

## Original Article



# Efficacy of Living Donor Liver Transplantation in Patients with Methylmalonic Acidemia

Jae Guk Jang ,<sup>1</sup> Seak Hee Oh ,<sup>1</sup> Yu Bin Kim ,<sup>1</sup> Seo Hee Kim ,<sup>1</sup> Han-Wook Yoo ,<sup>1</sup> Beom Hee Lee ,<sup>1</sup> Jung-Man Namgoong ,<sup>2</sup> Dae Yeon Kim ,<sup>2</sup> Ki-Hun Kim ,<sup>2</sup> Gi-Won Song ,<sup>3</sup> Deok-Bog Moon ,<sup>3</sup> Shin Hwang ,<sup>3</sup> Sung-Gyu Lee ,<sup>3</sup> and Kyung Mo Kim <sup>1</sup>

## OPEN ACCESS

**Received:** Sep 26, 2019

**1st Revised:** Nov 14, 2020

**2nd Revised:** Nov 16, 2020

**Accepted:** Feb 2, 2021

### Correspondence to

**Kyung Mo Kim**

Department of Pediatrics, Asan Medical Center Children's Hospital, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea.  
E-mail: kmkim@amc.seoul.kr

Copyright © 2021 by The Korean Society of Pediatric Gastroenterology, Hepatology and Nutrition

This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<https://creativecommons.org/licenses/by-nc/4.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

### ORCID iDs

Jae Guk Jang

<https://orcid.org/0000-0002-6093-0707>

Seak Hee Oh

<https://orcid.org/0000-0002-9672-8877>

Yu Bin Kim

<https://orcid.org/0000-0001-6325-6191>

Seo Hee Kim

<https://orcid.org/0000-0001-7564-7675>

Han-Wook Yoo

<https://orcid.org/0000-0001-8615-186X>

Beom Hee Lee

<https://orcid.org/0000-0001-9709-2631>

Jung-Man Namgoong

<https://orcid.org/0000-0002-9237-7440>

Dae Yeon Kim

<https://orcid.org/0000-0001-6130-1796>

<sup>1</sup>Department of Pediatrics, Asan Medical Center Children's Hospital, University of Ulsan College of Medicine, Seoul, Korea

<sup>2</sup>Department of Pediatric Surgery, Asan Medical Center Children's Hospital, University of Ulsan College of Medicine, Seoul, Korea

<sup>3</sup>Division of Hepato-Biliary Surgery and Liver Transplantation, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

## ABSTRACT

**Purpose:** Despite aggressive medical and nutritional management, patients with methylmalonic acidemia (MMA) often suffer from multi-organ damage. Early deceased donor liver transplantation (DDLT) has emerged as an intervention to prevent disease progression. We investigated the efficacy of living donor LT (LDLT) with a potential carrier of MMA and a small volume of graft in patients with MMA as an alternative to DDLT.

**Methods:** Of five patients (three male, two female; median age 5.7 years; range, 1.3–13.7 years), four underwent carrier LDLT, while one underwent non-carrier auxiliary LDLT. All patients received pre- and post-LT continuous renal replacement therapy and were provided with minimal restriction diet according to serum MMA level after LT. MMA levels in the serum and urine, the incidence of metabolic crisis, and clinical findings before and after LT were compared.


**Results:** The survival rate was 100% during 2.2 years of follow up period after LT. In all five cases, MMA titer in the serum after transplantation decreased with less restrictive diet. Metabolic crisis was not observed during the follow-up period. In addition, no patient showed progression of severe renal impairment requiring hemodialysis. Progression of delayed cognitive development was not observed. Social functioning with improved neuropsychiatric development was observed.

**Conclusion:** This study showed that LDLT achieved improved quality of life with less restrictive diet, therefore it could be a feasible alternative option to DDLT for the treatment of patients with MMA, even with an auxiliary LT.

**Keywords:** Methylmalonic acidemia; Living donors; Liver transplantation; Child

## INTRODUCTION

Methylmalonic acidemia (MMA) is a rare genetic metabolic disease, an autosomal recessive disorder, in most cases. The incidence of MMA in the Western population is estimated at 1:48,000 to 1:61,000, although it is much higher in some populations in the world [1].

