Table 4. LDLT for each metabolic disorders

Diagnosis (n)	Wilson's disease (n = 59)	Urea cycle deficiency (n = 51)	Organic acidemia (n = 29)	Glycogen storage disease (n = 15)	Primary hyperoxaluria (n = 9)
Family history	4 (6.8%)	17 (33.3%)	2 (6.9%)	1 (6.6%)	3 (33.3%)
Donor age (yr)	41.7 ± 8.7 (22–68)	35.8 ± 6.8	33.6 ± 5.0	36.4 ± 9.2	39.9 ± 5.3
ABO incompatibility	5 (8.5%)	6 (11.8%)	5 (17.2%)	3 (20.0%)	1 (11.1%)
Age at onset (yr)	11.0 ± 4.4 (6–16)	1.1 ± 1.5 (0–2)	0.6 ± 1.7 (0–6)	0.1 ± 0.3 (0–1)	1.0 ± 0.8 (0.4–2)
Age at transplantation (yr)	11.4 ± 2.8 (6–17)	3.8 ± 4.6 (0.2–16)	2.2 ± 2.8 (0.4–12)	4.9 ± 4.3 (0.8–13)	7.7 ± 6.2 (1–17)
Indication of LTx	Chronic liver failure 42 Fulminant 17	Frequent hyperammonemia 51 Poor QOL 30	Metabolic decompensation 29 Poor QOL 29	Hypoglycemia 11 Chronic liver failure 3 Acute liver failure 2	Renal failure 9 Poor QOL 9
Transplantation score*	17.7 ± 3.2	19.3 ± 4.11	18.6 ± 3.0	14.0 ± 2.0	13.0 ± 2.0
Immunosuppression	Tac 66.0%, Tac+MMF 18.8% CyA 7.5%	Tac 72%, Tac+MMF20%, CyA 10%	Tac 86.2%, Tac+MMF3.4%, CyA 10.3%	Tac 80%, Tac+MMF 20%	Tac 77.8%, Tac+MMF 11.1%, CyA 11.1%
Acute and chronic rejection (%)	11.9, 3.4	9.8, 0	0, 0	6.6, 0	11.1, 0
Post LTx complication					
Hepatic artery thrombosis	1	0	0	0	1
Portal vein thrombosis	1	0	0	1	1
Biliary	1	1	0	0	0
Renal insufficiency	0	1	4	0	–
Seizure	4	4	3	3	0
Cause of death	*Pneumocystis* pneumonia Recurrent hepatitis C De novo autoimmune hepatitis Hypoxic–ischemic encephalopathy (epilepticus) Sepsis 2	Hemophagocytic syndrome Traffic accident	Sepsis 4	Sepsis 5 Liver failure after PV thrombus	Sepsis 3 Liver failure after HA/PV thrombus
Patient survival					
1 yr	98.4	96.1	89.7	80.0	55.6
5 yr	96.6	96.1	85.2	66.7	55.6
10 yr	94.7	96.1	85.2	66.7	55.6
15 yr	77.5	96.1	–	–	–

QOL, quality of life, LTx, liver transplantation, Tac, tacrolimus, MMF, mycophenolate mofetil, CyA, cyclosporine A, HA, hepatic artery, PV, portal vein.
*See Table 2.

died from septic complications. Mortality was observed in older patients (seven, nine, 15, and 17 yr), and three of five isolated liver transplant patients died. The one-, five-, and 10-yr patient and graft survival rates were 55.6%, 55.6%, and 55.6%, respectively.

Thirteen patients underwent LDLT for tyrosinemia at a median age of 8.1 ± 5.7 (1–21) months. Two patients had a family history of newborn death. LDLT was indicated for acute and chronic liver failure in all cases, with a median transplantation score of 19.1 ± 10.2. Three patient mortalities were noted, including sepsis in two cases and a traffic accident in one case.

Six patients received LDLT for citrullinemia at a median age of two and a half yr. All patients are currently doing well. Three other mortalities were observed, including a case of multi-organ failure in a patient with mitochondrial respiratory chain disorder, a case of sepsis in a patient with a bile acid synthetic defect and a case of sepsis secondary to biliary leakage in a patient with protoporphyria. Two of three patients with auxiliary orthotopic LDLT patients are doing well, one patient with OTCD received native hepatectomy due to the portal steal phenomenon.

