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

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ABSTRACT

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

Methods. Retrospective study including 308 consecutive ACLF patients, listed in 20 centres across 8 European countries, from January 2018 to June 2019.

Results. 2677 patients received a LT, 1216 (45.4%) for decompensated cirrhosis (DC). Of these, 234 (19.2%) had ACLF at LT: ACLF-1, 58 (4.8%); ACLF-2, 78 (6.4%); and ACLF-3, 98 (8.1%). Wide variations were observed amongst countries: France and Germany had high rates of ACLF-2/3 (27-41%); Italy, Switzerland, Poland and Netherlands had medium rates (9-15%); and United Kingdom and Spain had low rates (3-5%) ($p < .0001$). One-year probability of survival after LT for patients with ACLF was 81% (95% CI 74-87). Pre-LT arterial lactate levels >4 mmol/L (HR 3.14, 95% CI 1.37-7.19), recent infection from multi-drug 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 WL. In an intention-to-treat analysis, one-year survival of ACLF patients on the LT WL was 73% for ACLF-1 or -2 and 50% for ACLF-3.

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

LAY SUMMARY

- The percentage of liver transplants (LT) performed in patients with acute-on-chronic liver failure (ACLF) grade 2-3 differed significantly between European countries, raising significant issues with access to transplantation across Europe.
- Prioritization on the waiting list should take into account the 25% mortality risk for patients with ACLF-2-3, to equitably allocate grafts to the more urgent cases.
- One-year post-LT survival of patients with ACLF was in excess of 80% independently of ACLF grade.
- Infections from multi-drug resistant organisms, either precipitating ACLF or complicating its clinical course, were relevant predictors of poor outcome.

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 extra-hepatic 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 the survival of patients with ACLF (3,4). However, most of the data has 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 role of donor and recipient characteristics in determining the outcome, healthcare burden of patient's management and the importance of concomitant infection with multi-drug resistant organisms (MDRO) are unknown. Importantly, clinical criteria to assess mortality risk of patients on the waiting list (WL) and after LT is 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 centers 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 was their survival after listing for LT on the WL and after LT?
- What were the determinants of mortality in both settings?

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 twenty LT centres participating in European Liver Transplant Registry from 8 European countries were included. In parallel, total LT activity in each center during the same time period was recorded. All adult patients listed for LT in the 20 participating centers 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 of ACLF

Diagnostic criteria of ACLF and its grades were those as described previously (2). ACLF grade 1 (ACLF-1) was defined by 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 normalized ratio [INR] ≥2.5; circulation: use of vasopressors; lungs: PaO2/FiO2 ≤200 or SpO2/FiO2 ≤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 PaO2/FiO2 >200) as the definition proposed by CLIF-Consortium was strictly followed. ACLF grade 2 (ACLF-2) and ACLF grade 3 (ACLF-3) were defined by the presence of 2 or ≥3 organ failures (OFs), respectively.

Data collection

The data that was collected for ACLF patients included demographics (age, sex), etiology of liver disease, number and type of OFs at listing and at LT, 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 from multiple

drug resistant organism (MDRO) 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 (DBD – donation after brain death donors, or DCD – donation after circulatory death donors), WIT (warm ischemic time) and CIT (cold ischemic time).

Definition of multi-drug resistant organisms

MDRO was defined as acquired non-susceptibility to at least one agent in 3 or more antimicrobial categories. The following bacteria were considered MDRO 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 (MRSA/VRSA) and vancomycin-resistant Enterococcus faecium (VRE) (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 summarized through percentages, while continuous variables through median, first quartile (Q1) and third quartile (Q3). Categorical variables 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 two-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 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 patients' characteristics was evaluated through univariate competing risks models, accounting for transplant as a competing event. All characteristics analyzed 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 patients' characteristics at transplant was evaluated through univariate and multivariate Cox proportional hazard 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 2677 LT, representing 25.8% (total number 10350) of the LT registered by ELTR, 1216 (1216/2677, 45.4%) of which being performed for DC, 895 (895/2677, 33.4%) for HCC, and 566 (566/2677, 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 with ACLF 1-3 at the time of listing and 81 (26.3%) who 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 ACLF patients WL for LT or with ACLF occurring while already listed, 68 (22.1%) were 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 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 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 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) ($p < 0.0001$) (Figure 1)**.**

