

# Evolution of Pediatric Liver Transplant - Report from a Pediatric Surgical Center

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**Abstract:** Liver transplant (LT) is a well-established treatment for children with end-stage liver disease (ESLD) in the western world and other developed countries. However, its acceptance in India has been discouraging more due to the financial and logistic reasons than the availability of expertise. This report outlines our journey and highlights issues pertinent to circumstances in an emerging economy like India. A retrospective analysis of all children who underwent LT since 2005 at our institute was done. The data was collected and was analyzed. A total of 43 children underwent LT. The mean Pediatric end-stage liver disease (PELD) score at the time of LT was 17.6 ranging from -6 to 45. Biliary atresia was the most common indication (> 50%). Forty children underwent live donor LT (mothers being the majority of the donors). None of the donors had any major post-operative complications. The major surgical complications in the post-operative period included bleeding (5 cases needing re-exploration), vascular complications (n=12), biliary (n=12) and bowel (n=10) complications. The major medical complications included infections and graft related complications like acute rejection, primary non-function and delayed function (16 cases). The overall survival after liver transplantation in our group is 72% with the survival rate being almost 85% in the recent years. About 31 patients are alive and well after their transplantation at a mean follow up of 32 months. Out of the 12 deaths, 8 were in the perioperative period (within 28 days of the transplant). Our experience demonstrates the feasibility of LT in children with ESLD in India with results comparable with those reported in the developed world.

## INTRODUCTION

Liver transplant (LT) is a well-established treatment for children with liver failure. Its acceptance in India, however, has been slow, more due to financial and logistic reasons than the availability of expertise. There are many well-established centers for adults in India; not all of them treat children in large numbers. Among the difficulties, the paramount one is the cost of the procedure in the absence of significant insurance cover. Some state-based insurance schemes offer support but the amount allotted barely covers the medical costs.

As pediatric surgeons we see a significant number of children with biliary atresia and other surgical pathologies that result in end-stage liver disease (ESLD). Add to this is an equal number of metabolic and infective conditions. Approximately 2500-3000 children need LT annually in India; but we are able to perform less than 1% of that number per year. It is in this background that we embarked on a program to develop an exclusive pediatric LT program in our center. This report outlines our journey and highlights issues pertinent to circumstances in an emerging economy like India and builds upon a previously published article from our center<sup>1</sup>.

## MATERIALS AND METHODS

A total of 43 children underwent LT in our center since October 2005. This is a descriptive study of our experience and is based on data from a structured database maintained since the inception of the program.

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## RESULTS

### Recipient Profile

Age of these 43 children ranged from 6 months to 12 years; of whom 31 were boys. Twenty-four children (55%) weighed less than 10 kg. Most of them were undernourished. Many had associated comorbidities. The mean pediatric end-stage liver disease (PELD) score was 17.6 (range -6 to 45). The indications for transplantation are listed in Table 1.

Table 1: Indications for liver transplantation

Diagnosis	n
Biliary Atresia	22
Metabolic disorders	6
Progressive Familial Intrahepatic Cholestasis	3
Cryptogenic cirrhosis	2
Budd Chiari Syndrome	2
Fulminant hepatic failure	1
Hepatoblastoma	1
Paucity of bile duct	2
Primary sclerosing cholangitis	1
Alagille syndrome	2
Caroli Disease	1

### Donor Profile

Only 3 of the 43 grafts were from deceased donors. One was from a size-matched child; the other two were reduced grafts from adult donors. The donor profile is detailed in Table 2. Mothers were the commonest live donors (n=29). Six fathers, four second degree relatives and one altruistic donor accounted for the rest. Two donors required early post-operative re-exploration, one for bleeding from the drain and the other for bile leak.

Table 2: Donor profile

Donor	Number
Father	6
Mother	29
Relative	4
Altruistic	1
Deceased	3

### Immunosuppression

Immuno-suppression is done with tacrolimus and steroids (which is weaned off by 3 months). Additional drugs such as Mycophenolate mofetil (MMF) and monoclonal induction was used in selected cases. Serum levels of Tacrolimus are maintained between 8 to 10 ng/ml in the early post transplant period and reduced to 5-6 ng/ml by the end of the first year.

