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Original Article

Impact of Donor Age on Liver Transplant Outcomes in Patients with Acute-on-Chronic Liver Failure: A Cohort Study

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Background/Aims: Liver transplantation is the most effective treatment for the sickest patients with acute-on-chronic liver failure (ACLF). However, the influence of donor age on liver transplantation, especially in ACLF patients, is still unclear.

Methods: In this study, we used the data of the Scientific Registry of Transplant Recipients. We included patients with ACLF who received liver transplantation from January 1, 2007, to December 31, 2017, and the total number was 13,857. We allocated the ACLF recipients by age into group I (donor age ≤17 years, n=647); group II (donor age 18–59 years, n=11,423); and group III (donor age ≥60 years, n=1,787). Overall survival (OS), graft survival, and mortality were compared among the three age groups and the four ACLF grades. Cox regression was also analyzed.

Results: The 1-, 3-, and 5-year OS rates were 89.6%, 85.5%, and 82.0% in group I; 89.4%, 83.4%, and 78.2% in group II; and 86.8%, 78.4%, and 71.4% in group III, respectively (p<0.001). When we analyzed the different effects of donor age on OS with different ACLF grades, in groups II and III, we observed statistical differences. Finally, the cubic spline curve told us that the relative death rate changed linearly with increasing donor age.

Conclusions: Donor age is related to OS and graft survival of ACLF patients after transplantation, and poorer results were associated with elderly donors. In addition, different donor ages have different effects on recipients with different ACLF grades. **(Gut Liver, 2025;19:398-409)**

Key Words: Liver transplantation; Overall survival; Graft survival; Age; Acute-on-chronic liver failure

INTRODUCTION

Acute-on-chronic liver failure (ACLF) is a syndrome that occurs in patients with cirrhosis. The characteristic of ACLF is acute hepatic decompensation, organ system failures, and 28-day mortality >15%.[1] Although liver failure is potentially reversible in ACLF if the precipitating factor can be controlled,[2] liver transplantation (LT) is the most useful way to save ACLF patients. Moreover, without transplantation, there is a high mortality rate in ACLF grade 3. However, owing to the great number of patients waiting for LT and lack of donor livers, a substantial number of patients drop out of the waiting list or die while waiting. Therefore, there is a strong incentive to increase the age limitation for liver donation.[3,4]

The proportion of elderly donors (>60 years old) for liver transplants significantly increased from the early 1990s to the early 2000s in the United States and then has slowly stabilized. For transplantations using donors >60 years, both recipient and graft survival (GS) have recently improved.[4,5] Several studies suggested that the difference between older and younger donors in survival rate after transplantation mainly occurred in the first year after LT and stabilized thereafter.[4,6-8] However, data from the United

Kingdom suggested that donor age remained a predictor of survival rate 1 year after transplantation.[4,9] Overall, there is no unified consensus on the upper age limit of LT donors, even though significant progress have been made with elderly donors.[4,5] Until now, the effect of donor age on LT has not been elucidated, especially in ACLF patients.

Here, we used data from the Scientific Registry of Transplant Recipients (SRTR) to evaluate the influence of donor age on liver transplant prognosis, including overall survival (OS), GS, and mortality in patients with ACLF.

MATERIALS AND METHODS

1. Study design

We used data from the SRTR for this study. The data about all donors, wait-listed candidates, and transplant recipients in the United States submitted by the members of the Organ Procurement and Transplantation Network, are from the SRTR database. The activities of the Organ Procurement and Transplantation Network and SRTR contractors were supervised by the Health Resources and Services Administration, U.S. Department of Health and Human Services. The Hennepin Healthcare Research Institute served as the contractor for the SRTR supplied the reported data here. The interpretation and reporting of these data were the responsibility of the author(s) and in no way should be seen as an official policy of or interpretation by the SRTR or the U.S. Government.[10] We did not use the organs from executed prisoners in this study. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the First Affiliated Hospital, College of Medicine, Zhejiang University, China (approval number 2019-1020) and individual consent for this retrospective analysis was waived.

We included patients with ACLF who received LT from January 1, 2007, to December 31, 2017. The inclusion criteria were as follows: recipients ≥18 years old. ACLF at the time of listing as well as at the time of LT was identified according to the European Association for the Study of the Liver Chronic Liver Failure criteria.[11] Specific organ failures including liver failure (total bilirubin ≥12.0 mg/dL), cerebral failure (grade 3 through 4 encephalopathy), coagulation failure (international normalized ratio ≥2.5), kidney failure (creatinine ≥2.0 mg/dL or dialysis) or dysfunction (creatinine 1.5 to 1.9 mg/dL) were determined based on Chronic Liver Failure-Sequential Organ Failure Assessment scores.[11] Since we did not have detailed information about circulatory and respiratory failure in the SRTR database, we took use of vasopressors as a proxy for circulatory failure, and mechanical ventilation as a proxy for respiratory failure. The number of organ failures determined ACLF grade.[11,12]

Patients with previous LT or multi-organ transplantation, or status 1a or hepatocellular carcinoma, or waiting time >28 days, or with no age recorded were excluded from this study. Finally, our study included a total of 13,857 recipients. Patients were followed up to death or the end of the study on March 1, 2019. The patient selection flowchart was shown in the Fig. 1.

