



## Short and Long Term Complications after Pediatric Liver Transplantation: A Review and Literature

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### Abstract

#### Background

Pediatric liver transplant (PLT) is a complex surgical procedure. Pediatric liver transplantation has evolved over the last two decades into an effective and widely accepted therapy for infants and children. We aimed to review the short and long term complications after oediatric liver transplantation.

#### Materials and Methods

The literature research was conducted in EMBASE, PubMed, Scopus, ISI Web of Science, Cochrane Library, and Google Scholar; were searched from January 1984 to January 2016. The following keywords were used: Liver transplantation, Pediatric Liver transplantation, Risk factors, Complication, and Mortality.

#### Results

The main complications after pediatric liver transplantation were: infections (51.4%) and surgical complications including (biliary complications [41.2%], and postoperative bleeding [27%]). In general, vascular complications were observed in 35% of studied children.

#### Conclusion

Infections and biliary complications were the most common outcome occurring in children after LT. Advances in post-transplant care and monitoring of the recipients, technical refinements enable the better results.

**Key Words:** Children, Complications, Liver transplantation, Systematic review.

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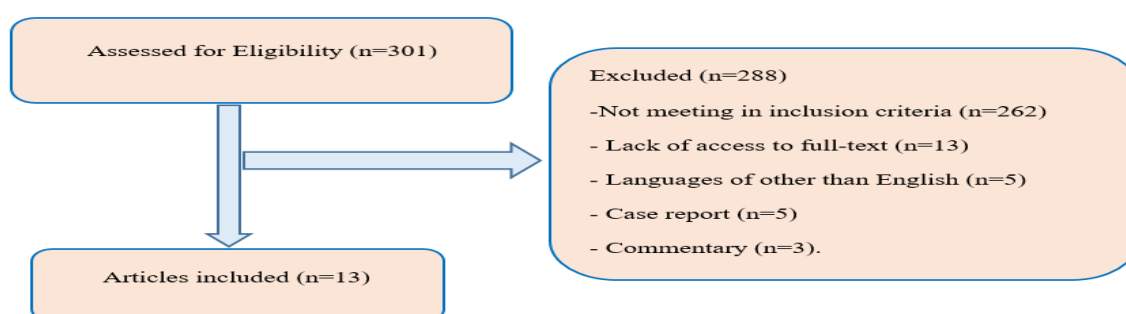
## 1- INTRODUCTION

The first human liver transplant was performed in 1963 by a surgical team led by Dr. Thomas Starzl of Denver, Colorado, United States. Dr. Starzl performed several additional transplants over a few years till the first short-term success was achieved in 1967 with one-year survival post transplantation. Despite the development of viable surgical techniques, liver transplantation remained experimental through the 1970s, with one year patient survival in the vicinity of 25%. The introduction of cyclosporin by Sir Roy Calne, Professor of Surgery Cambridge, markedly improved patient outcomes, and the 1980s was recognition of liver transplantation as a standard clinical treatment for both adult and pediatric patients with appropriate indications. Liver transplantation is now performed at over one hundred centers in the US, as well as numerous centers in Europe and elsewhere. One-year patient survival is 80–85%, and outcomes continue to improve, although liver transplantation remains a formidable procedure with frequent complications. The supply of liver allografts from non-living donors is far short of the number of potential recipients, a reality that has spurred the development of living donor liver transplantation. The first altruistic living liver donation in Britain was performed in December 2012 at St James University Hospital Leeds (1-3).

## MATERIALS AND METHODS

### 2-1. Method

The following databases were searched for relevant papers and reports: Medline, Cinahl, Embase, Cochrane Collection, Pubmed, ISI Web of Knowledge, and Google Scholar. Key references from extracted papers were also hand-searched. These searches focused upon papers published between Jan 1984 and Jan 2016. Terms to evaluate the texts and websites, the singular or combination forms of the following keywords were used to search for the relevant literature: "Liver transplantation", "Risk factors", "Pediatric liver transplantation", "Complication", and "Mortality" and equivalent Persian words using bulletin index such as AND, OR. Included were: all Persian and English articles which have the mentioned keywords in the title and abstract and related to the purpose of the research, published between Jan 1984 to Jan 2016. Articles with incomplete data, and also from other languages were excluded. In the initial review, 301 articles were found. Of the collected articles, 288 documents were excluded in several steps by processes of article selection. A total of 13 studies were ultimately included in this review. The procedure of the search and selection of studies is appeared in **Figure.1**.



