures the subtleties of sepsis (the virulence of the germ involved, the response to treatment), supersedes attempts to categorize complex critically ill transplantation candidates along a single, simplistic scale. Capturing the objective reason for which a critically ill patient in the ICU was deemed too sick to be transplanted is therefore extremely complex both retrospectively and prospectively.

To conclude, one of the aims of our study is not so much to provide an airtight scientific causal account of the variability observed across transplantation centers but rather to acknowledge and illustrate the practical lack of consensus that the transplantation community faces on this topic in Europe, leading to disparities of access to a life-saving treatment.

CONFLICT OF INTEREST

Rajiv Jalan owns stock in and is a founder of Yaqrit Ltd, Hepyx Ltd, and CyberLiver Ltd.

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SUPPLEMENTARY ARTICLE 2

Intensive Care Med
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WHAT'S NEW IN INTENSIVE CARE

Liver transplantation for patients with severe acute on chronic liver failure: it is time to change paradigms

Thierry Artzner[1*], Javier Fernandez[2,3] and Rajiv Jalan[3,4]

I. **Using liver transplantation to make the difference for patients with severe acute on chronic liver failure**

The outcome of critically ill cirrhotic patients in the intensive care unit (ICU) with life support is associated with high mortality rates. The development of the concept of acute-on-chronic liver failure (ACLF) over the past decade has underlined the importance of interactions between hepatic and extra hepatic organ failures [1, 2]. This condition, which occurs in hospitalized cirrhotic patients with multiorgan failure, is stratified into different prognostic groups dependent upon the number of organ failures and response to intervention (diagnostic criteria and grading are described in the ESM Table). It has also led to renewed interest in liver transplantation (LT) to cure this deadly condition and offer patients a chance of long-term survival. A number of granular and registry studies have reported one-year post-LT survival rates above 80% [3, 4] and 5-years post-LT survival rates above 60% for patients with the most severe form of ACLF: ACLF-3 (ACLF with three or more organ failures) [5]. These studies demonstrate a key concept: that LT is capable of reversing both hepatic and extra-hepatic organ failure in severe ACLF. This concept already supports the use of LT for acute liver failure (ALF) in ICUs and LT centers across the world and was described as nothing short of a miracle in its early days. To be sure, the etiology, natural history, prognosis, epidemiology and clinical management of ALF and ACLF are markedly different. ALF typically occurs in patients without preexisting liver disease, it is rarer and most often due to viral infection or acute drug toxicity. Nevertheless, LT delivers a similar promise in both cases: replacing the liver can resolve and reverse multiorgan failure. In practice, this effectively means that LT can save the lives of cirrhotic patients who require mechanical ventilation, vasopressors and renal replacement therapy, provided they are selected carefully.

Up to now, discussions over the use of LT for ACLF-3 patients have largely taken place within the field of hepatology and the subspecialty of transplant medicine. This article highlights the crucial role of critical care support for patients with ACLF-3 as a bridge to early transplant.

II. **Reducing inequity in access to LT for patient with ACLF-3: improving referrals to LT centers and pre-LT workup in the ICU**

Despite promising reports in the literature, epidemiological studies have shown that, in practice, LT for ACLF-3 patients varies across transplant centers, leading to inequities in access to this life-saving treatment [6–8]. A recent survey, conducted among LT specialists and intensivists, revealed that a majority of respondents considered that patients with ACLF-3 do not have adequate access to LT in their region [9]. Inadequate access to ICUs in secondary care centers and limited referral from these ICUs to transplant centers are identified as key obstacles in providing ACLF-3 patients with access to LT. Fostering new attitudes toward LT for ACLF-3 patients and

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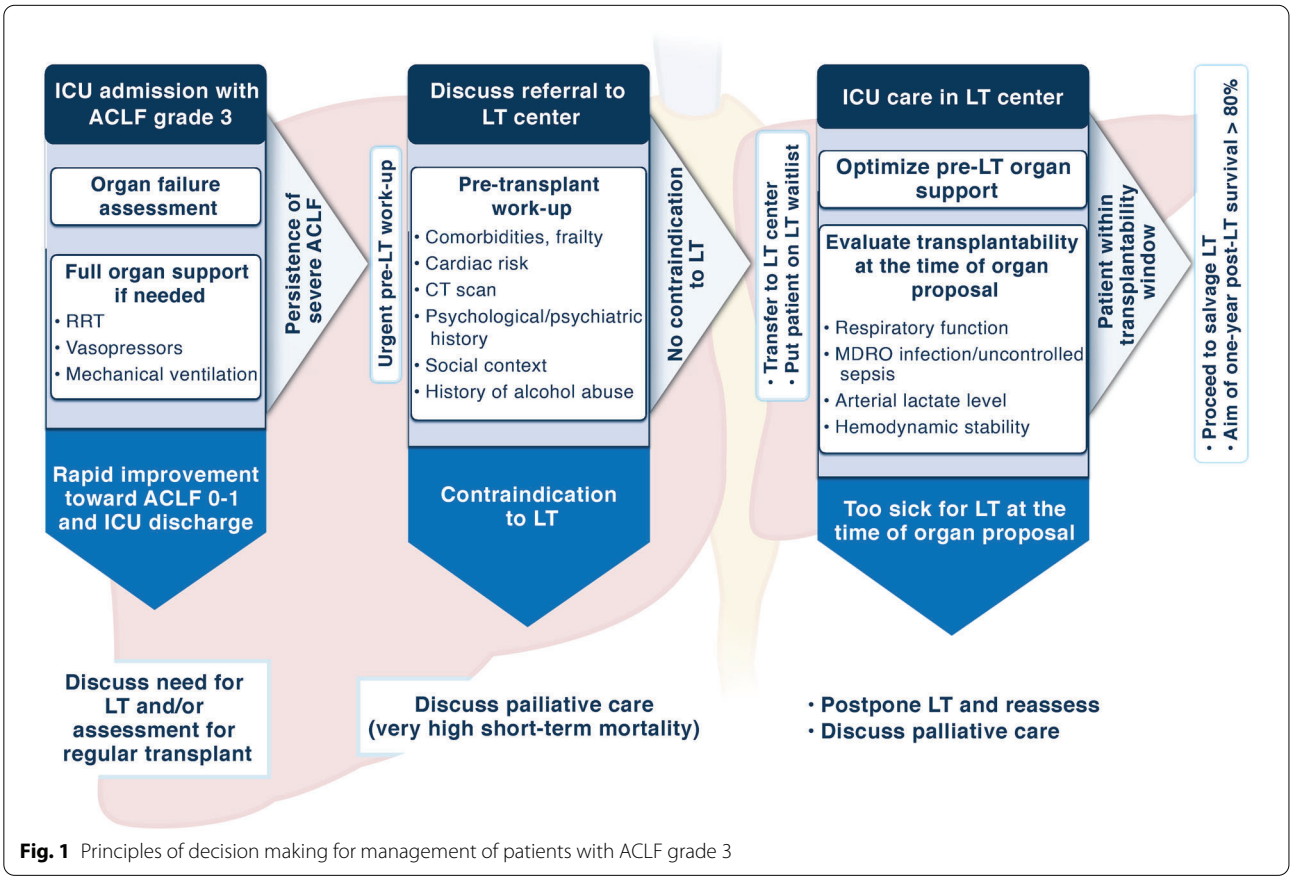

Fig. 1 Principles of decision making for management of patients with ACLF grade 3

promoting referral networks from peripheral ICUs to transplant centers is therefore a timely undertaking. This will undoubtedly lead to lively debates (in particular over the issue of transplanting patients with alcohol-related cirrhosis, especially when they are active drinkers), but it promises to provide more widespread and fairer access to a life-saving treatment.

A second key result derived from these studies is that giving access to LT for ACLF-3 patients relies on the capacity to undertake a full pre-LT workup in the ICU [7]. While this is customary for patients who need to be transplanted urgently with ALF, pre-LT workup of ACLF-3 patients is typically more complex, since these patients are generally older and have more comorbidities. In particular, evaluation of social status, psychological background and risk of relapse to alcohol abuse is challenging when patients are under multiorgan support (principles of clinical decision-making in these patients are summarized in Fig. 1).

Delivering LT to ACLF-3 patients does not rely on access to a particular drug, medical device or surgical technique; it relies on changing attitudes toward the care of ACLF-3 patients requiring organ support.

III. The ethical predicament of LT for patients with ACLF-3

Advocating access to LT for all patients with ACLF-3 is unrealistic, irresponsible and unfounded. Indeed, the field of solid organ transplantation is characterized by donor shortages. Thus, each and every individual decision to put a patient on an organ waitlist must take into consideration this situation as well as the collective utility of LT. Indeed, current 1-year post-LT survival in the general population of transplanted patients is well above 80%. All the studies reporting post-LT outcomes for ACLF-3 patients have relied on transplant candidates that had been selected by transplant teams. In addition, several small granular studies have reported significantly poorer post-LT results for such patients [10, 11]. While this does not question the individual benefit of LT for these patients, it highlights the importance of being able to deny access to LT for critically ill patients whose post-LT prognosis is poorest, in order

to avoid funneling scarce resources to patients with unacceptably low post-LT survival.

IV. Identifying the transplantability window in the ICU to optimize post-LT outcomes

The clinical course of ACLF-3 patients in the ICU is erratic and the exact timing of deceased donor organ availability is, in essence, unpredictable. Identifying the transplantability window, which is often narrow for these critically ill patients, is therefore crucial to ensure that LT is a reasonable clinical course of action.

Several pre-LT risk factors of post-LT mortality have been identified in ACLF-3 patients. These include both recipient baseline characteristics (age, history of diabetes, portal vein thrombosis and frailty) and specific ICU features (arterial lactate level, increasing vasopressor requirements, ongoing infection with multi-drug resistant or fungal organism, respiratory failure with $PaO_2/FiO_2 < 200$ mmHg) [6, 8, 12, 13]. In addition, clinical deterioration of patients prior to LT has been shown to be associated with lower post-LT survival [14, 15].

However, there is no consensus over the exact combination of factors defining the transplantability window. Ongoing [16] and future studies, involving both transplant specialists and intensivists will therefore be crucial to delineating more clearly the boundaries of LT for these patients.

Supplementary Information
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Declarations

Conflicts of interest
TA and JF have nothing to disclose. RJ 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.

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SUPPLEMENTARY ARTICLE 3

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ORIGINAL ARTICLE

Liver transplantation for critically ill cirrhotic patients: Stratifying utility based on pretransplant factors

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The aim of this study was to produce a prognostic model to help predict posttransplant survival in patients transplanted with grade-3 acute-on-chronic liver failure (ACLF-3). Patients with ACLF-3 who underwent liver transplantation (LT) between 2007 and 2017 in 5 transplant centers were included (n = 152). Predictors of 1-year mortality were retrospectively screened and tested on a single center training cohort and subsequently tested on an independent multicenter cohort composed of the 4 other centers. Four independent pretransplant risk factors were associated with 1-year mortality after transplantation in the training cohort: age ≥53 years (P = .044),

Abbreviations: ACLF, acute-on-chronic liver failure; AUROC, area under receiver operating characteristic; BAR, balance of risk; CLIF, Chronic Liver Failure Consortium; EASL, European Association for the Study of the Liver; G-CSF, granulocyte-colony stimulating factor; ICU, intensive care unit; IQR, interquartile range; LT, liver transplantation; MELD, model for end-stage liver disease; NASH, non-alcoholic steatohepatitis; P-SOFT, preallocation score to predict survival outcomes following liver transplantation; ROC, receiver operating characteristic; SD, standard deviation; SOFA, sequential organ failure assessment; TAM, transplantation for ACLF-3 model; UNOS, United Network for Organ Sharing.

Thierry Artzner and Baptiste Michard are co-first authors.

pre-LT arterial lactate level ≥4 mml/L (P = .013), mechanical ventilation with PaO_2/FiO_2 ≤ 200 mm Hg (P = .026), and pre-LT leukocyte count ≤10 G/L (P = .004). A simplified version of the model was derived by assigning 1 point to each risk factor: the transplantation for Aclf-3 model (TAM) score. A cut-off at 2 points distinguished a high-risk group (score >2) from a low-risk group (score ≤2) with 1-year survival of 8.3% vs 83.9% respectively (P < .001). This model was subsequently validated in the independent multicenter cohort. The TAM score can help stratify posttransplant survival and identify an optimal transplantation window for patients with ACLF-3.

KEYWORDS

acute-on-chronic liver failure, clinical research/practice, ethics, ethics and public policy, liver disease, liver transplantation, liver transplantation/hepatology, organ allocation, organ procurement and allocation

1 | INTRODUCTION

Liver transplantation (LT) for cirrhotic patients with grade-3 acute-on-chronic liver failure (ACLF-3) is a controversial procedure. The dismal transplant-free prognosis of these patients has been established repeatedly and a number of accurate tools are already available to assess their prognosis.[1-3] Salvage LT is currently the only specific treatment available that has demonstrated significant individual benefit for these patients.[4-7] However, the collective utility of LT in the context of organ shortage remains debated.

In recent years, LT for patients with ACLF-3 has been considered feasible, with reports of 1-year survival rates above 80%.[4-6] Some authors have therefore argued in favor of prioritizing access to livers for patients with ACLF by taking into account the organ failures that do not feature in the model for end-stage liver disease (MELD) score.[5,8] However, conflicting results have been reported for ACLF-3 patients with 1-year survival rates below 50%.[9,10] Such poor outcomes weigh against giving access to organs for ACLF-3 patients (let alone prioritizing them), given the organ shortage.

Two guiding principles need to be balanced in order to guarantee the equity and the performance of our transplantation programs in the context of critically ill cirrhotic patients. First, we should indeed prioritize access to LT for critically ill patients, provided they have high post-LT survival rates. Second, we should limit the access of those with poor post-LT survival rates in order to prevent a massive funneling of scarce resources to patients with potentially unacceptably low post-LT survival rates. To date, there is no model designed specifically to assess the post-LT prognosis of patients with ACLF-3. Such a model would be crucial to help clinicians who need to discriminate the patients who will benefit most from LT from those who are "too sick to be transplanted."

This study was specifically designed to address this issue. A number of pre-LT factors were screened in univariate analysis and entered into a multivariate regression. A model was subsequently developed and tested on an independent multicenter validation cohort.

2 | METHODS

2.1 | Study population

The consecutive patients who received LT between January 1, 2007 and June 30, 2017 from 4 transplant centers in France (Hôpital de Hautepierre in Strasbourg, Hôpital Beaujon in Clichy, Hôpital Henri Mondor in Créteil, Hôpital Trousseau in Tours) and 1 center in the United Kingdom (King's College Hospital in London) were retrospectively included if they fulfilled the following inclusion criteria: age >18 years, LT for cirrhosis with ACLF-3 at the time of transplantation. The criteria used to define ACLF-3 were based on the European Association for the Study of the Liver-Chronic Liver Failure (EASL-CLIF) consortium definition.[1] Exclusion criteria were as follows: (1) multivisceral transplantation, (2) retransplantation, and (3) LT for acute liver failure.

This study was approved by the institutional review board of the coordinating center.

2.2 | Training and validation cohorts

The cohort from Hôpital de Hautepierre in Strasbourg was used to determine a statistical model that was tested on a validation cohort composed of the 4 other centers. Investigators from each center retrospectively collected variables concerning the donor and the recipient. Prognostic scores (MELD, CLIF-SOFA, CLIF-C ACLF, and CLIF-OF) were calculated according to the published formulas.[1,2] Organ failures (liver, kidney, coagulation, brain, respiratory, and circulatory) were defined according to the CLIF-OF system.[2] Given the retrospective nature of the study and the subjectiveness of respiratory failure in the CLIF-OF system, we used an additional, more objective criterion to study the respiratory status of patients: mechanical ventilation with PaO_2/FiO_2 ≤ 200 mm Hg.

In the training cohort, the various clinical and biological constituents of the CLIF-OF system as well as additional laboratory data (arterial lactate levels, fibrinogen, D-dimers) were recorded on

admission and immediately prior to LT. In addition, demographic characteristics, data concerning the etiology of cirrhosis, and cause of decompensation were recorded.

The primary outcome was 1-year post-LT survival.

2.3 | Study design and statistical analysis

Continuous variables are presented as means ± SD and were compared using Student's *t* test or presented as medians with interquartile range (IQR) and were compared with the Mann-Whitney test as appropriate. Qualitative variables are presented as numbers and percentages and were compared using the χ^2 test or Fisher's exact test as appropriate. To assess prognostic factors of 1-year mortality in the training cohort, all potential factors with a $P < .1$ in univariate analysis were included in a multivariate regression model. Optimal cut-off points were determined for noncategorical variables using Youden's index in order to generate dichotomous variables. Backward stepwise selection procedure based on Akaike information criterion was subsequently performed. The Transplantation for Aclf-3 Model (TAM) score was generated by summing the rounded β coefficients derived from the multivariate analysis. The predictive accuracy of the TAM score was tested both on the training and on the validation cohorts using the Hosmer-Lemeshow test. Survival probabilities were computed using the Kaplan-Meier method and compared with the log-rank test. Patients who lacked one or more elements of the TAM score were excluded from the survival analysis. All analyses were performed using the R statistical software version 3.4.3.

3 | RESULTS

3.1 | Patients included in the training and validation cohorts

In total, 3587 patients with LT were screened over the study period (Figure 1). A total of 510 patients were excluded because they underwent multivisceral transplantation or because it was not their first LT (Figure 1). Among the 3077 patients who could be included in the study, there were 152 patients with ACLF-3 at the time of LT: 76 patients with ACLF-3 in the training cohort and 76 patients with ACLF-3 in the validation cohort (the fact that the number of patients in each cohort is the same is haphazard). All the patients were prioritized according to the MELD-based French and British allocation algorithms (prior to the introduction of the transplant benefit score in the United Kingdom in 2018), with no additional points allocated for pulmonary, circulatory, or neurological failure.

3.2 | Characteristics of LT recipients, outcome, and donor characteristics in the training cohort

In the training cohort, the 2 most frequent etiologies of cirrhosis were alcohol (n = 47, 61.8%) and hepatitis C (n = 11, 14.5%) (Table 1). The mean age was 54 ± 10 years. The most frequent organ failures (as defined by the CLIF-OF system) were kidney (n = 66, 86.8%), coagulation (n = 65, 85.5%), circulation (n = 61, 80.3%), and liver (n = 60, 78.9%). Sixty-seven patients (88.2%) were intubated and

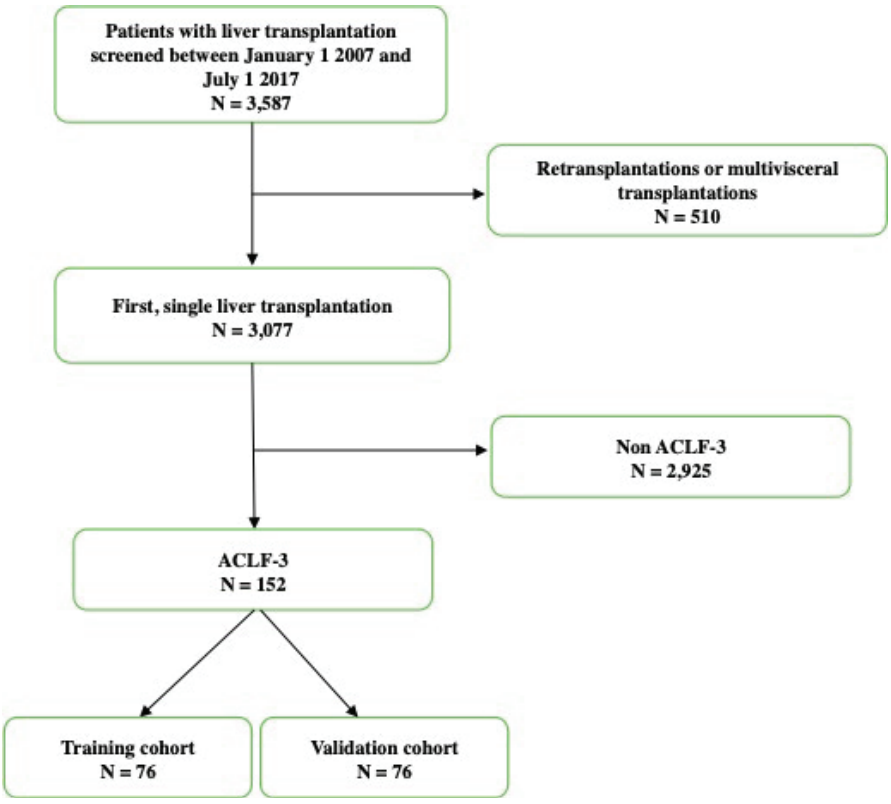

FIGURE 1 Study flowchart [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Comparison of preoperative characteristics of recipients, outcomes, and donor characteristics between training and validation cohorts

	All (N = 152)	Training cohort (N = 76)	Validation cohort (N = 76)	*P* value
Male sex	109 (71.7)	53 (69.7)	56 (73.7)	.59
Age (y)	53 ± 10	54 ± 10	52 ± 9	.29
Etiology of cirrhosis				
Alcoholic	89 (58.6)	47 (61.8)	42 (55.3)	.41
Hepatitis B	10 (6.6)	3 (3.9)	7 (9.2)	.19
Hepatitis C	29 (19.1)	11 (14.5)	18 (23.7)	.15
NASH	12 (7.9)	7 (9.2)	5 (6.6)	.55
Autoimmune hepatitis	9 (5.9)	4 (5.3)	5 (6.6)	1
Biliary	12 (7.9)	6 (7.9)	6 (7.9)	1
Other	12 (7.9)	7 (9.2)	5 (6.6)	.55
Alcoholic hepatitis	24 (15.8)	9 (11.8)	15 (19.7)	.18
Hepatocellular carcinoma	11 (7.2)	2 (2.6)	9 (11.8)	.028
Organ failures				
Liver	124 (81.6)	60 (78.9)	64 (84.2)	.40
Kidney	111 (73)	66 (86.8)	45 (59.2)	<.01
Cerebral	84 (55.6)	44 (57.9)	40 (52.6)	.57
Coagulation	122 (80.3)	65 (85.5)	57 (75)	.10
Circulation	106 (69.7)	61 (80.3)	45 (59.2)	<.01
Lung	77 (50.7)	41 (53.9)	36 (47.4)	.42
Number of organ failures				
3	55 (36.2)	17 (22.4)	38 (50)	<.01
4	48 (31.6)	27 (35.5)	21 (27.6)	.30
5	27 (17.8)	14 (18.4)	13 (17.1)	.83
6	22 (14.5)	18 (23.7)	4 (5.3)	<.01
Life support therapies				
Mechanical ventilation	111 (73)	67 (88.2)	44 (57.9)	<.01
Vasopressors	106 (69.7)	61 (80.3)	45 (59.2)	<.01
Dialysis	99 (65.1)	63 (82.9)	36 (47.4)	<.01
Laboratory data				
PaO_2/FiO_2 ≤ 200 mm Hg (with mechanical ventilation)	31 (20.4)	14 (18.4)	17 (22.4)	.55
Serum bilirubin (mg/dL)	23.7 (13.9-32)	23 (12-31.2)	24.7 (15.9-33.4)	.34
International normalized ratio	3.8 ± 1.9	3.8 ± 1.9	3.8 ± 1.9	.95
Platelet count (G/L)	57 (39-79)	58 (40.5-79)	55 (38-75)	.42
Arterial lactate level (mmol/L)	2.6 (1.6-3.6)	2.6 (1.7-4.1)	2.5 (1.6-3.4)	.42
Leukocyte count (G/L)	12.5 ± 7.6	13.4 ± 7.5	11.5 ± 7.6	.14
Predictive scores				
MELD	40 (37-40)	40 (39-40)	40 (36-40)	.29
CLIF SOFA	16 ± 4	17 ± 3	15 ± 4	<.01
CLIF OF	15 ± 2	16 ± 2	14 ± 2	<.01
CLIF C ACLF	65 ± 9	68 ± 8	61 ± 8	<.01
Donor characteristics				
Age (y)	59 (45-71)	58 (43-76)	60 (49-70)	.59
Cold ischemia time (min)	445 ± 109	465 ± 98	424 ± 117	.025

(Continues)

TABLE 1 (Continued)

	All (N = 152)	Training cohort (N = 76)	Validation cohort (N = 76)	*P* value
Delay between admission and LT (d)	8 (4-15)	8 (4-13)	10 (3-20)	.21
Outcome				
28-d survival	130 (85.5)	66 (86.8)	64 (84.2)	.65
90-d survival	117 (77)	60 (78.9)	57 (75)	.56
1-y survival	102 (67.1)	54 (71.1)	48 (63.2)	.30

Note: Binary variables are displayed as numbers (%) and continuous variables are displayed as means ± SD (normally distributed data) or median interquartile range (nonparametric testing).