### Survival

The overall survival after LT was 72%. In the initial 3 years, overall survival was 50%. Six out of the 14 cases died in the early post-operative period and one died later due to Post-transplant lymphoproliferative disease (PTLD). In subsequent years, 24 of 29 patients transplanted are doing well (85% survival). Overall, 31 patients are alive and well at a mean follow up of 32 months (range 4 months to 62 months). Seven deaths occurred within 28 days of surgery; and caused by sepsis (3), primary non-function, abdominal compartment syndrome, portal vein thrombosis and resistant pulmonary hypertension (1 each). Five children succumbed to various illnesses later on. Causes included biliary sepsis (n=2) and one each from Burkitt's lymphoma, unexplained respiratory arrest, and recurrent hepatocellular carcinoma

## COMPLICATIONS IN THE POSTOPERATIVE PERIOD

Complications are common in children under going LT and even more so in living donor LT because of smaller grafts and vessels. The problems encountered during this period are detailed below:

- Bleeding:** Five children required re-exploration for post-operative bleeding. Source of bleeding was the arterial anastomosis in one and from retroperitoneal veins in another. In the remaining 3 children no source of bleeding was found.
- Vascular complications:** Twelve recipients had vascular complications; these are detailed in Table 3.
- Biliary complications:** All the patients, except 2 who had duct-to-duct drainage, had biliary drainage into a jejunal roux-loop. Sixteen grafts had more than one duct anastomosed to the roux loop. Of 10 who had early bile leak, 9 responded to expectant management. Two patients developed late biliary strictures and died of biliary sepsis.
- Bowel complications:** 10 patients (23.8%) developed bowel complications (Table 4). Time of presentation ranged from 1 week to 2 years post LT. Nine (90%) out of these 10 patients were previously operated for biliary atresia.
- Graft related complications:** Graft related complications occurred in 16 children. One child who received a reduced cadaveric graft succumbed to primary non-function. Five had delayed graft function. Acute rejection was seen in 7 children - all responded to pulse steroid. Three patients developed chronic rejection.
- Infections:** Infection was the commonest complication after LT. Bacterial sepsis occurred in 25 children and fungal sepsis in 10. Other infections noted in the late post-operative period include tuberculosis, malaria, measles, dengue fever, herpes, chicken pox and cytomegalo virus (CMV) infection.
- PTLD and Lymphoma:** Post transplant lympho-proliferative disease (PTLD) was seen in one patient who was managed successfully with reduction in immunosuppression. One other child succumbed to Burkitt's lymphoma.
- Pulmonary complications:** Five patients developed lung infection and severe acute respiratory distress syndrome (ARDS) like features in the early post-operative period. The presence of pre-existing pulmonary hypertension and pulmonary arteriovenous fistulae were risk factors for pulmonary morbidity in the post-operative period. Three children required temporary tracheostomy.
- Renal dysfunction:** Acute renal failure was seen in 4 patients, which was managed with dialysis.

Table 3: Vascular complications

Complication	n	Management
Hepatic artery thrombosis	4	Re-do anastomosis (n=2) Endovascular thrombolysis and stenting (n=2)
Early portal vein thrombosis	2	Re-do anastomosis (n=1) Distal inferior vena cava-to-portal vein anastomosis (n=1)
Late portal vein Stenosis	5	Endovascular balloon dilatation (n=2) Conservative (n=3)
Hepatic vein outflow obstruction	1	Creation of ventral hernia (n=1)

Table 4: Causes of intestinal complications

Etiology-Obstruction(n=6)	Number of patients
Adhesive obstruction	3
PTLD*	1
Serosal hematoma	1
Roux loop kinking	1
<b>Etiology-Perforation (n=4)</b>	
Iatrogenic	1
PTLD	1
Cytomegalo viral enteritis	1
Infective	1

\* PTLD - Post-transplant lympho-proliferative Disease

10. **Pathological fracture:** It occurred in 5 patients in late post-operative period despite vitamin D supplementation.
11. **Drug toxicity:** Adverse effects of tacrolimus included CNS toxicity, renal impairment, hypertension and hyperkalemia. In these children tacrolimus levels were reduced and MMF added.

