Original Article

Outcomes of Liver Transplantation for Patients with Acute Liver Failure

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Abstract

Background: Liver transplantation is a treatment for patients who have acute liver failure (ALF). This study aims to evaluate the outcomes following liver transplantation in patients with ALF and compare them with cirrhotic patients who underwent liver transplantation.

Methods: This retrospective cross-sectional study was conducted at Shiraz Organ Transplant Center between June 2004 and March 2011 to evaluate the clinical presentation and underlying etiology of patients with ALF and their outcomes following liver transplantation.

Results: Out of 750 patients who underwent liver transplants, 12 (8 males and 4 females) had a diagnosis of ALF. The cirrhotic group (control) consisted of 20 transplanted patients. ALF patients were younger with a mean age of 18.7 ± 12.9 years compared to 37.4 ± 13.6 years in the cirrhotic group (P = 0.001). In the ALF group, 5 (41.66%) underwent partial living related liver transplantation compared to 1 (5%) in the cirrhotic group (P = 0.018). There were significantly more early post-transplant complications observed among patients with ALF compared to the cirrhotic group (P = 0.002).

Conclusion: Liver transplantation is safe, effective and should be considered in patients diagnosed with ALF.

Keywords: Acute liver failure, fulminant hepatic failure, liver transplantation

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Introduction

Acute liver failure (ALF), also known as fulminant hepatic failure, is a syndrome that occurs following abrupt onset of extensive loss of the liver cell mass which leads to jaundice and hepatic encephalopathy.[1] Patients typically do not have preexisting liver disease prior to this presentation. This condition has variable causes and in severe cases is associated with very high mortality. Death due to ALF is usually related to sepsis, cerebral edema and multiorgan failure. Mortality also significantly depends on the underlying disease that leads to ALF. While acetaminophen toxicity and acute hepatitis A and B have relatively good prognoses, seronegative hepatitis, and other causes with more insidious onset, are associated with higher mortalities.[2]

Liver transplantation has been established as the ultimate treatment of patients with ALF.[3] It has been recognized that early referral to transplantation centers is of utmost importance in these patients. Shiraz Organ Transplant Center is a leading transplant center in Iran with more than 18-year experience in liver transplantation. The aim of this study is to report the clinical course, presentation and outcomes of patients with ALF who have undergone liver transplantation in our center in comparison with patients who have liver cirrhosis.

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Materials and Methods

Definitions

The diagnosis of ALF was defined as proposed by O'Grady et al.[4] Accordingly, patients should have at least one episode of hepatic encephalopathy within 12 weeks after onset of their liver disease. We categorized ALF based on the time interval between jaundice and encephalopathy as follows: 1) hyperacute (0 to 7 days); 2) acute (8 to 28 days); and 3) subacute (29 days to 12 weeks).

Patients

This retrospective cross-sectional study evaluated the clinical presentation and underlying etiologies of patients with ALF and their outcomes following liver transplantation. We reviewed the charts of all patients who had undergone liver transplantation at the Shiraz Organ Transplant Center between June 2004 and December 2010 to identify those whose transplantations were due to ALF. An expert pathologist evaluated all explants from the identified patients. The diagnosis was made by review of clinical features, laboratory examinations, and explant pathology.

Patients' data that included: age, sex, primary diagnosis, history of using herbal medications, poisoning, clinical presentation, presence of ascites and gastrointestinal bleeding, time interval between jaundice and encephalopathy, time of transplantation, time interval between presentation and transplantation, result of pathology and source of allograft were collected by extensive chart review and questionnaire-based interviews with patients or their families when necessary. Outcomes, rejection episodes, and post-transplant surgical, and medical complications were also recorded. Laboratory profiles that included liver function test (LFT), complete blood count (CBC), prothrombin time (PT) and INR, partial thromboplastin time (PTT) electrolytes, blood urea nitro-

Table 1. Baseline characteristics of patients with acute liver failure (ALF) who underwent transplants at Shiraz Organ Transplant Center.