Baseline characteristics of patients with ACLF at listing or occurring after listing

Two-hundred and five patients were male (66.6%) and median age (IQR) at inclusion was 56 (48–62) years. The most frequent etiologies of cirrhosis were alcohol (53.9%), viral infection (hepatitis B or C viruses) (11.0%) and 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 the majority of patients (89.6%), at least one precipitating event could be identified, with infections (182/308, 59%) being the most frequent, 30% of which were from MDRO (55/182). A detailed description of MDRO is provided in Supplementary table 1. 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 (Figure 2). When considering ACLF-3 patients having 4 or more OFs, the 1-year survival further declined to 42.2% (95% CI 27.8% - 56.0%) (Figure 2)**.** The cumulative incidence of transplant or death by competing risk analysis is shown in Figure 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 Supplementary tables 2 and 3.

Predictors of mortality on the WL by competing risk model

Factors significantly associated with death by 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 MDRO were observed in 60% of the cases (28/47) with mortality being directly related to MDRO in 26; the

two remaining patients died of massive gastro-intestinal bleeding and of liver failure associated with HCC rupture (Supplementary Table 3).

Variability in wait-list 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) (Supplementary Table 4).

Characteristics of patients with ACLF 1-3 receiving a LT

Patients' 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 etiologies 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 Supplementary Table 5. Median arterial lactate level at LT was 2 mmol/L (1.4-2.7) and 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. Median WIT and CIT were 35 min (25-45) and 421 min (352-490), respectively.

Follow-up

Median follow-up time 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 having received a LT, 37 (37/234, 15.8%) died after LT. The KM 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) (Figure 4). Notably, the survival probability of ACLF-3 patients having 4 or more OFs did not differ significantly from that of patients with only 3 OFs (Figure 4).

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

The survival after LT did not differ when countries performing high, medium and low percentage of ACLF-2/3 were compared (Supplementary figure 1).

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 RRT. The ACLF-3 patients required a significantly more frequent intubation (44 patients, 44.9%) and RRT (46 patients, 46.9%) compare to ACLF-1 (10 (17.2%) intubation and 15 (25.9%) RRT) and ACLF-2 (18 (23.1%) intubation and 18 (23.1%) RRT) (Table 3). Patients with ACLF-3 also experienced significantly more infections in particular from MDRO compared with ACLF-1 and ACLF-2 patients (Table 3 and Supplementary table 4). Of the 23 patients having a MDRO infection pre-LT, 13 (56.5%) had a new infection from MDRO post-LT with 7 deaths. In 11 cases the post-LT MDRO infection was from the same organism isolated before LT (Supplementary table 6).

The median post-LT ICU stay was 12.5 (7 – 29) days for ACLF-3, 10 (6 – 17) for ACLF-2 and 7.5 (5 – 13) for ACLF-1, while the median total hospital stay was 37.5 (24.5 – 69.5), 30 (21 – 54) and 24 (18 – 39) days, respectively. ACLF-3 group had a statistically significantly longer stay only compared to ACLF-1 group for both ICU and hospital stay ($p <= 0.05$).

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 of dialysis at LT (Table 4). Multivariable analysis of factors associated with death demonstrated persisting positive associations with pre-LT MDRO 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 of RRT at LT (HR 2.74, 95% CI 1.37-5.51, p=0.0046)

DISCUSSION

This large international study involving 20 liver transplant centres across 8 European countries provides the current state of clinical practice and results of LT for patients with ACLF and provides several novel observations. 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 a 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 ACLF patients is likely to consume more resources as the post-LT hospital and ICU stay are high 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 rates 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 unfavorably 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 suggests 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. It is now time to consider harmonization 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 earlier appreciation of the risk of mortality allowing a change in referral and allocation policies.

