Transplant International

Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

Pediatric living-donor liver transplantation for acute liver failure: analysis of 57 cases

Walid Mohamed El Moghazy,[1,2,3] Yasuhiro Ogura,[1] Minata Mutsuko,[2] Kouji Harada,[2] Akio Koizumi[2] and Shinji Uemoto[1]

1 Department of Hepatobiliary, Pancreas and Transplant Surgery, Kyoto University, Kyoto, Japan
2 Department of Health and Environmental Sciences, Kyoto University, Kyoto, Japan
3 Department of Surgery, Sohag University, Sohag, Egypt

Keywords
graft loss, outcome, refractory rejection, survival.

Correspondence
Walid Mohamed El Moghazy, Department of Hepatobiliary, Pancreas and Transplant Surgery, Kyoto University Hospital, 54 Kawara-cho, Shogoin, Sakyo-ku, Kyoto city, Kyoto 606-8507, Japan. Tel.: +81 75 751 4324, +81 0806164 3079; fax: +81 75 751 4325; e-mail: moghazyw@gmail.com

Received: 27 October 2009
Revision requested: 17 November 2009
Accepted: 17 January 2010
Published online: 16 February 2010

doi:10.1111/j.1432-2277.2010.01059.x

Summary

We reviewed 57 pediatric patients admitted with acute liver failure to Kyoto University Hospital in Japan over a period of 15 years to compare the etiology and the long-term outcome of infants and children after living donor liver transplantation (LDLT). Patients were divided into two groups according to age at the time of liver transplantation, infants group (<1 year, $n = 20$), and children group (1–18 years, $n = 37$). The overall survival rates were 73.6%, 69.5% and 67.2% at 1, 5, and 10 years after LDLT respectively. Age of recipients at the time of LDLT had a strong impact on their outcome, Children had significantly better outcome than infants ($P = 0.001$). Surgical complications were comparable between both groups. Infants had higher rates of acute cellular rejection (ACR), which was associated with features of hepatitis in many cases. Refractory ACR was the leading cause of death in eight out of 12 infants, while it resulted in loss of one child only. Cox's proportional hazard regression model was used to examine potential risk factors for graft loss and it shows that age <1 year was associated with high risk of graft loss [hazard ratio (HR) = 11.393; CI = 1.961–76.1763] ($P < 0.05$). In conclusion, Infants had poorer prognosis than children and refractory ACR was the leading cause of death. Using additional immunosuppressant for cases with severe and atypical rejections is recommended.

Introduction

Acute liver failure (ALF) is a clinical syndrome characterized by severe impairment of liver function, which develops in patients without preceding chronic liver diseases. Massive or submassive necrosis is a typical pathological feature in the liver [1]. Hepatic encephalopathy is difficult to assess in many infants and children and may not be essential to the diagnosis of ALF in children [2]. ALF is rare and has multiple causes that vary in course and outcome [3]. Liver transplantation has revolutionized the management of ALF and improved survival rates considerably [4]. In Japan, where liver transplantation from brain-dead donor is performed very rarely, living donor liver transplantation (LDLT) is indicated for emergency cases such as ALF in pediatric patients [5]. Etiology of ALF and patient age may be important prognostic factors [6]. We reviewed 57 pediatric patients admitted with ALF to Kyoto University Hospital in Japan over a period of 15 years to compare the etiology and the long-term outcome of infants and children after LDLT.

Materials and methods

Patients

From June 1990 to July 2008, a total of 706 pediatric LDLTs were performed in 655 children (<18 years old) at Kyoto University Hospital. Fifty-seven pediatric patients

received LDLT as a result of ALF. Patients were divided in two groups according to age at the time of LDLT, infants group contained pediatric patients <1 year of age and children group included patients between 1 and 18 years of age.

Etiology of ALF

To investigate the etiology of ALF, a precise history including toxin- or drug exposure was taken, and serologic viral markers and examinations for metabolic disorders and autoimmune diseases were preoperatively performed as much as possible. In cases in which the symptoms and biochemical and histologic features were similar to those of viral hepatitis but in which no viral markers were detected and no history of toxin or drug exposure was found, the etiology of ALF was classified as cryptogenic hepatitis [7].