Mean age (years)	18.66 ± 12.94
Sex (male/female)	4/8
Underlying disease (primary diagnosis)	
Hallothane toxicity	1
AIH*	3
Wilson disease	3
Unidentified	5
Viral hepatitis	0
Clinical presentation	
Jaundice	9
Encephalopathy	6
Ascites	3
GI Bleeding*	1
Source of allograft	
Deceased donor	7
Living donor	5
History of herbal drug use	0

* AIH = autoimmune hepatitis, GI bleeding = gastrointestinal bleeding.

Table 2. Comparison between acute liver failure (ALF) and cirrhotic (control) groups.

	ALF[a]	Cirrhosis	*P*-value
Age (years)	18.66 ± 12.94	37.4 ± 13.63	0.001
Sex (male/female)	8/4	11/9	0.393
Source of allograft			0.018
Living-related	5	1	
Deceased	7	19	
Mean hospital stay (days)	23.58 ± 15.5	13.1 ± 5.2	0.007
Early rejection	7	4	0.034
Late complications			> 0.05
Diabetes	1	2	
Cytomegalovirus infection	1	3	
Renal failure	1	1	
Malignancy	1 (seminoma)	0	
Chronic rejection	3	2	
Hyperlipidemia	2	2	
Immunosuppressive regimen			
Prednisolone	12/12	20/20	
Mycophenolate mofetil	12/12	20/20	
Tacrolimus	9/12	14/20	
Cyclosporine	3/12	6/20	

[a] = acute liver failure

gen (BUN) and creatinine, viral markers for hepatitis A and B, autoimmune markers for autoimmune hepatitis, and serum ceruloplasmin and urine copper for Wilson disease were also gathered.

We compared these patients with 20 patients (controls) who had undergone transplantation for cirrhosis in the elective setting. Controls were those who had transplantations the week after transplantation of an ALF patient. We located control patients by conducting a search of our transplant list.

Statistical analysis

Results were expressed as mean ± SD. Data were analyzed by independent sample *t*-tests, and two-tailed Fisher's exact and Chi-square tests when appropriate by using SPSS software (version 12.0, SPSS Japan Inc., Tokyo). *P* values of < 0.05 were considered statistically significant.

Ethics

This study was approved by the Ethics Committee of the Shiraz University of Medical Sciences, Shiraz, Iran, where the work was undertaken. The study also conforms to the provisions of the Declaration of Helsinki (as revised in Edinburgh, 2000).

Results

During the study period there were 750 liver transplantations performed in our center. Of these, 12 (1.6%) patients had diagnoses of ALF. Other causes for liver transplantation during this period were HBV cirrhosis in 201 (26.8%), cryptogenic cirrhosis in 155 (20.6%), autoimmune hepatitis in 143 (19.1%), Wilson disease in 116 (15.4%), primary sclerosing cholangitis in 82 (10.9%), HCV cirrhosis in 35 (4.6%), and primary biliary cirrhosis in 18 (2.4%) patients.

There were 4 (33.33%) females and 8 (66.66%) males in the ALF group. There were 8 pediatric patients (< 18 years) and 4 who were over the age of 18 (range: 25 to 45) years. A total of 5 (41.7%) received allografts from living, related donors (4 patients from their fathers and 1 from her brother) and 7 (58.3 %) from deceased donors. Table 1 shows baseline characteristics of the patients.

We compared 12 ALF patients with 20 controls who had undergone liver transplantation for chronic liver disease (CLD) during the same period as the ALF cases. There were 8 patients in the ALF group and 11 in the control group who were male ($P = 0.393$). Mean age of patients in the ALF group was 18.66 ± 12.94 years while it was 37.4 ± 13.63 years in the control group ($P = 0.001$). In the ALF group, 5 (41.66 %) underwent partial living related liver transplantation compared to 1 (5 %) in the control group ($P=0.018$). Mean duration of hospital stay after liver transplantation was 21.58 ± 15.5 days for patients with ALF and 13.1 ± 5.2 days for patients with cirrhosis ($P = 0.007$). As seen in Table 2, in the first month after transplan-

Table 3. Early (1st month) post-transplant complications in patients with acute liver failure (ALF).