Abbreviations: ACLF, acute-on-chronic liver failure; CLIF, chronic liver failure; ICU, intensive care unit; LT, liver transplantation; MELD, model for end-stage liver disease; NASH, non-alcoholic steatohepatitis; OF, organ failure; SOFA, sequential organ failure assessment.

TABLE 2 Independent predictors of 1-y posttransplantation mortality in the training cohort (n = 76) and TAM score points

	β coefficient	Odds ratio	95% CI	*P* value	TAM score points
Age, y					
<53	0	1			0
≥53	1.76	5.79	1.05-32.04	.044	1
Pre-LT arterial lactate level, mmol/L					
<4	0	1			0
≥4	2.30	9.99	1.62-61.46	.013	1
Pre-LT respiratory failure[a]					
No	0	1			0
Yes	2.15	8.60	1.30-56.88	.026	1
Pre-LT leukocyte count, G/L					
>10	0	1			0
≤10	2.56	12.91	2.26-73.87	.004	1
TAM score = Σ					

Abbreviations: CI, confidence interval; LT, liver transplantation; TAM, transplantation for Aclf-3 model.

[a]Defined as mechanical ventilation with PaO_2/FiO_2 ≤ 200 mm Hg.

14 (18.4%) had a PaO_2/FiO_2 below 200 mm Hg. The median donor age was 58 years (IQR = 43-76) and the mean cold ischemia time was 465 ± 98 minutes. The 1-year survival rate was 71.1% and only one patient in the entire cohort required retransplantation within 1 year. An additional table compares the characteristics of LT recipients in each center (Table S2).

3.3 | Predictive model based on 1-year mortality risk factors in the training cohort

Fifteen factors were associated with 1-year mortality in the training cohort (Table S1). All of these factors were immediate pre-LT markers apart from age, spontaneous bacterial peritonitis, leukocyte count on admission, and cerebral failure on admission. It is noteworthy that neither the MELD score nor its individual components were associated with post-LT outcome in univariate analysis.

Optimal cut-off points were determined for noncategorical variables using Youden's index and stepwise logistic regression analysis was performed. Four factors were independently associated with post-LT mortality in multivariate analysis with no interaction between these factors (Table 2): age ≥53 years, pre-LT arterial lactate level ≥4 mml/L, mechanical ventilation with PaO_2/FiO_2 ≤ 200 mm Hg, and pre-LT leukocyte count ≤10 G/L.

The predictive model derived from the multivariate analysis in the training cohort was the following:

$$\text{probability of being dead one year after LT} = \frac{1}{1+\exp\left(4.592-1.76\times A-2.15\times B-2.30\times C-2.56\times D\right)}$$

where: A = 1 if age ≥53 years, A = 0 otherwise; B = 1 if the patient is intubated with PaO_2/FiO_2 ≤ 200 mm Hg, B = 0 otherwise; C = 1 if pre-LT lactate levels ≥4 mmol/L, C = 0 otherwise; D = 1 if pre-LT leukocyte count ≤10 G/L, D = 0 otherwise.

The area under receiver operating characteristic (AUROC) of the multivariate model was 0.889 (95% CI = 0.801-0.977), with greater predictive accuracy than the MELD, the CLIF-C ACLF, the CLIF-OF, the balance of risk score (BAR), or the preallocation score to predict

survival outcomes following LT (preallocation score to predict survival outcomes following liver transplantation [P-SOFT]) in this population (Figure 2).

3.4 | Simplified version of the model: the Transplantation for Aclf-3 Model (TAM) score

A simplified model was derived from the multivariate analysis by linear transformation of the β coefficients (β coefficients divided by 2 and rounded): the TAM score. Each risk factor was thereby assigned one point in this simplified, user-friendly model (Table 2). Two patients were excluded from the analysis in the training cohort because one factor from the model was missing for them. An optimal threshold was set >2 points to single out the subgroup of patients with poorest post-LT survival and maximize the specificity of the test (specificity = 98%, 95% CI = 90%-100%; sensitivity = 43%, 95% CI = 22%-66%; positive predictive value = 90%, 95% CI = 55%-100%, negative predictive value = 81%, 95% CI = 70%-90%). The fit between expected and observed 1-year mortality in the simplified model was measured by the Hosmer-Lemeshow test at a *P* value of 1 for the training cohort. One-year survival was significantly different between the high-risk group (TAM score >2) and the low-risk group (TAM score ≤2): 8.3% vs 83.9%, *P* < .001.

3.5 | Validation of the TAM score

Two patients were excluded from the analysis in the validation cohort because one factor from the model was missing for them. The cut-off value of 2 in the simplified model was supported by the validation cohort, with a fit between expected and observed 1-year mortality measured by the Hosmer-Lemeshow test at a *P* value of .55. One-year survival was significantly different between the high-risk group (TAM score >2) and the low-risk group (TAM score ≤2): 10% vs 71.9%, *P* < .001. Comparisons between baseline characteristics of patients with TAM scores >2 and patients with TAM scores ≤2 are shown in Table 3, which illustrates that these categories mainly differed on the elements of the TAM score and not on the etiology of their liver disease.

3.6 | TAM score-dependent survival plots in the training, validation, and total cohort

Log-rank analysis of the survival function of the high-risk and the low-risk group of patients found a significant difference both in the training and in the validation cohort (Figure 3).

Among the patients from the low-risk group, survival rate decreased as the TAM score increased (*P* < .001) in the entire cohort (Figure 4) and in the training and the validation cohorts (data not shown). There were no censored data in these survival analyses.

3.7 | Post-LT mortality model with continuous variables

A multivariate analysis of the entire cohort of 152 patients was conducted using the four risk factors identified with age, arterial

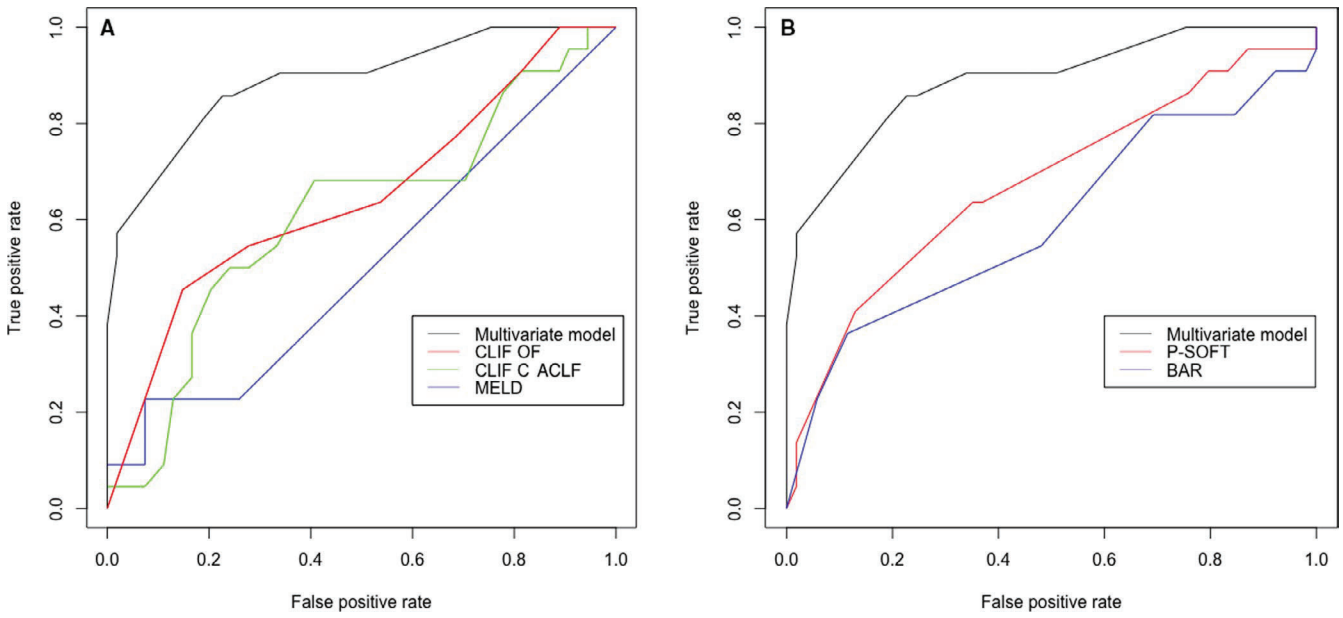

FIGURE 2 Receiver operating characteristic curves of the multivariate model (black line) compared to the model for end-stage liver disease (MELD), chronic liver failure (CLIF) C ACLF and CLIF OF scores (*blue*, *green*, and *red lines*) in the training cohort (A), and receiver operating characteristic curves of the multivariate model (*black line*) compared to the preallocation score to predict survival outcomes following liver transplantation (P-SOFT) and the balance of risk score (BAR) scores (*red* and *blue lines*) in the training cohort (B) [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Comparison of preoperative characteristics of recipients, outcome, and donor characteristics between patients with TAM ≤ 2 and TAM > 2

	Patients with TAM ≤ 2 (N = 126)[a]	Patients with TAM > 2 (N = 22)[a]	*P* value
Training cohort	62 (49.2)	12 (54.5)	.64
Male sex	92 (73)	15 (68.2)	.64
Age (y)	52 ± 10	59 ± 6	.002
Etiology of cirrhosis			
Alcoholic	78 (61.9)	9 (40.9)	.065
Hepatitis B	7 (5.6)	2 (9.1)	.62
Hepatitis C	20 (15.9)	8 (36.4)	.036
NASH	9 (7.1)	2 (9.1)	.67
Autoimmune hepatitis	8 (6.3)	1 (4.5)	1
Biliary	11 (8.7)	1 (4.5)	1
Other	9 (7.1)	3 (13.6)	.39
Alcoholic hepatitis	20 (15.9)	1 (4.5)	.20
Hepatocellular carcinoma	7 (5.6)	2 (9.1)	.62
Organ failures			
Liver	105 (83.3)	16 (72.7)	.24
Kidney	93 (73.8)	15 (68.2)	.58
Cerebral	65 (51.6)	17 (81)	.012
Coagulation	102 (81)	16 (72.7)	.39
Circulation	83 (65.9)	21 (95.5)	.005
Lung	56 (44.4)	19 (86.4)	<.001
Number of organ failures			
3	47 (37.3)	6 (27.3)	.37
4	44 (34.9)	3 (13.6)	.048
5	23 (18.3)	4 (18.2)	1
6	12 (9.5)	9 (40.9)	.0007
Life support therapies			
Mechanical ventilation	86 (68.3)	22 (100)	.002
Vasopressors	83 (65.9)	21 (95.5)	.005
Dialysis	81 (64.3)	15 (68.2)	.72
TAM score factors			
Age ≥53 y	63 (50)	21 (95.5)	<.001
PaO_2/FiO_2 ≤ 200 mm Hg (with mechanical ventilation)	14 (11.1)	17 (77.3)	<.001
Leukocyte count ≤10 G/L	52 (41.3)	16 (72.7)	.006
Arterial lactate level ≥4 mmol/L	17 (13.5)	17 (77.3)	<.001
Laboratory data			
Arterial lactate level (mmol/L)	17 (13.5)	17 (77.3)	<.001
Serum bilirubin (mg/dL)	24 (14-33)	21 (11-30)	.32
International normalized ratio	3.8 ± 1.9	3.8 ± 2.1	.97
Platelet count (G/L)	57 (39-80)	55 (38-73)	.50
Arterial lactate level (mmol/L)	2.3 (1.6-3)	4.9 (4-8.7)	<.001
Leukocyte count (G/L)	13 ± 7.6	9.8 ± 7.3	.065
Predictive scores			
MELD	40 (37-40)	40 (39-40)	.32
CLIF SOFA	16 ± 3	19 ± 2	<.001
CLIF OF	15 ± 2	16 ± 2	.001
CLIF C ACLF	64 ± 9	69 ± 10	.009
Donor characteristics			
Age (y)	58 (45-68)	67 (48-77)	.29
Cold ischemia time (min)	432 (363-512)	436 (355-518)	.56
Delay between admission and LT (d)	8 (3-15)	10 (5-20)	.31
Outcome			
1-y survival	98 (77.8)	2 (9.1)	<.001

Note: Binary variables are displayed as numbers (percentage) and continuous variables are displayed as means ± SD (normally distributed data) or median interquartile range (nonparametric testing).

Abbreviations: ACLF, acute-on-chronic liver failure; CLIF, chronic liver failure; ICU, intensive care unit; LT, liver transplantation; MELD, model for end-stage liver disease; NASH, non-alcoholic steatohepatitis; OF, organ failure; SOFA, sequential organ failure assessment; TAM, transplantation for ACLF-3 model.

[a]Four patients were left out of the analysis because they each were missing one element of the TAM score.

lactate, and leukocyte count as continuous variables, which confirmed that these factors are independently associated with 1-year mortality in the entire cohort (Table S3). The AUROC for this model was 0.844. A predictive model, based on this analysis, along with a TAM score calculator, is available at the following address: http://www.chru-strasbourg.fr/Transplantation-ACLF-3-patients-Model-TAM-score

4 | DISCUSSION

If no boundaries are set to how sick patients can be in order to be listed for transplantation, our organ allocation algorithms are at risk

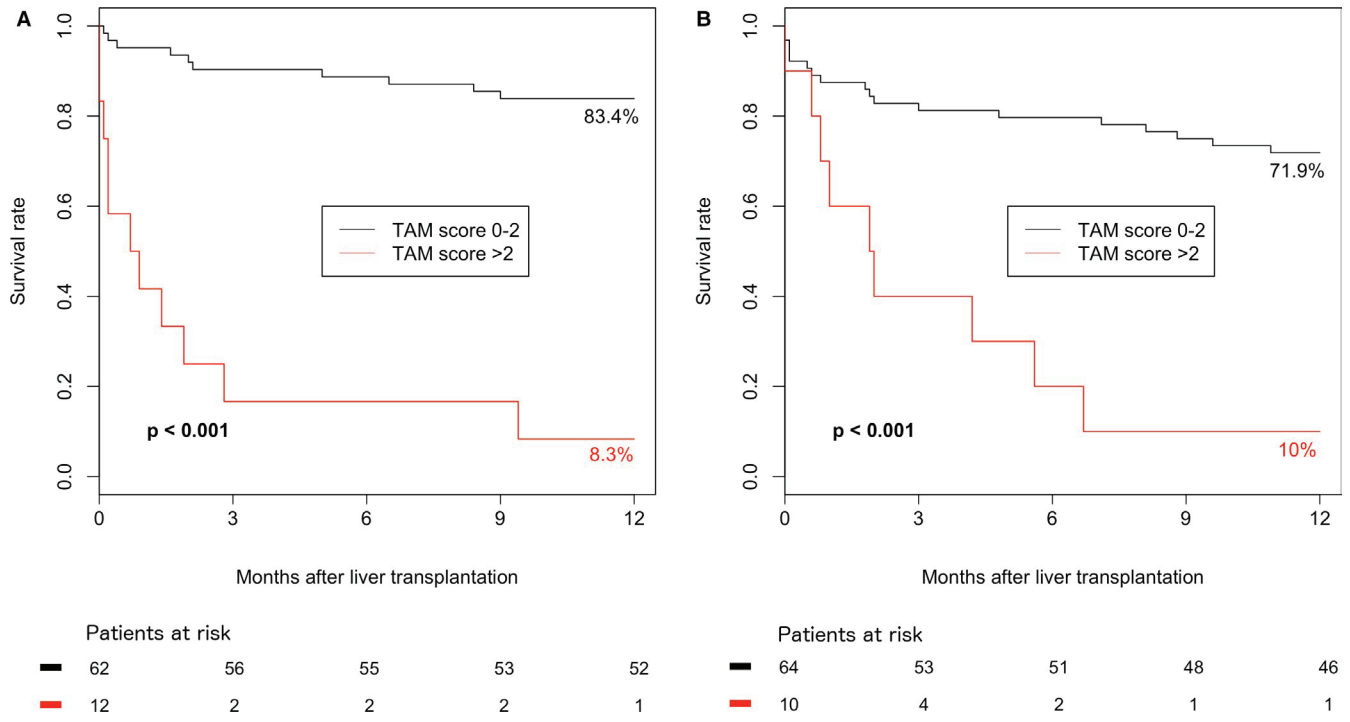

FIGURE 3 Survival rate after liver transplantation in the training cohort (A, n = 74) and in the validation cohort (B, n = 74) in high-risk (red line) and low-risk (black line) patients [Color figure can be viewed at wileyonlinelibrary.com]

	Points
Arterial lactate level (mmol/l)	
<4	0
≥4	1
Mechanical ventilation with PaO_2/FiO_2 ratio ≤ 200 mm Hg	
No	0
Yes	1
Age (years)	
<53	0
≥53	1
Leukocyte counts (G/l)	
>10	0
≤10	1
TAM score	= Σ

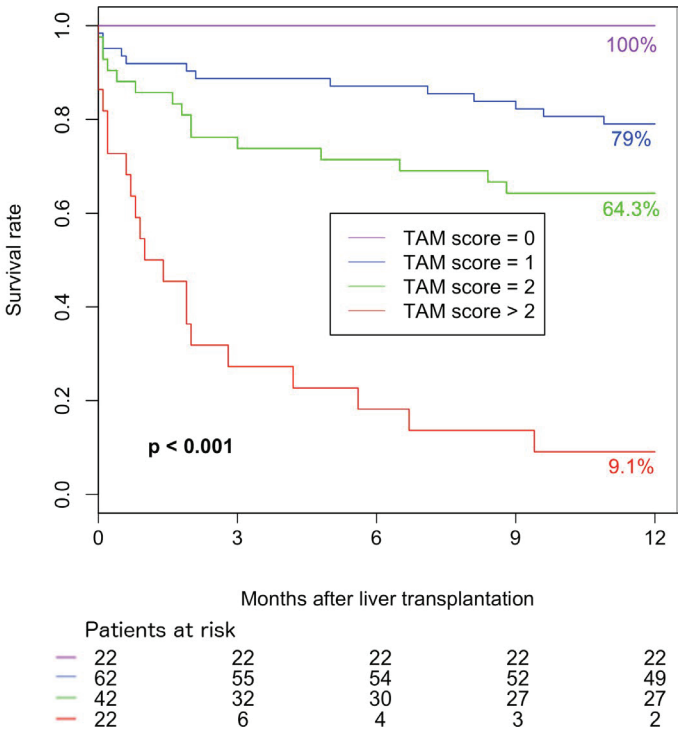

FIGURE 4 Survival rate after liver transplantation in the entire cohort (n = 148) depending on the transplantation for ACLF-3 model (TAM) score [Color figure can be viewed at wileyonlinelibrary.com]

of prioritizing patients who are "too sick to be transplanted." The TAM score, which is based on 4 factors independently associated with post-LT mortality, was developed specifically to address this issue for patients with ACLF-3.

