Living Donor Liver Transplantation for Acute on Chronic Liver Failure Based on EASL-CLIF Diagnostic Criteria

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Background: The European association for the study of the liver and chronic liver failure consortium (EASL-CLIF) recently proposed diagnostic criteria for acute on chronic liver failure (ACLF). There is lack of data regarding liver transplant outcomes in ACLF patients based on these criteria. The objective of this study was to determine outcome following living donor liver transplantation (LDLT) in ACLF patients. **Methods:** We retrospectively reviewed patients who underwent LDLT for ACLF based on European association for the study of the liver and chronic liver failure consortium (EASL-CLIF) diagnostic criteria (group 1) ($N = 60$) and compared them with ACLF patients who did not undergo transplantation (group 2) ($N = 59$). The primary outcome of interest was 30 day mortality. We also looked at one year survival in these patients. Survival was calculated using Kaplan–Meier curves and Log rank test was used to determine significance between variables. **Results:** Median MELD scores for group 1 and 2 patients in ACLF grade 1 was 28 (20–38) and 31 (24–36), in ACLF grade 2 was 35 (24–42) and 36 (24–42) and in ACLF grade 3 was 36 (29–42) and 38 (32–52). For group 1 and 2, 30 day mortality in ACLF grade 1, 2 and 3 was 2/43 (4.6%) versus 9/15 (60%) ($P < 0.001$), 1/15 (6.6%) versus 13/19 (68.4%), 0/2 (0%) versus 20/25 (80%) ($P < 0.001$). Actuarial 1 year overall survival was 92% versus 11% ($P < 0.001$) in patients who underwent transplantation versus those who did not. One year survival in patients with grade 1 and 2 ACLF who received transplant versus medical treatment was 91% versus 13% and 93% versus 15% ($P < 0.001$) respectively. **Conclusion:** LDLT has excellent outcomes in patients with EASL-CLIF grade 1 and 2 ACLF. Without transplantation, ACLF patients have a very poor prognosis. (J CLIN EXP HEPATOL 2018;8:136–143)

Acute decompensation is a common phenomenon in cirrhotic patients. But in some patients it is associated with organ failure and high short term mortality.^{1–3} These patients have been grouped together as acute on chronic liver failure (ACLF) patients.^{3–5} Short term mortality in ACLF patients is very high and ranges between 50 and 90%.^{6–9} Until recent past, ACLF remained a poorly defined clinical entity. A recent study by Moreau and colleagues greatly improved our understanding of ACLF and categorized organ failure into grades based

on increasing number of failing organs and mortality.¹⁰ ACLF represents an important clinical dilemma since it is a dynamic phenomenon and is potentially reversible but with risk of high short term mortality. Liver transplant is an option in patients who fail conservative treatment but can lead to prolonged waiting precluding eventual transplantation. Thus, judicious waiting time is recommended.¹¹ Previous reports on liver transplant in these patients have demonstrated acceptable outcomes but ACLF was not defined clearly and was not based on European association for the study of the liver and chronic liver failure consortium (EASL-CLIF) guidelines.^{11–16} Recently outcomes of liver transplantation (LT) for EASL-CLIF ACLF have been reported and a 90 day mortality of 20.7% was demonstrated.¹⁷

The objective of the current study was to determine outcome in patients with ACLF who underwent LDLT based on EASL-CLIF criteria and compare it with patients who received medical treatment alone.

METHODS

This was a review of patients who were admitted and managed at Shifa International Hospital between

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Abbreviations: ACLF: acute on chronic liver failure; ACR: acute cellular rejection; CIT: cold ischemia time; EAD: early allograft dysfunction; EASL-CLIF: European Association for the Study of the Liver-Chronic Liver Failure; HCV: hepatitis C virus; HOTA: human organ transplantation authority; LDLT: living donor liver transplantation; LT: liver transplantation; MELD: model for end-stage liver disease; MHV: middle hepatic vein; OS: overall survival; WIT: warm ischemia time

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April 2012 and September 2016 for decompensated liver disease. For diagnosis of ACLF, EASL-CLIF criteria were used.¹⁰ ACLF was graded as grade 1, 2 and 3 based on number of organ failures.¹⁰ A total of 119 patients were included in the study. Group 1 ACLF ($N = 60$) patients underwent LDLT while ACLF patients in group 2 ($N = 59$) were offered transplant but only received medical treatment. Primary reasons for not receiving transplantation included patient refusal, donor non-availability and financial constraints. Patients who had active infection, high ionotrope dependence ($>10 \mu\text{g}/\text{min}$ of nor-epinephrine, >1 ionotropic medications) or need for mechanical ventilation were not transplanted ($N = 3$) and not included in the study.

