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Original Article

Liver Transplants for Pediatric Metabolic Diseases in the Last Ten Years: Immediate and Long-Term Results

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ABSTRACT

Objective: Liver transplantation is an accepted treatment modality in the pediatric patient group due to metabolic diseases. Patients are a more special population due to the presence of concomitant metabolic problems and the pediatric age group. There is no consensus on the long-term prognosis of pediatric patients with various rare liver diseases and inherited metabolic diseases. For this reason, we retrospectively evaluated our pediatric patients who underwent liver transplantation for pediatric metabolic liver diseases between 2012 and 2021.

Methods: Seventeen patients were included in the study. The mean Pediatric End-Stage Liver Disease (PELD) score was 21.47 (±8.47). Eight (47,1%) children received cadaveric, and 9 (52,9%) children received living liver transplantation. The mean age was 8.03 years (±6.37) (13 months-18 years). Left lateral graft was used in 11 patients (64%), right lobe graft in 3 patients (18%) and left lobe graft in 3 patients (18%). Six patients had biliary strictures out of which, 5 (29.4%) had percutaneous transhepatic biliary dilatation, and ERCP was performed in 1 (5.8%) patient.

Results: Our early survival rate was 100% and 2 patients (11,7%) were exitus in the late period for reasons unrelated to liver transplantation. Our mean follow-up period after transplantation was 70,6 months (±20.75) and no additional metabolic crisis was detected during the follow-up of the patients, including patients whose donors were relatives.

Conclusion: Metabolic liver diseases have severe systemic effects, and it is important to be evaluated by a multidisciplinary team in their diagnosis and treatment and to perform planned liver transplants rapidly without delay. Liver transplantation performed at the right time can prevent permanent additional organ damage.

Keywords: Pediatric, metabolic diseases, pediatric liver transplantation

INTRODUCTION

Liver transplantation is an accepted treatment modality in pediatric patients with metabolic diseases. The reported incidence of liver transplantation in patients with inherited metabolic diseases is 8.0-20.2%.[1-3] Although this patient group represents a small group among transplant patients, it is a more special population because it includes accompanying metabolic problems and the pediatric age group.

In the pediatric age group undergoing liver transplantation for metabolic diseases, outcomes continue to improve with better survival rates and quality of life with improvements in perioperative transplantation management. One and 5-year survival rates reported in the literature range from 87% to 94% and 79% to 92%, respectively.[4-6]

The clinical presentation of metabolic disorders is variable. They may present with hepatocellular cancer including end-stage liver failure, renal tubular acidosis, seizures,

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encephalopathy, myopathy and similar clinical conditions. Therefore, liver transplant patients with inherited metabolic disease have many post-transplant related problems. In the case of living donor liver transplantation for these patients, there is no consensus on donor safety, given the possibility of the donor being a heterozygous carrier.[7-10] Although the prognosis of patients with urea cycle disorders after liver transplantation is known to be good because it is curative, the prognosis of patients with metabolic defects in other organs is not yet well defined.[3,11] In addition, although patients with hyperammonemia have potential intellectual development disorders and neurological sequelae, the outcomes for these patients remain uncertain.

There is no consensus on the long-term prognosis of pediatric patients with various rare liver diseases but not inherited metabolic diseases. In line with these aims, we aimed to retrospectively review our short and long-term outcomes in pediatric patients who underwent liver transplantation for pediatric metabolic liver diseases between 2012 and 2021 in our center.

METHODS

The available data were retrospectively reviewed through the electronic patient file (EHD). Patients with complete parameters and consent during treatment and follow-up were included in the study. Between 2012 and 2021, 91 pediatric patients who underwent liver transplantation at Ege University Faculty of Medicine Hospital were included in the study.

Liver disease etiology, age, gender, weight/size, Pediatric End-Stage Liver Disease (PELD) score, donor source, type of graft used, early and late postoperative technical and metabolic complications were analyzed. Patient consents were received for the study. Ege University ethics committee approved this study with 23-6.1T/2 and 23-9.1T/11 on June 22, 2023 and September 21, 2023.

MAIN POINTS

- Liver transplant patients with inherited metabolic diseases have many post-transplant related problems and timely transplantation with meticulous post-operative follow-up is required.
- Our study shows the potential to provide more information on the long-term prognosis of pediatric patients with inherited metabolic disorders with rare liver diseases.
- The results of this study show that the survival rate of these patients has increased and the quality of life of these patients has improved.
- Safety and ethical issues need to be carefully considered in the transplantation of liver from a living donor.