The patients transplanted in this study were all allocated an organ through a MELD-based algorithm. This reflects the general tendency of these algorithms to prioritize the sickest patients, which has led to a relentlessly growing proportion of patients transplanted with

high MELD scores.[11] Despite this context, the question of setting a cut-off beyond which an organ should not be allocated to a patient on the basis of the severity of his or her illness remains open.[12,13] The results of this study confirm that the MELD score and the scores derived from the CLIF Consortium have been shown to be poor predictors of post-LT outcome among critically ill patients.[4,14,15] The results from this study confirm these observations: neither the MELD score, nor its individual components were associated with post-LT outcome in univariate analysis and the scores from the CLIF-OF system were not associated with post-LT mortality in multivariate analysis. Limits need to be set on how sick ACLF patients can be before LT in order to ensure the equity and performance of our organ allocation algorithms. This has been done in the context of hepatocellular carcinoma[16] but it remains to be done for patients with severe ACLF.

The strength of this study relies on the size of the cohort. With 152 patients, this is by far the largest study of patients transplanted with ACLF-3 (apart from registry cohorts). We have identified four simple, objective, and clinically relevant prognostic factors: recipient age ≥53 years, arterial lactate level ≥4 mmol/L, mechanical ventilation with PaO_2/FiO_2 ≤ 200 mm Hg, and leukocyte count ≤10 G/L. These factors were derived and subsequently validated in two independent, heterogeneous cohorts. The TAM score can be used at the bedside as a rule of thumb to stratify the risk of post-LT mortality and assist clinicians who have to decide whether or not to allocate an organ to a particular patient in the urgent and critical circumstances of the intensive care unit (ICU). Its high specificity is particularly useful in deciding to exclude patients who have a high probability of post-LT mortality.

Age has been reported to be associated with poorer post-LT outcome among patients with ACLF-3[5] and in critically ill cirrhotic patients.[10,17,18] Naturally, the 53-year cut-off point should be interpreted with caution given the size of this cohort and larger, prospective cohorts could refine this model, possibly by including age as a continuous variable. High arterial lactate levels, which reflect an increase in lactate production, a decrease in clearance due to liver failure and possibly mesenteric ischemia in patients with severe portal hypertension[19] has recently been shown to be predictive of short-term mortality in critically ill patients with ACLF outside the context of LT.[20] This multicenter study confirms the finding described in a smaller study concerning the post-LT prognostic value of pre-LT high arterial lactate levels.[21]

Intubated cirrhotic patients in the ICU are known to have an increased risk of mortality whether they are transplanted[5,6,22] or not.[23] Although the proportion of intubated patients in this cohort was substantially higher than the proportion reported in the United Network for Organ Sharing (UNOS) registries (73% vs <40%, respectively), mechanical ventilation per se was not associated with increased mortality in this study. This could be due to lack of statistical power (mechanical ventilation increased the risk of mortality by roughly 10 points in the UNOS registry cohorts). This cohort cannot compare with large registries in terms of the number of patients included but it does have the granularity that registries lack, in particular concerning PaO_2/FiO_2 ratios that typically go unrecorded in registries.[24] Mechanical ventilation with PaO_2/FiO_2 ratio ≤200 mm Hg was associated with a 40-point increase in mortality compared to the rest of the patients in the entire cohort (64.5% vs 24.8%, respectively). The effect of respiratory failure is therefore probably incremental: mechanical ventilation alone (eg, for encephalopathy) affects post-LT outcome moderately whereas mechanical ventilation with low PaO_2/FiO_2 ratio affects it drastically. There are limits to the use of the PaO_2/FiO_2 ratio to assess respiratory failure, in particular, the fact that PaO_2/FiO_2 ratios vary according to intensive care management (in particular hemodynamic status and ventilator settings). It is therefore crucial to reassess PaO_2/FiO_2 ratios regularly for patients who require critical care before taking this factor into consideration for a decision to go forward with LT. Finally, it should be stressed that organ support per se should not constitute a contra-indication for LT. Although studies based on smaller cohorts have argued that the association of dialysis, intubation, and vasopressors could constitute a rebuttal for LT,[9] a large proportion of patients had this association in our cohort (67 out of 152), with similar post-transplant mortality as those without this association (36% vs 31% respectively). It is not so much the association of organ support that matters as the *level* of organ support (high FiO_2 requirements on the ventilator, in particular) and the *intensity* of multiple organ failure (arterial lactate level in particular).

Lower leukocyte count, the fourth independent prognostic factor identified in this cohort, has not previously been reported to be a pre-LT risk factor of post-LT mortality in the literature. This study reports an inverse relation between pre-LT leukocyte count and post-LT mortality. Immunoparesis is described in end-stage liver disease, especially in patients with portosystemic shunts and may be a risk factor for early postoperative sepsis. Lower leukocyte count could also be linked to portal hypertension and hypersplenism. Finally, this finding is compatible with the effects that have been reported with the use of granulocyte-colony stimulating factor (G-CSF) in patients with ACLF: G-CSF therapy is associated both with an increase in leukocyte count[25,26] and neutrophil count[27] and with better prognosis. The weight of this risk factor in our analysis should be interpreted with caution. Indeed, patients with uncontrolled sepsis (and potentially high leukocyte count) were de facto excluded from LT. Thus, it is only in the absence of uncontrolled sepsis that high leukocyte count may be interpreted as a favorable factor for LT.

This brings to light a major limitation of all the recent retrospective studies, including this one, that discuss LT for critically ill patients: these studies include only patients who received LT. Potential candidates who were evaluated by transplantation teams and finally denied access to an organ were de facto excluded from the analysis. The factors that are described in this study should therefore not be used to include (let alone prioritize) patients for LT but rather be taken as arguments to exclude patients from LT. Our results support the fact that ACLF-3 patients who have 3 or 4 risk factors should not be allocated organs given their poor post-LT outcome (9.1% 1-year survival in the total cohort). By contrast, a gray area remains concerning the outcome of patients with 2 risk

factors (64.3% 1-year survival in the total cohort). Although their results are substantially lower than the 1-year post-LT outcomes reported in the general population in French[28] and American registries,[29] this study does not bring enough evidence to rule them out on the sole basis of the TAM score. Finally, patients with 0-1 risk factors have a 1-year survival rate of 84.5% in the entire cohort, which is close to the survival rate in the global population of patients receiving LT. Naturally, this result does not entail that the absence of unfavorable criteria for patients with grade 3 ACLF-3 should automatically lead to LT. Other factors—such as a history of alcohol or illicit substance abuse, uncontrolled pre-LT sepsis, psychological evaluation, frailty, or sarcopenia—should continue to be taken into consideration by clinicians. In that respect, the question of transplanting patients with ACLF-3 and alcoholic hepatitis (and, more generally, active alcohol drinkers with ACLF-3) is still open and largely unexplored. In any case, the high survival rate of patients with 0-1 risk factors is an additional argument in favor of referring cirrhotic patients with organ failure into the ICU for a trial of organ support and expeditious evaluation for possible LT, irrespective of the cirrhosis' etiology, an attitude that is being increasingly defended.[30-33]

The overall survival of our cohort is in accordance with other post-LT predictive models, in particular the BAR and P-SOFT scores. However, these scores were derived from a general population of LT recipient within the UNOS registry and they fail to capture the specific dividing lines that run through the population of critically ill cirrhotic patients. Indeed, the strong homogeneity of BAR scores and P-SOFT scores in our cohort is striking and can be explained by the fact that the patients all had high MELD scores, they were all hospitalized in the ICU before transplant, there was a high proportion of patients under life support therapy, and we did not include any re-transplantations. Patients with BAR scores >18 in the training cohort had a 1-year posttransplant survival rate of 67% (vs 66% for patients with BAR scores >18 in the UNOS cohort[34]). The P-SOFT score of the bulk of the patients in the training cohort (73 out of 76) was between 16 and 35, with a 1-year posttransplant survival rate of 71%, which is very close to the 75% survival rate reported for this "high-moderate risk" group in the UNOS registry.[35] The cohort's homogeneity explains why both the BAR and the P-SOFT scores have low AUROCs. By contrast, within the very specific population of ACLF-3 patients who are candidate for LT, the TAM score allows clinicians to discriminate subgroups of patients according to their post-LT outcome with much greater accuracy than the BAR and P-SOFT scores.

Three issues that are almost certainly critical in dealing with decisions to move forward with LT were not addressed in this study. First, the impact of pre-LT sepsis in post-LT outcome remains difficult to apprehend in retrospective studies, even though it is intimately tied to ACLF.[36,37] Second, donor-recipient matching is probably critical both in terms of survival and also in terms of equity insofar as the most critically ill patients (who potentially have the poorest post-LT outcomes) may require high-quality organs in order to survive.[6,38] In our study, donor age and cold ischemia time were evaluated and did not predict outcome. The Donor Risk Index could not be calculated in the context of a European cohort. Finally, a dynamic apprehension of LT in critically ill patients with ACLF is essential in order to be able to determine at which stage patients should be transplanted. In a recent study from the UNOS registry, transplantation within 30 days from listing was associated with reduced mortality.[6] We also know that ACLF-3 is a dynamic process in which prognostication is best achieved within a few days after patients have been admitted in the ICU.[36,39] A critical question that clinicians regularly face is whether ACLF-3 patients should be transplanted when their clinical state worsens or ameliorates. There is, to this date, very little data and no consensus to guide clinical practice in this regard.

Prospective studies, with careful documentation of sepsis management, standardized assessment of alcohol use and protocolled selection management need to be conducted in order to improve post-LT prognostication and refine the selection process of critically ill cirrhotic patients who require LT.

5 | CONCLUSION

This is the first study that identifies subgroups of ACLF-3 patients according to their post-LT outcome based on four simple, independent pre-LT risk factors: age ≥53 years, arterial lactate level ≥4 mmol/L, mechanical ventilation with PaO_2/FiO_2 ≤ 200 mm Hg, and leukocyte count ≤10 G/L. We propose that these criteria can contribute to the assessment of organ utility and the identification of an optimal transplantability window by stratifying post-LT mortality risk. In particular, if a patient with ACLF-3 has more than 2 of these risk factors when an organ is available, it is reasonable to turn down the proposition on the basis of the foreseeably high post-LT mortality. These criteria need to be tested in other cohorts of ACLF-3 patients and in prospective studies in order to refine them (in particular the cut-off points) and, potentially, take them into account in organ allocation algorithms.

DISCLOSURES

The authors have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

AUTHOR CONTRIBUTIONS

Study concept and design: TA, BM, EL, and FF. Acquisition of data, analysis, and interpretation of data: TA, BM, EW, ZN, EL, FF, LB, and ET. Drafting of manuscript: TA and BM. Revision of manuscript: BM, EW, LB, ZN, JCM, CPB, CF, FD, OS, TP, ET, JOG, WB, NH, ES, PB, HB, FL, LS, CB, PB, FS, EL, and FF. Statistical analysis: TA, FL, and FF. Study supervision: BM and FF. All authors approved the final version of the article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the authors upon request. Restrictions may apply to the availability of these data based on current data use agreements with the institution.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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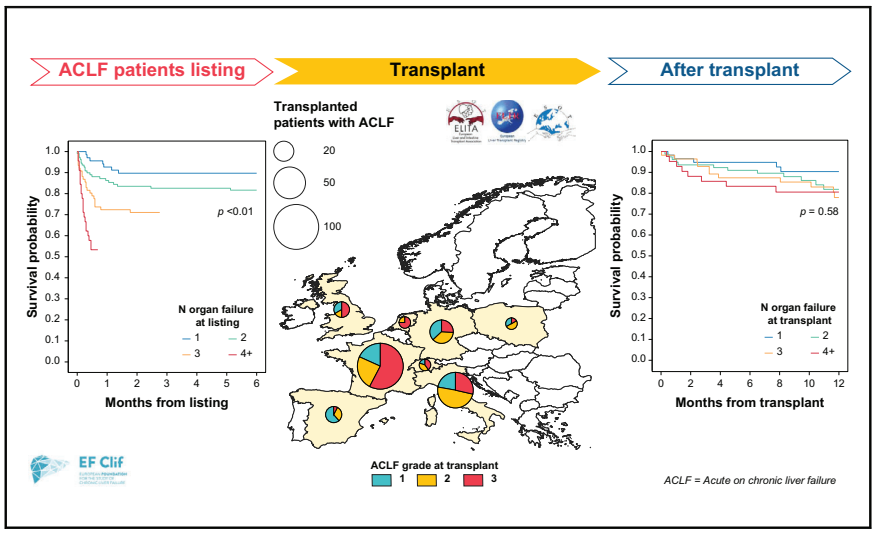
SUPPLEMENTARY ARTICLE 4

Research Article
Liver Transplantation

JOURNAL
OF HEPATOLOGY

Liver transplantation for patients with acute-on-chronic liver failure (ACLF) in Europe: Results of the ELITA/EF-CLIF collaborative study (ECLIS)☆

Graphical abstract



Highlights

- The percentage of LTs performed in patients with ACLF grade 2-3 differed significantly between European countries.
- Waiting list priority should account for the 25% mortality risk in patients with ACLF-2-3.
- One-year post-LT survival of patients with ACLF was in excess of 80%, independently of ACLF grade.
- Factors independently associated with post-LT mortality included lactate levels >4 mmol/L need for RRT at LT, and infections with MDROs while on the waiting list.
- Infections with MDROs, either precipitating ACLF or complicating its clinical course, were relevant predictors of poor outcome.

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Lay summary

Acute-on-chronic liver failure (ACLF) is a severe clinical condition for which liver transplantation is an effective therapeutic option. This study has demonstrated that in Europe, referral and access to liver transplantation (LT) for patients with ACLF needs to be harmonised to avoid inequities. Post-LT survival for patients with ACLF was >80% after 1 year and some factors have been identified to help select patients with favourable outcomes.

https://doi.org/10.1016/j.jhep.2021.03.030

Research Article
Liver Transplantation

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Liver transplantation for patients with acute-on-chronic liver failure (ACLF) in Europe: Results of the ELITA/EF-CLIF collaborative study (ECLIS)☆

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Background & Aims: Liver transplantation (LT) has been proposed as an effective salvage therapy even for the sickest patients with acute-on-chronic liver failure (ACLF). This large collaborative study was designed to assess the current clinical practice and outcomes of patients with ACLF who are wait-listed for LT in Europe.

Methods: This was a retrospective study including 308 consecutive patients with ACLF, listed in 20 centres across 8 European countries, from January 2018 to June 2019.

Results: A total of 2,677 patients received a LT: 1,216 (45.4%) for decompensated cirrhosis. Of these, 234 (19.2%) had ACLF at LT: 58 (4.8%) had ACLF-1, 78 (6.4%) had ACLF-2, and 98 (8.1%) had ACLF-3. Wide variations were observed amongst countries: France and Germany had high rates of ACLF-2/3 (27–41%); Italy, Switzerland, Poland and the Netherlands had medium rates (9–15%); and the United Kingdom and Spain had low rates (3–5%) (p <0.0001). The 1-year probability of survival after LT for patients with ACLF was 81% (95% CI 74–87). Pre-LT arterial lactate levels >4 mmol/L (hazard ratio [HR] 3.14; 95% CI 1.37–7.19),

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recent infection from multidrug resistant organisms (HR 3.67; 95% CI 1.63–8.28), and renal replacement therapy (HR 2.74; 95% CI 1.37–5.51) were independent predictors of post-LT mortality. During the same period, 74 patients with ACLF died on the waiting list. In an intention-to-treat analysis, 1-year survival of patients with ACLF on the LT waiting list was 73% for ACLF-1 or -2 and 50% for ACLF-3.

Conclusion: The results reveal wide variations in the listing of patients with ACLF in Europe despite favourable post-LT survival. Risk factors for mortality were identified, enabling a more precise prognostic assessment of patients with ACLF.

Lay summary: Acute-on-chronic liver failure (ACLF) is a severe clinical condition for which liver transplantation is an effective therapeutic option. This study has demonstrated that in Europe, referral and access to liver transplantation (LT) for patients with ACLF needs to be harmonised to avoid inequities. Post-LT survival for patients with ACLF was >80% after 1 year and some factors have been identified to help select patients with favourable outcomes.

Introduction

Acute-on-chronic liver failure (ACLF) is a life-threatening syndrome occurring in approximately 30% of hospitalised patients with cirrhosis. It combines acute decompensation (AD) of a patient with cirrhosis with the development of hepatic and/or extrahepatic organ failures (OFs) and high short-term mortality. There is a close relationship between the severity of ACLF as assessed by the ACLF grade and 28-day mortality, but outcome prediction can be further refined by reassessing the ACLF grade 3-7 days later. The 3-month mortality of patients with ACLF-2 or -3 at 3-7 days after hospitalisation is 57% and 87%, respectively.[1,2]

Liver transplantation (LT) has been shown to improve survival in patients with ACLF.[3,4] However, most of the data have been derived from retrospective studies including patients over a long period of time or from National registries, which fail to provide granular information, and important knowledge gaps remain.[3–9] In particular, the impact of donor and recipient characteristics on outcome, the healthcare burden of patient management and the importance of concomitant infection with multidrug resistant organisms (MDROs) are unknown. Importantly, clinical criteria to assess mortality risk of patients on the waiting list (WL) and after LT are also scarce.[5,10]

In order to address these issues, ELITA (European Liver and Intestine Transplant Association), ELTR (European Liver Transplant Registry), and EF-CLIF (European Foundation for the Study of Chronic Liver Failure) decided to combine their efforts in a retrospective study aiming to establish a detailed picture of the current use and results of LT for ACLF in LT centres across Europe. The specific questions that are addressed in this manuscript are as follows:

- How many patients with ACLF were listed and received a LT between January 2018 and June 2019 across Europe and how does practice vary between countries?
- What were survival rates after listing for LT and after LT?
- What were the determinants of mortality in both settings?

Patients and methods

Study cohort

This retrospective cohort included consecutive patients who had ACLF 1-3 at the time of listing or developed ACLF 1-3 while on the WL between January 1st 2018 and June 30th 2019. Patients from 20 LT centres participating in the ELTR from 8 European countries were included. In parallel, total LT activity in each centre during the same time period was recorded. All adult patients listed for LT in the 20 participating centres were identified and stratified into 3 groups: patients listed with decompensated cirrhosis (DC), patients listed with hepatocellular carcinoma (HCC) and patients listed for other indications. In patients listed for DC, patients presenting with ACLF at listing or developing ACLF on the WL were subsequently identified.

Diagnostic criteria for ACLF

The diagnostic criteria used to define ACLF and its grades have been described previously.[2] ACLF grade 1 (ACLF-1) was defined by the presence of kidney failure (serum creatinine ≥2 mg/dl) or other non-renal single OFs (liver: serum bilirubin >12 mg/dl; brain: grade III-IV hepatic encephalopathy [HE] based on West-Haven criteria; coagulation: international normalised ratio [INR] ≥2.5; circulation: use of vasopressors; lungs: PaO_2/FiO_2 ≤200 or SpO_2/FiO_2 ≤214 or use of mechanical ventilation for respiratory failure) if associated with kidney dysfunction (serum creatinine ranging from 1.5 to 1.9 mg/dl) and/or mild-to-moderate (grade I-II) HE. Ventilation for HE was not considered as respiratory failure (as long as PaO_2/FiO_2 >200) as the definition proposed by the Chronic Liver Failure-Consortium (CLIF-C) was strictly followed. ACLF grade 2 (ACLF-2) and ACLF grade 3 (ACLF-3) were defined by the presence of 2 or ≥3 OFs, respectively.

Data collection

Data collected for patients with ACLF included demographics (age, sex), aetiology of liver disease, number and type of OFs at listing and at LT, model for end-stage liver disease (MELD) and CLIF-C ACLF scores at listing and at LT, type of precipitating event, days from occurrence of ACLF to transplant/death/delisting and patient survival outcome. Granular information on the presence and type of infection with MDROs was also collected. The following variables were also obtained specifically for patients receiving LT: pre-LT arterial lactate, white blood cells, need of intubation >48 hours, need of renal replacement therapy, donor age, type of donor (donation after brain death [DBD] donors, or donation after circulatory death [DCD] donors), warm ischemic time (WIT) and cold ischemic time (CIT).

Definition of multi-drug resistant organisms

MDROs were defined as organisms with acquired non-susceptibility to at least 1 agent in 3 or more antimicrobial categories. The following bacteria were considered MDROs in the current study: extended-spectrum beta-lactamase (ESBL, mainly *Escherichia coli* and *Klebsiella pneumoniae*) or derepressed chromosomic Amp-C beta-lactamase-producing Enterobacteriaceae (*Enterobacter* or *Citrobacter* spp), carbapenem-resistant *Klebsiella pneumoniae*, carbapenem-resistant *Escherichia coli*, carbapenem-resistant *Pseudomonas aeruginosa, Stenotrophomonas maltophilia*, carbapenem-resistant *Acinetobacter baumanii*, *Burkholderia cepacia*, methicillin- or vancomycin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecium*.[11] Data about whether the infection was acquired prior to or after the onset of ACLF was not collected.

Ethical and regulatory approval

Data was collected in accordance with General Data Protection Regulation (GDPR), the European Union legislation and the ELTR

privacy declaration. All procedures were followed in accordance with STROBE guidelines.[12]

Statistical analysis

Analysis was led by the Research Centre on Public Health (CESP), University of Milan-Bicocca, Monza, Italy. A descriptive analysis of the cohort was carried out on the overall population and after stratifying by ACLF at listing or at ACLF occurrence, if it occurred after listing. A descriptive analysis was also performed on the overall patients receiving a LT and after stratifying by ACLF. Categorical variables were summarised through percentages, while continuous variables through median, first quartile (Q1) and third quartile (Q3). Categorical variable distributions were compared using the $\chi 2$ or the Fisher's exact tests; continuous variables were compared using the Mann-Whitney *U* test or the Kruskall-Wallis test, when appropriate. All tests were 2-sided and used a significance level of 0.05. The rates of missing data for each variable were reported.

