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Title

Acute on Chronic Liver Failure: Factors Associated With Transplantation.

Permalink

https://escholarship.org/uc/item/3f55505z

Journal

Transplantation Direct, 7(12)

ISSN

2373-8731

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Publication Date

2021-12-01

DOI

10.1097/TXD.0000000000001245

Peer reviewed

Acute on Chronic Liver Failure: Factors Associated With Transplantation

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Background. Acute on chronic liver failure (ACLF) carries a poor prognosis unless liver transplantation is offered. We present risk factors associated with proceeding with liver transplantation in patients with ACLF. **Methods.** A retrospective review of all patients with ACLF who presented to a single transplant center between January 2016 and December 2017 was performed. We compared patients who were transplanted with patients who were not. **Results.** During the study period, 144 patients with ACLF were identified, 86 patients (59.7%) were transplanted, and 58 were not. The transplanted patients had a lower number of failed organs (4 versus 5, $P < 0.001$) and lower incidence of ACLF grade 3 (76.7% versus 94.8%, $P = 0.014$) compared with nontransplanted patients. Liver transplantation offered a 1-y survival of 86% as compared to 12% in the nontransplanted group. Hospital charges were significantly higher among transplanted patients as compared with the nontransplanted patients ($227 886 versus $88 900, $P < 0.001$). Elevated serum lactate was a risk factor in not offering liver transplantation in ACLF patients. **Conclusions.** In appropriately selected patients with ACLF, liver transplantation is feasible and can provide above 86% 1-y patient survival even in grade 3 ACLF.

(*Transplantation Direct* 2021;7: e788; doi: 10.1097/TXD.0000000000001245. Published online 17 November, 2021.)

INTRODUCTION

Acute on chronic liver failure (ACLF) was first described in 1995 and has gained much attention in the hepatology and critical care literature over the last decade.[1,2] ACLF is believed to have a different pathophysiology and prognosis from decompensated chronic liver disease manifesting with rapid and severe deterioration in hepatic function and

poor outcome.[3,4] There is no consensus on the definition of ACLF, yet, irrespective, of the definition, it is a syndrome that is characterized by acute decompensation resulting in 1 or more organ failures (OF) and is associated with a high short-term mortality.[5-7] Different hepatic and extrahepatic insults are known to precipitate ACLF including infections, gastrointestinal bleeding, continued alcohol consumption, and viral hepatitis, although the etiology is unknown in up to 40% of cases.[7,8]

Management of ACLF patients is resource intensive and requires supporting all failing organs. Without liver transplantation, the outcome of ACLF patients is grim, with the 30-d mortality exceeding 80% in patients with 3 or more failed organs.[9,10] Liver transplantation offers the only treatment for patients with ACLF and multiple extrahepatic OF, and in selected patients, it can offer a 1-y survival that exceeds 80%, making it comparable with outcomes for patients with decompensated liver disease.[11,12] Moreover, the quality of life after liver transplant, as assessed by Karnofsky performance status, appears to be excellent in those patients who were transplanted in the presence of multiple organ failure.[13]

Organ shortage continues to be the major limiting factor for transplanting patients with chronic liver disease including ACLF patients and wise and judicious use of available organs is of paramount importance to achieve excellent outcomes. The purpose of this study is to identify pretransplant risk factors that are associated with proceeding with liver transplantation in the presence of ACLF.

MATERIALS AND METHODS

After institutional review board approval was obtained, a retrospective review of all patients who were referred for consideration for liver transplantation at our institution between January 1, 2016, and December 31, 2017, was performed. All patients with ACLF who presented to our institution as a direct admission or transfer from another facility were included. Patients with ACLF were identified based on the European Association for the Study of the Liver (EASL) definition "acute deterioration of preexisting, chronic liver disease, usually related to a precipitating event and associated with increased mortality at 3 mo due to multisystem organ failure."[4] Patients younger than 18 y of age and patients who were evaluated for dual organ transplantation and liver retransplantation were excluded. Liver transplantation candidacy was evaluated for all patients in a multidisciplinary meeting that involved liver transplant surgeons, transplant hepatologists, social workers, nutritionists, nurse coordinators, and pharmacists.

ACLF Cohort

Patients' demographics, comorbidities, and etiology of liver disease were recorded. Primary decompensating event, development of a secondary decompensating event during hospitalization, development of a secondary infection, model of end-stage liver disease-sodium (MELD-Na) score and laboratory values at admission and during hospitalization were evaluated. The primary decompensating event was defined as the initial event that caused the patient to be admitted to the hospital. The secondary decompensating event was defined as an event that developed a few days to a week after the primary event and during the same admission and caused further deterioration in the clinical status of the patient. The etiology of the secondary decompensating event was classified as either infection or bleeding. Secondary infection was defined as an infection that developed after the initial decompensation during the same hospitalization. Peak lactate and peak white blood cell count (WBC) were defined as the highest value before transplantation in the transplant group or the highest value during admission in the nontransplanted group.