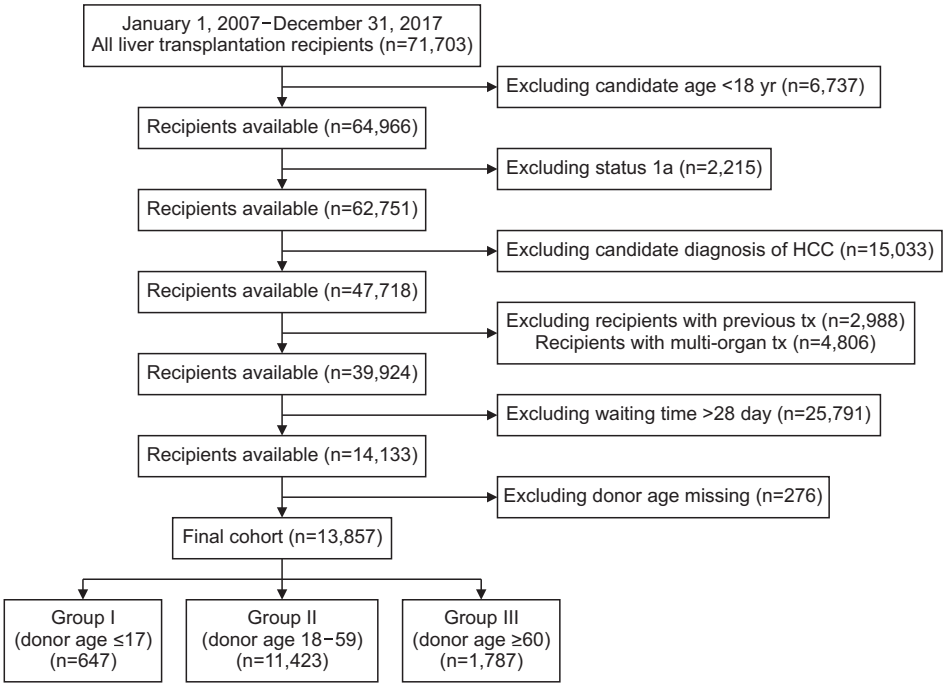


Fig. 1. Patient selection flowchart. HCC, hepatocellular carcinoma; tx, transplantation.

To evaluate how donor age affected liver transplant outcomes, we divided recipients into three groups on the basis of donor age: group I, donor age ≤17 years (n=647); group II, donor age 18–59 years (n=11,423); and group III, donor age ≥60 years (n=1,787). The donor and recipient data as well as OS, GS, and mortality were compared among the three groups. In each group, we also compared the OS, GS, and mortality among ACLF0, ACLF1, ACLF2, and ACLF3. OS was calculated from the time of LT to recipient death, and GS was measured from the date of LT to date of graft failure or re-transplantation, or last follow-up. Patient causes of death, including graft failure, cardio/cerebral disease, organ failure, hemorrhage, infection, malignancy or other, were compared among ACLF0, ACLF1, ACLF2, and ACLF3 in all patients and in every age group. Considering the comprehensive influence of the age of donors and recipients, we divided them into four groups according to donor-recipient age match. These groups were: young to young group (n=8,790): donor <60 years old to recipient <60 years old; young to elderly group (n=3,280): donor <60 years old to recipient ≥60 years old; elderly to young group (n=1,160): donor ≥60 years old to recipient <60 years old; elderly to elderly group (n=627): donor ≥60 years old to recipient ≥60 years old. In each group, we compared the OS and GS among ACLF0, ACLF1, ACLF2, and ACLF3.

2. Statistical analysis

For baseline characteristics comparison, we used one-way analysis of variance for continuous variables and the chi-square analyses for categorical variables. OS and GS were estimated by the Kaplan-Meier method and a log-rank test was used to compare differences among the groups. A univariate test was used to analyze prognostic factors for the multivariable Cox regression analysis model; significant factors in the univariate analysis were subsequently included in the multivariable Cox model to determine independent effects. Cubic smoothing splines (and 95% confidence intervals) were generated to estimate the hazard ratio of donor age for OS at each ACLF level.[13] To reduce the confounding bias of the baseline characteristics, we performed inverse probability of treatment weighting (IPTW), a method based on propensity scoring.[14] And IPTW-adjusted OS and GS in all cohorts and in different donor age groups were further analyzed. A two-sided p-value <0.05 was considered statistically significant. All the analyses were conducted with SPSS version 22.0 (IBM Corp., Armonk, NY, USA) and R for Windows (version 4.0.2; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

1. Baseline characteristics

The total number of recipients included was 13,857. The median follow-up time was 48 months (interquartile range, 24 to 84 months) for the entire study population. There were 163 living donor LT (1.2%) and 13,694 deceased donor LT (98.8%). Recipient characteristics including age, sex, race, underlying liver diseases, Karnofsky Performance Status (KPS), diabetes, Model for End-Stage Liver Disease score, circulatory failure, respiratory failure, liver failure, coagulation failure, renal failure, and ACLF stage at LT significantly differed among the three groups. Only ABO blood type, neurologic failure, and recipient body mass index were comparable among the three groups. For donor characteristics, sex, donor height, donor weight, donation

Table 1. Baseline Characteristics of Patients among Different Donor Age Groups

Variable	Donor age			p-value
	Group I (<18 yr, n=647)	Group II (18–59 yr, n=11,423)	Group III (≥60 yr, n=1,787)	
Recipient variable				
Age, yr	54 (47–60)	54 (47–60)	56 (49–62)	<0.001
Sex				<0.001
Female	285 (44.05)	4,015 (35.15)	612 (34.25)	
Male	362 (55.95)	7,408 (64.85)	1,175 (65.75)	
ABO blood type				0.379
A	232 (35.86)	3,945 (34.54)	608 (34.02)	
B	94 (14.53)	1,534 (13.43)	239 (13.37)	
O	272 (42.04)	5,242 (45.89)	839 (46.95)	
AB	49 (7.57)	702 (6.15)	101 (5.65)	
Race				0.003
White	447 (69.09)	8,172 (71.54)	1,332 (74.54)	
Black or African American	91 (14.06)	1,138 (9.96)	154 (8.62)	
Asian	23 (3.55)	371 (3.25)	60 (3.36)	
Hispanic/Latino	75 (11.59)	1,591 (13.93)	222 (12.42)	
Others	11 (1.70)	151 (1.32)	19 (1.06)	

