RESEARCH PAPER

Outcome of 200 Pediatric Living Donor Liver Transplantation in India

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ABSTRACT

Objectives: To describe our experience of pediatric living donor liver transplantation from India over a period of 12 year.

Materials and Methods: A retrospective analysis of 200 living donor liver transplantation in children (18 years or younger) was done for demographic features, indications, donor and graft profile and outcome.

Results: Between September 2004 and July 2016, 200 liver transplants were performed on 197 children. Fifty transplants were done in initial 6 years and 150 in next 6 years. All donors (51% mothers) were discharged with a mean stay of 7 days. The leading indications of liver transplants were cholestatic liver disease (46%) followed by metabolic liver disease (33%) and acute liver failure /acute on chronic liver failure (28.5%). Biliary leakage (8.5%), biliary stricture (9%), hepatic artery thrombosis (4.5%) and portal vein thrombosis (4%) were the most common surgical complications; all could be managed by surgical or interventional radiological measures, except in one child who died. Sepsis, acute rejection and CMV hepatitis in first 6 months were seen in 14.5%, 25% and 17% cases, respectively. Post-transplant lymphoproliferative disease was seen in only 1.5%. Re-transplant rate was 1.5%. The overall 1 year survival rate was 94% and 5 year actuarial survival was 87% with no statistically significant difference between children weight < 10 kg vs. > 10 kg. Outcome in acute liver failure did not differ significantly between those with acute on chronic liver failure *vs*. those with chronic liver disease.

Conclusions: Advances in medical and surgical techniques associated with multidisciplinary teams including skilled pediatric liver transplant surgeons, anesthetists, dedicated pediatric hepatologists, pediatric intensivists, interventional radiologists and pathologists resulted in an excellent outcome of living related liver transplants in children. Low age and weight of the baby does not seem to be a contraindication for liver transplantation as outcome were comparable in our experience.

Key words: *Acute Liver failure, Biliary Atresia,, Metabolic liver disease, Organ transplantation, Domino liver transplant*

INTRODUCTION

Liver transplantation (LT) has been well established in India for more than a decade now [1]. Common indications of pediatric LT are chronic liver disease (cholestatic, metabolic, autoimmune), acute liver failure and liver tumors. Over the years, the indications have extended to various inborn errors of metabolism [2]. We present our experience of 200 pediatric living donor liver transplantations (LDLT) in this large series from India.

METHODS

Data were collected from records of 200 children (<18 years of age) who underwent LDLT from September 2004 to July 2016. The initial 50 transplants were performed by the same team of surgeons and hepatologists at Sir Ganga Ram Hospital (New Delhi), and subsequent 150 transplants were performed at Medanta the Medicity (Gurgaon - Haryana).

Data was collected on age, sex, blood group, underlying liver disease, indications for liver transplant, vaccination status, and pre and post -transplant cytomegalovirus (CMV) and Ebstein Barr virus (EBV) serology status of the patient. Outcomes were recorded in terms of rejection (acute/chronic), surgical complications, blood culture positive sepsis, CMV hepatitis in the first 3 months, post-transplant lymphoproliferative disease (PTLD), retransplantation and survival. ALF was defined as per Pediatric Acute Liver Failure (PALF) study group as biochemical evidence of acute liver injury in a child with no known evidence of Chronic liver disease (CLD) with coagulopathy (defined as prothrombin time (PT) ≥15 sec or INR ≥ 1.5 not corrected by Vitamin K in the presence of encephalopathy, or PT >20 sec and INR>2.0 in patients without encephalopathy) [3]. Patients who had hepatic insult manifesting as jaundice and coagulopathy complicated within 4 weeks by ascites or encephalopathy in a previously diagnosed or undiagnosed CLD, were classified as having Acute on chronic liver failure (ACLF) as per Asia Pacific guidelines [4].