Almost two thirds of patients listed for ACLF or developing 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 prioritization 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 patients was because a graft was not available in due time, even with this level of prioritisation. The 1-year KM survival 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 of 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 ICU at the time of LT, which again suggests a possible association between pre-LT MDRO and 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 having infection from 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 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 optimize 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 rule a patient out from being transplanted.

Compared to patients with ACLF-1 and -2, those with ACLF-3 developed significantly more complications in the post LT period requiring prolonged intubation, RRT and more 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 increase in resource utilization that will result.

Evaluation of the role of LT for patients with ACLF needs to take into account their outcome from the time of wait listing. In the present cohort, the 1-year KM survival from wait listing with ACLF was 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 prioritization 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 MDRO 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 already having 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 MDRO are highly prevalent in patients with cirrhosis (21,22) and known to be associated with poor survival. Established risk factors for MDRO infections are recurrent hospitalizations, 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 ACLF patients, 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. Firstly, 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 characterization 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 realized 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 taken into account. Second, the dynamics of ACLF could not be analysed because it was available only for patients who developed ACLF after listing. Third, it was not possible to retrospectively assess whether patients on the waiting list died because they were 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 ACLF patients 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 multicenter 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 - emphasizing 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 MELD score do not always identify those at highest risk and that LT in these patients can yield favourable post-LT survival. Risk factors for mortality were identified both from the time of wait listing and also at time of transplant, which may permit more precise assessment of prognosis of patients with ACLF who are potential transplant recipients. The results of this study argue strongly for initiation of pilot programmes across Europe generating more prospective data for better selection of patients.

Abbreviations

ACLF: acute-on-chronic liver failure, ELITA: European Liver and Intestine Transplant Association, EF-CLIF: European Foundation for the study of chronic liver failure, LT: liver transplantation, WL: waiting list, DC: decompensated cirrhosis, HCC: Hepatocellular carcinoma, HE: hepatic encephalopathy, INR: international normalized ratio, PaO2: partial arterial oxygen, FiO2: fraction inspired oxygen, OF: organ failure, MELD: Mayo model for end stage liver disease, CLIF-C: chronic liver failure-consortium, DBD: donation after brain death, DCD: donation after circulatory death, WIT: warm ischemic time, CIT: cold ischemic time, MDRO: multi-drug resistant organisms, MRSA: methicillin resistant staphylococcus aureus, VRE: vancomycin resistant enterococci, GDPR: general data protection regulation, HR: hazard ratio, CI: confidence intervals, NASH: non-alcoholic steato-hepatitis, WBC: white blood cells, KM: Kaplan Meier, ICI: intensive care unit, RRT: renal replacement therapy, AD: acute decompensation.

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Figure legends

Fig 1. ACLF cases enrolled in the study by country. LT: Liver Transplant, DC: Decompensated Cirrhosis, ACLF: Acute-on-chronic liver failure. *Percentages referred to patients with DC

Fig 2. Survival curves from waitlisting for ACLF or from occurrence of ACLF if it occurred after listing. (A) survival probability stratified by ACLF grade at baseline, (B) survival probability stratified by number of organ failures at baseline. P-values refer to log-rank test.

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

Fig 4. Survival curves from liver transplant. (A) survival probability stratified by ACLF grade at liver transplant, (B) survival probability stratified by number of organ failures at liver transplant. P-values refer to log-rank test.

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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).

Supplementary materials.