Table 1. Continued

Variable	Donor age			p-value
	Group I (<18 yr, n=647)	Group II (18–59 yr, n=11,423)	Group III (≥60 yr, n=1,787)	
Underlying liver diseases				<0.001
HCV	143 (22.10)	2,522 (22.08)	262 (14.66)	
ALD	163 (25.19)	3,290 (28.80)	613 (34.30)	
NASH	113 (17.47)	2,052 (17.96)	322 (18.02)	
Others	228 (35.24)	3,559 (31.16)	590 (33.02)	
KPS*				<0.001
KPS I	330 (51.97)	6,951 (61.68)	931 (53.20)	
KPS II	237 (37.32)	3,212 (28.50)	602 (34.40)	
KPS III	68 (10.71)	1,106 (9.81)	217 (12.40)	
Recipient BMI, kg/m^2	26.63 (22.95–30.72)	28.25 (24.55–32.99)	28.12 (24.50–32.50)	0.806
Diabetes	155 (23.96)	2,516 (22.03)	438 (24.51)	0.041
MELD	27.00 (21.00–33.00)	29.00 (22.00–36.00)	26.00 (20.00–33.00)	<0.001
Circulatory failure	81 (12.52)	1,609 (14.09)	161 (9.01)	<0.001
Respiratory failure	49 (7.57)	949 (8.31)	107 (5.99)	0.003
Liver failure	261 (40.34)	5,471 (47.89)	650 (36.37)	<0.001
Neurologic failure	118 (18.24)	2,037 (17.83)	279 (15.61)	0.065
Coagulation failure	201 (31.07)	4,211 (36.86)	574 (32.12)	<0.001
Renal failure	216 (33.38)	4,716 (41.29)	595 (33.30)	<0.001
ACLF stage at transplantation				<0.001
ACLF-0	245 (37.87)	3,544 (31.03)	743 (41.58)	
ACLF-1	141 (21.79)	2,221 (19.44)	353 (19.75)	
ACLF-2	135 (20.87)	2,769 (24.24)	377 (21.10)	
ACLF-3	126 (19.47)	2,889 (25.29)	314 (17.57)	
Donor variable				
Sex				<0.001
Female	204 (31.53)	4,479 (39.21)	874 (48.91)	
Male	443 (68.47)	6,944 (60.79)	913 (51.09)	
ABO blood type				0.105
A	233 (36.01)	4,183 (36.62)	640 (35.81)	
B	83 (12.83)	1,105 (9.67)	176 (9.85)	
O	305 (47.14)	5,794 (50.72)	913 (51.09)	
AB	26 (4.02)	341 (2.99)	58 (3.25)	
Donor height, cm	169.50 (160.02–177.80)	172.72 (165.10–180.00)	168.00 (162.56–177.80)	<0.001
Donor weight, kg	65.83 (55.00–77.00)	80.00 (68.20–93.00)	79.00 (68.00–92.20)	<0.001
Cold ischemia time, hr	6.01 (4.72–7.62)	6.00 (4.70–7.60)	6.00 (4.80–7.40)	0.171
DCD	57 (8.81)	506 (4.49)	14 (0.78)	<0.001
Partial/split	46 (7.11)	215 (1.88)	1 (0.56)	<0.001
Organ share				<0.001
Local	489 (75.58)	7,034 (62.46)	1,119 (62.65)	
Regional	149 (23.03)	3,911 (34.73)	536 (30.01)	
National	9 (1.39)	316 (2.81)	131 (7.33)	
Race				<0.001
White	374 (57.81)	7,294 (63.85)	1,262 (70.62)	
Black or African American	146 (22.57)	2,195 (19.22)	309 (17.29)	
Asian	14 (2.16)	229 (2.00)	46 (2.57)	
Hispanic/Latino	107 (16.54)	1,614 (14.13)	166 (9.29)	
Others	6 (0.93)	91 (0.80)	4 (0.22)	
Cause of death				<0.001
Anoxia	205 (31.68)	3,269 (29.03)	298 (16.69)	
Cerebrovascular	40 (6.18)	3,657 (32.47)	1,214 (67.97)	
Head trauma	387 (59.81)	4,045 (35.92)	241 (13.49)	
CNS tumor	2 (0.31)	45 (0.40)	3 (0.17)	
Others	13 (2.01)	245 (2.18)	30 (1.68)	

Data are presented as median (interquartile range) or number (%).

HCV, hepatitis C virus; ALD, alcoholic liver disease; NASH, non-alcoholic steatohepatitis; KPS, Karnofsky Performance Status; BMI, body mass index; MELD, Model for End-Stage Liver Disease; ACLF, acute-on-chronic liver failure; DCD, donation after cardiac death; CNS, central nervous system.

after cardiac death, partial/split graft, organ share, race, and cause of death were all statistically different among the three groups. Donor ABO and cold ischemia time were comparable among the three groups. Table 1 presented the above specific data in detail.

2. Overall survival

We compared OS among the three groups. The 1-, 3-, and 5-year OS rates were 89.6%, 85.5%, and 82.0% in group I; 89.4%, 83.4%, and 78.2% in group II; and 86.8%, 78.4%, and 71.4% in group III, respectively (p<0.001) (Supplementary Fig. 1A). We found that the survival rate of group I recipients was better than that of the other two groups, and the difference among three groups became obvious with time. Then we compared OS among the grades of ACLF in every group. In group I, there was no statistically significant differences among the four grades (p=0.45) (Fig. 2A). However, we observed statistically significant differences in group II (p<0.001) and group III (p=0.01) (Fig. 2B and C).

