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Impact of acute-on-chronic liver failure on 90-day mortality following a first liver transplantation

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Abstract

Background: Acute-on-chronic liver failure (ACLF) is associated with a significant short-term mortality rate (23%-74%), depending on the number of organ failures. Some patients present with ACLF at the time of liver transplantation (LT). The aim of this study was to assess whether ACLF was also a prognostic factor after LT and, if applicable, to construct a score that could predict 90-day mortality.

Methods: Three hundred and fifty cirrhotic patients, who underwent LT between January 2008 and December 2013, were enrolled. We used ACLF grades according to EASL-CLIF consortium criteria to categorize the cirrhotic patients. A propensity score was applied with an Inverse Probability Treatment Weighting in a Cox model. A predictive score of early mortality after LT was generated.

Results: One hundred and forty patients (40%) met the criteria for ACLF. The overall mortality rate at 90 days post-transplant was 10.6% (37/350 patients). ACLF at the time of LT (HR: 5.78 [3.42-9.77], $P<.001$) was an independent predictor of 90-day mortality. Infection occurring during the month before LT, high recipient age and male recipient, the reason for LT and a female donor were also independent risk factors for early mortality. Using these factors, we have proposed a model to predict 90-day mortality after LT.

Conclusions: LT is feasible in cirrhotic patients with ACLF. However, we have shown that ACLF is a significant and independent predictor of 90-day mortality. We propose a score that can identify candidate cirrhotic patients in whom LT might be associated with futile LT.

KEYWORDS

acute-on-chronic liver failure, cirrhosis, liver transplantation, mortality, outcome

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Abbreviations: ACLF, acute-on-chronic liver failure; AIC, Akaiké Information criterion; CLIF-SOFA, chronic liver failure-sequential organ failure assessment; EASL, European association for the study of the liver; ICU, intensive care unit; IPTW, inverse probability of treatment weighting; LT, liver transplantation; MELD, model for end-stage liver disease; PS, propensity score; SD, standard deviation; SOFA, sequential organ failure assessment.

*Both authors contributed equally to the work.

1 | INTRODUCTION

The graft allocation system for liver transplantation (LT) is based on the recipient's Model of End-Stage Liver Disease (MELD) score, which has created a shift in donor liver allocation to the sickest recipients in order to minimize waiting list mortality.[1-3] In the current context of organ shortage, the strict selection of transplant candidates is mandatory in order to prevent early mortality after transplantation, defined as death within 90 days of LT. Recently, experience with LT in Intensive Care Unit (ICU)-bound patients[4] showed that those requiring intubation at the time of LT[5] or with a MELD score>30[6] or ≥40,[7,8] experienced acceptable results. However, each of these studies explored the impact of only one or two organ failures on outcome.

According to the CANONIC study, Acute-On-Chronic Liver Failure (ACLF) is characterized by an acute decompensation of cirrhosis associated with organ failure (liver, coagulation, kidney, brain, circulation or/and lung).[9-12] This condition is associated with a short-term mortality rate (within 28 days) that ranges from 23% to 74%, depending on the number of organ failures.[10] ACLF is a dynamic syndrome that resolves in about 50% of patients.[13] In contrast, a high risk of early death (ranging from 41.7% to 91.8% within 28 days) is observable among patients in whom ACLF persists for more than 7 days after its diagnosis.[13] These latter patients are potential candidates for LT.

LT in patients with ACLF has been reputed as feasible, yielding a survival rate similar to that seen in patients without ACLF.[14-16] However, the definition of ACLF was not standardized in these studies[14-18] and none of these authors applied the European Chronic Liver Failure-ACLF criteria.[12]

Because the data are scarce and only available in eastern populations, the purpose of this study was to assess the risk of 90-day mortality in a larger number of consecutive cirrhotic patients in a western country who were undergoing LT, and to evaluate the impact of ACLF at the time of LT.

Key points

- ACLF is associated with a significant short-term mortality rate without LT
- Very few data are available regarding the impact of organ failure at the time of LT on the outcome of liver transplant
- ACLF at the time of LT was an independent predictor of 90-day mortality
- Based on the risk factors (recipient and donor genders, recipient age, LT indication, infection and ACLF), a prognostic model could be proposed to help clinicians to identify cirrhotic patients on the waiting list with a risk of early mortality after LT.

2 | PATIENTS AND METHODS

This study population included all consecutive cirrhotic patients receiving a first LT in one centre (Henri Mondor University hospital) between January 2008 and December 2013. Cirrhotic patients who underwent combined organ transplantation were excluded. The data were collected through the patient records. This study was approved by the Henri-Mondor Ethics Committee, and informed consent was obtained from each patient included in this study. The database was declared to the Commission Nationale de l'Informatique et des Libertés (n° 1699340).