The presence and development of organ failure during hospitalization was defined based on a modified version of the Chronic Liver Failure-Sequential Organ Failure Assessment (CLIF-SOFA) scale as follows: (1) hepatic failure as serum bilirubin ≥12 mg/dL, (2) renal failure as serum creatinine (Cr) ≥2 mg/dL or being on intermittent or continuous hemodialysis, (3) coagulation failure as international normalized ratio (INR) ≥ 2.5, (4), neurologic failure as hepatic encephalopathy grade (HE) 3 or 4, (5) respiratory failure as being on a mechanical ventilator or $PaO_2/FiO2 ≤ 200$, and (6) circulatory failure as being on vasopressors.[5,11] The number of organ failures was assessed and the severity of ACLF was graded based on the number of OF: grade 1 with 1 OF, grade 2 with 2 OF, and grade 3 with 3 and more OF.[5]

Patients' outcomes including mortality within 30 d, transplantation status, hospital charges, and survival at last follow up were collected. Mortality within 30 d was defined as death during the index admission or within 30 d after discharge. Observation started at an index date, defined as admission date, and patients were followed until event date or 30 d of discharge. Hospital charges were obtained for the entire hospital stay.

Liver transplantation for patients with acute alcoholic hepatitis was offered in our institution without the need for a period of sobriety. All patients with first presentation of severe acute alcoholic hepatitis failing medical therapy were evaluated for liver transplantation after a thorough psychosocial assessment.

For patients who were not offered liver transplantation, the contraindication was categorized as medical, social, or recovered without transplantation. Medical contraindications included too sick for transplantation, presence of active malignancy, overwhelming sepsis, advanced systemic disease (cardiomyopathy, severe pulmonary hypertension, severe deconditioning, and malnourishment), or presumed technical difficulty (extensive mesenteric thrombosis or hostile abdomen). Social contraindications included active drug abuse, lack of insurance, or the lack of adequate support structure. Patients who recovered showed rapid improvement in their clinical status and organ function without the need for transplantation.

Artificial liver support devices were not used in our cohort.

Transplanted ACLF Cohort

For ACLF patients who underwent liver transplantation, donor and intraoperative details including cold ischemic time, donation type (donation after brain death [DBD] versus donation after cardiac death [DCD]), donor warm ischemic time in DCD donors, estimated blood loss, type of caval reconstruction (bicaval versus piggyback), transfusion requirements, presence of a native portal vein thrombus at the time of transplantation, need for an arterial jump graft, need for intra operative veno-venous bypass, and if the abdomen was temporarily left open were recorded. Cold ischemic time was defined from aortic cross clamp in the donor to portal reperfusion in the recipient. Donor warm ischemic time was defined from extubation to initiation of aortic flush.

Postoperative outcomes including hepatic artery thrombosis, portal vein thrombosis, primary allograft nonfunction, early allograft dysfunction, reoperation, need and duration of renal replacement therapy, biliary complications, respiratory failure, and need for tracheostomy, rejection, length of hospital and intensive care unit stay were evaluated. Primary allograft nonfunction was defined as development of liver failure within 7 d posttransplantation resulting in retransplantation or death in the absence of a major vessel thrombosis. Early allograft dysfunction was defined as peak AST/ALT above 2000 IU/L within the first week, INR > 1.6 or bilirubin > 10 mg/dL on posttransplant day 7.[14] Biliary complications included biliary stricture or leak identified on an ERCP. Patient and graft survival were observed from transplantation date. Graft failure was defined as death with a functioning graft or liver failure requiring retransplantation. Postoperative and long-term outcomes were compared between patients with ACLF grade 1 and 2 and ACLF grade 3.

Statistical Analysis

Descriptive statistics for characteristics of patients were presented as means with standard deviations (SDs) or medians with interquartile ranges (IQR) as appropriate for continuous variables and numbers with frequencies for categorical variables. Differences between 2 groups were assessed using the chi square test for categorical variables; normality was checked for all continuous variables, if the data were not

normally distributed, the nonparametric Wilcoxon test was used, and otherwise the t test was used. Significant variables ($P \leq 0.05$) were considered for multivariate analysis. A logistic regression model with feature selection using backward elimination to optimize the performance was applied to the data. Collinearity between variables were assessed before inclusion in the model, and highly correlated variables were tested separately. In addition, at each elimination step, multicollinearity among covariates was checked by using correlation analysis with a cutoff point of $r = 0.8$, and variance inflation factor with a cutoff value of 5. Variables with a significant effect ($P \leq 0.05$) were retained in the final model. Estimations of adjusted odds ratios (aORs) and 95% confidence intervals (CI) were reported. Unadjusted Kaplan–Meier survival curves were used for data illustration. All analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC).

RESULTS

During the study period, 807 patients with liver disease were evaluated at our transplant center, and 63 patients were excluded due to dual organ transplant evaluation (N = 51) and retransplantation evaluation (N = 12). We identified 144 patients with ACLF in this study; of these, 32 were not listed, and 112 were listed. Of the listed patients 86 were transplanted (Figure 1). The average age of our ACLF cohort was 53 y, and 86 (59.7%) were males. The most common cause of liver disease in our cohort was alcohol 84 (58.3%) patients. Infection as a primary decompensating event was seen in 87 (60.4%) patients.

