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REVIEW

# Post-transplantation Outcomes in Patients with PA or MMA: A Review of the Literature

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## ABSTRACT

***Introduction***: Liver transplantation is recognised as a treatment option for patients with propionic acidemia (PA) and those with methylmalonic acidemia (MMA) without renal impairment. In patients with MMA and moderate-to-severe renal impairment, combined liver–kidney transplantation is indicated. However, clinical experience of these transplantation options in patients with PA and MMA remains limited and fragmented. We undertook an overview of post-transplantation outcomes in patients with PA and MMA using the current available evidence.

***Methods***: A literature search identified publications on the use of transplantation in patients with PA and MMA. Publications were considered if they presented adequate demographic and outcome data from patients with PA or MMA. Publications that did not report any specific outcomes for patients or provided insufficient data were excluded.

***Results***: Seventy publications were identified of which 38 were full papers. A total of 373 patients underwent liver/kidney/combined liver–kidney transplantation for PA or MMA. The most typical reason for transplantation was recurrent metabolic decompensation. A total of 27 post-transplant deaths were reported in patients with PA [14.0% (27/194)]. For patients with MMA, 18 post-transplant deaths were reported [11% (18/167)]. A total of 62 complications were reported in 115 patients with PA (54%) with cardiomyopathy ($n$ = 12), hepatic arterial thrombosis (HAT; $n$ = 14) and viral infections ($n$ = 12) being the most commonly reported. A total of 52 complications were reported in 106 patients with MMA (49%) with viral infections ($n$ = 14) and renal failure/impairment ($n$ = 10) being the most commonly reported.

***Conclusions***: Liver transplantation and combined liver–kidney transplantation appears to benefit some patients with PA or MMA, respectively, but this approach does not provide complete correction of the metabolic defect and some patients remain at risk from disease-related and transplantation-related complications, including death. Thus, all treatment avenues should be exhausted before consideration of organ transplantation and the benefits of this approach must be weighed against the

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risk of perioperative complications on an individual basis.

**Keywords:** Kidney transplantation; Liver transplantation; Methylmalonic acidemia; Morbidity; Mortality; Propionic acidemia

**Key Summary Points**

A literature review was performed to ascertain the outcomes associated with liver and or kidney transplantation in patients with propionic acidemia (PA) or methylmalonic acidemia (MMA).

Thirty-eight papers and 32 abstracts were identified, totalling 373 patients.

Transplantation improved outcome in some patients with PA and MMA, but was also associated with appreciable mortality (14% PA, 11% MMA) and complications including cardiomyopathy, hepatic arterial thrombosis, renal failure/impairment, and viral infections.

While transplantation appears to be of some benefit in a subset of patients with PA/MMA, this approach does not provide a metabolic cure and patients remain at risk from disease-related and transplantation-related complications.

All treatment avenues should ideally be exhausted for PA/MMA before selecting transplantation.

## INTRODUCTION

Propionic acidemia (PA) and methylmalonic acidemia (MMA) are rare inborn errors of metabolism presenting in infancy with episodes of metabolic acidosis that can lead to early mortality and significant morbidity [1–3]. Both PA and MMA are characterised by the accumulation of propionic acid and/or methylmalonic acid in plasma, urine, and other body fluids, due to defects in the enzymes propionyl-CoA carboxylase and methylmalonyl-CoA mutase, respectively.

Patients with PA and/or MMA typically present shortly after birth with acute deterioration, metabolic acidosis, and hyperammonaemia leading to either severe intellectual disabilities or death [1]. For these patients with 'classical' PA and MMA, dietary restriction (a low-protein, high-energy diet) together with oral medication (typically carnitine) has remained the core therapy for decades. However, despite intensive medical efforts, frequent episodes of metabolic decompensation occur with inevitable complications [1].

Solid-organ transplantation, such as single liver or kidney transplantation, or combined liver–kidney transplantation, has become an effective alternative treatment for metabolic disease in recent decades [1]. The role of liver, kidney, or combined liver–kidney transplantation in patients with PA/MMA is currently evolving and, while not considered 'curative', is typically undertaken as an 'enzyme replacement therapy' [4]. However, any decision to carry out a transplantation is a complicated one which requires a comprehensive understanding of the underlying disease, the risks and benefits of transplantation, and current therapeutic alternatives [5]. Furthermore, clinical experience of transplantation in PA and MMA remains both limited and fragmented due to the low prevalence of these diseases [4, 6].

The purpose of this review is to provide an overview of post-transplantation outcomes in patients with PA and MMA.

