

# Adult Living Donor Liver Transplantation for Acute-on-Chronic Liver Failure in High-Model for End-Stage Liver Disease Score Patients

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**The large volume of adult living donor liver transplantations (ALDLTs) at our center affords a unique opportunity to examine the impact of acute-on-chronic liver failure (ACLF) among high-Model for End-Stage Liver Disease MELD score patients. From February 1998 to March 2010, 1958 cirrhotic recipients were analyzed to study the relationship between MELD scores and ALDLT outcomes. A total of 327 high-MELD score recipients were categorized into ACLF and non-ACLF groups, and their outcomes were compared. The 5-year graft and patient survival in the high-MELD group were 75.2% and 76.4%, respectively, which were significantly worse than the low and intermediate MELD groups. The presence of ACLF associated with higher MELD scores appeared to be the dominant factor responsible for the inferior results of patients with MELD score of 30–34 points. The 5-year graft survivals in the ACLF group was 70.5% and in the non-ACLF group it was 81.0% ( $p = 0.035$ ). Therefore, ALDLT should be performed as soon as possible in high-MELD score patients prior to ACLF development. Moreover, ACLF patients should be separately categorized when analyzing the outcomes of ALDLT. ALDLT for ACLF patients should not be discouraged because favorable outcomes can be expected through timely ALDLT and comprehensive management.**

**Abbreviations:** ACLF, acute-on-chronic liver failure; ALDLT, adult living donor liver transplantation;

DDLT, deceased donor liver transplantation; GRWR, graft-to-recipient weight ratio; HCC, hepatocellular carcinoma; HV, hepatic vein; ICU, intensive care unit; INR, international normalized ratio; LDLT, living donor liver transplantation; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; RBC, red blood cell; UNOS, United Network for Organ Sharing

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## Introduction

Adult living donor liver transplantation (ALDLT) for high-Model for End-Stage Liver Disease (MELD) scores patients has been controversial due to concerns about poor outcomes. In 2002, the New York State Committee on Quality Improvement in Living Liver Donation recommended that living donor liver transplantation (LDLT) for high-MELD score patients with more than 25 points should be prohibited (1). However, ALDLT for high-MELD score patients has been performed in East Asia, including Korea, Japan, Taiwan, and Hong Kong because it is the only solution to save recipients due to a scarcity of deceased donors. However, high-MELD score patients with over 30 points are more likely to require intensive care unit (ICU) stay, ventilator support, renal replacement therapy, and vasopressor treatment before transplantation. In addition, intraoperative transfusion requirements and vasopressors use are also significantly higher in high-MELD score patients than low-MELD score patients (2). Preoperative high-MELD score patients were associated with postoperative graft failure following LDLT (3), and post-LDLT survival was significantly different according to United Network for Organ Sharing (UNOS) status despite no difference in the MELD score (4). In contrast, high MELD scores did not impact graft and patient survival in reports from a few well-known large LDLT centers (5–7).

One possibility for these conflicting reports is related to the number of acute-on-chronic liver failure (ACLF) patients, characterized by decompensation from an underlying chronic liver disease associated with organ failure that carries a high short-term mortality.

At our institution, many ALDLTs for ACLF patients have been performed due to the scarcity of deceased organ donation in Korea. We have not applied a different liver transplantation (LT) indication between LDLT and deceased donor liver transplantation (DDLT) in contrast to the UNOS recommendation for LDLT in 2002. The reported LDLT outcomes from a few well-known LDLT centers describing no survival differences between low- and high-MELD score patients at the time of transplantation are unconvincing results compared to ours, which are the largest experiences in the world. In this preliminary study, we investigated the relationship between the recipient MELD scores and ALDLT outcomes of 1958 recipients with cirrhosis (confirmed by explanted liver histology). We excluded 111 fulminant hepatic failure patients from a total of 2069 primary ALDLTs performed at Asan Medical Center in Seoul, Korea between February 1998 and March 2010. We analyzed 327 recipients with a high MELD score ( $\geq 30$ ) after categorizing them according to the consensus definition of ACLF by the World Congress of Gastroenterology (8,9).

## Materials and Methods

We retrospectively analyzed our prospective database containing all ALDLTs performed on chronic liver disease patients at our institution since February 1998. Fulminant liver failure patients without cirrhotic liver pathology on explanted liver and retransplantation were excluded. All patients were followed up regularly by the same team of surgeons. No patients were lost to follow-up. The last census date for this study was June 30, 2015. This study was approved by the Institutional Review Board of our institution. All living donors were voluntary and altruistic. A total of 70% of all the donors were male with a median donor age of 30 years (range, 18–62). The type of liver graft varied to satisfy the metabolic demands of the cirrhotic recipients, including the right hemiliver ( $n = 1519$ , 77.6%), left hemiliver ( $n = 159$ , 8.1%), and dual grafts using two left hemilivers or a combination of the right and left hemiliver ( $n = 280$ , 14.3%). Venous drainage was reconstructed to avoid graft dysfunction related to venous congestion in 95.7% of the cases ( $n = 1874$ ). In 4.3% of the cases ( $n = 84$ ), the right lobe graft was not reconstructed due to the negligible size of middle hepatic vein (HV) tributaries with minimal congestion. We have applied strict donor selection criteria, particularly regarding the right hemiliver donation in consideration of donor safety. The minimally accepted expected remnant liver volume should be individualized from 30% to 35% according to the donor age and the degree of steatosis. Healthy volunteer donors aged up to 55 years and with less than 30% steatosis were possible candidates for right hemiliver donation (10). Currently, the degree of steatosis in the donor liver is primarily evaluated by nonenhanced plain computed tomography, and a preoperative liver biopsy is performed selectively (11). All ACLF patients, except those with full-blown sepsis, were registered for ALDLT. Preoperatively, we attempted to satisfy the 1% expected graft-to-recipient weight ratio (GRWR) if possible, using a living liver graft with minimal steatosis from a young donor. Otherwise, dual-graft LDLTs in consideration of donors' liver volume, hepatic steatosis, and age were often performed to meet the more stringent conditions compared to those for non-ACLF patients (12). However, under inevitable situations considering the available donors, ALDLT was also performed for ACLF patients when an available liver graft was expected to have the minimum 0.8% GRWR and minimal steatosis from a young donor. Detailed descriptions of our

