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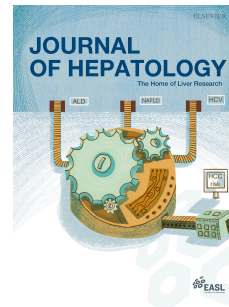
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Journal Pre-proof



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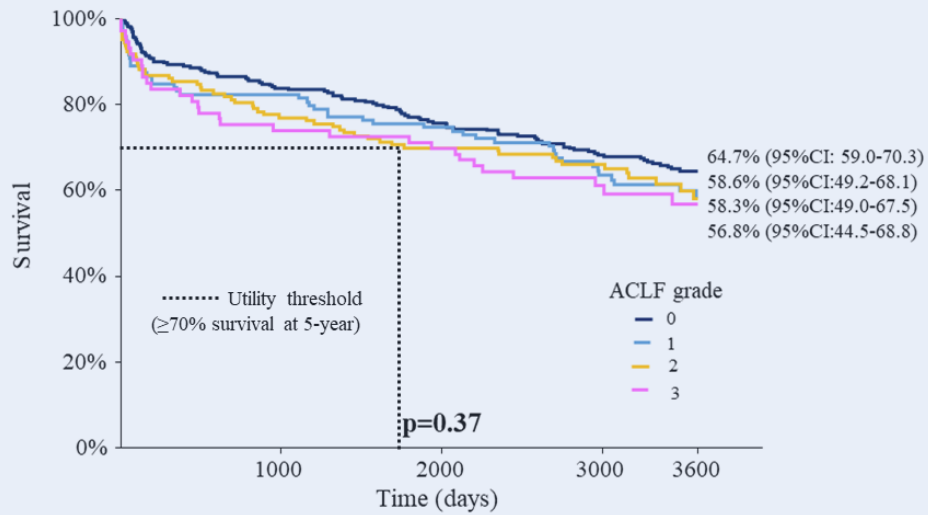
Graphical abstract.

73 patients with ACLF-3 at time of liver transplantation matched to 145 with ACLF-2

119 patients with ACLF-1

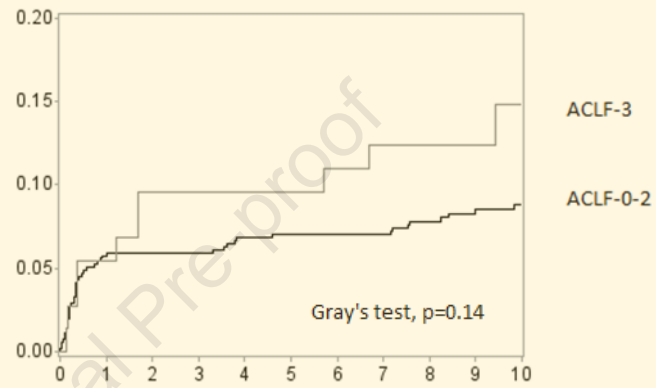
292 patients without ACLF

10-year survival following liver transplantation according to ACLF grade

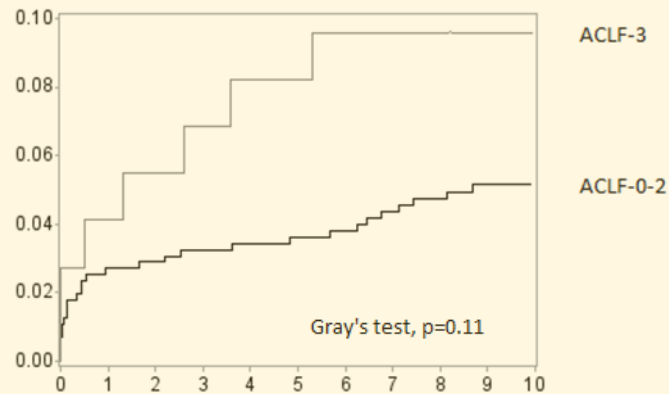


Two leading causes of deaths were

Infectious events

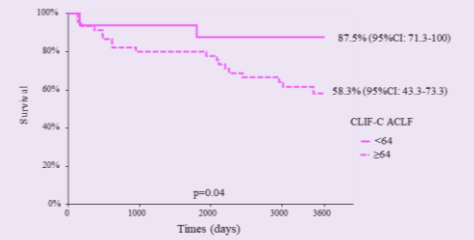


Cardiovascular events

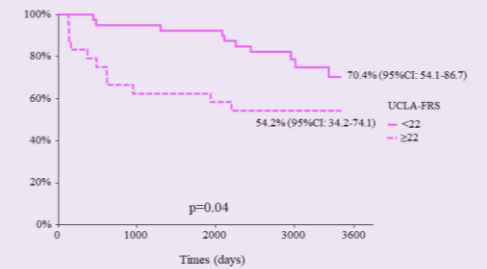


The three parameters independently associated with the 10-year risk of death were CLIF-ACLF, UCLA-FRS and age-adjusted Charlson comorbidity Index

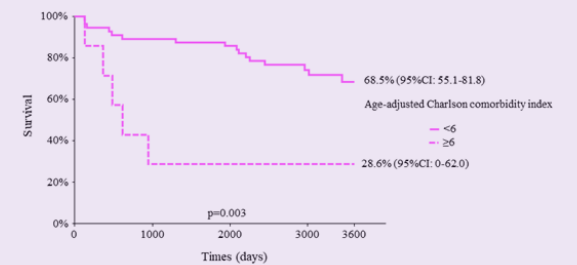
10-year survival following LT according to CLIF-C ACLF



10-year survival following LT according to UCLA-FRS score



10-year survival following LT according to age-adjusted Charlson comorbidity index



Long-term outcome following liver transplantation of patients with ACLF grade 3

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Design of the study: FA, FS, AL

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1 **Statistical analysis:** JL, FA, AL

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4 **Key words (max 12):** Cirrhosis, acute-on-chronic liver failure, liver transplantation, intensive care,
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6 **Electronic words count:** 4492 words

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8 **Data availability statement:** data will be made available upon reasonable request to the corresponding
9 authors.

10

Journal Pre-proof

1 **Abstract:**

2 **Background and Aims:** Utility, a major principle for allocation in the context of transplantation, is questioned in
3 patients with acute-on chronic liver failure grade 3 (ACLF-3) who undergo liver transplantation (LT). We aimed
4 to explore long-term outcomes of patients included in the three-center retrospective French experience published in
5 2017.

6
7 **Method:** All patients with ACLF-3 (n=73) as well as their transplanted matched controls with ACLF-2 (n=145),
8 1 (n=119) and no ACLF (n=292) that have participated in the princeps study published in 2017 were included. We
9 explored 5- and 10-year patient and graft survivals, causes of death and their predictive factors.

10
11 **Results:** Median follow-up of patients ACLF-3 patients was 7.5 years. At LT, median MELD was 40. In patients
12 with ACLF-3, 2, 1 and no ACLF, 5-year patients' survivals were respectively 72.6% vs. 69.7% vs. 76.4% vs.
13 77.0% (p=0.31). Ten-year patients' survival ACLF-3 was 56.8% and was not different from other groups (p=0.37)
14 Leading causes of death in ACLF-3 patients were infections (33.3%), and cardiovascular events (23.3%). After
15 exclusion of early death, UCLA frailty risk score, age-adjusted Charlson comorbidity index and Chronic Liver
16 Failure Consortium ACLF score were independently associated with 10-year patients' survival. Long-term grafts'
17 survivals were not different across the groups. Clinical frailty scale and WHO performance status improved over
18 time in patients alive after 5 years.

19
20 **Conclusion:** 5- and 10-year patients' and grafts' survivals in ACLF-3 patients were not different from their
21 controls. 5-year patients' survival is higher than that of the 50%-70% threshold defining the utility of liver graft.
22 Efforts should focus on candidates' selection based on comorbidities as well as the prevention of infection and
23 cardiovascular events standing as the main cause of death.

24

1 **Highlights**

- 2 - 5- and 10-year patients' and grafts' survivals in ACLF-3 patients were not different
- 3 from their matched controls.
- 4 - Within five years, 90% of deaths occurred before the end of the second year.
- 5 - Leading causes of deaths in ACLF-3 patients were infection and cardiovascular events
- 6 - UCLA-FRS and Charlson-comorbidity index were associated with the 10-year risk of
- 7 death highlighting the weight of comorbidities on the long-term
- 8 - An age-adjusted Charlson comorbidity index ≥ 6 was associated with a 10-year
- 9 survival rate $< 30\%$.