**Fig.1:** Flowchart of selection of studies.

### 3- RESULTS

During the 32-yr period between Jan 1984 and Jan 2016, we compared the complications of pediatric liver transplantation at different eras. **Table.1** (*Please see the table at the end of paper*), shows the general characteristics of the included studies. In terms of study sample size, three studies (27.07%) evaluated less than 100 patients and other studies (76.9%) assessed more than 100 patients. One study was a case control and others were retrospective review. Unfortunately, there are few studies with substantial numbers of patients that identify outcomes predictors. However the early recognition and correction of post-transplant complication improves graft and patient survival. The majority of complications and deaths occur within the first three months. Some of common complications after liver transplant include:

#### 3-1. Complications after liver transplant, collected from review of literatures (17)

##### 3-1-1. Bleeding

Poor graft function, coagulopathy, imperfect hemostasis, or slippage of a tie can result in postoperative bleeding that requires re-exploration. Postoperative bleeding is reported in 8.5% of patients (9). Even if easily controlled, postoperative bleeding leads to increased cost, morbidity, and mortality.

##### 3-1-2. Biliary complications

Biliary leak and stricture are the most common technical complications occurring in 22% to 47.3% of children (5, 12). Biliary drainage is re-established by bile duct to bile duct anastomosis, or more commonly hepaticojejunostomy.

##### 3-1-3. Rejection

About 25% of patients develop at least one episode of acute rejection in the first weeks after liver transplantation (9, 14). A

liver biopsy is required to confirm rejection. Acute rejection is characterized by the histological triad of endothelialitis, portal triad lymphocyte infiltration with bile duct injury, and hepatic parenchymal cell damage.

##### 3-1-4. Infections

Immunosuppressive medications interfere with a patient's natural immunity; therefore, the patient will be more susceptible to infections after transplant surgery. Infections were the most common complications occurring in 28–51.4% of children (6, 9). Wound infection and superficial wound dehiscence occurred in (2.1%) and (28%) cases respectively. The most frequent source of infection was bacteremia (53%), lungs (24%), and abdomen (22%). The most frequent pathogens were bacteria (79%), candida (18%), and viruses (8%) (6).

##### 3-1-5. Liver failure

Liver failure is a medical term meaning that the transplanted organ is not working properly. It's one of the most serious complications of a liver transplant and occurs in around one in 11.1% to 18% of children (11, 16). The most common cause is a disruption to the blood supply to the transplanted liver, caused by blood clots (thrombosis). Graft failure can develop suddenly, or slowly over a longer period of time. Symptoms can include jaundice, fluid retention (oedema), mental changes and a swollen abdomen.

##### 3-1-6. Vascular occlusions

In general, vascular complications in 11.4 to 35% of children who have had a liver transplant, was observed (9, 11).

##### 3-1-7. Hepatic artery thrombosis

Thrombosis of the hepatic artery is the most common vascular occlusion, especially for living donor transplants, in which anastomosis is performed between smaller arteries. That is a major

complication, which often leads to graft loss. The incidence varies (1.03%–12%) depending on the type of graft, being less common in cut down livers (10, 12). Causes include poor surgical technique or kinking of the artery, endothelial injury (poor handling during retrieval or implantation), increased coagulability, or liver swelling during acute rejection. Factors such as high haematocrit and raised blood viscosity, arterial hypotension, infection, or perfusion injury predispose to thrombosis. Early recognition and immediate surgical revascularisation may salvage the graft.

### **3-1-8. Portal vein thrombosis**

Portal vein thrombosis (PVT) occurs in approximately 3.2% to 9.8% of transplants, particularly in small children with hypoplastic portal veins (12, 15). Late portal vein complications present with signs of portal hypertension such as variceal haemorrhage or splenomegaly. The underlying cause may be technical, but on occasions remodelling of a “cut down” liver causes stretching of the portal vein.

