



## Pediatric liver transplantation: 10 years of experience at a single center in Brazil

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### Abstract

**Objectives:** To evaluate the first 10 years' experience of the liver transplantation department at the Alfa Institute, Hospital das Clínicas da Universidade Federal de Minas Gerais, Brazil.

**Methods:** A descriptive study, based on a retrospective analysis of 84 children and adolescents enrolled on a liver transplantation waiting list, from March 1995 to January 2006, based on the following variables: age, etiology of underlying liver disease, Child-Pugh, Malatack, model for end-stage liver disease (MELD) and pediatric end-stage liver disease (PELD) scores, time on waiting list, complications and survival after the procedure.

**Results:** Forty children had 42 liver transplants. Twenty six died while on the waiting list. Biliary atresia was the most frequent indication for transplant. The median age was 6.6 years (ranging from 1.9 to 16.8 years). Post liver transplant mortality was 32.5% (13 of 40 children). The median time on the liver transplant waiting list was 291 days. Complications related to the graft occurred in 24 of 42 transplants (57.1%), including vascular complications (30.8%), with thrombosis of the hepatic artery being the most frequent (16.6%); acute rejection occurred in 16.6%.

**Conclusions:** The overall results are similar to what can be found in the literature with relation to indications and post-transplant survival. However, there were elevated rates of complications unrelated to the graft and of complications involving the hepatic artery.

*J Pediatr (Rio J). 2008;84(5):395-402.* Liver transplantation, children, adolescents, mortality, outcome assessment, postoperative complication, survival analysis.

### Introduction

With 30 years' experience since its introduction to medical practice, liver transplantation has evolved, accumulating

progress and confirming its position as the only effective treatment for patients with advanced liver diseases.<sup>1,2</sup> Liver transplantation has greatly improved the survival rate of children

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and adolescents with terminal liver disease. Patients who previously would have had no prognosis of survival, nowadays undergo liver transplantation with 1-year survival rates that vary from 80 to 90%.<sup>3</sup>

Liver transplantation is indicated for all children with liver disease and progressive deterioration of health, before the appearance of complications that can make the procedure excessively risky. In this context, the following are indicators of a need for transplantation: cholestasis, pruritis and/or ascites that are untreatable from a clinical point of view; portal hypertension with bleeding from varices that is unresponsive to treatment; multiple episodes of cholangitis or episodes of spontaneous bacterial peritonitis; progressively deficient hepatic synthesis; impact on somatic growth and hepatic encephalopathy.<sup>3,4</sup> Biliary atresia is the primary indication in the pediatric age group.<sup>3,4,5</sup>

The objective of this study is to describe the 10 years of experience in pediatric liver transplantation accrued by the Transplantation Department at the Alfa Institute, Hospital das Clínicas da Universidade Federal de Minas Gerais (UFMG), in Brazil, in terms of the following variables: indications, severity of liver disease measured using the following scores: Child-Pugh, Malatack, model for end-stage liver disease (MELD) and pediatric end-stage liver disease (PELD), time on waiting list, post-transplant survival, complications, immunosuppression employed and length of hospital stay.

## Methods

This is a descriptive study of children and adolescents with indications for liver transplantation, enrolled on a waiting list between March of 1995 and January of 2006. The study included all patients less than 18 years old seen by the liver transplantation team at the Alfa Gastroenterology Institute, UFMG Hospital das Clínicas, and enrolled on the state of Minas Gerais transplantation list.

