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Title

Long-term outcomes of patients undergoing liver transplantation for acute-on-chronic liver failure

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Footnote page:

Abbreviations:
Acute on chronic liver failure (ACLF)
Alcoholic liver disease (ALD)
Hepatitis C virus (HCV)
Liver transplantation (LT)
Organ failure (OF)

United Network for Organ Sharing (UNOS)

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Abstract

Aims: Recent data have demonstrated greater than 80% one-year survival probability after liver transplantation (LT) for patients with severe acute on chronic liver failure (ACLF). However, long term outcomes and complications are still unknown for this population. Our aim was to compare long-term patient and graft survival among patients transplanted across all grades of ACLF.

Methods: We analyzed the UNOS database, years 2004-2017. Patients with ACLF were identified using the EASL-CLIF criteria. Kaplan-Meier and Cox regression methods were used to determine patient and graft survival and associated predictors of mortality in adjusted models.

Results: A total of 75,844 patients were transplanted of which 48,854 (64.4%) had no ACLF, 9,337 (12.3%) had ACLF-1, 9,386 (12.4%) had ACLF-2 and 8,267 (10.9%) had ACLF-3. Patients transplanted without ACLF had a greater proportion of hepatocellular carcinoma within (23.8%) and outside (12.7%) Milan criteria. Five-year patient survival after LT was lower in the ACLF-3 patients compared with the other groups (67.7%, $p<0.001$), although after year 1, the percentage decrease in survival was similar among all groups. Infection was the primary cause of death among all patient groups in the first year. After the first year, infection was the main cause of death in patients transplanted with ACLF-1 (31.1%), ACLF-2 (33.3%) and ACLF-3 (36.7%), whereas malignancy was the predominant cause of death in those transplanted with no ACLF (38.5%). Graft survival probability at 5 years was above 90% among all patient groups.

Conclusion: Patients transplanted with ACLF-3 have lower 5-year survival as compared to ACLF 0-2 but mortality rates were not significantly different after the first year following LT. Graft survival was excellent across all ACLF groups.

Introduction

Acute-on-chronic liver failure (ACLF) is a syndrome that is defined by acute hepatic decompensation, presence of organ failures (OFs), systemic inflammation, and 28-day mortality of greater than 15%.[1-3] Likelihood of death correlates with the number of OFs developed, with ACLF grade 3 (ACLF-3), defined as the presence of 3 or more OFs, having a mortality without liver transplantation (LT) approaching 80% at 28 days.[2]

Considering the high mortality without transplantation with ACLF-3, LT represents a potentially important intervention for these patients.[4-6] Recent studies have demonstrated that LT is feasible and associated with 1-year post-LT survival above 80% in patients with ACLF-3, thereby providing evidence of survival benefit with LT.[4, 6-8] However, given the limited supply of donor organs, information is additionally needed regarding whether patients who were transplanted with ACLF-3 also have acceptable long-term outcomes, to determine if organs are being utilized properly in this population. One such metric of "utility" is a greater than 50% 5-year survival rate following LT.[9] Therefore, the primary aims of our study were to report 5-year patient and graft survival in patients transplanted with ACLF-3 as compared to those transplanted with lower grades of ACLF or without ACLF. We additionally explored the etiologies of patient death and graft failure in this population.

Methods

The study protocol was approved as exempt from review by the institutional review board at Cedars-Sinai Medical Center. The study and analysis of this study were performed consistent with STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines.

United Network for Organ Sharing database analysis

From the United Network for Organ Sharing (UNOS) registry, we evaluated patients age 18 or older listed for LT from 2004 to 2017, to allow for one year of post-LT follow-up time. Patients listed as status-1a, had hepatocellular carcinoma (HCC), or who underwent multi-organ transplantation were excluded. We decided, however, to include patients who underwent simultaneous liver and kidney transplantation (SLKT) given the substantial rise in performance of this operation in the United States since 2002.[10] Additionally, we excluded patients who were re-transplanted, since the etiology of their organ dysfunction may be secondary to post-LT complications as opposed to end-stage liver disease. We collected data regarding patient characteristics at the time of waitlist registration and both patient and donor organ characteristics at transplantation, including donor risk index (DRI). Regarding etiology of liver disease, patients were considered as having nonalcoholic fatty liver disease as their primary etiology of cirrhosis if they were identified either as having nonalcoholic fatty liver disease induced cirrhosis or cryptogenic cirrhosis with a concurrent diagnosis of diabetes mellitus or a body mass index above 30 kg/m^2. Additional classifications included hepatitis C virus (HCV) and alcoholic liver disease (ALD). To avoid misclassification, patients who were categorized as having both HCV infection and ALD were considered as having HCV, due to lack of data regarding alcohol use.