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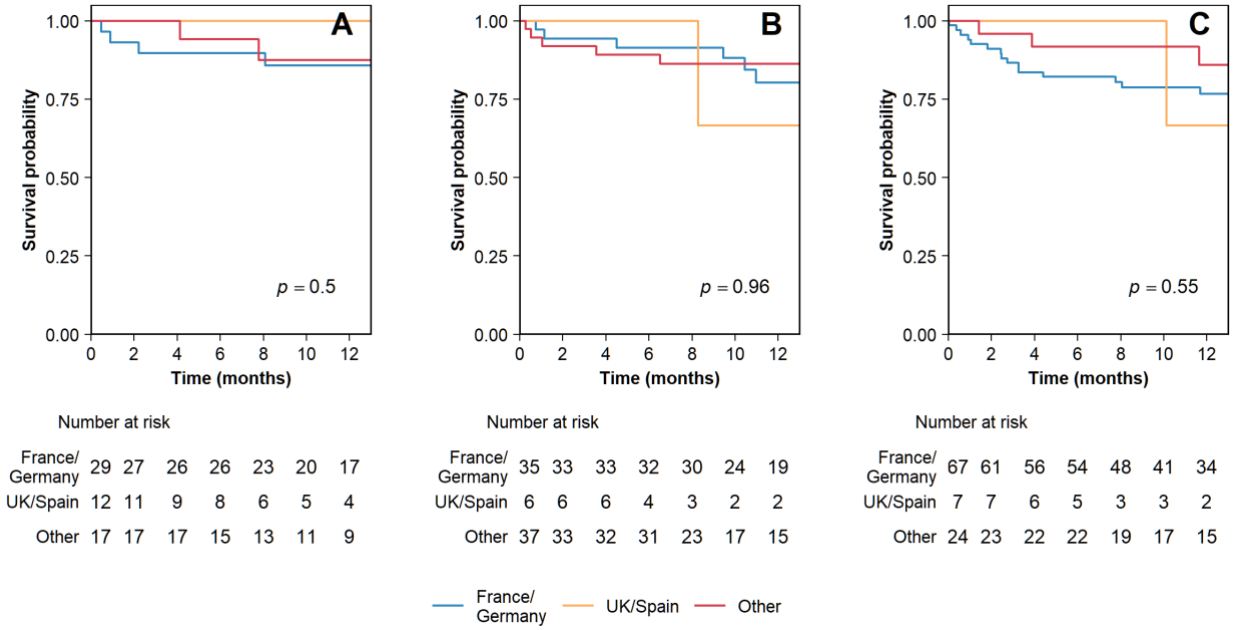
Supplementary figure

Figure S1. Survival curves from liver transplant, stratified by country. Survival curves for patients with ACLF grade 1 (A), with ACLF grade 2 (B), with ACLF grade 3 (C). P-values refer to log-rank test.



Supplementary tables

Table S1. Description of MDRO infections.

	ACLF at listing or at occurrence (if after listing)			Total (N=308)
	ACLF-1 (N=68)	ACLF-2 (N=109)	ACLF-3 (N=131)	
MDRO infection – N (%)				
Yes	10 (14.71%)	14 (12.84%)	31 (23.66%)	55 (17.86%)
Missing	*0 (0.00%)*	*1 (0.92%)*	*0 (0.00%)*	*1 (0.32%)*
Organisms (multiple organisms possible) – N (%*)				
Gram positive	1 (10.00%)	1 (7.14%)	4 (12.90%)	6 (10.91%)
VRE	*1 (10.00%)*	*0 (0.00%)*	*2 (6.45%)*	*3 (5.45%)*
MRSA/VRSA	*0 (0.00%)*	*1 (7.14%)*	*2 (6.45%)*	*3 (5.45%)*
Gram negative	7 (70.00%)	11 (78.57%)	22 (70.97%)	40 (72.73%)
Carbapenem resistant	*1 (10.00%)*	*0 (0.00%)*	*3 (9.68%)*	*4 (7.27%)*
ESBL	*6 (60.00%)*	*10 (71.43%)*	*18 (58.06%)*	*34 (61.82%)*
Amp-c Enterobacter or Amp-c Citrobacter	*0 (0.00%)*	*1 (7.14%)*	*1 (3.23%)*	*2 (3.64%)*
Other	2 (20.00%)	2 (14.29%)	7 (22.58%)	11 (20.00%)
Fungi	*1 (10.00%)*	*1 (7.14%)*	*4 (12.90%)*	*6 (10.91%)*
Other	*1 (10.00%)*	*1 (7.14%)*	*3 (9.68%)*	*5 (9.09%)*
Site (multiple sites possible) - N (%*)				
Spontaneous or secondary bacteremia	2 (20.00%)	7 (50.00%)	12 (38.71%)	21 (38.18%)
Spontaneous bacterial peritonitis	1 (10.00%)	4 (28.57%)	4 (12.90%)	9 (16.36%)
Pneumonia	3 (30.00%)	2 (14.29%)	9 (29.03%)	14 (25.45%)
Urinary tract infection	3 (30.00%)	1 (7.14%)	7 (22.58%)	11 (20.00%)
Skin or soft tissue	1 (10.00%)	1 (7.14%)	2 (6.45%)	4 (7.27%)
Cholangitis or liver abscesses	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (1.82%)

