Research Article
Liver Transplantation

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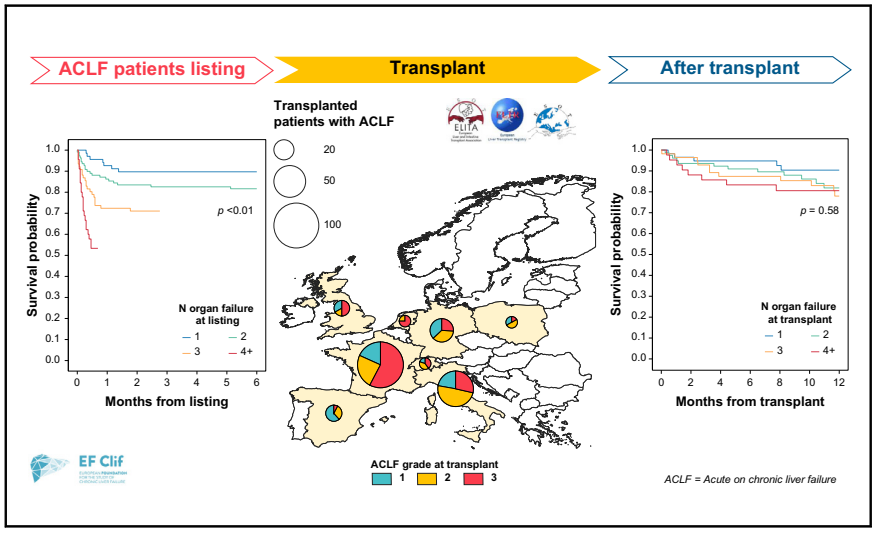
Liver transplantation for patients with acute-on-chronic liver failure (ACLF) in Europe: Results of the ELITA/EF-CLIF collaborative study (ECLIS)☆

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.

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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),

Keywords: Acute-on-Chronic Liver Failure; Liver transplantation; Waiting list; Predictive factors; Multi-drug resistant organisms.
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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%)