3. Graft survival

Similarly, we compared GS among the three groups. The 1-, 3-, and 5-year GS rates in group I were 94.7%, 93.2%, and 91.6%; 95.4%, 92.9%, and 91.1% in group II; and 93.4%, 90.4%, and 87.7% in group III, respectively (p<0.001) (Supplementary Fig. 1B). We observed that the GS of group III recipients was the worst. Then we compared GS among the different grades of ACLF in every group. In group I, there was no difference (p=0.85). There were significant differences among the four grades only in group II (p=0.014). And no difference was observed in group III (p=0.075) (Fig. 3).

4. Post-transplantation mortality

First, we analyzed cause of death among the different grades of ACLF in all patients. Cardio/cerebral disease, infection, and malignancy were found to be significantly different between the four grades (Table 2). Then, we analyzed cause of death among the grades in every group. Interestingly, there were no significant differences among

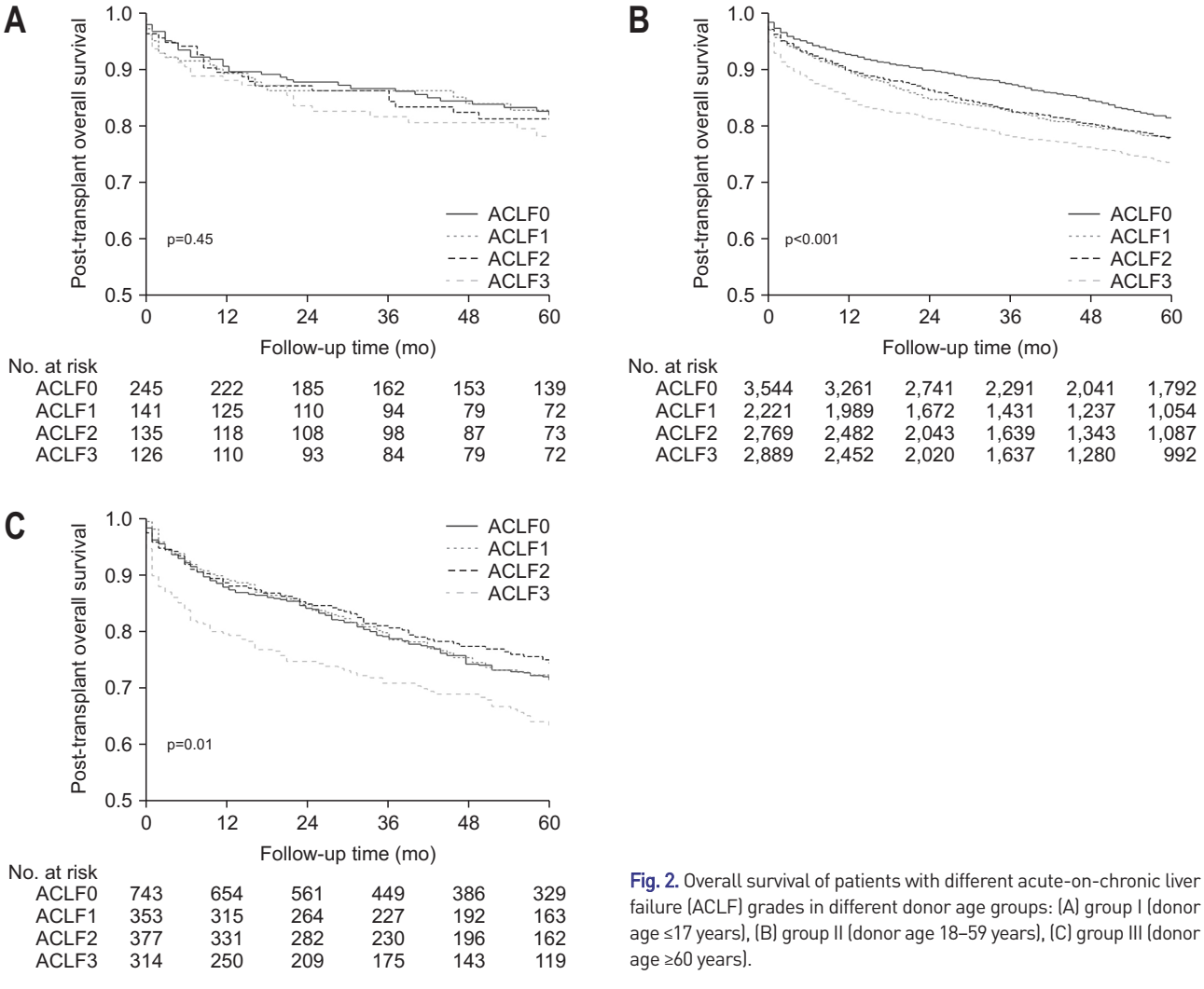
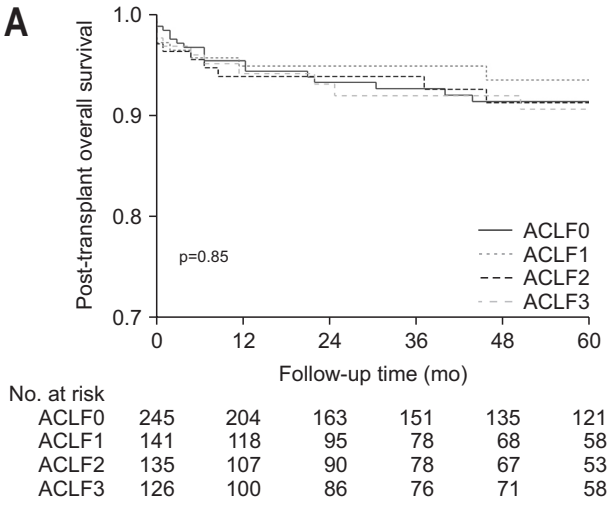
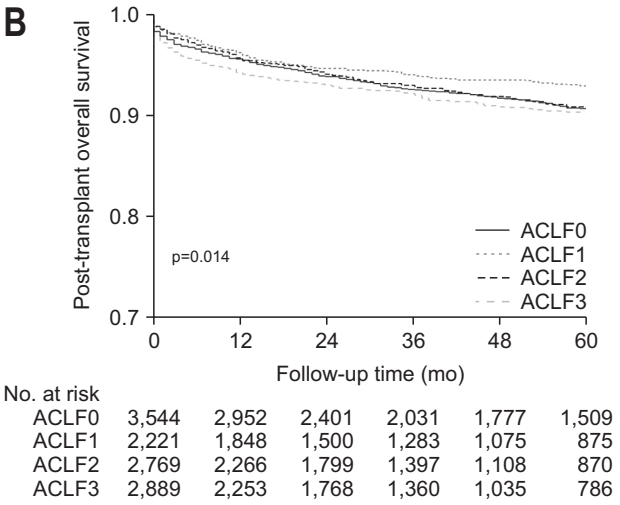