Survival analyses, both overall and stratified by ACLF grade at baseline, were based on the Kaplan-Meier method: for each patient, the follow-up time was computed as the difference between the date of listing or ACLF occurrence (if after listing) and death or end of follow-up. Further, the cumulative incidence of death and transplant was estimated based on a competing risk analysis, both overall and stratified by ACLF grade at baseline. The follow-up time was computed as the difference between the date of listing or ACLF occurrence (if after listing) and death or transplant. The association between mortality and baseline patient characteristics was evaluated through univariate competing risks models, accounting for transplant as a competing event. All characteristics analysed in univariate models were then included in a stepwise selection process that identified the best multivariate model. A similar process was repeated in patients receiving LT. For each of these patients, the time between the date of transplant and death or end of follow-up was computed, and Kaplan-Meier survival curves stratified by ACLF grade at LT were estimated. Finally, the association between mortality and patient characteristics at transplant was evaluated through univariate and multivariate Cox proportional hazards models.

All statistical analyses were conducted using SAS version 9.4 (The SAS institute, Cary, NC) and R version 4.0.0 (R Core Team, Vienna, Austria) with the specific packages cmprsk, ggplot2, survival, survminer and crrstep. The map was drawn using QGIS software version 3.10 (QGIS Development Team).

Results

Study population

During the study period, the 20 centres participating in this study performed a total of 2,677 LT, representing 25.8% (total number 10,350) of the LT registered by ELTR; 1,216 (1,216/2,677, 45.4%) transplants were performed for DC, 895 (895/2,677, 33.4%) for HCC, and 566 (566/2,677, 21.1%) for other indications.

The study cohort comprised 308 patients with ACLF 1-3 listed over the study period among whom 227 (73.7%) patients had ACLF 1-3 at the time of listing and 81 (26.3%) developed ACLF 1-3 after listing (Table 1).

The distribution of LT for ACLF in Europe

Characteristics of the study cohort are shown in Table 1. Of the 308 patients with ACLF on the LT WL or with ACLF occurring while already listed, 68 (22.1%) had ACLF-1, 109 (35.4%) had ACLF-2 and 131 (42.5%) had ACLF-3. Two-hundred and thirty-four (75.9%) patients underwent LT and 74 (24.1%) died without receiving a LT.

The proportion of patients receiving a LT for DC associated with ACLF varied greatly between countries. France and Germany reported high rates of ACLF 2-3 at LT (85/316, 26.9%, 95% CI 22.1–32.1; and 17/41, 41.5%, 95% CI 26.3–57.9, respectively); Italy, Switzerland, Poland and the Netherlands reported medium rates (49/359, 13.6%, 95% CI 10.3–17.6; 4/26, 15.4%, 95% CI 4.4–34.9; 4/45, 8.9%, 95% CI 2.5–21.2, and 4/59, 6.8%, 95% CI 1.9–16.5, respectively); and the United Kingdom and Spain had low rates (8/275, 2.9%, 95% CI 1.3–5.7; and 5/101, 5.0%, 95% CI 1.6–11.2, respectively) (p <0.0001) (Fig. 1).

Baseline characteristics of patients with ACLF

Two-hundred and five patients were male (66.6%) and median age (IQR) at inclusion was 56 (48–62) years. The most frequent aetiologies of cirrhosis were alcohol (53.9%), viral infection (hepatitis B or C viruses) (11.0%) and non-alcoholic steatohepatitis (NASH) (8.4%). The majority had ACLF-2 or 3 (77.9%) and median (IQR) MELD at listing was 30 (23–37). Median CLIF-C ACLF score was 53 (46–64) and it progressively increased from 44.5 (40–51) in ACLF-1 to 51 (45–58) in ACLF-2 and to 63 (54–72) in ACLF-3. In most patients (89.6%), at least 1 precipitating event could be identified, with infections (182/308, 59%) being the most frequent, 30% of which were from MDROs (55/182). A detailed description of MDROs is provided in Table S1. Median time from listing to LT was 8 days.[3–19] This interval progressively decreased from 20 (8–37) days in ACLF-1, to 8[4–18] days in ACLF-2, and to 5[2–11] days in ACLF-3. Median (IQR) follow-up was 9.8 (1.4–17.1) months (Table 1).

Survival of patients with ACLF 1-3 on the WL

Overall, 74 patients (74/308, 24%) died while on the WL. The 1-year intent-to-transplant survival from listing with a diagnosis of ACLF, stratified by ACLF grade, was 75.2% (95% CI 62.6–84.1%) for patients with ACLF-1; 71.6% (95% CI 61.5–79.5%) for those with ACLF-2; and 52.7% (CI 95% 43.7–61.0%) for those with ACLF-3 (Fig. 2). When considering ACLF-3 patients with 4 or more OFs, the 1-year survival further declined to 42.2% (95% CI 27.8–56.0%) (Fig. 2). The cumulative incidence of transplant or death by competing risk analysis is shown in Fig. 3, where patients are stratified according to ACLF grade (panel A) and number of OFs (panel B). Additional characteristics of patients who died on the WL are reported in Table S2 and S3.

Predictors of mortality on the WL using a competing risk model

Factors significantly associated with death on univariable analysis are reported in Table 2.

Multivariable analysis of factors associated with death demonstrated persisting positive associations with incidental ACLF after listing (HR 1.87; 95% CI 1.12–3.13; p = 0.0167), patient age >60 years (HR 1.89; 95% CI 1.15–3.11; p = 0.0118), number of OFs 3 *vs.* 1 (HR 2.85; 95% CI 1.33–6.12; p = 0.0073), number of OFs 4+ *vs.* 1 (HR 5.29; 95% CI 2.39–11.70; p <0.0001), and MDRO infections (HR 3.83; 95% CI 2.27–6.46; p <0.0001). Seventy-four patients with ACLF died after listing, with infection being the most frequent precipitant (63.5% [47/74]). In particular, infections from MDROs were observed in 60% of patients who died (28/47) with mortality being directly related to MDROs in 26

Table 1. Patients with ACLF at listing or occurring after listing: baseline characteristics.

	ACLF at listing or at occurrence (if after listing)			
	ACLF-1 (n = 68)	**ACLF-2 (n = 109)**	**ACLF-3 (n = 131)**	**Total (N = 308)**
Males	43 (63.24%)	74 (67.89%)	88 (67.18%)	205 (66.56%)
Age at listing/ACLF occurrence				
Median (Q1-Q3)	55.5 (47.5–63.5)	57.0 (49.0–63.0)	56.0 (48.0–61.0)	56.0 (48.0–62.0)
Classes				
≤50	28 (41.18%)	33 (30.28%)	42 (32.06%)	103 (33.44%)
50-60	15 (22.06%)	40 (36.70%)	56 (42.75%)	111 (36.04%)
>60	25 (36.76%)	36 (33.03%)	33 (25.19%)	94 (30.52%)
Aetiology				
Alcohol	35 (51.47%)	64 (58.72%)	67 (51.15%)	166 (53.90%)
HCV/HBV	5 (7.35%)	15 (13.76%)	14 (10.69%)	34 (11.04%)
NASH	8 (11.76%)	4 (3.67%)	14 (10.69%)	26 (8.44%)
Other	20 (29.41%)	26 (23.85%)	36 (27.48%)	82 (26.62%)
ACLF grade at listing[abc]				
No ACLF (incident cases)	19 (27.94%)	22 (20.18%)	40 (30.53%)	81 (26.30%)
1	49 (72.06%)	–	–	49 (15.91%)
2	–	87 (79.82%)	–	87 (28.25%)
3	–	–	91 (69.47%)	91 (29.55%)
Patients developing ACLF after listing (incident cases)	19 (27.94%)	22 (20.18%)	40 (30.53%)	81 (26.30%)
Number of organ failure[abc]				
1	68 (100.00%)	–	–	68 (22.08%)
2	–	109 (100.00%)	–	109 (35.39%)
3	–	–	76 (58.02%)	76 (24.68%)
4+	–	–	45 (34.35%)	45 (14.61%)
Missing	0 (0.00%)	0 (0.00%)	10 (7.63%)	10 (3.25%)
Type of organ failure				
Liver failure	55 (80.88%)	95 (87.16%)	102 (77.86%)	252 (81.82%)
Renal failure[abc]	9 (13.24%)	46 (42.20%)	86 (65.65%)	141 (45.78%)
Coagulation failure[abc]	0 (0.00%)	54 (49.54%)	90 (68.70%)	144 (46.75%)
Brain failure[bc]	3 (4.41%)	12 (11.01%)	58 (44.27%)	73 (23.70%)
Circulatory failure[bc]	1 (1.47%)	6 (5.50%)	55 (41.98%)	62 (20.13%)
Respiratory failure[bc]	0 (0.00%)	3 (2.75%)	43 (32.82%)	46 (14.94%)
MELD at listing[ab]				
Median (Q1-Q3)	27.0 (20.5–30.0)	31.0 (26.0–36.0)	33.0 (21.0–40.0)	30.0 (23.0–37.0)
CLIF-C ACLF score[abc]				
Median (Q1-Q3)	44.5 (40.0–51.0)	51.0 (45.0–58.0)	63.0 (54.0–72.0)	53.0 (46.0–64.0)
Missing (%)	0 (0.00%)	5 (4.59%)	20 (15.27%)	25 (8.12%)
Classes[abc]				
≤40	18 (26.47%)	12 (11.01%)	3 (2.29%)	33 (10.71%)
40-52	35 (51.47%)	46 (42.20%)	18 (13.74%)	99 (32.14%)
52-64	9 (13.24%)	31 (28.44%)	46 (35.11%)	86 (27.92%)
>64	6 (8.82%)	15 (13.76%)	44 (33.59%)	65 (21.10%)
Type of precipitating event (multiple events possible)*				
Infection	42 (61.76%)	62 (56.88%)	78 (59.54%)	182 (59.09%)
Alcohol	4 (5.88%)	18 (16.51%)	13 (9.92%)	35 (11.36%)
Bleeding	10 (14.71%)	19 (17.43%)	37 (28.24%)	66 (21.43%)
Other	4 (5.88%)	8 (7.34%)	13 (9.92%)	25 (8.12%)
Unknown	12 (17.65%)	11 (10.09%)	6 (4.58%)	29 (9.42%)
MDRO infection (multiple organisms possible)				
Yes	10 (14.71%)	14 (12.84%)	31 (23.66%)	55 (17.86%)
Gram positive	1 (10.00%)	1 (7.14%)	4 (12.90%)	6 (10.91%)
Gram negative	7 (70.00%)	11 (78.57%)	22 (70.97%)	40 (72.73%)
Other	2 (20.00%)	2 (14.29%)	7 (22.58%)	11 (20.00%)
Missing	0 (0.00%)	1 (0.92%)	0 (0.00%)	1 (0.32%)
Transplant[b]	60 (88.24%)	87 (79.82%)	87 (66.41%)	234 (75.97%)
Time (in days) from wait-listing for ACLF** to transplant/death/delisting[abc]				
Median (Q1-Q3)	20.0 (8.0–37.5)	8.0 (4.0–18.0)	5.0 (2.0–11.0)	8.0 (3.0–19.5)
Death[bc]	18 (26.47%)	31 (28.44%)	62 (47.33%)	111 (36.04%)
Follow-up time (in months) from wait-listing for ACLF* to death/end of follow-up[b]				
Median (Q1-Q3)	11.7 (7.5–18.3)	10.2 (5.7–16.2)	7.1 (0.3–16.5)	9.8 (1.4–17.1)

ACLF, acute-on-chronic liver failure; CLIF-C, Chronic Liver Failure-Consortium; MDRO, multidrug resistant organism; MELD, model for end-stage liver disease; NASH, non-alcoholic steatohepatitis.

The distributions of all categorical variables were compared among ACLF classes using Chi-square or Fisher's exact test, while those of continuous variables were compared using Mann-Whitney *U* test. Bonferroni's method was used to account for multiple comparisons. The significance of pairwise comparisons is reported as follows:

[a] *p* value ACLF 1 *vs.* ACLF 2 ≤0.05

[b] *p* value ACLF 1 *vs.* ACLF 3 ≤0.05

[c] *p* value ACLF 2 *vs.* ACLF 3 ≤0.05

In the absence of the aforementioned symbols, the corresponding pairwise comparison was not significant at 0.05 level.

*Combined precipitating factors reported in Table S6.

**or from time of ACLF occurrence if after listing.

Country	Centres	N of LTs	DC indication	ACLF 2/3 at LT*
Italy	7	891	359 (40.3%)	49 (13.6%)
France	4	613	316 (51.5%)	85 (26.9%)
United Kingdom	2	495	275 (55.6%)	8 (2.9%)
Spain	2	229	101 (44.1%)	5 (5.0%)
Poland	1	184	45 (24.5%)	4 (8.9%)
The Netherlands	1	114	59 (51.8%)	4 (6.8%)
Germany	2	85	41 (48.2%)	17 (41.5%)
Switzerland	1	66	26 (39.4%)	4 (15.4%)

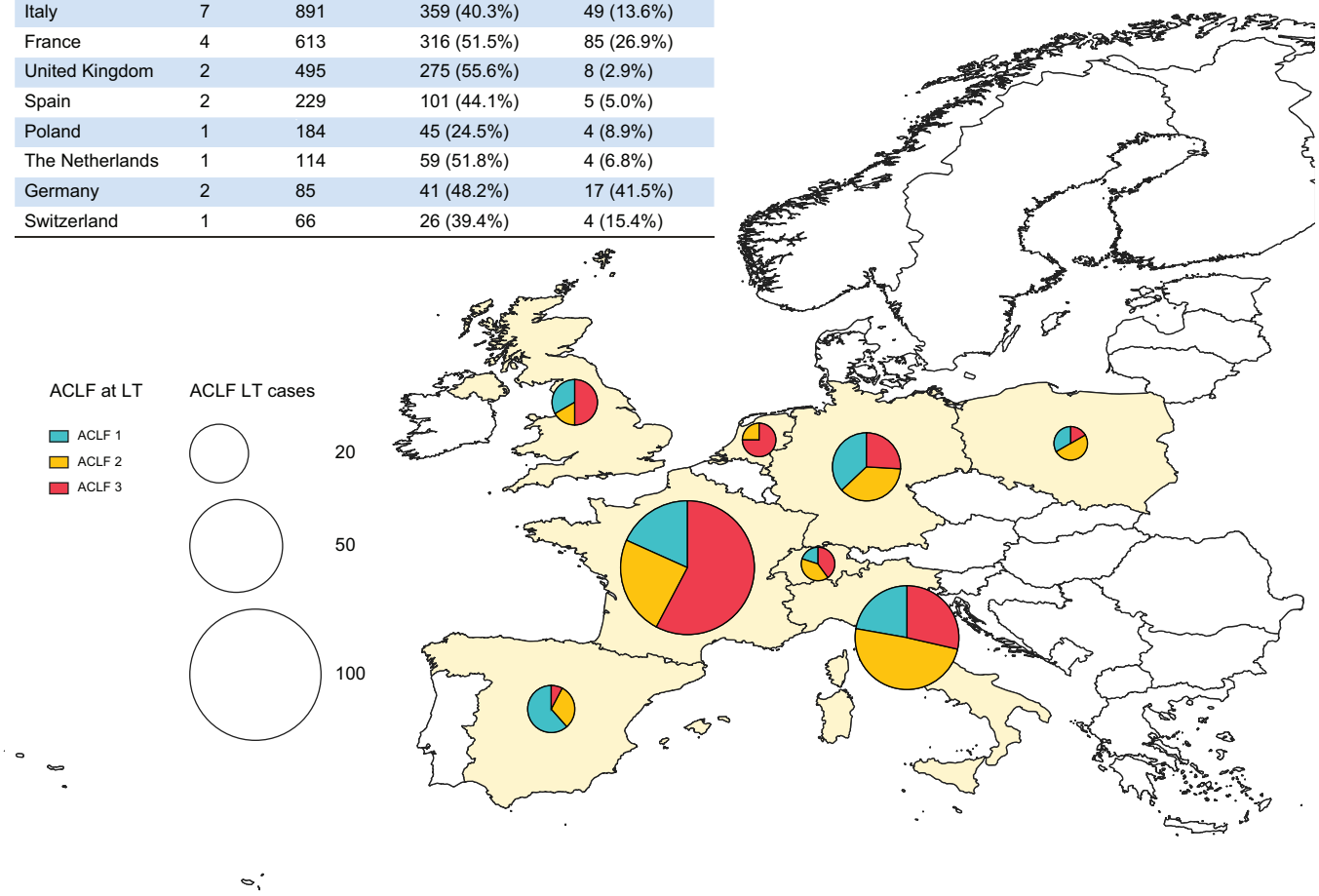


Fig. 1. ACLF cases enrolled in the study by country. *Percentages referred to patients with DC. ACLF, acute-on-chronic liver failure; DC, decompensated cirrhosis; LT, liver transplantation.

patients; the 2 remaining patients died of massive gastrointestinal bleeding and of liver failure associated with HCC rupture (Table S3).

Variability in WL mortality and organ donation rate across Europe

The WL mortality stratified by country varied from 7.6% in Spain to 28% in The Netherlands, which was inversely correlated with the donation rate that was also vastly variable (from 49 *vs.* 14.5 per million inhabitants). Wide variation in WL mortality was also confirmed for super-urgent cases (acute liver failure and urgent re-LT; from 4% in Italy to 25% in the Netherlands) and for patients with MELD >35 (from 5% in Spain to 33% in Italy) (Table S4).

Characteristics of patients with ACLF 1-3 receiving a LT

Patient characteristics at LT or before LT

One-hundred and fifty-five patients who underwent LT were male (66.2%) and median age (IQR) was 55 (47–61) years (Table 3). The most common aetiologies of cirrhosis were alcohol (41.6%), viral hepatitis (hepatitis B or C viruses) (7.1%) and NASH (6.2%). The great majority had ACLF-2 or 3 (75.2%) and the median MELD at LT was 34 (30-39). Median (IQR) CLIF-C ACLF score was 52 (45-61), progressively increasing from 43 (39-47) in ACLF-1 to 50 (46-55) in ACLF-2 and to 62 (55-67) in ACLF-3. In 23 patients (9.8%), ACLF was precipitated by a MDRO infection. A detailed description of MDRO infections is reported in Table S5. Median arterial lactate level at LT was 2 mmol/L (1.4–2.7) and white blood cell (WBC) count was $7.7*10^9$/L (5.1-11.1).

Donor and surgical variables

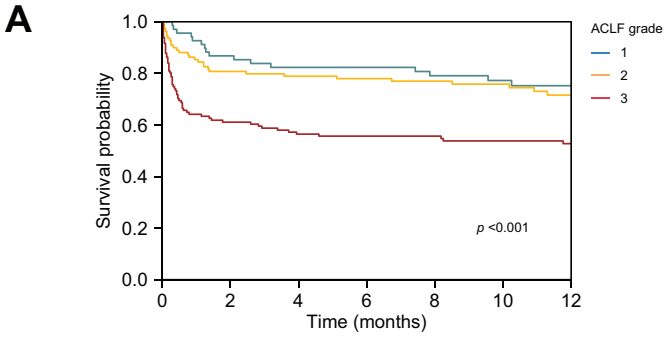
Median donor age was 58 years (46–70). The vast majority (95.7%) of organs were from DBD donors. Median WIT and CIT were 35 min (25–45) and 421 min (352–490), respectively.

Follow-up

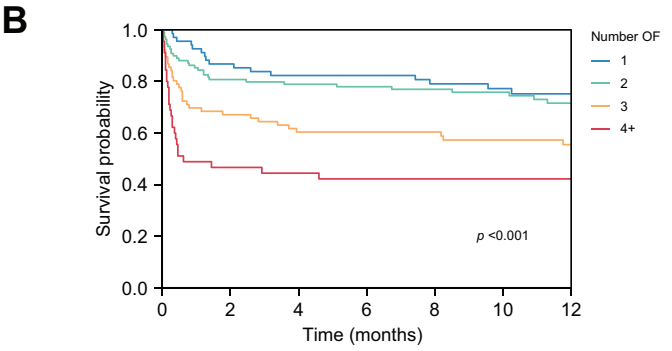
Median follow-up times from WL with ACLF or from ACLF occurrence (if after listing) and from LT were 13 months (8–18.4) and 12 months (7.5–17.6), respectively (Table 3).

Survival from LT

Of the 234 patients who received a LT, 37 (37/234, 15.8%) died after LT. The Kaplan-Meier 1-year survival stratified by ACLF grade varied between 78.9% (95% CI 68.7–86.1%) for ACLF-3 and 88.6% (95% CI 76.3–94.8%) for ACLF-1 (p value log-rank test = 0.38) (Fig. 4). Notably, the survival probability of ACLF-3 patients

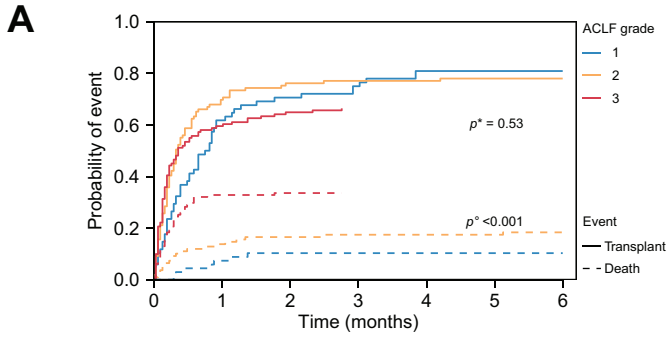


Number at risk							
ACLF1	68	59	54	52	47	40	3
ACLF2	109	88	85	80	69	58	4
ACLF3	131	80	73	71	60	54	4

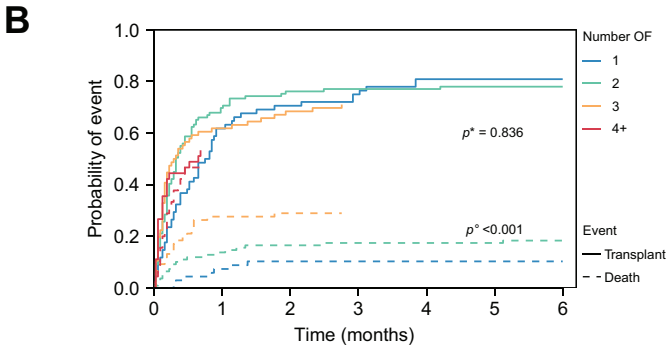


Number at risk							
OF1	68	59	54	52	47	40	3
OF2	109	88	85	80	69	58	4
OF3	76	51	45	45	39	35	3
OF4+	45	21	20	18	17	15	1

Fig. 2. Survival curves from wait-listing for ACLF or from occurrence of ACLF if it occurred after listing. (A) survival probability stratified by ACLF grade at baseline, and (B) survival probability stratified by number of organ failures at baseline. *p* values refer to log-rank test. ACLF, acute-on-chronic liver failure; OF, organ failure.