10

11 **Impact and implications**

12 While short-term outcomes following liver transplantation in the most severely ill cirrhotic
13 patients (ACLF-3) are known, long-term data are limited, raising questions about the utility of
14 graft allocation in the context of scarce medical resources. This study provides a favorable long-
15 term update, confirming no differences in 5- and 10-year patient and graft survival following
16 liver transplantation in ACLF-3 patients compared to matched ACLF-2, ACLF-1, and no-
17 ACLF patients. The study highlights the risk of dying from infection and cardiovascular causes
18 in the long-term and identifies scores including comorbidities evaluation, such as the age-
19 adjusted Charlson Comorbidity Index, as independently associated with long-term survival.
20 Therefore, physicians should consider the cumulative burden of comorbidities when deciding
21 to transplant these patients. Additionally, after transplantation, the study encourages mitigating
22 infectious risk with tailored immunosuppressive regimens and managing tightly cardiovascular
23 risk over time.

24

1 Introduction

2 Acute-on-chronic liver failure (ACLF) is a syndrome associated with intense systemic inflammation,
3 immune paresis, hepatic and extra-hepatic organ failures, and a high short-term mortality rate [1]. This
4 condition is highly prevalent. It is observed in about 30% of cirrhotic patients admitted to the hospital
5 and can occur in already hospitalised patients in about 10% of cases[1]. These patients often require
6 organ support and admission to an intensive care unit (ICU) due to organ failures. While ACLF is a
7 dynamic condition that can rapidly improve or worsen within hours, the chances of improvement are
8 very low in patients with persisting 3 or more organ failures after 3 to 7 days (i.e.ACLF grade 3, ACLF-
9 3) of medical management [2,3]. Consequently, these patients face a substantial risk of death at 28-day
10 (70 to 100%) and 90-day (80 to 100%) [2–4]. In this situation, approximately 2/3 of deaths occur before
11 15 days. Liver transplantation (LT) becomes therefore the only life-saving option in the absence of other
12 treatments to avoid imminent death. Initially, liver transplant centres were hesitant to offer liver grafts
13 to these patients as critical care factors (higher MELD score, life support, septic shock before LT) were
14 associated with poorer outcomes following LT based on large retrospective studies mainly from the
15 Organ Procurement and Transplantation Network (OPTN) in the United States (US) [5,6]. However,
16 over the past decade, several reports have shown favorable outcomes following LT in ACLF grade 3
17 patients, with a 1-year survival often exceeding 80% [2,7–14], while the outcome of matched controls
18 with a similar degree of organ failure had extremely poor 1-year survival estimated to be $\leq 10\%$ [2,14].
19 Nevertheless, LT in ACLF-3 patients is associated with an increased incidence of complications after
20 the procedure, such as higher infection rates, longer stays in the ICU and hospital, and an increased risk
21 of readmission [8,11,14].

22 Furthermore, patients with ACLF-3 face challenges in accessing LT under MELD-based allocation
23 policies, as their mortality risk is underestimated by the MELD score, which doesn't consider organ
24 failure evaluation [15,16]. Consequently, some countries, including Spain and the United Kingdom,
25 have implemented prioritisation policies, while debates regarding this issue continue in the United
26 States.

27 One of the main argument postponing the prioritisation of ACLF-3 patients is the paucity of long-term
28 data that provides reassurance regarding the utility of liver grafts which is a major principle for allocation
29 in the context of scarce medical resources [8,17]. Liver utility has been traditionally defined as a 5-year
30 survival rate of 50% after liver transplantation. However, this definition has been recently revised in the
31 context of hepatocellular carcinoma (HCC) to include indications for liver transplantation with survival
32 rates of up to 70% [18,19]. The largest available studies in patients with ACLF as per the definition of
33 EASL are issued from the OPTN [8,9], a database known to be associated with a significant risk of
34 misclassification of ACLF grades due to the lack of granularity in data collection [20,21]. The other
35 available data are either issued from single centre experience or report dismal prognosis after LT in this

1 population [17,22–24]. There is a current consideration from studying primarily only short-term post-
2 liver transplant results as important metrics to global medium-to-long-term patients' and grafts'
3 outcomes for the evaluation of liver transplant activity.

4 Hence, it is of critical importance to address this unmet need and determine the long-term outcomes of
5 patients and liver grafts after LT in the context of ACLF-3. In this study, we capitalised on the
6 prospective follow-up of our multicentric cohort in France to assess and report the long-term outcomes
7 of LT in the ACLF-3 population.

8

Journal Pre-proof

1 Patients and methods

2 Patients with ACLF-3 included in this study are the same as those included in our study published in
3 2017 [14]. Briefly, between January 1st 2008, and December 31st 2014, all liver transplant recipients in
4 three French transplant centers (Hôpital Huriez, Lille, Hôpital Paul-Brousse, Villejuif, and Hôpital
5 Saint-Eloi, Montpellier) were retrospectively included if they fulfilled the following inclusion criteria:
6 age ≥ 18 years old, LT for cirrhosis with ACLF grade 3 based on the European foundation for the study
7 of chronic liver failure (EF-CLIF) criteria [1]. Exclusion criteria were multiple organ transplantation,
8 LT for fulminant hepatic failure, and patients who underwent a re-transplantation in a context of primary
9 non-function of the graft. Patients were identified through the “CRISTAL database” of the French
10 Agency for transplantation (Agence de la Biomédecine - ABM).

11 At time of LT, the following data were collected: age, gender, body mass index (BMI), cause of
12 cirrhosis, comorbidities, primary single reason for admission in ICU, international normalised ratio
13 (INR), prothrombin rate (PT), leukocytes count, platelets count, haemoglobin, creatinine, albumin,
14 natremia, bilirubin, transaminases level, blood gas, and arterial lactate level, MELD, CLIF-C organ
15 failure (OF), CLIF-C ACLF, transplantation for ACLF-3 model (TAM) [10], balance of risk (BAR)
16 score [6] donor, preallocation survival outcomes following liver transplantation (P-SOFT) score [25],
17 university of California Los Angeles – futility risk score (UCLA-FRS) [5], cardiac risk as defined in [5]
18 and graft data (donor risk index [DRI], eurotransplant [ET]-DRI, cold ischemia time), red blood cells
19 (RBC) packs transfusion during the procedure.

20 During follow-up: date of the last follow-up and status (alive or dead, at home or hospitalised), ongoing
21 complications on the date of last follow-up, date and cause of re-transplantation, date and cause of death.
22 The donor and graft data as well as the outcome and post-LT complications of ACLF grade 3 patients
23 were obtained from the prospectively collected CRISTAL database of the ABM.

24 Case-control study

25 Transplanted controls are the same as those included in the second case-control part of the study
26 published in 2017. Briefly, each patient transplanted with ACLF-3 was matched to control patients who
27 were transplanted without ACLF (each case was matched to four controls), with ACLF-1 (each case
28 matched to one or two controls if possible), and with ACLF-2 (each case was matched to one or two
29 controls if possible) with the following matching criteria: age ± 5 years and sex. These control patients
30 were retrospectively included from a specific database between 2008 and 2014 including 1,611 patients
31 classified by the ACLF score and transplanted in the three participating centres. All control groups were
32 matched to the ACLF grade 3 case group using the optimal matching methods without replacement,
33 with no knowledge of their survival.

34 At the time of LT, the following data were collected: age, sex, ethnicity, BMI, cause of cirrhosis,
35 indication of LT, MELD score, ACLF grade. During follow-up: date of the last follow-up and status
36

1 (alive or dead, at home or hospitalised), ongoing complications on the date of last follow-up, date and
2 cause of re-transplantation, date and cause of death. The donor and graft data as well as the outcome and
3 post-LT complications of controls were obtained from the prospectively collected CRISTAL database
4 of the ABM.

5

6 Sarcopenia evaluation

7 Radiological parameters of sarcopenia were retrospectively assessed on CT scans performed at time of
8 LT (± 15 days) when available using psoas muscle index (PMI in cm^2/m^2) and transverse psoas muscle
9 thickness on height (TPMT/height) at the L3-L4 level as previously described [26]. CT scans allowing
10 for the assessment of PMI and TPMT/height were available in 584 patients (93%).

11

12 Deprivation status

13 Deprivation status was evaluated with a composite deprivation index (French Deprivation index or
14 FDep) provided by the French National Institute of Statistics and Economic Studies (INSEE) and
15 previously described [27]. This index was built at the smallest administrative level using data from the
16 2019 French census. The FDep index was defined as the first component of the PCA of the following
17 variables: median population, median household income, percentage of high school graduates in the
18 ≥ 15 -year-old population, and unemployment rate. This index was calculated for the overall cohort and
19 each group (no ACLF, ACLF 1, 2 and 3). In the present study, a higher FDep value meant less deprived
20 status.

21

22 Clinical frailty scale (CFS) and WHO performance status

23 CFS and WHO performance status were retrospectively collected three months before LT, at 1-year
24 following LT and at last follow-up in ACLF-3 groups and at last follow-up in the other groups

25

26 The study is in accordance with the Declaration of Helsinki and is within “non-RIPH” setting of the Loi
27 Jardé ruling the clinical research in the French public health code (article R.1121-1).