### **3-1-9. Renal Function**

CNIs, the principal immunosuppressive medications, used to prevent graft rejection, contribute to de novo acute and chronic posttransplant renal dysfunction. In children, the prevalence is not as well defined because serum creatinine is not a reliable measure of renal function and only a few studies have directly measured the glomerular filtration rate (GFR). Campbell et al. reported that renal dysfunction was present in 32% of children (13).

### **3-1-10. Other complications include**

Incisional hernia and diaphragmatic hernia reported by others in 0.7% and 1.1%, respectively (4), while bowel obstruction and perforation were seen in 3.2% and 2.5% of cases (4). The results of Berrocal et al. (12) showed that organ transplant

recipients are at risk for PTLD. Arnon et al. (16) reported the metabolic disease and neonatal hepatitis occurred in (10.9%) and (7.5%) of cases, respectively. Wisniewski et al. (7) showed that 8.5% of children after LT were diagnosed with FA and/or EGID. Shroff et al. (8) reported food allergy symptoms in 6% of children after LT with confirmatory specific IgE testing in 4%. Atopic disease was present in (14.2%) of patients. Food allergy and atopic skin disease symptoms were present in 40% and 56% of cases, respectively. Asthma, allergic rhinitis, or both were found in 66% of cases. Varela et al. (14) reported posttransplant lymphoproliferative disorders in (5.7%) of children after LT.

## **4- DISCUSSION**

### **4-1. Liver transplantation**

Liver transplant is a last resort treatment measure that can help save patient's life when the liver no longer works. Also called a liver or hepatic transplantation, the treatment involves the surgical removal of the entire organ. It is then replaced with a healthy donor liver. Having a healthy liver is essential to longevity because the liver is responsible for nutrient distribution and toxin removal in the body (18, 19).

This procedure is a treatment, used in appropriately selected patients, for acute and chronic liver failure due to any cause. It is not indicated if an acceptable alternative is available or if contraindications are present (eg, some cases of malignancy, terminal conditions, poor expected quality of outcome).

Pediatric patients account for about 12.5% of liver transplant recipients. When a pediatric patient is likely to require a liver transplant, the medical management is generally divided into pretransplant and posttransplant periods, with the

posttransplant period further separated into early and late time frames.

Medical treatment, surgery, and postsurgical care can be broken into 4 basic steps:

1. Candidate evaluation;
2. Waiting period;
3. Surgery;
4. Postsurgical care (18).

#### 4-2. Indications

Liver transplantation is potentially applicable to any acute or chronic condition resulting in irreversible liver dysfunction, provided that the recipient does not have other conditions that will preclude a successful transplant. Uncontrolled metastatic cancer outside liver, active drug or alcohol abuse and active septic infections are absolute contraindications. While HIV infection was once considered an absolute contraindication, this has been changing recently. Advanced age and serious heart, lung, or other disease may also prevent transplantation (relative contraindications). Most liver transplants are performed for chronic liver diseases that lead to irreversible scarring of the liver, or cirrhosis of the liver. Some centers use the Milan criteria to select patients with liver cancers for liver transplantation (20-22).

#### 4-3. Indications for pediatric liver transplantation

About 50% of the pediatric patients who require a liver transplant have biliary atresia. Other disease states that progress to end-stage liver disease among pediatric patients and require liver transplantation include metabolic disorders and progressive intrahepatic cholestasis.

Examples of metabolic derangements include Wilson disease, alpha 1-antitrypsin deficiency, tyrosinemia, and hemochromatosis. Other metabolic disease

states leading to hepatic dysfunction include the following (23-25):

- Crigler-Najjar syndrome;
- Glycogenosis;
- Hyperoxaluria;
- Metabolic respiratory chain deficiencies;
- Familial hypercholesterolemia
- Methylmalonyl aciduria

#### 4-4. Techniques

A liver transplant may involve the whole liver, a reduced liver, or a liver segment. Most transplants involve the whole organ but segmental transplants have been performed with increasing frequency in recent years. This would allow two liver recipients to be transplanted from one cadaveric donor or to allow for living donor liver donation. A reduced liver transplant may result if the donor liver is too large for the recipient (18, 26).