Statistical Analysis

The data obtained was analyzed with the Statistical Package for the Social Sciences, version 26.0 (IBM SPSS Corp., Armonk, NY, USA). In our study, the significance of *P* value was set as .05 and 95% confidence interval was used. After descriptive statistics, the normality distribution of the data was evaluated by Kolmogorov–Smirnov test and Shapiro-Wilk test. For comparisons between multiple groups, the Student's t test was used for independent groups if the data were normally distributed, while the Mann-Whitney-U test was used for non-normally distributed data.

RESULTS

Between 2012 and 2021, 91 patients underwent liver transplantation at Ege University Faculty of Medicine Hospital. 17 patients (18%) were transplanted for metabolic liver diseases. Among the liver transplant patients who underwent liver transplantation for metabolic diseases, 5 (29.4%) were male and 12 (70.6%) were female. The median PELD was 70.65 days (±20.75). The median waiting time for living donor group is 16.00 days (3.98-79.13) and 286 days (71.03-661.96) in cadaveric donor group (*P* = .015) children received living liver transplantation. The mean age was 8.03 years (±6.37) (13 months-18 years). The mean time from waiting list to transplantation 70.65 days (±20.75). The median waiting time for living donor group is 16.00 days (3.98-79.13) and 286 days (71.03-661.96) in cadaveric donor group (*P* = .015). Demographic data are summarized in Table 1. Etiologic reasons requiring liver transplantation are summarized in Figure 1 with their percentages.

The mean donor age was 25.8 (±12.9) years (5-46). Of the 9 living donors, 7 (77.7%) were transplants from the patients' own relatives (3 from the mother, 3 from the father, 1 from the brother). The median graft weight was 680 grams (380-1095). Left lateral grafts were used in 11 patients (64%), right lobe grafts in 3 patients (18%)

Table 1. Demographic Data

Gender	
Female	12 (71%)
Male	5 (29%)
Age (years)	
Mean ± SD	8.03 (±6.37)
Transplantation type	
Cadaveric	8 (47%)
Living donor	9 (53%)
Waiting time (months)	
Mean ± SD	103.75 (±343)
Donor age (years)	
Mean ± SD	25.8 (±12.9)

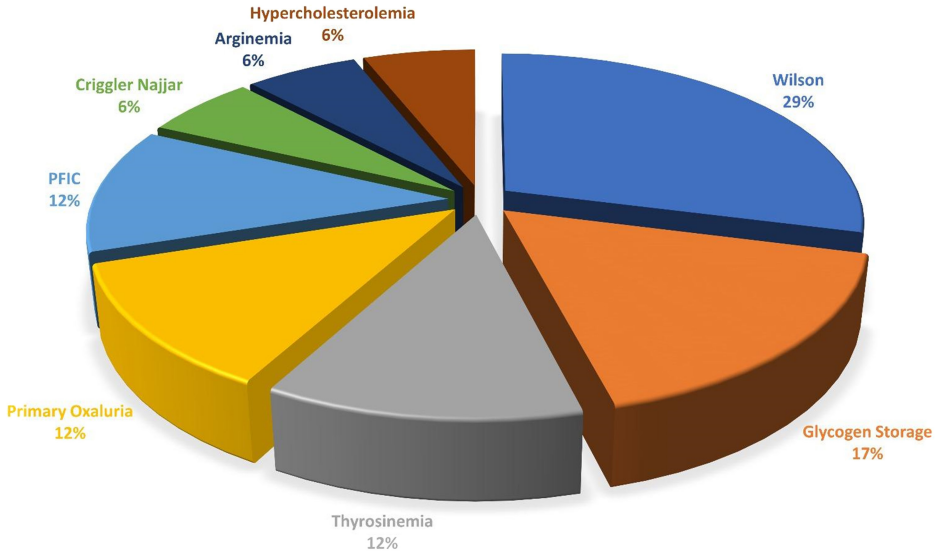

Figure 1. Etiologies in our pediatric population.
PFIC, Progressive familial intrahepatic cholestasis.

and left lobe grafts in 3 patients (18%). The mean duration of cold and warm ischemia was 93 minutes (±13.8) and 69 minutes (±19), respectively, in living transplants and 5.59 hours (±3.52) and 55 minutes (±12), respectively, in cadaveric transplants ($P < .001$). Nine patients (52.9%) were extubated after liver transplantation and admitted to the intensive care unit. Operative parameters are summarized in Table 2.

Prednisolone and tacrolimus were used routinely according to our center protocols, and it was standard in all patients. In case of any deterioration in renal function, immunosuppression was revised. Rejection occurred in 2 patients (12%) after liver transplantation, one of which was early acute rejection and the other was late chronic rejection. In 8 (47.1%) patients Mycophenolate mofetil (MMF) and in 2 (11.7%) patients everolimus treatment was added according to the clinical need.