The criteria for listing for LT in patients with CLD included pediatric end stage liver disease (PELD) score >10 age <12 years, and model for end-stage liver disease (MELD) score >15 in >12 years, as per AASLD guidelines [4]. Those patients with ALF who fulfilled King's College criteria and revised Wilson's prognostic index for Wilson's disease (WD) were listed for LDLT. However, the trend of INR either outside or within hospital was followed before proceeding for LT. None of the patients with INR <4 were transplanted. Significant portal hypertension not responding to medications or associated moderate to severe hepatopulmonary syndrome (HPS) with more than 20% shunt were listed irrespective of their PELD or MELD score [4]. Patients with organic acidemias, urea cycle disorders and factor VII deficiencies were excluded from PELD and MELD scoring criteria for transplantation [5].

The immunization of the patients with CLD included all vaccines as per Indian Academy of Pediatrics (IAP) guidelines along with few optional vaccines such as hepatitis A, pneumococcal, chickenpox and typhoid. Our protocol included Measles Mumps Rubella (MMR) vaccine at 6 months, if early transplant was attempted. Live vaccines were not given within 3 weeks prior to the LT [6]. Nutritional assessment was done by measuring weight and height (centile and *Z* score as per WHO standrads). In patients of CLD with associated malnutrition posted for elective LT, efforts were made for nutritional optimization for 3-8 weeks prior to transplant, depending on the clinical condition of the patient. Energy-dense (120-150 kcal) and high protein diets were initiated in all, and if required tube feeds were given in hospitalized patients. However, weight and vaccination was not a criterion to refuse transplant in cases with advanced liver disease / liver failure necessitating urgent LT.

As per government of India guidelines, all transplants were performed with related donors. Blood group matched liver donors were preferred. In the absence of suitable blood group or volume mismatch in the family members, swap transplantation was done, which means paired donor exchange thus benefitting both patients. In the absence of suitable swap transplantation, ABO mismatch LT was done. Immunosuppression protocol in all patients included triple immunosuppression which comprised of steroids (day 1), tacrolimus (day 3) and mycophenolate (day 3-5) unless any toxicity observed to that drug. Tacrolimus level of 7-10 ng/ml was maintained in the initial 1-2 months, followed by gradual tapering of the dose over time to achieve long term immunosuppression levels of 4-6 ngm/mL beyond 1 year post-LT. Mycophenolate was stopped 6-7 months post-LT in most patients. Antibiotic prophylaxis with broad spectrum antibiotics and antifungal prophylaxis with fluconazole were utilized in all children. Antiviral prophylaxis for CMV with intravenous gancyclovir or oral valgancyclovir was administered for initial one month post-transplant in high-risk cases (donor positive and recipient negative cases, patients who were CMV PCR positive prior to transplant, and in all infants in last 100 transplants). In the last 150 liver transplants, CMV and EBV PCR (quantitative) monitoring was done at 2, 4, 8, 12 and 24 weeks post-LT followed by 6monthly intervals or as and when viremia was suspected. Ultrasound-Doppler for hepatic vasculature was done twice a day for first 5 days post-LT; then daily till 7-10 days post surgery following which a protocol of twice a week was followed till discharge.

The donors underwent a complete medical and physical examination as per standard international living liver donation guidelines [7]. The following donor data was obtained from database: age, sex, blood group, relationship to recipient, graft type and outcome in terms of complications and survival.

Statistical analysis: Continuous variables were reported as median and categorical variable as proportions. The patient survival was shown as Kaplan Meier curve and comparison in different groups was performed using log rank tests. Categorical and continuous variables were compared using Fisher's

exact test, the Mann-Whitney U test and t test respectively. P <0.05 was considered statistically significant. Statistical analysis was performed with the SPSS version 19.0.

RESULTS

A total of 200 LDLT, including three retransplants, were performed on 197 patients (60% males). Indications of LDLT are shown in ***Table* I**. Biliary Atresia (BA) was the commonest indication for liver transplant. Forty-eight (66%) BA patients had undergone Kasai Portoenterostomy (PE) prior to transplant. Majority of WD cases had an ALF- or ACLF-like presentation. Three of them were unmasked by acute hepatitis A or E infection. Out of the three tyrosinemia cases presenting as ACLF, two had associated CMV infection as an acute event and one had associated hepatitis A infection.