Transplanted Versus Not Transplanted

Demographics and Comorbidities

In our ACLF cohort, 86 patients were transplanted, and 58 were not. There were no statistical differences between the 2 groups in demographics and the presence of comorbidities apart for a lower incidence of pulmonary hypertension in the transplanted group (2% versus 12%, $P = 0.018$) (Table 1).

Presentation and Organ Failure

There was no difference in MELD-Na score in the transplanted and nontransplanted group (33.6 versus 31.7, $P = 0.09$). The transplanted group had a lower median number of OFs during admission (4 versus 5, $P < 0.001$) and a lower incidence of grade 3 ACLF (76.7% versus 94.8%, $P = 0.01$). There was no statistical difference in the rate of hepatic failure (69% versus 78%, $P = 0.24$) and renal failure (83% versus 86%, $P = 0.57$) between the 2 groups, while the presence of coagulation failure (72% versus 86%, $P = 0.046$), neurologic failure (72% versus 93%, $P = 0.002$), respiratory failure (56% versus 88%, $P < 0.001$), and circulatory failure (49% versus 72%, $P = 0.005$) were lower in the transplanted group compared with the nontransplanted group.

On admission, the transplanted group had a lower serum lactate level (3.55 versus 4.84, $P = 0.04$) compared with the nontransplanted group. In addition, patients in the transplanted group had a lower peak serum lactate (4.83 vs. 9.60, $P < 0.001$) and lower peak WBC (18.6 versus 22.9, $P = 0.03$) compared with the nontransplanted group. During hospitalization, the development of a secondary infection (33% versus 51%, $P = 0.03$) and the development of a secondary decompensating event (41% versus 66%, $P = 0.003$) were less
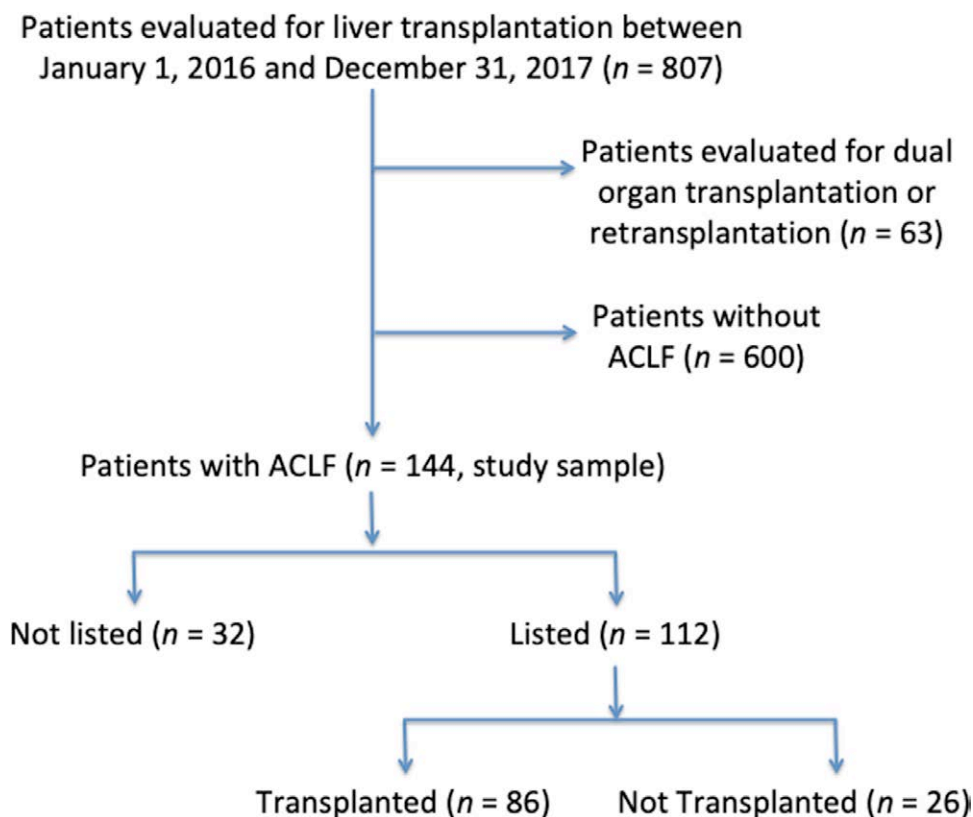

FIGURE 1. Flow chart of patients with liver disease evaluated at our institution during the study period. ACLF, acute on chronic liver failure.

TABLE 1.