Surgical procedure

Techniques for donor and recipient operations have been described previously [8,9]. The left lateral segment was the primary choice. However, if the estimated graft-recipient weight ratio (GRWR) was larger than 4%, a monosegment graft was used [10]. For larger recipients, graft selection was extended to the left lobe [11] and to the right lobe [12] according to GRWR and the residual liver volume in the donor after hepatectomy.

Immunosuppression

The immunosuppressive regimen consisted of tacrolimus (FK506) and low-dose steroids [13]. Target tacrolimus trough serum levels were initially >10 ng/ml, decreasing gradually to 6–8 ng/ml a few months after LDLT. Methylprednisolone (10 mg/kg body weight) was administered intraoperatively prior to reperfusion. During the postoperative period, 1 mg/kg of the same drug was given for the first 3 postoperative days, followed by 0.5 mg/kg for the next 3 days, and 0.3 mg on the 7th postoperative day. This was changed to oral prednisolone at a dose of 0.3 mg/kg 8 days after transplantation. Prednisolone was reduced to 0.1 mg/kg/day 4 weeks after transplantation if the postoperative course was free of liver dysfunction, and steroid therapy was routinely weaned by 3–6 months after transplantation, as long as graft function was maintained.

In cases of ABO-incompatible LDLT, additional immunosuppressants and preconditioning regimens were given to inhibit humoral rejection; drugs used included prostaglandin E1, cyclophosphamide, azathioprine, mycophenolate mofetil (MMF), and plasma exchange according to the active ABO incompatible protocol on LDLT.

Acute cellular rejection (ACR) was treated with high-dose methylprednisolone as pulse therapy. If rejection was steroid-resistant, OKT3 was used. If liver function was not clearly normalized with tacrolimus and steroids, azathioprine for earlier cases and MMF for more recent cases was added as the third drug for maintenance immunosuppression. Wherever liver biopsy specimens presented mixed features of ACR and hepatitis, we decided in consultation with transplant pathologists as to the type of management for ACR or hepatitis that was appropriate on a case-by-case basis [7].

Clinical data

All clinical and laboratory data were collected from patients' charts. The values used for analysis were from the last records before LDLT. Data for cross-matching using flow cytometry was available for cases who received transplantation after the year 2000.

Statistical analysis

Overall patient survival was described by Kaplan–Meier methods, and compared using log-rank tests. The outcome was defined as graft failure or patient death after LDLT and Cox's proportional hazard model was used for examining the prognostic factors. Comparison between groups was made by Student's *t*-test and chi-squared tests. A P value <0.05 was considered significant. SPSS software, version 16 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

Results

A total of 20 infants and 37 children with ALF received LDLT at Kyoto University between March 1992 and August 2008. Mean age of infants was 0.39 ± 0.27 years (mean ± SD) while children had mean age of 10.04 ± 4.98 years. The mean follow-up for all pediatric patients was 6.04 ± 4.84 years (range 0.05–15.86 years). Mean follow-up for infants and children was 3.39 ± 4.33 (range 0.05–12.16) and 8.07 ± 4.64 (range 0.20–15.86) respectively. Among infants, three patients were younger than 1 month at the time of LDLT. Table 1 shows recipient characteristics in both groups. Cryptogenic ALF (non-A–non-B–non-C hepatitis) showed major difference between both groups, it was the indication for LDLT in 16 out of 20 infants (80%) while it represented indications in 17 out of 37 children (45.9%) ($P = 0.010$). Infants received liver grafts from younger donors ($P = 0.001$) and had better renal function than children ($P = 0.001$).

Table 1. Characteristics of patients.