Identification of ACLF

ACLF at the time of LT was identified based on the European Association for the Study of the Liver-Chronic Liver Failure (EASL-CLIF) criteria of having a single hepatic decompensation and the presence of one or more of the following OFs: single renal failure, single non-renal OF with renal dysfunction or hepatic encephalopathy (HE), or two non-renal OFs. Regarding decompensating events, we only assessed for the presence of ascites or HE, as information

regarding variceal hemorrhage and bacterial infection were unavailable. Specific OFs were determined according to the CLIF consortium OFs score for coagulopathy, liver failure, renal dysfunction and renal failure, brain failure, and circulatory failure (Table S1). We used mechanical ventilation as a surrogate marker for respiratory failure. Grade of ACLF was determined based on the number of OFs at listing and transplantation.

Statistical analysis

All statistical analyses were performed using the Stata statistical package (version 14, Stata Corporations, TX). Comparisons were made utilizing Chi-square testing for categorical variables and Student's t-test or Rank sum testing for continuous variables between two groups. We compared five-year patient and graft survival probability among the different groups of transplanted patients, utilizing Kaplan-Meier methods, with differences in survival probabilities assessed by log-rank testing. We additionally developed univariable and multivariable Cox proportional hazards regression models to evaluate the association between ACLF grade and post-LT mortality. Variables were selected for the univariable model *a priori* based on review of the literature regarding patient and donor characteristics that affect survival after transplantation. After performing univariable analysis, the independent factors that were considered significant ($p<0.10$) were then incorporated into the multivariable model. As there were less than 5% missing data regarding the variables incorporated into our models, we did not pursue multiple imputation. Goodness of fit was tested using Cox-Snell residuals.

Results

Recipient and donor characteristics at transplantation

We identified a total of 56,801 patients who met our inclusion criteria at the time of transplantation, of whom 31,024 (54.6%) had no ACLF, 8,757 (15.4%) patients had ACLF-1, 9,039 (15.9%) patients had ACLF-2, and 7,981 (14.1%) patients had ACLF-3. Regarding demographic data, patients with ACLF-3 had the smallest proportion of men (62.1%), the fewest percentage of Caucasians (66.2%), and the greatest proportion of Hispanic individuals (18.1%). The percentage of patients with alcoholic liver disease was highest among ACLF-3 (27.5%) patients, whereas the prevalence of HCV-induced cirrhosis was highest in candidates without ACLF (31.5%). NASH was most prevalent among those with ACLF-1 (17.4%). Median MELD and MELD-Na scores were significantly greater among patients with ACLF-3 (40.1 for both scores). Among the patients with ACLF-3, 4,377 (54.9%) had 3-organ failure alone, whereas 2,115 patients (26.5%) had 4-organ failure, 1,147 patients (14.3%) had 5-organ failure, and 342 patients (4.2%) had 6-organ failure. Of note, there were 2,426 patients classified as no ACLF who had renal failure. These patients were categorized as not having ACLF as they did not have presence of ascites or hepatic encephalopathy, and we therefore believed their renal failure was due to chronic kidney disease. The median creatinine at LT for this group was 4.0 and median MELD-Na score was 26.1. Data were also compared regarding donor characteristics of the transplanted patients. Patients with ACLF-3 received younger donor organs (mean age 37.8 years) and the smallest percentage of organs from high-risk donors with DRI $\geq$1.7 (24.5%) (Table 1).

Post-transplant patient survival

After transplantation, 5-year patient survival was lowest among patients with ACLF-3 (67.7%) compared with the other patient groups (75-79%, P<0.001). However, the mortality of patients with ACLF-3 declined most rapidly within the first 12 months by 19.4% and then leveled off afterwards (Figure 1). In patients with no ACLF, ACLF-1, ACLF-2 and ACLF-3, survival after the 1st year up to 5 years post-LT decreased 13.1%, 14.3%, 13.7% and 12.9%, respectively (p=0.192). (Table S2)

Causes of death after transplantation

Table 2 describes causes of death after transplantation, stratified by ACLF category. Infection was the primary cause among all patient groups in the first year. After the first year,

infection was the main cause of death in patients transplanted with ACLF-1 (32.1%), ACLF-2 (33.9%) and ACLF-3 (37.6%). Among those transplanted without ACLF, infection (29.3%) and malignancy (28.5%) were the two predominant causes of death. In table 3, we further describe infectious causes of death within 1 year among patients transplanted with ACLF-3. Within the first 3 months post-LT, sepsis (72.4%) was the predominant cause followed by fungal infections (7.6%) and pneumonia (3.1%). Between 3-12 months after transplantation, sepsis remained the predominant infectious cause of death (76.1%), followed by fungal infection (3.1%) and bacterial peritonitis (3.1%).