Since prior to 2002 there was no specific legislation, enrollment on the list was decided at weekly transplant team clinical meetings based on the following general principles: patients with hepatic cirrhosis who exhibited progressively deficient hepatic synthesis, non-progressive liver disease with recognized morbidity and mortality and impact on weight-height growth, pruritis and/or ascites that were untreatable from a clinical point of view; portal hypertension with variceal bleeding and unresponsive to treatment; multiple episodes of cholangitis or episodes of spontaneous bacterial peritonitis; fulminating liver failure; and malignancy. From 2002 onwards, the decision was based on the criteria laid out in National Transplants System Directive 541, of the 14th of March 2002.<sup>6</sup>

Eighty-four patients were enrolled; 40 underwent liver transplantation, two of whom received repeat transplantations. Grafts were obtained from donor cadavers, 12 of the donors being children. In 31 transplants, the entire liver was

grafted, 10 reduced-size grafts were used and one split graft was performed. During the period that these transplants were carried out, the criterion used to decide priority when allocating grafts was chronological order.

For all 84 patients, the following were recorded: age at enrollment, sex and indications for liver transplantation. For patients enrolled due to chronic liver disease, the Child-Pugh, Malatack, PELD (patients less than 12 years old) and MELD (over 12 years old) scores were calculated. For the group of patients who received transplants, the following were also analyzed: age at time of transplant, time on waiting list, complications and post-transplant survival, type of immunosuppression employed, length of hospital stay and length of time in the intensive care unit for postoperative care.

The following criteria were used to classify postoperative complications unrelated to the graft: respiratory complications in pleural hemorrhage cases, airway obstruction after extubation, pneumocystosis, tracheostomy, barotrauma; hemodynamic complications in patients who had hemodynamic instability and required volume resuscitation or amines; infectious complications where antibiotics, antifungals or antivirals were needed (with the exception of prophylactic or pre-emptive use); neurological complications where patients had persistently altered states of consciousness postoperatively, exhibited motor or cognitive deficits or convulsive crises; and renal complications where renal function was abnormal as manifest by elevated creatinine and urea.

The following criteria were used to define complications that were related to the graft: primary non-function was where there was persistent coagulopathy, acidosis, hyperkalemia and progressively elevated aminotransferases; acute rejection was when there were abnormal laboratory results (aminotransferases, alkaline phosphatase, bilirubins, gamma glutamyl transferases) associated with hepatic histopathology; chronic rejection was abnormal laboratory results (aminotransferases, alkaline phosphatase, bilirubins, gamma glutamyl transferases) and confirmation with liver biopsy; vascular and biliary complications were documented by imaging studies and laboratory findings.

Data were collected by three researchers, who discussed their findings among each other and with the research supervisor if there were any doubts with relation to the criteria adopted. Data were analyzed using statistical resources available in the software package Epi-Info 6.04. Continuous variables without normal distribution were expressed as medians and 25-75% interquartile ranges (IQ25-75%) and compared using the Kruskal-Wallis non-parametric test. The distribution of dichotomous variables was analyzed using the chi-square test with Yates' correction, or Fisher's exact test, two-tailed, when necessary. The probability of significance was considered significant when less than 0.05 ( $p < 0.05$ ). Post-transplant survival was evaluated using the program KMSURV. The cutoff date for data was set at 31st January 2006

and for transplant patients the day of the transplant was considered day zero, while for the group on the waiting list the day of enrollment was considered day zero. The study was approved by Research Ethics Committee at UFMG.

## Results

A total of 84 children and adolescents enrolled on a liver transplantation list were evaluated. Of these, 40 patients underwent 42 transplants (two received repeat transplants), 26 died while waiting for a transplant and 18 patients were awaiting transplantation on the cutoff date set for this study.

The characteristics of the patients on the list, those who received transplants and those who died while on the waiting list are described in Table 1. There were no statistically significant differences between the group of patients who received transplantations due to chronic liver disease and those who died on a waiting list, in terms of sex ( $p = 0.78$ ), age at enrollment on the list ( $p = 0.16$ ) or Child-Pugh ( $p = 0.06$ ), Malatack ( $p = 0.19$ ), MELD ( $p = 0.68$ ) or PELD ( $p = 0.54$ ) classifications.

