Digestive and Liver Disease 53 (2021) 1004–1010

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Liver, Pancreas and Biliary Tract

Predictors and outcome of emergent Liver transplantation for patients with acute-on-chronic liver failure

Ji Eun Kim[a], Dong Hyun Sinn[a,*], Gyu-Seong Choi[b,*], Jong Man Kim[b], Jae-Won Joh[b], Wonseok Kang[a], Geum-Youn Gwak[a], Yong-Han Paik[a], Moon Seok Choi[a], Joon Hyeok Lee[a], Kwang Cheol Koh[a], Seung Woon Paik[a]

[a] Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
[b] Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

ARTICLE INFO

Article history:
Received 8 October 2020
Revised 24 March 2021
Accepted 25 March 2021
Available online 27 April 2021

Keywords:
Acute on chronic liver failure
Deceased donor liver transplantation
Living donor liver transplantation
Model for end-stage liver disease score
Survival
Acute-on-chronic liver failure progression

ABSTRACT

Background and aims: Controversy exists over whether emergent liver transplantation (LT) should be performed for patients with acute-on-chronic liver failure (ACLF), especially for patients with multiple organ failure.

Methods: A total of 110 ACLF patients, defined by the European Association for the Study of the Liver (EASL) Chronic Liver Failure-Sequential Organ Failure Assessment (CLIF-SOFA) criteria were analyzed. The primary outcome was overall survival after ACLF diagnosis.

Results: During follow-up, 76 patients received LT (59 received deceased-donor LT and 17 patients received living-donor LT). The overall survival was better for patients who received LT than patients who did not (82.9% vs. 17.6%, $P < 0.001$). Among the 76 patients who received LT, the overall survival was not different according to ACLF grade at diagnosis (70.0%, 85.3%, and 84.4% at one-year for ACLF grades 1, 2, and 3, respectively, $P = 0.45$). The baseline model for end-stage liver disease (MELD) score and progression of the ACLF grade during the pre-transplant period were independent factors for survival after LT. The one-year survival rate was 92.3% for patients with baseline MELD scores of ≤ 32 without ACLF grade progression, whereas it was 33.3% for those with baseline MELD scores of > 32 and ACLF grade progression.

Conclusions: Emergent LT provided a significant survival benefit to ACLF patients, regardless of the baseline ACLF grade. Post-LT outcomes were associated with baseline MELD scores and ACLF progression during the pre-transplant period, which might be used in the emergent LT plan for patients presenting with ACLF.

1. Introduction

Liver transplantation (LT) is indicated for patients with acute liver failure and patients with end-stage liver disease (ESLD) when the limits of medical therapy have been reached [1,2]. Emergent adult living donor LT (LDLT) has been shown to improve the survival rate greatly in patients with acute liver failure [3]. Emergent deceased donor LT (DDLT) or living donor LT (e.g., within two days from living liver donor evaluation) can be considered for patients with acute-on-chronic liver failure (ACLF). However, the role of LT in patients with ACLF is controversial. ACLF is a syndrome characterized by the acute decompensation of chronic liver disease associated with organ failure that includes extrahepatic organ failure [4–6]. Although extrahepatic organ failure is not an absolute contraindication for LT, it does confer high risks for LT [7]. The reported one year survival rate of ACLF patients with multiple organ failures are 43∼46% [8,10], which was lower than the threshold classically accepted for LT (> 50% expected five-year survival post-LT) [9]. Donor livers are a scarce, life-saving resource. Hence, the posttransplant mortality risk should be considered in decisions to proceed with an emergent LT in very sick patients [11]. The low post-LT survival rates among ACLF patients with multiple organ failure suggest that ACLF patients with multiple organ failure need careful consideration to prevent futile or inappropriate LT.

Abbreviations: LT, liver transplantation; ACLF, acute-on-chronic liver failure; EASL, European Association for the Study of the Liver; CLIF-SOFA, Chronic Liver Failure-Sequential Organ Failure Assessment; MELD, model for end-stage liver disease; LDLT, living donor liver transplantation; UNOS, United Network for Organ Sharing; DDLT, deceased donor liver transplantation.

* Corresponding author.
E-mail addresses: sinndhn@hanmail.net (D.H. Sinn), gyuseong.choi@samsung.com (G.-S. Choi).

https://doi.org/10.1016/j.dld.2021.03.030
1590-8658/

In contrast, some studies found comparable or excellent outcome in ACLF patients with multiple organ failures [12,13], suggesting that emergent LT can be an option to improve the outcome of patients with ACLF and multiple organ failure if selected appropriately. Presently, where the sickest candidates are prioritized and no delisting criteria are given, identifying patients who may benefit from an emergent LT is a clinically unmet need [14]. This critical question is more challenging in the setting of living donor LT (LDLT), as the timing of LT can be selected by the doctor in LDLT [15]. Hence, in a region where LDLT is a major mode of LT, determining the optimal timing, selection, and delisting criteria for LT in patients with ACLF is needed. In this study, we analyzed patients with ACLF on LT waiting lists to identify factors that could be used to guide the management plans of patients with ACLF.