institutional donor and recipient evaluation process, surgical techniques, and outcomes are published in other reports (10–23).

### ACLF versus non-ACLF

The MELD score was calculated purely based on the liver disease severity at the time of the transplant. As a preliminary study before the comparison of ACLF versus non-ACLF using our collected database, all 1958 ALDLT patients with cirrhosis displayed on the explanted liver pathology were stratified into three groups according to the MELD score: low MELD group,  $\leq 19$ ; intermediate MELD group, 20–29; high MELD group,  $\geq 30$ ; and the overall survival rates were compared among the MELD groups.

High-MELD score patients ( $\geq 30$ ) were categorized into the ACLF and non-ACLF group according to the consensus definition of the World Congress of Gastroenterology in 2014 (8,9). We used the cut-off levels of The Chronic Liver Failure Consortium organ failure score described by Bernal et al and Jalan et al (8,9) to categorize specific organ failure. A score of 3 is the definition of organ failure for each system, except for the kidney, for which a score of 2 or more is the definition. However, in the case of coagulation failure, we consider it to be one of the findings of liver failure itself and it was excluded for conditions of extrahepatic organ failure (Table S1). The total bilirubin and creatinine levels were based on  $\mu\text{mol/L}$  in the table and we used the cut-off levels after a conversion to mg/dL due to the different units of those levels at our institution. The cut-off levels are greater than 12.1 and 1.98 mg/dL, respectively. Hence, the liver failure was defined by the total bilirubin ( $>12.1$  mg/dL) and/or international normalized ratio ( $\geq 2.5$ ).

### Assessment of transplant outcomes

The surgical outcomes were measured by the intraoperative time and transfusion amount, postoperative peak level of biochemical markers depicting hepatocyte injury and liver function (aspartate aminotransferase [AST], alanine aminotransferase [ALT], and total bilirubin), the length of ICU and hospital stay, posttransplant complications (e.g. medical and technical complications), and the necessity of a reoperation. Regarding the posttransplant complications, when one of the recipients exhibited multiple complications, the most important and severe Clavien-Dindo complication grade (24) affecting the recipient's outcome was recorded for simplification of the analysis. The long-term transplant outcome was measured by the actuarial graft and patient survival at 1, 3, and 5 years.