* Refers to patients experiencing an infection (first row)

Table S2. Additional characteristics of patients who died on the waiting list.

	ACLF at listing or at occurrence (if after listing)			Total (N=74)
	1 (N=8)	2 (N=22)	3 (N=44)	
Subjects developing ACLF after listing (incident cases)[b]	0 (0.00%)	8 (36.36%)	25 (56.82%)	33 (44.59%)
Early death (before 3rd day)	0 (0.00%)	1 (4.55%)	8 (18.18%)	9 (12.16%)
Only for patients who survived up to the 3rd day				
ACLF grade at 3-7 days*				
2	1 (12.50%)	3 (14.29%)	1 (2.78%)	5 (7.69%)
3	7 (87.50%)	17 (80.95%)	35 (97.22%)	59 (90.77%)
Missing	*0 (0.00%)*	*1 (4.76%)*	*0 (0.00%)*	*1 (1.54%)*
Type of organ failure				
Missing	*0 (0.00%)*	*1 (4.76%)*	*0 (0.00%)*	*1 (1.54%)*
Liver failure	6 (75.00%)	18 (85.71%)	30 (83.33%)	54 (83.08%)
Renal failure	7 (87.50%)	15 (71.43%)	31 (86.11%)	53 (81.54%)
RRT	*4 (57.14%)*	*9 (60.00%)*	*23 (74.19%)*	*36 (67.92%)*
Coagulation failure	6 (75.00%)	13 (61.90%)	27 (75.00%)	46 (70.77%)
Brain failure	2 (25.00%)	8 (38.10%)	19 (52.78%)	29 (44.62%)
Circulatory failure	7 (87.50%)	12 (57.14%)	27 (75.00%)	46 (70.77%)
Respiratory failure	6 (75.00%)	11 (52.38%)	26 (72.22%)	43 (66.15%)
PaO2/FiO2				
Median (Q1-Q3)	*191.9 (136.0 - 230.0)*	*156.5 (142.0 - 213.9)*	*167.0 (148.7 - 215.0)*	*167.0 (142.0 - 215.0)*
Missing (%)	*0 (0.00%)*	*1 (9.09%)*	*1 (3.85%)*	*2 (4.65%)*
PaO2/FiO2 <200	3 (50.00%)	6 (54.55%)	16 (61.54%)	25 (58.14%)
CLIF ACLF score at 3-7 days*				
Median (Q1-Q3)	72.0 (64.0 - 73.5)	68.5 (54.0 - 78.0)	73.0 (61.0 - 76.0)	71.0 (58.0 - 77.0)
Missing (%)	0 (0.00%)	3 (14.29%)	3 (8.33%)	6 (9.23%)
Lactate at 3-7 days*				
Median (Q1-Q3)	4.6 (2.6 - 6.8)	4.1 (3.1 - 7.7)	5.0 (2.4 - 11.7)	4.3 (2.5 - 9.2)
Missing (%)	0 (0.00%)	1 (4.76%)	1 (2.78%)	2 (3.08%)
WBC at 3-7 days*				
Median (Q1-Q3)	14.5 (11.8 - 17.4)	13.7 (10.9 - 18.7)	13.1 (10.2 - 17.8)	13.5 (10.5 - 18.0)
Missing (%)	0 (0.00%)	1 (4.76%)	0 (0.00%)	1 (1.54%)
MDRO infection				
Yes	5 (62.50%)	10 (47.62%)	13 (36.11%)	28 (43.08%)
Gram positive	1 (20.00%)	1 (10.00%)	2 (15.38%)	4 (14.29%)
Gram negative	2 (40.00%)	8 (80.00%)	8 (61.54%)	18 (64.29%)
Other	2 (40.00%)	1 (10.00%)	5 (38.46%)	8 (28.57%)
Time (in days) from wait-listing for ACLF to death / delisting[b]**				
Median (Q1-Q3)	26.5 (11.5 - 38.5)	13.0 (5.0 - 37.0)	8.0 (4.5 - 13.5)	9.0 (5.0 - 18.0)