2. Methods

2.1. Study design, setting, and participants

This study was a retrospective cohort study performed at the Samsung Medical Center, Seoul, South Korea. We screened the LT waiting list between January 2014 and December 2018 ($n = 1989$) for potential study participants. Among them, we included adult patients with ACLF defined by the European Association for the Study of the Liver (EASL)-CLIF without malignancy or prior LT ($n = 130$). Among the eligible participants, 20 patients were excluded due to early referral to other hospitals. Finally, 110 patients were analyzed in this study (Supplementary Fig. 1). The detailed LT evaluation process in our institution are described in the Supplementary Method. The study protocol was reviewed and approved by the Institutional Review Board at Samsung Medical Center. As the study used only de-identified data routinely collected during hospital visits, the requirement to obtain informed consent from the patients was waived.

2.2. Study endpoints, variables, and definitions

The primary outcome was overall survival. The patients were monitored from the day of ACLF diagnosis to mortality or the last follow-up, whichever came first. The following variables were collected by reviewing the electronic medical record of each patient for the day of ACLF diagnosis, age, sex, etiology of chronic liver disease, potential triggers, the presence of liver failure, kidney failure, coagulation failure, cerebral failure, circulatory failure, respiratory failure, and model for end-stage liver disease (MELD) score. Organ failure was defined according to the CLIF-SOFA definition for each organ [16]. ACLF grade was assessed according to the CLIF-SOFA definitions (Supplementary Method: ACLF grade) [16]. The etiology of liver disease was classified into viral (chronic hepatitis B virus or chronic hepatitis C virus infection), alcohol-related liver disease, and chronic liver disease from other causes. To identify the potential triggering event for ACLF, we searched for information on a hepatitis B virus flare, active alcohol ingestion, infection, or gastrointestinal bleeding. Patients without an identifiable potential trigger for ACLF were classified as unknown causes. We also collected data on whether the patients received LT during follow-up, the type of LT (DDLT or LDLT), and the time from diagnosis of ACLF to LT. Among the patients who received LT, we additionally collected the ACLF grade at the time of LT. ACLF progression was defined by any increase in the ACLF grade at the time of LT compared to the grade at the time of ACLF diagnosis.

2.3. Statistical analyses

Variables were compared using t-tests, Chi-squared tests, and Fisher's extract test, as appropriate for the group comparisons. The overall survival was estimated with the Kaplan-Meier method and differences in survival between the groups were compared using a log-rank test. Cox regression was performed to identify the factors associated with survival. For the MELD scores, the patients were divided into two groups (MELD score > 32 or ≤ 32) and tested by Cox regression analysis. The cutoff value for MELD scores was determined by area under the receiver operating characteristics (AUROC) analysis. The difference in grade distribution at the time of diagnosis and transplantation was analyzed by the generalized estimating equation (GEE). Multivariable Cox regression analysis was performed using variables with p-values < 0.05 on univariable analysis. Statistical significance was declared for p-values < 0.05.

3. Results

3.1. Baseline characteristics

The baseline characteristics of the analyzed patients are summarized in Table 1. A potential trigger for ACLF was not identifiable in 54.5% of the participants and among those with identifiable triggers, infection was the most common cause. Acute alcoholic hepatitis was identified in 11 patients. The mean MELD score at ACLF diagnosis was 28 points. The ACLF grades were 1, 2, and 3 for 18.2%, 40.9%, and 40.9% of the patients, respectively. Of 110 patients, 17 patients had already been on the waiting list (15.4%), and 93 patients were on the waiting list at the time of the ACLF episode. During follow-up, 76 patients received LT and 34 patients did not receive LT. The specific reasons were: 1) no deceased donor allocation ($n = 24$, 70.6%); 2) recovered spontaneously ($n = 6$, 17.6%); 3) allocated deceased donor canceled by the patient or family members due to cost or other issues ($n = 2$, 5.9%); and 4) allocated deceased donor canceled by the physician due to high risk of futility (worsening of multi-organ failure) ($n = 2$, 5.9%). Of the 28 patients who died without LT, the median time from ACLF diagnosis to death was 25 days. A comparison of the baseline characteristics between those who received and did not receive LT is shown in Table 1.

3.2. Outcome and predictors of patients with ACLF

During the median 2.35 years of follow-up (range: 0.01 – 6.91 years), 42 patients died. Of 42 patients with mortality, 41 patients died within one year of the ACLF diagnosis. DDLT was performed in 59 patients and 17 patients received LDLT. In a comparison of those who received LDLT and DDLT, those who received LDLT were younger (48.0 ± 8.3 vs. 52.0 ± 10.8, $p = 0.004$), and more patients had ACLF grade 1 at baseline (ACLF grades 1, 2 and 3: 35.3%, 23.5%, and 41.2% for LDLT vs. 6.8%, 50.8% and 42.8% for DDLT, respectively, $p = 0.009$). There was no difference in sex, etiology, potential trigger, organ failure, MELD score, or LT waiting time between the LDLT and DDLT patients (data not shown). Sex, history of cirrhosis decompensation, MELD score, ACLF grade, and LT were associated with overall survival in univariable analysis. In multivariable analysis, LT was the only independent factor associated with overall survival (Supplementary Table S1). When stratified by LT, the survival rates were better for those who received LT (88.2% vs. 17.6% for LT vs. non-LT at 90 days; 82.9% vs. 17.6% for LT vs. non-LT at one year; 81.6% vs. 17.6% for LT vs. non-LT at five years, Fig. 1A, $p < 0.001$). When the type of LT was compared, there was no difference in survival between LDLT and DDLT patients (94.1% vs. 86.3% at one year, Fig. 1B, $p = 0.51$). When stratified according to ACLF grade and LT, survival was better for those who received LT than for those who did not, regardless of the ACLF grade (one-year survival rate: 70.0% vs. 20.0% for LT vs. non-LT for ACLF grade 1, $p = 0.028$; 85.3% vs. 36.4% for LT vs. non-LT for ACLF grade 2, $p < 0.001$; and 84.4% vs. 0% for LT vs. non-LT for ACLF grade 3, $p < 0.001$; Fig. 2A–C). When

Table 1
Baseline characteristics.