28

29 Statistical analyses

30 Quantitative variables were expressed medians (interquartile range) and categorical variables were
31 expressed as frequencies and percentages. Comparisons in patient’ characteristics at time of liver
32 transplantation according to ACLF grade were done using one-way analysis of variance (or using
33 Kruskal-Wallis test in case of non-gaussian distributions assessed by Quantile-Quantile plots and using
34 the Shapiro-Wilk test) for quantitative variables and using Chi-square test (or Fisher’s exact test in case
35 of expected cell frequency < 5) for categorical variables.

1 Overall survival at 5 and 10 years were estimated using the Kaplan-Meier method and compared
2 between the groups using Log-rank test. We estimated and compared the cumulative incidence rate of
3 specific mortality (cardiovascular and infection related mortality) according to groups using competing
4 risk survival approach treating the non-specific mortality as competing event. Cumulative incidences
5 were estimated using the using the Kalbfleisch and Prentice method [28] and between-group comparison
6 in incidences were done using Gray' test. We investigated the association of main patient characteristics
7 on the day of LT that with 10-year all-cause mortality using univariable and multivariable Cox
8 proportional hazards regression models. Before developing multivariable Cox's regression analysis, the
9 log-linearity assumption was assessed for quantitative characteristics using Martingale residual plots
10 and in case of deviation, the quantitative variable was analysed as a binary variable according to the
11 median cut-off value. We also evaluated the proportional hazards assumption for each characteristic
12 using Schoenfeld residuals plots and found no strong deviations. Hazard ratios (HRs) of all-cause
13 mortality were derived from Cox regression models as effect size measure. All patient's characteristics
14 associated with all-cause mortality at $p < 0.05$ were included into multivariable Cox's regressions using
15 the Firth's penalized likelihood to estimate hazard ratio to account the small number of events [29,30].
16 To better investigate the variables on day of LT associated with long-term outcome, univariate and
17 multivariate analyses were repeated after the exclusion of early deaths (< 3 months following LT).
18 Statistical analyses were performed with SAS software package, release 9.4 (SAS Institute, Cary, NC)
19 and using NCSS 2022 software (NCSS 2022 Statistical Software (2022). NCSS, LLC. Kaysville, Utah,
20 USA, ncss.com/software/ncss.)

1 **Results**

2 Seventy-three patients were transplanted with an ACLF grade 3 at time of LT and were included in the
3 study. They represented 40.6% of all liver transplant candidates placed on the waiting list with an ACLF-
4 3 over the study period. This cohort was mainly constituted by male patients (69.9%) with a median age
5 of 56.8 years old. Alcohol-related cirrhosis accounted for 53.4% of the underlying diseases and septic
6 shock (49.3%) and gastrointestinal bleeding (16.4%) were the main primary single reasons for admission
7 into the ICU. Median MELD at LT was 40 (40-40), with median CLIF-C ACLF at 67.3 (63.6-75.2).
8 Median follow-up of patients with ACLF-3 was 7.5 years (2.2-10.0). Main characteristics of the cohort
9 are provided in Table 1. Comparison with matched patients with ACLF grade 2, 1 and no ACLF are
10 provided in the Supplementary table 1. Besides liver disease severity related variables including
11 sarcopenia parameters, main differences between groups were causes of cirrhosis with an increased
12 prevalence of viral-related liver disease in non -ACLF group compared to the other (45.6% vs. 23.5%
13 vs. 18.6% vs. 27.4%). Hepatocellular carcinoma was also more often observed in non-ACLF group
14 (45.2% vs. 10.9% vs. 6.2% vs. 15.1%, $p<0.0001$). Social deprivation parameters highlighted a more
15 deprived status in ACLF-3 group illustrated by a decreased PCA ($p=0.0003$), high school graduate
16 ($p=0.002$) and income ($p=0.0007$) alongside with an increased unemployment rate ($p=0.006$). Regarding
17 comorbidities, some cardiovascular risk parameters were increased in ACLF-3 group including cardiac
18 risk. Importantly, liver graft parameters including DRI, ET-DRI and cold ischemia time were not
19 different between groups (Supplementary Table 1).

21 *5- year and 10-year patients' survival*

22 Overall survival at 5-year of patients transplanted with ACLF-3 was 72.6% (95%CI:62.0-77.0) and was
23 not different, in overall comparison, from patients with ACLF-2, ACLF-1 and no ACLF ($p=0.31$)
24 (Figure 1). Death occurred in 20 patients with ACLF-3 within the first 5 years following LT. Among
25 them, 7 (35.0%) deaths occurred within 3 months following LT, 12 (60.0%) within 1 year and 18
26 (90.0%) within 2 years. Overall survival at 10-year of patients transplanted with ACLF-3 was 56.8%
27 (95%CI:44.5-68.9) and was not different, in overall comparison, from patients with ACLF-2, ACLF-1
28 and no ACLF ($p=0.37$) (Figure 2). Death occurred in another 10 patients between the 5th and the 10th
29 year following LT.

31 *Causes of deaths*

32 In ACLF-3 patients, causes of death were cardiovascular for 7 (23.3%) patients (stroke, $n=1$; heart
33 failure, $n=3$; myocardial infarction, $n=2$; pulmonary embolism, $n=1$), infectious disease for 10 (33.3%)
34 patients (septic shock from bacterial origin, $n=9$; invasive fungal infection, $n=1$), graft complication for
35 5 (16.7%) patients (chronic rejection, $n=1$; recurrence of alcohol-related liver disease, $n=1$, ischemic
36 cholangitis, $n=1$; hepatocellular carcinoma, $n=2$), other cause for 6 patients (20.0%) including severe
37 refractory bleeding for 3 patients (iatrogenic after thoracic paracentesis, $n=1$; gastrointestinal bleeding

1 in the context of post endoscopic retrograde cholangiopancreatography severe acute pancreatitis, n=1;
2 leakage of arterial anastomosis, n=1), multiorgan failure in the context of mycophenolate mofetil
3 attributed severe acute pancreatitis for 1 patient, iatrogenic secondary to bleeding from dialysis circuit,
4 n=1 and suicide, n=1, cancer for 2 (6.7%) patients (prostate, n=1; cutaneous, n=1). After the exclusion
5 of early deaths, infections and cardiovascular events remained the leading causes of death in ACLF-3
6 patients representing respectively 5/23 (21.7%) and 8/23 (34.8%) of deaths.

7 We hence compared the two leading causes of death in the ACLF-3 with the other groups using
8 competing risk survival approach treating the non-specific mortality as competing event (Figure 3).
9 ACLF-3 patients experienced a non-significant greater risk of cardiovascular events and infectious
10 events as cause of death compared with the other groups (Gray's test $p=0.11$ and $p=0.14$ respectively).

11 *Factors associated with 10-year mortality*

12 In univariable Cox-regression analysis of factors associated with 10-year mortality in patients with
13 ACLF-3, the following variables on day of LT had a p -value <0.05 : UCLA-FRS score (HR 1.11, 95%CI:
14 1.01-1.22, $p=0.030$), and the number of red blood cell (RBC) packs transfused (HR 1.13, 95%CI: 1.05-
15 1.22, $p=0.0003$). In multivariable analyses, the only factor associated with 10-year mortality was the
16 number of RBC packs transfused (HR 1.16, 95%CI: 1.07-1.25, $p<0.001$) while the UCLA-FRS score
17 was not (HR 1.10, 95%CI: 0.99-1.22, $p=0.060$) (Table 2). When plotting survival curves of patients
18 according to the cut-offs of 10 RBC packs during LT, patients who received less than this threshold had
19 higher 10-year survival rates than that of patients who received ≥ 10 RBC packs: 62.1% (95%CI: 48.5-
20 75.8) vs. 28.6% (95%CI: 4.9-52.2), $p=0.0001$ (Figure 4).

21 After exclusion of early deaths, in univariable analysis, CLIF-C ACLF score (HR 1.08, 95%CI:1.01-
22 1.15, $p=0.012$), UCLA-FRS score (HR 1.18, 95%CI: 1.05-1.31, $p=0.003$), Age-adjusted Charlson
23 comorbidity index (HR 1.32, 95%CI: 1.01-1.71, $p=0.036$), and length of stay in ICU before LT (HR
24 0.92, 95%CI: 0.85-1.00, $p=0.047$) had a p value <0.05 (Table 3). In multivariable analysis the 3 score
25 were tested independently due to collinearity: UCLA-FRS score (HR 1.16, 95%CI: 1.05-1.29, $p=0.004$),
26 Age-adjusted Charlson comorbidity index (HR 1.29, 95%CI: 1.00-1.67, $p=0.047$), and CLIF-C ACLF
27 score (HR 1.09, 95%CI:1.02-1.16, $p=0.007$) were the independently associated with 10-year mortality.
28 Length of stay in ICU before LT was not associated with 10-year mortality in 2 of the 3 models
29 (Supplementary Table 2A and B). Patients who scored below the thresholds of 64 for the CLIF-CACLF,
30 22 for the UCLA-FRS, and 6 for the age-adjusted Charlson comorbidity index exhibited higher 10-year
31 survival rates when compared to patients who scored above these thresholds at the time of liver
32 transplantation respectively 87.5% (95%CI:71.3-100) vs. 58.3%(95%CI:43.3-73.3), $p=0.03$, 70.4%
33 (95%CI: 54.1-86.7) vs. 54.2% (95%CI:34.2-74.1), $p=0.03$ and 68.5% (95%CI:55.1-81.8) vs. 28.6%
34 (95%CI: 0-62.0), $p=0.003$ (Figure 5A-C).

