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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 2017;xx:1–8)**

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 μg/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 ≥10 mg/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.

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