	Infants	Children	*P*-value
Age (years)	0.39 ± 0.27	10.04 ± 4.98	0.000
Body weight (kg)	6.63 ± 1.96	37.05 ± 19.25	0.000
Male/Female	9/11	16/21	0.559
Cryptogenic ALF	16	17	0.010
Fulminant Wilson's	–	17	
Fulminant hepatitis	4	2	
Heat stroke	–	1	
ABO-incompatibility			
Identical/compatible/ incompatible	13/3/4	21/11/5	0.440
Graft type			
Mono/Lt Lat/ Left/Right	6/14/0/0	0/11/19/7	0.002
Donor age (years)	32.90 ± 9.11	38.97 ± 8.51	0.001
GRWR	3.39 ± 1.20	1.23 ± 0.48	0.001
Laboratory values			
WBCs ($\times 10^9$/l)	10.43 ± 7.06	7.62 ± 6.14	0.149
Platelets ($\times 10^4$/mm^3)	20.01 ± 26.05	21.16 ± 28.47	0.584
AST (IU/l)	369.06 ± 658.25	188.88 ± 249.716	0.813
ALT (IU/l)	247.21 ± 520.39	162.73 ± 296.9	0.472
Total bilirubin (mg/dl)	16.39 ± 10.24	17.94 ± 12.40	0.238
PT (s)	22.24 ± 5.93	22.75 ± 6.97	0.808
Creatinine (mg/dl)	0.28 ± 0.40	0.49 ± 0.31	0.001

Mono, monosegment; Lt Lat, left lateral segment; Left, left lobe; Right, right lobe; GRWR, graft recipient weight ratio; WBCs, white blood corpuscles; AST, aspartate aminotransferase; ALT, alanine aminotranferease; PT, prothrombin time; ALF, acute liver failure.

Patient and graft survival

The overall survival rates from the date of first LDLT to 1, 5, and 10 years after LDLT were 73.6%, 69.5% and 67.2% respectively. It was significantly lower when compared with survival of non-ALF pediatric patients who showed significantly better survival of 86.3%, 83.2% and 77.8% at 1, 5 and 10 years respectively; ($P = 0.038$). ALF pediatric recipients had graft survival of 73.6%, 65.3% and 62.5% at 1, 5 and 10 years respectively. Age of recipients at the time of LDLT had a strong impact on their outcome, Children had significantly better outcome than infants, they achieved patient survival of 94.5%, 85.3% and 81.9% at 1, 5 and 10 years respectively while infants had patient survival of 40%, 40% and 40% at 1, 5 and 10 years respectively ($P = 0.001$) (Fig. 1). Infants who sustained 1-year survival achieved better outcome. There was no difference between infants and children in term of patient survival after 1-year ($P = 0.245$).

Children had better graft survival of 94.5%, 85.3% and 81.9% at 1, 5 and 10 years respectively while infants achieved graft survival of 40%, 34.3% and 22.9% at 1, 5 and 10 years respectively (Fig. 2).

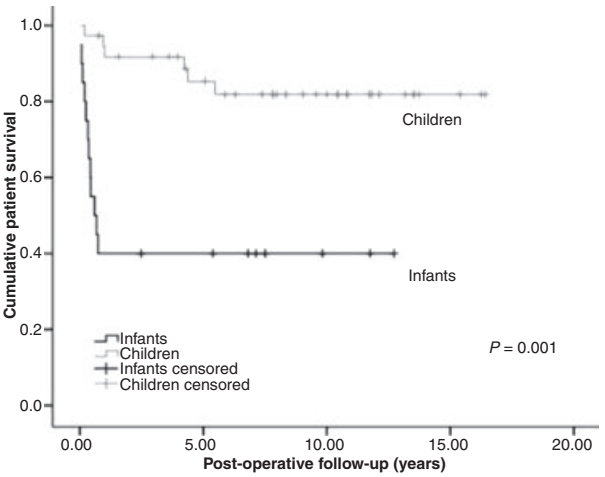

Figure 1 Survival of acute liver failure (ALF) pediatric patients after living donor liver transplantation (LDLT).

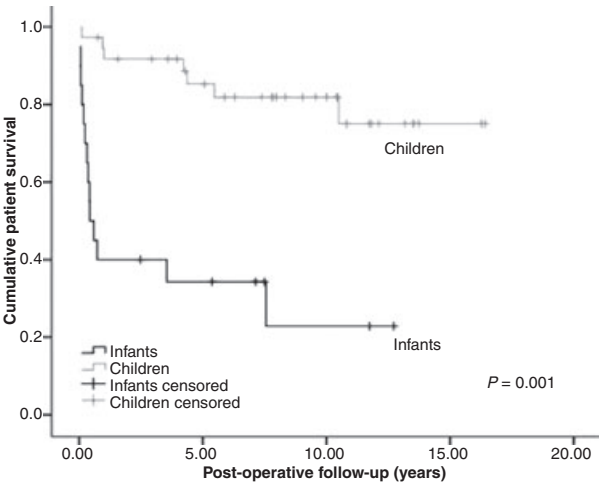

Figure 2 Graft survival of acute liver failure (ALF) pediatric patients after living donor liver transplantation (LDLT).