Number at risk							
ACLF1	68	21	13	10	6	6	6
ACLF2	109	18	8	6	6	5	4
ACLF3	131	10	2	0	0	0	0



Number at risk							
OF 1	68	21	13	10	6	6	6
OF 2	109	18	8	6	6	5	4
OF 3	76	8	2	0	0	0	0
OF 4+	45	0	0	0	0	0	0

Fig. 3. Cumulative incidence of transplant and death. (A) Cumulative incidence stratified by ACLF grade at baseline, and (B) cumulative incidence stratified by number of organ failure at baseline. Results from competing risks analysis. **p* values refer to Gray's test comparing cumulative incidence of transplant. °*p* values refer to Gray's test comparing cumulative incidence of death. ACLF, acute-on-chronic liver failure; OF, organ failure.

with 4 or more OFs did not differ significantly from that of patients with only 3 OFs (Fig. 4).

Main causes of death were sepsis and multiple organ failure in 21 patients, cardiac arrest in 3, tumour recurrence in 3, haemorrhagic shock in 2, surgical complications in 2, haemophagocytic syndrome in 1, primary graft non-function in 1, cerebral haemorrhage in 1, and unknown in 3.

The survival after LT did not differ when countries performing a high, medium and low percentage of transplants for ACLF-2/3 were compared (Fig. S1).

Complications in ICU and length of hospital stay

Overall, 72 patients (30.8%) required intubation for longer than 48 hours and 79 (33.8%) required renal replacement therapy (RRT). ACLF-3 patients required intubation and RRT (44 patients [44.9%] and 46 patients [46.9%], respectively) significantly more frequently than ACLF-1 patients (10 [17.2%] intubation and 15 [25.9%] RRT) and ACLF-2 patients (18 [23.1%] intubation and 18 [23.1%] RRT) (Table 3). Patients with ACLF-3 also experienced significantly more infections, particularly with MDROs, than ACLF-1 and ACLF-2 patients (Table 3 and Table S4). Of the 23 patients with a MDRO infection pre-LT, 13 (56.5%) had a new infection from MDRO post-LT, of whom 7 died. In 11 cases the post-LT MDRO infection was from the same organism isolated before LT (Table S6).

The median post-LT intensive care unit (ICU) stay was 12.5 (7–29) days for ACLF-3, 10[6–17] days for ACLF-2 and 7.5[5–13] days for ACLF-1, while the median total hospital stays were 37.5 (24.5–69.5), 30 (21–54) and 24 (18–39) days, respectively. The ACLF-3 group had a statistically significantly longer stay compared to the ACLF-1 group (for both ICU and hospital stay [$p \leq 0.05$]) but not the ACLF-2 group.

Predictors of mortality after LT

Factors significantly associated with death on univariable analysis were the following: kidney failure, MELD 1-point increase, pre-LT MDRO infections at listing or while listed, arterial lactate levels at LT >4 mmol/L, intubation >48 hours and need for dialysis at LT (Table 4). Multivariable analysis of factors associated with death demonstrated persisting positive associations with pre-LT MDRO

Table 2. Analysis of predictors of death or delisting before transplant (competing risks model).

	Univariate model		Multivariate model	
Variable	**HR (95% CI)**	***p* value***	**HR (95% CI)**	***p* value***
Incident case	2.77 (1.75–4.39)	<0.0001	1.87 (1.12–3.13)	0.0167
ACLF baseline				
2 *vs.* 1	1.82 (0.83–3.99)	0.1331		
3 *vs.* 1	3.47 (1.68–7.19)	0.0008		
Sex (male *vs.* female)	1.06 (0.66–1.72)	0.8043		
Age >60	2.03 (1.29–3.19)	0.0023	1.89 (1.15–3.11)	0.0118
Number of organ failure				
2 *vs.* 1	1.82 (0.83–4.00)	0.1329	1.97 (0.93–4.15)	0.0755
3 *vs.* 1	2.85 (1.30–6.26)	0.0091	2.85 (1.33–6.12)	0.0073
4+ *vs.* 1	5.53 (2.49–12.29)	<0.0001	5.29 (2.39–11.70)	<0.0001
Organ failure				
Liver failure	0.85 (0.45–1.59)	0.6006		
Kidney failure	2.32 (1.45–3.71)	0.0004		
Coagulation failure	1.11 (0.70–1.76)	0.6452		
Brain failure	1.92 (1.19–3.09)	0.0075		
Circulatory failure	2.31 (1.40–3.82)	0.001		
Respiratory failure	3.59 (2.19–5.87)	<0.0001		
MELD at listing (1-unit increase)	0.96 (0.93–0.99)	0.006		
CLIF-C ACLF score classes				
40-52 *vs.* ≤40	0.83 (0.16–4.32)	0.8249		
52-64 *vs.* ≤40	3.25 (0.74–14.23)	0.1177		
>64 *vs.* ≤40	12.94 (3.09–54.27)	0.0005		
Type of precipitating event (multiple events possible)				
Infection	1.02 (0.62–1.67)	0.9378		
Alcohol	0.38 (0.14–1.02)	0.0545		
Bleeding	1.44 (0.87–2.40)	0.1552		
Other	0.27 (0.07–1.10)	0.0668		
MDRO infection	4.55 (2.90–7.16)	<0.0001	3.83 (2.27–6.46)	<0.0001
Gram positive	4.09 (2.05–8.18)	<0.0001		
Gram negative	2.81 (1.69–4.66)	<0.0001		
Other	5.82 (3.18–10.64)	<0.0001		

ACLF, acute-on-chronic liver failure; CLIF-C, Chronic Liver Failure-Consortium; HR, hazard ratio; MDRO, multi-drug resistant organism; MELD, model for end-stage liver disease.
*p values refer to z-test from competing risk models.

infection (HR 3.67; 95% CI 1.63–8.28; p = 0.0017), arterial lactate levels at LT >4 mmol/L (HR 3.14; 95% CI 1.37–7.19; p = 0.0069) and need for RRT at LT (HR 2.74; 95% CI 1.37–5.51; p = 0.0046).

Discussion

This large international study involving 20 LT centres across 8 European countries provides crucial information regarding the state of clinical practice in Europe. First, we observed that the percentage of LT performed in patients with ACLF 2-3 differed significantly between countries, ranging from 25–40% of all LT for DC in France and Germany to fewer than 6% in the UK and Spain, indicating possible issues with access to transplantation across Europe. Second, 1-year post-LT survival of patients with ACLF, who are known to have a high risk of short-term mortality,[1] was in excess of 80%, providing evidence of transplant benefit. Factors independently associated with risk of post-LT mortality included lactate >4 mmol/L at LT, need for RRT at LT and MDRO infection while on the WL. Third, about 25% patients listed for LT die on the WL, indicating that each European country should balance the allocation to urgent cases, very high MELD and ACLF 2-3 to avoid inequities. Finally, LT for these patients with ACLF is likely to consume more resources as the post-LT hospital and ICU stay are long and increase with the severity of ACLF.

The striking differences in organs allocated to patients with ACLF is unlikely to be fully explained by the large variability in organ donation rates, from 11 per million inhabitants in Germany to 48 in Spain. It is therefore striking to note that transplantation rate for ACLF in Spain is one of the lowest. It is more likely that this variation is due to the perception that patients with ACLF have a poor outcome with transplantation and thus compete unfavourably with other LT candidates in whom a good outcome is more assured. The excellent results obtained by countries with a pro-active attitude towards LT for patients with ACLF suggest that this perception is erroneous and confirms that for selected patients with ACLF, in whom death is almost inevitable with intensive care alone, LT is lifesaving. An alternative hypothesis is that the number of patients with ACLF on the waitlist in Spain are low because of high organ donation rates. The answers to these questions will be addressed in the CHANCE study, which will prospectively evaluate outcomes of patients with ACLF listed for transplantation. The question of when LT is futile in patients with ACLF also remains unclear.[13] It is now time to consider harmonisation of practices across Europe, recognising that the limits beyond which LT becomes futile are still unclear.[13] ACLF classification is potentially an important tool in the LT setting that may allow for earlier appreciation of the risk of mortality, enabling a change in referral and allocation policies.

Almost two-thirds of patients listed for ACLF or who developed ACLF while listed received a LT after a median waiting time of 20 days for ACLF-1, 8 days for ACLF-2 and 5 days for ACLF-3, suggesting an overall level of prioritisation for LT. However, a median interval of 7 days or more was observed in patients who died while waiting for a liver between ACLF occurrence and death, suggesting that the cause of death in some very sick

Table 3. Characteristics of patients receiving a liver transplant.

	ACLF at LT			
	1 (n = 58)	2 (n = 78)	3 (n = 98)	Total (N = 234)
Patient features				
ACLF occurring after listing (incident cases)[ab]	21 (36.21%)	13 (16.67%)	14 (14.29%)	48 (20.51%)
Males	36 (62.07%)	54 (69.23%)	65 (66.33%)	155 (66.24%)
Age at LT				
Median (Q1-Q3)	55.5 (45.0–63.0)	54.5 (47.0–61.0)	55.5 (49.0–59.0)	55.0 (47.0–61.0)
Classes				
≤50	24 (41.38%)	28 (35.90%)	29 (29.59%)	81 (34.62%)
50-60	15 (25.86%)	30 (38.46%)	47 (47.96%)	92 (39.32%)
>60	19 (32.76%)	20 (25.64%)	22 (22.45%)	61 (26.07%)
Aetiology				
Alcohol	30 (51.72%)	41 (52.56%)	57 (58.16%)	128 (41.56%)
HCV/HBV	2 (3.45%)	9 (11.54%)	11 (11.22%)	22 (7.14%)
NASH	5 (8.62%)	7 (8.97%)	7 (7.14%)	19 (6.17%)
Other	21 (36.21%)	21 (26.92%)	23 (23.47%)	65 (21.10%)
Number of organ failure for ACLF3				
3	–	–	56 (57.14%)	56 (23.93%)
4+	–	–	42 (42.86%)	42 (17.95%)
Type of organ failure				
Liver failure[ab]	32 (55.17%)	69 (88.46%)	88 (89.80%)	189 (80.77%)
Renal failure[bc]	16 (27.59%)	23 (29.49%)	64 (65.31%)	103 (44.02%)
Coagulation failure[ab]	8 (13.79%)	50 (64.10%)	76 (77.55%)	134 (57.26%)
Brain failure[bc]	2 (3.45%)	8 (10.26%)	50 (51.02%)	60 (25.64%)
Circulatory failure[bc]	0 (0.00%)	5 (6.41%)	48 (48.98%)	53 (22.65%)
Respiratory failure[bc]	0 (0.00%)	1 (1.28%)	28 (28.57%)	29 (12.39%)
PaO_2/FiO_2 at LT				
Median (Q1-Q3)	–	–	253.5 (195.0–296.0)	253.5 (195.0–296.0)
Missing (%)	–	1 (100.00%)	6 (21.43%)	7 (24.14%)
PaO_2/FiO_2 at LT <200	–	–	6 (21.43%)	6 (20.69%)
Severe alcoholic hepatitis	6 (10.34%)	9 (11.54%)	14 (14.29%)	29 (12.39%)
Hospitalisation status at LT[abc]				
ICU	14 (24.14%)	30 (38.46%)	81 (82.65%)	125 (53.42%)
Ward	33 (56.90%)	47 (60.26%)	17 (17.35%)	97 (41.45%)
Home	11 (18.97%)	1 (1.28%)	0 (0.00%)	12 (5.13%)
MELD at LT[abc]				
Median (Q1-Q3)	28.0 (25.0–32.0)	34.0 (30.0–38.0)	38.5 (33.0–40.0)	34.0 (30.0–39.0)
MELD at LT >30[ab]	20 (34.48%)	57 (73.08%)	84 (85.71%)	161 (68.80%)
MELD at LT >35[abc]	5 (8.62%)	30 (38.46%)	61 (62.24%)	96 (41.03%)
CLIF-C ACLF score at LT[abc]				
Median (Q1-Q3)	43.0 (39.0–47.0)	50.5 (46.0–55.0)	62.0 (55.0–67.0)	52.0 (45.0–61.0)
Missing (%)	0 (0.00%)	0 (0.00%)	1 (1.02%)	1 (0.43%)
Classes[abc]				
≤40	22 (37.93%)	7 (8.97%)	2 (2.04%)	31 (13.25%)
40-52	32 (55.17%)	38 (48.72%)	17 (17.35%)	87 (37.18%)
52-64	4 (6.90%)	30 (38.46%)	43 (43.88%)	77 (32.91%)
>64	0 (0.00%)	3 (3.85%)	35 (35.71%)	38 (16.24%)
Pre-LT MDRO infection				
Yes	6 (10.34%)	4 (5.13%)	13 (13.27%)	23 (9.83%)
Gram positive	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (4.35%)
Gram negative	5 (83.33%)	3 (75.00%)	12 (92.31%)	20 (86.96%)
Other	0 (0.00%)	1 (25.00%)	1 (7.69%)	2 (8.70%)
Lactate before LT (mmol/L)				
Median (Q1-Q3)	1.6 (1.4–2.5)	2.1 (1.6–2.8)	2.0 (1.5–2.9)	2.0 (1.4–2.7)
Missing (%)	16 (27.59%)	8 (10.26%)	2 (2.04%)	26 (11.11%)
Lactate >4	2 (3.45%)	4 (5.13%)	14 (14.29%)	20 (8.55%)
WBC before LT[bc]				
Median (Q1-Q3)	6.4 (3.7–10.4)	7.1 (4.4–10.0)	8.6 (6.1–12.0)	7.7 (5.1–11.1)
Missing (%)	1 (1.72%)	0 (0.00%)	0 (0.00%)	1 (0.43%)
Donor & graft characteristics				
Donor age				
Median (Q1-Q3)	59.5 (50.5–70.5)	56.5 (46.0–65.0)	59.0 (45.0–71.0)	58.0 (46.0–70.0)
Missing (%)	2 (3.45%)	8 (10.26%)	13 (13.27%)	23 (9.83%)
DBD or DCD				
DBD	52 (89.66%)	77 (98.72%)	95 (96.94%)	224 (95.73%)
DCD	6 (10.34%)	1 (1.28%)	3 (3.06%)	10 (4.27%)

(*continued on next page*)

Table 3. (*continued*)

	ACLF at LT			
	1 (n = 58)	**2 (n = 78)**	**3 (n = 98)**	**Total (N = 234)**
WIT in min				
Median (Q1-Q3)	37.0 (26.5–60.0)	30.0 (24.0–41.0)	40.0 (25.0–46.0)	35.0 (25.0–45.0)
Missing (%)	30 (51.72%)	33 (42.31%)	29 (29.59%)	92 (39.32%)
CIT in min				
Median (Q1-Q3)	422.0 (345.0–503.0)	440.0 (356.0–490.0)	406.5 (358.0–482.0)	421.0 (352.0–490.0)
Missing (%)	7 (12.07%)	9 (11.54%)	4 (4.08%)	20 (8.55%)
Post-LT features				
Intubation >48 hr[bc], N of pts (%)	10 (17.24%)	18 (23.08%)	44 (44.90%)	72 (30.77%)
Days of intubation				
Median (Q1-Q3)	7.0 (3.0–15.0)	6.0 (4.0–12.0)	9.5 (4.0–23.0)	8.0 (4.0–20.0)
Missing (%)	0 (0.00%)	0 (0.00%)	2 (2.04%)	2 (0.85%)
RRT[bc], N of pts (%)	15 (25.86%)	18 (23.08%)	46 (46.94%)	79 (33.76%)
Days of RRT				
Median (Q1-Q3)	8.0 (3.0–22.0)	13.0 (6.0–19.0)	11.0 (4.0–24.0)	11.0 (4.0–22.0)
Missing (%)	2 (3.45%)	0 (0.00%)	0 (0.00%)	2 (0.85%)
Length (days) of total hospital stay after LT[b]				
Median (Q1-Q3)	24.0 (18.0–39.0)	30.0 (21.0–54.0)	37.5 (24.5–69.5)	32.0 (21.0–55.0)
Missing (%)	5 (8.62%)	6 (7.69%)	10 (10.20%)	21 (8.97%)
Length (days) of ICU stay after LT[b]				
Median (Q1-Q3)	7.5 (5.0–13.0)	10.0 (6.0–17.0)	12.5 (7.0–29.0)	11.0 (6.0–20.0)
Missing (%)	2 (3.45%)	3 (3.85%)	2 (2.04%)	7 (2.99%)
Post-LT MDRO infections				
Yes	14 (24.14%)	15 (19.23%)	30 (30.61%)	59 (25.21%)
Gram positive	3 (21.43%)	2 (13.33%)	1 (3.33%)	6 (10.17%)
Gram negative	11 (78.57%)	10 (66.67%)	28 (93.33%)	49 (83.05%)
Other	1 (7.14%)	3 (20.00%)	3 (10.00%)	7 (11.86%)
Death	6 (10.34%)	12 (15.38%)	19 (19.39%)	37 (15.81%)
Follow-up time (in days) from wait-listing for ACLF* to transplant[ab]				
Median (Q1-Q3)	17.0 (8.0–32.0)	6.5 (3.0–17.0)	6.0 (2.0–13.0)	7.0 (3.0–20.0)
Follow-up time (in months) from transplant to death/end of follow-up				
Median (Q1-Q3)	13.1 (7.4–17.4)	10.7 (7.4–16.7)	12.7 (7.6–17.9)	12.0 (7.5–17.6)
Follow-up time (in months) from wait-listing for ACLF* to death/end of follow-up				
Median (Q1-Q3)	15.5 (8.2–18.7)	11.8 (8.0–17.7)	13.0 (7.7–18.2)	13.0 (8.0–18.4)

ACLF, acute-on-chronic liver failure; CIT, cold ischemic time; CLIF-C, Chronic Liver Failure-Consortium; DBD, donation after brain death; DCD, donation after circulatory death; LT, liver transplantation; MDRO, multi-drug resistant organism; MELD, model for end-stage liver disease; NASH, non-alcoholic steatohepatitis; RRT, renal replacement therapy; WBC, white blood cell; WIT, warm ischemic time.

The distributions of all categorical variables were compared among ACLF classes using Chi-square or Fisher's exact test, while those of continuous variables were compared using Mann-Whitney *U* test. Bonferroni's method was used to account for multiple comparisons. The significance of pairwise comparisons is reported as follows:

[a] *p* value ACLF 1 *vs.* ACLF 2 ≤0.05

[b] *p* value ACLF 1 *vs.* ACLF 3 ≤0.05

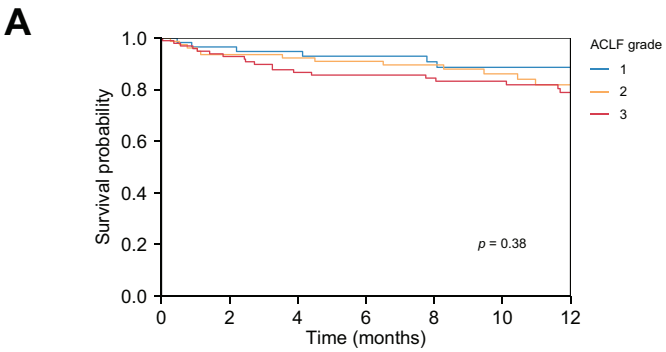
[c] *p* value ACLF 2 *vs.* ACLF 3 ≤0.05

In the absence of the aforementioned symbols, the corresponding pairwise comparison was not significant at 0.05 level.

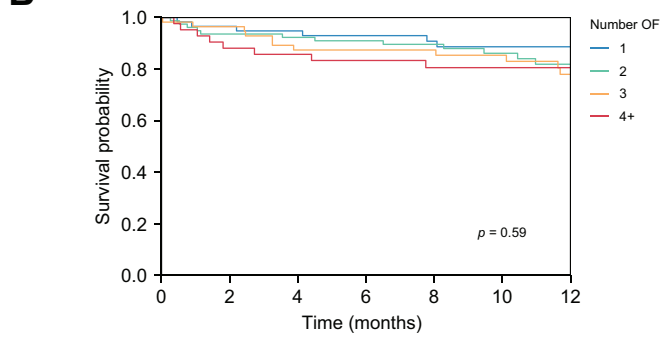
*or from time of ACLF occurrence if after listing.

patients was because a graft was not available in due time, even with this level of prioritisation. The 1-year Kaplan-Meier survival rate after LT was about 80% across all ACLF grades, confirming that LT is an excellent therapeutic option for patients with ACLF. These results are even more relevant in terms of transplant benefit, considering the very high short-term mortality without transplant, particularly for patients with ACLF-3.[4,8]

Three factors emerged as independent predictors of mortality after transplant, namely pre-LT MDRO infections, arterial lactate level >4 mmol/L at LT and pre-LT need for RRT. The issue of MDRO infections pre-LT is intriguing since all patients being offered a LT were considered clear from overt active infection and eligible for LT. Notably, approximately 80% of patients with pre-LT infection from MDRO were ACLF-3 patients either on RRT or already in the ICU at the time of LT, which again suggests a possible association between pre-LT MDRO and a complicated disease course. From our data, it is unclear whether these infections precipitated ACLF or developed after the occurrence of ACLF. In addition, of the 23 patients infected with a MDRO, 11 had a recurrent infection from the same organism post-LT, of whom 7 died. This finding reinforces the importance of establishing an antibiotic escalation plan prior to LT. The observation that arterial blood lactate concentration is a predictive marker of post-LT survival is not unexpected.[10,14,15] In other critical illnesses, lactate is an important marker of disease severity and is associated with higher mortality. Biologically, arterial blood lactate is accepted as a surrogate for physiological stress, reflecting microcirculatory dysfunction and or tissue dysoxia.[16] In liver failure, lactate clearance may be further impaired by mechanisms yet to be fully understood but likely to involve impairment of mitochondrial function.[17] Since arterial lactate can be rapidly and accurately measured using point-of-care techniques and is a widely used parameter in the ICU setting, it would be straightforward to integrate this variable into



Number at risk							
ACLF1	58	55	52	49	42	36	3
ACLF2	78	72	71	67	56	43	3
ACLF3	98	91	84	81	70	61	5



Number at risk							
OF1	58	55	52	49	42	36	3
OF2	78	72	71	67	56	43	3
OF3	56	54	48	47	43	37	2
OF4+	42	37	36	34	27	24	2

Fig. 4. Survival curves from liver transplant. (A) survival probability stratified by ACLF grade at liver transplant, and (B) survival probability stratified by number of organ failures at liver transplant. *p* values refer to log-rank test. ACLF, acute-on-chronic liver failure; OF, organ failure.

transplantation candidacy scores for patients with ACLF-3, as has been suggested by Artzner *et al.*[10] Previous studies that have focused specifically on transplantation of patients with ACLF-3 have not found a negative association between the use of RRT and post-LT survival.[10,17] This is likely explained by RRT being frequently used prior to transplantation as a way to optimise the clinical condition of ACLF-3 patients in the ICU. Thus, the observed prognostic value of RRT in this study is difficult to explain and is perhaps a reflection of severity of multiorgan failure. The identification of these risk factors for post-LT mortality may be of help for clinicians, keeping in mind that that none of them by themselves should prevent a patient from being transplanted.