35 *5- and 10-year graft survivals*

1 Fifty-nine out of the 73 patients with ACLF-3 (80.8%) received induction with IL-2 receptor antibodies.
2 Long-term treatment was association of calcineurin inhibitors (CNI) and mycophenolate mofetil (MMF)
3 in 56 (78.9%) patients, CNI alone in 9 (12.7%) patients, MMF and steroids in 1 (1.4%) patient and
4 mTOR inhibitors alone or in combination with MMF in 5 (7.0%) patients (2 patients died before the
5 introduction of CNI and MMF). Within 10 years, no patients experienced primary non function of the
6 graft and 5 patients underwent re-transplantation that happened at 185 days (ischemic cholangitis), 332
7 days (B lymphoma of the graft), 432 days (ischemic cholangitis, patient die 179 after re-do from
8 cutaneous cancer), 1421 days (chronic rejection) and 2471 days (chronic rejection). One of these patients
9 died 179 days after re-transplantation. In patient with ACLF-3, graft survivals at 5- and 10-years were
10 respectively 67.1% (95%CI:56.3-77.9) and 49.9% (95%CI:37.7-62.0). In overall comparison, they were
11 not different than that of patients with ACLF-2, ACLF-1 and no ACLF ($p=0.43$ and $p=0.34$ respectively)
12 (Figure 5A and B). In univariable logistic regression analysis, CNI regimen alone was associated with
13 an increased risk of re-transplantation over time (OR 7.7, 95%CI:1.01-63.8, $p=0.05$).

14

15 *Evolution of clinical frailty scale and WHO performance status*

16 We finally investigated the evolution of CFS and WHO performance status over time in ACLF-3
17 patients alive after 5-years. Between 3-months before LT, 1-year after LT and last-follow-up after LT,
18 CFS decreased from 4 (3-4) to 3 (2.2-4, $p=0.08$) to 3 (2-3.5, $p=0.007$) and in parallel to the WHO
19 performance status from 2 (1-2) to 1 (1-2, $p=0.31$) to 1 (1-2, $p=0.01$). In patients alive after 5 years, at
20 last follow-up, both CFS and WHO performance status were not different between groups
21 (Supplementary Figure 2).

22

1 **Discussion**

2 In this current matched control study, we present favorable long-term patient and graft outcomes after
3 liver transplantation in patients with ACLF-3. These outcomes show no significant differences when
4 compared to patients with ACLF-2, ACLF-1, and those without ACLF. Significantly, in this study, the
5 ACLF-3 group achieved a survival rate that aligns with the most recent definition of liver utility. The
6 leading causes of death in this population were cardiovascular and infectious diseases while the risk of
7 developing extra-hepatic cancer was low. Furthermore, in this study, UCLA-FRS score and the age-
8 adjusted Charlson comorbidity index, which is included in the UCLA-FRS score, were among the most
9 influential factors associated with long-term mortality. Overall functioning, as evaluated by the CFS and
10 the WHO performance status, improved after LT in long-term surviving patients with ACLF, with no
11 significant difference compared to other groups.

12 While so far, a definitive consensus on a unified definition of the syndrome reconciling western and
13 eastern perspectives has not been achieved, the existing definitions have been beneficial in identifying
14 patients showing the greatest risk of death among patients with acute decompensation of cirrhosis.
15 Notably, most of these patients are encompassed within the EASL definition of ACLF [31]. Therefore,
16 those with persistent ACLF-3 after few days of management in the ICU face an exceptionally high risk
17 of death with no life-saving alternatives other than LT. This procedure has been regularly reported
18 feasible in carefully selected patients achieving short-term favourable outcome following LT [7,9–
19 11,13,14]. Based on these findings, many experts have drawn attention to the lack of equity in access to
20 liver transplantation for this population. This inequity arises from an underappreciation of the risk of
21 death on the waiting list within MELD-based allocation programs as well as centre dependant disparities
22 in the promotion of LT for this patients population [12,15,32]. In our cohort, the median MELD score
23 at LT was very high (40). It suggests that LT candidates with ACLF-3 and lower MELD score and
24 ACLF-3 were indeed unlikely to access an organ. While addressing the issues of equity and access to
25 liver transplantation for ACLF-3 patients is undoubtedly essential, it is also crucial to consider the
26 limited availability of long-term data questioning utility of the liver graft, which is one of the
27 fundamental principles of allocation policies.

28 In this match-controlled survival analyses, patients and graft survivals were not different across the
29 different groups, underlining that the results observed at 1-year after LT in our cohort were not modified
30 on the long-term. Given that ACLF-3 patients demonstrated lower long-term survival rates for both
31 patients and grafts in this study, it emphasizes the critical importance of maintaining a stringent selection
32 process to identify the best candidates who have the highest likelihood of survival after LT. Importantly
33 90% of deaths observed at 5 years occurred within the first 2 years following LT. This finding is
34 particularly noteworthy considering that the scoring systems developed in the field have predominantly
35 focused on very short-term (3 months) or short-term (1 year) outcomes [5,10,33]. Consequently, in the
36 pursuit of the goal of long-term survival after LT, it becomes necessary to develop scoring systems
37 ideally based on the 2-year mortality risk, which better reflect 5-year mortality, rather than solely relying

1 on the 1-year data. This approach would potentially lead to improvements in long-term outcomes and
2 allow for a comprehensive evaluation of variables associated with such outcomes at the time of LT.

3 In this cohort, the long-term outcomes were predominantly influenced by the UCLA-FRS score and the
4 age-adjusted Charlson comorbidity index. Notably, MELD score, cardiac risk and septic shock before
5 LT, which were not associated with outcomes in the present study, played a lesser role in predicting
6 long-term survival. Cardiac risk is defined by presence of severe valvular disease, severe coronary artery
7 disease, history of ventricular and/or atrial arrhythmias, elevated pre-OLT troponin I, and/or new wall
8 motion abnormalities on echocardiography [5]. Given the increased prevalence of major cardiovascular
9 events and cardiovascular death in patients with ACLF-3, the causality of cardiac risk should be further
10 examined in larger prospective cohorts. Moreover, an age-adjusted CCI score of 6 or higher markedly
11 distinguished a cohort of patients at significant risk of long-term mortality. This observation aligns with
12 previous reports of short-term mortality in patients with a MELD score of 40 or above [5]. While it is
13 widely recognized that a single comorbidity should not be a sole determinant for denying access to liver
14 transplantation, considering comorbidities collectively (especially age, diabetes, cardiovascular disease,
15 chronic kidney, and pulmonary disease) can be valuable in identifying patients who may not be
16 candidates for LT. Taking these comorbidities into account together can provide a more comprehensive
17 assessment of a patient's overall condition and potential for long-term survival after LT. This approach
18 allows for a more nuanced evaluation of patient suitability for the procedure and helps in making
19 informed decisions to optimize outcomes. The retrospective design of the study precluded unfortunately
20 to evaluate the proportion of patients denied to LT based on high level of comorbidities. Frailty, an
21 emergent parameter of patients with advanced liver disease and ACLF that is associated with outcome
22 before and after LT is not included in the age-adjusted Charlson comorbidity index. It would be
23 interesting in the future to evaluate their correlation and independent predicting values in this population.

24 Cardiovascular events represent one of the primary causes of long-term death in this population after
25 liver transplantation. This observation may explain the effectiveness of the comorbidity scores, and it
26 should encourage physicians to improve patient selection for LT and focus on preventing such events
27 after the procedure. Currently, a significant number of patients who undergo LT in the context of severe
28 ACLF have their pre-transplantation workup performed in the ICU, particularly in cases of multiple
29 organ failure. Although there is no available data on the specifics of how this workup is conducted, it is
30 generally accepted that a single transthoracic echocardiography is performed at the bedside.
31 Interestingly, LT from the ICU has been associated with an increased risk of major adverse
32 cardiovascular events after transplantation [34]. Whether it is due to the presence of cirrhotic
33 cardiomyopathy, the risk of developing atrial fibrillation, or the ICU stay itself remains to be elucidated.
34 In the present study, ACLF-3 patients had increased cardiac risk mainly relying on the prevalence of
35 elevated troponin level before LT and history of atrial fibrillation or ventricular arrhythmia.