Details of donor/patient selection and operative technique have been explained elsewhere.^{18,19} In general, donors were between 18 and 45 years of age, blood group compatible and related to the recipient. All transplants were performed after approval from Human organ transplant authority (HOTA) and hospital transplant committee. This committee included members from the departments of transplant surgery, hepatology, anesthesia, physiotherapy and critical care. All non-transplanted patients were managed by transplant hepatology team.

The two groups were compared for demographics, etiology of liver failure, MELD scores, acute decompensation and precipitating factors. Graft variables including graft type, use of middle hepatic vein (MHV) and number of biliary and hepatic venous anastomoses were assessed in transplanted patients. We also assessed operative variables including cold ischemia time (CIT), warm ischemia time (WIT), duration of surgery and blood loss in transplanted patients. We used 90 day morbidity to report post-transplant complications and severity was assessed based on Clavien-Dindo grading.²⁰ Cause of death in transplanted and non-transplanted patients was assessed. Early allograft dysfunction (EAD) was defined as presence of total bilirubin $\geq 10 \text{ mg}/\text{dl}$ on day 7, INR ≥ 1.6 on day 7, AST ≥ 2000 , ALT ≥ 2000 within first 7 days as defined previously.²¹ Primary outcome of interest was 30 day and 90 day mortality. Interval variables were represented as medians and range. We also looked at 1 year survival in these patients. Overall survival was defined as time when decision to transplant was made and date of death or last follow up. For categorical variables, chi square or fisher exact test was used while for interval variables Mann-Whitney U test was applied. Survival was calculated using Kaplan-Meier curves and Log rank test was used to determine significance. A P value <0.05 was considered statistically significant. The hospital ethics committee approved the study. All analysis was performed on SPSS version 20.

RESULTS

Demographics

Median follow up was 7.7 (0–51.3) months. Median age was 48 (13–75) years. Median BMI was 25.5 (15.6–46.1) kg/m^2 . Median MELD score was 33 (20–52). Median time to transplant was 5.5 (1–41) days after hospital admission.

Patient Characteristics

Distribution of patients in various grades of ACLF based on underlying organ failure is shown in Table 1. Out of 60 patients who underwent transplantation, 43/60 (71.6%) had grade 1 ACLF. In group 2, grade 3 ACLF (25/59) (42.3%) was more frequent. A total of 119 patients developed 210 organ failures. The most common was liver failure in 87/119 (73.1%) patients followed by renal failure in 50/119 (42%) patients. In grade 1 ACLF patients, renal failure was seen more frequently in group 2 patients i.e. 6/15 (40%) versus (6/43) (14%) ($P < 0.01$). In ACLF grade 2, significant difference was seen for coagulation ($P = 0.03$) and cerebral failure ($P = 0.005$).

Table 2 represents various patient characteristics at the time of transplantation between group 1 and 2. Ascites was seen more frequently in group 2 i.e. 53/59 (89.8%) versus 31/60 (51.7%) patients ($P < 0.001$). A significant difference was present between group 1 and 2 with regards to age i.e. 45 (13–65) years versus 55 (24–75) years ($P = 0.002$) and MELD scores 28 (20–42) versus 36.5 (24–52) ($P < 0.001$). Median MELD score for group 1 and 2 patients in ACLF grade 1 was 28 (20–38) and 31 (24–36) ($P = 0.01$); in ACLF grade 2 was 35 (24–42) and 36 (24–42) ($P = 0.7$) and in ACLF grade 3 was 36 (29–42) and 38(32–52) ($P = 1$).

Graft and Operative Variables

Graft and operative variables are shown in Table 3. Majority of patients had a right lobe graft 58 (96.7%) without MHV 52 (86.7%). There was a single biliary anastomoses in 30/60 (50%) patients and more than 1 outflow anastomoses in 48/60 (80%) patients.