Analysis of factors associated with long-term mortality

Univariable and multivariable Cox proportional hazards regression for mortality after the first year post-LT are displayed in Table 4. For this analysis, we created a variable regarding the time period of transplantation, to account for the improvement in post-LT care over time. This variable was categorized as years 2004-2011 and years 2012-2017, which provided a relatively even distribution of patients. On univariable analysis, age >40 years, presence of diabetes, and high DRI were associated with long-term mortality, while undergoing LT in years 2012-2017 was associated with survival. On multivariable analysis, the presence of ACLF-1 (HR 1.17; 95% CI 1.09–1.25), ACLF-2 (HR 1.19; 95% CI 1.09–1.29), and ACLF-3 (HR 1.34; 95% CI 1.21–1.48), age >60 years (HR 1.23; 95% CI 1.13–1.34), the presence of diabetes (HR 1.36; 95% CI 1.29–1.42), and a DRI ≥1.7 (HR 1.22 95% CI 1.17–1.28) were associated with an increased hazard of long-term mortality.

Subgroup analysis of 3 versus 4-6 organ failures

We performed an additional subgroup analysis, after categorizing patients with ACLF-3 according to the presence of 3 (n=4,548) or 4-6 organ failures (n=3,179) at the time of transplantation. The characteristics of these subgroups at LT are displayed in table S3. Patients with 3 organ failures had a 71.5% survival probability at 5 years after LT, while recipients with 4-6 organ failures had a 63.0% survival probability (p<0.001). (Figure S1) Cox regression revealed that patients with ACLF-3 at transplantation with 3 organ failures have greater post-LT mortality relative to patients without ACLF (HR=1.22, 95% CI 1.09-1.36), however the hazard ratio was numerically similar to that of ACLF-1 (HR=1.17, 95% CI 1.10-1.26) and ACLF-2 (HR=1.20, 95% CI 1.10-1.29). For patients with 4-6 organ failures at transplantation, however, the risk of long-term

mortality was greatest (HR=1.55, 95% CI 1.37-1.75). (Table S4). In table S5, we report the most common infectious etiologies of death beyond 1-year after LT in the two patient groups, of which sepsis was the most prevalent cause of mortality.

Risk factors for mortality due to infection

In table S6, we display our analysis regarding risk factors for mortality due to infection within 90-days and after 1-year post-LT. We included a variable for SLKT in this part of the analysis, as patients who underwent SLKT often require a greater amount of immunosuppression to prevent kidney allograft rejection. Within 90-days after LT, we did not identify particular recipient characteristics associated with infection related mortality, though there was a trend towards significance among those transplanted with 4-6 organ failures (HR=1.27, 95% CI 0.98-1.64). Beyond 1 year after transplantation, the risk of death from infection was significantly higher in recipients with 2 organ failures (HR=1.20, 95% CI 1.07-1.33), 3 organ failures (HR=1.23, 95% CI 1.10-1.36) and 4-6 organ failures (HR=1.37, 95% CI 1.06-1.77) at LT. Additional recipient characteristics associated with infection related mortality included age > 60 (HR=1.19, 95% CI 1.07-1.31) and diabetes (HR=1.11, 95% CI 1.02-1.14).

Sensitivity analysis

As the post-LT course differs among those receiving SLKT, we performed an additional survival analysis restricted to patients who underwent SLKT (n=6,339). Similar to recipients who did not receive SLKT, the presence of ACLF-3 at LT yielded the lowest post-transplant survival at 5-years (66.6%), though the greatest decline in survival for this group occurred within the first year post-LT. (Table S7) In multivariable Cox regression (table S8), we found that the presence of ACLF-3 (HR=1.38, 95% CI 1.02-1.76), diabetes (HR=1.53, 95% CI 1.24-1.74), and transplantation with a high DRI organ (HR=1.35, 95% CI 1.14-1.59) were associated with an increased risk of mortality beyond 1 year after LT.

Post-transplant graft survival

We evaluated graft survival among patients who did not die during post-LT follow up. After transplantation, 5-year graft survival was lowest among patients with ACLF-3 (90.7%) compared with the other patient groups (p<0.001) (Figure 2). This was numerically similar to the overall mortality suggesting that the presence of ACLF-3 at transplantation is not associated with greater percentage of graft loss (Table S9). In table S10, we display causes of graft failure among the four patient groups. The predominant cause of graft failure was recurrent hepatitis. However, there was significant missing data regarding etiologies of graft failure in the entire study population.

