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Improvement in organ failure in acute on chronic liver failure (ACLF) upon liver transplantation

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***Abstract*---**Background &Aim: The prognostic factors determining the outcome of patients with cirrhosis and multi-organ failure are currently under evaluation. Reversal of organ failure pattern in

response to Liver Transplant has not been studied much. It is an understood phenomenon that different organs that failed as consequence of ACLF will ultimately recover from injury upon liver transplantation. The aim of the study was to determine the mean number of days a failing organ in a pre-transplanted patient will take to recover after liver transplantation. Methods: Data was collected from April 2013 till February 2020 in the department of Liver Transplantation, Hepatobiliary and Pancreatic Services, Shifa International Hospital, Islamabad. In this cross-sectional retrospective study, 82 ACLF patients of both genders of age >15 years who fulfilled EASL-AASLD definition and underwent liver transplantation were included in the study. And patients who fulfilled APASL criteria but did not fulfilled EASL-AASLD criteria of definition of ACLF or those who required ventilator support or triple inotropic support before surgery were excluded. Patients with serum creatinine level >1.5mg/dl were labeled as having renal failure. Those with total bilirubin level of >12 mg/dl were labeled as hepatic failure and those with INR >2.5 were having coagulation failure. Time to recover for each organ after transplant was noted. Results: Among these 82 patients, 84.1% (69/82) were males and 15.9% (13/82) were female patients. Mean age was 43.17+11.6 years. 24.4% (20/82) patents had pre-transplant renal failure, 72% (59/82) had pre-transplant hepatic failure and38% (32/82) had coagulation failure before the transplant. With grading of ACLF, 4 (4.8%) were of grade 1, 48 (58.5%) of grade 2 and 30 (36.7%) were of grade 3. Kidneys recovered in 5.8+6.07days with 85% patients had early recovery (within 2 weeks) and INR became normal in 6.9 + 3.7 days with 96.8% had early recovery. Hepatic recovery of 50/59 took 19.46+ 11.9 days with 31% patients showing early recovery. Few patients went into complications like post liver transplant biliary leaks and stricture formation further complicating our results by masking the recovery period of organs. Majority of the patients with hepatic failure in grade 2 ACLF, hepatic failure recovered late (>2 weeks) or went into complications. Conclusion: Authors reached on a conclusion that the renal function and coagulation system revived earlier than the hepatic function after live liver transplant. Liver of most of the ACLF patients with grade 2 ACLF, either recovered late or developed complications hence masking recovery period after liver transplantation.

***Keywords*---**live liver transplant, ACLF, organ failure.

Introduction

A recognized syndrome defined as; “an acute deterioration of liver function in patients with cirrhosis, which is usually associated with a precipitating event and results in the failure of one or more organs and high short-term mortality”.[1] From pathological standpoint; altered host response to injury and infection play important roles in its development and culminating in the end organ dysfunction. Occasionally, no specific precipitating event can be found. An important feature of

ACLF is its rapid progression, leading to multi-organ failure and a very high short-term mortality of 50-90%.[2,3]

ACLF syndrome remains undefined but two consensus working definitions exists: APASL forwarded, “Liver Failure is defined as Jaundice (serum bilirubin >5mg/dl) and coagulopathy (INR>1.5 or PT<40%). Liver failure is complicated within 4 weeks by clinical ascites and/or encephalopathy in patients with previously diagnosed or undiagnosed chronic liver disease” and EASL-CLIF stated, “Acute Liver Failure in a patient with chronic liver disease due to an acute insult and decompensation leading to one or more organ failure (serum bilirubin > 12mg/dl, INR > 2.5, serum creatinine > 1.5 along with grade 1/ 11 encephalopathy or isolated serum creatinine level of > 1.9, grade 111/ 1V encephalopathy, inotropic support for maintaining MAP > 65mmHg, ventilatory support for maintenance of saturation above 92%”.[4] These definitions are too imprecise to allow homogenous diagnostic criteria and clinical studies are currently underway to reach an evidence-based definition.[1]