Of the 200 transplants, there were 2 domino donors. These domino donors were 2-and 3- year-old maple syrup urine disease (MSUD) cases whose explanted whole liver was used as a graft for children with biliary cirrhosis. Out of 217 potential donors evaluated for 198 liver transplants, four were medically unfit and 15 were rejected because of fatty liver. The characteristics of recipients and grafts, donors are shown in ***Table* II**. Majority (61%) of donors were females. The median (IQR) age and weight of donors were 34.7 (29, 40) years and 65.4 (58, 74) kg, respectively. Majority (51%) of donors were mothers, followed by close relatives (26%), father (18%) and swap donors (3.5%). Almost three-fourths (77.5%, n=155) donor were of same blood group as recipient, 21% (n=42) had compatible but non-identical blood group, and 3 (1.5%) had incompatible blood group. The median hospital stay for donors was 7 days. There were no major complications in them, except for biliary leak in two, which was managed conservatively and an incision hernia in one which was repaired surgically.

Median age and weight in CLD group (**Table II**) was significantly less as compared to patients in ALF (P<0.001) and ACLF group (P≤0.001) with no statistically significant difference between ALF and ACLF. Mean PELD score in children<12 years of age was 21.5, and mean MELD in >12 years was 27. The mean (range) INR in ALF group was 8.1 (4.3-14). Pre-transplant CMV IgG and EBV IgG were positive in 90% and 74% of recipients, excluding initial 60 transplants where these were not done. There was no significant difference in mean hospital stay between the various groups. Graft details are given in ***Table* II**. A total of 63 patients weighed <10 kg and nearly half of them received reduced left lateral segments. Gore-Tex mesh closure of the abdominal wall, followed by delayed closure 2 weeks later, was done in three of our patients who weighed <6 kg.

Blood culture positive sepsis was seen in 14.5% of which 8 patients (27%) died and rest responded to antibiotics. Majority (76%) of these were multidrug-resistant gram negative organisms (*Klebsiella pneumoniae* 9, *Acinetobacter baumannii* 7, *Burkholderia cepacia* 3, *Salmonella paratyphi*1 and *Pseudomonas aeruginosa* 2) followed by gram positive cocci in 20% (*Enterococcus faecium* 3 and *Staphylococcus* 5) and Candida (n=2). There was no statistically significant difference in the incidence of

sepsis in ALF versus decompensated CLD (*P*=0.23) or <10 kg versus more than 10 kg patients (*P*=0.5). CMV hepatitis occurred in 34 (17%) children and all responded to gancyclovir. The incidence of CMV hepatitis was higher (*P*=0.041) in children age <2 years (22.5%) in comparison to older age. Acute rejection during the first 4 weeks post-LT was seen in 25% of our patients, of which 64% were biopsy proven. All responded to pulse steroid therapy except one who required anti thymocyte globulin (ATG) but still progressed to chronic rejection. Drug-induced complications in the postoperative period included transient hyperglycemia and hypertension in 22% and 29%, respectively. Clinical seizures in immediate post-transplant period were seen in 10% of our patients, all of whom responded to anticonvulsants and the medications were stopped within 3 months. Two of these patients had changes suggestive of posterior reversible encephalopathy syndrome (PRES) on neuroimaging, and responded well to antihypertensive therapy. Late complications in our series included PTLD in 3 patients (2 of them had EBV viremia within 6 months post-LT while one developed Burkitt's lymphoma 2 year post-LT with no EBV viremia). Two of these PTLD patients died, including the child with Burkitt's lymphoma in whom parents refused chemotherapy; one recovered with use of Rituximab and is doing well on more than 5 year follow-up . Chronic rejection was seen in five patients; three died, one underwent retransplant and another one responded to modified immunosuppression. Recurrence of autoimmune hepatitis post-LT was seen in 2 of 23 patients (8.6%) with one retransplant being done in a case of autoimmune hepatitis with sclerosing cholangitis within 2 years of primary transplant. She is doing well 3 years post second transplant.