Discussion

Due to the scarcity of donor organs, the potential benefit of LT must always balance the best possible outcome for a given patient with the maximum utility of an organ.[11] In general, most transplantation groups accept that patients should be offered LT if there is more than a 50% expectancy of 5-year survival post-LT with an acceptable quality of life.[12-15] This is also consistent with recent survey data of both medical and non-medical respondents, who regard LT as worthwhile if a patient achieves a survival benefit on the timeline of 1-5 years at minimum.[16] Although LT represents the only definitive therapeutic option for patients with ACLF-3, the early reported results were poor.[1, 17] However, recently there seems to be agreement regarding better outcomes of LT in patients with ACLF-3, with acceptable to excellent 1-year post-LT survival.[4, 6, 8, 18] Our study is the first to focus on long term patient survival, graft survival and complications after LT for patients with ACLF and showed that even patients with ACLF-3 had a 5-year post-LT survival of 67.7%, which justifies both 'transplant benefit' for these patients as well as acceptable 'utility' of the donor organs. Even among patients with 4-6 organ failures, the 5-year survival was 63.0% indicating that such recipients still have transplant benefit. Finally, among patients transplanted with ACLF-3, the steepest decline in mortality occurred within the first year and was primarily due to infectious complications. Therefore, appropriate infection management and prophylaxis is important for long-term survival in this population.

Infection was the primary cause of death among all patient groups in the first year and it represents the main cause of death in patients with all ACLF grades after the first year. On the contrary, malignancy was the predominant cause of death in patients transplanted with no ACLF. The impact of infections in our study is higher than that reported by other literature. Artru and colleagues showed that acquired infections are common among patients with ACLF-3 at the time of transplantation, as 80.8% of patients developed bacterial infections, 35.6% acquired viral infections, 15.1% had fungal infections, and 6.8% of patients transplanted with ACLF-3 died from infection within the first year after LT.[4] The high incidence of bacterial infection after ACLF diagnosis justifies the implementation of infection control practices, such as bundles on prevention of ventilator-associated pneumonia, catheter-related bacteremia, and hand hygiene.[19] Treatments aimed at restoring the patients' immune function could also be beneficial

in these patients.[20] Fernández and colleagues recently demonstrated that adequacy of empiric antibiotic strategies is also a key factor in the management of infected patients with ACLF, and that inappropriate first-line therapies were associated with increased mortality.[21] Therefore, broad antibiotic schemes covering all potential pathogens should be considered within the first 48–72 hours after the diagnosis of infection, to improve clinical efficacy to minimize the selection of resistant strains.[19] While such measures would be expected to potentially improve peri-operative and short-term post-LT outcomes, the impact on longer-term post-LT outcomes is less clear and could be the subject of future research.

Risk factors regarding reduced long-term survival following LT were also identified in this study. On multivariable analysis there was an association between ACLF and long-term mortality between one- and five-years post-LT when compared to no ACLF. The rise in mortality, although marginal, increased in a stepwise fashion for ACLF 1-3. Given the similar stepwise increase in infection-related mortality after 12-months post-LT in no ACLF to ACLF3 patients, it is tempting to hypothesize that the increased observed ACLF mortality may be attributable to long-standing ACLF-induced immunoparesis.[22] Additionally, sepsis is a common driver of ACLF and may further drive immune dysfunction through bone marrow suppression.[23] Second, the rapid introduction of immunosuppression following LT may further inhibit immune reconstitution following the initial insult, in a manner that is protracted in patients with ACLF. Finally, as an alternative to the above hypothesis, we noted that post-LT graft failure was significantly higher in patients with increasing grades of ACLF, though this effect was modest. Therefore it is theoretically possible that higher requirements for immune suppression in these patients over time results in increased rates of infection and sepsis.

Pre-existing diabetes is a risk factor for death from one year onwards after LT, and this finding is in concordance with previous data.[24] Diabetes is expected to worsen following LT due to immunosuppressive regimens, and this has a distinct effect on renal injury, infection risk, and cardiovascular-related death.[25] Notably, the presence of pre-existing diabetes prior to LT confers an equivocal-to-higher long-term mortality after LT than the presence of ACLF-3, and a higher mortality than ACLF-1 or ACLF-2, versus no ACLF at the time of LT. The association between increasing age and post-LT mortality was observed and is also consistent with previous data.[26, 27] This may be an expected finding due to increasing co-morbidity, natural deterioration of

physiological processes, and increasing frailty with advancing age. Durand *et al* reported that older patients (>60 years old) receiving LT had increased cardiovascular and malignancy-related mortality compared with their younger (<60 years old) counterparts.[26] These factors add to and are independent of ACLF-3 in defining the long-term post-LT mortality.