[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*

**from ACLF occurrence*

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

Table S3. Description of MDRO infections of patients who died in the waiting list.

	ACLF at listing or at occurrence (if after listing)			Total (N=74)
	1 (N=8)	2 (N=22)	3 (N=44)	
MDRO infection – N (%)	5 (62.50%)	10 (47.62%)	13 (36.11%)	28 (43.08%)
Organism (multiple organisms possible) – N (%*)				
Gram positive	1 (20.00%)	1 (10.00%)	2 (15.38%)	4 (14.29%)
VRE	1 (20.00%)	0 (0.00%)	1 (7.69%)	2 (7.14%)
MRSA/VRSA	0 (0.00%)	1 (10.00%)	1 (7.69%)	2 (7.14%)
Gram negative	2 (40.00%)	8 (80.00%)	8 (61.54%)	18 (64.29%)
Carbapenem resistant	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)
ESBL	1 (20.00%)	8 (80.00%)	8 (61.54%)	17 (60.71%)
Other	2 (40.00%)	1 (10.00%)	5 (38.46%)	8 (28.57%)
Fungi	1 (20.00%)	0 (0.00%)	3 (23.08%)	4 (14.29%)
Other	1 (20.00%)	1 (10.00%)	2 (15.38%)	4 (14.29%)
Site (multiple sites possible) – N (%*)				
Spontaneous or secondary bacteremia	2 (40.00%)	6 (60.00%)	5 (38.46%)	13 (46.43%)
Spontaneous bacterial peritonitis	0 (0.00%)	3 (30.00%)	0 (0.00%)	3 (10.71%)
Pneumonia	3 (60.00%)	1 (10.00%)	6 (46.15%)	10 (35.71%)
Urinary tract infection	0 (0.00%)	0 (0.00%)	3 (23.08%)	3 (10.71%)
Skin and soft tissue infection	1 (20.00%)	1 (10.00%)	0 (0.00%)	2 (7.14%)

* Refers to patients experiencing an infection (first row)

Table S4. Donation rate and waiting-list mortality in each country participating in the study referred to 2019.

	Donors / million	WL mortality* - overall	WL mortality* - superurgent	WL mortality* - MELD>35
France	28.5	18%	12%	24%
Germany	11	23%	NA	NA
The Netherlands	14.5	28%	25%	NA
Italy (NITp)	27	9.3%	4%	33%
Spain	49	7.6%	5.5%	5%
UK	13.8	12%	6%	0%
Poland	17	15%	15%	20%
Switzerland	18.4	11.4%	5.3%	28%

*Mortality or drop-out from waiting-list.