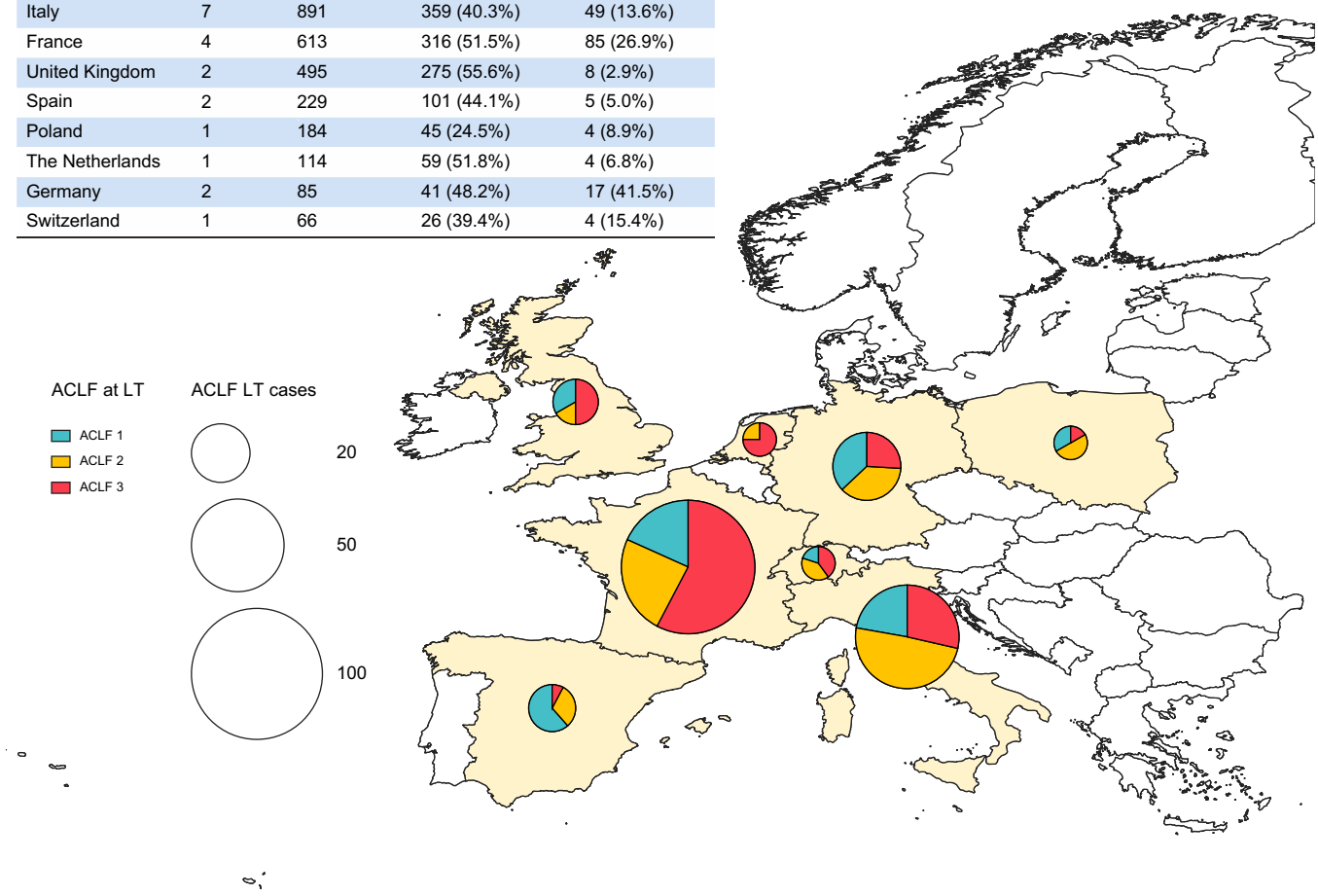


Fig. 1. ACLF cases enrolled in the study by country. *Percentages referred to patients with DC. ACLF, acute-on-chronic liver failure; DC, decompensated cirrhosis; LT, liver transplantation.

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

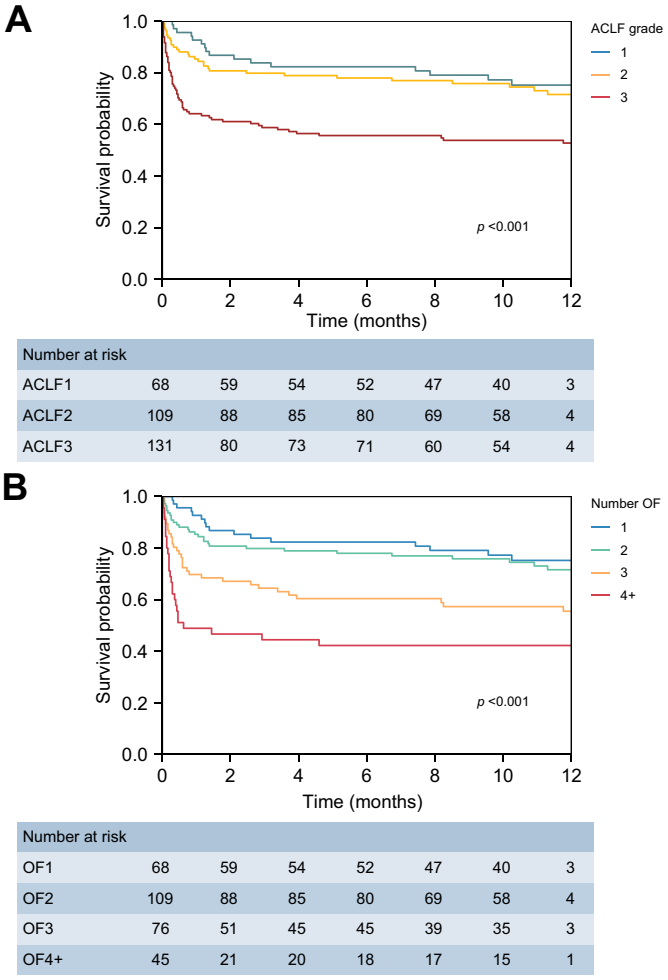


Fig. 2. Survival curves from wait-listing for ACLF or from occurrence of ACLF if it occurred after listing. (A) survival probability stratified by ACLF grade at baseline, and (B) survival probability stratified by number of organ failures at baseline. *p* values refer to log-rank test. ACLF, acute-on-chronic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