Cirrhosis is characterized by histological development of regenerative nodules surrounded by fibrous bands in response to chronic liver injury, which leads to portal hypertension and end stage liver disease.[4]Nearly all causes of chronic liver injury can produce fibrosis and lead to the development of cirrhosis. Alcoholic liver disease and Hepatitis C are the most common causes in developed countries, whereas Hepatitis B is the prevailing cause worldwide. Fibrosis of the liver is mediated by the same molecular signals and cellular processes that govern the normal wound healing response. It is the location, duration and intensity of liver injury that dictate outcome.[4]

ALF, ACLF and ESLD are distinct physiologically, the molecular mechanisms dictating their pathogenesis are overlapping, and clinically liver transplantation remains the only definitive treatment for patients who fail to demonstrate recovery. To stratify potential liver recipients more objectively, UNOS (United Network for Organ Sharing) developed a modified listing criterion in 1997.[5] The new criteria were based on the CTP score (Child-Pugh-Turcotte) and candidates were scored as status 1 (fulminant liver failure) or status 2A, 2B, 3 in deteriorating order of priority. This system had several shortcomings and did not account for renal function and did not measure severity of liver illness on a linear scale. This ultimately led to the use of MELD (Model for End Stage Liver Disease) for allocation of liver in Feb.’ 2002.[6]

Meld score was initially developed to estimate the 3 month mortality risk in patients with cirrhosis undergoing TIPSS procedure.[7] An increasing score indicates increasing mortality, for example patient with a MELD score of 10 have a 3 month mortality rate of close to 0%, compared to around 90% for those with a score of 40.[8] The prognostic factors determining the outcome of patients with cirrhosis and multi-organ failure are currently under evaluation, but it seems that the scoring systems addressing the severity of liver disease, such as CTP, or MELD for ESLD[9] perform less well than the scoring systems addressing organ dysfunction such as SOFA (sequential organ system failure assessment) or APACHE[10] scores.

The rationale of this study was to observe reversal of organ failure pattern in response to Liver Transplant. It is an understood phenomenon that different organs that failed because of ACLF will ultimately recover from injury upon liver transplantation. This study would also help generate local statistics and would be a source for sharing experience of 82 cases undergoing Liver Transplantation for ACLF at Shifa International Hospital, Islamabad.

Materials and Methods

The data collected for this study was done during April 2013 till February 2020 in the department of Liver Transplantation, Hepatobiliary and Pancreatic Services, Shifa International Hospital, Islamabad. In this cross-sectional retrospective study, 82 ACLF patients of both genders of age >15 years who fulfilled EASL-AASLD definition[11] and underwent liver transplantation were included in the study. All those patients with serum creatinine level > 1.5mg/dl were labeled as having renal failure. All those patients with total bilirubin level of > 12 mg/dl were labeled as hepatic failure and those with INR > 2.5 were having coagulation failure. Time to recover for each organ after transplant was noted.

ACLF cases were graded as 1, 2 and 3 based on the number of organ failures. Those patients with creatinine 1.5-1.9mg/l and with grade 1/ 2 encephalopathy were labeled as grade 1. Those with two failing organs (liver, kidney, coagulation, brain, circulatory etc.) were labeled as grade 2. Those patients of ACLF with three or more of the failing organs were labeled as grade 3.[11] Chronic liver disease (Cirrhosis) was defined as a condition characterized by the presence of regeneration nodules along with fibrotic bands seen on history. Patients can end up into portal hypertension and end-stage-liver-disease (ESLD).

All those patients who fulfilled APASL criteria but did not fulfilled EASL-AASLD criteria of definition of ACLF and those who required ventilator support or triple inotropic support before surgery were excluded. Patients with active infection or on high ionotropic dependent (>10 mg/min of nor-epinephrine, more one ionotropic medications) were also not included in the study. Details regarding the donor as well as patient selection along with the operation procedure have been discussed elsewhere.[12,13]

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, which includes members of various departments including transplant surgery, hepatology, anesthesia, physiotherapy, and ICU/critical care. Demographics along with etiology leading to liver failure, MELD scoring and aggravating factors were noted.