Super-urgent: acute liver failure and urgent re-transplantation.

NITp: Nord Italia Transplant

NA: not available

Table S5. Description of MDRO infections of transplanted patients.

	ACLF at LT			Total (N=234)
	1 (N=58)	2 (N=78)	3(N=98)	
Pre-LT MDRO infection – N (%)	6 (10.34%)	4 (5.13%)	13 (13.27%)	23 (9.83%)
Organism (multiple organism possible) – N (%*)				
Gram positive	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (4.35%)
VRE	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%)
Carbapenem resistant	0 (0.00%)	0 (0.00%)	2 (15.38%)	2 (8.70%)
ESBL	4 (66.67%)	3 (75.00%)	9 (69.23%)	16 (69.57%)
Amp-c Enterobacter or Amp-c Citrobacter	1 (16.67%)	0 (0.00%)	1 (7.69%)	2 (8.70%)
Other	0 (0.00%)	1 (25.00%)	1 (7.69%)	2 (8.70%)
Fungi	0 (0.00%)	1 (25.00%)	1 (7.69%)	2 (8.70%)
Site (multiple sites possible) - N (%*)				
Spontaneous or secondary bacteremia	1 (16.67%)	0 (0.00%)	4 (30.77%)	5 (21.74%)
Spontaneous bacterial peritonitis	0 (0.00%)	2 (50.00%)	4 (30.77%)	6 (26.09%)
Pneumonia	1 (16.67%)	0 (0.00%)	2 (15.38%)	3 (13.04%)
UTI	4 (66.67%)	1 (25.00%)	3 (23.08%)	8 (34.78%)
Skin or soft tissue	0 (0.00%)	0 (0.00%)	2 (15.38%)	2 (8.70%)
Cholangitis or liver abscesses	0 (0.00%)	1 (25.00%)	0 (0.00%)	1 (4.35%)
Post-LT MDRO infection – N (%)	14 (24.14%)	15 (19.23%)	30 (30.61%)	59 (25.21%)
Germ (multiple germs possible) – N (%°)				
Gram positive	3 (21.43%)	2 (13.33%)	1 (3.33%)	6 (10.17%)
VRE	3 (21.43%)	1 (6.67%)	0 (0.00%)	4 (6.78%)
MRSA/VRSA	0 (0.00%)	1 (6.67%)	0 (0.00%)	1 (1.69%)
Gram negative	11 (78.57%)	10 (66.67%)	28 (93.33%)	49 (83.05%)
Carbapenem resistant	1 (7.14%)	2 (13.33%)	8 (26.67%)	11 (18.64%)
ESBL	6 (42.86%)	8 (53.33%)	15 (50.00%)	29 (49.15%)
Amp-c Enterobacter or Amp-c Citrobacter	4 (28.57%)	0 (0.00%)	7 (23.33%)	11 (18.64%)
Other	1 (7.14%)	3 (20.00%)	3 (10.00%)	7 (11.86%)
Fungi	1 (7.14%)	3 (20.00%)	2 (6.67%)	6 (10.17%)
Other	0 (0.00%)	0 (0.00%)	1 (3.33%)	1 (1.69%)
Site (multiple sites possible) – N (%°)				
Spontaneous or secondary bacteremia	4 (28.57%)	6 (40.00%)	7 (23.33%)	17 (28.81%)
Spontaneous bacterial peritonitis	3 (21.43%)	4 (26.67%)	7 (23.33%)	14 (23.73%)
Pneumonia	5 (35.71%)	4 (26.67%)	14 (46.67%)	23 (38.98%)
Urinary tract infection	3 (21.43%)	4 (26.67%)	6 (20.00%)	13 (22.03%)
Skin or soft tissue	0 (0.00%)	1 (6.67%)	4 (13.33%)	5 (8.47%)
Cholangitis or liver abscesses	3 (21.43%)	1 (6.67%)	1 (3.33%)	5 (8.47%)

* Refers to patients experiencing a pre-LT infection

° Refers to patients experiencing a post-LT infection

Table S6. Description of pre-LT infections and post-LT re-infections for MDRO and deaths, among patients who experienced a pre-LT MDRO infection. In the columns are reported the pre-LT MDRO infection and in rows the post-LT MDRO infections, the intersection between columns and rows describes how many patients have that specific combination of pre- and post-LT infections and how many of them died post-LT.

