



Pediatric Liver Transplantation Outcomes for Metabolic and Non-metabolic Diseases in Turkey: A Single Center Experience

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ABSTRACT

Aim: Liver transplantation (LT) is performed for several indications in the pediatric population, including malignancy and acute hepatic failure among others. LT has become an important treatment alternative for metabolic diseases. In most pediatric transplant centers, metabolic liver disease is the second most common indication for LT after biliary atresia. Our studies aim is to compare the post-transplant outcomes of those patients with metabolic and other liver diseases in our transplant program.

Materials and Methods: One hundred eighty-nine patients who underwent LT between 1997 and 2015 due to metabolic diseases and acute or chronic liver failure were included in the study. This study was performed retrospectively.

Results: We enrolled 189 patients in our study. 54% (n=102) male and 46% (n=87) female patients were included in the study. The metabolic disease group included 56 patients and the non-metabolic disease group contained 133 patients. Progressive familial intrahepatic cholestasis is the most common disease among metabolic diseases resulting in LT and Wilson disease is the second most common. Post-transplant immunosuppression was similar for both groups. There was no difference in both groups regarding the onset of post-transplant complications for graft type or recipient age. Biliary and portal vein complications were most particularly defined in the group with non-metabolic diseases. There was no significant difference in survival between the two groups.

Conclusion: LT is an important treatment option for acute hepatic failure and end-stage liver diseases. In addition, LT is an alternative treatment option for some metabolic diseases.

Keywords: Complications, non-metabolic diseases, metabolic diseases, liver, survival, transplantation

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Introduction

In children, liver transplantation (LT) can be performed at many indications, including malignancy and acute hepatic failure. LT is an important treatment option, especially in children with biliary atresia, progressive familial intrahepatic cholestasis (PFIC), Wilson disease and some metabolic diseases (1,2). In metabolic diseases, multiorgan failure may occur due to an accumulation of toxic metabolites in organs. In inherited metabolic diseases, LT has two main purposes: to keep the patient alive in progression to hepatic failure and to completely eliminate the underlying metabolic defect for some metabolic diseases. Some metabolic disorders cause progressive liver damage and may require LT (3). Other metabolic disorders do not cause structural liver damage, but toxic metabolites have extra hepatic effects in some diseases such as urea cycle defects, primary hypercalcemia Type I, and Crigler-Najjar syndrome Type I. (3-6). LT can be performed to relieve the enzyme deficiency if alternative treatment options are not sufficient or metabolic decompensation could not be prevented in metabolic diseases (3,7). During the last few decades, LT has become an alternative treatment in metabolic diseases. In most pediatric transplant centers, metabolic liver disease is the second most common indication for LT after biliary atresia (8,9).

Due to progress in the field, long-term survival rates of pediatric LT are now over 80% with the majority of mortalities occurring within 6 months of the transplant procedure (10,11). The survival rates for 1 and 5 years after LT in children are 77-86%, 73% and 87%, respectively (12-14). These rates may be better for children with LT for metabolic diseases. The 1- and 5-year survival rates of children with LT due to metabolic disease vary between 87-94%, 79% and 92%, respectively (15-17). The purpose of this study is to compare the treatment and follow-up results of patients who underwent LT for metabolic disease and other causes in our transplantation program.

Materials and Methods

One hundred eighty-nine patients who underwent LT between 1997 and 2015 due to metabolic diseases and acute or chronic liver failure were included in the study. This retrospective study reviewed the records of these patients. After the LT, all the recipients were followed monthly during the first six months, every three months in the next six months and after the first year they were followed up every six months.

Gender, age, age at transplantation, type of transplantation, type of donor, rejection and complications were evaluated. This study was performed retrospectively. The study was prepared in accordance with the Helsinki Declaration. An informed consent form was obtained from the patients' relatives.

Statistical Analysis

The results are expressed as mean values where indicated; a paired Student t-test was used to assess differences between the two groups. The Kaplan-Meier method was used to assess patient survival rates. Differences in survival were compared using a log-rank analysis. $P < 0.05$ was considered significant. All the statistical analyses were performed using MedCalc Software (Ostend, Belgium, <https://medcalc.org/>; 2013) version 12.7.7.

Results

A total of 189 patients, 54% (n=102) male and 46% (n=87) female were included in the study. Fifty-six patients in the Metabolic disease group were enrolled (PFIC: 22 patients, Wilson disease: 11 patients, tyrosinemia Type I: 9 patients, familial hyperlipidemia: 4 patients, alpha 1 antitrypsin deficiency: 3 patients, glycogen storage disease (GSD) Type I: 3 patients, Crigler Najjar syndrome Type I: 2 patients, GSD Type III: 1 patient, GSD Type IV: 1 patient) in the study. Details are given in Figure 1. In the non-metabolic liver disease group; there were 133 patients (biliary atresia: 55 patients, autoimmune hepatitis: 13 patients, fulminant hepatitis: 32 patients, tumor: 10 patients, other cholestatic disease: 19 patients and others: 4 patients). The diagnosis of these patients is detailed in Figure 2.