Compared to patients with ACLF-1 and -2, those with ACLF-3 developed significantly more complications in the post-LT period; as such, they more often required prolonged intubation and RRT, and more frequently acquired infections. This increased risk of complications was associated with a median ICU stay and hospital stay of 12 days and 37 days, respectively, which is similar to those reported by Artru *et al.*[4] and Levesque *et al.*[8] (median ICU and hospital stay of 18 and 51 days and of 29 and 62 days, respectively). Therefore, the major survival benefit of LT must be weighed against the resulting increase in resource utilisation.

Evaluation of the role of LT for patients with ACLF needs to consider their outcome from the time of wait-listing. In the present cohort, the 1-year Kaplan-Meier survival rates from wait-listing with ACLF were 75.2% and 71.6% for patients with ACLF-1 or -2, but only 52.7% for those with ACLF-3, once again pointing to the possible inadequate prioritisation of these patients while on the WL. Analysis of risk factors for mortality by competing risk analysis revealed age, ACLF grade 3, ACLF occurring after listing and infections from MDROs as independent predictors of mortality. The associations of age and ACLF grade are not unexpected, reflecting the extreme physiologic stress of both ACLF and urgent transplantation as widely reported.[1,10,18–20] The negative impact of ACLF after listing is a novel finding which may at least in part be explained by some patients having a rapidly progressive course precluding transplantation. Patients with incidental ACLF-3 more frequently have respiratory failure compared to those that have ACLF-3 prior to listing (35% *vs.* 10%, respectively). Respiratory failure has previously been shown to be independently associated with mortality.[10] In contrast, patients who already had ACLF at the time of listing may follow a better course as they were pre-selected, with patients displaying adverse clinical features or comorbidity already being excluded. Infections caused by MDROs are highly prevalent in patients with cirrhosis[21,22] and are known to be associated with poor survival. Established risk factors for MDRO infections are recurrent hospitalisations, ICU admission, need for invasive procedures and repeated exposures to antibiotics.[23] Once again, a pre-LT MDRO infection may identify a subgroup of patients with a more complicated disease course who are exposed to a greater mortality risk. Notably, in the present study, patients with incidental ACLF precipitated by a MDRO infection had a mortality risk after 7 days of 22.2% (95% CI 9.0–48.9) and after 14 days of 66.7% (95% CI 45.5–86.3). Finally, all 6 cases with fungal infections died, 4 pre-LT and 2 post-LT, supporting the ominous prognosis of such infections both pre- and post-LT and raising the issue of initiating specific antifungal prophylaxis in patients with ACLF, whether listed or not, to improve prognosis. It is not clear from our analysis whether these MDRO infections were a trigger for the occurrence of ACLF or developed as a consequence.

This study has several strengths. First, at the time of writing, this is the largest European cohort of consecutive patients with ACLF being offered LT over a very recent and relatively short period of time, 18 months from January 2018 through June 2019. As such it provides a perspective of the current practice and results. Second, the registry was specifically designed for this study, thus avoiding the limitations of studies based on 'general' registries where clear identification of patients with AD evolving to ACLF and precise characterisation of each OF is not possible. Third, the quality of the data was guaranteed by maintaining constant communications with the contributing centres.

Some limitations are also to be acknowledged. First, although we attempted to collect data on major co-variables, upon analysing the results it was realised that some aspects regarding sarcopenia, frailty, quality of the graft, origin of infection and differentiating MDRO infections between those triggering or complicating ACLF, were not adequately considered. Second, the dynamics of ACLF could not be analysed because it was available

Table 4. Analysis of predictors of death after transplant.

	Univariate models		Multivariate model	
Variable	**HR (95% CI)**	***p* value***	**HR (95% CI)**	***p* value***
Incident case	1.81 (0.89–3.66)	0.1		
ACLF at LT				
2 *vs.* 1	1.51 (0.57–4.03)	0.4071		
3 *vs.* 1	1.89 (0.75–4.73)	0.1743		
Sex (male *vs.* female)	1.02 (0.51–2.03)	0.9545		
Age >60	0.54 (0.23–1.30)	0.1717		
Number of organ failure				
2 *vs.* 1	1.51 (0.57–4.03)	0.4071		
3 *vs.* 1	1.87 (0.69–5.05)	0.2193		
4+ *vs.* 1	1.92 (0.67–5.54)	0.2261		
Organ failure				
Liver failure	1.01 (0.44–2.29)	0.9879		
Kidney failure	1.99 (1.03–3.83)	0.0401		
Coagulation failure	0.96 (0.50–1.85)	0.9114		
Brain failure	1.87 (0.96–3.64)	0.0643		
Circulatory failure	1.30 (0.63–2.69)	0.4746		
Respiratory failure	0.59 (0.18–1.93)	0.387		
PaO_2/FiO_2 at LT <200	0.95 (0.13–6.90)	0.9562		
Severe alcoholic hepatitis	0.59 (0.18–1.93)	0.3833		
MELD at LT (1 unit increase)	1.05 (1.00–1.11)	0.0436		
MELD >30	1.66 (0.76–3.63)	0.2047		
MELD >35	1.73 (0.91–3.31)	0.096		
CLIF-C ACLF score at LT (classes)				
40-52 *vs.* ≤40	3.06 (0.71–13.32)	0.1353		
52-64 *vs.* ≤40	2.39 (0.53–10.80)	0.2561		
>64 *vs.* ≤40	3.67 (0.78–17.27)	0.1002		
Type of precipitating event (multiple events possible)				
Infection	1.28 (0.61–2.68)	0.5192		
Alcohol	0.17 (0.02–1.21)	0.0764		
Bleeding	1.36 (0.63–2.92)	0.4328		
Other	1.51 (0.58–3.91)	0.3974		
Pre-LT MDRO infection	3.86 (1.82–8.21)	0.0004	3.67 (1.63–8.28)	0.0017
Gram positive	2.33 (0.32–16.99)	0.4051		
Gram negative	2.89 (1.20–6.95)	0.0178		
Other	26.25 (5.71–120.63)	<.0001		
Lactate before LT (1-unit increase)	1.07 (0.96–1.20)	0.1944		
Lactate at LT >4 mmol/L	3.63 (1.64–8.04)	0.0015	3.14 (1.37–7.19)	0.0069
WBC before LT (1-unit increase)	1.01 (0.97–1.06)	0.6503		
Intubation >48 hr	4.11 (2.11–7.99)	<.0001		
RRT	2.86 (1.49–5.48)	0.0016	2.74 (1.37–5.51)	0.0046
Donor age (1-unit increase)	1.02 (0.99–1.04)	0.1668		
WIT in min (1-minute increase)	1.00 (0.99–1.01)	0.4667		
CIT in min (1-minute increase)	1.00 (1.00–1.00)	0.7306		
Time from listing to LT (1-day increase)	1.00 (0.99–1.01)	0.8561		

ACLF, acute-on-chronic liver failure; CIT, cold ischemic time; CLIF-C, Chronic Liver Failure-Consortium; LT, liver transplantation; MDRO, multi-drug resistant organism; MELD, model for end-stage liver disease; RRT, renal replacement therapy; WBC, white blood cell; WIT, warm ischemic time.
*p values refer to z-test from Cox proportional hazards models.

only for patients who developed ACLF after listing. Third, it was not possible to retrospectively assess whether patients on the WL died because they had become too sick for LT or because an organ was not available in due time. Fourth, transplant centres applied different criteria to decide whether or not to list patients with ACLF for LT, indicating a possible selection bias. This centre-dependent pre-selection implies that it was impossible to retrospectively extract all mortality risk factors rigorously. These limitations can only be addressed with large properly designed multicentre prospective studies.

In conclusion, the results of the present study revealed wide variations in the practice of wait-listing and transplantation of patients with ACLF across Europe, despite clear evidence for favourable post-LT survival and remarkable transplant benefit, emphasising the need for harmonisation. As ACLF is a newly defined entity, there is urgent need for more widespread recognition that the syndrome is extremely dynamic, the currently used prognostic scoring systems, such as the MELD score, do not always identify those at highest risk, for whom an LT can yield favourable post-LT survival. Risk factors for mortality were identified both from the time of wait-listing and transplant, which may permit more precise assessment of prognosis in potential transplant candidates with ACLF. The results of this study argue strongly for initiation of pilot programmes across Europe to generate more prospective data and to improve patient selection.

Abbreviations

ACLF, acute-on-chronic liver failure; AD, acute decompensation; CIT, cold ischemic time; CLIF-C, Chronic Liver Failure-

Consortium; DBD, donation after brain death; DC, decompensated cirrhosis; DCD, donation after circulatory death; ELITA, European Liver and Intestine Transplant Association; EF-CLIF, European Foundation for the study of chronic liver failure; FiO_2, fraction inspired oxygen; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; HR, hazard ratio; ICU, intensive care unit; INR, international normalised ratio; LT, liver transplantation; MDRO, multidrug resistant organism; MELD, model for end-stage liver disease; NASH, non-alcoholic steatohepatitis; OF, organ failure; PaO_2, partial arterial oxygen; RRT, renal replacement therapy; WIT, warm ischemic time; WL, waiting list; WBC, white blood cell.

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Conflict of interest
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Authors' contributions
Concept and design: LSB, CD, PA, VA and RJ. Collection of data: LSB, TA, WB, SCS, GPP, SR, JT, JF, GP, SA, SN, MCM, SM, WGP, KZ, CT, MB, CI, FI, RV, FF, LR, FS, LM, ML, FEU, CF, BM, AC, MM, DM, and AS. Analysis and interpretation of data: SC, PC, LSB, GP, CD, TA, WB and RJ. Writing: LSB, TA, WB and RJ. Revision for important intellectual content and final approval of the version to be published: LSB, TA, WB, SC, PAC, SCS, GPP, SR, JT, JF, GP, SA, SN, MCM, SM, WGP, KZ, CT, MB, CI, FI, RV, FF, LR, FS, LM, ML, FEU, CF, BM, AC, MM, DM, AS, PA, VK, RA, PA, VA and RJ.

Data availability statement
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supplementary data

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Author names in bold designate shared co-first authorship

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SUPPLEMENTARY
ARTICLE 5

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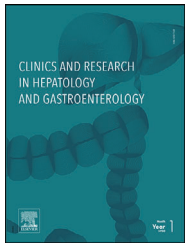

ORIGINAL ARTICLE

Liver transplantation for critically ill cirrhotic patients: Results from the French transplant registry

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Abstract

This study describes the population of cirrhotic patients who were transplanted from the ICU in France, identifying pre-transplant risk factors of post-transplant mortality and describing geographic variations in ICU transplant activity.

Cirrhotic patients transplanted between 2008 and 2018 were included through the national transplant registry. The demographic, clinical and biological characteristics of the patients transplanted from the ICU were compared to cirrhotic patients who were transplanted from home or from the hospital. Risk factors of post-transplant one-year mortality were identified in uni- and multivariable analysis within the population transplanted from the ICU. Funnel plots were used to illustrate center-specific differences in ICU transplant activity.

1,047 cirrhotic patients were transplanted from the ICU during the study period. While the national rate of transplants performed from the ICU was 14.3% the absolute number and the rate of cirrhotic patients transplanted from the ICU varied significantly from one center to another, ranging from 6.6% to 22.8% ($p < 0.05$). Three recipient-associated independent risk factors one-year post-LT mortality were identified in the population transplanted from the ICU: age > 50 years (HR 1.65, 95%CI 1.16−2.36), $p = 0.005$), diabetes (HR 1.46, 95%CI 1.07−1.98, $p = 0.02$) and intubation (HR2.12, 95%CI 1.62-2.78), $p < 0.001$). Donor age was also independently associated with mortality (HR 1.01, 95%CI 1.01−1.02, $p < 0.001$). Funnel plots showed significant differences in the proportion of patients transplanted from the ICU and the distribution of risk

Abbreviations: ACLF, Acute-on-chronic liver failure; BMI, Body mass index; HCC, Hepatocellular carcinoma; ICU, Intensive care unit; LT, Liver transplantation; MELD, Model for end-stage liver disease.

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factors across French transplant centers, especially the inclination to transplant intubated patients.

This study underlines the increased post-transplant mortality among cirrhotic patients transplanted from the ICU. It identifies four clinically pertinent independent risk factors associated with post-transplant mortality in this specific sub-group of transplant candidates. Finally, it illustrates how diverse the landscape of liver transplantation for critically ill cirrhotic patients is across a single country, despite a unified allocation algorithm.

1. Introduction

Liver transplantation (LT) for critically cirrhotic patients is a complicated ethical and medical question. Mortality of cirrhotic patients increases with the number of organ failures, reaching one-month mortality rates above 80% when patients have three or more organ failures [1]. Recently, a number of retrospective studies have shown that patients with grade 3 acute-on-chronic liver failure (ACLF) could dramatically benefit from LT, with potential one-year post-transplant survival rates above 80% [2—5]. While there is an undoubtable *individual* benefit to transplant these patients, current organ shortage demands that the decision to transplant individual patients meet standards of *collective* utility. In practice, this requires selecting LT candidates who are not too sick to be transplanted in order to maximize both the individual and the collective utility of available organs. There is to this day very little literature dedicated to helping clinicians balance the terms of this predicament and make the right choice for the patients they take care of. The aim of this study is to describe the patients who have access to LT from the ICU in France and to identify pre-LT risk factors of post-LT mortality from the data available in the French registry.

Organ allocation for liver transplantation in France relies on a single, centralized system that allocates donors to individual recipients [6,7]. National emergency priorities aside (e.g. fulminant hepatitis), patients are prioritized according to a national allocation score. Three algorithms assign points to transplant candidates according to distinct clinical situations: (i) decompensated cirrhosis, which relies on the Model for End—Stage Liver Disease (MELD) score, (ii) exceptions from the MELD score, where mortality risk is not adequately predicted by the MELD score and patients are therefore assigned points after review of their cases by experts (e.g. refractory ascites, chronic or recurrent encephalopathy, recurrent bacterial cholangitis — see supplementary table for details), and (iii) hepatocellular carcinoma (HCC), which depends on the alfa—fetoprotein score [8], the MELD score and waiting time.

One of the general characteristics of most organ allocation systems for LT [9,10], including the French one, is that their aim is to prioritize the access to LT for the sickest patients. However, apart from the HCC-related scores, they do not include an opt-out mechanism that prevents patients who are potentially too sick to be transplanted from having access to organs. The task of identifying these patients, in particular in the case of critically ill cirrhotic patients, therefore relies solely on the judgement of individual clinicians or transplant teams.

There is no single, straightforward definition of what counts as a critically ill cirrhotic patient. Some studies have focused on patients with high MELD scores [11—13]. The MELD score takes into account bilirubin, INR and creatinine. It therefore captures the severity of liver failure (bilirubin and INR) and takes into account kidney failure, which is the most frequent extra-hepatic organ failure in cirrhotic patients [1]. The MELD score therefore does not reflect other organ failures that affect critically ill cirrhotic patients, in particular cerebral, circulatory and respiratory failure. The ACLF classification, which was introduced in 2013, aims precisely at describing both hepatic and extra hepatic organ failures [1]. While registry studies derived from national or international databases give access to large numbers of patients, they often lack granularity to assess precisely the level of organ failure of transplant candidates and recipients. In this registry cohort study, we considered that admittance to the intensive care unit (ICU) was indicative of critical illness and therefore chose to focus on cirrhotic patients who were in the ICU prior to LT.

The aim of this study is to describe the population of cirrhotic patients who were transplanted from the ICU in France between 2008 and 2018 and to report post-LT survival according to pre-LT hospitalization status (ICU vs. hospitalization vs. home). It also identifies pre-LT factors of post-LT mortality in the population of patients transplanted from the ICU. Finally, it compares centers in terms of proportions of patients transplanted from the ICU and in terms of pre-LT risk factors.

2. Patients and methods

2.1. Study population

This study is a cohort analysis using the French national CRISTAL database. It includes all consecutive patients aged 18 years and above who underwent single liver transplantation between January 1, 2008 and May 31, 2018. A total of 11,114 patients were transplanted during the study period. The exclusion criteria were as follows: (i) retransplantation (n = 989), (ii) patients transplanted with national priority status in an emergency setting (n = 898), (iii) patients transplanted with a graft coming from a living donor, or donation after circulatory death (n = 272) and (iv) patients transplanted without cirrhosis (n = 1,643).

In addition, 4 patients were excluded from the study because there was no post-transplant follow up data and 147 patients were excluded because the variable concerning the pre-transplantation hospitalization status was missing.

At least one of the four elements that are taken into account to compute the MELD score (bilirubin level, INR, creatinine level and whether the patient is under dialysis or no) was missing on the day of transplantation for 596 patients. When the missing data were available within the 7 days prior to transplantation, they were used to compute the pre-transplantation MELD score (n = 63). Patients for whom these data were not available were excluded from the study (n = 533).

A total of 7,312 patients from 18 transplantation centers were finally included in the cohort.

2.2. Data collection and variables recorded

The national database CRISTAL, which is run by the Agence de la Biomédecine, prospectively collects data on all organ transplantat candidates, recipients, and donors in France together with candidate and recipient outcomes. The study was conducted in accordance with French legislation. According to French legislation, studies based on the national CRISTAL registry constitute part of the assessment of transplant outcomes and do not require ethics committee approval. Each center is responsible for entering data into the registry. Demographic, clinical, and laboratory data are collected at the time of listing, during pretransplant follow−up and at the time of transplant. Post-transplant data are also collected prospectively. Queries were performed to extract and subsequently analyze the following data: recipient gender, age, indication for LT, pre−LT hospitalization status, MELD score at the time of LT, donor gender, age and body mass index (BMI).

2.3. Statistical analysis

Demographic, clinical and biological characteristics were compared between patients in the ICU, in the hospital or at home at the time of transplantation. Continuous variables are expressed as median and interquartile range and categorical variables as frequencies (percentages). Qualitative variables were compared using a chi−square test or a Fisher's exact test, as appropriate. Quantitative variables were compared using a Wilcoxon test or a Kuskal-Wallis test (when comparing more than 2 variables). Survival curves were estimated using the Kaplan−Meier method and were compared using the log−rank test. To identify the predictors associated with 1−year post−transplant mortality in the ICU group, survival analysis was performed using a Cox proportional hazards model. We examined the relation between continuous variables and the hazard ratio for the outcome graphically with restricted cubic splines and the determined the cutoff points for continuous variables based on these graphs and clinical relevance. Multivariable analysis included all variables associated with 1−year post−transplant mortality in univariable analysis at $P < 0.1$. The variables of the final model were selected by means of a backward stepwise procedure and all clinically relevant interactions between independent factors were tested. Observations with missing values for at least one of the predictive factors were excluded from the multivariable

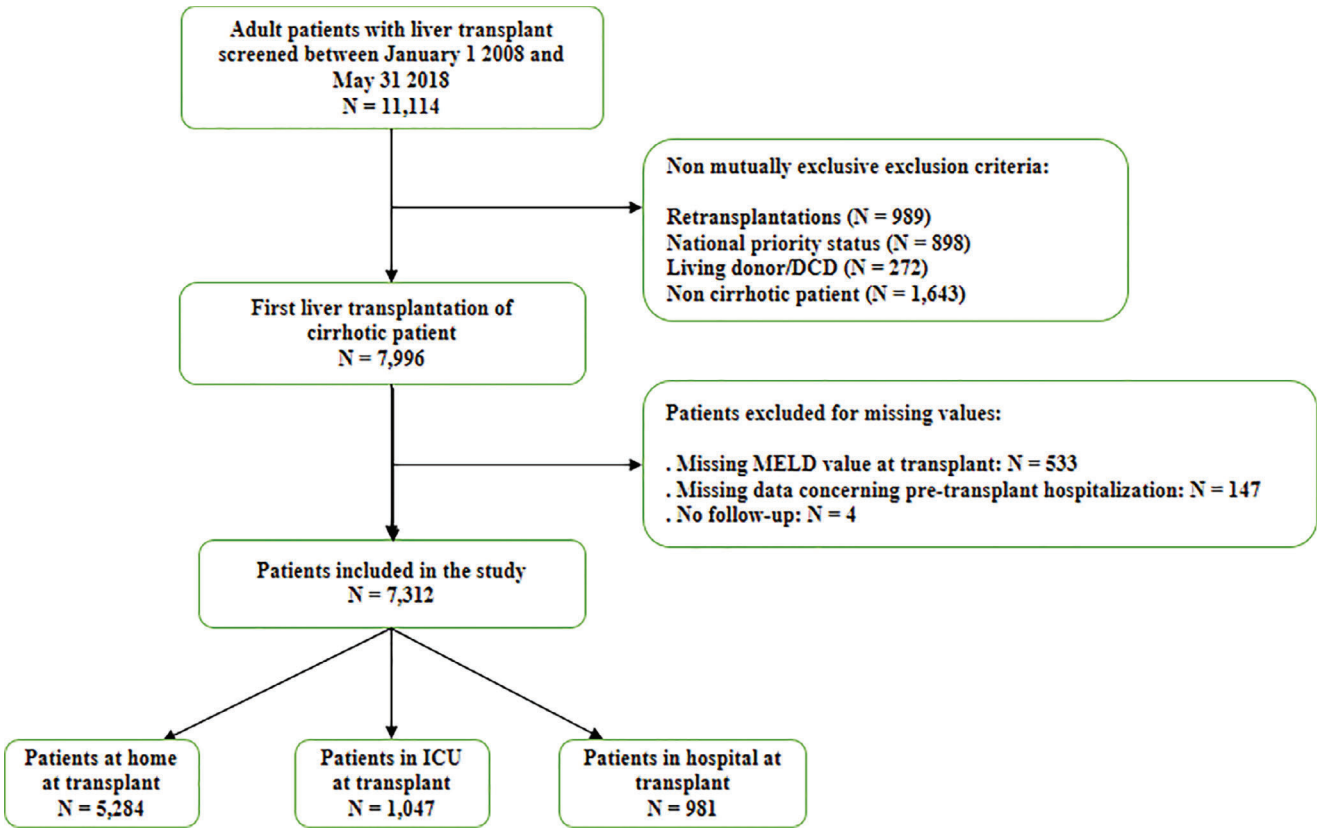

Figure 1 Study flow chart.