The UNOS registry has certain advantages for this investigation, particularly the availability of a large sample size of patients with ACLF-3 across multiple regions in the United States. However, several limitations exist regarding our analysis of this database, given the nature of retrospectively analyzing a large public database. First, there is the potential for misclassification at transplantation. In particular, there are patients with renal failure who are categorized as no ACLF, because there is no documented ascites or hepatic encephalopathy. It is likely that most of these patients had compensated cirrhosis with chronic kidney disease, since they did not have ascites, which is a necessary component of hepatorenal syndrome. It is also possible that certain individuals classified as no ACLF had a decompensating event such as variceal bleeding or bacterial infection, which is not captured in the UNOS database. Similarly, misclassification may also occur regarding grade of hepatic encephalopathy and the presence of mechanical ventilation as an indicator for respiratory failure, since the indication for mechanical ventilation is not available. For example, certain patients may have been mechanically ventilated for airway protection rather than for a reduced partial pressure of arterial oxygen, which is the original definition of respiratory failure used to identify ACLF. Second, data regarding immunosuppression is not well captured in the UNOS database, and we were therefore unable to account for differences in immunosuppressive regimens as a potential reason for infection. However, we do not have strong reasons to suspect that the immunosuppression protocols would be substantively different among the four patient groups, although this could be explored in future studies. Finally, in this study we do not provide a detailed analysis of geographic or center-level variation in post-LT outcomes for patients with or without ACLF. However, in principle there may be institutional practices or differences in wait listing or LT selection that may impact expected outcomes, even among patients with ACLF-3. This is another area where future research may be of benefit.

In conclusion, the results of this study provide new evidence that long term post-LT survival of patients with ACLF-3 are sufficient to confirm transplant benefit for the patient and

utility of the donated organ. Refinement in criteria for selection and better understanding of whether this improvement in survival benefit is associated with improved quality of life requires additional study. Further improvement in post-LT outcomes can be expected with improved understanding of immune reconstitution after LT and factors associated with infection acquisition.

Figure legends

Figure 1. Post-transplant patient survival by pre-transplant ACLF status

Figure 2. Post-transplant graft survival by pre-transplant ACLF status

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Table 1. Recipient and donor characteristics at the time of liver transplantation, categorized by ACLF grade.

Recipient characteristics	No ACLF (n=31,024)	ACLF-1 (n=8,757)	ACLF-2 (n=9,039)	ACLF-3 (n=7,981)	p-value*
Age, mean (SD)	53.8 (9.9)	52.1 (10.7)	52.3 (10.7)	54.5(10.5)	<0.001
Male, n (%)	20,519 (66.1)	5,682 (64.8)	5,703 (63.1)	4,957 (62.1)	<0.001
Diabetes mellitus, n (%)	7,985 (25.7)	2,582 (29.5)	2,214 (24.5)	1,811 (22.7)	<0.001
Race/ethnicity:					<0.001
Caucasian, n (%)	23,528 (75.9)	6,451 (73.7)	6,150 (68.0)	5,280 (66.2)	
African-American, n (%)	2,693 (8.7)	834 (9.5)	1,001 (11.1)	785 (9.8)	
Hispanic, n (%)	3,482 (11.2)	1,146 (13.1)	1,455 (16.1)	1,448 (18.1)	
Etiology, n (%)					<0.001
HCV	9,768 (31.5)	2,562 (29.3)	2,396 (26.5)	2,159 (27.1)	
ALD	6,379 (20.6)	2,281 (26.1)	2,399 (26.5)	2,193 (27.5)	
NASH	5,389 (17.4)	1,740 (19.9)	1,396 (15.5)	1,205 (15.1)	
Cholestatic	4,199 (13.5)	1,164 (13.3)	1,349 (14.9)	928 (11.6)	
MELD score, median (IQR)	18.0 (14.2-20.0)	26.8 (23.7-30.3)	33.9 (29.9-37.6)	40.1 (35.7-43.6)	<0.001
MELD-Na score, median (IQR)	20.7 (16.2-24.9)	29.0 (25.8-32.1)	34.8 (31.5-37.9)	40.1 (36.1-43.2)	<0.001
Albumin, median (SQ)	3.0 (2.6-3.5)	2.9 (2.4-3.4)	3.0 (2.5-3.5)	3.1 (2.6-3.7)	<0.001
Liver failure, n (%)	1,667 (5.4)	2,266 (25.9)	5,803 (64.7)	6,521 (81.9)	<0.001
Mechanical ventilation, n (%)	0 (0)	0 (0)	185 (2.1)	3,049 (38.2)	<0.001
Circulatory failure, n (%)	43 (0.1)	44 (0.5)	699 (7.7)	4,272 (53.5)	<0.001
Coagulation failure, n (%)	970 (3.1)	2,008 (22.9)	4,273 (47.9)	4,779 (63.3)	<0.001
Neurologic failure, n (%)	1,672 (5.4)	0 (0)	1,905 (21.1)	4,208 (52.7)	<0.001
Renal failure, n (%)	2,426 (7.8)	4,439 (50.7)	5,213 (57.7)	6,549 (82.2)	<0.001
Number of organ failures (n,%):					
Three				4,377 (54.8)	