2.1 | Recipients

The following recipient characteristics were taken into account: age, gender, ABO blood group, time from listing on the French national waiting list to LT, aetiologies of liver disease, presence of hepatocellular carcinoma, patient's location before LT (home, hepatology ward or ICU), scores (MELD, Child Pugh, SOFA and CLIF-SOFA) measured at the time of LT (the day of liver transplantation), presence of organ failures defined as a CLIF-SOFA score of 3 or 4 for each organ,[12] biological parameters (determined just before LT). For each patient, the biological assessment was conducted on the day of liver transplantation, just before his transfer in the operating room and the clinical assessment was evaluated on his arrival in the operating room. The diagnostic criteria for ACLF are detailed below.

Chronic morbidities and acute morbidity factors, including cardiac risk and the Charlson Comorbidity Index, were recorded. Cardiac risk was evaluated using criteria defined by the presence of severe valve disease, coronary artery disease with more than 70% stenosis or previous revascularization, a history of myocardial infarction, a history of ventricular and/or atrial arrhythmia, elevated pre-LT troponin I levels and/or new wall motion abnormalities on echocardiography.[7] Infection during the month prior to LT was recorded, based on the following criteria: (i) spontaneous bacterial peritonitis defined when the ascitic fluid neutrophil count was >250/mm^3; (ii) positive urine culture for urinary tract infection; (iii) positive blood cultures (two blood cultures for Staphylococcus epidermidis) for bacteraemia; (iv) suspicion of pneumonia based on combined criteria including elevated leucocytes (>12 000/mm^3), elevated C-reactive protein (>50 mg/L), fever or hypothermia (<36.5°C or >38.5°C), tracheal secretions, need for oxygen supply or mechanical ventilation, lung infiltrates or opacities on a chest X-ray.[19]

2.2 | Diagnostic criteria for ACLF

The diagnosis of ACLF was based on the consensus statement published by Moreau et al.[12] in 2013 (EASL-CLIF consortium/CANONIC study): patients with previously known chronic liver disease and an onset of organ failure defined by the CLIF-SOFA score (Circulation: need for epinephrine, norepinephrine or dopamine; lungs: $PaO_2/FiO_2 \leq 200$ or $SpO_2/FiO_2 \leq 214$; kidney: serum creatinine >176 μmol/L or use of renal replacement therapy; coagulation: INR≥2.5 or platelet count <20×10^3/mm^3; liver: bilirubin >204 μmol/L; brain: hepatic encephalopathy Grade III or IV).[12] Patients were then classified according to their ACLF score (From 0 to 3).[12]

2.3 | Liver transplantation

All donors were brain-dead and haemodynamically stable at multi-organ harvesting. Donor data included: age, gender, ABO blood group, cause of death, length of ICU stay, organ location, cold ischaemia time, height, weight and biological parameters.

The liver grafts were perfused and preserved using University of Wisconsin solution, Celsior solution or IGL-1 solution, depending on the preference of the harvesting centre. A mandatory wedge biopsy was performed at the beginning of organ procurement prior to aorto-caval clamping. This biopsy was examined urgently when the harvesting surgeon considered the liver graft to be abnormal. Grafts with macrosteatosis >40% or necrosis were discarded.

All operations were performed using standard surgical techniques, and the same anaesthetic protocol was applied for all transplanted patients. Intraoperative parameters were recorded and included cold ischaemia time, transfusions and duration of the procedure.

2.4 | Post-transplantation management

All patients received similar post-operative ICU with a routine triple immunosuppressive regimen including corticosteroids, mycophenolate mofetil and FK506 (Tacrolimus) or ciclosporin, with basiliximab (day 1 and day 4) in the event of rising or initially elevated serum creatinine levels. All patients received post-operative antibiotic therapy for 48 hours (piperacillin), and valganciclovir or ganciclovir for 6 months (in CMV-negative recipients and CMV-positive donors). Graft and recipient outcomes were recorded for all transplanted patients. No patients were lost to follow-up.

2.5 | Statistical analysis

Continuous data are presented as mean±SD or number of patients (%). Fisher's exact test (categorical variables) and the Mann-Whitney test (continuous variables) were used to compare data.

A propensity score was applied with an Inverse Probability Treatment Weighting in a Cox model. In addition, a prognostic score of early mortality after LT (90-day mortality) was generated. To build this score, we used a three-step methodology detailed in a submitted work. These steps were: a propensity score[20] and a weighted Cox model (Inverse Probability of Treatment Weighting), which enabled to perform an internal validation of the model.[21] It showed good performance. Finally, the score was defined as the predicted probability of death at 90 days: Score $= 1 - S_0(t)^{\exp(\beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_n X_n)}$, with $S_0(t)$ the month 3 baseline survival estimated thanks to Breslow estimator, β_i the coefficients of the model and X_i the covariates. Finally, Kaplan-Meier curves were fitted to two groups of patients according to the median of the model and to ACLF grade, then compared using the log-rank test. All analyses were performed using R statistical software version 3.3.0 (https: //r-project.org/).