Biliary atresia is the most common transplant indication for LT. The other important indications for LT are fulminant hepatic failure, autoimmune hepatitis and cholestatic liver diseases.

From a total of 189 patients; 29.6% (n=56) of cases were diagnosed as metabolic diseases including Wilson disease, Tyrosinemia and PFIC. Median age at diagnosis was 11.8 (1-31) months in the non-metabolic group and 2.2 (5 months-17 years) years in the metabolic group. In the metabolic diseases group, mean age at transplantation was 5.52 ± 4.75 (6 months-17 years) years and the non-metabolic group mean age at transplantation was 5.6 ± 5.4 (6 months-14 years) years. The characteristics of the patients diagnosed with non-metabolic and metabolic diseases are shown in Table I. The characteristics of the patients diagnosed with Metabolic diseases are shown in Table II.

Only one patient with familial hyperlipidemia and one patient with PFIC underwent a second transplant. In the group of patients with metabolic diseases (n=56), 5 cases were diagnosed with tyrosinemia Type I and developed hepatocellular carcinoma. PFIC was the most common disease among the patients with metabolic diseases who underwent LT, and Wilson disease was the second most common. In the non-metabolic group, 69.8% (n=92) of patients had a transplant from a living donor, while the rest of the patients (n=41) received a transplant from cadavers. More than two-thirds of patients with metabolic disease had a LT from a live donor. Rejection was found in 15% of those

patients with metabolic disease while the percentage of organ rejection in the other group was 18%. Post-transplant immunosuppression was similar for both groups. There was no difference in both groups regarding the onset of the post-transplant complications, graft type or recipient age. Biliary

and portal vein complications were most particularly defined in the group with non-metabolic diseases. There were three patients with gastrointestinal system complications in the metabolic diseases group, however no patient developed gastrointestinal complications in the non-metabolic disease