Morbidity

There was no donor mortality. Overall six donors had pleural effusion needing aspiration, one donor had bile leak requiring per cutaneous drain placement and one donor had intra abdominal collection who underwent aspiration.

Post-transplant recipient complications are shown in Table 4. Most common grade 2 complication was acute cellular rejection seen in 5/60 (8.3%) patients. Pleural effusion was the most common grade 3A complication while biliary leak/stricture was the most common grade 3B complication with 7/60 (11.6%) patients each.

Table 1 Organ Failures in ACLF Patients.

Organ failures		Percentage		Group 1		Group 2		P value
				N = 60		N = 59		
				Number	Percent	Number	Percent	
ACLF grade 1								
N = 58	N = 58			N = 43		N = 15		
	36	62.1	Liver failure (bilirubin ≥ 12 mg/dl)	28	65	8	53.3	0.7
	12	20.6	Kidney failure (creatinine ≥ 2 mg/dl)	6	14	6	40	0.01*
	3	5.2	Coagulation failure (platelets $\leq 20 \times 10^9$ /L)	3	7	0	0	0.5
	7	12.1	Coagulation failure (INR ≥ 2.5 IU)	6	14	1	6.7	0.6
ACLF grade 2								
N = 34	N = 68			N = 15		N = 19		
	28	41.2	Liver failure (bilirubin ≥ 12 mg/dl)	14	93.3	14	73.7	0.1
	17	25	Kidney failure (creatinine ≥ 2 mg/dl)	5	33.3	12	63.2	0.08
	16	23.5	Coagulation failure (INR ≥ 2.5 IU)	11	73.3	5	26.3	0.03*
	7	10.3	Cerebral failure (grade 3/4 encephalopathy)	0	0	7	36.8	0.005*
ACLF grade 3								
N = 27	N = 84			N = 2		N = 25		
	23	27.4	Liver failure (bilirubion > 12 mg/dl)	2	100	21	84	0.3
	21	25	Kidney failure (creatinine ≥ 2 mg/dl)	1	50	20	80	0.4
	5	5.9	Coagulation failure (platelets $\leq 20 \times 10^9$ /L)	0	.	5	20	1
	18	21.5	Coagulation failure (INR ≥ 2.5 IU)	2	100	16	64	0.5
	17	20.2	Cerebral failure (grade 3/4 encephalopathy)	1	50	16	64	0.1

*P value < 0.05.

Mortality

Sepsis was the most common cause of death and was seen in 4/60 (6.6%) patients post transplantation. EAD was seen in 7/60 (11.6%) patients. Causes of death in non-transplanted patients included sepsis (19/54) (32.2%), renal failure (7/54) (11.8%), multi organ failure (3/54) (5%), cardiac event (6/54) (10.1%), gastrointestinal bleeding (6/54) (10.1%), metabolic causes (7/54) (11.8%) and pneumonia (6/54) (10.1%).

Table 5 demonstrates the 30 and 90 day mortality in group 1 and 2 patients with respect to ACLF grades. A statistically significant difference was present for both 30 and 90 day mortality in all grades of ACLF as shown in the table. Actuarial 1 year OS for group 1 and 2 patients is shown in Figure 1(a). There was a statistically significant difference in 1 year OS in group 1 and 2 i.e. 92% and 11% ($P < 0.001$). This difference in survival was present for both ACLF grade 1 and 2 as shown in Figure 1(b) and (c).

DISCUSSION

The current study demonstrates excellent outcomes with LDLT for ACLF patients. Without transplantation, patients identified as potential candidates for LT are unlikely to survive. The current study also validates

EASL-CLIF ACLF grading in cirrhotic patients as there was a sequential increase in mortality with increasing ACLF grades in non-transplanted patients. In majority of patients precipitating factors for acute decompensation were not identifiable.