Etiology of ALF was unknown in 16 out of 20 infants (80%) and in 17 out of 37 children (45.9%). Cryptogenic ALF had significantly better graft survival in children group than in infants ($P = 0.001$). During follow-up period, 12 out of 16 grafts with cryptogenic ALF were lost in group of infants with overall graft survival of 25% while four out of 17 grafts were lost with overall graft survival of 76.5% in the children group.

Surgical complications

Biliary complications were the most common complication, it occurred in 13 patients, four infants and nine children ($P = 0.710$). Bile leakage ($n = 4$) was managed

by drainage and revision of the Roux-en-Y limb, whereas balloon dilatation and revision of the hepaticojejunostomy were used in cases of strictures ($n = 9$). Hepatic artery thrombosis (HAT) was reported in four cases, two cases in each group ($P = 0.517$). Portal vein complications in the form of stenosis at the anastomotic site, obstruction, partial thrombosis, and twisting of anastomotic site were detected in three infants and five children ($P = 0.877$). Interventional venoplasty was performed for all cases but additional therapy (i.e., thrombolytic therapy) was required for failed venoplasty. Surgical complications were comparable between both groups.

Rejection

According to Banff criteria, 34 patients (61.8%) had ACR in the first year after transplantation. Infants had markedly higher rate, where 20 patients (87%) had ACR in group 1 in contrast to 14 patients (43.8%) from group 2 ($P = 0.001$). Although the first attack of ACR tended to occur early in the group of infants (37.2 ± 63.0 days), there was no significant difference from older children (95.9 ± 273.4 days) ($P = 0.349$).

Moreover, infants had more severe attacks of rejection with mixed cellular infiltration at portal and central venous areas and other centrilobular injuries (necrosis and hemorrhage) observed at the same time with ACR [13 infants (56.5%) versus seven children (20.6%), $P = 0.015$] (Fig. 3). Presence of centrilobular injuries was associated with poor response to steroid pulse therapy and rapid deterioration of graft function in many cases and progression to ductopenic rejection in others. A total of five patients, [two infants (8.7%) and three children (8.8%), $P = 0.494$], developed ductopenic rejection. For ABO-incompatible grafts, antibody-mediated rejection (humoral rejection) was detected in two cases only and ACR incidence was not significantly different from other graft types ($P = 0.927$).

In our recent cases, augmented immunosuppressant regimens (with OKT3 or other immunosuppressive drugs such as MMF) were used with subsequent better outcome. When we compared pediatric patients, who received additional immunosuppressant immediately after LDLT, and those who received the standard regimen, the former group had significantly better survival ($P = 0.016$).

Risk factors for graft loss after LDLT

A univariate proportional hazard regression model was used to examine potential risk factors for association with graft loss. Univariate analysis revealed five potential risk factors at a statistical level of $P < 0.05$ (Table 2). Young age (infants), small body weight, cryptogenic liver failure as indication for transplantation, GRWR, and the type of the graft were associated with poor graft survival. Grade of encephalopathy, onset of liver failure (acute versus subacute), donor and plasmapheresis before LDLT, and human leukocyte antigen(HLA) A, B and DR mismatches showed no effect on graft survival. Cross-matching was negative for all cases after 2000, which made it difficult to examine its contribution to graft loss.