Fig. 2. Overall survival of patients with different acute-on-chronic liver failure (ACLF) grades in different donor age groups: (A) group I (donor age ≤17 years), (B) group II (donor age 18–59 years), (C) group III (donor age ≥60 years).





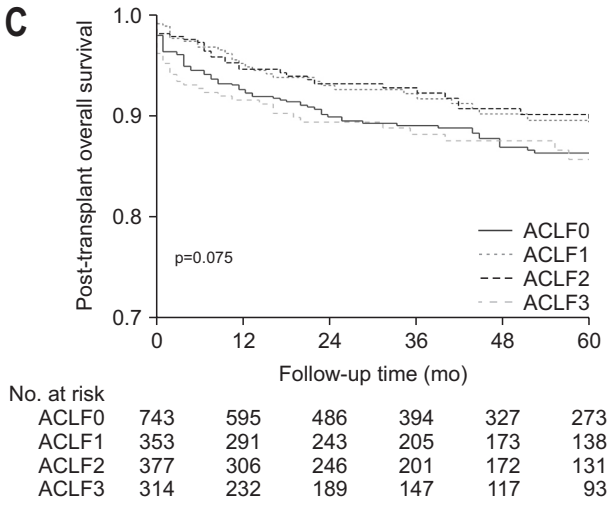


Fig. 3. Graft survival of patients with different acute-on-chronic liver failure (ACLF) grades in different donor age groups: (A) group I (donor age ≤17 years), (B) group II (donor age 18–59 years), (C) group III (donor age ≥60 years).

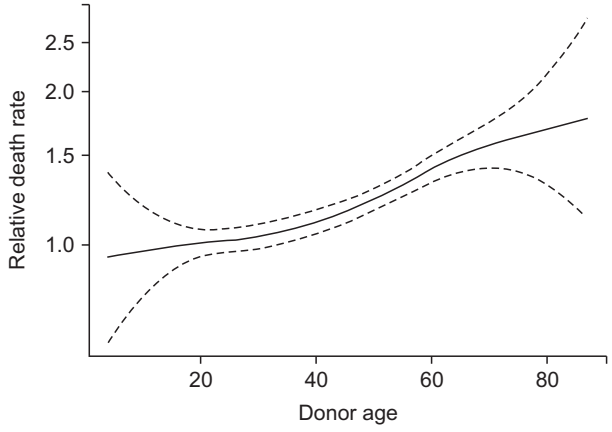


Fig. 4. Cubic spline curve analysis of relative death rate according to donor age.

the four grades in group I; and in group II, cardio/cerebral disease, organ failure, infection, and malignancy were to be found statistically different among the four grades; in group III, only cardio/cerebral disease was statistically different (p=0.017) (Supplementary Table 1).

5. Univariate analysis for OS

Then, in order to study the potential risk factors for recipient OS, we performed a univariate analysis. Donor age, cold ischemia time, organ share, cause of death and recipient age, KPS, race, underlying liver diseases, diabetes, Model for End-Stage Liver Disease score, and ACLF grade were all found to be significantly related to the OS. Detailed information was shown in Supplementary Table 2. We also performed univariate analysis in each donor age group, detailed information was shown in Supplementary Tables 3-5.

6. Multivariable analysis for OS

The multivariable Cox regression analysis revealed that donor age, cause of death, cold ischemia time and recipient age, race, underlying liver diseases, diabetes, KPS, and ACLF grade were all independent predictors of OS. Detailed information was shown in Table 3. Similarly,

Table 2. Post-Transplant Mortality in All Recipients

Variable	ACLF-0 (n=4,532)	ACLF-1 (n=2,715)	ACLF-2 (n=3,281)	ACLF-3 (n=3,329)	p-value
Graft failure	112 (2.47)	66 (2.43)	75 (2.29)	76 (2.28)	0.929
Cardio/cerebral disease	136 (3.00)	103 (3.79)	114 (3.47)	160 (4.81)	<0.001
Organ failure	145 (3.20)	104 (3.83)	114 (3.47)	143 (4.30)	0.069
Hemorrhage	25 (0.55)	24 (0.88)	22 (0.67)	31 (0.93)	0.183
Infection	129 (2.85)	82 (3.02)	112 (3.41)	147 (4.42)	0.001
Malignancy	129 (2.85)	70 (2.58)	55 (1.68)	59 (1.77)	0.001
Others	336 (7.41)	212 (7.81)	223 (6.80)	255 (7.66)	0.435

Values are presented as number (%). The number of organ failures determined ACLF grade.
ACLF, acute-on-chronic liver failure.