1 The other leading cause of long-term death is represented by infectious events. These are probably
2 promoted by the chronic inflammatory status of patients with ACLF associated with its compensatory
3 anti-inflammatory response syndrome leading to immune exhaustion and dysfunction before LT. On the
4 other side, the risk rejection leading to graft loss and re-transplantation appears low but not null. Indeed,
5 while we observed homogeneous strategies regarding the management of the immunosuppressive
6 regimens in these patients, there was an association between the use of CNI alone and the risk of re-
7 transplantation. In our series, while patients have a significant risk of dying from infectious cause in the
8 first years following LT, they still exhibited a risk of graft failure from chronic rejection on the long
9 term. These data suggest that patients with ACLF-3 are at risk for both events, but in a distinct temporal
10 manner. We currently lack reliable markers of immune status and function in the context of ACLF.
11 Hence, this study stressed the need to recall that tailored immunosuppressive regimen shall be applied
12 to this very fragile population especially during the first two years following LT to balance between the
13 mitigation of the risk of severe infectious events and the risk of re-transplantation over time. Finally, we
14 did not observe a selection of high-quality donor livers in patients with ACLF-3. This observation aligns
15 with a recent study reporting that early access to LT was more determinant of post-LT outcomes than
16 waiting for an optimal donor organ [35].

17 Some limitations must be acknowledged. First, the limited sample size and the number of deaths
18 observed in the ACLF-3 group restricted the analysis of factors associated with long-term outcomes.
19 Second, important factors, such as mitigation of risk behaviours (e.g., alcohol or tobacco consumption),
20 oncological screening practices, and post-transplantation overall management and treatments, were not
21 available and hence not considered in our analysis. Third, HCV-related cirrhosis was prevalent across
22 the different groups, especially in the non-ACLF one, and may have negatively impacted outcomes
23 following LT, especially during a time when direct-acting antiviral therapies were not available.
24 Therefore, given the evolving landscape of cirrhosis causes in LT candidates, we can expect improved
25 long-term outcomes following LT.

26 In summary, LT in carefully selected ACLF-3 patients is associated with satisfactory long-term patient
27 and graft outcomes, achieving the commonly accepted standard for utility. Moreover, there were no
28 significant differences observed when compared to patients with lower grade ACLF or no ACLF. The
29 study indicates that long-term mortality is primarily influenced by cardiovascular and infectious events,
30 with comorbidities, illustrated by UCLA-FRS score and age-adjusted Charlson comorbidity index, at
31 the time of LT playing a key role. Given that 90% of deaths occur within the first two years following
32 LT, it is suggested to shift the focus towards this endpoint to identify variables that would aid in the
33 selection process of these patients. By targeting the two-year mortality risk, it would be possible to better
34 assess patient suitability for liver transplantation and potentially improve long-term outcomes for
35 patients with ACLF-3. This approach would be instrumental in optimising patient selection and
36 enhancing post-transplant survival rates in this specific population.

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25

26

1 **Legends to figures**

2 Legend to Figure 1: 5-year patients' survival following liver transplantation (LT) in patient with ACLF
3 grade 3 at time of LT (n=73) and their matched controls on sex and age without ACLF (n=292), ACLF
4 grade 1 (n=119) and ACLF grade 2 (n=145). Survivals estimated by Kaplan-Meier method and
5 compared with the log-rank test. Level of significance: p=0.31.

6
7 Legend to Figure 2: 10-year patients' survival following liver transplantation (LT) in patient with ACLF
8 grade 3 at time of LT (n=73) and their matched controls on sex and age without ACLF (n=292), ACLF
9 grade 1 (n=119) and ACLF grade 2 (n=145). Survivals estimated by Kaplan-Meier method and
10 compared with the log-rank test. Level of significance: p=0.37

11
12 Legend to Figure 3: A Cumulative incidence of cardiovascular-related mortality following liver
13 transplantation in patients with ACLF grade 3 and with ACLF grade 0-2. B. Cumulative incidence of
14 infection-related mortality following liver transplantation in patients with ACLF grade 3 and with ACLF
15 grade 0-2. Cumulative incidences were estimated using the using the Kalbfleisch and Prentice method
16 and between-group comparison in incidences were done using Gray' test. Level of significance: p=0.11
17 and p=0.14 respectively.

18
19 Legend to Figure 4: 10-year patients' survival following liver transplantation (LT) in patient with ACLF
20 grade 3 at time of LT after exclusion of patients with early death occurring before the 90th day following
21 LT and according to A. the Chronic Liver Failure Consortium ACLF score at time of LT (threshold of
22 64 according to [2]) B. the University of California Los Angeles- Futility Risk Score (UCLA-FRS) at
23 time of LT (threshold of 22 according to [5]) C. the Age-adjusted Charlson comorbidity index (AA-
24 CCI) at time of LT (threshold of 6 according to [5]). Survivals estimated by Kaplan-Meier method and
25 compared with the log-rank test. Levels of significance p=0.04, p=0.04 and p=0.003.

26
27 Legend to Figure 5: A. 5- and B. 10-year grafts' survival following liver transplantation (LT) in patient
28 with ACLF grade 3 at time of LT (n=73) and their matched controls on sex and age without ACLF
29 (n=292), ACLF grade 1 (n=119) and ACLF grade 2 (n=145). Survivals estimated by Kaplan-Meier
30 method and compared with the log-rank test. Level of significance: p=0.43 and p=0.34 respectively.

31
32

Characteristics	
Age (years)	56.8 (48.6-62)
Sex (male), n (%)	51 (69.9)
BMI (kg/m ²)	25.0 (22.0-30.0)
Diabetes, n (%)	14 (19.2)
Aetiology	
Alcohol, n (%)	39 (53.4)
Viral, n (%)	20 (27.4)
Auto immune or cholestatic, n (%)	11 (15.1)
Other, n (%)	3 (4.1)
Primary single reason for admission in ICU	
Septic shock, n (%)	36 (49.3)
Bleeding, n (%)	12 (16.4)
Neurological failure, n (%)	4 (5.5)
Respiratory failure, n (%)	7 (9.6)
Renal failure, n (%)	10 (13.7)
Other cause, n (%)	4 (5.5)
Laboratory on day of LT	
Leukocytes (G/l)	9.2 (5.2-13.2)
Platelets (G/l)	48.0 (29.5-66.0)
INR (IU)	3.4 (3.0-4.8)
Bilirubin (µmol/l)	449.8 (263.0-592.0)
Albumin (g/l)	31.7 (28.8-36.0)
Creatinine (µmol/l)*	93.5 (64.3-168.0)
Lactate (mmol/l)	1.8 (1.3-2.4)
Organ failure on day of LT	
Liver, n (%)	61 (83.6)
Kidney, n (%)	45 (61.7)
Brain, n (%)	48 (65.8)
Coagulation, n (%)	65 (89.0)
Circulation, n (%)	45 (61.6)
Respiratory, n (%)	8 (11.0)
Organ support on day of LT	
RRT, n (%)	34 (46.6)
Vasopressors, n (%)	45 (61.6)
Mechanical ventilation, n (%)	46 (63.0)
Scores on day of LT	
MELD	38.0 (33.0-40.0)
CLIF-C ACLF	67.3 (63.6-75.2)
TAM score	1.0 (1.0-2.0)
BAR score	19.0 (16.0-20.2)
P-SOFT score	30.0 (27.0-32.5)
UCLA-FRS score	20.0 (18.0-23.0)
Charlson Comorbidity Index	2.0 (2.0-4.0)
Cardiac risk, n (%)	15 (20.8)
Characteristics of ICU stay before LT	
Placement on waiting list while in the ICU, (%)	50 (68.5)
Length of stay in ICU before LT (days)	9.0 (5.0-14.0)
MDROs infection before LT	18 (24.6%)
Sarcopenia parameters at LT	
PMI (cm ² /m ²)	5.5 (4.6-6.5)

TPMT/height (mm/m)	16.1 (14.1-18.6)
Liver graft and LT parameters	
DRI	2.0 (1.6-2.4)
ET-donor risk index	1.8 (1.5-2.0)
Cold ischemia time (hours)	7.7 (6.8-8.5)
Number of RBC packs transfused	8.0 (5.0-10.0)

Table 1: characteristics of the 73 patients transplanted with acute on chronic liver failure (ACLF) grade 3 at time of liver transplantation. Continuous and categorical variables expressed respectively in median (interquartile range) and N (percentages). *variable analysed only in patients who were not under renal replacement therapy. BMI, body mass index; ICU, intensive care unit; INR, international normalised ration; RRT, renal replacement therapy; MELD, model for end-stage liver disease; CLIF-C ACLF, chronic liver failure consortium ACLF score; TAM, transplantation for ACLF-3 model; BAR, balance of risk score; P-SOFT, pre-allocation survival outcomes following liver transplantation; UCLA-FRS, university of California Los Angeles futility risk score; PMI, psoas muscle index; DRI, donor risk index; ET-DRI, Eurotransplant-DRI; RBC, red blood cells; TPMT, transverse psoas muscle thickness.