Patient demographics and comorbidities of transplanted and nontransplanted patients

Variable	Transplanted (N = 86)	Not Transplanted (N = 58)	P
Age	52.52 ± 10.67	53.95 ± 11.41	0.45
Gender (male)	53 (61.6%)	33 (56.9%)	0.57
BMI	29.36 ± 6.96	30.93 ± 7.06	0.19
Race			0.53
White	70 (81.4%)	43 (74.1%)	
Black	11 (12.8%)	10 (17.2%)	
Hispanic	4 (4.7%)	4 (6.9%)	
Other	1 (1.1%)	1 (1.7%)	
Insurance			0.18
Medicaid	25 (29.1%)	22 (37.9%)	
Medicare	17 (19.8%)	9 (15.5%)	
Private	42 (48.8%)	22 (37.9%)	
VA/Tricare	2 (2.3%)	5 (8.6%)	
Comorbidities			
Hypertension	32 (37.2%)	20 (34.5%)	0.74
Diabetes mellitus	22 (25.6%)	14 (24.1%)	0.84
Chronic kidney disease	3 (3.5%)	6 (10.3%)	0.09
Coronary artery disease	4 (4.7%)	7 (12.0%)	0.10
COPD	5 (5.8%)	3 (5.2%)	0.87
Pulmonary hypertension	2 (2.3%)	7 (12.0%)	0.02
TIPS	5 (5.8%)	2 (3.5%)	0.52
Hepatocellular carcinoma	2 (2.3%)	3 (5.2%)	0.36
Prior abdominal surgeries	35 (40.7%)	23 (39.7%)	0.90
Etiology of liver disease			0.22
Alcohol	50 (58.1%)	34 (58.6%)	
HCV	10 (11.6%)	5 (8.6%)	
NASH	7 (8.1%)	10 (17.2%)	
HCV and alcohol	8 (9.3%)	1 (1.7%)	
Autoimmune	6 (7.0%)	2 (3.5%)	
Other	5 (5.8%)	6 (10.3%)	
Decompensating event			0.11
Infection	54 (62.8%)	33 (56.9%)	
Bleeding	13 (15.1%)	19 (32.8%)	
Alcohol	7 (8.1%)	4 (6.9%)	
Surgery	3 (3.5%)	1 (1.7%)	
Dehydration	1 (1.2%)	0 (0.0%)	
Portal vein thrombosis	2 (2.3%)	0 (0.0%)	
TIPS	1 (1.2%)	0 (0.0%)	
Tylenol overdose	0 (0.0%)	1 (1.7%)	
Unknown	5 (5.8%)	0 (0.0%)	
MELD_Na at admission	33.6 ± 5.8	31.7 ± 7.4	0.09
Lactate at admission	3.6 ± 2.2	4.8 ± 3.7	0.04
Albumin at admission	3.03 ± 0.74	2.76 ± 0.71	0.03
WBC at admission	14.1 ± 9.8	14.6 ± 8.7	0.77
Outpatient medications at admission			
SBP prophylaxis	8 (11.0%)	2 (3.7%)	0.13
Rifaximin	21 (28.8%)	14 (25.9%)	0.72
Lactulose	37 (50.7%)	21 (38.9%)	0.19
Proton pump inhibitors	34 (46.6%)	21 (38.9%)	0.39
Hepatic failure	59 (68.6%)	45 (77.6%)	0.23
Renal failure	71 (82.6%)	50 (86.2%)	0.56
Coagulation failure	62 (72.1%)	50 (86.2%)	0.05
Neurologic failure	62 (72.1%)	54 (93.1%)	0.002
Respiratory failure	48 (55.8%)	51 (87.9%)	<0.001
Circulatory failure	42 (48.4%)	42 (72.4%)	0.005

Continued next page

TABLE 1. (Continued)

Patient demographics and comorbidities of transplanted and nontransplanted patients

Variable	Transplanted (N = 86)	Not Transplanted (N = 58)	P
Number of organ failure	4 (2)	5 (2)	<0.001
ACLF grade			0.01
1	2 (2.3%)	0 (0.0%)	
2	18 (20.9%)	3 (5.2%)	
3	66 (76.7%)	55 (94.8%)	
Peak lactate	4.8 ± 2.8	9.6 ± 5.2	<0.001
Peak WBC	18.6 ± 11.5	22.9 ± 11.2	0.03
Peak INR	3.49 ± 1.48	4.55 ± 2.64	0.007
Secondary decompensating event	35 (40.7%)	38 (65.5%)	0.003
Secondary infection	28 (32.6%)	29 (50.0%)	0.03

Data are presented as numbers (%), means ± standard deviations and medians (interquartile ranges).

ACLF, acute on chronic liver failure; BMI, body mass index; COPD, chronic obstructive pulmonary disease; HCV, hepatitis C virus; MELD, model of end stage liver disease; NASH, nonalcoholic steatohepatitis; SBP, spontaneous bacterial peritonitis; TIPS, transjugular intrahepatic portosystemic shunt; VA, veterans affairs; WBC, white blood cell.

common in the transplanted group compared with the nontransplanted group (Table 2).