Table 2. Operation Parameters

Graft type	
Left lateral graft	11 (64%)
Right lobe graft	3 (18%)
Left lobe graft	3 (18%)
Graft weight (g)	680 (380-1095)
Cold Ischemia	
Living donor	
Mean ± SD	93 minutes (±13.8)
Cadaveric	
Mean ± SD	5.59 hours (±3.52)
Warm Ischemia	
Living donor	
Mean ± SD	69 minutes (±19)
Cadaveric	
Mean ± SD	55 minutes (±12)

Postoperative vascular problems and early bile leakage were not detected in routine postoperative imaging. Percutaneous transhepatic biliary dilatation was performed in 5 of 6 (83.3%) patients and Endoscopic retrograde cholangiopancreatography (ERCP) was performed in 1 patient (16.7%) who had anastomotic stenosis in the bile ducts during follow-up. Cold and warm ischemia times were not found to be significantly different between the anastomotic stenosis groups ($P = .315$). Also found that there was not a significant difference between anastomatic stenosis and etiologies of transplantations ($P = .640$). Our early survival rate was 100% and 2 patients (12%) died in the late period for reasons not related to liver transplantation. Our mean follow-up period after transplantation was 70.65 months (±20.75), and no additional metabolic crisis was detected in the follow-up of the patients, including those whose donors were related.

DISCUSSION

In a 2010 review study by Binita M. Kamath et al.[12] titled liver transplantation in Alagille syndrome, 1-year survival rates were found to be between 71% and 100% except for early series and the median survival rate was 79%. In our study, our early survival rate was 100% and our result is in line with the literature.[12]

Furthermore, in a single-center study of 54 pediatric metabolic liver patients in Seoul between 1995 and 2015, the 1,5 and 10-year survival rates after living-to-living pediatric liver transplantation were 90.7%, 87.5% and 87.5%,

respectively, and graft survival rates were 88.8%, 85.5% and 85.5%, respectively.[1]

In our study, a group of 17 patients underwent liver transplantation for metabolic disorders between 2012 and 2021 and the findings reveal important implications for pediatric gastroenterology and liver transplantation. In terms of survival, our results are consistent with the literature. However, the small number of patients and the fact that the study was conducted in a single center may limit the generalizability of these results, so it would be useful to conduct multi center similar studies.

Prenatal genetic testing facilitates the diagnosis of metabolic diseases, and early detection and diagnosis of metabolic disorders is crucial in the course and treatment of the disease. It has the potential to be a new source of light for early intervention and possible preventive treatment modalities. This may reduce the need for liver transplantation in the pediatric population in the future. With the development of new preventive treatment modalities, new ethical issues related to these modalities will need to be meticulously addressed.[13]

As in adult liver transplantation, the issues in pediatric liver transplantation are complex. These dilemmas include decisions such as the appropriate length of time to wait before transplantation and whether to transplant in non-acute cases that are likely to deteriorate as the prognosis progresses. Effective, rapid, and comprehensive assessment by a multidisciplinary team on a case-by-case basis is critical to appropriately address these issues.[14]

With timely, effective, and multidisciplinary liver transplants, 100% survival rates can be achieved in the early stages, as demonstrated in our study. However, exitus may occur in the later stages for reasons unrelated to liver transplantation. Multidisciplinary management of the process is of great importance in preventing recurrent metabolic crises in transplants in which relatives are donors.

Percutaneous transhepatic biliary dilatation and ERCP procedures were performed with the support of interventional radiology and gastroenterology in patients who developed biliary strictures during follow-up. A study by Darius et al. highlighted the prognostic importance of biliary strictures and the need for effective and rapid intervention. In this context, developing technological methods allow patients to be treated earlier and with minimally invasive methods. It is known that minimally invasive interventions contribute less to the increase in mortality and have less impact on the patient's quality of life than surgical interventions.[15]

Metabolic liver diseases are a group of diseases with severe systemic effects, and it is important that their diagnosis and treatment are assessed by a multidisciplinary team and that planned liver transplantation is performed quickly and without delay. Timely liver transplantation can prevent permanent additional organ damage. The most important factors influencing the success of transplantation are the patient's adherence to the post-transplant diet and the prevention of metabolic problems that can develop at risk through regular follow-up.

Our study shows the potential to provide more information about the long-term prognosis of pediatric patients with inherited metabolic disorders with rare liver diseases. At this point, studies with larger sample sizes and long-term follow-up are needed.

In conclusion, liver transplantation for metabolic diseases is an important treatment modality for pediatric patients. The results of this study show that the survival rate of these patients is increased, and their quality of life is improved. However, safety and ethical issues need to be carefully addressed in living donor liver transplantation.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Ege University (Date: June 22, 2023 and September 21, 2023, Number: 23-6.1T/2 and 23-9.1T/11).

Informed Consent: Written informed consent was obtained from patients and their parents who participated in this study.

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