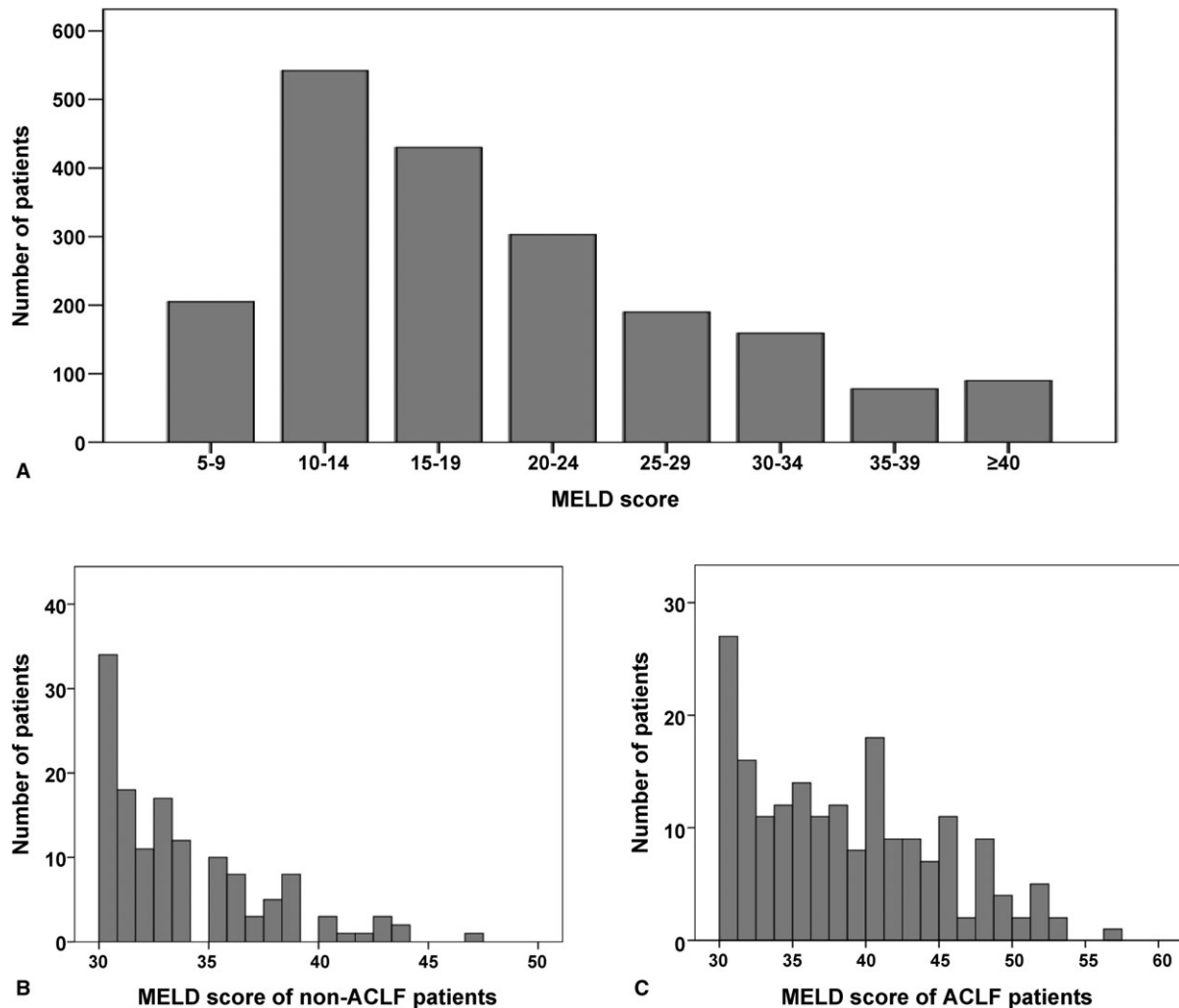
### Statistical analysis

Statistical analysis was performed using the IBM SPSS Statistics 21 program. All values are expressed as the means  $\pm$  standard deviation. The categorical variables were compared with a Fisher's exact test, and the continuous variables were compared with a Student's *t*-test. We used the Kaplan–Meier method with a log-rank test for the analysis of graft and patient survival. The variables reaching statistical significance via the univariate analysis were then included in the multivariate analysis. In the multivariate analyses, we used the Cox proportional hazards regression method with a stepwise procedure to determine the survival rates when a *p*-value was  $\leq 0.1$  in the univariate analysis. A *p*-value  $\leq 0.05$  was considered to be significant.

## Results

### Outcome of ALDLT according to the MELD scores

The MELD scores at the time of the transplant ranged from 6 to 57 (mean,  $19.6 \pm 9.5$ ). A total of 1149 (58.9%)



**Figure 1: Distribution of the MELD score.** (A) Indicates the 1958 adult living donor recipients, (B) indicates the high-MELD score non-ACLF patients, and (C) indicates the high-MELD score ACLF patients. MELD, Model for End-Stage Liver Disease; ACLF, acute-on-chronic liver failure.

and 488 recipients (24.7%) belonged to the low- and intermediate-MELD group, respectively, while 327 patients (16.4%) had a high MELD score ( $\geq 30$ ). The detailed distribution of the MELD score is depicted in Figure 1. The low-MELD group ( $\leq 19$ ) graft and patient survival rates at 1, 3, and 5 years were 92.7%, 87.6%, and 86.2%, and 93.3%, 88.1%, and 86.7%, respectively. The intermediate-MELD group (20–29) also had similar graft and patient survival rate at 1, 3, and 5 years as follows: 90.2%, 85.5%, and 85.1%, and 91.0%, 86.5%, and 86.1%, respectively. However, in the high MELD group ( $\geq 30$ ), the graft and patient survival rates at 1, 3, and 5 years were significantly worse than the low and intermediate MELD: 82.9%, 76.7%, and 75.2% ( $p = 0.002$ ), and 84.7%, 77.7%, and 76.4% ( $p = 0.003$ ), respectively (Figure S1).

**Demographics of the high-MELD ( $\geq 30$ ) score recipients**

The mean recipient age was  $46.7 \pm 8.8$  years, with 64.8% of all recipients being male. Among the recipients, hepatitis B virus (HBV) (79.5%) was the most common etiology of primary liver disease, followed by alcohol (8.6%). Hepatocellular carcinoma (HCC) was present in 10.7% of the recipients. The mean total bilirubin, creatinine, international normalized ratio (INR), and MELD score at the time of transplantation were  $30.5 \pm 13.5$  mg/dL,  $2.0 \pm 1.8$  mg/dL,  $3.2 \pm 1.5$ , and  $36.4 \pm 6.2$ , respectively. Pretransplant hepatic encephalopathy grade 3 and 4 (32.7%), hepatorenal syndrome with  $>2.0$  mg/dL (32.7%), hemodialysis (24.8%), ventilator support (20.8%), vasopressor (11.3%), and need for ICU stay (39.8%) were common features. The types of liver