## METHODS

A literature search was undertaken on 10 April 2019 to identify suitable papers for inclusion in the present review. The literature search tools used were PubMed, Embase and Biosys. The search string was [(propionic OR methylmalonic) AND acidemia*] AND [(transplant OR transplantation) AND aciduria*]. No date limitations were applied. Suitable references for inclusion included abstracts and full papers, clinical studies, case studies, and retrospective

analyses of patients with PA and/or MMA. Any references which included patients with PA or MMA as part of a pooled population of patients with inherited metabolic disorders but did not report any specific outcomes for these patients were excluded, as were abstracts providing insufficient data. Given the methodology used, this review was undertaken to assess any trends arising from the use of liver/kidney/combined liver–kidney transplantation in patients with PA/MMA.

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

## RESULTS

### Patient Demographics and Follow-up

Seventy suitable references (retrospective analyses and case studies) were identified, 32 of which were meeting abstracts. A summary of transplantation type and median patient age taken from these references is shown in Table 1. A total of 195 and 167 patients underwent liver/kidney/combined liver–kidney transplantation for PA and MMA, respectively (a total of 373 transplantations). In addition, a total of nine and two retransplantations were required in patients with PA and MMA, respectively. Single organ liver transplantation was performed more commonly in both PA and MMA (total $n = 307$, PA $n = 193$; MMA $n = 114$), when compared with kidney (PA $n = 2$; MMA $n = 21$) or combined liver–kidney transplantation (PA $n = 0$; MMA $n = 32$) (retransplantations not included). Median age at transplantation ranged from 0.25 to 42 years in patients with PA and from 0.4 to 28.0 years in patients with MMA. The most typical reason for any type of transplantation in patients with PA and MMA was recurrent metabolic decompensation. Follow-up data to show outcomes by type of transplantation were available for all PA ($n = 195$; available follow-up range 0–22 years) and MMA ($n = 167$; range 0.04–16 years) patients, although specific timings of follow-up were not always provided.

Of the 70 references identified, 38 were full papers which contained sufficient patient information, both pre-operatively and post-transplantation, along with a suitable follow-up duration to enable a more detailed overview. A summary of key findings from these references is shown in Tables 2 and 3. Available data from the identified abstracts were limited and are summarised in the "Appendix".

**Table 1** Overall characteristics of reviewed patients

| Characteristic | PA | MMA |
|---|---|---|
| Liver transplantation | 193 | 114 |
| Kidney transplantation | 2[a] | 21 |
| Combined transplantation | 0 | 32 |
| Retransplantation | 9 | 2 |
| Total transplantation | 204 | 169 |
| Median age at transplant, range, years[b] | 0.25–42.0 | 0.4–28.0 |
| Mortality | 27/195 (14%) | 18/167 (11%) |
| Complications[c] | 62/115 (54%) | 52/106 (49%) |

*MMA* methylmalonic acidemia, *PA* propionic acidemia

[a] One patient had a liver transplantation followed approximately 3 years later by a kidney transplant [7]

[b] Based on available data

[c] Publications not reporting complications and their associated patient numbers were excluded

**Table 2** Overview of data from published papers of PA studies/case studies

| References | *n* | Transplant type[a] | Median (range) transplant age (years) | Post-transplant metabolic control | Post-transplant neurological health | Complications | Median (range) duration of follow-up | Deaths (cause and number) |
|---|---|---|---|---|---|---|---|---|
| Arrizza et al. [8] | 1 | OLT | 22 (n/a) | No decompensations | Reversal of severe cardiomyopathy ($n = 1$) | None reported | 10 (n/a) | None reported |
| Barshes et al. [9] | 2 | OLT | 1.7 (1.3–2.0) | No decompensations | Improvement in bilateral ganglia lesions ($n = 1$)<br>Improved cognition ($n = 1$) | HAT requiring retransplant ($n = 1$) | 1.4 (0.3–2.4) | None reported |
| Charbit-Henrion et al. [10] | 12 | LT | 3.2 (1.6–6.8) | No decompensations | Reversal of cardiomyopathy ($n = 3$) | Repeat transplantation required ($n = 4$): biliary cirrhosis secondary to HAT ($n = 2$), primary non-function of the graft ($n = 1$), hepatic dysfunction after HAT ($n = 1$)<br>Moderate renal failure ($n = 1$)<br>PTLD ($n = 2$)<br>Bipolar disorder ($n = 1$)<br>Kidney transplant ($n = 1$)<br>Chronic hepatitis ($n = 1$)<br>Biliary cirrhosis ($n = 2$)<br>Biliary stricture ($n = 1$ after second transplant)<br>ARDS ($n = 4$)<br>Acute encephalopathy ($n = 1$)<br>Biliary sepsis ($n = 1$) | 17 (0–21) | Multi-organ failure ($n = 4$)<br>Hepatic failure ($n = 3$) |