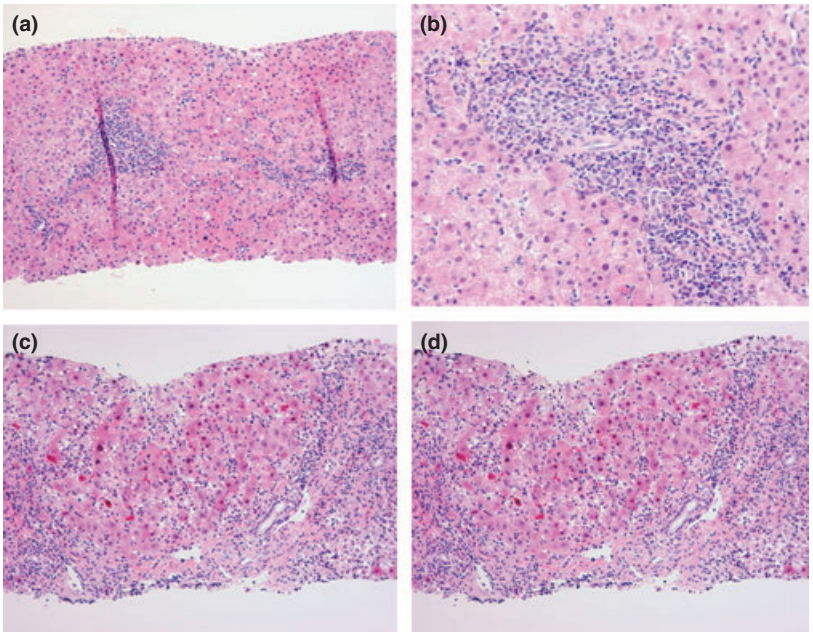

Figure 3 Histopathological examination for liver biopsy specimens, (a) and (b) show the mixed features of moderate acute cellular rejection (ACR) and lobular inflammation obtained on day 12 after living donor liver transplantation (LDLT) in female patient who was 5 months old. (c) and (d) show the second specimen which was obtained on day 24 and revealed severe ACR with massive hepatocyte dropout, which we called 'recurrence of acute liver failure (ALF)'.

Table 2. Risk factors for graft loss after LDLT by univariate analysis.

	Lost grafts	Functioning	*P*-value	Hazard ratio	95% Confidence interval	
Age						
≤1 year	15	8	<0.001	1	2.430	16.417
>1 year	6	28		6.316		
Gender						
Female	8	17		1		
Male	13	19	0.465	0.72	0.297	1.743
Recipient weight			0.004	0.96	0.928	0.986
ALF (known cause)	5	19		1		
Cryptogenic LF	16	17	0.013	3.623	1.317	9.967
Total bilirubin			0.998	1.00	0.961	1.040
Creatinine			0.074	0.15	0.018	1.205
Prothrombin time			0.674	0.99	0.919	1.056
C-reactive protein			0.123	0.16	0.016	1.638
Age donor			0.210	0.97	0.920	1.019
Gender donor (female versus male)	10	21	0.715	0.810	0.290	2.355
Onset (acute versus subacute)	21	36	0.260	1.724	0.668	4.449
Grade						
1	10	10	0.274			
2	6	17	0.841	0.876	0.241	3.188
3	2	7	0.186	0.393	0.098	1.571
4	3	2	0.224	0.329	0.055	1.973
Clinical status						
Hospitalized	7	10		1		
ICU-bound	14	25				
GRWR			0.003	1.35	1.104	1.641
Graft						
Left lateral	13	12	0.015			
Left lobe	3	16	0.219	0.49	0.157	1.529
Right lobe	1	6	0.004	0.11	0.024	0.502
Monosegment	4	2	0.044	0.10	0.012	0.943
ABO						
Identical	13	21	0.922			
Compatible	5	9	0.725	1.25	0.356	4.403
Incompatible	3	6	0.912	1.09	0.259	4.549
HLA-B mismatches						
1	4	8	0.763	1	0.308	4.985
2	4	8		1.239		
HLA-DR mismatches						
0	1	3	0.824	1		
1	5	7	0.970	0.954	0.086	10.540
2	2	6	0.600	1.555	0.299	8.097

ALF, acute liver failure; GRWR, graft recipient weight ratio; LDLT, living donor liver transplantation.

The five potential risk factors derived from the univariate analyses were further assessed by multivariate analysis. The multivariate analysis revealed that young age (<1 year) is the only variable ($P < 0.05$) with independent prognostic significance (HR = 11.393; CI = 1.961–76.1763) (Table 3).

Graft loss and re-LDLT

A total of 14 grafts were lost in infants group during follow-up period whereas seven grafts were lost in children group. In infants, 12 out of 14 grafts (85.7%) were lost within 1-year after LDLT while in children only two out of seven grafts (28.6%) were lost by the end of the first year.