**Table 1:** Clinical features of the high-MELD score recipients in adult living donor liver transplantation

	Total (n = 327)	Non-ACLF (n = 137)	ACLF (n = 190)	p
Age (years)	46.7 ± 8.8	45.8 ± 8.6	47.2 ± 8.9	0.173
Male	212 (64.8%)	87 (63.5%)	125 (65.8%)	0.440
Etiology, HBV	260 (79.5%)	110 (80.3%)	150 (78.9%)	0.773
Alcoholic	28 (8.6%)	11 (8.0%)	17 (8.9%)	
HCV	8 (2.4%)	1 (0.7%)	7 (3.7%)	
AIH	6 (1.8%)	3 (2.2%)	3 (1.6%)	
Wilson's	6 (1.8%)	3 (2.2%)	3 (1.6%)	
SBC	5 (1.5%)	3 (2.2%)	2 (1.1%)	
PBC	4 (1.2%)	2 (1.5%)	2 (1.1%)	
Others	10 (3.1%)	4 (2.9%)	4 (3.2%)	
HCC	35 (10.7%)	11 (8.0%)	24 (12.6%)	0.125
MELD score	36.4 ± 6.2	33.7 ± 3.8	38.4 ± 6.9	<0.001
Total bilirubin	30.5 ± 13.5 mg/dL	31.0 ± 10.4 mg/dL	30.1 ± 15.3 mg/dL	0.529
Creatinine	2.0 ± 1.8 mg/dL	1.1 ± 0.4 mg/dL	2.6 ± 2.2 mg/dL	<0.001
INR	3.2 ± 1.5	3.3 ± 1.2	3.1 ± 1.7	0.226
HEP grade 3, 4	107 (32.7%)	0 (0%)	107 (56.6%)	<0.001
HRS	130 (39.8%)	0 (0%)	130 (68.8%)	<0.001
Hemodialysis	81 (24.8%)	0 (0%)	81 (42.9%)	<0.001
Ventilator	68 (20.8%)	0 (0%)	68 (36.0%)	<0.001
Vasopressor	37 (11.3%)	0 (0%)	37 (19.5%)	<0.001
ICU-bound	130 (39.8%)	3 (2.2%)	127 (67.2%)	<0.001
Graft type, RL	233 (71.3%)	91 (65.9%)	142 (75.1%)	0.028
LL	33 (10.1%)	21 (15.2%)	12 (6.3%)	
Dual	61 (18.7%)	26 (18.8%)	35 (18.5%)	
Graft weight	691 ± 142 g	671 ± 148 g	705 ± 135 g	0.054
GRWR	1.0 ± 0.21%	1.0 ± 0.20%	1.0 ± 0.23%	0.231
Operation time	926 ± 201 min	935 ± 161 min	919 ± 226 min	0.580
Red blood cells	19.9 ± 15.8 U	17.2 ± 9.8 U	21.9 ± 19.0 U	0.014
Platelet	14.8 ± 9.1 U	14.9 ± 7.4 U	14.6 ± 10.3 U	0.771
Fresh-frozen plasma	25.8 ± 17.2 U	24.4 ± 12.3 U	26.9 ± 20.1 U	0.761
Cold ischemia	77.9 ± 28.3 min	78.0 ± 28.3 min	77.4 ± 28.1 min	0.673
Warm ischemia	45.0 ± 15.6 min	44.9 ± 15.7 min	45.5 ± 15.4 min	0.382

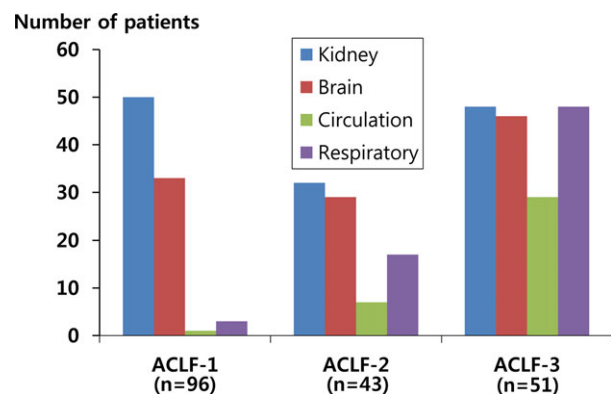
HBV, hepatitis B virus; HCV, hepatitis C virus; AIH, autoimmune hepatitis; ACLF, acute-on-chronic liver failure; SBC, secondary biliary cirrhosis; PBC, primary biliary cirrhosis; MELD, Model for End-Stage Liver Disease; INR, international normalized ratio; HEP, hepatic encephalopathy; HRS, hepatorenal syndrome; ICU, intensive care unit; HCC, hepatocellular carcinoma; GRWR, graft-to-recipient weight ratio; U, units; RL, right hemiliver; LL, left hemiliver; Dual, dual graft with two left livers or right and left liver

graft for ALDLT were the right hemiliver (71.3%), left hemiliver (10.1%), and dual grafts (18.7%). The mean weight of the liver graft was 691 ± 142 g with a mean GRWR of 1.0% ± 0.21%. The operation time from the skin incision to closure was 926 ± 201 min and the amount of red blood cell (RBC) transfusion was 19.9 ± 15.8 units (Table 1).