**Table 2** continued

| References | *n* | Transplant type[a] | Median (range) transplant age (years) | Post-transplant metabolic control | Post-transplant neurological health | Complications | Median (range) duration of follow-up | Deaths (cause and number) |
|---|---|---|---|---|---|---|---|---|
| Critelli et al. [11] | 3 | LDLT | 8.7 (1.2–11.8) | No decompensations | Not reported | HAT ($n$ = 1)<br>CMV infection ($n$ = 1)<br>Colonic perforation ($n$ = 1)<br>EBV viremia ($n$ = 2) | 2.1 (1.6–2.1) | None reported |
| Kasahara et al. [12] | 3 | LDLT | 2 (0.6–2.2) | No decompensations | Normal mental development ($n$ = 3) | CMV infection ($n$ = 2)<br>Intestinal perforation which necessitated relaparotomy ($n$ = 1) | 3.3 (n/s) | None reported |
| Kasahara et al. [13] | 9 | LDLT | 2.2 (0.4–12.0) | Recurrent metabolic decompensation ($n$ = 9) | No episodes of cardiac insufficiency reported | Septic complications ($n$ = 4) | Not reported | Sepsis ($n$ = 4) |
| Kayler et al. [14] | 1 | LT | 3 (n/a) | Not specified | Not specified | Not specified | 0.25 (n/a) | Cause not specified ($n$ = 1) |
| Lam et al. [15] | 1 | KT | 42 (n/a) | n/s | n/s | n/s | 3 (n/a) | None reported |
| Moguilevitch and Delphin [16] | 1 | LT | 1 (n/a) | Not reported | Not reported | Increase in liver function tests ($n$ = 1) | n/s | None reported |
| Morioka et al. [17] | 3 | LDLT | 2 (1–5) | No decompensations | Not reported | None reported | 2.5 (1.8–4.9) | None reported |
| Nagao et al. [18] | 1 | LDLT | 0.6 (n/a) | No decompensations | Improved neurologic function ($n$ = 1) | Intestinal perforation ($n$ = 1)<br>CMV infection ($n$ = 1) | 18 (n/a) | None reported |

**Table 2** continued

| References | *n* | Transplant type[a] | Median (range) transplant age (years) | Post-transplant metabolic control | Post-transplant neurological health | Complications | Median (range) duration of follow-up | Deaths (cause and number) |
|---|---|---|---|---|---|---|---|---|
| Quintero et al. [19] | 6 | LDLT | 5.2 (1.3–7.5) | No decompensations | Stabilisation/ improvement of baseline neurological impairment (*n* = 6) | HAT (*n* = 2)<br>Arterial vasospasm without thrombus during surgery (*n* = 2)<br>Delayed biliary anastomosis (*n* = 2) | 1.5 (0.5–4.0) | None reported |
| Rammohan et al. [20] | 6 | APOLT (*n* = 5)<br>OLT (*n* = 1) | n/s | n/s | Stabilisation of cardiomyopathy (*n* = 1) | HAT (*n* = 1; APOLT)<br>Graft dysfunction leading to severe metabolic decompensation (*n* = 1; OLT) | 4.2 (n/s) | Severe metabolic decompensation (*n* = 1) |
| Rela et al. [21] | 1 | ALT | 2 (n/a) | Metabolic decompensation (*n* = 1) | Acceptable neurological development (*n* = 1) | None reported | 10 (n/a) | None reported |
| Romano et al. [22] | 2 | OLT | N/a | No decompensations | Reversal of cardiomyopathy (*n* = 2) | Cardiac arrest (recovered) (*n* = 1) | 14.5 (7.0–22.0) | None reported |
| Schlenzig et al. [23] | 2 | OLT | 8.0 (7.0–9.0) | No decompensations | Neurological sequelae involving basal ganglia (*n* = 1) | Acute rejection (*n* = 1)<br>Chronic rejection (*n* = 1)<br>CMV infection (*n* = 2)<br>Incomplete HAT (*n* = 1)<br>Persistent insulin-dependent diabetes mellitus (*n* = 1) | 1.3 (n/s) | Incomplete HAT (*n* = 1) |
| Shanmugam et al. [24] | 5 | APOLT | 2.75 (0.7–4.6) | No decompensations | Progressive improvement in developmental scores (*n* = 5) | HAT (*n* = 1)<br>High ammonia without encephalopathy (*n* = 1)<br>Acute cellular rejection (*n* = 4) | 2.7 (1.6–4.2) | None reported |