Biliary atresia was the most common subjacent disease (Table 2). The indications for transplantation for the four patients with Child-Pugh class A were untreatable pruritis (in a patient with Alagille syndrome) and upper digestive hemorrhage secondary to portal hypertension in three patients. Just five of the 10 patients with fulminating hepatitis who received transplants had a definite etiology: hepatitis A virus (two cases), hepatitis medicamentosa from fenproporex (one case), autoimmune hepatitis (one case) and Wilson's disease (one case).

The causes of death of the children who died on the waiting list were sepsis (38.1%), multiple organ failure secondary to liver failure (30.1%), disseminated intravascular coagulation (9.5%), upper digestive hemorrhage (9.5%), acute abdomen (6.4%) and pulmonary hemorrhage (6.4%). Figure 1 illustrates the mortality curve of the patients on the waiting list. Analysis of the survival curve for the 44 patients who were enrolled but did not receive transplants demonstrates that 25% of the deaths occurred during the first 95 days after enrollment and 50% took place within 354 days of waiting on the list.

### **Description of patients who underwent transplantation**

Age at transplantation varied from 1.9 to 16.8 years, with a median of 6.6 years (IQ25/75% = 3.8/12.6), with a length of time on the waiting list that varied from 2 to 1,567 days, with a median of 291 days (IQ25/75% = 16/554 days). The length of time waiting on the list for the 30 patients whose transplants were for chronic liver disease varied from 16 to 1,567 days, with a median of 492 days (IQ25/75% = 215/641 days). The length of time that the group of patients with

fulminating hepatitis waited varied from 2 to 18 days with a median of 4 days (IQ25/75% = 3/4).

Two patients received repeat transplants due to thrombosis of the hepatic artery; one was a patient with fulminating hepatitis who was progressing well after the second operation; the second had cryptogenic cirrhosis and died from thrombosis of the hepatic artery after the second transplant.

### **Post-transplant survival**

Thirteen (32.5%) of the 40 transplant recipients died, at ages that varied from 1.8 to 13.6 years (median of 6.7 years). These patients died between 0 and 204 days after the transplant, at a median of 7 days (IQ25-75% 4-12). Analysis of the 40 transplant recipients demonstrated that probability of survival to 180 days was 70%, and that 67.2% survived 5 years after transplantation.

For the subset with chronic disease, the probability of survival for the 30 patients was 79.8% to 180 days and 76.2% up to 5 years after transplantation (Figure 2). There were seven deaths, three due to primary non-function, two cases of thrombosis of the hepatic artery, one death from septic shock and one death during the postoperative period of surgery for a biliary fistula.

The probability of patients with fulminating hepatitis surviving to 365 days post-transplantation was 40%. There were six deaths, five due to multiple organ failure and one due to primary non-function.

### **Length of hospital stay and post-transplant complications**

The length of time spent in the intensive care unit (ICU) by the 29 patients who were discharged to the wards (11 patients died in the ICU) varied from 2 to 80 days, with a median of 7 days. The length of hospital stay for the 28 patients who were discharged to go home varied from 8 to 123 days, with a median of 21.5 days.

Post-transplant complications unrelated to the graft occurred in 17 of the 42 transplant cases (40.5%). Hemodynamic complications affected 40.5% of the transplants, there were neurological complications in 38%, infectious in 35.7%, respiratory complications in 33.3% and renal complications in 23.8%. There was one case of lymphoproliferative disease (LPD, 2.3%).

Complications related to the graft were observed in 24 (57.1%) of the 42 transplants performed: acute rejection in seven (16.6%); thrombosis of the hepatic artery in seven (16.6%); stenosis of the hepatic artery in four (9.5%); primary non-function in four (9.5%); biliary complications in three (7.1%, two of which were associated with complications of the hepatic artery); there was portal vein thrombosis in two (4.7%) and chronic rejection in one case, who exhibited good progress after immunosuppression was adjusted. In three cases of hepatic artery thrombosis, liver function and

**Table 1** - Patient characteristics: sex, age at enrollment on the transplant list and Child-Pugh, Malatack, PELD and MELD scores