Variables	Overall($n=110$)	LT($n=76$)	Non-LT($n=34$)	p value
Age (years)	51.0 ± 10.1	51.1 ± 10.3	50.9 ± 9.8	0.90
Men	72 (65.5)	43 (56.6)	29 (85.3)	0.004
Etiology				0.48
Viral	29 (26.3)	20 (26.3)	9 (26.5)	
Alcohol	57 (51.8)	37 (48.7)	20 (58.8)	
Others	24 (21.8)	19 (79.2)	5 (14.7)	
History of cirrhosis decompensation	51 (46.4)	27 (35.5)	24 (70.6)	0.001
Potential trigger				0.57
HBV flare	2 (1.8)	2 (2.6)	0	
Active alcohol use	11 (10.0)	8(10.5)	3 (8.8)	
Infection	28 (25.5)	17 (22.4)	11 (32.4)	
Bleeding	9 (8.1)	5 (6.6)	4 (11.7)	
Unknown	60 (54.5)	44 (57.9)	16 (47.1)	
Hepatic encephalopathy				0.019
None	47 (42.7)	38 (50.0)	9 (26.5)	
Grade 1/2	25 (22.7)	18 (23.7)	7 (20.6)	
Grade 3/4	38 (34.5)	20 (26.3)	18 (52.9)	
Renal replacement therapy	24 (21.8)	17 (22.3)	7 (20.6)	1.00
Mechanical ventilator	12 (10.9)	12 (15.8)	0	0.017
Vasopressor use	46 (41.8)	30 (39.4)	16 (44.1)	0.53
International normalized ratio	2.61 ± 1.12	2.75 ± 0.97	2.29 ± 1.36	0.043
Bilirubin (mg/dl)	17.8 (11.4–28.9)	20.5 (12.3–28.7)	17.3 (4.3–30.8)	0.21
Creatine (mg/dl)	1.84 ± 1.32	1.69 ± 1.06	2.18 ± 1.72	0.068
Organ failure				
Liver failure	81 (73.6)	59 (77.6)	22 (64.7)	0.17
Kidney failure	51 (37.3)	26 (34.2)	15 (44.1)	0.39
Coagulation failure	58 (52.7)	46 (60.5)	12 (35.3)	0.022
Cerebral failure	38 (34.5)	20 (26.3)	18 (53.0)	0.009
Circulation failure	47 (42.7)	31 (40.8)	16 (47.1)	0.68
Lung failure	6 (5.5)	4 (5.3)	2 (5.9)	1.00
ACLF grade				0.13
Grade 1	20 (18.2)	10 (13.2)	10 (29.4)	
Grade 2	45 (40.9)	34 (44.7)	11 (32.4)	
Grade 3	45 (40.9)	32 (42.1)	13 (38.2)	
MELD	28.2 ± 3.5	28.6 ± 3.3	27.2 ± 3.8	0.07
≤ 32	97 (88.2)	67 (88.2)	30 (88.2)	
> 32	13 (11.8)	9 (11.8)	4 (11.8)	
LT waiting time	12 (5.0–19.8)			
Within 2 wks	48 (63.2)			
Beyond 2 wks	28 (36.8)			

NOTE: Values are expressed as number (%), mean ± standard deviation or median (quartile), as appropriate.
Abbreviation: LT = liver transplantation; LDLT = living donor liver transplantation; DDLT = deceased donor liver transplantation; ACLF = Acute on chronic liver failure.

Table 2
Factor associated with post-LT outcome ($n=76$).

Variables	Univariable	p value	Multivariable	p value
Age (per year)	1.04 (0.99–1.10)	0.11		
Men (vs. female)	1.47 (0.49–4.37)	0.49		
Etiology				
Viral	Reference			
Alcohol	0.33 (0.10–1.06)	0.064		
Others	0.25 (0.05–1.22)	0.087		
Potential trigger				
Hepatic insult	Reference			
Non-Hepatic insult	1.19 (0.12–11.4)	0.87		
Unknown	2.09 (0.26–16.3)	0.48		
History of cirrhosis decompensation (vs.no)	1.05 (0.35–3.15)	0.92		
Baseline factors				
MELD score >32 (vs.≤32)	4.75 (1.48–15.2)	0.009	3.54 (1.01–12.5)	0.049
ACLF grade				
Grade 1	Reference			
Grade 2	0.53 (0.13–2.13)	0.37		
Grade 3	0.47 (0.11–1.97)	0.30		
Factors at the time of LT				
ACLF progression (yes vs. no)	4.91 (1.70–14.1)	0.003	3.75 (1.16–12.1)	0.027
ACLF grade 3 (vs. grade 0–2)	4.52 (1.26–16.2)	0.021	1.87 (0.42–8.34)	0.40
Type of LT				
DDLT	Reference			
LDLT	0.54 (0.12–2.42)	0.42		

Abbreviation: See Table 1.