**Table 2** continued

| References | *n* | Transplant type[a] | Median (range) transplant age (years) | Post-transplant metabolic control | Post-transplant neurological health | Complications | Median (range) duration of follow-up | Deaths (cause and number) |
|---|---|---|---|---|---|---|---|---|
| Vara et al. [25] | 5 | LT | 1.5 (0.8–7.0) | No decompensations | Neurological decompensation ($n = 1$) | HAT requiring retransplantation ($n = 1$)<br>Metabolic stroke ($n = 1$) | 7.3 (2.2–15.0) | None reported |
| Yorifuji et al. [26] | 3 | LDLT | 2 (1.2–5.1) | Reduced metabolic decompensation | Improvement in neurological health ($n = 1$)<br>Data n/a for other patients | Acute metabolic decompensation ($n = 1$) | 1.4 (0.7–3.8) | None reported |

*ALT* auxiliary liver transplantation, *APOLT* auxiliary partial orthotopic liver transplantation, *ARDS* acute respiratory distress syndrome, *CMV* cytomegalovirus, *EBV* Epstein–Barr virus, *HAT* hepatic artery thrombosis, *KT* kidney transplantation, *LDLT* living-donor liver transplantation, *LT* liver transplantation, *OLT* orthotopic liver transplantation, *PTLD* post-transplant lymphoproliferative disease, *n/a* not available, *n/s* not specified

[a] Various types of liver transplantation used

**Table 3** Overview of data from published papers of MMA studies/case studies

| References | *n* | Transplant type[a] | Median (range) transplant age years) | Post-transplant metabolic control | Post-transplant neurological health | Complications | Median (range) duration of follow-up | Deaths (cause and number) |
|---|---|---|---|---|---|---|---|---|
| Brassier et al. [27] | 4 | KT | 7.9 (5–10.2) | No decompensations | Neurological stability (*n* = 2) | Hepatoblastoma followed by neurological complications (*n* = 1)<br>Acute rejection responsive to prednisone (*n* = 1)<br>Movement disorder (*n* = 1) | 2.8 (1.8–4.6) | Hepatoblastoma followed by neurological complications (*n* = 1) |
| Chen et al. [28] | 4 | LT | 1.4 (0.7–2.1) | 0.08 per year | Continued development (*n* = 4) | None reported | 3.5 (0.2–7.7) | None reported |
| Clothier et al. [29] | 1 | KT | 12 (n/a) | No decompensations | Not reported | Mild focal interstitial fibrosis (*n* = 1) | 6 (n/a) | None reported |
| Critelli et al. [11] | 6 | OLT (*n* = 1)<br>Combined LT/KT (*n* = 5) | 8.4 (1.9 –21.6) | No decompensations | Not reported | Near-complete stenosis of the right hepatic vein at its junction with the inferior vena cava (*n* = 1)<br>HAT (*n* = 1)<br>Renal rejection (*n* = 1)<br>Biliary anastomotic stricture (*n* = 1)<br>EBV viremia (*n* = 1)<br>Mild tubulointerstitial injury (*n* = 1) | 3.4 (1–11.6) | None reported |

**Table 3** continued

| References | *n* | Transplant type[a] | Median (range) transplant age years) | Post-transplant metabolic control | Post-transplant neurological health | Complications | Median (range) duration of follow-up | Deaths (cause and number) |
|---|---|---|---|---|---|---|---|---|
| Duclaux-Loras et al. [30] | 1 | Combined LT/KT | 10.4 (n/a) | No decompensations | Not reported | Renal arterial thrombosis ($n$ = 1) | 10 (n/a) | None reported |
| Hirotsu et al. [31] | 1 | LDLT | 1.8 (n/a) | No decompensations | Not reported | None reported | 0.2 (n/a) | None reported |
| Kasahara et al. [13] | 20 | LDLT | 2.2 (0.4–12) | Recurrent metabolic decompensation ($n$ = 20) | Not reported | Progressive renal insufficiency ($n$ = 4)<br>New onset of seizures ($n$ = 3) | Not specified | None reported |
| Kayler et al. [14] | 2 | LT ($n$ = 1)<br>Combined LT/KT ($n$ = 1) | 14.5 (13–16) | Not specified | Not specified | Liver retransplantation ($n$ = 1)<br>EBV viremia ($n$ = 1)<br>Potential PTLD ($n$ = 1) | 2.5 (1.1–3.9) | None reported |
| Khanna et al. [32] | 1 | Cadaveric LT | 28 (n/a) | No decompensations | Not reported | None reported | > 1 (n/a) | None reported |
| Lubrano et al. [33, 34] | 1 | KT | 17 (n/a) | No decompensations | Not reported | Chronic allograft nephropathy ($n$ = 1) | 10 (n/a) | None reported |