Characteristics	Patients enrolled (total = 84)	Transplanted due to chronic liver disease (total = 30)	Transplanted due to fulminating liver failure (total = 10)	Patients who died while on the waiting list (total = 26)
Male	44 (52.4)*	16 (55)*	4 (40)*	12 (46)*
Age at enrollment (years)				
Median	4.7	6.6	10.5	4.6
p (25%)/p (75%)	2/11.9	3.8/12.6	8/12	2.6/17.7
Child-Pugh				
A	8 (9.50)*	4 (13.3)*	- <sup>†</sup>	2 (7.8)*
B	44 (52.4)*	21 (70.0)*	- <sup>†</sup>	12 (46.1)*
C	27 (32.0)*	5 (16.7)*	- <sup>†</sup>	12 (46.1)*
Losses	5 (6.0)*	0	- <sup>†</sup>	0
Malatack				
Low risk	52 (61.9)*	23 (76.7)*	- <sup>†</sup>	11 (42.3)*
Moderate risk	10 (11.9)*	4 (13.3)*	- <sup>†</sup>	6 (23.1)*
High risk	7 (8.3)*	3 (10.0)*	- <sup>†</sup>	4 (15.3)*
Not classified	15 (17.9)*	0	- <sup>†</sup>	5 (19.3)*
PELD	59 children	24 patients	- <sup>†</sup>	21 patients
Median	13	14.5	- <sup>†</sup>	14
p (25%)/p (75%)	-7/48	-2/48	- <sup>†</sup>	-7/43
MELD	17 patients	5 patients	- <sup>†</sup>	5 patients
Median	19	15	- <sup>†</sup>	24
p (25%)/p (75%)	9/44	10/19	- <sup>†</sup>	21/31

\* Total (%).

<sup>†</sup> Not applicable.

the biliary tree remained normal and repeat transplantation was not necessary. In two of the hepatic artery stenosis cases, stents were fitted, in the remainder conservative treatment was chosen; all are progressing well.

### **Immunosuppression**

Thirty-four of the 40 liver transplant recipients started immunosuppression (six died before that point). In all cases

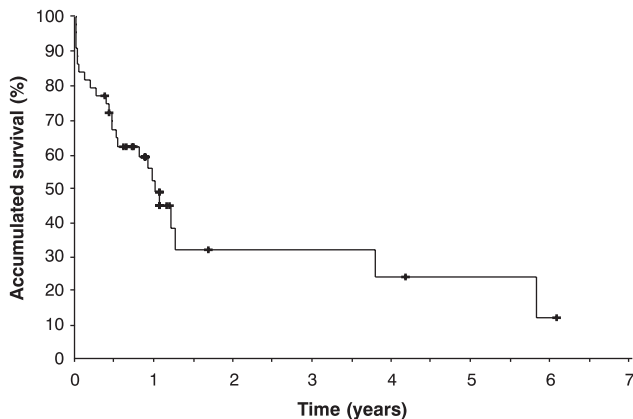
**Table 2** - Liver disease diagnoses of patients enrolled on transplant waiting list and of subset who have already received a transplant

Liver disease	On waiting list Total = 84 patients n (%)	Transplanted Total = 40 patients n (%)
Biliary atresia	30 (35.7)	14 (35)
Fulminating hepatitis	15 (17.9)	10 (25)
Cryptogenic cirrhosis	13 (15.5)	6 (15)
Autoimmune hepatitis	6 (7.1)	2 (5)
Alpha-1-antitrypsin deficiency	6 (7.1)	3 (7.5)
Choledochal cyst	3 (3.6)	2 (5)
PFIC	2 (2.4)	-
Sclerosing cholangitis	2 (2.4)	-
Alagille syndrome	2 (2.4)	1 (2.5)
Others	5 (6.0)*	2 (5) <sup>†</sup>

PFIC = progressive familial intrahepatic cholestasis.

\* Glycogenosis, Wilson's disease, ductal hypoplasia, Crigler-Najjar syndrome, Budd Chiari syndrome.