Early graft loss in infants was related to severe ACR and subsequent HAT in one case, to Epstein–Barr virus (EBV)-related acute hepatitis in one case, chronic rejection in one case and nine cases showed severe lobular inflammation suggestive of recurrence of fulminant hepatitis; however, possibility of ACR could not be ruled out (Fig. 3). On the contrary, early graft loss in pediatric patients was caused by chronic rejection.

Table 3. Risk factors for graft loss after LDLT by multivariate analysis.

	P-value	Hazard ratio	95% Confidence Interval	
Cryptogenic liver failure	0.106	0.354	0.101	1.248
Recipient weight	0.255	1.066	0.955	1.190
GRWR	0.668	0.897	0.546	1.474
Graft type				
Left lateral	0.786	1	–	–
Left lobe	0.848	1.247	0.130	11.958
Right lobe	0.575	0.292	0.004	21.608
Monosegment	0.433	0.085	0.000	40.402
Age ≤1 year	0.012	11.393	1.691	76.763

GRWR, graft recipient weight ratio; LDLT, living donor liver transplantation.

Late graft loss in infants was related to chronic ischemic damage in one case and submassive necrosis and fulminant hepatitis-like pathology in the other case. Late graft loss in pediatric patients was related to vascular complications in three cases, and chronic rejection in two cases.

Five re-transplants were performed in both groups. Three infants received a second transplant because of graft failure, severe rejection with subsequent HAT, and portal vein thrombosis and two children had re-transplantation because of chronic rejection and chronic cholangitis.

Discussion

This study represents an important update on our experience with LDLT for ALF in pediatric patients. It showed that recipient age at the time of LDLT is a determinant for graft loss where infants had poorer graft survival compared with older children.

In this study, we examined the outcome of LDLT in 57 pediatric patients with ALF and we found a significant difference in the outcome where children (over 1 year) had an excellent survival of 81.9% at 10 years while infants had a poor survival of 40% at 10 years after LDLT.

There is no doubt that liver transplantation dramatically improved the outcome of ALF, as survival rates without transplant range from 10% to 30% [1,14,15]. Nevertheless, subjects with ALF have a poorer survival rate compared with subjects with non-ALF [5]. In this study, survival of children (>1 year) after LDLT exceeded 80% after 10 years which was comparable to those achieved for less emergent indications in the same age group [16].

Goss *et al.* [17] reported results for subjects with ALF that were comparable to those of subjects with non-ALF. However, compared with our study, only 12% of the patients in the study by Goss *et al.* [17] were infants, and there were few cases of cryptogenic ALF. In contrast, infants represented 35% of our patients, and cryptogenic ALF was the main indication for transplantation. Both indeterminate etiology and infancy are associated with poor prognosis as reported by other authors [2,18].

Etiology of ALF in pediatric patient is age-dependant [17], in a recent multicenter, multinational study [2], the cause of ALF was indeterminate in 49% of all cases and in 54% of children under 3 years of age. Although the medical history and laboratory examinations, including serologic viral markers and examinations for metabolic disorders and autoimmune diseases, were meticulously reviewed, 80% of infants and 46% of children were still classified as cryptogenic hepatitis in this patient cohort.

As shown in our previous report [7], cryptogenic ALF was associated with poorer outcome in infants. In this updated study, we confirmed the previous finding; however studying all pediatric patients showed that cryptogenic ALF was not associated with the same dismal prognosis in case of older children.

Infants with cryptogenic ALF had poor outcome with 25% graft survival while children achieved significantly better graft survival of 76.5%. Although infants are expected to have a higher rate of surgical complications (especially vascular) after liver transplantation, there was no difference between infants and children regarding surgical complications. Surgical innovations have led to lower incidence of vascular complications [16].

In our study, refractory ACR and chronic rejection contributed to 75% of the causes of death in infants and 33.3% of death in children. These figures look incomparable to figures of <6% for refractory ACR and chronic rejection in pediatric patients undergoing LDLT for non-acute liver diseases in our center [16]. ACR could not be controlled with pulse therapy in many cases and presence of mixed features of ACR and hepatitis impeded appropriate management. In our early experience, priority was given to management of hepatitis which was associated with poor prognosis as many cases progressed to refractory ACR and others to ductopenic rejection [5,7].