**Table 3** continued

| References | *n* | Transplant type[a] | Median (range) transplant age years) | Post-transplant metabolic control | Post-transplant neurological health | Complications | Median (range) duration of follow-up | Deaths (cause and number) |
|---|---|---|---|---|---|---|---|---|
| McGuire et al. [35] | 1 | LT/KT | 5 (n/a) | One metabolic decompensation at 10 months post transplantation | Neurological deterioration (hemiplegia, truncal ataxia and speech dyspraxia) (*n* = 1) | Cerebellar stroke (*n* = 1) | ≥ 10 months (n/a) | None reported |
| Morioka et al. [17] | 2 | LDLT | 6.5 (1–12) | Metabolic stroke (*n* = 1) | Not reported | Metabolic stroke (*n* = 1)<br>Aspergillosis (*n* = 1) | 0.1 (0.04–0.17) | Metabolic stroke (*n* = 1)<br>Aspergillosis (*n* = 1) |
| Morioka et al. [36] | 7 | LDLT | 4.3 (0.6–7.5) | Metabolic acidosis (*n* = 2) | Cognitive deficit improved (*n* = 7) | Sepsis (*n* = 1)<br>Graft dysfunction (*n* = 1)<br>CMV viremia (*n* = 2)<br>EBV viremia (*n* = 1) | 0.9 (0.3–1.75) | Sepsis (*n* = 1) |
| Nagarajan et al. [37] | 2 | LT/KT | 15.5 (10–21) | No decompensations | Mental status changes (*n* = 1)<br>Tremors (*n* = 1) | Mild reversible acute rejection of the liver (*n* = 1)<br>CMV gastritis (*n* = 1)<br>Mental status changes (*n* = 1)<br>Tremors (*n* = 1)<br>Mild glucose intolerance (*n* = 1) | 3.3 (1.5–5) | None reported |

**Table 3** continued

| References | *n* | Transplant type[a] | Median (range) transplant age years) | Post-transplant metabolic control | Post-transplant neurological health | Complications | Median (range) duration of follow-up | Deaths (cause and number) |
|---|---|---|---|---|---|---|---|---|
| Niemi et al. [38] | 14 | LT ($n$ = 6)<br>Combined LT/KT ($n$ = 8) | 7.4 (0.8–20.7) | No decompensations | All patients maintained or improved neurological health | HAT requiring liver retransplantation ($n$ = 1)<br>Bleeding requiring re-exploration ($n$ = 2)<br>Drainage of subphrenic abscess ($n$ = 1),<br>Seizure ($n$ = 1)<br>Diabetes mellitus ($n$ = 1) | 3.25 (0.25–14)[b] | None reported |
| Nyhan et al. [39] | 1 | OLT | 22 (n/a) | No decompensations | Neurologic manifestations ($n$ = 1) | Progression of pre-surgery renal failure ($n$ = 1)<br>Neurologic manifestations ($n$ = 1) | 2 (n/a) | None reported |
| Sakamoto et al. [40] | 13 | LDLT | 9 (0.7–7) | Several metabolic episodes ($n$ = 3) | Normal growth reported | Severe adhesive intestinal obstruction ($n$ = 1)<br>Strangulation ileus ($n$ = 1)<br>Bile duct stenosis ($n$ = 2)<br>Acute renal failure ($n$ = 1)<br>Convulsion ($n$ = 2)<br>Portal vein stenosis ($n$ = 1)<br>Sepsis ($n$ = 1)<br>Cholangitis ($n$ = 2) | 8.1 (4–16) | None reported |

**Table 3** continued

| References | *n* | Transplant type[a] | Median (range) transplant age years) | Post-transplant metabolic control | Post-transplant neurological health | Complications | Median (range) duration of follow-up | Deaths (cause and number) |
|---|---|---|---|---|---|---|---|---|
| Spada et al. [41] | 2 | Whole LT ($n$ = 1)<br>Split LT ($n$ = 1) | 1.9 (0.75–3) | No decompensations | Adequate neurological development ($n$ = 2) | None reported | 7 (2–12) | None reported |
| Stevenson et al. [42] | 3 | Combined LT/KT | 10.8 (n/s) | No decompensations | Not reported | Decreased renal function ($n$ = 1) | > 1 (n/s) | None reported |