Discussion

We reviewed the outcomes of 194 pediatric LDLT recipients with metabolic disorders. The one-, five-, 10-, and 15-yr patient and graft survival rates of the patients with metabolic disorders undergoing LDLT were 91.2%, 87.9%, 87.0%, and 79.3%, and 91.2%, 87.9%, 86.1%, and 74.4%, respectively. The present results compare favorably with recently published data from an outstanding series regarding deceased LT (16–18). Patient survival was significantly better for patients undergoing LDLT more recently, with a five-yr survival rate of 89.9%. The recent achievement of better patient survival might be due to perioperative nutritional, immunological, and surgical management. Non-Wilson, non-urea cycle patients appear to be more associated with medical complications in their mortality causes. These patients necessitate lifelong strict medication and protein restriction even after successful LDLT, and this might be associated with worse patient survival.

Due to the unavailability of deceased donors, LDLT has been employed as a major organ resource for LT in our country. In the present study, 95.6% of the donors were parents, and an obligate heterozygous carrier of the recipient's disorder may be used as a live donor. There have been limited numbers of LDLT series using heterozygous donors in the literature, and the long-term risks of heterozygous carrier donors have not been fully documented (19, 20). Most cases of inherited metabolic disorders are autosomal recessive, and transplantation from carrier parents with autosomal recessive diseases (50% enzyme activity) has demonstrated successful LDLT results (21). It has been reported that the use of genetically proven heterozygous donors in patients with autosomal recessive disease shows no negative impact on either the donors or recipients (6, 7, 9–11, 19). With regard to X-linked OTCD, it has been reported that heterozygote females are at risk of the disease, presumably due to liver mosaicism (22). In the present study, 19 of the 48 patients with OTCD (39.6%) received maternal grafts, given the potential for heterozygote carriers, and no morbidities or mortalities related to the use of heterozygous carriers were observed. Recently, Wakiya et al. (7) reported that the liver tissue in asymptomatic maternal carriers should be extracted via liver biopsies for enzymatic analyses prior to LDLT. Inui et al. (23) demonstrated that the OTC activity is different in each segment of the liver in OTCD recipients, ranging from 9.7% in segment VI to 34.2% in segment II. Moreover, intrahepatic variation of enzyme activity was reported in a study of affected carriers (24). With respect to these studies, it is obvious that symptomatic carriers should not be as potential donor candidates for LDLT to avoid potential hyperammonemic event. A portion of the liver tissue should be used to investigate the correlation between genetic errors and the enzyme activity, while the remainder must be preserved for future analyses to precisely evaluate the impact of the use of heterozygous carriers of disorders on the risk and safety of the procedure in both donors and recipients.

The present study clearly demonstrated a significant increase in the number of LDLT procedures for inborn errors of metabolism and changes in the indications for LDLT over the past two decades. Although there are differences between the JLTS series and other outstanding series of patients with original liver disease (16–18), the proportion of recipients with Wilson's disease decreased from 43.9 to 12.7% over the most recent 10 yr in the present series. The development of conventional medical treatment with copper chelate (D-penicillamine, trientine hydrochloride) and zinc salt combined with early diagnosis means that the number of patients who can be maintained with medications without undergoing LT is expected to increase in Japan (25). Patients with Wilson's disease should

undergo a trial of treatment with medications together with considering LDLT.

On the other hand, the number of cases of urea cycle disorder is increasing from 15.5 to 30.9% over the most recent 10 yr. Even after successful treatment of severe hyperammonemia with pharmaceutical therapy with/without hemodiafiltration, most patients require a considerable treatment regimen and may have handicaps, such as impaired development, due to recurrent episodes of hyperammonemia (26). It has been reported that patients with neonatal onset of urea cycle disorders exhibit remarkable gains in their development after undergoing successful LT (1). Given the risk of continued neurological compromise, the potential to improve development represents a major benefit of early LDLT. In the present JLTS study, although there were no significant differences, the proportion of transplanted recipients with urea cycle disorders less than six months of age increased from 0% to 30.8% over the past two decades.

The use of LDLT for organic acidemia has also increased in recent years. Although implanted liver grafts produce deficient enzymes in patients with organic acidemia, the procedure only partially corrects the biochemical defects, as the enzymes are expressed in most cells and surgery may not prevent the development of progressive renal and neurological deterioration (27). However, the use of LDLT for organic acidemia showed acceptable patient and graft survival, with a rate of 85.2% at 10 yr, in the present study. Charkrapani et al. (27) reported that the benefits of an improved quality of life associated with the elimination of episodes of decompensation and improved protein tolerance must be weighed against the potential for renal and neurological injury. We agree with these results that LDLT does not cure the disease, although it may decrease the disease severity.