Secondary Decompensating Event and Secondary Infection

Seventy-three patients developed a secondary decompensating event. Infection was the most common etiology of decompensating event (77% in transplanted patients versus 68% in nontransplanted patients, $P=0.70$), while the rest were due to bleeding. In the transplanted group, pneumonia was the most common secondary infection (58%) encountered, followed by a urinary tract infection (22%). While in the nontransplanted group, pneumonia most commonly encountered (58%) followed by intraabdominal infections (23%). No patient in the transplanted group developed fungal infections, while 2 patients in the nontransplanted group developed fungemia. There were no differences in preadmission characteristics between patients that developed secondary decompensating event versus patients that did not except for a lower use of rifaximin preadmission (19.7% versus 36.1%, $P=0.04$) and a higher incidence of bleeding as a primary decompensating event (28.8% versus 15.5%, $P=0.02$).

Survival and Hospital Charges

Among the transplanted patients, 78 patients (90.7%) survived at least 30 d postdischarge as opposed to only 14 patients (24%) in the nontransplanted group. The 1-y survival in the transplanted group was 86%, while only 12% were alive in the nontransplanted group (Figure 2). Ten transplanted patients died within 1 y, 8 patients died from sepsis, 1 from unknown etiology and 1 from cardiogenic shock. The graft survival was similar to patient survival as none of the patients in our cohort required retransplantation. Regarding hospitalization charges, the hospital stay for the transplanted patients was significantly more expensive compared with the nontransplanted group ($227 886 versus $88 900, $P<0.001$).

Reasons for Not Listing or Transplanting

There were 26 patients that were listed but not transplanted; 20 were not transplanted for medical reasons, 5

Postoperative and long-term outcomes in transplanted patients based on ACLF grade

Variable	ACLF grade 1 and 2 (N = 20)	ACLF grade 3 (N = 66)	P
Length of stay pretransplantation (d)	12 (10)	9 (11)	0.94
Duration at outside hospital (d)	5.5 (8.5)	5 (13)	0.69
Open abdomen	1 (5.0%)	15 (22.7%)	0.07
Reoperation	2 (10.0%)	29 (43.9%)	0.006
Early allograft dysfunction	3 (15.0%)	19 (29.2%)	0.20
Hepatic artery thrombosis	0 (0.0%)	2 (3.0%)	0.43
Bile leak	0 (0.0%)	1 (1.5%)	0.58
Biliary stricture	3 (15.0%)	5 (7.6%)	0.32
Pneumonia postoperation	4 (20.0%)	20 (30%)	0.37
Days on the ventilator	1 (1)	2 (3)	0.001
Tracheostomy	2 (10.0%)	8 (12.1%)	0.80
Rejection	5 (25.0%)	17 (25.8%)	0.95
Dialysis posttransplantation	8 (40.0%)	44 (66.7%)	0.03
Dialysis at 3 mo posttransplantation	0 (0.0%)	6 (15.4%)	0.24
Dialysis at 1 y posttransplantation	0 (0.0%)	3 (8.1%)	0.40
Kidney transplanted	0 (0.0%)	2 (3.0%)	0.43
ICU LOS postTransplantation (d)	5 (5)	6 (7)	0.02
Hospital LOS posttransplantation (d)	12 (15)	22.5 (8)	0.04
Discharged home	11 (55.0%)	14 (21.2%)	0.004
Charges (USD)	173 240.5 ± 50 621.95	244 444.8 ± 122 618.7	<0.001

Data are presented as numbers (%), means ± standard deviations and medians (interquartile ranges).
ACLF, acute on chronic liver failure; ICU, intensive care unit; LOS, length of stay; USD, US dollar.

recovered without the need for transplantation, and 1 was not transplanted for social reasons. Thirty-two patients were not listed; 18 for medical reasons, 12 for social reasons, 1 for both medical and social reasons, and 1 recovered.

Factors Associated With Likelihood to Proceed With Transplantation

A multivariable analysis was performed to assess risk factors associated with transplantation. Only higher MELD-Na score at admission (aOR, 1.08; 95% CI, 1.00-1.16; $P = 0.048$) and a lower peak lactate level during hospitalization (aOR, 0.77; 95% CI, 0.69-0.86; $P < 0.001$) were significantly associated with proceeding with liver transplantation in patients presenting with ACLF.

Subanalysis of Transplanted Patients Based on ACLF Grade

During the study period, our center performed 330 liver transplants; 86 patients (26%) were patients with ACLF included here. Twenty patients had grade 1 or 2 ACLF, while 66 had grade 3 ACLF.