3 | RESULTS

3.1 | Overall population

Between January 2008 and December 2013, 399 consecutive cirrhotic patients were listed for LT in our centre. Twenty-one patients were withdrawn from the waiting list because of their worsening clinical condition, and 28 died while on the list. The most common reasons were uncontrolled infection (n=24), the progression of hepatocellular

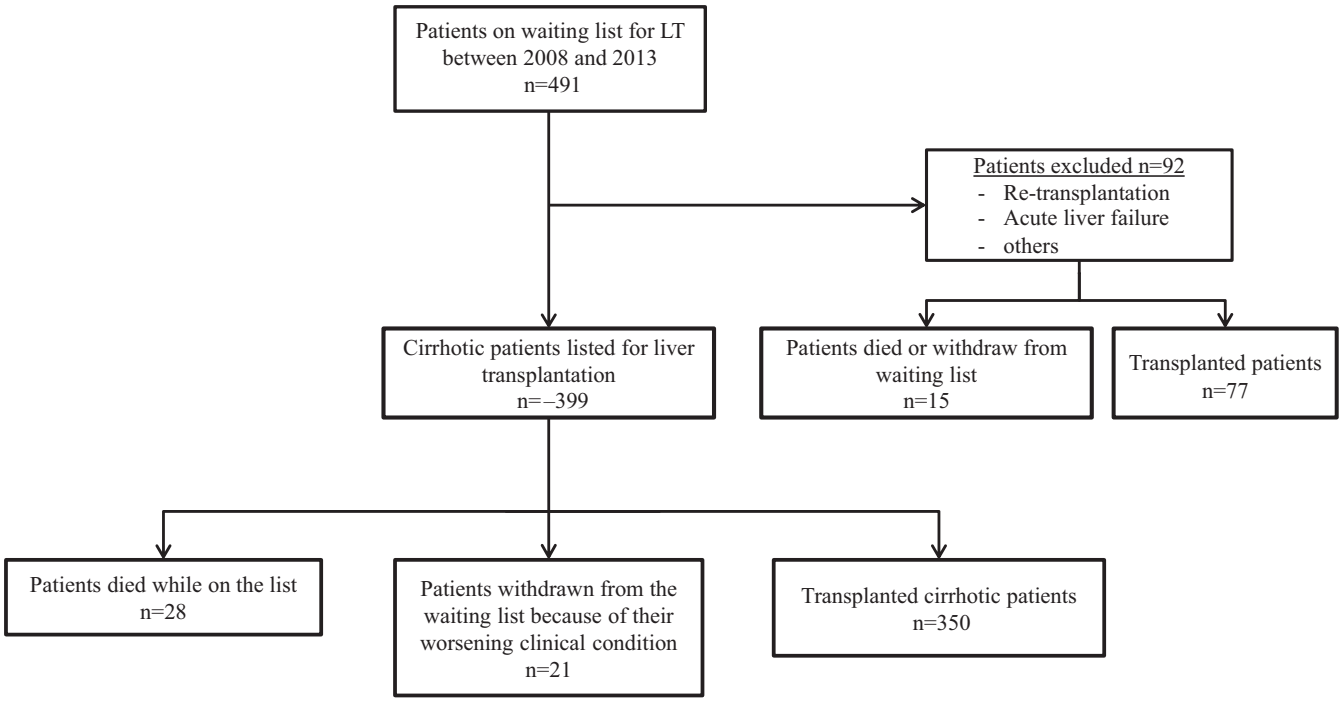

FIGURE 1 A flow chart illustrates the number of patients identified for this study

carcinoma (n=16) and haemorrhagic shock because of gastrointestinal bleeding (n=5). This study population thus included the remaining 350 transplanted patients (Figure 1).

The characteristics of the study population are shown in Table 1. One hundred and fifty-six patients (44.6%) underwent LT for a primary diagnosis of hepatocellular carcinoma, and 194 (55.4%) for end-stage liver disease. The two most common aetiologies were alcohol-induced disease (55.1%) and hepatitis C (26.3%). The mean age of the recipients was 55.5±9.5 years, and most of them (79.4%) were male. At the time of LT, 52 patients (15%) were ICU-bound, 58 (16.5%) were hospital-bound and 240 (68.5%) were at home. Sixty-four patients (18.6%) had an age-adjusted Charlson Comorbidity Index>6. The cardiac risk was markedly elevated in 52 patients (14.9%). At the time of transplantation, the mean CLIF-SOFA and MELD scores were 6.7±4.4 and 20.4±10.6 respectively. The MELD score was ≥30 in 84 (24%) and ≥40 in 40 (11.4%) patients.

The median ICU and hospital stays after LT were 13.9±17.8 and 38.7±28.2 days respectively. The median follow-up was 53 months. Mortality within 90 days of LT occurred in 37 patients (10.6%). The primary cause of death was infection/multi-organ failure (65%). Patient and graft survival rates at 3 months, 1 year and 5 years after LT were 89.4%, 82.9% and 75.4% and 87.1%, 82% and 71% respectively.

3.2 | Patients with or without ACLF

According to the EASL-CLIF consortium, 140 of our 350 patients (40%) fulfilled the criteria for ACLF at the time of LT. Between 2008 and 2013, the annual proportion of cirrhotic patients with ACLF undergoing LT rose from 32% to 51% (*P*=.04).