Table 3. Multivariable Analysis of Predictors for Overall Survival

Variable	HR (95% CI)	p-value
Donor age (reference group I)*		<0.001
Group II	1.081 (0.906–1.290)	0.387
Group III	1.412 (1.158–1.721)	0.001
ACLF grade (reference ACLF-0)†		<0.001
ACLF-1	1.088 (0.980–1.207)	0.114
ACLF-2	1.074 (0.965–1.196)	0.188
ACLF-3	1.353 (1.215–1.506)	<0.001
Recipient age	1.016 (1.012–1.020)	<0.001
Recipient race (reference white)		<0.001
Black or African American	1.225 (1.097–1.367)	<0.001
Asian	0.638 (0.504–0.806)	<0.001
Hispanic/Latino	0.798 (0.714–0.891)	<0.001
Others	0.936 (0.682–1.286)	0.683
Underlying liver diseases (reference HCV)		<0.001
ALD	0.748 (0.677–0.826)	<0.001
NASH	0.827 (0.743–0.922)	0.001
Others	0.759 (0.691–0.835)	<0.001
Recipient diabetes	1.234 (1.137–1.339)	<0.001
Donor cause of death (reference anoxia)		<0.001
Cerebrovascular/stroke	1.148 (1.047–1.259)	0.003
Head trauma	0.947 (0.861–1.041)	0.26
CNS tumor	1.011 (0.557–1.835)	0.97
Others	0.801 (0.603–1.064)	0.126
KPS (reference KPS I)		<0.001
KPS II	0.842 (0.770–0.920)	<0.001
KPS III	0.676 (0.591–0.774)	<0.001
Cold ischemia time	1.031 (1.020–1.043)	<0.001

HR, hazard ratio; CI, confidence interval; ACLF, acute-on-chronic liver failure; HCV, hepatitis C virus; ALD, alcoholic liver disease; NASH, non-alcoholic steatohepatitis; CNS, central nervous system; KPS, Karnofsky Performance Status.
*Group I: donor age ≤17 years; group II: donor age 18–59 years; group III: donor age ≥60 years; †The number of organ failures determined ACLF grade.

we performed a multivariable analysis in each donor age group. In group I, only recipient age and diabetes were the independent predictors for OS. In group II, recipient variables including age, KPS status, race, underlying liver diseases, diabetes as well as ACLF grades, and donor variables including cold ischemia time, donation after cardiac death, and cause of death were independent predictors, which were similar to the multivariable analysis in the entire cohort. In group III, although ACLF grade was associated with OS in the univariate analysis, it was not independently associated with OS in the multivariable analysis. Recipient age, KPS status, race, underlying liver diseases as well as donor gender were independent predictors in group III. The detailed information on univariate and multivariable analysis were depicted in Supplementary Table 6.

7. OS and GS in four donor-recipient age matched groups

We firstly compared OS among different ACLFs in the four donor-recipient age matched groups. The 5-year OS rates were 83.2% in ACLF0, 81.2% in ACLF1, 80.3% in ACLF2, and 76.9% in ACLF3, respectively in young to young group (p<0.001); 79.0% in ACLF0, 72.1% in ACLF1, 72.5% in ACLF2, and 65.6% in ACLF3 in young to elderly group (p<0.001); 73.6% in ACLF0, 75.7% in ACLF1, 76.3% in ACLF2, and 66.8% in ACLF3 in elderly to young group (p=0.11); and 70.0% in ACLF0, 66.5% in ACLF1, 73.3% in ACLF2, and 56.1% in ACLF3 in elderly to elderly group (p=0.037) (Supplementary Fig. 2). There were statistical differences in young to young group, young to elderly group, elderly to elderly group. However, no significant difference was observed in elderly to young group. Detailed information was shown in Supplementary Table 7. We then analyzed GS in the same way. Only in young to young group, we found statistical differences, with 5-year GS rates at 90.0% in ACLF0, 92.4% in ACLF1, 90.1% in ACLF2, and 89.8% in ACLF3 (p=0.042). There were no statistical differences in young to elderly group with 5-year GS rates at 92.9% in ACLF0, 94.6% in ACLF1, 93.6% in ACLF2, and 92.2% in ACLF3 (p=0.45) and in elderly to young group with 5-year GS rates at 82.2% in ACLF0, 88.2% in ACLF1, 88.9% in ACLF2, and 85.2% in ACLF3 (p=0.11) as well as in elderly to elderly group with corresponding 5-year GS rates at 92.7% in ACLF0, 91.5% in ACLF1, 93.5% in ACLF2, and 87.4% in ACLF3 (p=0.27) (Supplementary

Fig. 3). Detailed information was shown in Supplementary Table 8.

8. Cubic spline curve analysis of relative death rate according to donor age

The restricted cubic spline curve showed that relative death rate increased linearly with increasing donor age in all patients (Fig. 4). Then, we evaluated the relationship between relative death rate and donor age among every ACLF grade. In ACLF0, the trend was the same in all patients. In ACLF1, it remained the same until age 20 and decreased between age 20 to 40; in ACLF2, it decreased up to age 30 and then increased; and in ACLF3, the trend was the same as ACLF0 (Supplementary Fig. 4).