Donor Factors

The average age of the donor was 42.2 y (range 15–77 y), 61.6% were males, 67.4% were White, and the average BMI was 28.6 (range 13.7–45.8). Eighty-one grafts were procured from DBD donors, while 5 grafts were from DCD donors. Thirty-seven grafts (43%) were allocated from local donors, while the rest were regional. The average cold ischemic time
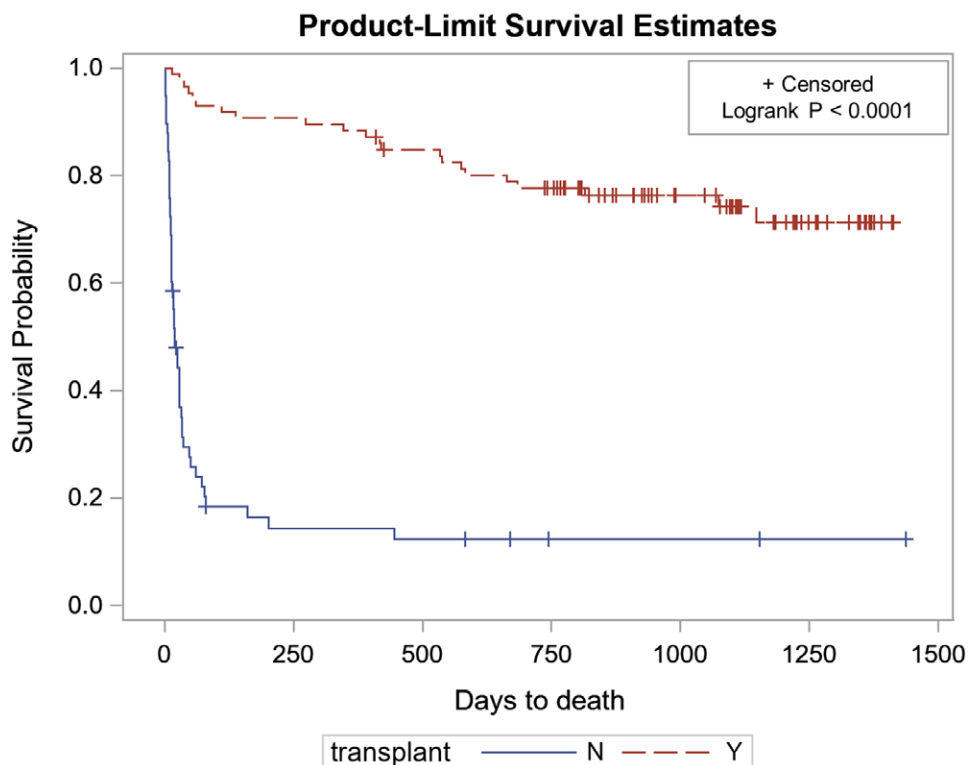

FIGURE 2. Kaplan–Meier patient survival curve with log rank test in transplanted and nontransplanted patients with ACLF. ACLF, acute on chronic liver failure.

was 253 min (range 140–383 min). For the DCD donors, the average donor warm ischemic time was 23 min (range 16–40 min).

Surgical Technique

The piggyback technique for caval reconstruction without systemic venous bypass was used in 75 cases, bicaval reconstruction was performed in 10 cases, and 1 case was performed in a piggyback fashion with systemic veno-venous bypass, which was initiated during the case due to excessive bleeding. A deceased donor arterial iliac graft was used in 1 case to create an arterial jump graft from the infra-renal aorta to the donor hepatic artery due to poor quality of the inflow artery. Primary end-to-end portal venous anastomosis was performed between the donor and recipient portal vein in all cases. Ten patients had a native portal vein thrombus that was evacuated with an eversion endovenectomy. Primary end-to-end choledocho-choledochostomy was performed in all cases.

Outcomes of Transplanted ACLF Grade 3 Versus ACLF Grade 1 and 2

Among the 86 patients who were transplanted, 66 patients (77%) had grade 3 ACLF, and 20 patients (23%) had ACLF grade 1 and 2. There was a trend towards a higher MELD-Na score at the time of transplantation in ACLF grade 3 group compared with ACLF grade 1 and 2 group (36.7 versus 34, $P = 0.06$). The average intra-operative estimated blood loss was not statistically different between both groups (4380 vs. 5410 mL, $P = 0.33$). There was no primary nonfunction or postoperative portal vein thrombosis of the entire cohort. Two patients in the ACLF grade 3 (3%) had hepatic artery thrombosis, while there was none in the ACLF grade 1 and 2. There was a statistically higher reoperation rate (44% vs. 10%, $P = 0.006$), higher need for postoperative renal replacement therapy (67% vs. 40%, $P = 0.03$), longer duration on the ventilator (2 d vs. 1 d, $P = 0.001$), longer postoperative ICU length of stay (6 d vs. 5 d, $P = 0.02$), longer postoperative hospital length of stay (22.5 d vs. 12 d, $P = 0.04$), lower percentage of patients discharged to home (55% vs. 21%, $P = 0.004$), and higher hospitalization charges ($244 445 vs. $173 241, $P < 0.001$) in the transplanted patients with ACLF grade 3 as compared with ACLF grade 1 and 2 (Table 2). There was no difference in overall survival after transplantation between ACLF 1 and 2 and ACLF 3 (log rank test $P = 0.50$), there was no significant difference in 30 d (log rank $P = 0.44$) and 1-y (log rank test $P = 0.07$) survival (Figure 3).