To explain this poor outcome, there are several possibilities; one possibility is technical problems related to reduced monosegment grafts used in infants however there is evidence in this study that type of graft is not a prognostic factor. In a previous report from our center [19], reduced monosegments were not significantly different from left lateral segments regarding graft survival however ALF as indication was associated with a poor prognosis.

Another possibility may be related to the underlying pathogenesis, cryptogenic liver failure represents the main

indication and it may be caused by viral infection, which could not be identified by the ordinary methods because of mutation of known viruses or a new virus. It is suspected that a long-lasting unknown hepatitis viral infection may have caused accelerated immune response in those patients [5]. Most ALF cases in pediatric patients are caused by hepatitis without an identifiable specific viral agent. There is a strong circumstantial evidence that non A-G ALF is a viral disease, but to date no viral agent has been identified [20]. Recently, Ishikawa *et al.* [21] reported a high prevalence of herpesviridae viruses in Japanese pediatric patients with fulminant hepatitis of unknown cause, and Palacios *et al.* [22] found a new virus after fatal transplants using unbiased high-throughput sequencing. Presence of histopathological evidence of hepatitis in specimens together with recurrence of the same picture in the graft after LDLT support this possibility; accordingly, we are studying the available samples to check the presence of undetected viruses using the previously referred technique.

Whether this infection is donor-derived or not is a difficult question to answer; however, donors should be considered for thorough screening for existence of viral infection. Donor-derived infections accounted for two cases of hepatitis B, who received their grafts from HBcAb-positive donors; however, both the transplant recipients are living with good functioning grafts.

Another possibility is antibody-mediated rejection; in this study, ABO-incompatible grafts represented about 15.8% of all cases and showed comparable outcome to other graft types with low incidence of humoral and cellular rejections. This favorable finding is most probably attributable to the use of preconditioning regimens including plasma exchange to decrease anti-donor blood group A/B antibody titers and using drugs like MMF [23].

Presensitization of pediatric patients (by their mothers) remains a remote possibility, patients who received grafts from their mothers and those with HLA-mismatches had graft survivals comparable to other cases and had no higher incidence of rejection.

A recent study from Pittsburgh [24] showed that early ACR of liver allografts in children is associated with enhanced donor-specific alloreactivity and requires additional immunosuppression. This observation supports our recent approach of increasing immunosuppression using MMF for patients who had severe early rejection, which was associated with better outcome.

Although LDLT provides a valuable resource for transplantation recipients, it also poses a risk to an otherwise healthy donor. Therefore, it is essential to select candidates carefully for LDLT [25,26].

In summary, infants, transplanted for ALF, had poorer prognosis than children as the infants have a much higher risk of graft loss after LDLT. Cryptogenic hepatitis remains a mystery and understanding the underlying pathogenesis may be the key to achieve a better outcome. Refractory ACR is the main contributing factor for this poor outcome and using additional immunosuppressant for transplant recipients with severe and atypical rejections is recommended.

Authorship

El Moghazy WM proposed the study and wrote the draft, Ogura Y and Uemoto S supervised the study. All authors contributed to the design and interpretation of the study and to further drafts.

Funding

We did not receive any grant or financial support to perform this retrospective study.

References

1. Fujiwara K, Mochida S, Matsui A, Nakayama N, Nagoshi S, Toda G. Fulminant hepatitis and late onset hepatic failure in Japan. *Hepatol Res* 2008; **38**: 646.
2. Squires RH Jr, Shneider BL, Bucuvalas J, *et al.* Acute liver failure in children: the first 348 patients in the pediatric acute liver failure study group. *J Pediatr* 2006; **148**: 652.
3. Akamatsu N, Sugawara Y. Acute liver failure and living donor liver transplantation. *Hepatol Res* 2008; **38**(s1The 6 Japan Society of Hepatology Single Topic Conference: Liver Failure: Recent Progress and Pathogenesis to Management. 28–29 September 2007, Iwate, Japan): S60.
4. Takikawa Y, Suzuki K. Clinical epidemiology of fulminant hepatitis in Japan. *Hepatol Res* 2008; **38**(s1The 6 Japan Society of Hepatology Single Topic Conference: Liver Failure: Recent Progress and Pathogenesis to Management. 28–29 September 2007, Iwate, Japan): S14.
5. Uemoto S, Inomata Y, Sakurai T, *et al.* Living donor liver transplantation for fulminant hepatic failure. *Transplantation* 2000; **70**: 152.
6. Lee WS, McKiernan P, Kelly DA. Etiology, outcome and prognostic indicators of childhood fulminant hepatic failure in the United kingdom. *J Pediatr Gastroenterol Nutr* 2005; **40**: 575.
7. Sakamoto S, Haga H, Egawa H, *et al.* Living donor liver transplantation for acute liver failure in infants: the impact of unknown etiology. *Pediatr Transplant* 2008; **12**: 167.
8. Tanaka K, Uemoto S, Tokunaga Y, *et al.* Surgical techniques and innovations in living related liver transplantation. *Ann Surg* 1993; **217**: 82.
9. Tanaka K, Inomata Y. *Living-Donor Liver Transplantation Surgical Techniques and Innovations*. Barcelona: Prous Science, 2003.