Ki-Hun Kim <https://orcid.org/0000-0002-4016-0995>Gi-Won Song <https://orcid.org/0000-0002-1581-7051>Deok-Bog Moon <https://orcid.org/0000-0002-8209-3540>Shin Hwang <https://orcid.org/0000-0002-9045-2531>Sung-Gyu Lee <https://orcid.org/0000-0001-9161-3491>Kyung Mo Kim <https://orcid.org/0000-0001-7896-6751>**Conflict of Interest**

The authors have no financial conflicts of interest.

MMA is caused by metabolic defects in methylmalonyl-CoA mutase (MCM) or cobalamin (Cbl)/vitamin B12. This is an inborn error of metabolism that can be classified as an organic acidemia caused by a dietary Cbl deficiency [2].

Similar to other metabolic disorders, the accumulation of MMA, a metabolite, causes hyperammonemia, vomiting, and neonatal death. Despite early conservative therapy, MMA requires management of developmental disorders caused by progressive damage to the heart, kidney, and neurological system [3]. The efficacy of deceased donor liver transplantation (DDLTL) for inborn errors of metabolism (IEM) resulting from a deficiency of enzymes that mediate specific metabolic processes in the body is well-known [4]. While LT can cure the IEM such as Wilson disease in which the metabolism occurs solely in liver, it can not cure the other IEM such as MMA in which the metabolism occurs partly in liver but improve the quality of life with improving the metabolic control and less restrictive diet [4-6] and quality of life because part of metabolism can be improved. The Korea Network for Organ Sharing (KONOS) allocation system is determined by Pediatric End-stage Liver Disease [7] and Model for End-stage Liver Disease score [8] in Korea. The chances of DDLTL for MMA is very low, therefore LDLT is inevitable in Korea. Despite a promising report about the feasibility efficacy of LDLT for MMA by Morioka et al. [9], there is no consensus regarding LDLT for MMA.

This study reports the experiences with LDLT, a potential carrier of MMA with related donors, and a small volume of graft with auxiliary LDLT for the treatment of MMA instead of DDLTL at a single center.

## MATERIALS AND METHODS

This is a case series of five patients with MMA among 49 patients who underwent LDLT at the Asan Medical Center Children's Hospital between March 2015 and March 2019.

The patients included three boys and two girls with a median age of 5.7 years (range, 1.3–13.7 years). All patients were genetically diagnosed as MMA (**Table 1**). LDLTs were performed, including auxiliary transplant in one case in a family with proven genotypes (one sibling was non-carrier, both parents were genetically heterozygous).

We investigated the following parameters before and after LDLT through the electronic medical records: serum MMA, urine MMA, intensive care unit (ICU) stay in days, hospital stay in days, immunosuppressant use, postoperative complications, metabolic decompensation number, protein intake per kilogram, feeding route, medication for MMA, weight, height, echocardiography findings, and glomerular filtration rate (GFR).

The study was approved by the Institutional Review Board of Asan Medical Center (No. 2019-1080).

**Table 1.** Genetic typing of the patients

Case	Genetics
1	Compound heterozygote with two MUT0 (R228* and L494*)
2	Compound heterozygote with two MUT0 (E117* and V502fs)
3	Compound heterozygote with two MUT0 (I697F and E117*)
4	Compound heterozygote with two MUT0 (R108H and L494*)
5	Compound heterozygote with two MUT0 (R108H and L494*)