Characteristics	Univariable analysis			Multivariable analysis		
	HR	95% CI	p value	HR	95% CI	p value
Characteristics						
Age \geq 57 years*	0.67	0.32-1.38	0.28			
Sex (male as reference)	0.66	0.28-1.55	0.34			
BMI (per 1 kg/m ² increase)	0.94	0.86-1.03	0.17			
Diabetes	1.75	0.75-4.10	0.19			
Aetiology			0.11			
Alcohol as reference	1.00	reference	-			
Viral	1.41	0.64-3.06	0.39			
Other	0.28	0.06-1.20	0.085			
Primary single reason for admission in ICU						
Septic shock vs. other	0.98	0.48-2.02	0.97			
Scores on day of LT						
MELD	1.05	0.97-1.13	0.23			
CLIF-C ACLF	1.05	0.99-1.11	0.063			
TAM score [#]	1.70	0.51-5.65	0.38			
BAR score	1.02	0.90-1.16	0.77			
SOFT score	1.01	0.93-1.10	0.82			
UCLA-FRS score	1.11	1.01-1.22	0.030	1.10	0.99-1.22	0.060
Age-adjusted Charlson-Comorbidity Index	1.23	0.97-1.55	0.075			
Cardiac risk	1.00	0.40-2.45	0.99			
Characteristics of ICU stay						
Placement on waiting list while in the ICU	1.15	0.53-2.47	0.71			
Length of stay in ICU before LT	0.96	0.90-1.03	0.20			
MDROs infection before LT	1.96	1.90-4.22	0.088			
Sarcopenia parameters at LT						
Sarcopenia according to PMI sex specific cut-offs	1.75	0.80-3.80	0.16			
Sarcopenia according to TPMT/height sex specific cut-offs	0.61	0.27-1.34	0.22			
Liver graft and LT parameters						
DRI	1.23	0.47-3.19	0.68			
ET-donor risk index	1.34	0.44-4.06	0.61			
Cold ischemia time (hours)	0.77	0.58-1.02	0.060			
Number of RBC packs transfused	1.13	1.05-1.22	0.0003	1.16	1.07-1.25	<0.001

Table 2: Uni- and multivariable Cox regression analysis of variables associated with 10-year mortality following liver transplantation in patients with ACLF grade 3 at time of LT (n=73). * Tested as categorical using the median cut-off value to acknowledge the non-log-linear assumption # Tested as categorical with a threshold of 2 (≤ 2 vs. > 2). [¥]not included to acknowledge the collinearity with UCLA-FRS score.

Abbreviations: BMI, body mass index; LT, liver transplantation; MELD, model for end-stage liver disease; CLIF-C ACLF, chronic liver failure consortium ACLF score; TAM, transplantation for ACLF-3 model; BAR, balance of risk score; P-SOFT, preallocation survival outcomes following liver transplantation; UCLA-FRS, university of California Los Angeles futility risk score; ICU, intensive care unit; MDROs, multidrug resistant organisms; PMI, psoas muscle

index; DRI, donor risk index; ET-DRI, Eurotransplant-DRI; RBC, red blood cells; TPMT, transverse psoas muscle thickness.

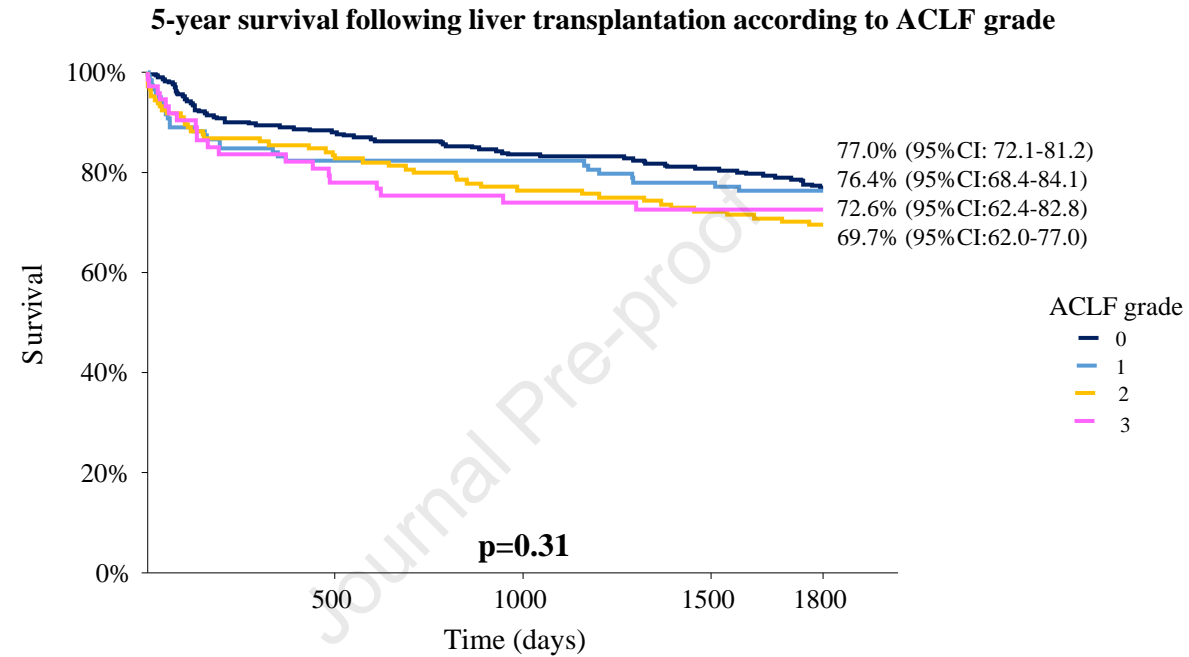
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Characteristics	HR	95% CI	p value	HR	95% CI	p value
Characteristics						
Age \geq 57 years	1.09	0.47-2.49	0.84			
Sex (male as reference)	0.45	0.15-1.32	0.15			
BMI (per 1 kg/m ² increase)	0.95	0.86-1.05	0.26			
Diabetes	1.66	0.61-4.48	0.32			
Aetiology			0.16			
Alcohol as reference	1.00	reference	-			
Viral	1.27	0.51-3.12	0.61			
Other	0.16	0.02-1.24	0.079			
Primary single reason for admission in ICU						
Septic shock vs. other	0.74	0.31-1.71	0.48			
Scores on day of LT						
MELD	1.05	0.96-1.15	0.23			
CLIF-C ACLF	1.08	1.01-1.15	0.012		Not included [¥]	
TAM score [#]	2.47	0.72-8.40	0.15			
BAR score	1.06	0.90-1.23	0.47			
SOFT score	1.03	0.94-1.12	0.57			
UCLA-FRS score	1.18	1.05-1.31	0.003	1.16 [¥]	1.051-1.28	0.004
Age-adjusted Charlson-Comorbidity Index	1.32	1.01-1.71	0.036		Not included [¥]	
Cardiac risk	1.37	0.53-3.47	0.51			
Characteristics of ICU stay						
Placement on waiting list while in the ICU	1.25	0.53-2.95	0.61			
Length of stay in ICU before LT	0.92	0.85-1.00	0.047	0.93	0.86-1.003	0.059
MDROs infection before LT	2.09	0.88-4.94	0.093			
Sarcopenia parameters at LT						
Sarcopenia according to PMI sex specific cut-offs	1.64	0.66-4.07	0.29			
Sarcopenia according to TPMT/height sex specific cut-offs	0.93	0.39-2.22	0.88			
Liver graft and LT parameters						
DRI	1.40	0.46-4.24	0.55			
ET-donor risk index	1.65	0.44-6.04	0.45			
Cold ischemia time (hours)	0.75	0.55-1.03	0.074			
Number of RBC packs transfused	1.11	0.98-1.25	0.088			

Table 3: Uni- and multivariable Cox regression analysis of variables associated with 10-year mortality following liver transplantation in patients with ACLF grade 3 at time of LT (n=66) after exclusion of early death occurring before 90 days. * Tested as categorical using the median cut-off value to acknowledge the non-log-linear assumption # Tested as categorical with a threshold of 2 (≤ 2 vs. > 2). [¥]not included to acknowledge the collinearity with UCLA-FRS score.