High-MELD score recipients were categorized as 137 (41.9%) non-ACLF and 190 (58.1%) ACLF patients, in which the ACLF group exhibited a significantly higher value for the MELD score, creatinine, INR and amount of RBC transfusion, as well as a higher frequency of hepatic encephalopathy 3 and 4, hepatorenal syndrome, preoperative intensive care unit-bound, use of hemodialysis, ventilator, and right hemiliver graft.

We subdivided the ACLF patients into ACLF-1, 2, and 3 according to the number of extrahepatic organ failures. ACLF-1 (n = 96) denotes one extrahepatic organ failure; ACLF-2 (n = 43) indicates a double extrahepatic organ

failure; and ACLF-3 (n = 51) means that three or more organs have failed. More detailed data concerning the combination of extrahepatic organ failures are depicted in Figure 2.

**Figure 2:** Types of extrahepatic organ failure by ACLF grade. ACLF, acute-on-chronic liver failure.

**Impact of the pretransplant status on graft survival in high-MELD score recipients**

We analyzed the impact of pretransplant variables on the posttransplant graft survival. In the univariate analysis, age  $\leq 59$  years, male sex, GRWR 0.8–0.99%, non-ACLF group, and the absence of HCC, hepatorenal syndrome, preoperative ICU-stay, and vasopressor use were associated with significantly improved 1-, 3-, and 5-year graft survival rates. However, in multivariate analysis, male

sex, absence of HCC, and the non-ACLF group revealed significantly improved survival rate with a hazard ratio of 1.84, 1.795, and 1.61, respectively (Table 2).

**Impact of ACLF on the short-term outcome**

The peak AST and ALT within 48 h of reperfusion were not different between the ACLF and non-ACLF group. The ACLF group stayed longer in the ICU during the posttransplant period than the non-ACLF group ( $15.2 \pm 16.2$  days

**Table 2:** Posttransplant graft survival according to the pretransplant variables

	Univariate analysis				Multivariate analysis		
	1-YSR (%)	3-YSR (%)	5-YSR (%)	p	HR	95% CI	p
Age							
$\leq 59$ years	82.9	77.7	76.4	0.005	1.92	0.97–3.79	0.060
$\geq 60$ years	70.6	52.9	47.1				
Sex							
Male	84.6	79.2	77.6	0.005	1.84	1.19–2.84	0.006
Female	75.3	66.7	65.4				
Etiology							
HBV	83.5	77.7	76.2	0.251			
Non-HBV	76.1	70.0	70.0				
HCC							
None	82.9	78.1	76.7	0.018	1.795	1.04–3.11	0.037
Yes	77.1	62.3	59.3				
ACLF							
None	89.8	82.5	81.0	0.035	1.61	1.03–2.50	0.035
Yes	76.8	72.1	70.5				
Graft							
RL	83.7	76.4	75.5	0.324			
LL	75.8	72.7	66.7				
Dual	82.0	77.0	77.0				
GRWR (%)							
$< 0.8$	81.8	66.7	63.6	0.010	1.06	0.77–1.47	0.729
0.8–0.99	89.5	85.1	84.2				
$\geq 1.0$	78.3	72.2	71.1				
HRS							
None	85.3	80.2	79.2	0.042	0.80	0.41–1.58	0.523
Yes	77.7	69.9	68.4				
HD							
None	84.6	78.0	76.4	0.204			
Yes	75.3	70.3	70.3				
HEP							
Grade 0, 1, 2	85.4	77.6	76.3	0.457			
Grade 3, 4	75.9	74.1	72.2				
Ventilator							
None	84.2	76.8	75.6	0.405			
Yes	75.0	73.5	72.1				
ICU stay							
None	87.3	80.7	79.2	0.017	0.76	0.42–1.39	0.376
Yes	74.6	70.0	68.4				
Vasopressor							
None	84.5	78.3	76.5	0.021	1.95	1.12–3.40	0.19
Yes	64.9	62.2	62.2				

Univariate analysis using the Kaplan–Meier method with log rank test, multivariate analysis using Cox proportional hazards regression method with a stepwise procedure. 1-,3-,5-YSR, 1, 3, and 5-year graft survival rate; HR, hazard ratio; CI, confidence interval; p, p-value; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; ACLF, acute-on-chronic liver failure; RL, right hemiliver; LL, left hemiliver; Dual, dual-graft with two left livers or right and left liver; GRWR, graft-to-recipient weight ratio; HRS, hepatorenal syndrome; HD, hemodialysis; HEP, hepatic encephalopathy; ICU, intensive care unit.



vs.  $9.5 \pm 10.3$  days,  $p = 0.008$ ); however, the total hospital days, including ICU stay after ALDLT, was not different between the two groups (ACLF  $48.2 \pm 32.2$  days vs. non-ACLF  $41.9 \pm 31.9$  days,  $p = 0.156$ ).

The frequency of total complications was similar between the ACLF and non-ACLF groups (74.7% vs. 70.8%,  $p = 0.446$ ). However, the ACLF group had a higher grade of complications categorized via the Clavien-Dindo classification ( $p = 0.018$ ) (24), as well as a higher hospital mortality (15.8% vs. 6.6%,  $p = 0.011$ ). Reoperation and retransplantation were performed more frequently in the ACLF group, but this did not reach significance ( $p = 0.064$  and 0.313, respectively) (Table S2).