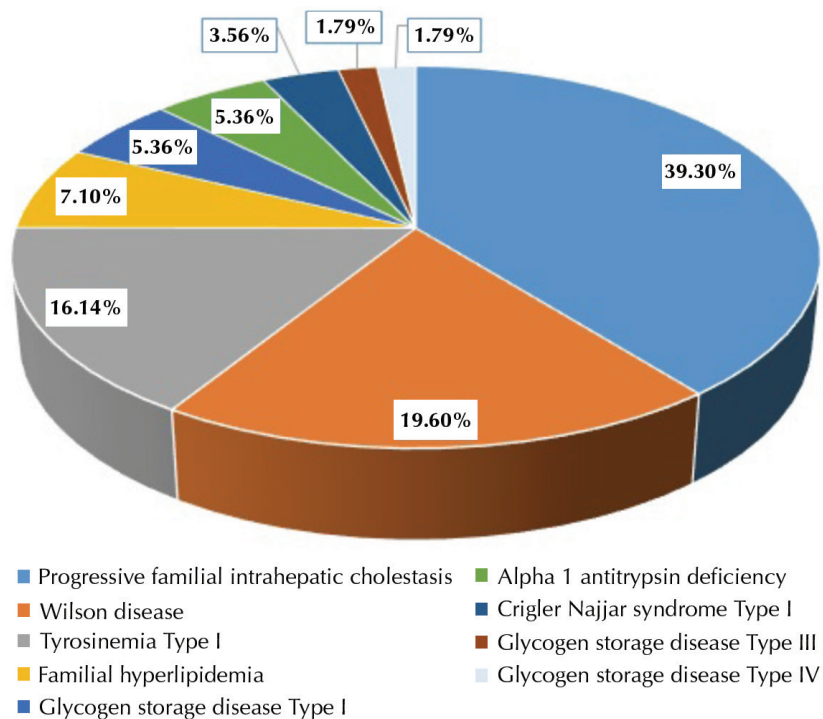


Figure 1. Metabolic diseases groups

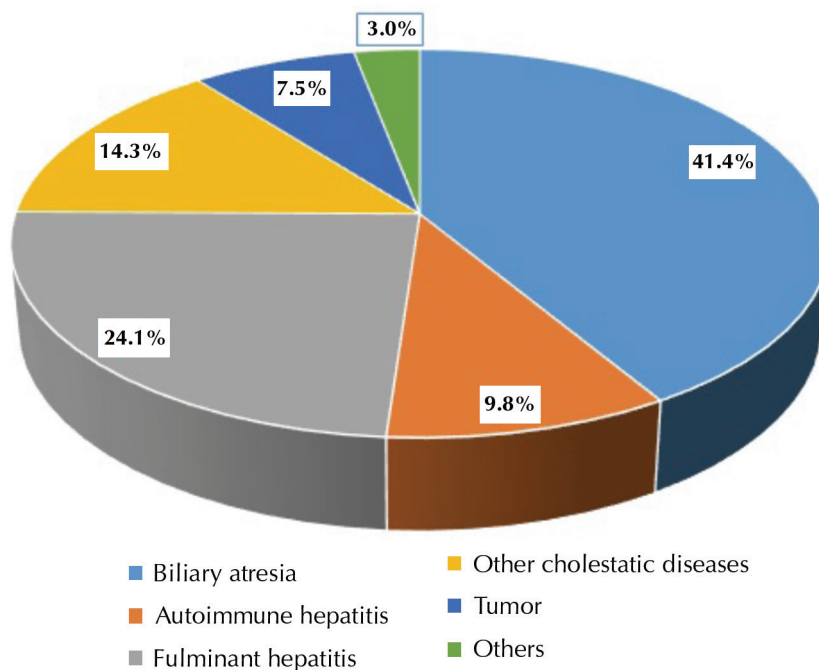


Figure 2. Non-metabolic diseases groups

group. Post-transplant complications of the patients diagnosed with metabolic diseases are given in Table III.

The rate of immunosuppressive drugs which were used for LT due to metabolic disease varied as follows: 60.7% tacrolimus, 28.5% sirolimus and 10.8% cyclosporine. The rate of immunosuppressive drugs which were used for LT due to non-metabolic disease varied as follows; 71.4% tacrolimus, 18% cyclosporine and 9.8% sirolimus. In terms of ongoing medication, no statistically significant difference was detected between the two groups.

In the non-metabolic disease group, the survival rate for the first year after transplantation was 82%, but in the fifth year this rate dropped to 79%; In the group of patients with metabolic disease, the survival rate at one year after transplantation was 80%, while in the fifth year it was 77% (Figure 3). No significant difference was detected between the two groups.

Group	Non-metabolic disease	Metabolic disease	p value
Gender (female/male)	64/69	30/26	0.96
Mean age at transplantation	5.6±5.4	5.52±4.75	0.92
Donor type			
- Cadaveric	40	19	0.90
- Living donor	93	37	-
- Rejection	31	5	0.44
Treatment			0.38
- Siklosporin	24	16	-
- Tacrolimus	95	36	-
- Sirolimus	14	4	-
Number of patients with post-transplant complications (%)	38 (28.6)	15 (26.7)	0.56

Discussion

This study reviewed the experience and long-term follow up of pediatric patients with metabolic and non-metabolic diseases who underwent LT at our center during the last 18 years. In the literature, post transplantation survival rates of patients who had inborn defects of metabolism appear to be higher, when compared to survival following transplantation for other indications, such as extrahepatic biliary atresia, acute liver failure, or post necrotic liver cirrhosis (16). Most studies regarding LT for metabolic liver diseases involve pediatric patients. In our study, the survival rate for the first year after transplantation was 82%, but in the fifth year this rate dropped to 79%; in the group of patients with metabolic disease, the survival rate one year after transplantation was 80%, while in the fifth year, it was 77%. According to our analysis, the patient survival rate was similar for children with metabolic and non-metabolic diseases. The survival rate was the same in both groups, which might be related to accompanying pre-transplant and post-transplant factors and the diseases which caused parenchymal liver disease in both groups. Pre-transplant health status affects post-transplant survival (2). The one- and five-year patient survival rates were reported as between 92% and 94% in the United States (18) whereas

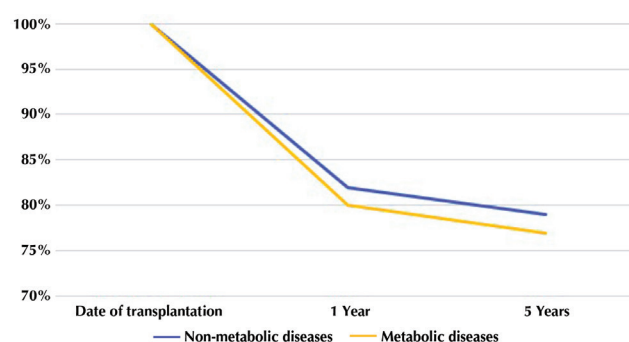


Figure 3. Survival rate of metabolic and non-metabolic diseases

	CNS Type I	GSD Type III	Wilson disease	PFIC	Alpha 1 antitrypsin deficiency	GSD Type I	GSD Type IV	Tyrosinemia	Hyperlipidemia
Number of patients	2	1	11	22	3	3	1	9	4
Number of living patients	2	1	8	15	3	3	1	8	4
Median age (year)	2	4	12.44±4.04	3.9±2.64	0.8±0.28	8.3±4.93	4	2.75±2.41	5.5±3.5
Donor type numbers, cadaveric/living	1/1	-/1	5/6	8/14	-/3	1/2	-/1	1/8	-/4

CNS: Crigler-Najjar syndrome Type I, GSD: Glycogen storage disease, PFIC: Progressive familial intrahepatic cholestasis

Sze et al. (19) reported survival rates of 91% and 86%, respectively, in the United Kingdom. The survival rates at 1, 5, and 10 years in these studies were similar to other studies. (16,17,20).