Biliary and vascular complications were among the most common surgical complications. Seventeen (8.5%) children developed biliary leak and 18 (9%) developed biliary stricture at the anastomotic site. Biliary complications could be addressed conservatively /by interventional radiology/surgery with good outcome. Vascular complications included hepatic artery thrombosis in 9 (4.5%) and portal vein thrombosis in 8(4%) patients. Two patients with hepatic artery thrombosis died while rest of the patients with vascular complications could be successfully managed by surgical / interventional radiological techniques. Bowel perforation requiring laparotomy was observed in 9 patients. Eight of these patients were post-Kasai who had severe intraabdominal adhesions noted at the time of transplant. One patient had perforation secondary to sepsis and intussusception. Chylous ascites was seen in 15 patients. All recovered on medium-chain-triglycerides (MCT)-based dietary therapy within 3 weeks except one in whom improvement was seen over 10 weeks . In 7 of these 15 patients, total parenteral nutrition was used in the first week of onset of chylous ascites.

Retransplants were done in three patients. These were done for hepatic artery thrombosis, recurrence of autoimmune disease and chronic rejection at 4 weeks, 2 years and 4 years post primary LT respectively. In our series of 200 liver transplants, 19 recipients died (9.5%). Death within 4 weeks of surgery was seen in 9 (<5%); 1 due to hepatic artery thrombosis, 1 due to massive intracranial bleed in a

case of hepatopulmonary syndrome, 2 patients of WD-related acute kidney injury, 5 due to sepsis. Another 5% died beyond 1 month post-LT; 3 due to sepsis, 2 with PTLD, 3 with chronic rejection, 1 with disseminated tuberculosis, and 1 with bleeding from ectopic varices despite PV stenting. There were 2 patients on high dose of tacrolimus beyond 1 year post-LT who developed diabetes requiring insulin, which responded to reduction of tacrolimus and use of mycophenolate mofetil. Our overall patient and graft survival rates were 90.5% and 89%, respectively. Actuarial survival at 1 and 5 year was 94% and 87%, respectively (***Fig.* 1a**). The actuarial 5-year survival in age < 1 yr was 84% in comparison to 91.5% in age >1 year (P=0.08). The survival was 100% for ALF, 90.4% for CLD and 85% for ACLF (**Fig. 1b**). There was no significant difference in survival between these groups (P=0.375).

DISCUSSION

In majority of our cases mothers were the donor. To answer organ shortage we did swap and ABO incompatible LT. We did 2 domino LT from grafts of our MSUD patients [8].

The leading indications of pediatric LT at our center were BA followed by metabolic liver disease (MLD) and ALF. Biliary atresias followed by MLD were also the commonest indications in 808 children transplanted in Pittsburgh [9]. Data from Southern India by Safwan, *et al.* reported a primary LT in 43% of their series of 58 children with BA [10], suggesting delayed referral as a major issue in management of BA in India. However, in another study from Northern India on 20 BA children undergoing LDLT, primary LT was done in only 10% cases [11].

Biliary complications including bile leak and anastomotic stricture have historically been a major problem of partial liver grafts resulting from very small/multiple bile ducts or thrombosis of hepatic artery. Technical surgical advances have significantly lowered these complications. Studies from India, USA and Japan have reported an overall incidence of 6-27% bile leaks after LDLT [12]. Mesquita, *et al.* [13] reported biliary complication rate as low as 7.5%. This may be due to the fact that their patients were older (mean age of 6 years) in comparison to those in our series.

In our study, incidence of hepatic artery thrombosis was relatively low (4.5%) and all could be salvaged by innovative surgical techniques except two cases. Recent studies from New York and Brazil had vascular complications ranging from 12–31% [14, 15]. The high-risk factors of HAT discussed in literature include children <3 years of age and weight <15 kg [16]. Reported incidence of portal vein thrombosis in pediatric LT is 44-12% [17,18]. In our series, we had 4% incidence and 92% of these cases were post-Kasai BA. The portal vein in children, especially after a Kasai procedure, is often narrow, fibrotic or encased in inflammatory lymph nodes causing high risk of PVT. We had 4.5% enteric

perforations; all but one occurred in post- Kasai patients with repeated cholangitis and ascites, suggesting that previous surgery and abdominal infections are high-risk cases.

The incidence of CMV / EBV infection and PTLD was low in our series as compared to 4-15% in western literature [19]. Most of our patients and donors were CMV IgG and EBV IgG positive, thus were at relatively low risk.