Common technical complications of the ACLF group included bleeding from the operation fields requiring embolization or reoperation (29.6%), HV stenosis (21.0%), biliary complications including stricture and leakage (20.0%), hepatic artery complications including stenosis, dissection, thrombosis, and pseudoaneurysms (10.8%), and wound complications (7.4%). In the 30 cases of hospital mortality in the ACLF group, the cause of death was predominantly due to medical complications, such as pneumonia and acute rejection (23, 76.7%) rather than technical complications (7, 23.3%). Concerning technical complications, hepatic artery complications were the most common cause of hospital mortality.

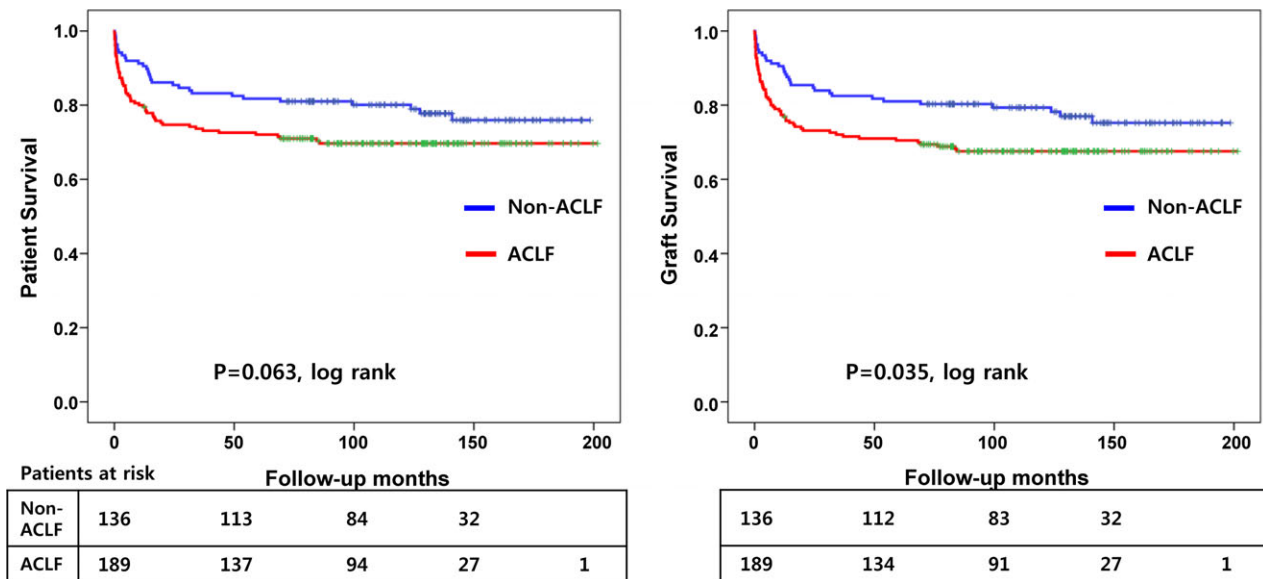
**Impact of ACLF on graft and patient survival**

When we analyzed the survival between the ACLF and non-ACLF groups, the posttransplant graft survival at 1, 3, and 5 years were significantly worse in the ACLF group (76.8%, 72.1%, and 70.5%, respectively)

compared to the non-ACLF group (89.8%, 82.5%, and 81.0%, respectively) ( $p = 0.035$ ), however, the patient survival at 1, 3, and 5 years were not statistically different between the ACLF group (79.5%, 73.6%, and 72.1%, respectively) and the non-ACLF group (90.5%, 83.2%, and 81.8%, respectively) ( $p = 0.063$ ) (Figure 3). Among the ACLF-1, -2, and -3 patients according to the number of extrahepatic organ failures, the 1-, 3-, and 5-year graft survival rates were 81.3%, 76.0%, and 75.0% for ACLF-1; 72.3%, 70.2%, and 68.0% for ACLF-2; and 76.0%, 71.5%, and 71.5%, for ACLF-3, respectively ( $p = 0.296$ ). ACLF-2 and -3 tended to exhibit a worse survival than ACLF-1, but this did not reach statistical significance.

**Prognostic interrelationship between ACLF and the MELD score**

To clarify the prognostic interrelationship between ACLF and the MELD score among high-MELD score patients, we performed an additional analysis after subgrouping the high-MELD score patients into a lower group ( $n = 169$ ) indicating a MELD score of between 30 and 34 points, and a higher group ( $n = 158$ ) indicating a MELD score of  $\geq 35$  points. The ACLF patients comprised 45 patients (32.8%) in the lower group and 124 patients (65.3%) in the higher group. In the higher group, the 1-, 3-, and 5-year graft survival between the non-ACLF and ACLF groups were 86.7%, 80.0%, and 75.6%, and 76.6%, 71.0%, and 69.4%, respectively ( $p = 0.289$ ). In the lower group, the 1-, 3-, and 5-year graft survival between the non-ACLF and ACLF groups were 91.3%, 83.7%, and 83.7%, and 77.3%, 74.2%, and 72.6%, respectively ( $p = 0.088$ ). In the multivariate analysis, the higher group did not exhibit any significant prognostic



**Figure 3: Survival differences between ACLF and non-ACLF recipients following ALDLT.** ACLF, acute-on-chronic liver failure; ALDLT, adult living donor liver transplantation.