## DISCUSSION

The program demonstrates feasibility of LT in developing countries like India. Increasing experience has improved outcomes. Biliary atresia was the commonest indication for LT, followed in frequency by metabolic liver disease. This is similar to other larger programs.<sup>(2,3)</sup> The low median weight of 8.5 kg at a median age of 2 years reflects the severe malnutrition and poor health of these children. Nutritional rehabilitation should form part of the ongoing care of these children-irrespective of whether they come to transplant or not. Children weighing less than 10 kg are a high-risk group to transplant. This occurred in 23 of 43 children in our group; however, outcomes were at par with the rest.

Living donor LT accounts for over 90% of transplants. Similar experience has been reported from other Asian countries<sup>4</sup>. As most children require a left lateral segment graft, the morbidity and risks to the donor are less than those donating their right lobes. Living donor transplants are ideally suited to children as it allows for a planned procedure, allows for a near optimal size graft for the child and reduces the risk to the donor. The incidence of rejection is also reduced.

Mothers were the predominant donors in our group. However, our recent experience has shown that increasingly fathers are willing to be donors. This trend increases the donor pool and gives options to choose either of the parents and the possibility of re-transplantation. Our preferred policy is to use group specific donors and availability of such is often a limiting factor. Altruistic and unrelated donation in case of liver transplantation is an ethically difficult problem as risks associated with the donor procedure remain significant. Ideally we should strive to develop the deceased donor program with the expertise to use split-liver grafts and reduced grafts. This has been possible only twice in our group.

Most patients with chronic liver disease, especially those with biliary atresia, are in very poor general health. Previous surgery is followed by development of portal hypertension, ascites, bacterial peritonitis and severe malnutrition. They have marginal renal and pulmonary functions. They have often been hospitalized and are colonized with hospital pathogens. Performing a liver transplant on them, as expectedly, puts them at risk of variety of complications<sup>4</sup>.

Bleeding is one of the major reasons for re-exploration in the immediate post-operative period. It occurs from the areas of vascular anastomosis, raw surface of the liver or from the retroperitoneal vessels. A combination of portal hypertension, previous surgery and pre-existing coagulopathy increase the risk of post-operative bleed. They are coagulopathic to start with and continue to remain so until the liver begins synthetic functions and sepsis is controlled. However, a majority can be managed conservatively. Careful management of their coagulation status is vital and thrombo-elastography provides a functional indicator of the coagulation status in these children.

The incidence of hepatic artery thrombosis (HAT) in our series was 9.3 % (n=4). Risk of HAT is high due to small caliber vessels, low flow states (e.g. splanchnic vasoconstriction secondary to low fluid status), diuretic use, hemodynamic instability, imbalanced

coagulation and disseminated intravascular coagulation (DIC)<sup>5,6</sup>. Over the last 20 cases, hepatic artery anastomosis has been performed with micro-vascular techniques, resulting in significant reduction in incidence of HAT. In the early post-operative period HAT can potentially impact graft and patient survival. The two children who were recanalized after HAT have been on follow-up for over 2 years and are well. Delayed effects of arterial insufficiency such as biliary strictures have not been detected. Wamaar *et.al* reported a HAT incidence of 13.7%, about a third of whom were recanalized successfully<sup>5</sup>.

Incidence of portal vein thrombosis is reported as 4.6%<sup>2</sup>. Portal vein in children, especially after a Kasai procedure, is often narrow, fibrotic and encased in inflamed lymph nodes. A high risk of portal vein thrombosis exists in these children. Acute portal vein thrombosis in the early post-operative period can be devastating as is demonstrated in the one child who developed it in this series. Late portal vein stenosis is usually anastomotic and children present with features of portal hypertension. Trans-hepatic endovascular balloon dilatation is the procedure of choice<sup>7</sup>. Other procedures such as operative repair, porto-caval shunts have an unacceptably high morbidity and graft loss.

Biliary problems are the commonest surgical problems in the post-operative period with a reported incidence of 27.9%<sup>4</sup>. The bile ducts on the graft are often very small and multiple. A roux-en-Y drainage of all these ducts is the procedure of choice. Occasionally, a duct-to-duct anastomosis is possible; but care needs to be taken to preserve vascularity of the recipient duct during the explantation procedure. Children with arterial problems often manifest with bile leaks because the biliary blood supply is almost entirely from the hepatic artery<sup>8</sup>. Intestinal obstruction in the early post-operative period can result in dilatation of the roux loop and disruption of the new biliary enteric anastomosis as was noted in 2 children in this series. Majority of the bile leaks respond to drainage and time.