Before transplantation, liver-support therapy might be indicated (bridging-to-transplantation). Artificial liver support like liver dialysis or bio-artificial liver support concepts are currently under preclinical and clinical evaluation. Virtually all liver transplants are done in an orthotopic fashion, that is, the native liver is removed and the new liver is placed in the same anatomic location. The transplant operation can be conceptualized as consisting of the hepatectomy (liver removal) phase, the anhepatic (no liver) phase, and the post-implantation phase. The operation is done through a large incision in the upper abdomen. The hepatectomy involves division of all ligamentous attachments to the liver, as well as the common bile duct, hepatic artery, hepatic vein and portal vein. Usually, the retro-hepatic portion of the inferior vena cava is removed along with the liver, although an alternative technique preserves the recipient's vena cava ("piggyback" technique) (27). The donor's

blood in the liver will be replaced by an ice-cold organ storage solution, such as University of Wisconsin solution (UW; Viaspan) or Histidine-tryptophan-ketoglutarate, or Custodiol HTK until the allograft liver is implanted. Implantation involves anastomoses (connections) of the inferior vena cava, portal vein, and hepatic artery. After blood flow is restored to the new liver, the biliary (bile duct) anastomosis is constructed, either to the recipient's own bile duct or to the small intestine. The surgery usually takes between five and six hours, but may be longer or shorter due to the difficulty of the operation and the experience of the surgeon. The large majority of liver transplants use the entire liver from a non-living donor for the transplant, particularly for adult recipients.

A major advance in pediatric liver transplantation was the development of reduced size liver transplantation, in which a portion of an adult liver is used for an infant or small child. Further developments in this area included split liver transplantation, in which one liver is used for transplants for two recipients, and living donor liver transplantation, in which a portion of a healthy person's liver is removed and used as the allograft. Living donor liver transplantation for pediatric recipients involves removal of approximately 20% of the liver (Couinaud segments 2 and 3). Further advance in liver transplant involves only resection of the lobe of the liver involved in tumors and the tumor-free lobe remains within the recipient. This speeds up the recovery and the patient stay in the hospital quickly shortens to within 5–7 days. Many major medical centers are now using radiofrequency ablation of the liver tumor as a bridge while awaiting for liver transplantation. This technique has not been used universally and further investigation is warranted (28-30).

#### **4-5. Types of liver transplant**

There are three main ways a liver transplant can be carried out:

- **4-5-1. deceased organ donation:** involves transplanting a liver that has been removed from a person who died recently.
- **4-5-2. living donor liver transplant:** a section of liver is removed from a living donor; because the liver can regenerate itself, both the transplanted section and the remaining section of the donor's liver are able to regrow into a normal-sized liver.
- **4-5-3. split donation:** a liver is removed from a person who died recently and is split into two pieces; each piece is transplanted into a different person, where they will grow to a normal size (23, 27).

#### **5- CONCLUSIONS**

Liver transplantation is life saving for patients with end stage liver disease. Post liver transplantation complications may occur in all recipients. Patients should be followed by gastroenterologist for postoperative care, medications and tests. Parents are responsible to administer transplant medications to children up to age 18 to prevent liver transplant rejection. This is because teenage patients may stop taking the medications without mentioning it to their parents. Patients should be tested for allergies after liver transplantation, because of a higher chance in these group of patients. Acute and chronic liver failure, cirrhosis of the liver, chronic active hepatitis, acute and chronic rejection may happen post liver transplantation. These could be eliminated and controlled by close patients observation, evaluations, and treatment.

#### **6- CONFLICT OF INTEREST**

All the authors declare that they have no conflict of interest.