Complications	ALF group	Cirrhotic group	*P*-value
Diabetes	1	1	—
Cytomegalovirus infection	0	0	—
Rejection	7	4	—
Biliary leakage	2	1	—
Renal failure	0	0	—
Convulsion	2	1	—
Malignancy	0	0	—
Gastrointestinal bleeding	2	0	—
Early mortality	2	0	—
Cardiomyopathy	1	0	—
ARDS*	1	0	—
Intra-abdominal bleeding	1	0	—
Biliary necrosis	1	0	—
Number	22	7	0.002

*Acute respiratory distress syndrome

tation 7 patients in the ALF group and 4 patients in the cirrhotic control group had acute rejections, all of whom received methylprednisolone pulse therapy ($P = 0.034$). Early post-transplant complications during the first month following transplant in both groups are outlined in Table 3. No statistically significant difference was observed in the frequency of complications after the first month of transplantation between the two groups (Table 2).

Discussion

This study is the first Iranian study that evaluates outcomes of ALF after liver transplantation. Although Shiraz Organ Transplant Center is the first and most active liver transplant center in the country; the number of transplanted patients for ALF is considerably low in comparison with the large numbers of transplanted patients for CLD. This might have been due to the fact that many patients with ALF must refer from other regions of the country, which was often not feasible. Those who had the chance to seek medical care in this center were usually in the late stages of the disease, sometimes with grave complications that precluded transplantation.

We have shown that partial living donor transplantation was more significant in ALF patients. Due to organ shortage and the urgent nature of transplantation in this specific group this policy seems warranted.

ALF patients were younger with many of them under the age of 18 years, therefore their mean age was lower. Although this could have been a referral bias, as referral and willingness for transplantation are more likely for younger patients, it could also implicate a higher likelihood of ALF among this age group. This needs to be confirmed in larger prospective studies that register all ALF patients.

Acute rejection during the first month after transplantation was significantly higher among patients with ALF. The cause of this finding was unclear, however it could be related to the state of immunosuppression due to malnutrition, an altered immune system, and immunosuppressive treatment in those with CLD.

Patients with ALF had longer durations of hospital stay after surgery. Early post-operative complications were defined as any complication during the first month of the post-transplant period. There were more early post-transplant complications among ALF patients which agreed with other reports. Most were probably related to the grave condition of the patients at the time of transplantation. However, after the first month the outcomes did not differ between ALF and cirrhotic patients.

Only one patient had a history of drug toxicity by halothane. In contrast to other centers where acetaminophen-induced ALF was the most common cause for ALF,[4] no patient underwent transplantation for acetaminophen poisoning in our center. This was probably related to a lower rate of acetaminophen poisoning in our community. The high rate of Wilson disease in this group (25%) was considerable. As consanguineous marriages are quite common in this country, we see more cases of Wilson disease compared to Western countries. In our series of CLD we had higher rates of Wilson disease.[5]

In this study the cause of ALF was not identified in 5 out of 12 patients. There was a possibility of un-reported drug exposure, particularly to herbal drugs, in these patients. Some might also be unusual presentations of autoimmune hepatitis (AIH). Although workups for HAV, HBV, and HCV were performed for all patients there could be acute cases of hepatitis E virus (HEV). Although HEV was believed to present only during epidemics in Iran, recent data has shown that it might sporadically occur, primarily amongst those involved in raising animals.[6]

Our study population was too small to investigate the variables that influenced outcomes of ALF; however, apparent cause and lower grade of coma at admission have been associated with outcomes in other studies.[7]

ALF is a rapidly progressive, fatal condition. Few treatments are available and the mainstay of management is mostly supportive. It has been recently shown that N-acetylcysteine, which is utilized for acetaminophen toxicity, may increase the transplant-free survival rate in non-acetaminophen-induced ALF.[8] In hepatology centers that lack transplant facilities, the use of N-acetylcysteine has been associated with significantly higher survival rates.[9] Other interventions such as plasmapheresis and artificial liver support systems have not changed outcomes.[10,11] However, despite these efforts liver transplantation is still the only reliable treatment for most severe cases.

In conclusion, this study shows that liver transplantation is an effective treatment in patients with ALF. Although the early post-transplant complications are higher in ALF patients in comparison to CLD, the overall survival and complications do not differ.

Conflict of interest: Nothing to declare.

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