Four				2,115 (26.5)	
Five				1,147 (14.4)	
Six				342 (4.3)	
Days from listing to LT (median, IQR)	103 (29-303)	48 (12-181)	22 (7-119)	12 (4-60)	<0.001
Liver-Kidney transplant	1,830 (5.9)	1,839 (21.1)	1,520 (16.8)	1,150 (14.4)	<0.001
Donor characteristics					
Age, mean (SD)	41.8 (17.2)	39.8 (16.1)	39.1 (15.6)	37.8 (15.4)	<0.001
Male, n (%)	18,543 (59.9)	5,189 (59.3)	5,448 (60.3)	4,868 (61.6)	0.130
Donor risk index >= 1.7	10,117 (32.6)	2,228 (25.3)	2,205 (24.4)	1,962 (24.5)	<0.001

* Evaluation of differences across all ACLF categories using ANOVA and Chi-square testing

Table 2. Causes of death after transplantation, according to ACLF category

	No ACLF	**ACLF-1**	**ACLF-2**	**ACLF-3**
< 3 months post-LT	**n=930**	**n=371**	**n=421**	**n=785**
Vascular embolism	38 (4.1)	14 (3.8)	13 (2.9)	25 (3.1)
Infection	388 (41.7)	169 (45.2)	219 (49.6)	416 (51.7)
Cardiovascular disease	435 (32.9)	129 (32.4)	133 (30.9)	202 (25.1)
Respiratory insufficiency	87 (6.6)	25 (6.3)	30 (6.8)	37 (4.6)
Renal failure	5 (0.4)	2 (0.5)	2 (0.5)	2 (0.4)
Malignancy	15 (1.3)	8 (2.0)	5 (1.1)	7 (0.9)
Perioperative death	33 (2.4)	10 (2.5)	9 (2.0)	13 (1.6)
Graft failure	156 (11.8)	30 (7.5)	30 (6.8)	98 (12.2)
3-12 months post-LT	**n=924**	**n=338**	**n=362**	**n=439**
Vascular embolism	4 (0.4)	5 (1.5)	1 (0.3)	3 (0.7)
Infection	392 (42.4)	156 (46.1)	179 (49.6)	248 (56.5)
Cardiovascular disease	108 (11.7)	45 (13.3)	45 (12.4)	59 (13.2)

Respiratory insufficiency	69 (7.5)	27 (7.9)	27 (7.5)	34 (7.5)
Renal failure	28 (3.0)	9 (2.6)	7 (1.9)	9 (2.1)
Malignancy	136 (14.7)	21 (6.2)	28 (7.7)	37 (8.4)
Graft failure	187 (20.2)	75 (22.3)	75 (20.7)	51 (11.6)
>12 months post-LT	**n=3,204**	**n=929**	**n=809**	**n=713**
Vascular embolism	17 (0.5)	6 (0.7)	4 (0.5)	9 (1.2)
Infection	937 (29.3)	298 (32.1)	274 (33.9)	268 (37.6)
Cardiovascular disease	455 (14.2)	161 (17.3)	116 (14.3)	114 (15.9)
Respiratory insufficiency	237 (7.4)	71 (7.6)	52 (6.4)	50 (7.1)
Renal failure	112 (3.5)	58 (6.1)	44 (5.3)	30 (4.2)
Malignancy	914 (28.5)	201 (21.5)	163 (20.2)	131 (18.4)
Graft failure	528 (16.5)	135 (14.5)	157 (19.4)	110 (15.4)

Table 3. Infectious causes of death within one year of transplantation, among patients transplanted with ACLF-3

	<3 months post LT n=251	3-12 months post LT n=159
Bacterial peritonitis	7 (2.8)	5 (3.1)
Pneumonia	8 (3.2)	4 (2.5)
Sepsis	182 (72.4)	121 (76.1)
Fungal	19 (7.6)	5 (3.1)
Mixed	5 (1.9)	2 (1.3)
Opportunistic	4 (1.6)	2 (1.3)
Viral	2 (0.8)	2 (1.3)
Other	24 (9.6)	18 (11.3)