The clinical characteristics and outcomes of patients with and without ACLF at the time of LT are shown in Table 1. Coagulation failure was the most prevalent organ failure among patients with ACLF (65% of recipients), followed by liver and renal failure (53.6% and 19.3% of patients respectively). Twenty-four patients with ACLF (17%) were being treated with vasopressors (eg epinephrine, norepinephrine or dobutamine) at the time of LT. Twenty-nine patients (21%) required mechanical ventilation, the main reasons being respiratory insufficiency secondary to infection (n=16) and hepatic encephalopathy (n=7). Sixteen patients (11%) required renal replacement therapy (RRT) at the time of LT. Infection during the month prior to LT (precipitating event) was more common in patients with ACLF than in those without (36.4% vs 1.9%; *P*<.001). Preoperative MELD and CLIF-SOFA scores were significantly higher in patients with ACLF than in those without ACLF: 29.5±9.4 vs 14.3±6.1, *P*<.001, and 10.3±4.4 vs 4.3±2.2, *P*<.001 respectively.

The survival rates at 3 and 12 months among patients with ACLF vs those without ACLF were 79.3% vs 96.2% (*P*<.001) and 70% vs 91.4% (*P*<.001) respectively.

Compared to patients without ACLF, those with ACLF experienced a significantly longer stay in the ICU (11.5±16.5 vs 17.5±19 days; *P*<.001) and a longer stay in hospital (32.9±20.4 vs 47.5±35.3 days; *P*<.001) following LT.

ACLF at LT (140 cases) was graded 1 in 68 (19%), 2 in 42 (12%) and 3 in 30 (8.5%) recipients. Table 2 shows the mortality after LT in recipients according to their ACLF grade. The 90-day and 1-year survival probability in patients with ACLF grade 1 or 2 was 84.5% and 77.2%, respectively, while it was 60% and 43.3% in patients with ACLF grade 3 (Figure 2). These patients were more often hospitalized in the ICU before LT and had a higher prevalence of infection during the month prior to LT. Among patients with ACLF grade 3, 33% experienced three organ failures and 66% had four or more organ failures, without any difference in terms of mortality.

3.3 | Risk factors for 90-day mortality following LT

Using a weighted Cox model and the IPTW method, six independent predictors of 90-day mortality were identified: five were related to recipients' characteristics, age, gender, primary diagnosis at listing (end-stage liver disease or hepatocellular carcinoma), infection during the month prior to LT and the presence of ACLF at the time of LT. Gender was the only donor variable independently predictive of 90-day mortality. Table 3 shows the values of the regression coefficients and corresponding hazard ratios for each independent predictor of 90-day mortality. ACLF conferred an increase in mortality by a factor 5.78 within 90 days.

3.4 | Model to predict the early mortality (90-day mortality)

Using the six factors retained in the weighted Cox model, the 90-day mortality risk was calculated according to following equation (Supporting information):

$$\text{Score} = 1 - 0.937^{[A]}$$

Where:

$$\begin{aligned}[A] = \exp(&-0.28 \times (1 \text{ if the recipient is male, 0 otherwise})\\ &+0.29 \times (1 \text{ if the donor is male, 0 otherwise})\\ &-0.29 \times (1 \text{ if the LT indicationis end- stage liver disease,}\\ &0 \text{ if LT is hepatocellular carcinoma on cirrhosis})\\ &+0.44 \times (1 \text{ if the recipient has infection, 0 otherwise})\\ &+0.40 \times (1 \text{ if the recipient is older than 57.2 years, 0 otherwise})\\ &+1.75 \times (1 \text{ if the recipient is ACLF, 0 otherwise}).\end{aligned}$$

Model performance (C-index) was 0.71 [0.66-0.75] and the optimism-corrected model estimate of performance using a bootstrapping procedure was 0.65 [0.58-0.71].

As shown in Table 4, "recipient gender: male" and "LT indication: end-stage liver disease" were protective while other covariates such as the "presence of infection", "presence of ACLF", "recipient age ≥57.2 years" and "male donor" increased the score and the risk of mortality within 90-days. These five examples suggest a pattern of an increasing risk of death at 90 days post-transplantation. Therefore, being a 43-year-old male with end-stage liver disease, without infection or ACLF, and transplanted with a liver from a female donor produced a 4% risk of mortality. Conversely, being a 67 year old female with cancer on cirrhosis, with infection and ACLF, and transplanted with a liver from a male donor, indicated a 69% risk of mortality at 90 days post-LT.