Levesque and colleagues have recently reported outcomes of liver transplantation in ACLF patients based on EASL-CLIF criteria.¹⁷ They have shown a 90 day mortality of 20.7% and 1 year mortality of 30% in patients transplanted for ACLF which is higher than a 5% 90 day and 8% 1 year mortality observed in the current study. A small number of patients underwent LDLT for grade 3 ACLF in our center and might have resulted in improved outcomes. However, better outcomes were seen even in grade 1 and 2 ACLF patients when compared to this study. This might be due to difference in patient selection for transplantation. We did not perform LDLT for ACLF patients who needed high doses of ionotropes or mechanical ventilation at the time of transplant. It has been shown that patients requiring ionotropic support or mechanical ventilation have lower survival rates.^{22,23} Levesque and colleagues concluded that ACLF was an independent predictor of poor post-transplant outcomes. It has been shown that 28 day mortality increases once ACLF persists for more than 7 days.²⁴ We did have more patients

Table 2 Demographics, Etiology of Liver Failure, MELD Scores, Acute Decompensation and Precipitating Events in the Two Groups.

		Transplant group		Non-transplant group		P value
		(N = 60)		(N = 59)		
		Number	Percent	Number	Percent	
Gender	Male	48	80	43	72.9	0.3
	Female	12	20	16	27.1	
Etiology	HCV	36	60	39	66.1	<0.001*
	HBV	4	6.7	8	13.6	
	NBNC	0	–	10	16.9	
	Cryptogenic	8	13.3	0	0	
	Others	12	20	2	3.4	
Acute decompensation	GI bleed	9	15	9	15.2	0.9
	Encephalopathy	41	68.3	39	66.1	0.7
	Jaundice	58	96.6	57	96.6	1
	Ascites	31	51.7	53	89.8	<0.001*
Acute insult	Bacterial infection	2	3.3	9	15.2	0.1
	Alcohol	0	–	3	5.1	
	Medications	3	5	1	1.7	
	Others	1	1.7	4	6.8	
	Unknown	54	90	42	71.2	
		Median (range)		Median (range)		
Age (years)		45	13–65	55	24–75	0.002*
BMI (kg/m ²)		25	(15.4–46.1)	26	18–38	0.4
MELD scores		29	20–42	36	24–52	<0.001*

*P < 0.05.

Table 3 Demonstrates Graft and Operative Variables in the Transplanted Group.

		Number (N = 60)	Percent (%)
Lobe used	Right	58	96.7
	Left	2	3.3
MHV used	Yes	8	13.3
	No	52	86.7
Biliary anastomoses	1	30	50.0
	2	19	31.7
	Ductoplasty	11	18.3
Outflow anastomoses	1	12	20.0
	2	34	56.7
	3	14	23.3
		Median (range)	
CIT (min)		35 (9–124)	
WIT (min)		40 (5–93)	
Surgery duration (h)		9.5 (6–16)	
Blood loss (ml)		2050 (400–30000)	

Table 4 Post Transplant Morbidity and Mortality in ACLF Patients.

	Number N = 46	Percent (%)
Grade 2		
Seizures	3	5
Pneumonia	3	5
Psychosis	2	3.3
ACR	5	5
Mucormycosis	1	1.7
HCV recurrence	1	1.7
Grade 3A		
Pleural effusion	7	11.7
Intra abdominal collection	3	5
Grade 3B		
Biliary complications	7	11.7
Bleeding	3	5
Grade 4A		
Renal failure	4	6.7
Grade 5		
Sepsis	4	6.7
Graft dysfunction	1	1.7
Bleeding	1	1.7
Rejection	1	1.7

in the transplant group that were ACLF 1. Most ACLF grade 3 patients did not survive until transplant (finances + donor) could be arranged. The median time to transplant was 5.5 days and is apparently short because we calculated days only from the last admission. Many of the grade 1 ACLF patients got discharged when they were a little better due to financial constraints and then got re-admitted before transplant when they were sick again.

Role of LDLT in ACLF has been previously explored.^{12,13} However, ACLF was not defined as per EASL-CLIF guidelines and patients predominantly had HBV related ACLF. On the contrary, the most common underlying etiology in the current study was HCV related cirrhosis. Despite these differences, liver transplantation had excellent outcomes in our cohort.