LDLT for GSD has recently been indicated by the JLTS. As a result of early diagnosis and radical treatment with nocturnal nasogastric feeding and uncooked cornstarch, the prognosis of GSD has improved dramatically. After starting radical dietary treatment, however, the development of neurological impairment as a consequence of metabolic derangement has been reported in 40% of patients with GSD (28). LT can be recommended from this point of view because the procedure can reduce the magnitude of progressive neurological disability caused by poor metabolic control. The patient and graft survival of patients with GSD are not sufficient due to septic complications. Proper infectious management (including neutropenia management in patients with GSD 1b) and the administration of regimens of immunosuppression are necessary in this population.

PH1 is a very rare inherited metabolic disorder characterized by a deficiency of the liver-specific enzyme alanine, alanine-glyoxylate aminotransferase, resulting in the overproduction and excessive urinary excretion of oxalate with end-stage renal disease. Although the number of cases was limited, four of the nine patients in this study who received sequential liver–kidney transplantation from a living donor are doing well. Mortality was observed in the patients transplanted much too late. It has been reported that combined liver–kidney transplantation is the best treatment for patients with PH1 with end-stage renal disease (29). In our country, small deceased donors are less likely to become available, and living donor liver–kidney transplantation is often the only treatment modality for patients with pediatric liver–kidney disease (12). Due to the unequivocal risks of the potential live donor candidate, especially liver–kidney donors, efforts should be made for early LT and to increase the number of deceased donors in order to minimize the need for living donors.

There is no clear score system for indications for LT in patients with inherited metabolic disorders. We retrospectively analyzed a grading score system (Table 2) and found that the system is an effective indicator for LT for patients with metabolic disorders. The mean transplant score was 16.3 ± 8.2 (3-37), while five patients (2.5%; Wilson's disease in two cases, familial hypercholesterolemia in two cases, and tyrosinemia in one case) demonstrated transplantation scores of <10. Although this study was a retrospective analysis, the transplantation score is useful for considering the indications and timing of LT because it reflects the effectiveness of conventional medical treatment, the quality of life, and the mental/physical status.

In conclusion, the present study confirmed that LDLT performed to treat inherited metabolic disorders can provide an acceptable survival rate over 15 yr, although most donors in the present series were heterozygous for their respective recipient's disorder. As neither mortality nor morbidity related to heterozygosis was observed, an intensive investigation should be conducted in this donor population. Improving understanding of the long-term suitability of this treatment modality will require the registration and ongoing evaluation of all patients with inherited metabolic disease considered for LT.

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Conflicts of interest

No conflicts of interest.

Appendix

The following constitute the pediatric JLTS research group enrolled in this study:

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References

1. Stevenson T, Millan MT, Wayman K, et al. Long-term outcome following pediatric liver transplantation for metabolic disorders. Pediatr Transplant 2010: 14: 268–275.
2. Treem WR. Liver transplantation for non-hepatotoxic inborn errors of metabolism. Curr Gastroenterol Rep 2006: 8: 215–223.
3. Lee V, Fecteau A, Shepherd R, et al. Outcomes of 5-year survivors of pediatric liver transplantation: Report on 461 children from a North American multicenter registry. Pediatrics 2008: 122: 1128–1135.
4. Morioka D, Kasahara M, Takada Y, et al. Living donor liver transplantation for pediatric patients with inheritable metabolic disorders. Am J Transplant 2005: 5: 2754–2763.
5. Cheng F, Li GQ, Zhang F, et al. Outcomes of living-related liver transplantation for Wilson's disease: A single-center experience in China. Transplantation 2009: 87: 751–757.
6. Yoshitoshi EY, Takada Y, Oike F, et al. Long-term outcomes for 32 cases of Wilson's disease after living-donor liver transplantation. Transplantation 2009: 87: 261–267.
7. Wakiya T, Sanada Y, Mizuta K, et al. Living donor liver transplantation for ornithine transcarbamylase deficiency. Pediatr Transplant 2011: 15: 390–395.
8. Kasahara M, Sakamoto S, Shigeta T, et al. Living-donor liver transplantation for carbamoyl phosphate synthetase 1 deficiency. Pediatr Transplant 2010: 14: 1036–1040.
9. Kasahara M, Sakamoto S, Kanazawa H, et al. Living-donor liver transplantation for propionic academia. Pediatr Transplant 2012: 16: 230–234.
10. Morioka D, Kasahara M, Horikawa R, Yokoyama S, Fukuda A, Nakagawa A. Efficiency of living donor liver transplantation for patients with methylmalonic academia. Am J Transplant 2007: 7: 2782–2787.
11. Kasahara M, Horikawa R, Sakamoto S, et al. Living donor liver transplantation for glycogen storage disease type 1b. Liver Transpl 2009: 15: 1867–1871.
12. Nakamura M, Fuchinoue S, Nakajima K, et al. Three cases of sequential liver-kidney transplantation from living-related donors. Nephrol Dial Transplant 2001: 16: 166–168.
13. Iwama I, Baba Y, Kagimoto S, et al. Case report of a successful liver transplantation for acute liver failure due to mitochondrial respiratory chain complex III. Transplant Proc 2011: 43: 4025–4028.
14. Kasahara M, Umeshita K, Inomata Y, Uemoto S. Long-term outcomes of pediatric living donor liver transplantation in japan: An analysis of more than 2,200 cases listed in the registry of the Japanese liver transplantation society. Am J Transplant 2013: 13: 1830–1839.
15. Kasahara M. Living donor liver transplantation for metabolic liver disease. J Pediatr Practice 2013: 76: 110–116.
16. Arnon R, Kerkar N, Davis MK, et al. Liver transplantation in children with metabolic disease: The studies of pediatric liver transplantation experience. Pediatr Transplant 2010: 14: 796–805.
17. Sze YK, Taylor RM, Bansal S, et al. Pediatric liver transplantation for metabolic liver disease; experience at King's college hospital. Transplantation 2009: 87: 87–93.
18. Kaylar LK, Rasmussen CS, Dykstra DM, et al. Liver transplantation in children with metabolic disorders in the United States. Am J Transplant 2003: 3: 334–339.
19. Morioka D, Takada Y, Kasahara M, et al. Living donor liver transplantation for noncirrhotic inheritable metabolic liver diseases: Impact of the use of heterozygous donors. Transplantation 2005: 80: 623–628.
20. Braegger C, Florman S, Shneider B. Living-related liver transplantation in inherited metabolic liver disease: Feasibility and cautions. J Pediatr Gastroenterol Nutr 2001: 33: 520–521.
21. Wong DA. Ornithine transcarbamylase deficiency: Are carrier females suitable donors? Pediatr Transplant 2012: 16: 535–537.
22. Yorifuji T, Muroi J, Uematsu A, et al. X-inactivation pattern in the liver of manifesting female with ornithine transcarbamylase (OTC) deficiency. Clin Genet 1998: 54: 349–353.

23. Inui A, Fujisawa T, Mogi A, et al. Living related liver transplantation for a ornithine transcarbamylase deficiency. Jap J Pediatr 1997: 101: 963–967.
24. Tuchman M. The clinical, biochemical, and molecular spectrum of ornithine transcarbamylase deficiency. J Lab Clin Med 1992: 120: 836–850.
25. Oya Y, Okajima H, Honda M, et al. Re-evaluation of the indications for liver transplantation in Wilson's disease based on the outcomes of patients referred to a transplant center. Pediatr Transplant 2013: 17: 369–373.
26. Maestri NE, Hauser ER, Bartholomew D, Brusilow SW. Prospective treatment of urea cycle disorders. J Pediatr 1991: 119: 923–928.
27. Chakrapani A, Sivakumar P, McKienan PJ, Leonard JV. Metabolic stroke in methylmalonic acidemia five years after liver transplantation. J Pediatr 2002: 140: 261–263.
28. Rake JP, Visser G, Labrune P, Leonard JV, Ullrich K, Smit GPA. Glycogen storage disease type 1: Diagnosis, management, clinical course and outcome. Results of the European Study on Glycogen Storage Disease Type 1 (ESGSD1). Eur J Pediatr 2002: 161: S20–S30.
29. Ellis SR, Hulton SA, McKiernan PJ, De Goyet JVD, Kelly DA. Combined liver-kidney transplantation for primary hyperoxaluria type 1 in young children. Nephrol Dial Transplant 2001: 16: 348–354.