## RESULTS

**Table 2** shows details of patients. All five cases of LDLT were living related donors, four by carrier parents and one by non-carrier a brother. Auxiliary liver transplantation was performed in one case and whole liver transplantation in four cases. The mean graft recipient weight ratio (GRWR) was 1.50% (range, 0.7–2.2%). In all cases, elective surgery was preceded by continuous renal replacement therapy (CRRT). The mean ICU stay was 19 days (range, 8–51 days), and the mean hospital stay was 49 days (range, 28–65 days). Immunosuppressive agents for induction were based on tacrolimus (TAC), prednisolone, and basiliximab. Those for maintenance included were based on TAC. In cases 1, 4, and 5, sirolimus was added to reduce the dose of TAC to minimize renal toxicity. Degree of dietary restriction was determined by the results of serum and urine MMA level. Graft and patient survival rates were 100%. Post-transplant complications included acute cellular rejection (ACR; cases 1, 2, 3, and 5), Epstein-Barr virus infection (case 2), stress-induced cardiomyopathy resulting in cardiac arrest requiring ECMO therapy (case 3), intestinal necrosis (case 3), and hepatic vein stenosis (case 4).

**Table 3** shows details of perioperative characteristics of the patients. Mean annual number of episodes of metabolic crisis before LT was 2.32 however that after LT was zero. Dietary protein intake allowance improved with less restriction up to 2.5 g/kg/day according to the result of serum MMA levels (**Fig. 1** and **Fig. 2**). Carnitine supplementation was maintained in all patients before and after the surgery, and the ammonia-lowering agent could be discontinued in all two patients (cases 2 and 4) who were taking it preoperatively. The Z score of height improved from a mean of -2.6 (range, -5.3 to -0.5) to a mean of -1.9 (range, -4.9 to -0.5). The Z score of weight also improved from a mean of -1.0 (range, -2.7 to 0.2) to a mean of -0.7 (range, -2.5 to 0.6). Before and after the surgery, the echocardiography findings were normal, except one episode of stress-induced cardiomyopathy in case 3. On postoperative day (POD) 5, emergency ECMO was done due to cardiac arrest, which continued until POD 41. Stress-induced cardiomyopathy was diagnosed because there was no surges in the serum and urine MMA performed at this time. The GFR based on cystatin C decreased from a mean of 78.8 mL/min/1.73 m<sup>2</sup> (range, 34–120) to a mean of 57.8 mL/min/1.73 m<sup>2</sup> (range, 21–93) during follow up, but no one needed renal replacement therapy.

Cases 2, 3, 4, and 5 were MUTO heterozygotes. In these four cases, changes in the serum MMA level after transplantation decreased from a mean of 447.7 µmol/L (range, 67.4–1,165.7 µmol/L) to a mean of 188.5 µmol/L (range, 27.1–622.9 µmol/L) even with much less protein restriction over a mean observation period of 1.5 years (range, 0.2–3.0 years).

Cases 2, 3, 4, and 5 were MUTO heterozygotes. In these four cases, changes in the urine MMA level after transplantation decreased from a mean of 15,670.1 mmol/mol creatinine (range, 1,308.7–30,831.1 mmol/mol) to a mean 1,541.2 mmol/mol creatinine (range, 675.4–2,174.7 mmol/mol) over a mean observation period of 1.5 years (range, 0.2–3.0 years).

## DISCUSSION

In patients with MMA, the phenotypes vary in severity; however, the symptoms usually occur in newborns or infants, with repeated metabolic crises. Without appropriate management, it can lead to the progression of brain lesions, coma, and even death [3]. In the 1980s, the mortality rate of MMA was nearly 60%; by the 2000s, it only slightly progressed to 40% [10].

**Table 2.** Individual characteristics of patients with methylmalonic acidemia

Case no.	Sex	LDLT follow-up age (yr)	Donor	ABO identical or compatible*	Graft type†	Auxiliary	Recipient weight (kg)	GRWR (%)	Duration of pre-LT CRRT (d)	Duration of post-LT CRRT (d)	ICU stay (d)	Hospital stay (d)	Immuno-suppressant induction	Immuno-suppressant maintenance	TAC induced nephrotoxicity	Complication	
1	Female	13.7	4.3	Brother	1	LLS	Yes	34.0	0.7	2	2	11	57	TAC+PD+BSX	TAC+mTORi+PD	0	ACR
2	Male	9.6	3.3	Father	0	LL	No	27.1	1.5	2	3	9	54	TAC+PD+BSX	TAC+mTORi+PD	0	ACR, EBV infection
3	Male	2.3	1.7	Mother	1	LL	No	12.2	2.2	1	3	51	65	TAC+PD+BSX	TAC+PD	0	SIC, IN, ACR
4	Male	1.3	1.5	Mother	0	LLS	No	11.3	2.0	2	5	15	43	TAC+PD+BSX	TAC+PD	0	HVS
5	Female	5.7	0.3	Mother	0	LL	No	21.0	1.1	1	2	8	28	TAC+PD+BSX	TAC+mTORi+PD	0	ACR