9. Baseline characteristics, OS and GS adjusted by IPTW

To balance the baseline variables, we conducted the IPTW analysis. After IPTW adjustment, we could observe that the differences in baseline characteristics among the three age groups were largely avoided and the standardized mean difference were <10% (Supplementary Table 9). We then conducted the IPTW-adjusted survival analysis firstly in the entire cohort, and then in different donor age groups. We found statistical difference in OS among the three donor age groups ($p<0.001$). And the survival rate of group III recipients was worse than that of the other two groups. GS among the three donor age groups was similar to the OS ($p<0.001$) (Supplementary Fig. 5). Then we compared OS among the ACLF grades in every donor age group. In group I, there was no statistically significant differences among the four grades ($p=0.62$). However, we observed statistically significant differences in group II ($p<0.001$) and group III ($p<0.01$) (Supplementary Fig. 6). For GS among ACLF grades in every donor age group, we observed statistically significant differences only in group II ($p=0.017$) and no difference in group I ($p=0.77$) and group III ($p=0.059$) (Supplementary Fig. 7).

DISCUSSION

In our study, we demonstrated that OS and GS in LT in patients with ACLF differed with age. Although the actual survival differences were minimal among the three groups at 2 years post-transplant, the influence of donor age on OS became more substantial with time. There was some difference in GS but this was minimal between groups I and II.

We also analyzed the different effects of donor age on OS and GS with different ACLF grades in every group. In group I, there was no statistically significant difference in OS among the four grades. That is, a younger donor age meant a smaller effect of ACLF severity on recipient survival. In terms of GS, a significant difference was only seen in group II. Indeed, the differences of actual survival were minimal among the four grades. This might be due to the large cohort of transplantation recipients, which might not necessarily mean it was clinically relevant.[15]

Other studies found that advanced donor age potentially predicted graft loss and a worse post-transplant outcome.[4,16-22] They showed that a donor age as young as 40 affected post-transplant mortality, and that this increased progressively thereafter. Reports from the European Liver Transplant Registry and the SRTR have suggested that donor age greater than 40 years was associated with decreased 3-month GS.[23] They also suggested that older donor age impacted early mortality after transplantation.[4,22] However, some results have been reported that the 5-year survival rates of older donors exceeding 70% after transplantation in most cases, similar to younger donors.[4,5,24] And using elderly liver donor can achieve good outcomes in short-term and midterm rates of survival.[25] Goldaracena *et al.*[24] suggested that a donor age over 50 or even 60 had little effect on survival after living donor LT.[4,26-29] Overall, there was no widely accepted view about the limit of donor age in LT. In our study, in all, the 5-year survival rate of group III was 71.4%, proving that recipients who accept donors over 60 years old can also achieve favorable transplantation prognosis. And our current study investigated the influence of donor age on the transplant prognosis, with a specific focus on recipients with different ACLF grades. We found that in group II, statistical differences existed among different ACLF grades. In the group I, there was no statistical difference. And in the group III, the prognosis of recipients with ACLF0, 1, and 2 grades was similar, but that of recipients with ACLF3 grade was obviously worse.

For IPTW-adjusted OS and GS analysis, we observed similar results with those before matching. On the other hand, the results based on IPTW analysis also needed to be interpreted with caution. Because after IPTW, the sample size in each group was reduced, possible because of the loss of patients due to unsuitable match during matching. This would lead to patient information loss and artificial bias. So the results after IPTW should be analyzed together with multivariable analysis in the entire cohort.

Next, we analyzed cause of recipient death after transplantation, especially among the four ACLF grades. Significant differences were observed in cardio/cerebral disease, infection and malignancy in different ACLF grades. When divided into three groups according to donor age, in group II the proportion of patients who died of cardio/cerebral

disease, organ failure and infection were higher in ACLF3. However, the number of patients who died due to malignancy was higher in ACLF0 but lower in ACLF3. These may be related to underlying disease and medical conditions in ACLF3 patients.

This study also identified independent risk factors associated with reduced long-term survival following LT: donor age, cause of death, cold ischemia time and recipient age, race, underlying liver diseases, diabetes, KPS, and ACLF grade. Two previous studies hypothesized that long-standing ACLF could induce immune suppression, influencing OS and GS.[30,31] And ACLF patients with systemic inflammation had a high chance of developing sepsis, leading to multiple organ failure.[32] Additionally, sepsis was a common driving factor of ACLF and might aggravate immune suppression through bone marrow suppression.[30,33]

KPS, a subjective "eyeball" assessment of the overall performance status of patients, was recently shown to be a predictor of transplant waitlist mortality.[34] Thuluvath *et al.*[35] believed that KPS scores were good surrogate markers of the overall physical and mental status of LT recipients. The OS rate of patients with high KPS score was better than that of patients with low KPS score.[34] Moreover, KPS score would affect the intubation time, hospitalization time and the incidence of pulmonary infection.[36] This was similar to our results, KPS would affect the prognosis of LT patients.

Longer cold ischemia time was associated with higher graft loss rate, higher primary non-function rate, longer post-transplant hospitalization, and early higher serum total bilirubin levels after transplant.[37] The ability of old donor liver to adapt to ischemia was poor, and the influence of cold ischemia time might be more serious.[22] In recent years, many studies explored ways to shorten cold ischemia time, thus to reduce ischemia-reperfusion injury and improve the prognosis of transplantation.