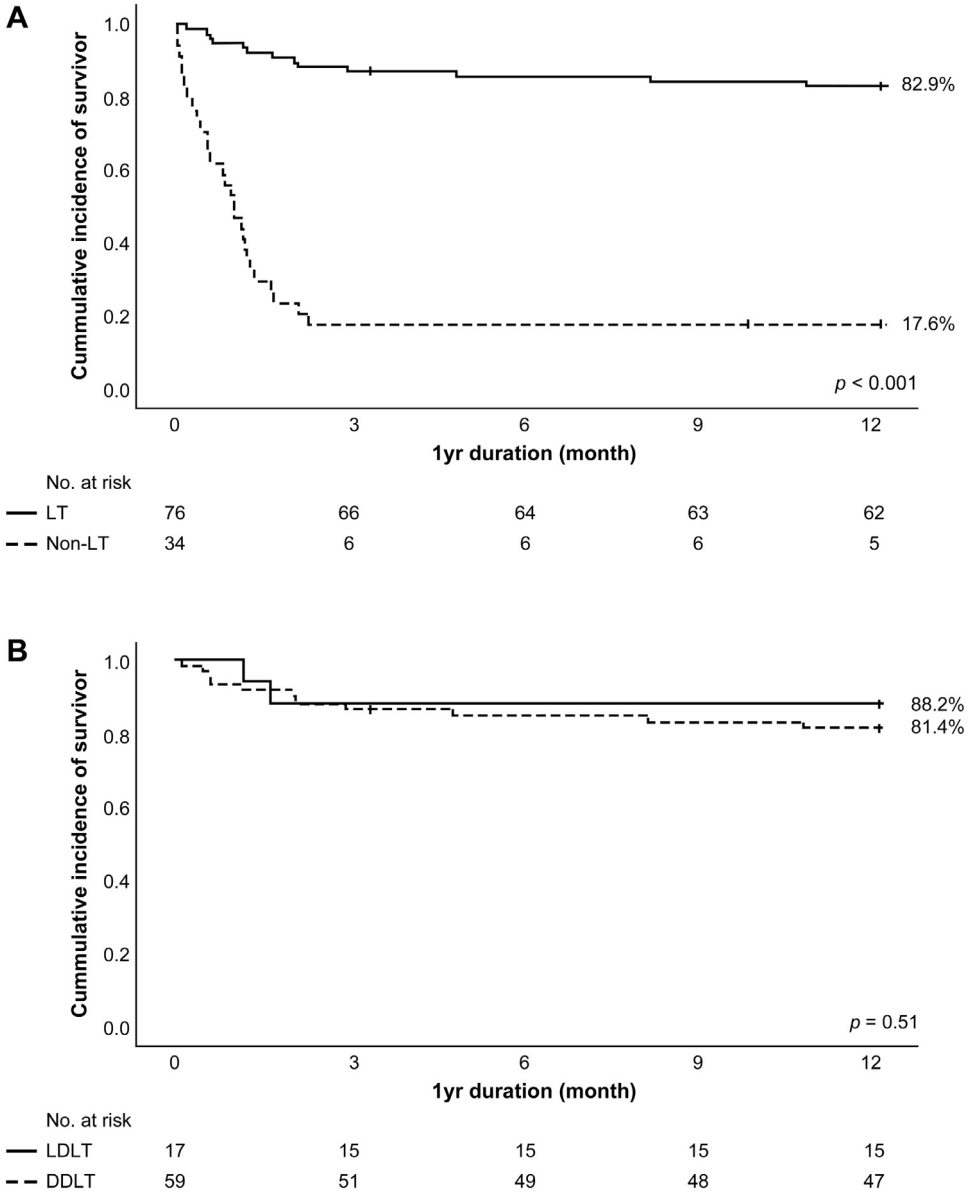

Fig. 1. Overall survival according to the type of liver transplantation.

stratified according to MELD scores and LT, survival was better for those who received LT than for those who did not, regardless of the MELD score (one-year survival rate: 86.6% vs. 20.0% for LT vs. non-LT for MELD $\leq$ 32, $p < 0.001$; and 55.6 vs. 0% for LT vs. non-LT for MELD score $>$ 32, $p = 0.048$).

3.3. Outcomes and predictors in patients with ACLF who received LT

Among the 76 patients who received LT, the median waiting time was 12 days. There was no difference in waiting time between the LDLT (median 12 days, interquartile range: 5.0–20.0 days) and DDLT patients (median 12 days, interquartile range: 6.5–20.5 days, $P = 0.49$). The variables at the time of ACLF diagnosis and at the time of LT are shown in Supplementary Table S2. The mean MELD score was 28.5 at the time of ACLF diagnosis and 28.0 at the time of LT. Notably, 21 patients (27.6%) showed improvement in ACLF grade, 37 patients (48.7%) had no change in ACLF grade, and 18 patients (23.7%) showed progression in their ACLF grade at the time of LT (Supplementary Table S2). Detailed post-LT outcomes according to changes in the ACLF grade during the pre-transplant period are shown in Fig. 3. The post-LT mortality rate was highest (50%) in 12 patients with ACLF grade 2 at diagnosis who progressed to ACLF grade 3 on the day of LT. Those with ACLF grade progression from the pre-transplant period showed worse post-LT mortality (44.4%, 10.8%, and 9.5% for patients with ACLF grade progression, no change, and improvement, respectively, $p = 0.015$).