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**Table-1:** Characteristics of included studies during (1984-2016)

Author Country Year Reference	Study design	Inclusion criteria	Sample size	Sample age	Complication
Ziaziaris, Australia 1986- 2014 (4)	Retrospective review	All children who underwent LT	242	Median age 31-month	General surgical complications were observed in 33 cases (11.7%). Wound infection 7(2.5%); Wound dehiscence 6 (2.1%); Incisional hernia 2(0.7%); Bowel perforation 9(3.2%); Bowel obstruction 7(2.5%); Diaphragmatic hernia 3(1.1%).
Cortes, Spain 1989-2013 (5)	Retrospective review	All children who underwent LT and subsequently presented with a DH	1032	<18 years	The most common indications for LT in children in the overall series were: extrahepatic biliary atresia (EHBA; 488 or 47.3%), acute liver failure (ALF; 135 or 13.1%), and cholestatic liver disease (66 or 6.4%).
Kukreti, Canada 1988-2011 (6)	Retrospective review	All children who underwent LT	145	Median age 2.7 years	Forty one patients (28%) had infections. The most frequent source of infection was bacteremia (26/49, 53%), lungs (12/49, 24%), and abdomen (11/49, 22%). The most frequent pathogens were bacteria (79%), candida (18%), and viruses (8%).
Wisniewski, USA 1990- 2010 (7)	Retrospective review	All children who underwent LT	352	<18 years	30 (8.5%) of children were diagnosed with FA and/or EGID.
Shroff USA 1995-2010 (8)	Review and follow-up	All children receiving chronic immunosuppression after orthotopic LT (OLT).	176	<18 years	Reported food allergy symptoms in 6% of children after LT with confirmatory specific IgE testing in 4%. Atopic disease was present in 25 (14.2%) patients. Food allergy and atopic skin disease symptoms were present in 40%, and 56% of cases, respectively. Asthma, allergic rhinitis, or both were found in 66% of cases.
Deng, China 2006- 2009 (9)	Retrospective review	All children received LT	35	<14 years	The most common postoperative complications were infections, 51.4% (18 cases), gastrointestinal bleeding, 8.5% (3 cases), and vascular complications 11.4% (4 cases). Rejection occurred in 25% of patients. There was one perioperative death from primary graft non-function, 2.8%. The most common isolated bacteria of the pathogen spectrum were Staphylococcus epidermidis.
Jones Australia. 1986- 2007 (10)	Retrospective review	All children who underwent LT	194	<18 years	Two of 194 (1.03%) patients developed mycotic aneurysms of the hepatic artery.

Complications After Pediatric Liver Transplantation

Farmer, USA 1984- 2006 (11)	Retrospective review	All children who underwent PLTx	657	<18 years	The most common causes of patient death were sepsis (28%), multisystem organ failure (16%), and liver failure (18%) and vascular complications (35%).
Berrocal, Spain 1989-2004 (12)	Retrospective review	All children who underwent LT	321	Age range, 6-204 months	Portal vein thrombosis (3.2%). Hepatic Artery Stenosis (12%). Vascular complications (35%). Portal Vein Stenosis (4%). IVC Thrombosis in less than (1%). Biliary complications (27%). Organ transplant recipients are at risk for PTLT(3%).
Campbell, USA. 1986- 1999 (13)	Case-control study	All children who received a primary LT and who survived for at least 3 years after transplant.	117	Age range, 3-14.6 years	Renal dysfunction was present in 32%.
Varela, Mexico. 1998-2004 (14)	Retrospective review	All children who received an OLT	35	Age range 0.7- 17.2 years	Biliary complications (22%). Posttransplant cytomegalovirus infection or reactivation (28%), acute rejection (25%), posttransplant lymphoproliferative disorders (5.7%).
Tiao, USA. 1986-2003 (15)	Retrospective review	All children who received an OLT	81	<1 year	Hepatic artery thrombosis: 6.2% and Portal vein thrombosis: 9.8%.
Arnon, USA. 1987-2008 (16)	Retrospective review	The Infants $\leq 5$ kg who had LT	570	<5 year	Biliary atresia (41.2%); Acute liver failure (11.1%); Metabolic disease (10.9%); Neonatal hepatitis (7.5%); TPN(6.5%).

FA: Food allergy; EGID: Eosinophilic gastrointestinal disorders; TPN: Total parenteral nutrition.