The patients and family were already counseled regarding future use of data for research purpose and benefits of the study explained to all patients and a written informed consent obtained. All patients were already subjected to detailed history and clinical examination. All patients were followed up at regular intervals to detect recovery pattern of outcome i.e., duration of time of recovery of different organs from time of liver transplantation. All the above-mentioned information

including name, age, address, and telephone number was recorded on a pre-designed proforma. Strictly exclusion criteria were followed to control confounders and bias in the study results. All the above-mentioned observations were conducted under supervision of an expert Transplant Surgeon with at least 5 years' experience.

Statistical Analysis

All the collected data was stored and analyzed in SPSS version 25 for windows. Mean + standard deviation was calculated for numerical variables like age, grades of ACLF and recovery time. Frequencies and percentages were calculated for categorical variables like gender. Common outcomes were stratified among age, organs recovery and duration to see the effect modifications. Qualitative variables were compared between two groups were done by Chi Square / Fischer exact test. Independent sample T test or one way ANOVA test were used to compare means of quantitative variables like mean hospital stay duration, Bilirubin level, Albumin level, ALT level and INR value. P value less than 0.05 was considered statistically significant.

Results

Among these 82 patients, 84.1% (69/82) were males and 15.9% (13/82) were female patients. Mean age of the patients was 43.17+11.6 years and mean BMI of the patients of 25.25 ± 5.05. Mean age and BMI among males was43.12 ± 11.4 years and 25.41 ± 4.98, respectively. Similarly, mean age and BMI among the female patients was 44 ± 12.88 years and 25.55 ± 7.76, respectively. Among the males, 12.1% were under-weight, 36.4% normal BMI, 37.9% over-weight and 13.6% were obese. Similarly, among the females, 20% were under-weight, while 26.7% were having normal BMI, over-weight and obese each. With grading of ACLF, 4 (4.8%) were of grade 1, 48 (58.5%) of grade 2 and 30 (36.7%) were of grade 3.

Several preoperative parameters such as hypertension, diabetes mellitus, ischemic heart disease, asthma, CTP score, CTP grade, different etiologies, MELD score, presence or absence of ascites, hematemesis and portosystemic encephalopathy were compared among the groups of patients with different grades of ACLF and most of the parameters were statistically comparable among the groups ($p>0.05$). Only CTP score appeared to have a statistically significant difference between the different groups with $p<0.05$ (Table 1).

Table 1: Comparison of study population characteristics in recipient groups

Characteristic	Grade 1 ACLF	Grade 2 ACLF	Grade 3 ACLF	p value
Mean Age (years)	44 ± 11.40	42.81 ± 12.21	43.36 ± 11.20	0.947
Mean BMI (kg/m^2)	24.05 ± 4.39	24.67 ± 4.70	26.39 ± 5.64	0.326
Gender				0.549
Male	4	39	26	

Female	0	9	4	
Hypertension				0.521
Present	0	8	2	
Not present	4	40	19	
Diabetes mellitus				0.640
Present	0	8	4	
Not present	4	40	17	
Ischemic heart disease				0.768
Present	0	1	0	
Not present	4	47	21	
Asthma				0.000
Present	1	0	0	
Not present	3	48	21	
CTP score	9.00 ± 1.41	10.76 ± 1.49	11.67 ± 1.21	0.025
CTP grade				0.262
Child A	0	1	0	
Child B	2	5	0	
Child C	2	31	6	
Etiology				0.188
HBV	0	3	11	
HCV	3	34	12	
NBNC	0	0	3	
Cryptogenic	0	2	0	
ALF	0	2	1	
PBC	0	0	1	
Wilson disease	0	2	0	
AIH	0	1	0	
Budd-Chiari syndrome	0	1	0	
ALD	0	1	0	
NASH	0	1	0	
Graft failure				
Ascites				0.099
Present	1	32	3	
Not present	3	16	5	
PSE				0.911
Present	1	16	3	
Not present	3	32	5	
Hematemesis				0.371
Present	0	7	0	
Not present	4	41	8	
Type of lobe				0.685
Right	4	45	28	
Left	0	0	1	
Dual	0	3	1	
MHV				0.974