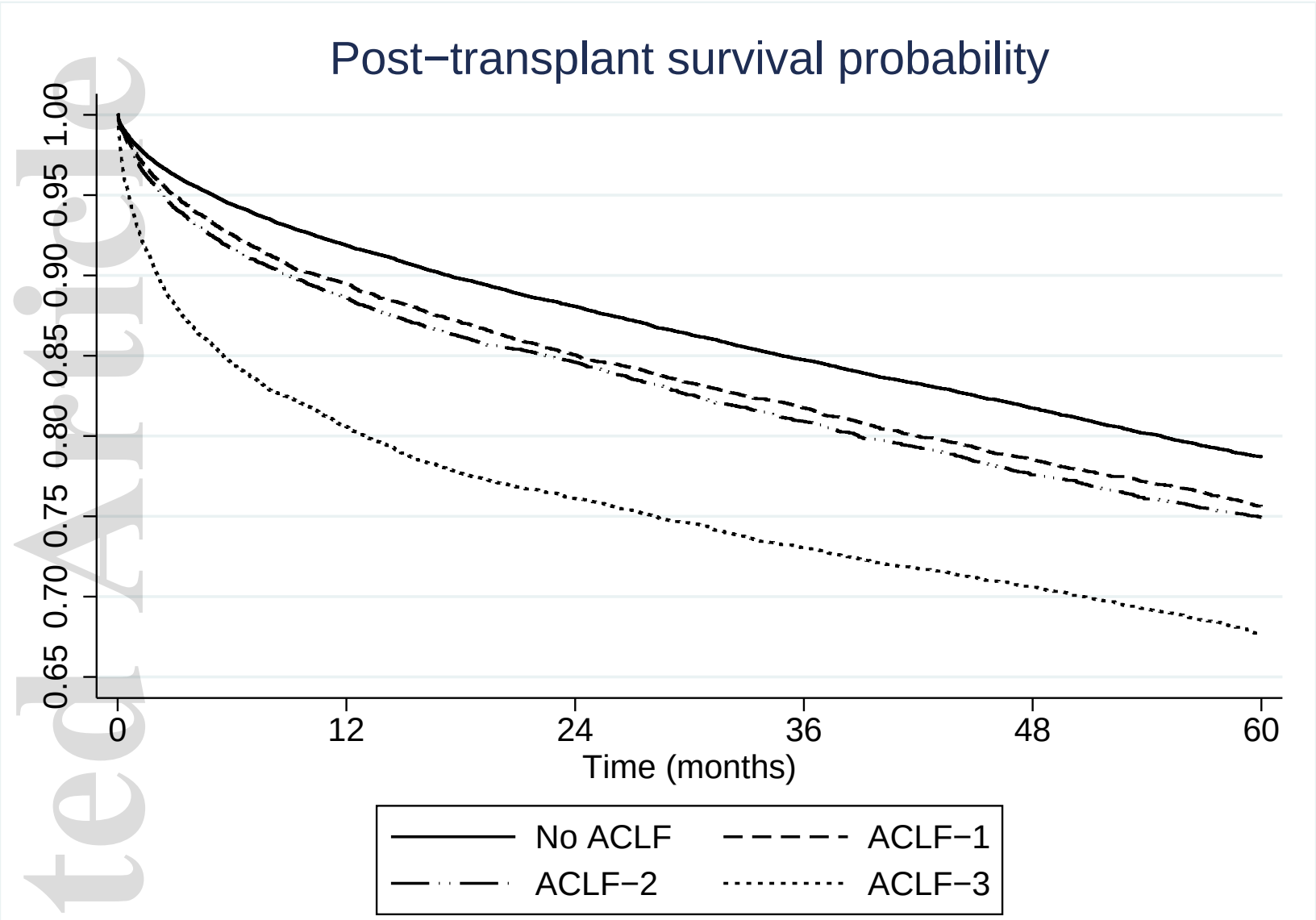
Table 4. Cox regression analysis for post-transplant mortality beyond 1 year after LT