*CMV* cytomegalovirus, *EBV* Epstein-Barr virus, *HAT* hepatic artery thrombosis, *KT* kidney transplantation, *LDLT* living-donor liver transplantation, *LT* liver transplantation, *LT/KT* liver/kidney transplantation, *OLT* orthotopic liver transplantation, *PTLD* post-transplant lymphoproliferative disease, *n/a* not available, *n/s* not specified

[a] Various types of liver transplantation used

[b] Mean (range) transplant age shown

## Mortality

A total of 27 post-transplant deaths were reported in patients with PA, which equated to a mortality rate of 14.0% (27/194). For patients with MMA, 18 post-transplant deaths were reported, which equated to a mortality rate of 11% (18/167). Causes of death for PA and MMA are presented in Tables 2 and 3, respectively.

### *PA*

A retrospective analysis of 12 patients with PA who underwent liver transplantation reported that while the graft survival rate was 60% at 5 years, seven of the 12 patients (58%) died within the first year after transplantation (multi-organ failure, $n = 4$; hepatic failure, $n = 3$) [10]. Infection is reported as a major cause of post-transplant deaths in patients with PA: Kasahara et al. [13] reported that liver transplantation in nine patients with PA resulted in four sepsis-related deaths, equating to a mortality rate of 44%. However, some studies suggest that transplantation appears to be less of a risk in some patients with PA. For example, a recent retrospective analysis of liver transplantation by Shanmugam et al. [24] reported survival in patients with PA to be 100% at a median follow-up of 32 months. It appears that survival following transplantation in patients with PA seems to be improving with greater experience of the procedure. Indeed, the expertise and experience of the surgical team is an important prognostic factor for general paediatric liver transplantation [43–46].

### *MMA*

Patient mortality following transplantation was less frequently reported in patients with MMA compared with patients with PA, with most studies reporting 100% patient survival. However, three studies identified a post-transplantation mortality risk in patients with MMA. For kidney transplantation, Brassier et al. [27] reported four patients with MMA [median transplantation age 7.9 years (range 5–10.2 years)] who received a kidney graft following repeated metabolic decompensations, with progression to chronic kidney disease (CKD) in three of these patients (end-stage kidney disease in two patients and CKD stage III in one patient; normal renal function in one patient) prior to transplantation. One patient developed a hepatoblastoma at the age of 11 (less than 2 years post-surgery), followed by neurological complications and death. The three other patients remained alive, with two achieving neurological stability. Morioka et al. [17] reported on two patients with MMA who both died after receiving a liver transplantation, equating to a 100% mortality rate; these deaths were caused by metabolic stroke and aspergillosis. One death caused by a metabolic crisis was identified in a patient with MMA following combined liver–kidney transplantation [47].

## Complications

A total of 62 complications (various types) were reported in 115 patients with PA. This equates to an approximate complication rate of 54% given that some patients experienced more than one complication. Cardiomyopathy ($n = 12$), hepatic arterial thrombosis (HAT; $n = 14$) and viral infections ($n = 12$) were most commonly reported complications among patients with PA. A total of 52 complications were reported in 106 patients with MMA. This equates to an approximate complication rate of 49% given that some patients experienced more than one complication. Viral infections ($n = 14$) and renal failure/impairment ($n = 10$) were most commonly reported complications among patients with MMA. Of note, the definition of what constituted a 'complication' varied widely between publications. Post-transplant complications for patients with PA and MMA are presented in Tables 2 and 3, respectively.

### *PA*

Complications related to the transplant procedure along with subsequent post-surgery infection appeared to be most commonly reported in

patients with PA (Table 2). A retrospective study reported that out of 17 liver transplantation procedures in 12 patients with PA, HAT was reported in a total of six transplants (equating to a 35% risk of HAT), and occurred in successive grafts in two patients [10]. Similarly, Critelli et al. [11] reported that two of three patients with PA who received a liver transplant developed a recurrent left HAT (equating to a 66% chance of HAT), one that required Fogarty catheter thrombectomy and one that did not resolve despite placement of an aortic conduit graft, resulting in an associated hepatic allograft infarction. The same study noted that one patient developed cytomegalovirus (CMV) viremia, while a similar retrospective review of children with PA noted that two of three patients developed CMV infection following liver transplantation [12]; all episodes of CMV infection were successfully treated with intravenously administered ganciclovir.

### *MMA*

Post-transplantation complications varied amongst patients with MMA, although most studies reported at least one complication (Table 3). Complications following combined liver/kidney transplantation included renal artery thrombosis (Duclaux-Loras et al. [30]) and cerebellar stroke [35]. For liver transplantation, complications such as infection (sepsis, CMV and Epstein-Barr virus [EBV]) [36] and HAT [11, 38] were reported. Complications following kidney transplantation included hepatoblastoma [27] and chronic allograft nephropathy [33].