During follow-up, 14 patients died after LT. The specific causes of mortality after LT are shown in Supplementary Table S3. MELD score, ACLF progression during the pre-transplant period, and ACLF grade on the LT day were factors associated with post-LT mortality in univariable analysis. Post-LT mortality was higher for patients with higher baseline MELD scores (44.4% vs. 14.9 for MELD $\geq$ 32 vs. $<$ 32, $p = 0.054$), and for patients with ACLF progression (44.4% vs. 10.3 for ACLF progression vs. no change/improved, $p = 0.003$). When stratified according to ACLF grade on the LT day, the duration of hospital stay was similar between the two groups (median 26.5 vs. 27.5 days for ACLF grade 3 vs. ACLF grade 0–2, $p = 0.94$), whereas the post-LT mortality was higher for patients with ACLF grade 3 than ACLF grades 0 to 2 on the LT day (30.6% vs. 7.5%, $p = 0.016$). Notably, there was no difference in post-LT survival

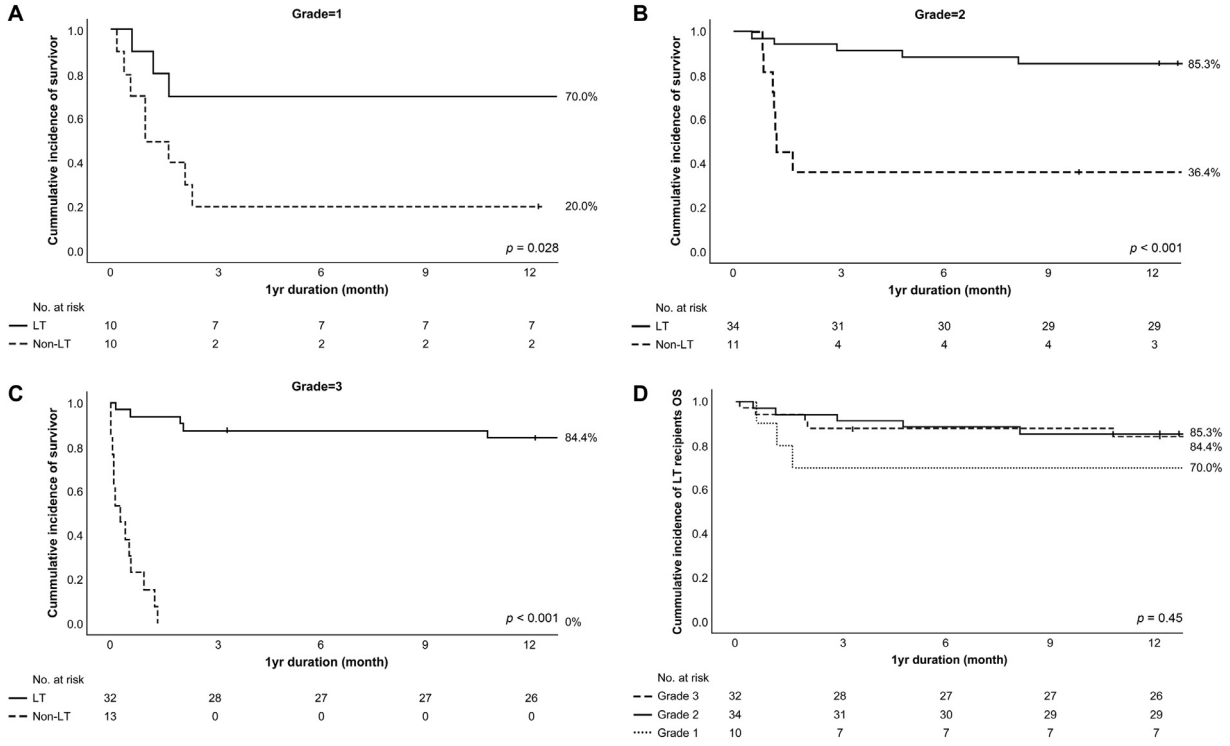

Fig. 2. Outcome of liver transplantation according to ACLF grade.

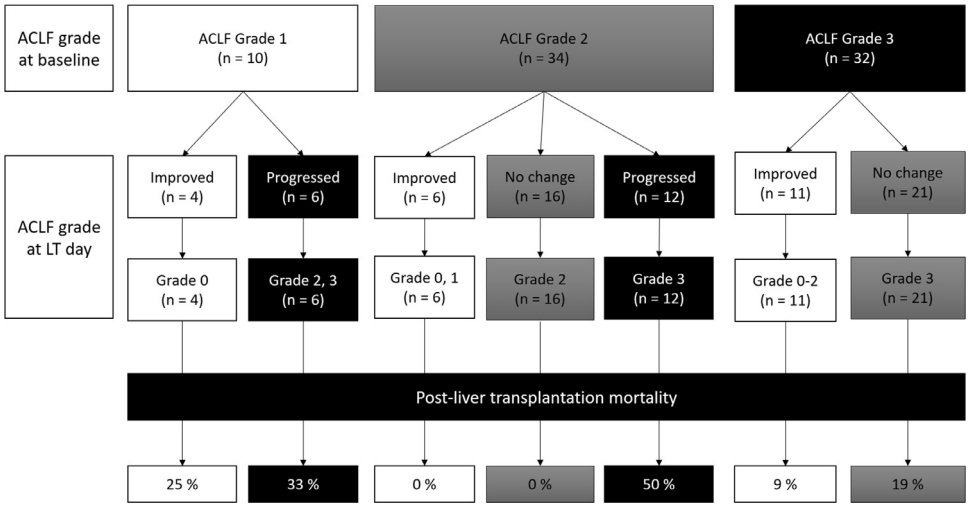

Fig. 3. Change in acute on chronic liver failure grade and post-liver transplantation mortality among patients who received liver transplantation.