TABLE 1 Preoperative characteristics of recipients, donor characteristics and outcomes for the overall population and for recipients with or without ACLF at the time of liver transplantation

	Total cohort (n=350)	Without ACLF (n=210)	With ACLF (n=140)	*P*
Age (years, mean±SD)	55.5±9.5	56.8±8.7	53.4±10.1	.0013
Gender (M/F)	278/72	172/38	106/34	.17
Body mass index (kg/m^2)	26.1±4.8	26.3±4.9	25.9±4.6	.53
Aetiology of liver disease n (%)				
Alcoholic	193 (55.1)	109 (51.9)	84 (60)	.09
Hepatitis B	24 (6.9)	16 (7.6)	8 (5.7)	
Hepatitis C	92 (26.3)	56 (26.7)	36 (25.7)	
Others	41 (11.7)	29 (13.8)	12 (8.6)	
Hepatocellular carcinoma	156 (44.6)	124 (59)	32 (22.9)	<.001
End-stage liver disease	194 (55.4)	86 (41)	108 (77.1)	
Location n (%)				
Home	240 (68.8)	186 (88.6)	43 (30.7)	<.001
Ward	58 (16.6)	20 (9.5)	36 (25.7)	
ICU	52 (14.8)	4 (1.9)	42 (30)	
Prognostic score before LT				
MELD score	20.4±10.6	14.3±6.1	29.5±9.4	<.001
SOFA score	5.8±4.5	3.7±1.9	9±4.6	<.001
CLIF-SOFA score	6.7±4.4	4.3±2.2	10.3±4.4	<.001
Child Pugh score	9.7±2.5	8.3±2.33	11.8±2.8	<.001
Child Pugh Class (A/B/C)	60/102/188	58/85/67	2/17/121	<.001
Laboratory data				
Serum sodium (mmol/L)	135.7±5.3	135±5	135±6	.9
Serum creatinine (μmol/L)	93.4±66.3	76±24	118±95	<.001
Serum bilirubin (mmol/L)	131.5±176.2	43±36	263±215	<.001
INR	2.1±1.3	1.5±0.4	3±1.7	<.001
Albumin (g/L)	31.7±6.9	32.1±6.3	30.9±7.8	.015
Platelets (/mm^3)	91.9±56.4	106±63	70±35	<.001
Leucocytes (/mm^3)	6.3±3.9	5.6±2.9	7.2±4.9	.035
Morbidity before LT n (%)				
Infection	55 (15.7)	4 (1.9)	51 (36.4)	<.001
Cardiac risk	52 (14.9)	26 (12.4)	26 (18.6)	.12
CCI Age-adjusted>6	64 (18.6)	34 (16.2)	30 (21.4)	.25
Ascites	200 (57.1)	93 (44.3)	107 (76.4)	<.001
Hepatic encephalopathy[a]	63 (18)	21 (10)	42 (30)	<.001
Acute variceal bleeding[b]	53 (15)	32 (15)	21 (15)	.95
Donor characteristics				
Age (years, mean±SD)	56.01±19	56.1±19.7	55.9±17.9	.94
Gender (M/F)	197/153	111/99	86/54	.12
Cold ischaemia time (min.)	479±138	496±135	452±139	.0013
Donor risk index	1.88±0.42	1.9±0.4	1.8±0.42	.11
Outcome				
ICU length of stay	13.9±17.8	11.5±16.5	17.5±19	<.001
Hospital length of stay	38.7±28.2	32.9±20.4	47.5±35.3	<.001

(Continues)

TABLE 1 (Continued)

	Total cohort (n=350)	Without ACLF (n=210)	With ACLF (n=140)	*P*
90-day mortality n (%)	37 (10.6)	8 (3.8)	29 (20.7)	<.001
1-year mortality n (%)	60 (17.1)	18 (8.6)	42 (30)	<.001

Data are expressed as mean±SD or number of patients (%). ACLF, Acute-on-Chronic Liver Failure; MELD, Model for End-Stage Liver Disease; SOFA, Sequential Organ Failure Assessment; CCI, Charlson Comorbidity index; BMI, body mass index; INR, International normalized Ratio; ICU, Intensive Care Unit.

[a]Hepatic encephalopathy: number of patients had at least one episode of encephalopathy in the year prior LT.

[b]Acute variceal bleeding: number of patients had at least one episode of acute variceal bleeding in the year prior LT.

Finally, Kaplan-Meier curves (Figure 3) were fitted for the two groups of patients according to the median of the model and compared using the log-rank test. A difference (P<.05) was seen in favour of patients with a predictive score lower than the median.

4 | DISCUSSION

This is the first study to have applied the new EASL-CLIF consortium criteria (CANONIC study) to explore early mortality after LT in a cohort of Caucasian cirrhotic patients undergoing a first non-combined LT. The presence of ACLF at the time of LT constituted a major risk of 90-day mortality. In addition, based on the risk factors and our prognostic model, we have been able to propose a score that could help clinicians to identify cirrhotic patients on the waiting list with a risk of early mortality after LT.

It has been shown, and further confirmed, that the presence of organ failure according to the definition of ACLF through EASL-CLIF consortium criteria is predictive of mortality in cirrhotic patients.[12] In contrast, in transplanted patients with ACLF defined using other criteria, several studies have suggested that the survival rate is similar to that obtained in patients without ACLF.[14-18] The difference between our study and those previous reports could be explained by the different definitions of ACLF (Asian-Pacific criteria[22] vs EASL-CLIF consortium criteria[12]) and the large cohort of patients studied here.