	Pre-LT MDRO infection											
	Gram-positive		**Gram-negative**						**Fungi (N=2)**		**Total (N=23)**	
	VRE (N=1)		*Carbapenem resistant (N=2)*		*ESBL(N=16)*		*Amp-c Enterobacter or Amp-c Citrobacter (N=2)*					
Post-LT MDRO infection	**N**	**Deaths (%)**	**N**	**Deaths (%)**	**N**	**Deaths (%)**	**N**	**Deaths (%)**	**N**	**Deaths (%)**	**N**	**Deaths (%)**
Gram-positive												
VRE (N=1)	1	0 (0.0%)									1	0 (0.0%)
Gram-negative												
Carbapenem resistant (N=2)			2	1 (50.0%)							2	1 (50.0%)
ESBL (N=8)					7	3 (42.9%)	1	1 (100.0%)			8	4 (50.0%)
Amp-c Enterobacter or Amp-c Citrobacter (N=1)					1	1 (100.0%)					1	1 (100.0%)
Fungi (N=1)									1	1 (100.0%)	1	1 (100.0%)
Total with post-LT MDRO infection (N=13)	**1**	**0 (0.0%)**	**2**	**1 (50.0%)**	**8**	**4 (50.0%)**	**1**	**1 (100.0%)**	**1**	**1 (100.0%)**	**13**	**7 (53.9%)**
None post-LT MDRO (N=10)	-	-	-	-	8	1 (12.5%)	1	0 (0.0%)	1	1 (100.0%)	10	2 (20.0%)
Total (N=23)	**1**	**0 (0.0%)**	**2**	**1 (50.0%)**	**16**	**5 (31.3%)**	**2**	**1 (50.0%)**	**2**	**2 (100.0%)**	**23**	**9 (39.1%)**

Tables

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

	ACLF at listing or at occurrence (if after listing)			Total (N=308)
	ACLF-1 (N=68)	ACLF-2 (N=109)	ACLF-3 (N=131)	
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%)
Etiology				
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)

[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*

**Combined precipitating factors reported in supplementary table 6*

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

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

Variable	Univariate model		Multivariate model	
	Hazard Ratio (95% Confidence Interval)	p-value	Hazard Ratio (95% Confidence Interval)	p-value
Incident case	**2.77 (1.75 - 4.39)**	**<.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)**	**<.0001**	**5.29 (2.39 - 11.70)**	**<.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)**	**<.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)**	**<.0001**	**3.83 (2.27 - 6.46)**	**<.0001**
Gram positive	**4.09 (2.05 - 8.18)**	**<.0001**		
Gram negative	**2.81 (1.69 - 4.66)**	**<.0001**		
Other	**5.82 (3.18 - 10.64)**	**<.0001**		

Table 3. Characteristics of patients receiving a liver transplant

	ACLF at LT			Total (N=234)
	1 (N=58)	2 (N=78)	3 (N=98)	
PATIENTS' 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%)
Etiology				
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 (23.93%)
4+	-	-	-	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%)
PaO2/FiO2 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%)*
PaO2/FiO2 at LT <200	-	-	6 (21.43%)	6 (20.69%)
Severe alcoholic hepatitis	6 (10.34%)	9 (11.54%)	14 (14.29%)	29 (12.39%)
Hospitalization 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 & I.O. 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%)
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 hrs[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)

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

Table 4. Analysis of predictors of death after transplant.

Variable	Univariate models		Multivariate model	
	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		
PaO2/FiO2 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 hrs	**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		