**Table 3:** Multivariate analysis of graft survival in the high-MELD score patients depending on each subgroup

Variable	p-value	Hazard ratio	95% CI
Low MELD group (30–34 points)			
Age, ( $\geq 60$ years)	0.76	0.83	0.25–2.80
Sex (female)	0.20	1.34	0.86–2.07
HCC (present)	0.74	0.89	0.45–1.78
ACLF (present)	0.01	2.46	1.28–4.72
GRWR (0.8–0.99%)	0.70	1.15	0.56–2.38
GRWR ( $\geq 1\%$ )	0.70	1.15	0.56–2.36
HRS (yes)	0.89	1.05	0.54–2.02
ICU-bound (yes)	0.36	0.76	0.42–1.36
Vasopressor (yes)	0.17	0.54	0.22–1.31
High MELD group ( $\geq 35$ points)			
Age ( $\geq 60$ years)	0.22	2.03	0.66–6.23
Sex (female)	0.97	1.01	0.61–1.66
HCC (present)	0.31	0.65	0.29–1.48
ACLF (present)	0.93	0.97	0.48–1.95
GRWR (0.8–0.99%)	0.69	0.86	0.40–1.83
GRWR ( $\geq 1\%$ )	0.87	1.06	0.51–2.21
HRS (yes)	0.56	1.19	0.66–2.13
ICU-bound (yes)	0.98	0.99	0.59–1.66
Vasopressor (yes)	0.42	1.31	0.68–2.52

MELD, Model for End-Stage Liver Disease; CI, confidence interval; HCC, hepatocellular carcinoma; ACLF, acute-on-chronic liver failure; GRWR, graft-to-recipient weight ratio; HRS, hepatorenal syndrome; ICU, intensive care unit.

variables; however, the lower group was significantly affected by the presence of ACLF ( $p = 0.01$ ) (Table 3).

## Discussion

Since the implementation of the MELD system by the UNOS in February 2002, there has been an ongoing debate regarding the posttransplant outcome of high-MELD score patients in the series of DDLT (25–28). In 2005, Habib et al reported a conclusive outcome that the pretransplant MELD score was inversely correlated with posttransplant survival based on a larger study with a longer follow-up (29). In contrast, the prevailing opinion from a few well-known LDLT centers is that there is no correlation between the pretransplant MELD score and posttransplant survival despite some conflicting results (3–7). In light of our clinical experiences based on the largest ALDLT series in the world, the prevailing opinions conflict with ours and we performed the present study to determine the effect of MELD scores on the survival outcome of patients in a large single-center series of ALDLT. Furthermore, we aimed to investigate the reasons for the conflicting results of the reported LDLT series by an analysis of perioperative data and survival outcomes between ACLF and non-ACLF groups of high-MELD score recipients.

In our series, the high MELD ( $\geq 30$ ) group exhibited a significantly lower graft and patient survival rate than the

low and intermediate MELD groups. This might be a natural outcome because a high MELD score reflects the severity of the recipients' pretransplant illness. However, we achieved a minimum of 10% superior graft and patient survival in comparison with the DDLT series in the high MELD group (27–29). Timely ALDLT for the urgent high-MELD score patients at our institution played a substantial role for achieving a better outcome in the scarcity of deceased donor livers in Korea (30). The selection of donors displaying a good quality of liver graft with less steatosis and a median age of 30 years, as well as the sustained efforts to satisfy  $\geq 1\%$  GRWR using various graft types (e.g. single-graft ALDLT with right or left hemi-liver, or dual-graft ALDLT with two left hemi-livers or right and left hemiliver) made it possible to achieve unique and excellent survival outcomes for high-MELD score recipients (12,18). Innovations in the operative techniques and intensive perioperative care by the dedicated team members also resulted in a favorable outcome (10,31). In addition, the predominant etiology related to HBV (79.5%) might have an important role for achieving a better survival rate (6) because recipients with an HBV etiology had superior survival rates compared to the non-HBV etiology despite no statistical significance.

We have performed multiple ALDLTs for high-MELD score patients, and the presence of ACLF might be an important prognostic factor associated with the patient outcome. The definition was first established by the Asian Pacific Association for the study of liver disease (APASL) in 2009 (32), in which it was defined as "acute hepatic insult manifesting as jaundice (serum bilirubin  $>5$  mg/dL) and coagulopathy (INR  $>1.5$ ), complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease." The European and American Association for the study of liver disease (EASL) also proposed a different definition in 2011 (33), which defined it as an "acute deterioration of pre-existing, chronic liver disease, usually related to a precipitating event and associated with increased mortality at 3 months due to multi-system organ failure." The differences were resolved as part of a consensus meeting organized under the auspices of the World Congress of Gastroenterology, and a new definition was created as a distinct clinical entity in 2014 (9). Using this consensus definition of ACLF, we were able to categorize high-MELD score cirrhotic recipients who had undergone ALDLT into ACLF and non-ACLF groups, and analyze the clinical data. To our knowledge, this study is the first report demonstrating the impact of ACLF on the post-ALDLT outcome using a newly established consensus definition.