Our findings corroborate the results of several other authors who studied the impact of a single organ failure on post-LT outcomes. Cerebral failure defined by grade 3-4 hepatic encephalopathy at the time of LT is associated with a lower post-LT survival rate, and an association has been proposed between severe HE before LT and increased rates of post-LT infections.[23] Similarly, acute kidney injury at the time of LT has been associated with increased post-operative morbidity and mortality.[24,25] As shown previously by Umgerter et al., the risk of mortality in these cirrhotic patients undergoing LT varied with the number of organ failures.[26] Indeed, the number of organ failures should be considered when determining candidacy for transplantation in order to optimize the efficient use of a scarce resource.[27] We observed that the risk of mortality was greater in patients with ACLF grade 3 than in those with ACLF grade 1. The risk of death in non-transplanted cirrhotic patients with ACLF 2-3 is so high (between 57.1% and 77.2% at 28 days) that the benefits of transplantation are obvious in these candidates.[13,28] But this needs to be weighed against the potential increase in resource utilization. ACLF patients have been seen to experience a higher incidence of post-transplant infections and longer ICU and hospital stays, which imply higher overall costs.[29] An analysis of the number of failing organs seems more relevant than use of a composite score. Prognostic scores such as MELD or SOFA do not help to identify either the appropriate timing or the correct LT candidates. Indeed, they have been shown to poorly predict 90-day survival after LT in critically ill cirrhotic patients,[30-32] including those with a MELD score>40.[7,33]

An original statistical methodology was used to develop our model for short-term mortality. In order to reduce selection bias, a propensity score analysis was used to explain hospitalization in an ICU, and logistic regression with backward elimination by AIC based on comorbidity covariates (Charlson Comorbidity index and cardiac risk evaluation). Logistic regression is usually applied to short-term prognostic outcomes, and Cox regression to long-term prognostic outcomes. Here, we used a weighted Cox model together with the IPTW method. Moreover, the model might enable an improved assessment of an indication for LT in cirrhotic patients. The 90-day risk is a model with six factors, including ACLF at the time of LT, infection, the primary diagnosis at listing, recipient age and donor and recipient genders. According to our model, LT candidates with high scores should not be transplanted because of the higher risk of 90-day mortality.

Among the risk factors, we showed that infection was associated with a higher risk of futile transplantation (90-day mortality), in accordance with the findings of Petrowsky et al.[7] Unlike some authors,[34] we think that even if a patient's infection is successfully treated, he/she remains at risk of short-term mortality and requires intensive post-LT management. Like several other authors, we observed an impact of recipient age on the post-transplant outcome.[34] Finally, as in the case of hepatitis C and some other liver conditions, we observed a gender-based difference in post-transplant outcomes.[35] In the MELD era, our results agree with those of Bruns et al.,[36] who found that a female donor was a strong and independent risk factor for 90-day post-LT mortality. The impact of donor gender on outcome has also been studied, but it is still necessary to clarify whether this is related to donor quality rather than donor gender per se, or a gender mismatch that actually impacts post-transplant outcome.[35] However, the size of our cohort did not allow us to analyse the mismatch between recipient and donor and additional studies are needed.

Our study had some limitations. The set of variables used to build the PS was limited, and more covariables might have helped to deal with any selection bias. Some clinically sound parameters were not

TABLE 2 Preoperative characteristics of recipients, donor characteristics and outcomes of recipients according to ACLF grade at the time of liver transplantation