No	3	37	23
Partial	1	6	5
Full	0	1	1
NA	0	3	1

(Abbreviations: BMI, Body mass index; CTP, Child-Turcotte-Pugh; HBV, Hepatitis B virus; HCV, Hepatitis C virus; NBNC, Non hepatitis B and non-hepatitis C; ALF, Acute liver failure; PBC, Primary biliary cirrhosis; AIH, Autoimmune hepatitis; ALD, Acute liver disease, NASH (Nonalcoholic steatohepatitis); PSE, Portosystemic encephalopathy; MHV, Middle hepatic vein).

About 24.4% (20/82) patients had pre-transplant renal failure with mean serum creatinine of 1.4 ± 1.08, 72% (59/82) had pre-transplant hepatic failure with mean serum bilirubin of 20.45 ± 12.35 mg/dl and 38% (32/82) had coagulation failure before the transplant with mean INR of 2.28 ± 1.25. Different preoperative labs such as Sodium levels, INR, creatinine, Albumin, platelet count, bilirubin, AFP level, MELD score and GRWR were compared among the groups of patients with varying grades of ACLF and the difference between none of the values appeared to be statistically significant (Table 2).

Table 2: Comparison of pre-operative labs in recipient groups

Parameter	Grade 1ACLF	Grade 2 ACLF	Grade 3 ACLF	p value
Mean Na^+ level (mEq/l)	124.75 ± 9.81	130.31 ± 8.22	129.25 ± 8.07	0.411
Mean INR	1.70 ± 0.53	1.45 ± 2.19	0.94 ± 2.28	0.529
Mean Creatinine level (mg/dl)	1.38 ± 0.75	1.48 ± 1.18	1.26 ± 0.94	0.695
Mean Albumin level (g/dl)	2.75 ± 0.53	2.74 ± 0.76	2.46 ± 0.49	0.209
Mean Platelet count ($\times 10^4$ cells/µl)	12.05 ± 10.85	10.36 ± 9.28	18.47 ± 44.26	0.458
Mean Bilirubin level (mg/dl)	25.22 ± 15.74	20.63 ± 13.21	19.48 ± 10.90	0.681
Mean AFP level (ng/ml)	5.57 ± 4.37	10.84 ± 15.76	9.82 ± 12.91	0.775
Mean MELD score	30 ± 8.16	30.09 ± 5.64	30.30 ± 5.54	0.986
Mean GRWR	1 ± 0.20	1.05 ± 0.25	1.03 ± 0.22	0.531

Abbreviations:(INR, International normalized ratio; AFP, Alpha fetoprotein; MELD, Model for end stage liver disease; GRWR, Graft to recipient weight ratio). Post-operative labs were also compared among the groups of patients. Only the difference among platelet counts were found to be statistically significant among the study groups (Table 3).

Table 3: Comparison of post-operative labs (7th day post op)

Parameter	Grade 1ACLF	Grade 2 ACLF	Grade 3 ACLF	p value
Mean Na^+ level (mEq/l)	136 ± 3.74	137.86 ± 5.37	140.46 ± 3.58	0.762
Mean INR	1.36 ± 0.28	1.30 ± 0.29	1.34 ± 0.27	0.888
Mean Creatinine level (mg/dl)	0.78 ± 0.29	1.09 ± 0.59	0.96 ± 0.44	0.504
Mean Platelet count ($\times 10^4$ cells/µl)	3.56 ± 1.27	4.07 ± 2.49	7.10 ± 5.32	0.011
Mean Bilirubin level (mg/dl)	13.40 ± 7.70	9.79 ± 9.65	7.91 ± 4.61	0.549
Mean AST level (Units/l)	128.33 ± 162.80	74.93 ± 57.88	68.75 ± 30.07	0.281
Mean ALT level (Units/l)	248.33 ± 251.95	133.06 ± 207.36	79.11 ± 53.88	0.287

Abbreviations:(INR, International normalized ratio; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase).