Abbreviations: BMI, body mass index; LT, liver transplantation; MELD, model for end-stage liver disease; CLIF-C ACLF, chronic liver failure consortium ACLF score; TAM, transplantation for ACLF-3 model; BAR, balance of risk score; P-SOFT, preallocation survival outcomes following liver transplantation; UCLA-FRS, university of California Los Angeles utility risk score; ICU, intensive care unit; MDROs, multidrug resistant organisms; PMI, psoas muscle index; DRI, donor risk index; ET-DRI, Eurotransplant-DRI; RBC, red blood cells; TPMT, transverse psoas muscle thickness.

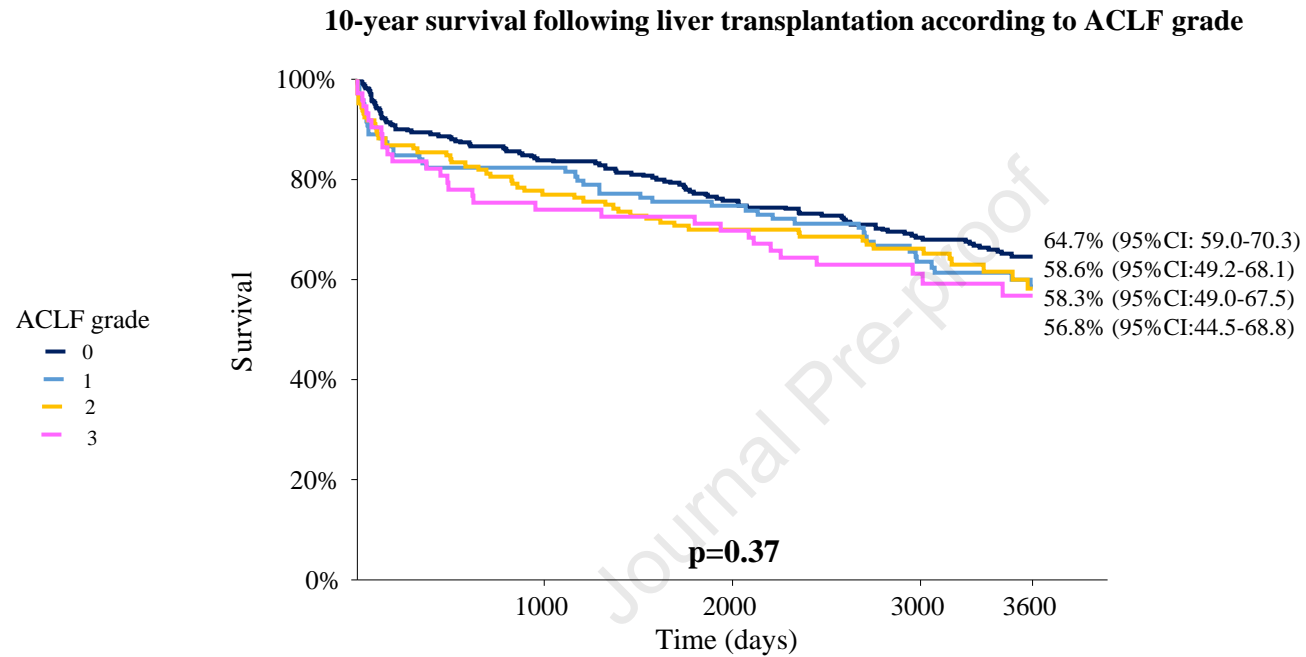
Figure 1.



Number At Risk

Grade ACLF = 0	292	256	242	234	223
Grade ACLF = 1	119	96	96	91	89
Grade ACLF = 2	145	119	110	104	104
Grade ACLF = 3	73	57	54	53	53

Figure 2.

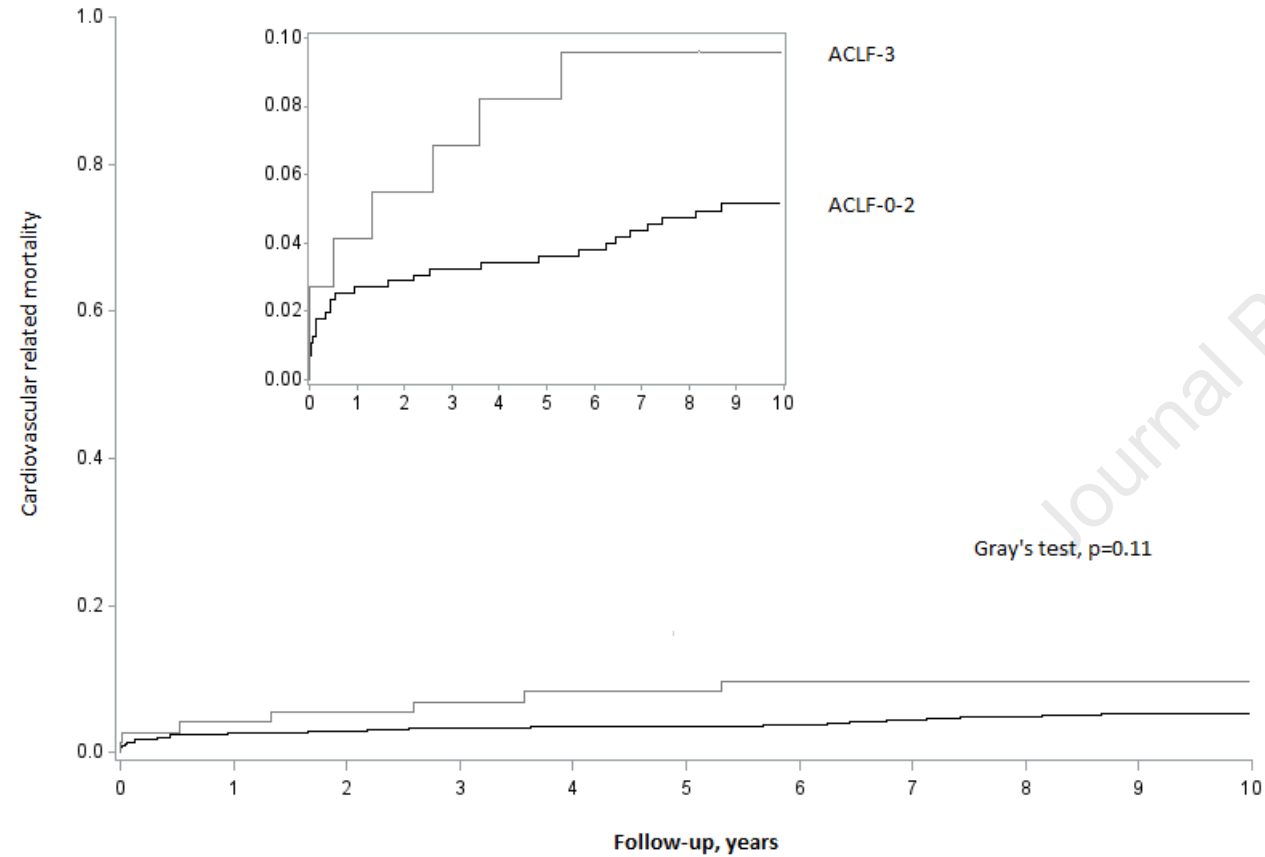


Number At Risk

Grade ACLF = 0	292	242	219	180	141
Grade ACLF = 1	119	96	87	60	41
Grade ACLF = 2	145	110	99	70	33
Grade ACLF = 3	73	54	51	32	20

Figure 3.

A Cumulative incidence of cardiovascular-related mortality following liver transplantation in patients with ACLF grade 3 and with ACLF grade 0-2



B Cumulative incidence of infection-related mortality following liver transplantation in patients with ACLF grade 3 and with ACLF grade 0-2