DISCUSSION

The prognosis of patients with ACLF and OF is usually poor with an escalating mortality rate as the number of failed organs increased unless patients were offered expedited liver transplantation.[3,4] Our current single-center study confirms the outcomes of prior studies and demonstrates a significant 1-y survival advantage of transplanted patients with ACLF and OF as opposed to patients that were not transplanted (86% versus 12%).[15–18] In addition, we report factors that influence the decision to proceed with liver transplantation and the outcomes associated with transplanting those with ACLF. Various risk factors have been studied to predict prognosis and survival in hospitalized patients with liver disease including grade 3 or 4 HE that has been associated with a higher in-hospital and 30-d mortality irrespective of the presence of other organ failures.[19] Using the United Network for Organ Sharing (UNOS), Thuluvath et al showed increasing mortality in ACLF patients with OF as the number of failed organs increased.[11] Moreover, liver transplantation is associated with excellent survival even in the presence of 3 or more OF.[11]
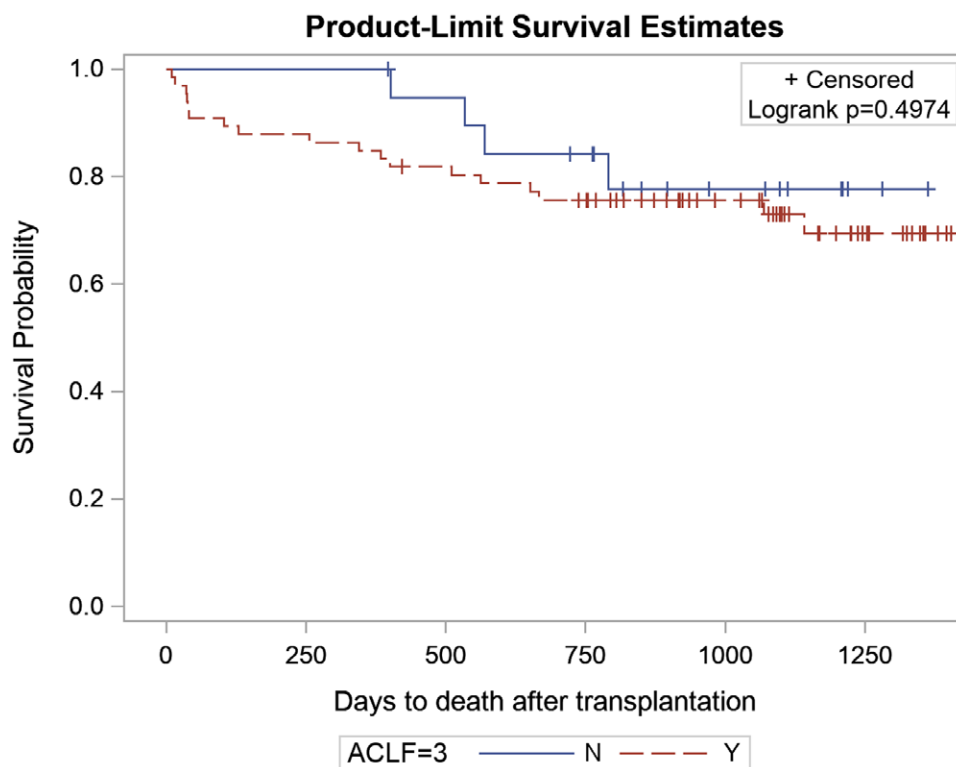

FIGURE 3. Kaplan–Meier patient survival curve with Log rank test by ACLF grade after transplantation. ACLF, acute on chronic liver failure.

We have corroborated those observations in our study also. However, there could be a strong selection bias when a decision is made to proceed with liver transplantation in the presence of multiple OF, and previous studies did not have sufficient granularity of data to examine the potential bias in the selection process. In our cohort, we found that ACLF patients who were much sicker on admission or during hospitalization, as manifested by a higher number of failed organs and a higher ACLF grade, were not likely to be transplanted. We examined multiple objective parameters that could have influenced the decision not to offer liver transplantation. One such surrogate marker was elevated peak lactate levels during hospitalization, which was identified as an independent risk factor for not offering liver transplantation in our study. Elevation in serum lactate is a probably a surrogate for increasing number and severity of organ failure, and it is most likely a result of a secondary decompensating event. This is similar to a recently published report that identified elevated serum lactate as an independent factor of decreased survival after liver transplantation in patients with ACLF grade 3.[20] Although we did not study the effect of a prolonged admission before transplantation, we believe, as has been previously suggested, that longer duration of hospitalization before transplantation is associated with worse outcomes in patients with ACLF, and this is likely the result of a "second hit" that renders these patients sicker and unfit for transplantation.[15,16]

We believe that patients with ACLF and OF should be evaluated for liver transplantation promptly once they are admitted. After ruling out nonmodifiable surgical, medical,

and psychosocial factors, a through in-depth evaluation is performed to judge the physiologic status of the patient by assessing the number and severity of failed organs (Figure 4). The presence of renal, hepatic, coagulation, and neurologic failure is seen in a large percentage of our cohort, and it usually does not affect our decision to proceed with liver transplantation directly, as we believe that these failed organs can be supported temporarily after transplantation until full recovery is achieved. However, assessing the cardiopulmonary status is of paramount importance in our pretransplant evaluation, and we pay special attention on the type and amount of respiratory support and the number and doses of vasoactive medications the patients are on. We tend to avoid transplanting patients who are on high vent settings (high FiO_2, high pressure support) and patients who are on high doses of multiple vasoactive medications, as these patients usually do not tolerate the surgical stress of liver transplantation and are likely to have an unfavorable outcome. After this evaluation, expedited listing should be done to these patients in an effort to transplant them rapidly. We believe that offering an expedited evaluation and listing process will decrease the pretransplant hospital length of stay and thus potentially prevent development of a second hit that might preclude patients from transplantation.