The ACLF group in our series comprised 51.8% high-MELD score recipients and the preoperative clinical data revealed a more severe clinical status than in the non-ACLF group. Moreover, the ACLF group required a larger amount of intraoperative RBC transfusion and had worse

short-term outcomes compared to the non-ACLF group. Considering the higher preoperative disease severity of ACLF, these are reasonable results. In the multivariate analysis, unexpectedly good outcomes in the men was related to a higher frequency of HBV-related liver cirrhosis (82.9%), which is associated with a better outcome after LT than other etiologies (6) in comparison to the female recipients (69.1%) ( $p = 0.008$ ); this was also related to relatively less severe sarcopenia, which has a poorer outcome (34,35). Although the presence of HCC unfavorably affected patient survival, the distribution and stage of the HCC patients was similar between ACLF and non-ACLF groups and we did not exclude HCC patients for the survival analysis between the two groups. Although hepatorenal syndrome, preoperative ICU stay, and vasopressor use were not significant prognostic variables in the multivariate analysis, the clinical importance was reflected by ACLF, which was a significantly worse prognostic factor in the multivariate analysis.

In contrast to the superior graft survival rate in the non-ACLF group, the patient survival rate was not significantly better because four out of seven patients in the ACLF group survived for a long period after retransplantation, despite the uncommon frequency; this offset the difference in the patient survival between the ACLF and non-ACLF groups.

Regarding the postoperative complications in ACLF patients, technical complications related to hospital mortality decreased further in the later period, but hepatic artery complications, which typically resulted from trauma to the arterial wall during hilar dissection under operative fields involving copious bleeding, were still important causes of hospital-related mortality. During the study period from February 1998 to March 2010, 21% of the high-MELD score patients underwent HV stenting following ALDLT due to suspicion of HV stenosis. During the later study period, the rate of HV stenting was decreased to approximately 9% following the introduction of HV plasty into the recipient side and further decreased less than 2% following the routine application of HV plasty in both the liver graft and recipient side in 2010 (36,37). The portal vein (PV) complication rates were low at approximately 2%, which was related to the introduction of an intraoperative cine-portogram since 2003 for recipients experiencing preoperative complications such as PV thrombosis and/or stenosis (38). When indicated (despite PV thrombectomy and/or plasty), PV stent placement is performed (39).

Regarding the prognostic interrelationship between the ACLF and MELD score, the presence of ACLF was not a significant prognostic factor in the higher MELD group ( $\geq 35$  points) but was a significant prognostic factor in the lower MELD group (30–34 points) after ALDLT in the multivariate analysis. In addition, when we excluded 190 ACLF recipients from total 1958 ALDLT recipients during the

study period, the posttransplant graft and patient survival at 1, 3, and 5 years in the high-MELD ( $\geq 30$  points) group did not differ from the graft and patient survival of the low- and intermediate-MELD groups (Figure S2). These findings are in line with the prevailing opinions of a few well-known LDLT centers (5–7). The conflicting worse outcome after ALDLT for the high-MELD score patients in our series could be explained by the high percentage of ACLF patients (58.1%) in the high-MELD ( $\geq 30$  points) group compared to a few well-known LDLT centers.

In conclusion, timely ALDLT using various graft types with good quality to satisfy the  $\geq 1\%$  GRWR for high-MELD score patients when there is a scarcity of deceased donor livers guaranteed excellent short-term and long-term survival rates. Considering the prognostic significance of the presence of ACLF in high-MELD score patients, particularly in the lower-grade group (30–34 points), ALDLT should be performed as soon as possible in high-MELD score patients prior to the development of ACLF. Moreover, ACLF patients should be categorized separately when analyzing the outcomes of ALDLT. In addition, ALDLT for ACLF patients should no longer be discouraged because favorable outcomes can be expected through performing timely ALDLT and comprehensive management.

## Author Contributions

Lee S-G, Moon D-B, Park G-C, Song G-W, Ha T-Y: Study conception and design; Moon D-B, Kang W-H, Jung D-H, Song G-W, Park G-C, Kim W-J, Cho H-D, Jwa E-K: Acquisition of data; Moon D-B, Lee S-G, Jung D-H, Kim W-J, Cho H-D, Jwa E-K, Kim H-J: Analysis and interpretation of data; Moon D-B, Lee S-G, Ha T-Y, Jung D-H, Song G-W, Kim H-J: Drafting of manuscript; Moon D-B, Lee S-G, Ha T-Y, Park G-C, Song G-W, Jung D-H, Kim H-J: Critical revision; Lee S-G, Moon D-B, Song G-W, Jung D-H: Final approval of the version to be published; Moon D-B, Lee S-G, Kang W-H, Park G-C: Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

## Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

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## Supporting Information

Additional Supporting Information may be found in the online version of this article.

**Figure S1: Overall survival following ALDLT according to MELD score.**

**Figure S2: Overall survival following ALDLT according to MELD score when excluding ACLF patients from the high-MELD score recipients.**

**Table S1:** Modified version of the Chronic Liver Failure Consortium organ failure score.

**Table S2:** Postoperative data according to the acute-on-chronic liver failure following adult living donor liver transplantation.