Intestinal problems in the post-operative period are common. A combination of previous exploration for the Kasai procedure and serositis increases the risk of bowel complications in these children<sup>9</sup>. Two children with ante-colic roux loops were particularly difficult to manage. When the roux loop is freshened and re-used to drain the graft biliary tree, the pull on the mesentery of this loop compressed the transverse colon resulting in obstruction. We now follow a policy of converting an ante-colic loop to a retrocolic one prior to the biliary enteric anastomosis. This intestinal failure needs time to recover and often total parenteral nutrition (TPN), along with all its problems, becomes unavoidable. Bowel perforation occurs in 6.4–20% of cases and has a poor prognosis with a mortality of 30–50%<sup>10-12</sup>. One child developed small bowel perforation due to invasive CMV infection.

Acute rejection was seen in 16.2% (n=7). All responded to pulse steroid and intensification of immune suppression. There have been no long term adverse effects in these patients and their course has been similar to those who did not have acute rejection. In the living donor liver transplant (LDLT) scenario, acute rejection is less common and usually completely reverses with adequate therapy. Incidence of acute rejection has been reported to be between 40%-70%<sup>2,4</sup>.

Other medical problems such as pulmonary failure, renal dysfunction and coagulopathy are common in the immediate post-operative period. A majority of these problems are controlled and reversed once the grafted liver begins to function normally.

Extreme caution is necessary when administering any medications as these could interact with immune suppression and raise or lower serum levels and could cause additive renal damage. Being in a tropical environment, the children are exposed to the usual tropical infections; malaria, measles, dengue fever and tuberculosis have all occurred in our series. Once again treatment needs to be tailored to reduce exposure to drugs that interact with immune suppression and also lay undue stress on the kidneys and transplanted liver.

The graft in most cases is the left lateral segment. Left hepatectomy was done in a few cases. The graft weight ranged from 150 gm to 550 gm. The average graft-to-body weight ratio was 2.6% (range from 0.8 to 7.76%). In those over 5% we prefer not to reduce the graft if it is well perfused after unclamping.

All the patients are on regular follow-up as per our institution protocol. Geographical and social factors impact on the nature of this follow-up. A combination of interaction with local physicians, laboratories and communication through email and telephone is used to ensure ongoing care and follow-up for these children.

Overall survival is 72%. Early in the program, 6 deaths occurred within 28 days of post-operative period. Sepsis, primary non-function and vascular problems are the usual causes of death in the early post-transplant period. Late complications include chronic rejection<sup>13</sup> renal damage in up to 20%<sup>14</sup>, drug toxicity, sepsis and PTL<sup>15</sup>.

Six patients presented to us with fulminant hepatic failure. One baby responded to medical management. Only one was successfully transplanted. The remaining four patients died while awaiting transplantation due to inability to complete the required legal formalities in time. A concerted effort is essential from the appropriate authority to hasten the process in such situations.

Over the last 29 cases, there have been only 2 post-operative mortalities. This is a reflection of maturation of the program and completion of the steep learning curve at all stages of management. Refinement of protocols has made long-term care more thorough and cost-effective. All the surviving children of our series are doing well. They have caught up with growth and development and are pursuing age appropriate activities. It is often the sickest children who make the most dramatic recoveries. Survival after liver transplantation has been reported as 91%, 87% and 81% at 1, 5 and 10 years respectively<sup>16</sup>. If a child makes it past the first year after transplant, it is very likely that he will get on to 10 years.

## CONCLUSIONS

Our experience demonstrates the success of LT in Indian children. The outcomes are comparable to other established programs, even in those children weighing less than 10 kg. Complications though

frequent, are mostly treatable. Most children can expect an excellent quality of life and longevity after LT. There are several special issues that the program has had to address. These include limited financial resources, skepticism from the medical and lay community, problems such as tuberculosis and tropical diseases that are specific to developing countries. However, all these issues can be addressed systematically and this is reflected in the improving outcomes and more physicians and parents opting for this treatment.

## DISCLAIMER

All the authors declare no vested financial interest in publishing this article.

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