LDLT: living donor liver transplantation, GRWR: graft-recipient weight ratio, CRRT: continuous renal replacement therapy, ICU: intensive care unit, LLS: left lateral segmentectomy, LL: left lobectomy, TAC: tacrolimus, PD: prednisolone, BSX: basiliximab, mTORi: mammalian target of rapamycin inhibitor, ACR: acute cellular rejection, EBV: Epstein-Barr virus, SIC: stress-induced cardiomyopathy, IN: intestinal necrosis, HVS: hepatic vein stenosis.

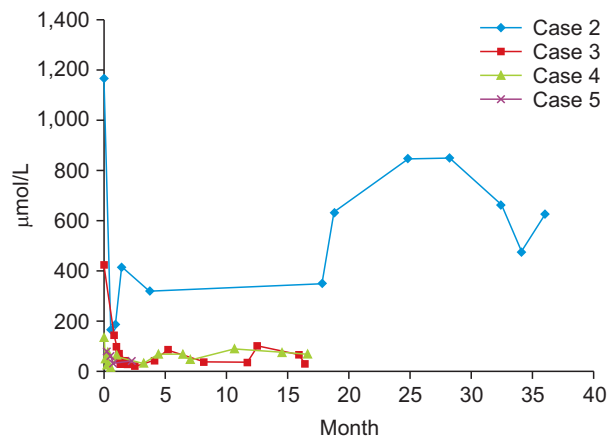
\*ABO identical or compatible: identical=0, compatible=1. †Graft type: LLS=0, LL=1.

**Table 3.** Perioperative characteristics of the patients

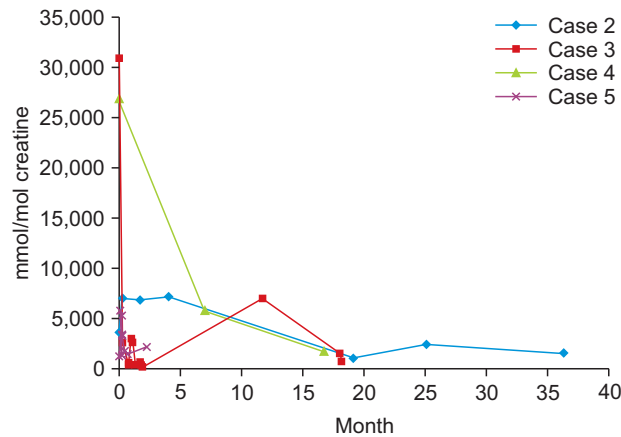
WNL	Follow-up period (yr)	Metabolic decompensation rate (number/year)		Dietary protein intake (g/kg/day)		Feeding route		Carnitine supplementation		Ammonia lowering agent		Height (cm) (Z-score)		Weight (kg) (Z-score)		Echocardiography		Cystatin C (mL/min/1.73 m <sup>2</sup> )	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	4.3	2.5	0	1.0-1.5	1.5-2.0	Oral+	Oral+	Yes	Yes	Yes	Yes	125.0 (-5.3)	136.3 (-4.9)	33.0 (-2.7)	39.5 (-2.5)	WNL	WNL	34	21
2	3.3	1.2	0	1.0-1.5	1.5-2.0	Oral	Oral	Yes	Yes	Yes	No	121.5 (-3.1)	139.7 (-2.5)	27.1 (-1.4)	38.5 (-1.5)	WNL	WNL	37	21
3	1.6	3.4	0	1.5-2.0	2.0-2.5	Oral	Oral	Yes	Yes	No	No	84.0 (-2.0)	100.9 (-0.5)	11.4 (-1.1)	16.0 (-0.5)	WNL	CMP*	120	93
4	1.5	9.0	0	2.0-2.5	2.0-2.5	Oral	Oral	Yes	Yes	Yes	No	75.0 (-2.0)	91.4 (-0.9)	10.8 (0.2)	14.0 (0.1)	WNL	WNL	99	76
5	0.3	1.7	0	1.5-2.0	1.5-2.0	Oral	Oral	Yes	Yes	Yes	Yes	112.1 (-0.5)	113.5 (-0.6)	19.8 (-0.4)	23.5 (0.6)	WNL	Not done	104	78