Arnon et al. (21) showed that survival rates of their patients with metabolic and non-metabolic diseases were 94.6% and 90.7% at one year respectively and 88.9% and 86.1% respectively at year five. The cumulative survival rates in pediatric patients with non-metabolic disease were 91.9%, 87.2%, and 85.8% at one, five, and 10 years, respectively (22). The survival rate was lower in both the metabolic and non-metabolic disease groups in our study, which was different from the study by Kayler et al. (15). Kayler et al. (15) and Arnon et al. (21) had patients without metabolic disease due to parenchymal liver disease, which may account for the lower survival rate in our study. However, we had more patients with PFIC and Wilson Disease than other studies. The study by Kayler et al. (15) conspicuously contained a lot of patients with alpha 1 antitrypsin deficiency (n=261). However, Kayler et al. (17) defined the metabolic group as only patients with biliary atresia, which meant that he compared biliary atresia to a non-metabolic group. These results may be due to the involvement of patients with LT due to tumor, autoimmune hepatitis, fulminant hepatitis, which might worsen the outcomes compared with postoperative transplantation due to BA. (23,24). We classified those patients with PFIC into the metabolic disease group, which may be why the survival rate is lower in our study than in other studies.

In our work, in accordance with other studies, we found that Pediatric End-stage Liver Disease scores were statistically significantly lower in children with metabolic diseases (25). As a result of very good survival rates, complications after LT can be seen in children. In the Arnon et al. (21) study, gastrointestinal and hematological

complications were more frequent. Peeters et al. (1) reported less gastrointestinal complications post-LT in patients with metabolic disease than in those with BA. In our study, autoimmune hemolytic anemia was more common in patients with metabolic disease after transplantation than in the non-metabolic disease group. Gastrointestinal complications were more common in those patients in the non-metabolic liver diseases group (1). According to Kasahara et al. (24), seizure was one of the common problems, related with patients with metabolic diseases. The effects on systems were different from each other in metabolic diseases. In our study, we did not observe any seizure after LT.

In terms of acute rejection rates, we found a rate of approximately 15%, whereas Rosencrantz et al. (25) found a rate of approximately 22%, which was more than ours. This fact could be related to different treatment procedures. In our study, 61% of patients were on tacrolimus treatment.

The present study has several limitations that are the result of its single-center, retrospective design. In our study, biliary complications were the most common cause of post-transplant complications in both groups, the latter was portal vein complications. The reason which may cause a difference from the results of the other studies might be due to the low cadaver rates, especially among child cadavers, and the tendency to prefer living donors for LT in our country.

Conclusion

In hereditary metabolic diseases, orthotopic LT has very good survival outcomes. These children should be carefully monitored for the timing of transplantation. LT is one of the curative treatments in hepatic failure and end stage of liver failure. Also, we want to mention that LT is an alternative treatment for some metabolic diseases.

Table III. Post-transplant complications of the patients diagnosed with metabolic diseases

	CNS Type I	GSD Type III	Wilson disease	PFIC	Alpha 1 antitrypsin deficiency	GSD Type I	GSD Type IV	Tyrosinemia	Familial hyperlipidemia
Number of patients	2	1	11	22	3	3	1	9	4
Biliary complications	-	1	5	2	-	-	-	-	-
Renal stone	-	-	-	-	-	1	-	-	-
Portal thrombosis	-	-	-	1	-	-	-	-	-
HLH	-	-	-	1	-	-	-	-	-
CRF	-	-	-	1	-	1	-	-	-
OIH	-	-	-	1	-	-	1	-	-

CNS: Crigler-Najjar syndrome Type-I, GSD: Glycogen storage disease, PFIC: Progressive familial intrahepatic cholestasis, HLH: Hemophagocytic lympho histiocytosis, CRF: Chronic renal failure, OIH: Autoimmune hemolytic anemia

Ethics

Ethics Committee Approval: This study was performed retrospectively. The study was prepared in accordance with the Helsinki Declaration.

Informed Consent: An informed consent form was obtained from the patients' relatives.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.K., O.E., F.Ç., S.A., M.K., Concept: S.A., Design: S.A., M.K., E.C., S.K., Data Collection or Processing: M.K., E.C., Analysis or Interpretation: M.K., Literature Search: M.K., E.C., S.K., Writing: M.K., E.C.

Conflict of Interest: There is no conflict of interest.

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