Table 1 Recipient and donor characteristics depending on the place of care at the time of transplantation (ICU/hospital/home).

	TOTAL (*N* = 7312)	ICU (*N* = 1047)	Hospital (*N* = 981)	Home (*N* = 5284)	*p*-value[1]
Recipient characteristics					
Female gender, n (%)	7312	288 (28%)	276 (28%)	1,055 (20%)	<0.001
Age (year), median (IQR)	7312	56 (49, 61)	56 (50, 61)	58 (52, 63)	<0.001
Age>50, n (%)	7312	748 (71%)	725 (74%)	4,274 (81%)	<0.001
BMI (kg/cm^2), median (IQR)	6437	25.6 (22.6, 29.4)	25.6 (22.5, 29.1)	26.2 (23.4, 29.7)	<0.001
Diabetes, n (%)	7208	205 (20%)	223 (23%)	1,394 (27%)	<0.001
HCC, n (%)	7312	125 (12%)	203 (21%)	2,826 (53%)	<0.001
Etiology of cirrhosis [2]					
Alcohol, n (%)	7312	710 (68%)	661 (67%)	3,391 (64%)	0.022
HCV, n (%)	7312	179 (17%)	176 (18%)	1,460 (28%)	<0.001
HBV, n (%)	7312	62 (5.9%)	72 (7.3%)	430 (8.1%)	0.044
Other	7312	171 (16%)	146 (15%)	557 (11%)	<0.001
Pre-transplant complications					
Gastrointestinal bleeding, n (%)	6914	202 (20%)	101 (11%)	244 (4.9%)	<0.001
Hydrothorax, n (%)	6854	136 (14%)	78 (8.4%)	214 (4.3%)	<0.001
Hepatorenal syndrome, n (%)	6900	403 (41%)	184 (20%)	203 (4.1%)	<0.001
Pulmonary hypertension, n (%)	6794	52 (5.4%)	33 (3.6%)	146 (3.0%)	<0.001
Bacteremia, n (%)	6880	188 (19%)	87 (9.4%)	93 (1.9%)	<0.001
Pneumonia, n (%)	6866	141 (14%)	67 (7.2%)	130 (2.6%)	<0.001
Ascitic fluid infection, n (%)	6798	196 (20%)	134 (14%)	262 (5.3%)	<0.001
Infection, n (%)[3]	6773	376 (38%)	229 (25%)	417 (8.6%)	<0.001
Recipient characteristics at the time of transplant					
MELD at LT, n (%)	7312				<0.001
<20		79 (7.5%)	232 (24%)	3,886 (74%)	
20-24		117 (11%)	197 (20%)	825 (16%)	
25-29		209 (20%)	254 (26%)	387 (7.3%)	
30-34		192 (18%)	156 (16%)	137 (2.6%)	
35-40		450 (43%)	142 (14%)	49 (0.9%)	
Bilirubin (μmol/l), median (IQR)	7312	292 (144, 492)	134 (59, 286)	33 (17, 74)	<0.001
INR, median (IQR)	7312	2.49 (1.95, 3.38)	2.29 (1.73, 3.06)	1.45 (1.20, 1.90)	<0.001
GFR (glomerular filtration rate)	7312				<0.001
>90		304 (29%)	470 (48%)	3,214 (61%)	
60-89		175 (17%)	260 (27%)	1,512 (29%)	
30-59		218 (21%)	204 (21%)	522 (9.9%)	
15-29		99 (9.5%)	35 (3.6%)	34 (0.6%)	
<15 or dialysis		251 (24%)	12 (1.2%)	2 (<0.1%)	
Dialysis, n (%)	7312	240 (23%)	11 (1.1%)	0 (0%)	<0.001
Serum sodium (mmol/l), median (IQR)	7281	137 (133, 141)	134 (130, 138)	137 (134, 140)	<0.001
Intubation, n (%)	6831	332 (35%)	0 (0%)	0 (0%)	<0.001
Time on waiting list (days), median (IQR)	1047	10 (4, 40)	33 (9, 134)	183 (71, 351)	<0.001
Modality of prioritisation, n (%)	6345				<0.001
Cirrhosis-MELD score, n (%)		823 (84%)	597 (70%)	1,360 (30%)	
HCC, n (%)		104 (11%)	160 (19%)	2,333 (52%)	
MELD exception, n (%)		51 (5.2%)	99 (12%)	818 (18%)	
Post-LT ICU stay (days), median (IQR)	7138	14 (7, 25)	9 (5, 15)	6 (4, 10)	<0.001

Table 1 (*Continued*)

	TOTAL (*N* = 7312)	ICU (*N* = 1047)	Hospital (*N* = 981)	Home (*N* = 5284)	*p*-value[1]
Donor characteristics					
Female gender, n (%)	1047	38 (48%)	62 (53%)	402 (47%)	0.5
Age (year), median (IQR)	7311	60 (46, 73)	59 (46, 71)	59 (45, 72)	0.2
BMI (kg/m^2), median (IQR)	7311	24.7 (22.0, 27.8)	24.9 (22.2, 28.1)	24.9 (22.4, 28.0)	0.2
Cold ischemia time (min), median (IQR)	7238	450 (378, 546)	450 (378, 540)	458 (369, 565)	0.4

[1] Statistical tests performed: chi-square test of independence; Kruskal–Wallis test; chi-square test of independence.
[2] Etiologies are not mutually exclusive.
[3] Infection is a composite variable which is positive if the patient has pneumonia or ascitic fluid infection or bacteremia.

analysis. All tests were two-sided and $P < 0.05$ was considered statistically significant. Funnel plots were used to assess disparity between centers by plotting rates (of LTs from the ICU and of pre-LT risk factors) against the population size of each center. Mean rates, 95% and 99% control limits were added to the plots. Statistical analyses were performed with R 3.6.2 and R studio 1.3.1.

3. Results

3.1. Description of the population of cirrhotic patients transplanted over the study period

Of 7,312 cirrhotic patients identified in the registry, 1,047 (14.3%) were transplanted from the ICU, 981 (13.4%) were in a hospital ward at the time of LT and 5,284 (72.3%) were at home (Fig. 1). The characteristics of cirrhotic patients transplanted from the ICU, from home and from the hospital are summarized in Table 1. Patients in the ICU had significantly more complications due to cirrhosis than patients in the hospital or at home (e.g. 403 (41%) had hepatorenal syndrome, compared to 184 (20%) and 203 (4.1%), respectively, $p < 0.001$). Patients in the ICU had higher MELD scores, with higher INR (2.49 (1.95, 3.38), vs. 2.29 (1.73, 3.06) and 1.45 (1.20, 1.90), respectively, $p < 0.001$) and higher bilirubin (292μmol/l (144, 492), vs. 134 (59, 286) and 33 (17, 74), respectively, $p < 0.001$). The severity of their extra-hepatic condition is reflected by the number of patients under dialysis and the number of patients intubated in the ICU prior to LT (240 (23%) and 332 (35%), respectively). The time between listing and LT was significantly shorter in the ICU group than in the hospital and the home group (10 days (4,40) vs. 33 (9, 134) and 183 (71, 351), $p < 0.001$, respectively) and relied significantly less often on prioritization based on MELD exception (51 (5.2%) vs. 99 (12%) and 818 (18%), respectively, $p < 0.001$) or HCC prioritization (104 (11%), vs. 160 (19%) and 2,333 (52%), respectively, $p < 0.001$) – see introduction and supplementary table concerning prioritization based on MELD exception.

3.2. Disparities among transplant centers in France

While the national rate of LTs performed from the ICU was 14.3% (Table 1), the absolute number and the rate of cirrhotic patients transplanted from the ICU varied significantly

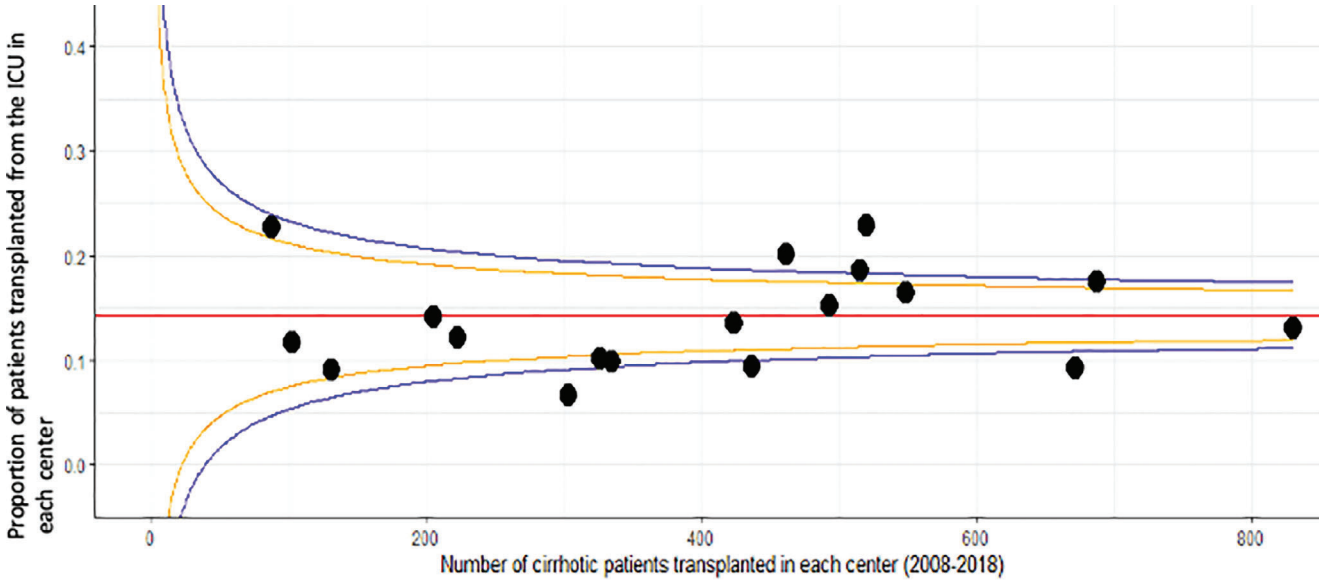

Figure 2 Funnel plot of the proportion of patients transplanted from the ICU, by center (blue lines = 99% limits, yellow lines = 95% limits).

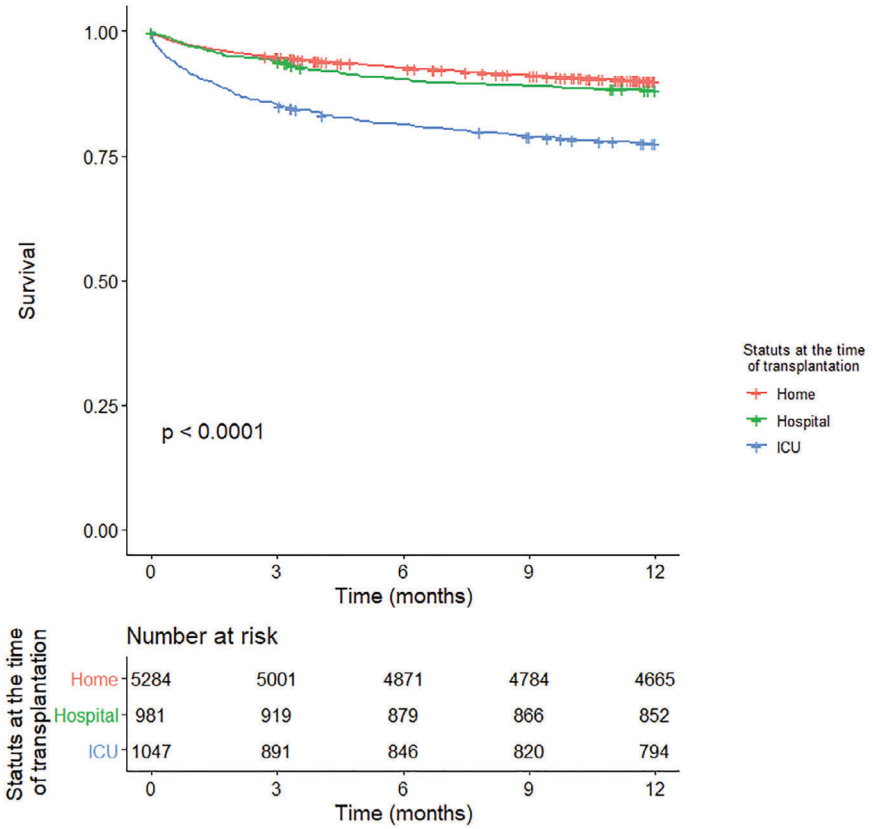

Figure 3 Survival plots according to the hospitalization status at the time of liver transplantation.

from one center to another, ranging from 6.6% to 22.8% (Fig. 2). Among the 18 centers scattered over the country, 6 fell outside the 99% prediction limit around the average rate of transplant from the ICU (3 above and 3 below).

3.3. Survival of patients according to the pre-LT hospitalization status

One-year post-LT survival varied according to pre-LT status with significantly lower post transplant survival for patients transplanted from the ICU than for patients transplanted from the hospital or from home (77.1% vs 88.0% and 89.8% respectively, $p < 0.0001$) (Fig. 3).

3.4. Risk factors of post-LT mortality in the population of patients transplanted from the ICU

Four independent risk factors of one-year mortality were identified in multivariable analysis (Table 2): recipient age $>$ 50 years (HR 1.65, 95%CI 1.16−2.36), $p = 0.005$), diabetes (HR 1.46, 95%CI 1.07−1.98, $p = 0.02$), intubation (HR2.12, 95%CI 1.62−2.78), $p < 0.001$) and donor age (HR 1.01, 95%CI 1.01−1.02, $p < 0.001$). There was no significant interaction between these factors.

The one-year post-LT survival rate of patients with none of the risk factors identified in this study was 89.9% (Fig. 4). This survival rate decreased with the number of pre-LT recipient-associated risk factors (i.e. recipient age $>$50 years, diabetes and intubation): 79.9% for patients with 1 risk factor, 68.9% for patients with 2 risk factors and 53.5% with 3 risk factors.

3.5. Disparities in distribution of risk factors among transplant centers in France

The distribution of risk factors (plotted against the number of cirrhotic patients transplanted in in the ICU in each center over the study period) is not homogeneous across French transplant centers. This is particularly clear concerning the inclination of transplant centers to move ahead with LT for intubated patients (Fig. 5). While the national proportion of patients in the ICU who were intubated at the time of LT was 35%, this rate varied significantly from one center to another, ranging from 0% to more than 70%. Among the 18 centers scattered over the country, 6 fell outside the 99% prediction limit around the average rate of transplant from the ICU (3 above and 3 below).

4. Discussion

This study shows that there is a strong heterogeneity in LT practices for cirrhotic transplant candidates who are in the ICU across French transplant centers. While the national rate of LTs performed from the ICU was 14.3%, this rate varied significantly from one center to another, ranging from 6.6% to 22.8%. This absence of standardization was also observed in the proportion of intubated patients in the ICU who had access to LT, ranging from 0% to 70%. Finally, this study reports significantly higher post-LT mortality among patients transplanted from the ICU compared to patients transplanted from home or from a regular ward, and

Table 2 Cox regression for 1-year mortality after liver transplantation (univariable and multivariable) in patients transplanted for cirrhosis from the ICU (*N* = 1047).

	Univariable analysis		Multivariable analysis	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Recipient age >50 years	1.62 (1.17−2.23)	0.003	1.65 (1.16−2.36)	0.005
Diabetes	1.53 (1.14−2.04)	0.004	1.46 (1.07−1.98)	0.02
Intubation	1.89 (1.45−2.47)	<0.001	2.12 (1.62−2.78)	<0.001
Donor age	1.01 (1.01−1.02)	0.001	1.01 (1.01−1.02)	<0.001
Recipient characteristics				
Female gender	1.20 (0.91−1.58)	0.20		
BMI	1.0 (0.99−1.0)	0.43		
HCC	1.1 (0.77−1.6)	0.54		
Etiology of cirrhosis		0.16		
Alcohol (reference)	1			
HCV	1.26 (0.85−1.87)	0.24		
HBV	0.57 (0.25−1.28)	0.17		
Pre-transplant complications				
Gastrointestinal bleeding	1.06 (0.77−1.46)	0.74		
Hydrothorax	1.09 (0.76−1.58)	0.62		
Hepatorenal syndrome	1.14 (0.87−1.48)	0.34		
Bacteremia	1.17 (0.85−1.61)	0.33		
Pneumonia	1.25 (0.88−1.77)	0.21		
Ascitic fluid infection	1.10 (0.80−1.52)	0.55		
Pulmonary hypertension	1.25 (0.73−2.14)	0.42		
Infection[1]	1.15 (0.87−1.50)	0.32		
Recipient characteristics at the time of transplant				
MELD category		0.29		
MELD<20	1.62 0.83−3.14	0.15		
MELD 20-24 (reference)	1			
MELD 25-29	1.58 (0.91−2.8)	0.11		
MELD 30-34	1.78 (1.02−3.1)	0.04		
MELD 35-40	1.75 (1.05−2.92)	0.03		
Serum sodium	1.01 (0.99−1.04)	0.18		
Dialysis	1.71 (1.30−2.24)	<0.001		
Time on waiting list (days), median (IQR)	1.0 (1.0−1.0)	0.49		
Modality of prioritisation		0.29		
Cirrhosis-MELD score (reference)	1			
MELD exception	1.48 (0.86−2.55)	0.15		
HCC	1.16 (0.77−1.74)	0.47		
Donor characteristics				
Female gender	0.90 (0.70−1.17)	0.44		
Donor BMI	0.99 (0.97−1.03)	0.96		
Cold ischemia time	0.99 (0.99−1.0)	0.77		

[1] Infection is a composite variable which is positive if the patient has pneumonia or ascitic fluid infection or bacteremia.

identifies pre-LT risk factors of post-LT mortality within this subgroup of critically ill patients.

Several recent articles have addressed the issue of LT for critically ill cirrhotic patients, using various criteria to identify these patients [2,13−16]. Our study assumes that studying cirrhotic patients who were in the ICU prior to LT is an objective way (among others) of shedding light on this clinically complex question. This is the first study that underlines the variability of LT practices for critically ill cirrhotic patients across transplant centers. Previous works, whether they were derived from registry cohorts or granular, multicenter cohorts have always described populations of critically ill cirrhotic patients *in bulk*. There are two general ways of making sense of this disparity. The first supposes that epidemiological factors are the driving force behind local differences among centers. Regional differences in cirrhosis prevalence and in the incidence of cirrhosis decompensations would explain the differences observed among centers. The alternative position assumes that center-specific attitudes and strategies toward LT for critically ill cirrhotic patients and regional disparities in the way these patients have access to ICU and are potentially referred to transplant centers explain the disparities observed across French transplant centers. The fact that LT for critically ill cirrhotic patients remains a contentious issue, with little consensus, no guidelines and no built-in mechanism to rule

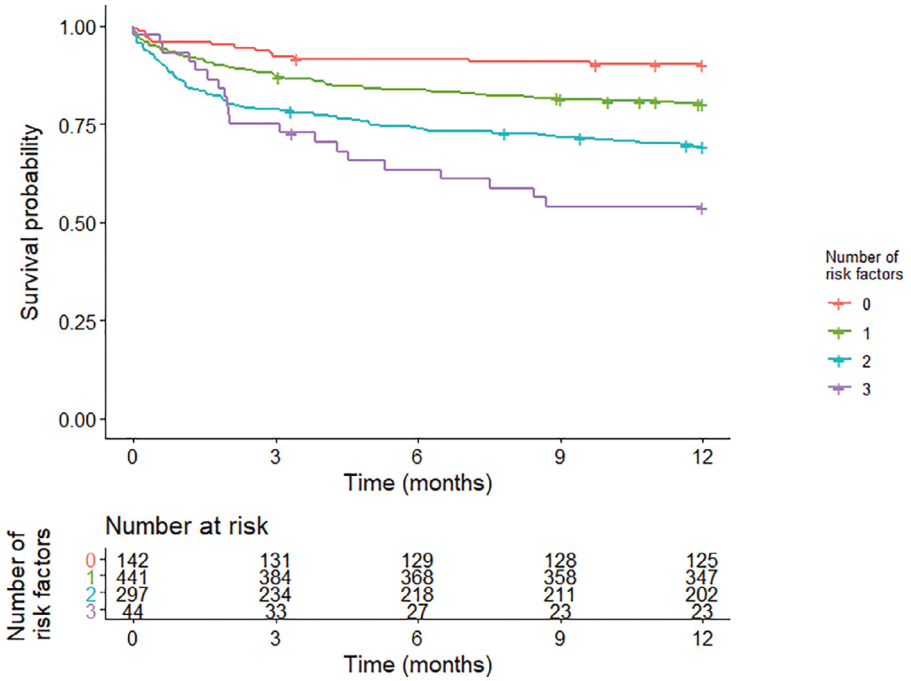

Figure 4 Post-transplant survival according to the number of pre-transplant risk factors for patients transplanted from the ICU.

out patients who are too sick to be transplanted from our allocation algorithms weighs in favor of this second explanation. This study is unable to draw the line between these positions and the truth probably lies somewhere between them. In any case, what this study clearly draws our attention to is that ensuring equity and fairness in LT for critically ill cirrhotic patients will almost certainly require looking into this issue way deeper into this question in years to come.