WNL: within normal limit, CMP: cardiomyopathy.

\*History of stress-induced cardiomyopathy, however, on the recent echocardiography, ejection fraction and fraction shortening were within the normal range.



**Fig. 1.** Serum methylmalonic acid level ( $\mu\text{mol/L}$ , month). In four cases, changes in the serum methylmalonic acidemia level after transplantation decreased from a mean of  $447.7 \mu\text{mol/L}$  (range,  $67.4$ – $1,165.7 \mu\text{mol/L}$ ) to  $188.5 \mu\text{mol/L}$  (range,  $27.1$ – $622.9 \mu\text{mol/L}$ ) over a mean observation period of 1.5 years (range, 0.2–3.0 years).



**Fig. 2.** Urine methylmalonic acid level (mmol/mol creatinine, month). Cases 2, 3, 4, and 5 were MUTO heterozygotes. In these four cases, changes in the urine methylmalonic acidemia level after transplantation decreased from a mean of  $15,670.1 \text{ mmol/mol creatinine}$  (range,  $1,308.7$ – $30,831.1 \text{ mmol/mol creatinine}$ ) to a mean of  $1,541.2 \text{ mmol/mol creatinine}$  (range,  $675.4$ – $2,174.7 \text{ mmol/mol creatinine}$ ) over a mean observation period of 1.5 years (range, 0.2–3.0 years).

Cases of MMA with the highest severity and earliest onset are caused by variations in the *MUT* gene located on chromosome 6p21, which is called isolated MMA [11]. MCM defects are divided into MUTO, with no enzyme function, and MUT, with some enzyme function. MMA expressed by MUTO has a worse prognosis [3].

The genotype of patients with MMA in this study was the MUTO homozygote. In other words, four parent donors provided the liver, and one sibling donor was a non-carrier. However, in sibling donor case, the GRWR fell short of 0.8% and was conducted with auxiliary LT. In summary, in five cases in this study, LT was performed in relatively unprepared conditions, but the liver-based essential activity was not in the prepared condition. According to a recent study, the postoperative monitoring of pathogenic metabolites in patients with MMA who underwent LT for correction of enzyme deficiency replacement suggested that preoperative CRRT was less frequently required [12]. However, in our study, pre- and postoperative dialysis was performed due to the relatively high risk of metabolic inefficiency, as we believe that

different perioperative management strategies are necessary to treat the various enzymatic activities in patients with MMA. In this regard, more studies with a higher number of cases of LDLT for MMA, with the data of pre and postoperative MMA are required.

One patient required extracorporeal membrane oxygenation due to stress-induced cardiomyopathy. We believe that it was not due to metabolic decompensation but MMA activity. However, the conventional complications associated with LT, including ACR, did not differ from those in the existing literature.

Under these conditions, patients with MMA who undergo LDLT experience improved quality of life through improvements in bowel habits and diet and a decreased incidence of metabolic crisis [4]. There were no significant differences in pre- versus postoperative carnitine supplementation; however, the improvements in Z-scores of the weight and height were significant. Early LDLT for patients in whom the prognosis is expected to be poor can improve the quality of life. The pre- versus postoperative serum and urine MMA levels (compared only in cases 2–5, which had MUTO homogeneity) generally decreased, while a moderate increase was induced by the LT complications but not by the metabolic crisis.