## Post-transplant Metabolic Episodes

### *PA*

In the literature available for patients with PA, reports of metabolic episodes ranged from 0% to 100% following liver transplantation (Table 2). A retrospective analysis of 12 patients with PA reported no further episodes of acute metabolic decompensation following liver transplantation even with a less restricted dietary protein intake [10]. Similarly, Shanmugam et al. [24] reported that of five children with PA and a median of eight episodes of decompensation per year prior to transplantation, no episodes of metabolic decompensation occurred either intraoperatively or immediately after transplantation when receiving a protein-unrestricted diet. In contrast, Kasahara et al. [13] reported that following liver transplantation in Japanese patients with PA/MMA, recurrent metabolic decompensation was observed in 100% of patients despite the administration of protein restriction with medications (cobalamin, carnitine supplementation, and antibiotics to eradicate gut flora). Thus, post-transplant medication for the original liver disease had to be continued in all patients.

### *MMA*

In the literature available for patients with MMA, episodes of metabolic decompensation varied by transplantation type (Table 3). For patients with MMA, the risk of further episodes of metabolic decompensation appeared to be higher following liver transplantation compared with kidney or combined kidney/liver transplantation. Kasahara et al. [13] reported recurrent metabolic decompensation in 100% of patients with MMA following liver transplantation despite the administration of protein restriction with medications, leading to the continuation of pre-surgery medication. Sakamoto et al. [40] reported that while the number of acidosis attacks significantly decreased following liver transplantation in Japanese patients with MMA, this was not deemed to be a 'curative' approach as most patients remained on a protein-restricted diet. Morioka et al. reported episodes of metabolic stroke [17] and metabolic episodes [36] following liver transplantation. In contrast, Niemi et al. [38] reported no further episodes of metabolic decompensation following liver transplantation in patients with MMA. patients with MMA who received kidney transplantation or combined liver/kidney transplantation typically reported no further metabolic decompensations. McGuire et al. [35] reported the case study of a

patient who received a combined liver/kidney transplant at 5 years, with subsequent metabolic decompensation at 10 months post-surgery; however, no further episodes of metabolic decompensation were reported.

### Can Transplantation Reverse Cardiomyopathy in Patients with PA?

Overall, liver transplantation was shown to effectively reverse baseline cardiomyopathy in approximately 50% of patients at post-transplant follow-up. Romano et al. [22] reported that of patients with PA who survived their first year of life, a dilated cardiomyopathy developed in six patients at a median age of 7 years (range 5–11 years), although this was reversed in two patients within 1 year following liver transplantation. Charbit-Henrion et al. [10] similarly reported reversal of cardiomyopathy in three patients with PA following liver transplantation, although three patients with normal heart ultrasound prior to transplantation subsequently developed unexpected heart failure and died at 1–4 weeks following surgery. Of note, transplantation is typically contraindicated in patients with severe heart disease.

## DISCUSSION

This review has shown that liver, kidney, or combined liver–kidney transplantation can significantly improve metabolic outcomes for patients with PA or MMA. However, data from retrospective and case studies suggest that this approach cannot be considered to be a cure, and all three types of transplantation are associated with significant risks of subsequent complications or death.

A number of factors influence the choice of therapy (liver or kidney transplant alone or combined liver–kidney transplantation) in patients with PA or MMA. In general, liver transplantation is deemed to be a suitable treatment option for patients with PA and those patients with MMA but without renal impairment. In contrast, combined liver–kidney transplantation is considered more suitable in those patients with MMA and renal impairment. In addition, it is important to recognise the indications and contraindications for the use of transplantation in PA/MMA. Traditionally, transplants have been reserved for the most 'brittle' patient, in whom it is difficult to achieve reasonable metabolic control or that their dietary restriction is very severe and still not achieving metabolic control. More recently, there has been a tendency to transplant at an earlier stage, regardless of the level of metabolic control. One reason behind this approach is the increased availability of transplant units. However, to support the optimal outcome of patients with PA/MMA, it is important that these transplant units have relevant and suitable experience in transplanting patients with metabolic disorders rather than patients with organ failure alone.