With the development of people's living standards, the prevalence of type 2 diabetes mellitus (DM), one of the types of DM, has increased significantly in recent decades, resulting in the coexistence of DM and the prevalence of chronic liver disease.[33,38] Like many other studies, our study showed DM in candidates was a significant risk factor leading to increased mortality of ACLF patients. Sarcopenia caused by malnutrition, protein consumption, and chronic inflammation in chronic liver disease was related to DM and influenced the prognosis of ACLF. Also, sarcopenia was related to the progression of liver cirrhosis in ACLF patients, which was more obvious in young patients.[39] Therefore, it is vital to prevent and control infection, give adequate nutritional support to patients with concurrent DM, and control DM in patients with ACLF.[38]

In order to further investigate the relationship between donor age and liver transplant outcomes, we performed univariate and multivariable analysis in each donor age group. In different donor age groups, we observed different predictors for OS, which was valuable for us to understand the different outcomes in these groups. And the results needed to be interpreted with caution, because patients in group II made up the majority of the current cohort, so the multivariable analysis in this group was mostly similar to that in the entire cohort. And due to the relatively small number in group I and group III, the multivariable analysis in these two groups needed to be validated in further studies.

With regard to OS among the four grades of ACLF in the four donor-recipient age matched group, young to young group, young to elderly group, elderly to elderly group were found statistically different. From these four figures (Supplementary Fig. 3), we could see that the prognosis of ACLF3 is the worst. If we compared the four matched groups, the prognosis of ACLF3 in the elderly to elderly group was the worst. For other grades, the difference was relatively insignificant.

Lastly, we used a cubic spline curve to analyze the influence of donor age on mortality. There was no doubt that elderly donor liver could increase recipient death rate after transplantation. As a result, reasonable allocation of the limited quantity of donor livers was difficult. However, since different ACLF grades were affected differently by donor age, this could inform allocation protocols.

Overall, our current study observed that different donor ages have different effects on recipients with different ACLF grades. The prognosis of patients with ACLF0-2 grade who received elderly donor livers had comparable outcomes with those who received young ones. However, the prognosis of patients with ACLF3 who received young donor livers was significantly better than those who received elderly ones. Relatively speaking, accepting a young donor liver may achieve a better prognosis, but for patients with ACLF3, it is not always possible to get a young donor. Previous study by Sundaram *et al.*[40] has demonstrated that patients with ACLF3 at the time of listing have greater 14-day mortality than those listed as status 1a. In this case, if patients with ACLF3 could accept an elderly donor, they would also get survival benefits compared with refusing an elderly donor liver in order to wait for a younger donor liver and losing the transplant opportunity. So in the current status of organ shortage, in order to obtain better transplant prognosis, donor allocation and recipient selection process should be carefully evaluated under different situations with regard to recipients with different ACLF grades in the clinical practice.

Our study has several inherent limitations due to the

retrospective nature of the SRTR database. Firstly, there is a risk of misclassification at listing. For example, some patients with renal failure might be classified as ACLF0. This is possibly due to the factor that they had compensated cirrhosis, and had no record of ascites or hepatic encephalopathy in the database.[29] Also, hepatic encephalopathy is a subjective assessment variable, which would also lead to misclassification. Moreover, the SRTR database did not have records of decompensating events such as variceal bleeding or bacterial infection, which some patients with renal failure would have. Secondly, due to such limitation of the SRTR database, our study takes obligatory use of vasopressors as a marker for circulatory failure, and mechanical ventilation for respiratory failure, as the SRTR database did not have recorded variables such as mean arterial pressure, the dose of vasopressors or partial pressure of oxygen/fraction of inspired oxygen, oxygen saturation/fraction of inspired oxygen. On the one hand, the indication for mechanical ventilation is not clear, and certain patients may have been mechanically ventilated for altered mental status to protect their airways; on the other hand, those patients with severe lung injury diagnosed as respiratory failure may not have received intubation treatment at the time of LT. Similarly, the use of vasopressors does not equate to circulatory failure.[12] Thirdly, we could not analyze the other important donor related factors such as severity of donor liver steatosis, detailed donor past medical history such as diabetes or hypertension control, which were identified as important predictors for prognosis in previous literature but not included or data incomplete in the SRTR. Fourthly, as living donor LT constituted only a small percent of the total transplant population in the current study, our results needed to be interpreted with caution, which should be largely applied in deceased donor LT practice. We admitted the potential risk of introduced bias. Nonetheless, our study has provided the most comprehensive analysis of the effect of donor age on patients with different ACLF grades to date, based on the availability of large sample size in the SRTR database, which could provide detailed information for donor allocation in clinical practice. Further prospective studies based on precise assessment of ACLF grade through single center as well as multicenter analysis are needed to validate those findings.

In conclusion, our study demonstrated that elderly donor age was associated with decreased OS in ACLF recipients following LT. In terms of GS, the influence was less obvious. More attention should be paid to patients' conditions. But in different ACLF grade, it had different situations. These findings may help decision-making with regards to marginal donor allocation and recipient selection to achieve better liver transplant outcomes. In the future, more prospective studies could be performed to investigate the effect of donor age, to further expand the donor pool and benefit more patients.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Study concept and design: J.Z. Data acquisition: Z.H. Data analysis and interpretation: J.Z., D.Y., S.R. Drafting of the manuscript: J.Z., D.Y., J.D., T.Z. Critical revision of the manuscript for important intellectual content: Z.C., S.Z. Statistical analysis: J.Z., F.X., H.Z. Obtained funding: Z.H., J.Z., Y.Z. Administrative, technical, or material support; study supervision: J.Z., Y.Z., Z.H. Approval of final manuscript: all authors.

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SUPPLEMENTARY MATERIALS

Supplementary materials can be accessed at https://doi.

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DATA AVAILABILITY STATEMENT

The data reported here have been supplied by the Minneapolis Medical Research Foundation, the contractor for the Scientific Registry of Transplant Recipients (SRTR). The interpretation and reporting of these data are the responsibility of the authors and should in no way be seen as an official policy of or interpretation by the SRTR or the U.S. Government.

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