	Reference	Hazard ratio, 95% CI*	Hazard ratio, 95% CI**	p-value***
ACLF-1	No ACLF	0.98 (0.92-1.03)	1.17 (1.09-1.25)	<0.001
ACLF-2		0.97 (0.92-1.01)	1.19 (1.09-1.29)	<0.001
ACLF-3		1.06 (0.99-1.13)	1.34 (1.21-1.48)	<0.001
Age 40-60	Age<40	1.09 (1.02 -1.17)	1.00 (0.93 -1.08)	0.941
Age > 60		1.38 (1.27-1.49)	1.23 (1.13-1.34)	<0.001
MELD-Na score		0.99 (0.99-1.00)	0.98 (0.96-1.00)	0.322
Diabetic	Non-diabetic	1.40 (1.34-1.46)	1.36 (1.29-1.42)	<0.001
DRI ≥ 1.7	DRI < 1.7	1.21 (1.16 -1.26)	1.22 (1.17 -1.28)	<0.001
Years 2012-2017	Years 2004-2011	0.88 (0.83-0.93)	0.86 (0.81-0.91)	<0.001

** Univariable analysis*

*** Multivariable analysis*

****p-value for multivariable analysis*



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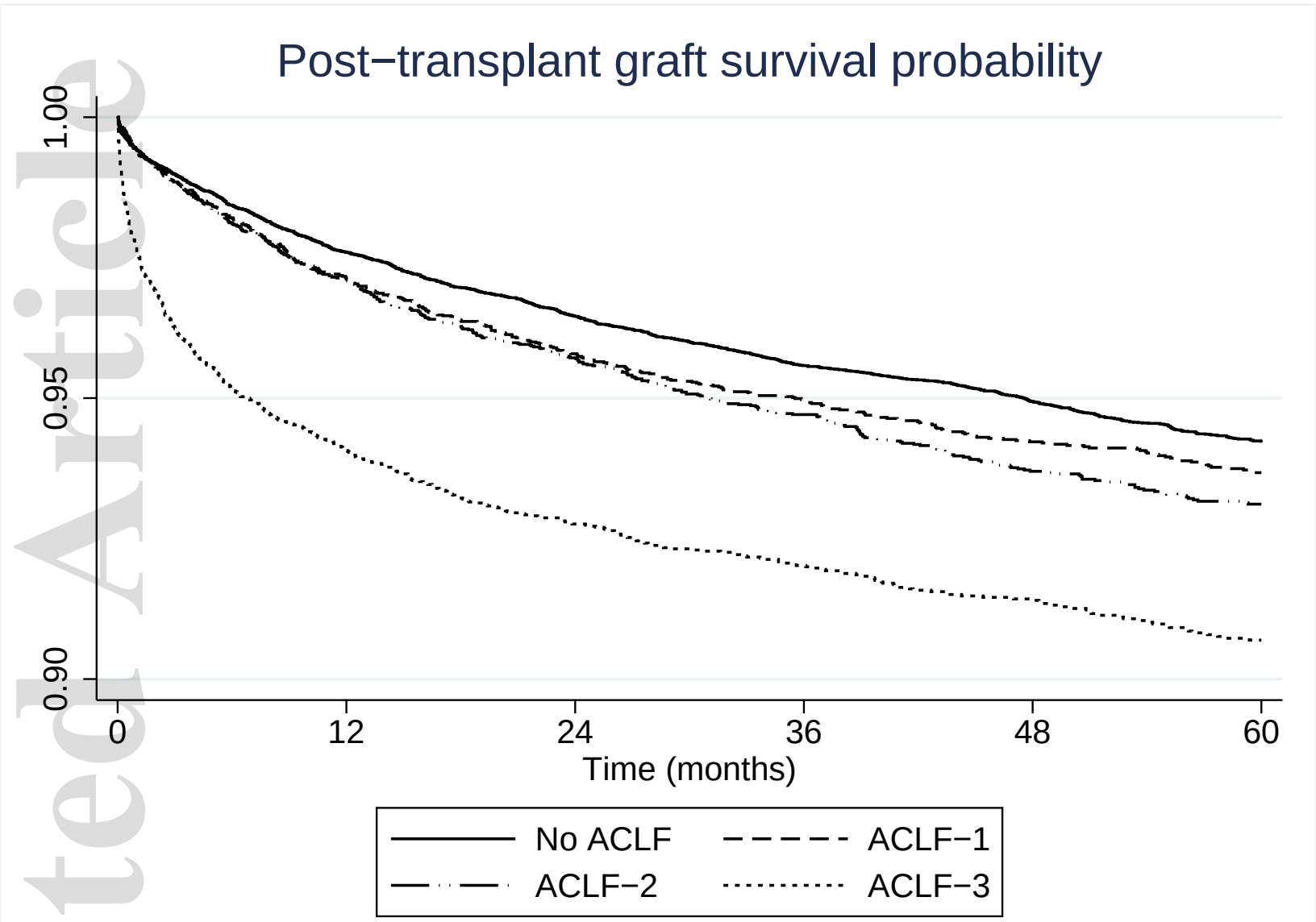

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