when stratified according to ACLF grade at diagnosis (Fig. 2D, $P = 0.45$). In the multivariable analysis, a baseline MELD score of 32 and ACLF progression during the pre-transplant period were two independent factors for post-LT outcome (Table 2). When the patients were grouped according to the two identified risk factors (baseline MELD scores and ACLF grade changes during follow-up), the post-LT survival was low (33.3% at one year) for those with high baseline MELD scores with ACLF grade progression at the time of LT compared to those with either risk factor (66.7% at one year) or no risk factors (92.3% at one year, $p < 0.001$, Fig. 4).

4. Discussion

In this study, we found that emergent LT was feasible with excellent outcomes in patients with ACLF, including patients with multiple organ failure. LT provided an excellent survival benefit regardless of ACLF grade, including patients with ACLF grade 3, whereas survival without LT was poor, especially for patients with ACLF grade 3. Our findings are consistent with previous studies that reported high mortality rates without LT in patients with ACLF [17], and improved outcomes by LT regardless of ACLF grade [13,18]. These findings indicate that LT can be an effective option to improve the outcome of patients with ACLF, including patients with multiple organ failure. Thus, LT should be considered for ACLF patients regardless of ACLF grade.

However, careful interpretation is required as all the data were from observational studies. The studied populations, which reported excellent outcomes of LT for ACLF patients, started from LT waitlists [13,18], as in this study. There are no universally accepted criteria to add patients to the LT waitlist. Yet, it is very likely that very sick patients may not have been added to the LT waitlist. In a study of 218 ACLF patients, fewer patients with ACLF grade 3 re-

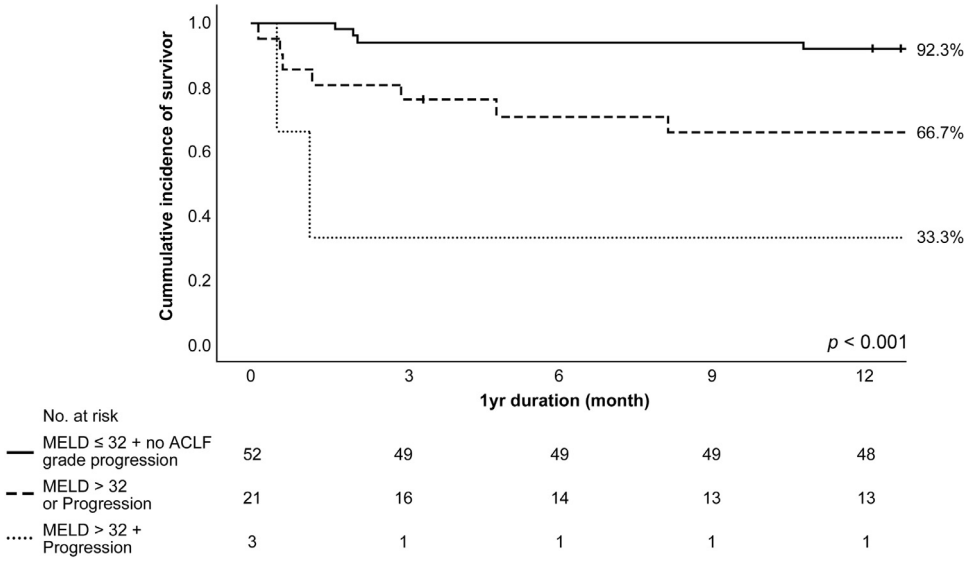

Fig. 4. Outcome of liver transplantation according to baseline MELD score and ACLF grade progression.

ceived LT compared to those with ACLF grades 2 or 1 (35%, 72.7%, and 80% for ACLF grade 3, 2, and 1, respectively) [19]. Circulatory and respiratory system failures were higher in the nontransplant group and none of the patients on high support for circulatory and respiratory failure underwent LDLT [19]. In addition, the dropout rate from waitlists is higher for those with multiple organ failure. Again, there are no universally accepted criteria to delist patients from the LT waitlist. Hence, excellent post-LT outcomes may come from selection bias by listing and delisting from the LT waitlist. In our center, there are no criteria for delisting and the decision to proceed with LT is decided at a multidisciplinary conference on a case-by-case basis. For LDLT, the time of LT was selected at a multidisciplinary conference. For DDLT, the decision to "go or stop" for LT was discussed at the time of allocation of the deceased donor, considering the recipient condition, as well as the donor characteristics. Thus, selection bias might have been present in this process. Taken together, the current data suggest that ACLF patients with multiple organ failure are not too sick to be considered for LT. However, the decision to proceed with LT should be made for carefully selected patients, not for all patients [20].