<sup>†</sup> Crigler-Najjar and Budd Chiari.



**Figure 1** - Survival curve for the 44 patients of the waiting list who did not receive transplants

prednisone was used (for the first 6 months after transplantation), in combination with calcineurin inhibitors. Twenty-three patients (67.6%) were prescribed tacrolimus, and 11 (32.4%) took cyclosporine. More recently, cyclosporine was substituted in all patients by tacrolimus.

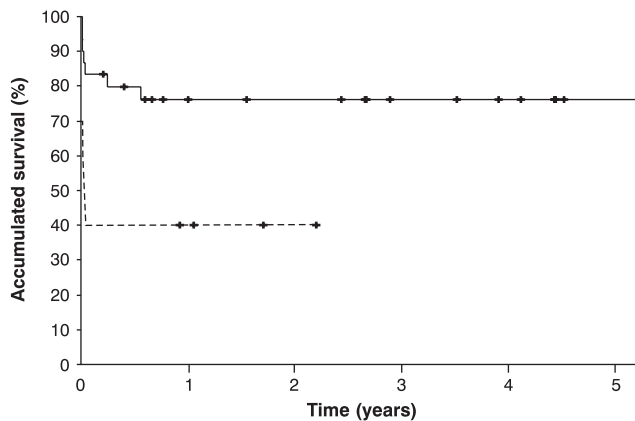
**Discussion**

Pediatric liver transplantation has become a reality in Brazil, after a major expansion that started in the 1990s. The first

pediatric liver transplantation carried out at the Hospital das Clínicas da UFMG took place in September of 1995. Since then, 84 children and adolescents have been enrolled on the waiting list for this procedure, although a low proportion them have received transplants, less than 50%, which is primarily related to the scarcity of donors and has resulted in a high rate of mortality while on the waiting list.

We observed that 50% of the deaths on the waiting list took place within 354 days of enrollment on the list, which is shorter than the median length of time waited by chronic liver disease patients before receiving a transplant, this being 492 days. This finding emphasizes the importance of reducing the length of time spent on waiting lists, by increasing awareness of the importance of donation and harvesting of organs, and also by implementation of surgical techniques such as live donation and split transplants. Such measures have been applied in other countries, with waiting list mortality rates reduced to as little as 5%.<sup>7-9</sup>

Enrolling patients in advanced stages of liver disease can contribute to increasing waiting list mortality, but this was not the case with our patient sample, according to severity scores for the patients enrolled for chronic liver disease, the great majority of whom were enrolled in good time according to what can be found in the literature.<sup>6,10-12</sup>



**Figure 2** - Post-transplant survival curve for the 30 patients with chronic liver disease and 10 patients with fulminating hepatitis

In common with what is reported by the majority of pediatric transplant centers, with the exception of Turkey where the primary cause is metabolic diseases, biliary atresia was the most common indication in this sample.<sup>8,13-17</sup> The fact that the second most common diagnosis among the group of transplant recipients was fulminating hepatitis is related to the priority that these patients are given, receiving donor organs that would probably go to adult recipients, and other studies have also listed this as their second most common indication.<sup>14,16,17</sup>

For the subset of patients transplanted due to chronic liver disease, the five-year survival rate is within the range of results obtained by leading transplant centers, where survival rates can reach 90% during the first year and 64.3 to 83.3% after 5 years.<sup>8,13,18-22</sup> Primary non-function and thrombosis of the hepatic artery were the principal causes of death of patients transplanted for chronic liver disease, which is a result that differs from other pediatric transplant centers, where infections tend to be the principal cause of death.<sup>3,8,14,18,22,23</sup> This difference can be attributed to the increased frequency of hepatic artery thrombosis found in this sample.