With good infection control policies, blood culture positive sepsis rate at our center was low (14.5%). Varghese, *et al.* [20] in a series of 35 liver transplant patients from Chennai reported sepsis in 20%. Other centers from Korea and France have reported blood culture positive infections in about one-third of their patients post-LT [21, 22]. We upgraded antibiotics empirically on clinical suspicion of sepsis; this could probably have lead to poor blood culture yield. We found a higher incidence of infection with gram negative organisms similar to observations by Varghese, *et al.* [20], whereas western centers have reported higher incidence of infection with gram positive bacteria [22]. Sepsis was the cause in 42% of our deaths, which is similar to the finding by Ueda, *et al.* [23] from Japan. Incidence of acute rejection in DDLT (Deceased Donor Liver Transplant) has been reported between 40% to 70% while in LDLT it is less, ranging from 15-30% [24]. In our series, acute rejection was seen in 25% responding to pulse steroid therapy in all but one patient. Chronic rejection was seen in 2.5% of our patients, and in most it was due to poor compliance with drugs, especially in adolescent age. We added Sirolimus in them with no great benefit.

Survival rates in our patients was at par with busy pediatric transplant centers in the world [25]. In our study, outcome was 100% in patients undergoing emergency transplant for ALF. In our setup, the donor work up could be done within 6-8 hours if required. We used KCH criteria which have been shown to have a better performance than the Clichy criteria and is widely used. The KCH criteria appear to have a higher specificity than sensitivity for acetaminophen-induced ALF, while its negative predictive value for non-acetaminophen induced ALF is low [26]. We always looked at the trend of INR either outside/inside the hospital before proceeding for LT.

Limitation of our study is that nutrition assessment was based on weight and height z score and not by the preferred modality in CLD patients of assessing muscle mass and skin fold thicknesses. Post transplant nutritional status and quality of life was not addressed in this study. Retrospective nature of data is also a potential limitation.

We conclude that LDLT is an available modality of treatment for ESLD, inborn errors of metabolism and ALF in Indian setting with outcomes comparable with the best centers of world. Morbidity and mortality due to vascular, biliary complications and sepsis post-liver transplant have reduced due to technical and medical advances. Multidisciplinary involvement from trained pediatric LT

surgeons, hepatologists, anesthetists, intensivists, interventional radiologists, pathologists has lead to a good outcome.

Contributors: NM – Interpretation of data, drafting and editing the manuscript; SK- Data analysis and drafting of manuscript; AR, MS, VR, DG, SG, PB, VV – Helping in management of patient and revision of manuscript; VS, TP , SSB – In analysis of radiology data; DG – reviewed the biopsy slides; AS – Transplant surgeon and critical revision of manuscript. All authors approved the final version of manuscript.

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TABLE I: INDICATIONS OF LIVER TRANSPLANT (*n*=200) IN PRESENT SERIES

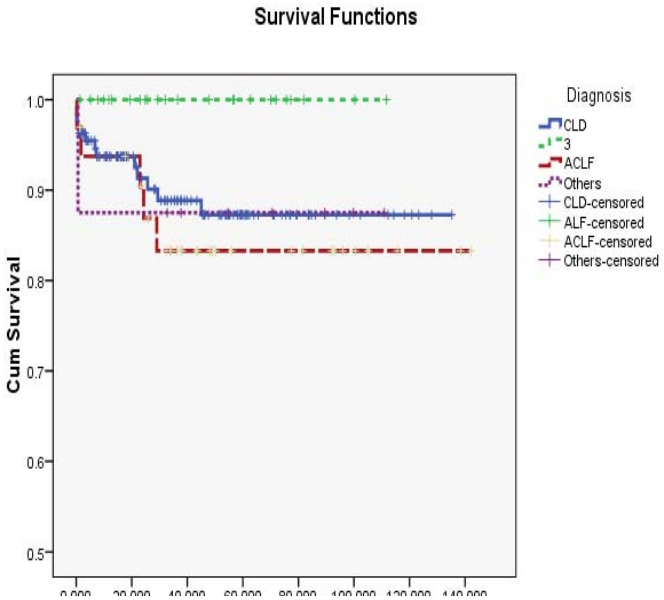
Indication	*Number*
• Chronic liver disease	133
Biliary atresia	72 (75%)
Progressive Familial Intrahepatic Cholestasis	10
Carolis disease	2
Allagille syndrome	3
Sclerosing Cholangitis (LCH)	3
Choledochal cyst IV	1
Budd- Chiari Syndrome	3
Portal Biliopathy with Biliary cirrhosis	1
Chronic Rejection with Biliary cirrhosis	1
Autoimmune hepatitis	15
Chronic hepatitis B	1
Wilsons disease	5
Tyrosinemia	7
Glycogen storage disease	1
Cryptogenic	8
Acute Liver Failure[#]	57
Hepatitis A virus	8
Hepatitis E virus	3
Cryptogenic	13
Wilsons	24
Autoimmune	8
Tyrosinemia	5
Neonatal hemachromatosis	1
Drug (ATT)	1
Tumours	2
Giant cavernous hemangioma	1
Hepatoblastoma	1
Others	8
Primary hyperoxaluria 1	2
Maple syrup urine disease	2
Citrullinemia type 1	3
Factor VII deficiency	1