In a study of 159 patients who underwent LT for ACLF, the MELD-Na scores (≥ 35 points) were the only risk factor associated with post-LT mortality [21]. In a study of 98 patients with ACLF, clinical improvement in the pre-transplant period, defined as the recovery of at least one previously failed organ systems (observed in 37 patients), was associated with significantly better survival than those without improvement (86.5% vs. 55.7% 90-day transplant-free survival, $p < 0.001$) [22]. In this study, we noticed that the MELD score at ACLF diagnosis and ACLF grade progression during the pre-transplant period were independent factors associated with poorer post-LT outcomes (Table 2). Of note, ACLF grade at diagnosis was not associated with post-LT outcome, while ACLF grade at LT was associated with post LT outcome. ACLF grade is a dynamic variable during clinical course of ACLF patients, and in multivariable analysis we observed that change in ACLF grade (ACLF progression) as a strong risk factor for post-LT outcome. In this study, we noticed very poor outcomes for those with high baseline MELD scores with ACLF grade progression. In the case of LDLT where the timing of LT can be selected, the risk-benefit of performing LT should be carefully evaluated when the ACLF grade progresses in patients with high MELD scores. The optimal time should be selected when the ACLF does not progress, although this observation needs further validation. These findings have some clinical implications in LT strategies regarding go or stop and deciding when to transplant in the setting of ACLF. While preparing for LT, progression or improvement in the ACLF grade should be carefully assessed daily. The decision to go or stop might be guided by assessing the progression of or improvement in the ACLF grade during the pre-transplant period. If the time of LT can be selected, high MELD score patients warrant an urgent approach before the ACLF grade progresses. Nevertheless, this concept is based on retrospective studies with relatively small numbers of patients and requires prospective validation.

Other factors are associated with the post-LT mortality of patients transplanted in the setting of ACLF. In the UNOS data, mechanical ventilation at LT, a marginal donor liver, and early LT were factors associated with post-LT outcomes [18]. Early LT (within two weeks from the ACLF diagnosis) was also associated with better post-LT outcomes [23,24]. In a study of 84 patients (29 with acute liver failure and 55 with ACLF) requiring ICU care prior to LT, the pretransplant lactate levels and the presence of acute respiratory distress syndrome (ARDS) were independent factors for post-transplant mortality [25]. In our study, there was no difference in post-LT outcome according to the type of donor (deceased donor vs. living donor), mechanical ventilation at LT, or early LT within two weeks from ACLF diagnosis. In addition, we did not observe a difference in outcome according to potential trigger or subsequent organ failure. There is an on-going debate on the definition of ACLF [26,27] and the impact of specific types of organ failure and triggers (e.g., infection) on patient outcomes [28,29]. However, considering the study size and retrospective nature of the current study, further studies are required to identify the most important clinical factors for guiding LT plans for patients with ACLF.

There were some other limitations to this study. Although performed in a single center, several physicians and transplant surgeons took care of the patients, and the decision to list a patient was at the discretion of the doctors in charge of the patient, indicating potential selection bias. In this study, we used two time points (ACLF grade at diagnosis and on the LT day) to classify changes in the ACLF grade. The clinical course of patients with ACLF is dynamic and the ACLF grade can change daily (one may deteriorate, recover, and deteriorate again). Using two time points (at diagnosis and on the LT day) may not fully capture the dynamic nature of ACLF patients. The relatively small study sample size lim-

ited us from performing more accurate statistical analyses (e.g., time-dependent analysis). Hence, further larger-scale studies are needed to better understand the prognostic significance of ACLF grade changes during the pre-transplant period, and the best way to classify ACLF changes during the pre-transplant period. By using AUROC analysis, we chose a MELD cutoff point of 32 but the specific MELD score cutoff point to predict post-LT outcomes needs to be determined. One great advantage of LDLT is that the time of LDLT can be selected early in the course of ACLF. However, we did not notice a difference in the LT waiting time between LDLT and DDLT patients and the exact reason for undergoing LDLT at a specific time point (e.g., two weeks after ACLF diagnosis) could not be accurately assessed (e.g., whether it was a donor issue or a recipient issue). In addition, the number of patients who received LDLT was small ($n = 17$). Hence, although the post-LT outcome was similar between LDLT and DDLT patients, further studies on the safety of LDLT for ACLF patients are needed. There also may have been unmeasured factors associated with the post-LT outcomes, including donor quality, operation time, and sarcopenia. In this study, the number showing ACLF progression was relatively small ($n = 18$). The strength of the study was the careful assessment of variables and identification of the importance of ACLF grade progression during the pre-transplant period.

In conclusion, we observed that LT provided a significant survival benefit to ACLF patients, regardless of the ACLF grade. The survival advantage of LT for ACLF patients was so large that LT should be considered for ACLF patients, regardless of the ACLF grade. The post-LT outcome was associated with MELD scores and ACLF grade progression during the pre-transplant period. These factors can be used to guide LT planning and counseling for patients presenting with ACLF and the decision to go or stop for LT. These findings warrant further validation.

Declaration of Competing Interest

All authors declare that they have no conflicts of interest regarding the content of this manuscript.

Authorship

Guarantor of the article: Sinn DH, Choi GS.

Author contributions

Study concept and design: Kim JE, Sinn DH, Choi GS

Contribution and acquisition of data: Kim JE, Choi GS, Kim JM, Joh JW, Kang W, Gwak GY, Paik YH, Choi MS, Lee JH, Koh KC, Paik SW

Data analysis, draft-writing: Kim JE, Sinn DH

Critical revision for intellectual content: Choi GS, Kim JM, Joh JW, Kang W, Gwak GY, Paik YH, Choi MS, Lee JH, Koh KC, Paik SW

All authors read and approved the final manuscript.