Management of ACLF patients requires heavy utilization of critical care resources to support the function of failing organs.[10] To our knowledge, this is the first study that reports on the financial ramifications of managing ACLF patients. In this study, we found out that there was a significant increase
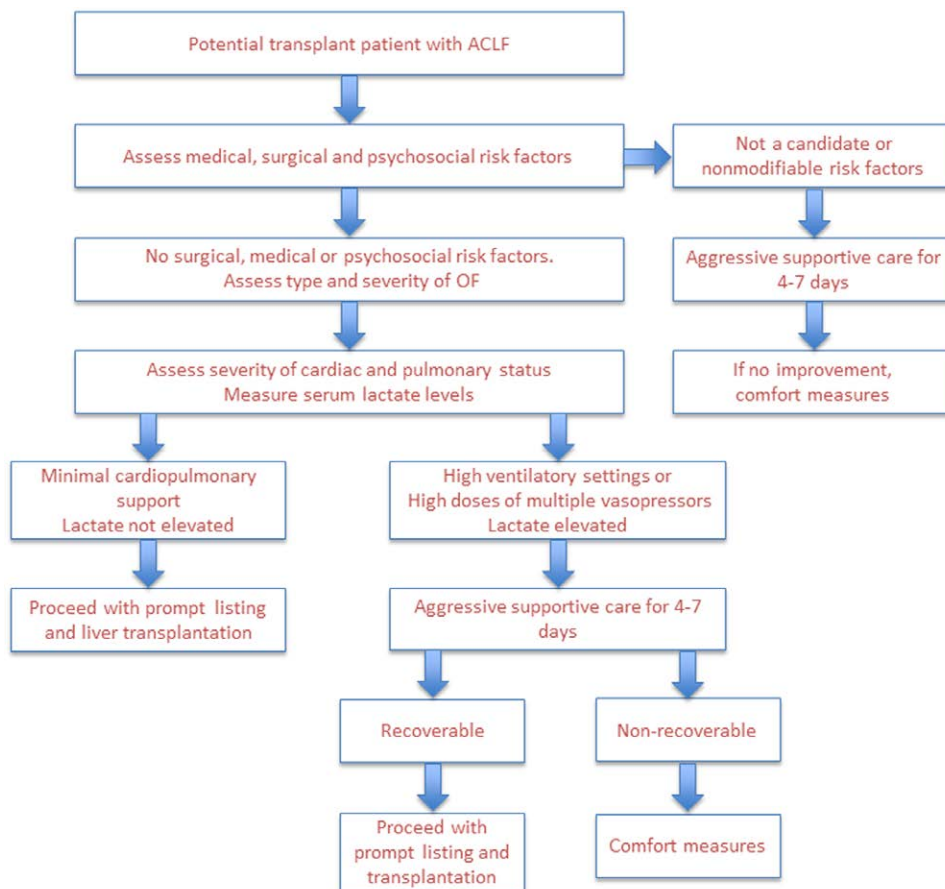

FIGURE 4. Management algorithm for patients with ACLF at the author's institution. ACLF, acute on chronic liver failure; OF, organ failure.

in-hospital charges for patients who underwent liver transplantation as opposed to patients who were not ($227 886 vs. $88 900, $P < 0.001$). Although this cost analysis is important, we strongly believe that it should not be a barrier to offer patients with ACLF liver transplantation.

Our study has multiple limitations. First, despite being the first study to report on the financial aspect of taking care of patients with ACLF, we only included hospital charges and failed to provide an in-depth breakdown of charges. Second, when assessing the severity of ACLF, we failed to provide granularity to the timing when organ failure developed as we combined the number of failed organs present on admission to the ones that developed during the admission. Given our expedited evaluation process for ACLF patients, all our patients were evaluated in the same hospitalization, and the time from admission to transplantation was very short, limiting our ability to provide a more descriptive timeline for organ failure development before transplantation. Third, we failed to provide details regarding the degree of vasopressor support and reasons for intubation, thus potentially overestimating the number and degree of organ failure. Forth, this is a retrospective single-center study with a limited number of patients, making it difficult to draw a cause and effect relationship. Future prospective multicenter studies are needed to provide a more standardized approach in evaluating patients for liver transplantation.

In conclusion, our study emphasized that liver transplantation in patients with ACLF offers a 1-y survival of 86% even in patients with 3 or more failed organs. We showed that elevated serum lactate during admission is a risk factor for not offering liver transplantation to patients with ACLF. Management of ACLF patients is an expensive and a resource intensive process, so careful selection of patients who undergo liver transplantation is of paramount importance to have good outcomes and ascertain judicious use of a scarce resource.

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