With relation to the fulminating hepatitis cases, the low survival rate during the first 365 days after transplant is similar to published data in which post-transplant mortality is high among such patients, fluctuating around 50%, probably due to their clinical severity at the time of transplantation.<sup>23,24,25</sup>

In the literature, infections are the principal cause of complications unrelated to the graft, occurring in 60 to 70% of cases.<sup>3,18,19,23</sup> Although we found a high frequency of infections, it was below what is found in published data, despite prolonged post-transplantation hospital stays with relation to other reports, where the mean stay varies from 17 to 24 days.<sup>14,25,26</sup>

With relation to post-transplant complications related to the graft, we observed similar frequencies to other samples of pediatric transplant patients, with cases of acute rejection and vascular complications predominating.<sup>19,27</sup> The incidence of acute rejection has reduced over the years in response to the use of ever more powerful immunosuppressors.<sup>19,27</sup> Thrombosis of the hepatic artery is a severe vascular complication that results in loss of the graft and an indication of immediate repeat transplantation.<sup>3,13,14,17,18</sup> It is more common in the pediatric age group (7 to 8%), to a great extent because of technical difficulties, such as the disproportionate diameters of donor and recipient blood vessels, with greater risk of stenosis and thrombosis at the anastomoses.<sup>3</sup> The rate of hepatic artery thrombosis in this patient sample was 16.6%, which is above what is described in the literature. We also observed that in three cases of hepatic artery thrombosis there was collateral arterial reperfusion and no need for repeat transplantation. This fact has also been reported with relation to other samples, and up to 40% of cases of thrombosis of the hepatic artery may not need repeat transplantation due to the development of collateral arteries that supply the liver and biliary tree.<sup>3,20</sup>

Portal vein thrombosis is rare in adults, but occurs in more than 33% of pediatric liver transplantation recipients, in contrast with what was observed in our study, where there were just two cases.<sup>13</sup> The great majority of biliary complications are secondary to thrombosis of the hepatic artery,<sup>28</sup> and were observed in 7.1% of our cases, which is comparable to what is reported in the literature (5 to 30%).<sup>3</sup>

One of our patients had lymphoproliferative disease (2.3%), which is described as affecting 5 to 15% of children after transplantation,<sup>10,22,29,30</sup> with 90% of these children having an Epstein-Barr virus infection. The risk of development of the disease is greater among patients with a primary Epstein-Barr infection,<sup>10,30</sup> which could affect up to 75% of children susceptible to the virus during the first 6 months after the procedure, increasing the risk of development of post-transplant LPD.<sup>22,29,30</sup> Pre-transplant serological evaluation is obligatory with the intention of monitoring patients for primary infection and providing post-transplant prophylaxis, since a diagnosis of primary infection is an important reason for reducing immunosuppressor dosages in order to avert progression to LPD.<sup>29</sup>

The principal causes of immediate repeat transplants are primary non-function of the graft and thrombosis of the hepatic artery,<sup>3,8,13,18,22</sup> while, over the long term, chronic rejection is the number one indication.<sup>8</sup> In our sample there were two repeat transplants due to thrombosis of the hepatic artery. The fact that there were no repeat transplants due to primary non-function is because none of these patients proved able to wait for a new donor. Primary non-function of the liver is a severe complication of the post-transplant period, which can occur in 5 to 16% of cases,<sup>3,16-18,22</sup> and is an indication

for immediate repeat transplantation. The reasons may be based in technical problems related to surgery, the donor, the organ harvesting process (which may contribute to ischemic damage to the graft) and the recipient, such as hyper-acute rejection. Prevention is difficult since there are so many possible causes.

There are certain limitations to the study design adopted here that should be taken into consideration, primarily with relation to minor complications, since reviewing medical records only makes it possible to record major complications. Therefore, there may be situations in which less relevant complications that took place during these patients' treatment have not been reported on their medical records.

It can be concluded that the results of this patient sample are similar to those that can be observed in the literature, in terms of indications for transplantation and post-transplantation survival and complications. Nevertheless, we need to improve our results in terms of reducing the number of complications unrelated to the graft and improving our rates of vascular complications.

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