Grants and financial support

No grants supported the current study.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2021.03.030.

References

[1] Martin P, DiMartini A, Feng S, et al. Evaluation for liver transplantation in adults: 2013 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. Hepatology 2014;59:1144–65.
[2] European association for the study of the Liver. EASL clinical practice guidelines: liver transplantation. J Hepatol 2016;64:433–85.
[3] Park SJ, Lim YS, Hwang S, et al. Emergency adult-to-adult living-donor liver transplantation for acute liver failure in a hepatitis B virus endemic area. Hepatology 2010;51:903–11.
[4] Kim TY, Kim DJ. Acute-on-chronic liver failure. Clin Mol Hepatol 2013;19:349–59.
[5] Sy E, Ronco JJ, Searle R, et al. Prognostication of critically ill patients with acute-on-chronic liver failure using the Chronic Liver Failure-Sequential organ failure assessment: a Canadian retrospective study. J Crit Care 2016;36:234–9.
[6] Moreau R. Acute-on-chronic liver failure: a new syndrome in cirrhosis. Clin Mol Hepatol 2016;22:1–6.
[7] Southern PB, Davies MH. Indication and assessment for liver transplantation. Clin Med (Lond) 2002;2:313–16.
[8] Umgelter A, Lange K, Kornberg A, et al. Orthotopic liver transplantation in critically ill cirrhotic patients with multi-organ failure: a single-center experience. Transplant Proc 2011;43:3762–8.
[9] Fernandez J, Saliba F. Liver transplantation in patients with ACLF and multiple organ failure: time for priority after initial stabilization. J Hepatol 2018;69:1004–6.
[10] Levesque E, Winter A, Noorah Z, et al. Impact of acute-on-chronic liver failure on 90-day mortality following a first liver transplantation. Liver Int 2017;37:684–93.
[11] Merion RM. When is a patient too well and when is a patient too sick for a liver transplant? Liver Transpl 2004;10:S69–73.
[12] Artru F, Louvet A, Ruiz I, et al. Liver transplantation in the most severely ill cirrhotic patients: a multicenter study in acute-on-chronic liver failure grade 3. J Hepatol 2017;67:708–15.
[13] Thuluvath PJ, Thuluvath AJ, Hanish S, et al. Liver transplantation in patients with multiple organ failures: feasibility and outcomes. J Hepatol 2018;69:1047–56.
[14] Linecker M, Krones T, Berg T, et al. Potentially inappropriate liver transplantation in the era of the "sickest first" policy - A search for the upper limits. J Hepatol 2018;68:798–813.
[15] Shukla A, Vadeyar H, Rela M, et al. Liver transplantation: east versus West. J Clin Exp Hepatol 2013;3:243–53.
[16] Moreau R, Jalan R, Gines P, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology 2013;144:1426–37 37 e1-9.
[17] Sundaram V, Shah P, Wong RJ, et al. Patients With Acute on Chronic Liver Failure Grade 3 Have Greater 14-Day Waitlist Mortality Than Status-1a Patients. Hepatology 2019;70:334–45.
[18] Sundaram V, Jalan R, Wu T, et al. Factors associated with survival of patients with severe acute-on-chronic Liver Failure before and after liver transplantation. Gastroenterology 2019;156:1381–91 e3.
[19] Yadav SK, Saraf N, Choudhary NS, et al. Living donor liver transplantation for acute-on-chronic liver failure. Liver Transpl 2019;25:459–68.
[20] Gustot T, Agarwal B. Selected patients with acute-on-chronic liver failure grade 3 are not too sick to be considered for liver transplantation. J Hepatol 2017;67:667–8.
[21] Zhang QK, Wang ML. Value of model for end-stage liver disease-serum sodium scores in predicting complication severity grades after liver transplantation for acute-on-chronic liver failure. Transplant Proc 2019;51:833–41.
[22] Huebener P, Sterneck MR, Bangert K, et al. Stabilisation of acute-on-chronic liver failure patients before liver transplantation predicts post-transplant survival. Aliment Pharmacol Ther 2018;47:1502–10.
[23] Sundaram V, Jalan R. Reply. Gastroenterology 2019;157:1163–4.
[24] Choudhary NS, Saraf N, Saigal S, et al. Factors associated with survival of patients with severe acute-on-chronic liver failure before and after liver transplantation: unanswered questions. Gastroenterology 2019;157:1162–3.
[25] Michard B, Artzner T, Lebas B, et al. Liver transplantation in critically ill patients: preoperative predictive factors of post-transplant mortality to avoid futility. Clin Transplant 2017:31.
[26] Choudhary NS, Saraf N, Saigal S, et al. Letter to the Editor: incidence and mortality of acute on chronic liver failure using two definitions in patients with compensated Cirrhosis. Hepatology 2019;70:2235–6.
[27] Kim TY, Song DS, Kim HY, et al. Characteristics and Discrepancies in Acute-on-Chronic Liver Failure: need for a Unified Definition. PLoS ONE 2016;11:e0146745.
[28] Bertuzzo VR, Giannella M, Cucchetti A, et al. Impact of preoperative infection on outcome after liver transplantation. Br J Surg 2017;104:e172–ee81.
[29] Choudhary NS, Saraf N, Soin AS. Liver transplantation for grade 3 acute-on-chronic liver failure: type of organ failure is important. J Hepatol 2018;68:621–2.