	ACLF Grade 1 (n=68)	ACLF Grade 2 (n=42)	ACLF Grade 3 (n=30)	*P*
Age (years, mean±SD)	54.9±10.5	51±10.8	53.4±7.8	.15
Gender (M/F)	52/16	30/12	24/6	.07
Body mass index (kg/m^2)	25.6±4.8	26.2±4.5	26.3±4.3	.49
Aetiology of liver disease n (%)				
Alcoholic	39 (57.4)	26 (61.9)	19 (63.3)	.51
Hepatitis B	3 (4.4)	3 (7.1)	2 (6.7)	
Hepatitis C	17 (25)	10 (23.8)	9 (30)	
Others	9 (13.2)	3 (7.2)	0 (0)	
Hepatocellular carcinoma	20 (29.4)	6 (14.3)	6 (20)	.16
End-stage liver disease	48 (70.6)	36 (85.7)	24 (80)	
Location n (%)				
Home	46 (67.6)	8 (19)	0 (0)	<.001
Ward	13 (19.1)	24 (57.1)	1 (3.3)	
ICU	9 (13.3)	10 (23.9)	29 (96.7)	
Prognostic score before LT				
MELD score	23.6±8.1	33.3±6.7	37.4±6.5	<.001
SOFA score	6.3±1.9	8.3±2	16±4	<.001
CLIF-SOFA score	7.6±1.6	9.9±1.7	17.3±3.9	<.001
Child Pugh score	11.1±2.3	12±1.8	13.6±1.4	<.001
Child Pugh Class (A/B/C)	2/13/53	0/3/39	0/1/29	.17
Organ failure n (%)				
Liver	14 (20.6)	37 (88.1)	24 (80)	<.001
Kidney	7 (10.3)	3 (7.1)	17 (56.7)	<.001
Cerebral	5 (7.4)	4 (9.5)	24 (80)	<.001
Coagulation	38 (55.9)	34 (81)	19 (63.3)	<.001
Circulation	5 (7.4)	1 (2.4)	18 (60)	<.001
Lungs	1 (1.5)	5 (11.9)	23 (76.7)	<.001
Laboratory data				
Serum sodium (mmol/L)	135±6	134±5	138±5	<.001
Serum creatinine (μmol/L)	105±91	88.5±42.3	190±120	<.001
Serum bilirubin (mmol/L)	138±138	342±192	437±222	<.001
INR	2.3±0.7	3.9±2	3.4±2.1	<.001
Albumin (g/L)	31.2±8.2	30.4±7.1	30.2±8.5	.81
Platelets (/mm^3)	74±39	69±27	62±33	.25
Morbidity before LT n (%)				
Infection	13 (19.1)	17 (40.5)	21 (70)	<.001
Cardiac risk	13 (19.1)	6 (14.3)	7 (23.3)	.98
CCI Age-adjusted>6	17 (25)	9 (21.4)	4 (13.3)	.43
Ascites	49 (72.1)	31 (73.8)	27 (90)	.13
Hepatic encephalopathy[a]	9 (13)	7 (16)	26 (86)	<.001
Acute variceal bleeding[b]	9 (13)	6 (14)	6 (20)	.73
Donor characteristics				
Age (years, mean±SD)	57.9±18.7	51.7±18.8	57.4±13.7	.17
Gender (M/F)	38/30	30/12	18/12	.26
Cold ischaemia time (min.)	463±151	443±126	437±129	.29

(Continues)

TABLE 2 (Continued)

	ACLF Grade 1 (n=68)	ACLF Grade 2 (n=42)	ACLF Grade 3 (n=30)	*P*
Donor risk index	1.9±0.45	1.7±0.37	1.9±0.4	.06
Outcome				
ICU length of stay	13.3±13.02	16±15.3	29.3±28	.0004
Hospital length of stay	41.4±31.12	46±36.5	62±39	.0045
90-day mortality n (%)	10 (14.7)	7 (16.7)	12 (40)	.013
1-year mortality n (%)	16 (23.5)	9 (21.4)	17 (56.7)	.0015

Data are expressed as mean±SD or number of patients (%). ACLF, Acute-on-chronic liver failure; MELD, model for end-stage liver disease; SOFA, sequential organ failure assessment; CCI, Charlson comorbidity index; BMI, body mass index; INR, International normalized Ratio; ICU: intensive care unit.
[a]Hepatic encephalopathy: number of patients had at least one episode of encephalopathy in the year prior LT.
[b]Acute variceal bleeding: number of patients had at least one episode of acute variceal bleeding in the year prior LT.

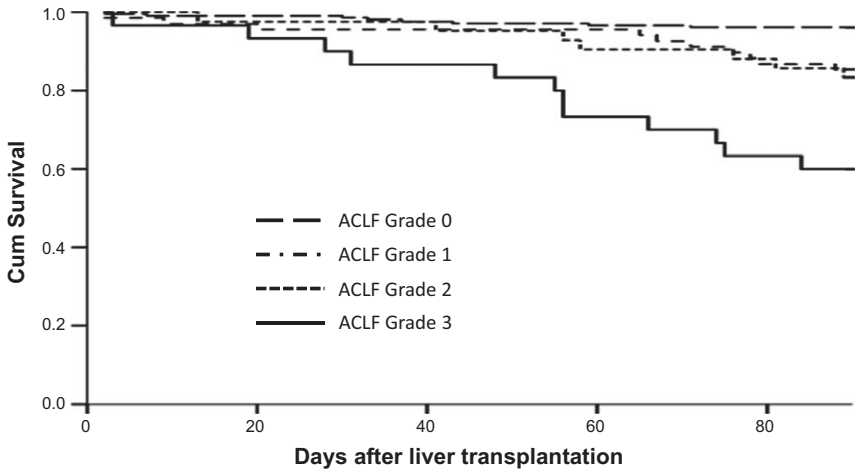

FIGURE 2 Cumulative 90-day survival of the 350 cirrhotic patients who underwent liver transplantation according to ACLF grade at the time of LT

TABLE 3 Weighted Cox model for mortality at 90 days after the backward elimination of covariates by AIC (reference group on the left-hand side)

Variable	Beta coefficient	HR	CI 95%	*P*
Recipient Age (≤57.2 vs >57.2 years)	0.40	1.49	1.10-2.03	.010
Infection (no vs yes)	0.44	1.56	1.13-2.14	.006
ACLF (no vs yes)	1.75	5.78	3.42-9.77	<.001
Recipient gender (F vs M)	−0.28	0.76	0.54-1.06	.104
Donor gender (F vs M)	0.29	1.34	0.98-1.83	.065
Aetiology LT (1 vs 2)	−0.29	0.75	0.53-1.04	.088