Four independent risk factors of post-LT mortality were identified in this study. Two of them, age and intubation have already been reported several times in the context of LT for critically ill cirrhotic patients and patients with high MELD scores [3,4,11,17]. Diabetes has been identified as a post-LT mortality risk factor in general populations of transplanted patients [18,19], but this association has not been described in critically ill cirrhotic patients [4,20]. Our observation raises a number of hypotheses and perspectives for

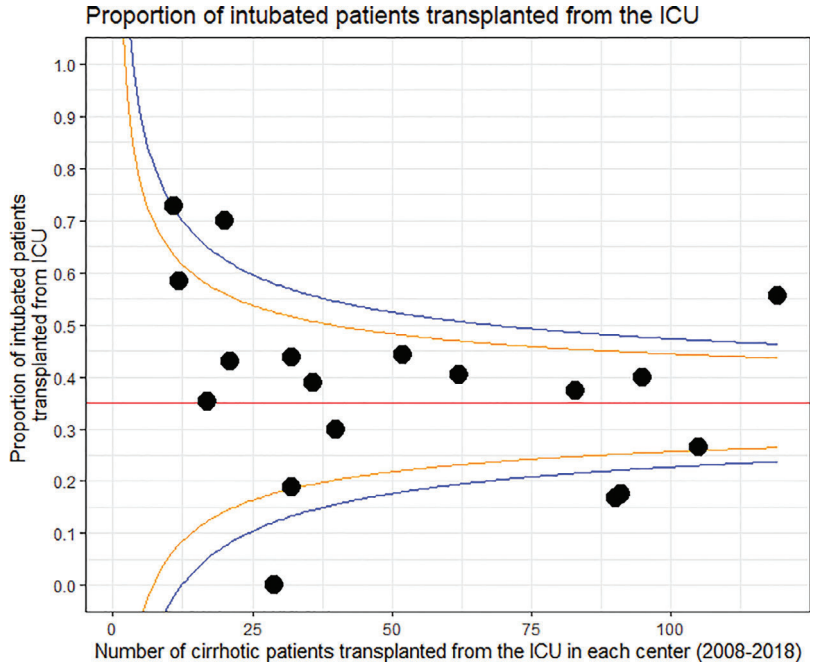

Figure 5 Funnel plot of the proportion of intubated patients transplanted from the ICU, by center (blue lines = 99% limits, yellow lines = 95% limits).

future studies. It seems particularly interesting to identify the mechanisms responsible for this increase in mortality: for example, whether micro or macro vascular lesions are involved, whether certain obesity profiles are associated with higher rates of post-LT mortality (BMI was not associated with post-LT mortality in our analysis) and whether biomarkers such as glycated hemoglobin levels could contribute to refining the risk assessment of LT for critically ill cirrhotic patients with diabetes. It is noteworthy that pre-LT kidney failure (defined as GFR $<$ 15 or 30 mL/min/1.73 m^2 or dialysis) was not independently associated with lower post-LT prognosis in multivariable analysis. While kidney failure and/or dialysis have repeatedly been reported to be associated with lower post-LT prognosis in the general populations of transplanted patients [21] and in the subgroup of cirrhotic patients with MELD scores $>$35 derived from the French registry cohort [11], the relevance of this factor has generally not been upheld in studies focusing on critically ill transplant candidates [3–5,14]. Our study confirms that in the specific clinical circumstance that constitutes the assessment of the indication and contra indication of LT for a critically ill cirrhotic patient, there is no evidence that dialysis should be put into the balance. In fact, bedside observations suggest that dialysis can constitute an extremely useful tool for intensivists to avoid fluid overload, optimize respiratory function and enable potentially massive blood products transfusion in the days and hours that precede LT. The final factor associated with post-LT mortality is donor age, which underlines the importance of donor-recipient matching to optimize post-LT outcome in the context of critically ill cirrhotic patients [4].

There are two main limits in this study. The first is that we focused only on patients who underwent LT and, as in all the recent publications focusing on post-LT mortality risk factors for critically ill cirrhotic patients, we cannot analyze the population of potential LT candidates who were not transplanted (because they were listed but they were not transplanted, or because they were never listed, or because they were never referred to the ICU). This pre-selection bias remains a crucial limit of the literature on this topic. The second major limit of this study has to do with the fact that it relies on a registry cohort. Some explicative variables are therefore potentially absent from the database (such as pre-LT arterial lactate levels for example). This study lacks granularity to assess key findings related to respiratory failure in the context of decompensated cirrhosis: the indication of intubation (e.g. respiratory failure, encephalopathy, or both) and PaO_2/FiO_2 levels, which are both pivotal and pragmatic factors that are used routinely to grasp the degree of respiratory failure at the bedside of intubated patients [5,14].

5. Conclusion

This study of critically ill cirrhotic patients who underwent LT identifies some of the specificities of this population in terms of management and prognosis. First, it confirms that the MELD score is not a predictor of post-LT survival. Second, it underlines the importance of extra-hepatic organ failures (in particular respiratory failure) in terms of post-LT prognosis and points to the relevance of recipient-donor matching. Finally, it illustrates that LT for critically ill cirrhotic patients is characterized by center-specific differences in terms of the percentage and type of patients who are transplanted from the ICU.

Data statement

Authors agree to make data and materials supporting the results or analyses presented in their paper available upon reasonable request.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.clinre.2021.101817.

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Résumé

Cette thèse de doctorat s'intéresse à la place de transplantation hépatique chez les patients cirrhotiques réanimatoires et à la place que ces patients occupent et sont susceptibles d'occuper dans le futur dans le champ de la transplantation hépatique.

I. Introduction

Dans sa forme la plus grave, la décompensation de cirrhose entraîne des défaillances d'organes extra hépatiques. L'atteinte des fonctions métaboliques du foie peut en effet se compliquer d'une atteinte rénale, hémodynamique, neurologique, immunitaire et respiratoire. En s'associant entre elles, ces défaillances s'amplifient les unes les autres en un cercle vicieux qui entraîne la mort du patient. Les traitements et techniques de réanimation ne permettent malheureusement que très rarement d'enrayer cette histoire naturelle. Le pronostic de la cirrhose décompensée associée à des défaillances d'organes extra hépatique fait par conséquent partie des plus sombres dans le champ de la réanimation.

L'espoir singulier que suscite la transplantation hépatique dans ce contexte est de permettre une résolution non seulement de la défaillance hépatique, mais également des défaillances extra hépatiques en restaurant les fonctions du foie. Ce principe thérapeutique est déjà au cœur de l'indication de greffe dans l'hépatite fulminante et, par exemple, dans le syndrome hépato rénal. Dans le cas du syndrome hépato rénal, le score de priorisation d'accès à la greffe utilisé de manière quasi ubiquitaire, le score de MELD, reflète la place de la greffe de foie dans le traitement de la défaillance rénale associée à la défaillance hépatique. Quant à l'hépatite fulminante, l'indication de greffe de foie pour résoudre les défaillances extra hépatiques est largement consacrée. Ces deux situations sont néanmoins très différentes de la cirrhose décompensée compliquée de défaillance multiviscérale. Lorsque le syndrome hépato rénal n'est pas associé à d'autres défaillances d'organes, la défaillance extra hépatique reste relativement circonscrite et ne nécessite pas de prise en charge réanimatoire lourde. Dans le cas de l'hépatite fulminante, la physiopathologie, l'histoire naturelle et l'épidémiologie de cette maladie se distinguent manifestement de la cirrhose

décompensée et la place de la greffe ne pas être transposée telle qu'elle de la première situation vers la seconde.

L'élaboration d'un nouveau cadre nosologique (l'Acute-on-chronic liver failure, ou ACLF) pour décrire et classifier la cirrhose décompensée associée à des défaillances d'organes extra hépatiques a conduit à un regain d'intérêt scientifique pour la question de la greffe dans la cirrhose réanimatoire. En effet, dans sa forme la plus grave (ACLF-3), il a été montré que le pronostic sans greffe de ces patients était catastrophique (de l'ordre de 10% de survie à trois mois) et que leur pronostic suite à la greffe était majoré (entre 43% et 85% de survie à un an de la greffe selon les études). Si cette fourchette de survie post greffe reste largement supérieure à la survie rapportée sans greffe, elle soulève néanmoins un problème éthique majeur. En effet, toute réflexion portant sur la transplantation d'organe solide se doit d'envisager son utilité non pas seulement sur le plan individuel du patient qui y a accès, mais également sur le plan collectif. En effet, compte tenu de la pénurie de greffons et de la mortalité des candidats sur liste d'attente, toute indication de greffe doit pouvoir démontrer un bénéfice pour le patient qui soit aussi proche que possible du bénéfice moyen de greffe. Dans le cas de la greffe de foie en France, la survie moyenne à un an est actuellement supérieure à 85%. Dans ces circonstances, l'horizon médical et éthique de la transplantation hépatique en réanimation est exceptionnel car il est double. Il ne se borne pas à l'exigence du soin le plus approprié pour le patient, mais s'élargit à la prise en compte d'une situation de pénurie d'accès à au meilleur traitement.

II. Positionnement de la thèse dans la littérature actuelle sur le sujet

La littérature consacrée à la greffe chez les patients cirrhotiques en réanimation a semblé présenté trois limites importantes :

1. L'absence relative de données granulaires concernant l'état clinique précis des patients avant la transplantation hépatique. En effet, la majorité des études sur ce sujet émanaient du registre des patients greffés américain (l'UNOS – united network for organ sharing). Cette base de données ne permet pas d'avoir accès à de nombreuses données fondamentales concernant les patients en réanimation ;

2. L’absence de consensus concernant le pronostic précis post greffe et l’absence d’identification de facteurs permettant d’estimer celui-ci afin de pouvoir identifier des sous-groupes de patients selon l’utilité escomptée de la greffe ;
3. L’absence d’attention portée à la variabilité d’accès à la greffe pour ces patients entre les différents centres de transplantation hépatique.

Un tour d’horizon épidémiologique du paysage de la transplantation hépatique chez les patients cirrhotiques en réanimation en France (à travers les données du registre CRISTAL de l’Agence de la Biomédecine) a rapidement fait apparaît que l’expérience strasbourgeoise dans ce domaine était très particulière puisque le centre de greffe alsacien était celui qui comptait la plus grande proportion de patients greffés depuis la réanimation dans le registre national.

La cohorte strasbourgeoise des patients greffés en ACLF-3 a été colligée et elle constitue de loin la plus grande cohorte monocentrique publiée dans la littérature. En s’associant avec 4 autres centres de transplantation hépatique (Beaujon, Henri Mondor, Tours et King’s College à Londres), une cohorte multicentrique a été constituée pour décrire plus en détail le pronostic post transplantation des patients cirrhotiques greffés en ACLF-3. L’analyse de cette cohorte a permis d’élaborer un algorithme simple (le score TAM - Transplantation for ACLF-3 Model) qui repose sur l’évaluation du risque de mortalité post transplantation et dont l’objectif est d’aider les cliniciens à décider d’accepter une proposition de greffon ou non chez un candidat à la greffe en réanimation.

Par ailleurs, une analyse plus détaillée du registre CRISTAL a permis de décrire l’activité de greffe pour cirrhose en réanimation en France et de souligné les variabilités d’activité entre les centres.

Cette thèse a pour objectif de poursuivre l’analyse granulaire des facteurs prédictifs de survie post greffe des patients transplantés depuis la réanimation à Strasbourg et d’élargir l’étude épidémiologique de cette question à travers l’analyse d’une cohorte européenne. Enfin, elle vise à préciser les obstacles actuels à la greffe à travers l’étude qualitative d’un questionnaire envoyé dans des centres de greffe à travers le monde.

III. Optimiser les résultats post transplantation des patients cirrhotiques transplantés en défaillance multiviscérale (étude granulaire unicentrique strasbourgeoise)

L'analyse d'une cohorte de 100 patients en ACLF-3 au moment de la greffe à Strasbourg a permis d'affiner le pronostic post-transplantation de ces patients et de préciser la place du score TAM dans leur prise en charge. En particulier, cette étude montre que :

- Le pronostic post greffe s'est largement amélioré avec le temps (survie à un an post greffe à 66% pour les 50 premiers patients et 86% pour les 50 suivants, $p = 0.02$), décrivant une courbe d'apprentissage dans ce domaine ;
- Le nombre de patients transplantés a augmenté de manière significative au cours du temps, suggérant l'importance de la constitution d'un réseau de centres périphériques adressant ces patients au centre de greffe ;
- La gravité des patients au moment de l'admission ou de la greffe entre les deux périodes était similaire, en dehors du nombre de patients avec un score TAM>2 à la greffe (1 patient dans la première moitié vs. 11 dans la secondaire, $p<0.01$), reflétant une meilleure appréciation de la fenêtre de transplantabilité par l'équipe dans la seconde période de l'étude ;
- Le score TAM est prédictif de la survie post greffe lorsqu'il est appliqué au moment de la proposition de greffon et non pas à l'admission en réanimation, ce qui plaide en faveur de ne pas juger de la transplantabilité des patients trop hâtivement au moment de leur admission en réanimation ;
- Les patients dont le score TAM s'est amélioré au cours de la prise en charge réanimatoire avaient une survie post transplantation plus élevée que celle du groupe des patients dont le score TAM restait le même ou augmentait (88% vs. 70% à un an, $p = 0.04$).

Au total, cette étude plaide à la fois en faveur donner un accès large à la réanimation pour les patients potentiellement candidat à la greffe hépatique et à appliquer des critères de sélection strictes à l'acceptation d'une proposition d'organe afin d'optimiser le pronostic post transplantation de ces patients. Elle montre également qu'un programme de greffe dédié à ces patients est susceptible d'être caractérisé par une courbe d'apprentissage, avec des résultats post transplantation largement inférieurs à la moyenne observée dans la population générale des patients transplantés du foie en

France. Elle montre enfin l'importance de constituer un réseau entre le centre de greffe et les centres périphériques afin d'optimiser l'adressage des patients cirrhotiques réanimatoires au centre de greffe.

IV. L'accès à la greffe chez les patients cirrhotiques en défaillance multiviscérale (étude granulaire multicentrique européenne)

Le deuxième volet de cette thèse aborde la question de la transplantation chez les patients cirrhotiques en réanimation sous un angle épidémiologique. Il repose sur l'analyse de l'activité de greffe d'une cohorte de 20 centres de transplantation européens, sous l'égide de deux sociétés savantes : ELITA (European Liver and Intestine Transplant Association) et EF-Clif (European Foundation for the study of chronic liver failure). Cette étude s'intéresse à l'accès à la réanimation chez les patients en ACLF-3, l'inscription sur liste de greffe et l'accès effectif à la greffe. En particulier, cette étude montre que :

- Il y a une inégalité d'accès à la greffe pour les patients en ACLF-3 à travers les centres de greffe en Europe ;
- L'accès à la réanimation est une condition nécessaire mais pas suffisante à l'accès à la greffe de foie chez les patients cirrhotiques en ACLF-3 et il n'y a pas de corrélation entre le nombre de patients admis en réanimation et le nombre de patients greffés/mis sur liste d'attente de greffe en ACLF-3 ;
- La majorité des patients transplantés en ACLF-3 étaient mis sur liste alors qu'ils étaient en ACLF-3 ;
- Le pourcentage de patients mis sur liste d'attente de greffe en ACLF-3 qui ont effectivement eu accès à la greffe est élevé (79%) ;
- C'est l'accès à la liste de greffe pendant que le patient est en ACLF-3 qui est déterminant pour l'accès effectif à la transplantation.

Au total, cette étude suggère que la promotion de l'accès à la greffe pour les patients en ACLF-3 passe par une refonte en profondeur de la manière dont on envisage l'activité de greffe chez les patients cirrhotiques en état critique. En effet, elle souligne à quel point il est crucial d'être en mesure de réaliser le bilan pré transplantation du patient *depuis le service de réanimation* si l'on veut pouvoir faire accéder à la greffe

ce groupe de patients. Ceci implique notamment une collaboration multidisciplinaire entre les équipes de greffe et de réanimation.

V. Obstacles pratiques et institutionnels à la transplantation hépatique chez les patients cirrhotiques réanimatoire (étude qualitative internationale)

Le dernier volet de cette thèse repose sur l'analyse d'un questionnaire qualitatif qui a été envoyé aux investigateurs de l'étude CHANCE (il s'agit d'une étude prospective qui s'intéresse à la greffe chez les patients en ACLF-2 et ACLF-3). L'analyse des 100 premières réponses (émanant de 26 pays différents) met notamment en évidence que :

- La majorité des sondés considèrent que leur centre de greffe n'offre pas un accès suffisant à la transplantation chez les patients en ACLF-3 ;
- La majorité des sondés considèrent que les patients cirrhotiques en état critique n'ont pas assez accès à la réanimation dans la région où ils travaillent ;
- La majorité des sondés considèrent que les centres périphériques n'adressent pas assez de patients cirrhotiques en état critique au centre de greffe ;
- La majorité des sondés considèrent qu'il convient d'intégrer un « filtre utilitariste » pour écarter certains candidats à la greffe lorsque leur état clinique est trop grave ;
- Il n'y a pas de consensus quant à la nécessité ou non de prioriser davantage l'accès à la greffe des patients en ACLF-3.

Au total, cette étude met en évidence certaines des pistes qu'il convient de suivre pour diminuer les inégalités d'accès à la greffe chez les patients cirrhotiques réanimatoires. Ces pistes reposent notamment sur la transformation de la manière dont les cliniciens envisagent le traitement et le pronostic de ces patients et donc sur une transformation de la manière dont cette pathologie est enseignée.

VI. Conclusion et perspectives

Cette thèse de doctorat confirme que la cirrhose réanimatoire est une excellente indication à la transplantation hépatique sur le plan individuel et précise certaines des conditions qui doivent être remplies pour s'assurer qu'elle constitue également une

indication raisonnable et justifiée sur le plan collectif. Elle met en lumière l'inégalité frappante d'accès à la greffe dans ce contexte entre les centres de greffe et identifie certaines pistes de réflexion pour réduire ces inégalités. Enfin, elle souligne l'importance de la collaboration multidisciplinaire dans ce domaine afin de transformer à la fois la manière dont la médecine de transplantation envisage les patients cirrhotiques réanimatoires et la manière dont la médecine intensive/réanimation envisage la transplantation hépatique.

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Résumé

La place de la transplantation hépatique chez les patients cirrhotiques en défaillance multiviscérale fait débat. D'un côté, il s'agit du seul traitement qui peut radicalement améliorer le pronostic vital de ces patients. D'un autre côté, compte tenu d'une survie post transplantation globalement inférieure à la survie moyenne de la population générale des candidats à une transplantation hépatique, l'accès de ces patients à la greffe doit faire l'objet de précautions particulières pour ne pas péjorer l'utilité globale de l'activité de transplantation hépatique.

Dans un premier temps, trois études identifient différents éléments cliniques pertinents pour aider les praticiens à identifier une fenêtre de transplantabilité optimale chez les patients cirrhotiques en défaillance multiviscérale.

Dans un second temps, nous avons analysé des données épidémiologiques concernant l'accès effectif à la transplantation hépatique de ces patients à travers plusieurs pays européens. Ces analyses soulignent une hétérogénéité des pratiques dans ce domaine qui conduit à une inégalité d'accès au traitement salvateur que constitue la greffe. Une enquête qualitative a également été réalisée auprès de praticiens travaillants dans des centres de transplantation pour identifier des pistes potentielles pour réduire cette inégalité d'accès à la greffe. Pour finir, les différentes analyses tirées de cette thèse permettent d'une part d'éclaircir la place potentielle que pourraient jouer les algorithmes de répartition d'organes chez ces patients et d'autre part d'ouvrir des perspectives de recherche clinique dans ce domaine clé pour l'avenir de la transplantation hépatique.

Mots clés : transplantation hépatique, cirrhose, acute on chronic liver failure, réanimation, éthique, santé publique

Abstract

There is considerable debate over the indication of liver transplantation for critically ill patients with cirrhosis. On the one hand, liver transplantation is the only treatment that can radically improve the prognosis of these patients. On the other hand, given current organ shortage and the potentially poor post-transplant prognosis of this subgroup of patients, access to liver transplantation for critically ill patients can only be justified and supported if their post-transplant survival approaches that of the general population of transplant candidates.

This dissertation includes three studies that identify clinical tools that can contribute to identifying the optimal transplantability window of critically ill transplant candidates with cirrhosis.

It also describes and analyses the effective access that this subgroup of patients has to liver transplantation. In particular, this epidemiological approach shows that there is inequity in access to this life-saving treatment across transplant centers in France and in Europe. A qualitative survey among transplant professionals complements these results and identifies obstacles and potential solutions to reducing the inequity of access to liver transplantation for these patients.

Finally, the results of this dissertation shed light on the potential role that organ allocation algorithms could or should play in the context of critically ill patients with cirrhosis. It also offers new research perspectives on this topic that will doubtless play a key part in the future of liver transplantation.

Keywords : liver transplantation, cirrhosis, acute on chronic liver failure, intensive care, ethics, public health