Kidneys recovered in 5.8 + 6.07 days with 85% patients had early recovery (within 2 weeks) and INR became normal in 6.9 + 3.7 days with 96.8% had early recovery. Hepatic recovery of 50/59 took 19.46 + 11.9 days with 31% patients showing early recovery (Table 4). Few patients went into complications like post liver transplant biliary leaks and stricture formation further complicating our results by masking the recovery period of failed organs. Majority of the patients with hepatic failure in grade 2 ACLF, hepatic failure recovered late (>2 weeks) or went into complications.

Table 4: Time of failed organ systems to recover after liver transplant

Organ system	Mean Recovery time
Recovery of Renal system	5.8 ± 6.07 days
Recovery of coagulation system	6.9 ± 3.7 days
Recovery of hepatic system	19.46 ± 11.9 days

Discussion

Sudden and rapid loss or malfunction of the hepatic parenchyma can lead to acute decompensated liver disease. This sudden hepatic malfunction can further

end-up into secondary organ system failure. One or more of the organs can get involved including kidneys, circulatory system, encephalopathy (brain), lungs and can even lead to hepatic shutdown. It is difficult to define decompensated liver disease along with multi-organ failure. Pathologist is now calling this condition as Acute on Chronic Liver Failure (ACLF). Based on the affected organs, ACLF is classified into four grades. The outcome of ACLF and its mortality is proportional to no. of failed organ systems;30 days mortality ranging to more than 70% when >3 organs disturbed. After lot of debate liver transplant in these cases have be labeled as a safe option.[14]

Among the failing organs most common are kidneys (in about 56% of patients), liver (44%), coagulation failure (28%), brain (24%), circulatory failure (17%) and the lungs (9%) as reported by Moreau R, et al. [15]They studied mortality of the liver transplant patients with prior ACLF and compared with non-ACLF patients. 28 days mortality of ACLF group was about 34% and 2% of non- ACLF group. Risk factors significant in the ACLF group were alcohol intake, bacterial infections, and raised WBCs and C-reactive protein (CRP).

In this study, about 24.4% (20/82) patients had pre-transplant renal failure with mean serum creatinine of 1.4 + 1.08, 72% (59/82) had pre-transplant hepatic failure with serum bilirubin of 20.45 + 12.35 mg/dl and 38% (32/82) had coagulation failure before the transplant with mean INR of 2.28 + 1.25. With grading of ACLF, 4.8% were of grade 1, 58.5% of grade 2 and 36.7% were of grade 3. Kidneys recovered in 5.8 + 6.07 days with 85% patients had early recovery (within 2 weeks) and INR became normal in 6.9 + 3.7 days with 96.8% had early recovery. Hepatic recovery of 50/59 took 19.46 + 11.9 days with 31% patients showing early recovery. Few patients went into complications like post liver transplant biliary leaks and stricture formation. Majority of the patients with hepatic failure in grade 2 ACLF, hepatic failure recovered late (>2 weeks) or went into complications.