10. Kasahara M, Kaihara S, Oike F, *et al.* Living-donor liver transplantation with monosegments. *Transplantation* 2003; **76**: 694.
11. Ikai I, Morimoto T, Yamamoto Y, *et al.* Left lobectomy of the donor: operation for larger recipients in living related liver transplantation. *Transplant Proc* 1996; **28**: 56.
12. Inomata Y, Uemoto S, Asonuma K, Egawa H. Right lobe graft in living donor liver transplantation. *Transplantation* 2000; **69**: 258.
13. Inomata Y, Tanaka K, Egawa H, *et al.* The evolution of immunosuppression with FK506 in pediatric living-related liver transplantation. *Transplantation* 1996; **61**: 247.
14. Ikegami T, Taketomi A, Soejima Y, *et al.* Living donor liver transplantation for acute liver failure: a 10-year experience in a single center. *J Am Coll Surg* 2008; **206**: 412.
15. Devlin J, Wendon J, Heaton N, Tan KC, Williams R. Pretransplantation clinical status and outcome of emergency transplantation for acute liver failure. *Hepatology* 1995; **21**: 1018.
16. Ueda M, Oike F, Ogura Y, *et al.* Long-term outcomes of 600 living donor liver transplants for pediatric patients at a single center. *Liver Transpl* 2006; **12**: 1326.
17. Goss JA, Shackleton CR, Maggard M, *et al.* Liver transplantation for fulminant hepatic failure in the pediatric patient. *Arch Surg* 1998; **133**: 839.
18. Durand P, Debray D, Mandel R, *et al.* Acute liver failure in infancy: a 14-year experience of a pediatric liver transplantation center. *J Pediatr* 2001; **139**: 871.
19. Ogawa K, Kasahara M, Sakamoto S, *et al.* Living donor liver transplantation with reduced monosegments for neonates and small infants. *Transplantation* 2007; **83**: 1337.
20. Whitington PF, Alonso EM. Fulminant hepatitis in children: evidence for an unidentified hepatitis virus. *J Pediatr Gastroenterol Nutr* 2001; **33**: 529.
21. Ishikawa K, Hasegawa K, Naritomi T, *et al.* Prevalence of herpesviridae and hepatitis virus sequences in the livers of patients with fulminant hepatitis of unknown etiology in Japan. *J Gastroenterol* 2002; **37**: 523.
22. Palacios G, Druce J, Du L, *et al.* A new arenavirus in a cluster of fatal transplant-associated diseases. *N Engl J Med* 2008; **358**: 991.
23. Haga H, Egawa H, Fujimoto Y, *et al.* Acute humoral rejection and C4d immunostaining in ABO blood type-incompatible liver transplantation. *Liver Transpl* 2006; **12**: 457.
24. Sindhi R, Magill A, Bentlejewski C, *et al.* Enhanced donor-specific alloreactivity occurs independently of immunosuppression in children with early liver rejection. *Am J Transplant* 2005; **5**: 96.
25. Broering DC, Wilms C, Bok P, *et al.* Evolution of donor morbidity in living related liver transplantation: a single-center analysis of 165 cases. *Ann Surg* 2004; **240**: 1013; discussions 1024–6.
26. Umeshita K, Fujiwara K, Kiyosawa K, K, Kiyosawa K, *et al.* Operative morbidity of living liver donors in Japan. *Lancet* 2003; **362**: 687.