ACLF, acute-on-chronic liver failure, Aetiology 1: cancer on cirrhosis, 2: end-stage liver disease.

analysed because of their retrospective nature. Indeed, important physiological parameters (such as nutritional issues), laboratory values and recipient characteristics[37] were lacking, even though they are of unquestionable value as a guide to clinical decision-making relative to liver organ allocation and transplantation in patients with decompensated cirrhosis receiving support in a critical care setting.[31] The design of the model was based only on transplanted patients. Therefore, it is still necessary to validate in, or adapt the score to, the population of patients not yet listed for transplantation, and particularly those admitted for the first time to the ICU. Nevertheless, our study may provide one answer to the question "when is a listed patient too sick to be transplanted?".[38] Moreover, assessing the weight of each of the components of ACLF would be informative in terms of detecting the right candidate for LT, but the size of our cohort did not allow us to answer this question categorically with respect to organ failure. Finally, this model is derived from a single cohort experience, and thus likely to be highly influenced by clinical decisions made by that single centre regarding management, organ acceptance criteria and clinical care post-LT. These findings should be validated in a larger cohort preferably multicentre and in another healthcare system.

TABLE 4 Specific combinations of risk factors, according to the predictive model, expressed as percentages of predicted mortality at 90 days post-LT

Risk factors	Reference patient	Example 1	Example 2	Example 3	Example 4	Example 5	Example 6
Recipient gender	Female	**Male**	Female	Female	Female	Female	Female
Donor gender	Female	Female	Female	Female	Male	Female	Male
LT indication	1	**2**	1	1	1	1	1
Infection	No	No	**Yes**	**Yes**	**Yes**	No	**Yes**
Recipient age	50	43	50	**58**	**60**	46	**67**
ACLF	No	No	No	No	No	**Yes**	**Yes**
Score	0.06	0.04	0.10	0.14	0.18	0.31	0.69
Risk of mortality at 90 days post-LT	**6%**	**6%**	**10%**	**14%**	**18%**	**31%**	**69%**

ACLF, acute-on-chronic liver failure, Aetiology 1: cancer on cirrhosis, 2: end-stage liver disease.
Values in bold differ from the values of the reference patient.

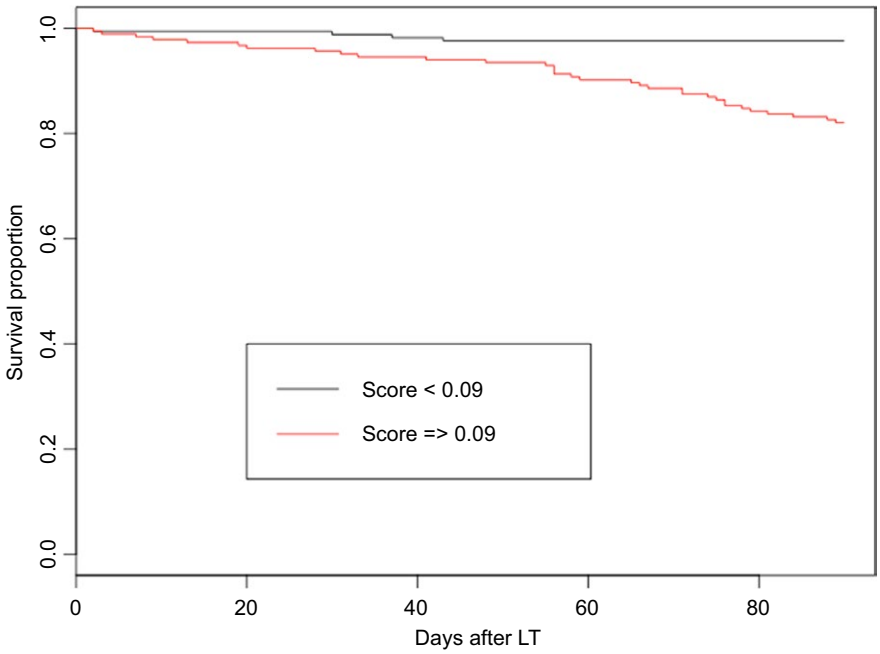

FIGURE 3 Comparison of survival curves at 90 days for a score <0.09 (black) vs ≥0.09 (red). A difference can be seen in favour of patients with a score lower than the median (0.09; Log-rank test $P<0.05$)

In conclusion, LT in cirrhotic patients with ACLF is associated with higher early mortality. Improving our ability to better identify those patients presenting with ACLF who might benefit from LT is a challenge, particularly in view of the increasing proportion of candidates with high MELD scores and/or with ACLF. For example, the number of organ failures (grade to ACLF) influences early mortality which can reach 40% in patients with three or more organ failures. In addition, as an aid to clinicians, we propose a model that can help to identify patients who will benefit from LT and might prevent 90-day mortality. Before introducing our model into clinical practice, it still needs to be refined and tested in other large multicentre cohorts and probably adapted to the number and type of organ failures.

CONFLICT OF INTEREST

No conflict of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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