It is known that the MUTO homozygote, which is expressed as an isolated MMA, progresses faster and has a worse prognosis [3]. Therefore, there is a need for prompt enzyme replacement therapy such as LT [11]; however, finding a deceased donors is difficult in Korea. Therefore, LDLT could be a feasible option, and the patient prognosis would be superior to that without LT.

This study has some limitations. The number of cases is small, this was a single-center study with a retrospective design, and the follow-up period was short. Further prospective studies with larger sample sizes and longer follow-up periods are required. Neurological evaluation was not performed using an objective assessment tool, and future studies should include this for the neurological evaluation.

In conclusion, this study showed that LDLT could be a feasible alternative to DDLT for the treatment of patients with MMA, even with an auxiliary graft.

## REFERENCES

1. Baumgartner MR, Hörster F, Dionisi-Vici C, Haliloglu G, Karall D, Chapman KA, et al. Proposed guidelines for the diagnosis and management of methylmalonic and propionic acidemia. *Orphanet J Rare Dis* 2014;9:130.  
[PUBMED](#) | [CROSSREF](#)
2. Fowler B, Leonard JV, Baumgartner MR. Causes of and diagnostic approach to methylmalonic acidurias. *J Inher Metab Dis* 2008;31:350-60.  
[PUBMED](#) | [CROSSREF](#)
3. Hörster F, Baumgartner MR, Viardot C, Suormala T, Burgard P, Fowler B, et al. Long-term outcome in methylmalonic acidurias is influenced by the underlying defect (mut0, mut-, cblA, cblB). *Pediatr Res* 2007;62:225-30.  
[PUBMED](#) | [CROSSREF](#)
4. Oishi K, Arnon R, Wasserstein MP, Diaz GA. Liver transplantation for pediatric inherited metabolic disorders: considerations for indications, complications, and perioperative management. *Pediatr Transplant* 2016;20:756-69.  
[PUBMED](#) | [CROSSREF](#)

5. Kim JS, Kim KM, Oh SH, Kim HJ, Cho JM, Yoo HW, et al. Liver transplantation for metabolic liver disease: experience at a living donor dominant liver transplantation center. *Pediatr Gastroenterol Hepatol Nutr* 2015;18:48-54.  
[PUBMED](#) | [CROSSREF](#)
6. Mazariegos G, Shneider B, Burton B, et al. Liver transplantation for pediatric metabolic disease. *Mol Genet Metab* 2014;111:418-27.  
[PUBMED](#) | [CROSSREF](#)
7. McDiarmid SV, Anand R, Lindblad AS; Principal Investigators and Institutions of the Studies of Pediatric Liver Transplantation (SPLIT) Research Group. Development of a pediatric end-stage liver disease score to predict poor outcome in children awaiting liver transplantation. *Transplantation* 2002;74:173-81.  
[PUBMED](#) | [CROSSREF](#)
8. Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. *Hepatology* 2000;31:864-71.  
[PUBMED](#) | [CROSSREF](#)
9. Morioka D, Kasahara M, Horikawa R, Yokoyama S, Fukuda A, Nakagawa A. Efficacy of living donor liver transplantation for patients with methylmalonic acidemia. *Am J Transplant* 2007;7:2782-7.  
[PUBMED](#) | [CROSSREF](#)
10. Nicolaidis P, Leonard J, Surtees R. Neurological outcome of methylmalonic acidemia. *Arch Dis Child* 1998;78:508-12.  
[PUBMED](#) | [CROSSREF](#)
11. Ledley FD, Lumetta MR, Zoghbi HY, VanTuinen P, Ledbetter SA, Ledbetter DH. Mapping of human methylmalonyl CoA mutase (MUT) locus on chromosome 6. *Am J Hum Genet* 1988;42:839-46.  
[PUBMED](#)
12. Porta F, Romagnoli R, Busso M, Tandoi F, Spada M. Differential intraoperative effect of liver transplant in different inborn errors of metabolism. *J Pediatr Gastroenterol Nutr* 2019;69:160-2.  
[PUBMED](#) | [CROSSREF](#)