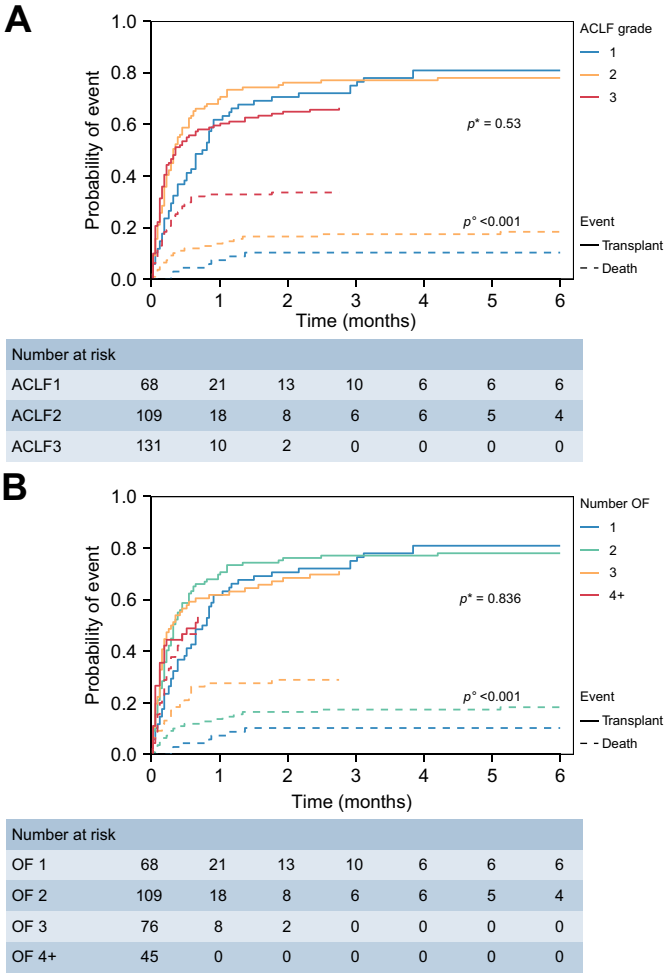


Fig. 3. Cumulative incidence of transplant and death. (A) Cumulative incidence stratified by ACLF grade at baseline, and (B) cumulative incidence stratified by number of organ failure at baseline. Results from competing risks analysis. **p* values refer to Gray's test comparing cumulative incidence of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

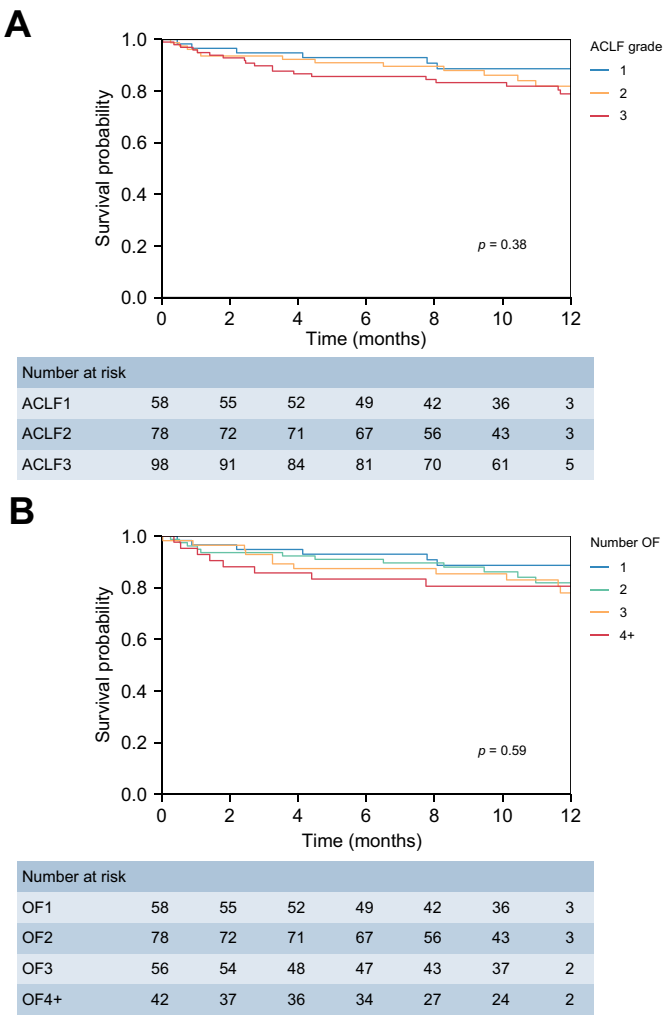
[c] *p* value ACLF 2 *vs.* ACLF 3 ≤0.05

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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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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