Patients in our study showed improvement in renal function within 1st week. Storm C, et al. reported the return of normal renal function after living donor liver transplantation, within first 18 days of transplantation.[16]In another study, on renal dysfunction in patients of LT, on 3 months follow-up, about 80% of the patients with hepatorenal syndrome had normal renal function and none of the remaining patients was on long-term dialysis; thus, showing excellent outcome among the survivors of these liver transplant cases.[17]

Iwatsuki S, et al. studied few cases of combined renal and hepatic failure cases requiring liver transplant. After the LT, renal function starts to improve on the 5th day and became normal with the end of 2nd weeks. Hepatic function also improved within first 2 weeks.[18]House AK, et al.[19] reported a case of 19 years old female with hepatic failure had liver transplant with improvement in liver function in 6 days. But later after 2 months had biliary stricture for which she was operated. Kobayashi S, et al. [20] reported recovery of hepatic function within 2 weeks of liver transplant. In the post-transplant period, response of the recipient was quite excellent.

More than 100 cases were studied by Spanier TB, et al. who had multiorgan failure and had liver transplant. They defined multiple-organ-failure as failure of >2 organs. Those with multi-organ failure were compared with those who did not. Complications included mortality among patients with multiple failing organs was about 40% as compared to only 2% in the opposite group ($p < .0001$). They concluded that pre transplant assessment of severity using APACHE II and UNOS scoring can predict post-operative outcome.[21]

Bajaj JS, et al. reported after studying patients of ACLF that among all the patients, 55% had higher grade of encephalopathy, about 18% developed circulatory failure, and 15% had renal failure, while about 16% had respiratory failure. About 40% patients did not develop any type of organ failure. In the other group, about 37% had one failing organ system, 10% with two organ system failures, 10% with three organ failures, and 4% with four organ failures.

More the number of involved failing organs more the risk of death in 30 days of discharge. About 20% died within a month and 20% had secondary complications including infections. Survival of these patients depends on presence of nosocomial infections, low arterial pressure (MAP). MELD score, raised WBCs and low level of serum albumin.[22]

It is difficult to predict that patients with renal failure prior to liver transplant will have full recovery after transplant. Laskey HL, et al.[23]studied liver transplant patients with some degree of renal injury for more than 10 years. Among the 40 recipients, 65% recovered and 35% could not. Huebener P, et al. [24]analyzed 250 ACLF patients with cirrhosis who had liver transplant. Among these, 98 were having liver failure 3-months prior to transplant; and about 30% of these patients could not improve after the transplant and had a 90-day survival of 72.4% when compared to the survival of transplant patients without any prior ACLF. They reported that patients with organ failure(s) in the pre-transplant period if improved before transplant during stay in ICU had excellent post-transplant survival.

Choudhary[25]and colleagues report that circulatory failure and respiratory failures lead to significant mortality even after liver transplant in patients of ACLF, similar findings noted by Michard B, et al. [26]Levesque et al.[27] recently reported that those patients with ACLF before liver transplant had poor outcome (about 40% one-year survival). They concluded that those with respiratory failure should not be taken for liver transplantation. Artru F, et al contradicted this conclusion and reported that those with controlled respiratory failure fulfilling the transplant criteria window can get a liver transplant.[28]

Durand F, et al proposed guidelines for prevention and management of post- liver transplantation (LT) renal failure. Pre-transplant renal failure can lead to significant morbidity after the transplant and even chronic renal failure (CRF). With the prevention of renal failure, long-term improvement and survival can be achieved. Exact assessment of the renal function at the baseline is important. New criteria for the diagnosis of renal failure in these patients have been designed to identify acute renal failure earlier for better outcomes.[29]

With the advancement in the transplant surgery and techniques of liver transplant along with ICU care of the patients before and after the surgery, the outcome of the LT is improving. Patients of ACLF recover from mild renal insult and disturbance of coagulation profile in the body within a week but those with decompensated liver failure take time to recover, still prognosis of patients who survive transplant surgery and their body accept the liver graft recover sooner or later. Studies should be done to see the risk factors associated with the delayed recovery of organ systems.

Conclusion

Authors reached on a conclusion that the renal function and coagulation system revived earlier than the hepatic function after live liver transplant. Liver of most of the ACLF patients with grade 2 ACLF, either recovered late or went into complications after liver transplant.

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