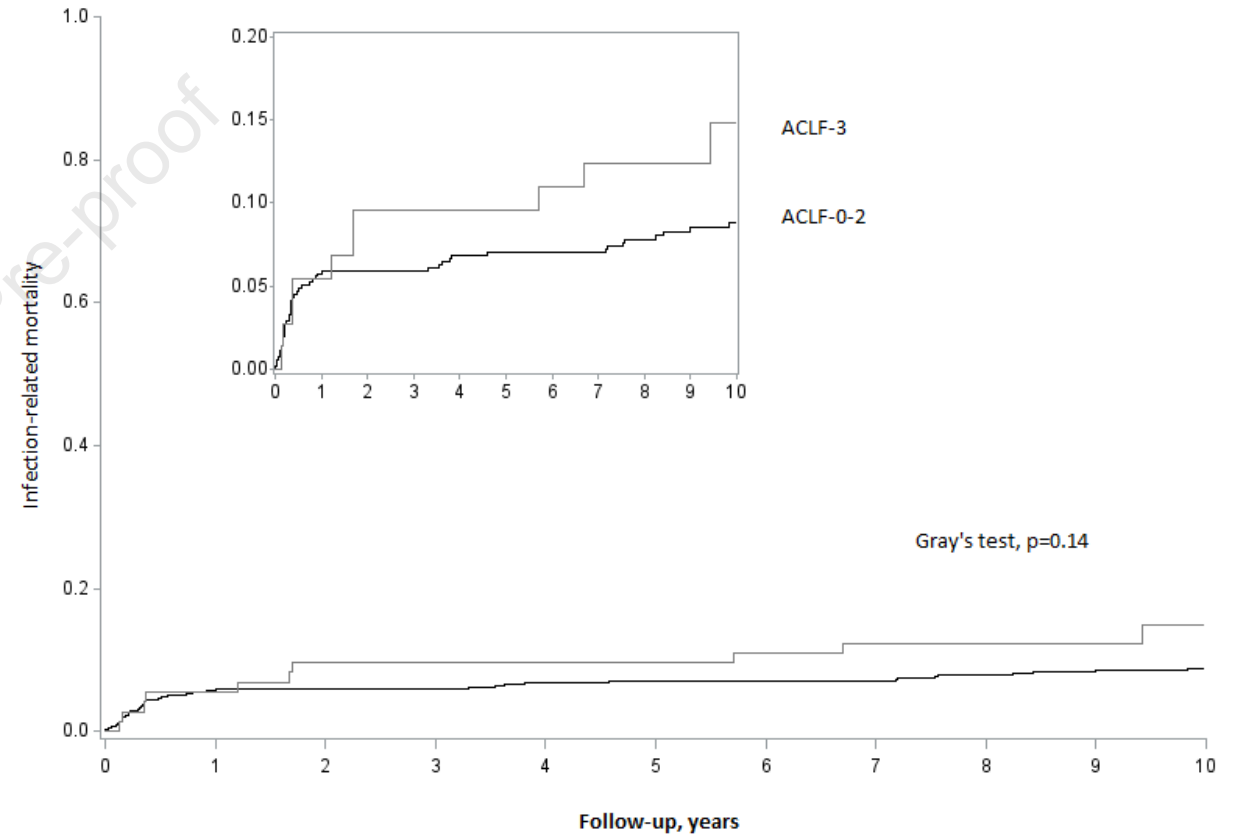
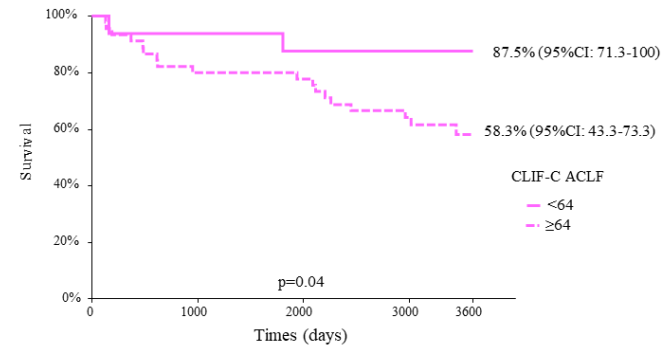


Figure 4.

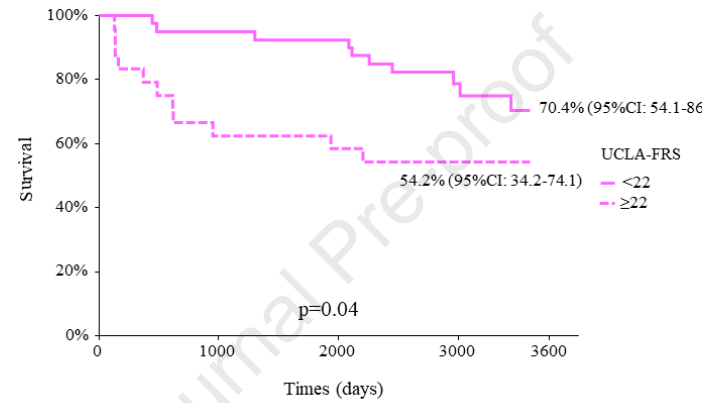
A 10-year survival following LT according to CLIF-C ACLF



Number At Risk

CLIF-C ACLF<64	18	16	14	5	5
CLIF-C ACLF≥64	45	36	35	25	15

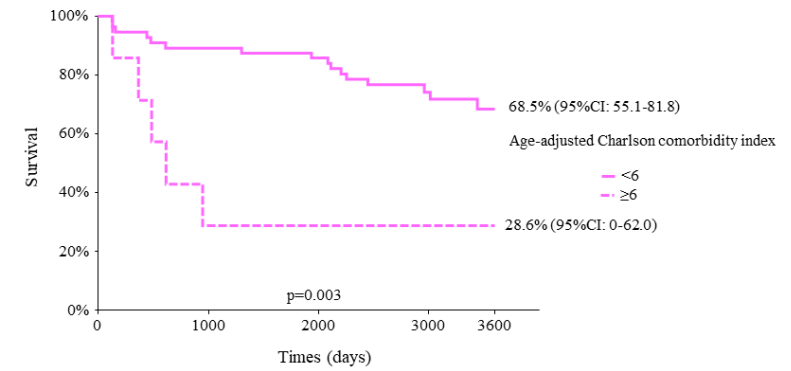
B 10-year survival following LT according to UCLA-FRS score



Number At Risk

UCLA-FRS<22	40	38	37	21	12
UCLA-FRS≥22	24	15	14	11	8

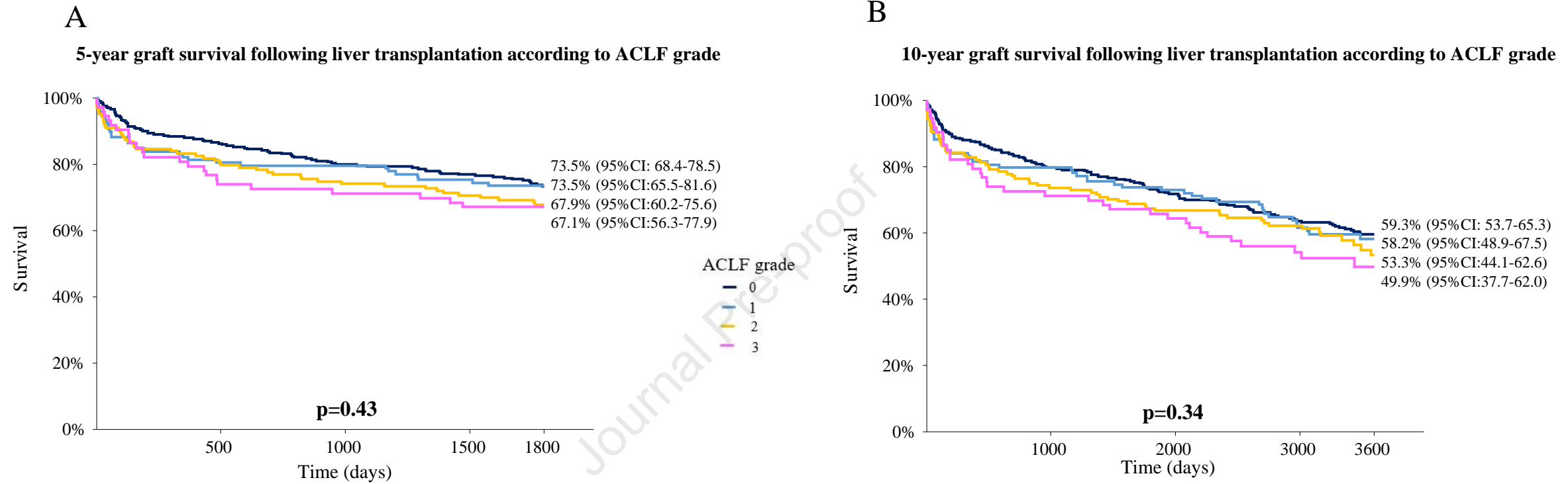
C 10-year survival following LT according to age-adjusted Charlson comorbidity index



Number At Risk

AA-CCI <6	56	50	48	29	18
AA-CCI≥6	7	2	2	2	2

Figure 5.



Number At Risk

Grade ACLF = 0	292	250	231	222	212
Grade ACLF = 1	119	95	93	87	85
Grade ACLF = 2	145	114	106	101	97
Grade ACLF = 3	73	54	52	49	49

Number At Risk

Grade ACLF = 0	292	231	208	167	131
Grade ACLF = 1	119	94	84	58	41
Grade ACLF = 2	145	106	96	68	33
Grade ACLF = 3	73	52	47	29	17

Long-term outcome following liver transplantation of patients with ACLF grade 3

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Highlights

- 5- and 10-year patients' and grafts' survivals in ACLF-3 patients were not different from their matched controls.
- Within five years, 90% of deaths occurred before the end of the second year.
- Leading causes of deaths in ACLF-3 patients were infection and cardiovascular events
- UCLA-FRS and Charlson-comorbidity index were associated with the 10-year risk of death highlighting the weight of comorbidities on the long-term
- An age-adjusted Charlson comorbidity index ≥ 6 was associated with a 10-year survival rate $< 30\%$.