[#]*including 33 patient with acute on chronic liver failure*

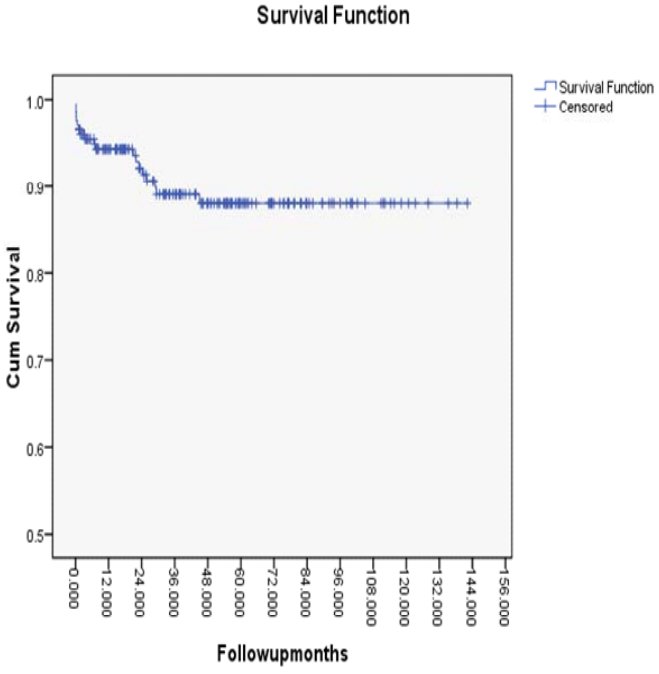
TABLE II: THE CHARACTERISTICS OF THE RECIPIENTS, AND GRAFTS

Recipient	*Total (n=200)*	*Chronic liver disease[#] (n=133)*	*Acute liver failure (n=24)*	*Acute on chronic liver failure (n=33)*	*Others (n=10)*
Male/female	120/80	76/56	18/6	19/14	7/3
Median (IQR) age (months)	60 (17-112)	28 (12-96)	90 (63-146)	108 (83-120)	34 (18-84)
Median (IQR) weight (kg)	16 (9-27)	12 (8-21)	25.5 (20-40)	25 (19-36.5)	12 (9.5-19.7)
Z score (weight)	0.020	-0.102	0.498	0.235	0.166
Z score (height)	0.459	0.399	0.994	0.236	0.625
Left lateral segment, n (%)	78 (39%)	60	5	8	5
Reduced graft, n (%)	26 (13%)	22	3	1	-
Left lobe, n (%)	68 (34%)	36	10	18	4
Right lobe, n (%)	26 (13%)	13	6	6	1
Domino, n (%)	2 (1%)	2	-	-	-
Median (IQR) stay (days)(	21 (5-90)	21(18-28)	20 (17-25)	23 (17-25)	24 (20-32)

 # 2 Patients with liver tumors were 'grouped' in others.



(a)



b)

Fig 1. Kalplan Meir curve for (a) acute liver failure, acute on chronic liver failure, chronic liver disease and others; and (b) for overall survival