There was an increase in mortality with increasing number of organ failures in cirrhotic patients with acute decompensation. However, it did not identify which patients could benefit from liver transplantation.¹⁰ The current study extends the utility of EASL-CLIF criteria to potential LDLT candidates. Only ACLF patients with stable cardiopulmonary function were considered eligible for LDLT since related factors have been shown to negatively impact survival post-transplantation.^{22,23} Failure to proceed with transplantation in the non-transplanted group was due to patient refusal, donor non-availability and financial constraints. Although these patients had a stable cardiopulmonary function, there was increasing mortality with increasing number of organ failures i.e. the 30 day mortality for ACLF grade 1, 2 and 3 patients was 60%, 68.4% and 80% respectively. This underscores the dismal prognosis in this select group of ACLF patients without transplant. In our experience, 80–90% patients are dead within 90 days if not transplanted. This is a high percentage compared to previous reports on 30 day mortality in ACLF patients.^{17,25} We can hypothesize that our patients were generally malnourished and presented to the hospital at later stage.²⁶ Nutritional status has been linked with post-transplant outcomes.²⁷ Inability to afford a transplant corresponds well to failure to bear expenses for medical management of ACLF. It is possible that they did not seek medical attention once discharged due to financial limitations and hence the poor outcome. This high mortality implies that liver transplant should be considered in all patients with ACLF but especially in those who have stable cardiopulmonary status. It can be argued that there was a difference in MELD scores

Table 5 Overall 30 Day and 90 Day Mortality in ACLF Patients Who Underwent Transplant or Received Medical Treatment.

		Transplant group		Non-transplant group		P value
		N = 60		N = 59		
		Number	Percent	Number	Percent	
30 day mortality	ACLF 1	2/43	4.6	9/15	60	<0.001*
	ACLF 2	1/15	6.6	13/19	68.4	
	ACLF 3	0/2	0	20/25	80	
90 day mortality	ACLF 1	2/43	4.6	12/15	80	<0.001*
	ACLF 2	1/15	6.6	16/19	84	
	ACLF 3	0/2	0	23/25	92	

*P < 0.05.

Figure 1 (A) One year OS in transplanted versus non-transplanted patients. (B) OS in transplanted versus non-transplanted grade 1 ACLF patients. (C) OS in transplanted versus non-transplanted grade 2 ACLF patients.

and organ failure type in patients who underwent transplant versus medical management. Despite this difference, a median MELD score of 29 (24–42) in transplant group is very high and a 30 day mortality of 5% in these patients reflects well on the utility of LDLT in these patients.

There was no difference in 30 day, 90 day and 1 year mortality in grade 1 and 2 ACLF patients who eventually underwent transplantation at our center. For grade 3 ACLF, although no post-transplant mortality was observed, the number was too small to draw meaningful

conclusions. Although high ACLF grade has been linked with poor post-transplant outcomes¹⁷; with better patient selection comparable survival can be expected for various grades of ACLF.

Limitations of the current study include its retrospective design. A small number of patients were transplanted for grade 3 ACLF and limit our ability to understand effectiveness of LDLT in this high acuity sub group of ACLF patients. We could not determine independent predictors of outcomes due to limitations in sample size which would make strength of association weaker. Acute insult could not be determined in majority of the patients. This is due to the retrospective nature of the study and missing documentation. However, these patients were in a reasonably stable condition before the episode of decompensation and that is why they were labeled as ACLF. It is difficult to demonstrate pre decompensation MELD scores since patients were not in regular follow up with us or at another facility. It is logical to assume that there were differences between patients in the two groups. Transplanted patients were in better condition than the other group. However, on subgroup analysis, MELD score was only significantly different for grade 1 patients. Moreover this small difference in MELD scores alone cannot be solely responsible for the striking difference in mortality between the two groups.

The current study reports outcomes of LDLT in ACLF patients based on EASL-CLIF criteria. More than 90% survival at 1 year is promising and demonstrates a definitive role of LDLT in ACLF patients. This study also demonstrates dismal prognosis in ACLF patients who are transplant candidates but do not receive one. Due to high short term mortality, liver transplantation should be considered early in the course of the disease as these patients are more likely to die than to have resolution of organ failure. It is critical to determine factors that can have a negative impact on post-transplant survival in these patients. Perhaps, larger studies with multi center collaboration can help us determine contraindications and appropriate timing of transplantation in ACLF patients.

CONFLICTS OF INTEREST

The authors have none to declare.

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