The use of transplantation in patients with PA/MMA typically occurs at a young age, although transplantation at adult age has been reported when other management approaches have proven to be unsuccessful. Frequent metabolic decompensations tend to be the most common indication for transplantation in PA/MMA, although other reasons include suboptimal metabolic outcomes despite medical therapy, elective transplantation in view of the natural history of the disease, and the prevention of ongoing long-term complications of the disease. Current Scottish Intercollegiate Guidelines Network (SIGN) guidelines for the management of PA and MMA recommend that liver and/or kidney transplantation should be considered in patients with frequent metabolic decompensations where the clinical condition is difficult to stabilise with dietary/pharmacological treatment [1]. A catabolic state or active metabolic decompensation would be a potential contraindication to transplantation; thus clinicians need to carefully consider related risks and benefits prior to surgery.

The success of transplantation in PA/MMA remains varied, with substantial rates of associated complications and deaths being reported. While the risk of episodes of metabolic decom-

pensation are reduced, a proportion of transplanted patients continue to have episodes (approx. 15%). Martinelli et al. [48] note that while transplanted organs (liver and/or kidney) are an enzyme source, they only partially correct the biochemical defect. However, the small amount of enzyme activity gained by kidney transplantation appears sufficient to improve the metabolic balance in patients with MMA [1]. This could explain why metabolic acidosis was more commonly reported after liver transplantation compared with kidney or combined liver–kidney transplantation. In addition, the risk of subsequent episodes of metabolic acidosis following transplantation may be higher in those patients offered a less restricted dietary protein intake, in contrast with those who remain on a protein-restricted diet and/or receive appropriate pharmacotherapy to support metabolic stabilisation.

As transplantation is not curative in PA/MMA, it is important to recognise that any improvement in metabolic control has to be balanced with the possibility of complications during surgery and following transplant, along with the need for prolonged immunosuppressive therapy. A number of factors may influence the occurrence of post-operative mortality and/or complications. For example, high-level expertise of the transplant team and transplant centre has the potential to reduce post-operative mortality and an experienced team would also recognise that patients with PA/MMA undergoing transplantation would need careful and prolonged management following surgery. As such, the transplant team should aim to work closely with the metabolic team to support the optimal peri- and post-operative management of the patient's primary metabolic disorder, be it PA or MMA. The use of immunosuppressive therapy, along with the management of any associated tolerability issues, also remains important following transplantation. Extra-hepatic risks remain following surgery in patients with PA and MMA, with transplantation simply aiming to provide a milder and more manageable phenotype of the disease. Patients will therefore be required to remain on a protein-restricted diet, albeit a less stringent one. Of note, patients with PA or MMA should avoid prolonged fasting and dextrose infusions following transplantation in order to promote anabolism and prevent metabolic decompensation perioperatively. In addition, regular renal surveillance is also advised post-transplant in the long term.

Preoperative conditions associated with PA and MMA, such as intellectual disability, pre-existing neurological impairment, and cardiomyopathy, may influence the lifespan of a patient following transplantation. However, the optimal management of metabolic status both perioperatively and following transplantation would serve to minimise any further deterioration of these preoperative conditions. In addition, existing cardiac complications in patients with PA have the potential to improve following liver transplantation. It should be noted that liver and/or kidney transplantation does not reverse any neurologic injury that has accumulated prior to surgery. Of note, SIGN guidelines suggest that transplantation should ideally occur prior to any severe neurological deterioration and under stable metabolic conditions [1]. Thus, residual neurologic injury remains a persistent disease complication suggesting that postponing a transplant to a later stage may lead to additional neurologic insults and possibly inferior neurodevelopmental outcomes. However, post-transplant neurological deterioration in organic acidurias has also been reported (e.g. [39, 49]. De novo MMA production in the central nervous system may contribute to neurological dysfunction given that organ transplantation does not affect the concentration of MMA in the cerebrospinal fluid [48].

Worsening renal function was reported in some patients with PA following liver transplantation, although combined liver–kidney transplantation appeared more likely to result in stable renal function. In addition, significant recovery of cardiac function/reversal of severe cardiomyopathy was reported in some patients

with PA following transplantation, although heart failure was reported as the cause of death in other patients. Thus, cardiac and renal function should be assessed before transplantation and monitored closely afterward, with consideration given to the use of renal-sparing immunosuppression following surgery.

This review identified that the transplantation process itself was associated with several surgical complications, with liver transplantation associated with a higher level of mortality compared with kidney and combined liver–kidney transplantation. HAT remains a serious life-threatening complication in liver transplantation as noted in our findings. The overall incidence of HAT following liver transplantation varies from 2% to 9% and represents one of the main causes of graft loss and transplant recipient mortality [50]. The mechanism of HAT development is not fully understood, although young donor age and small liver graft are reported as risk factors in paediatric deceased-liver transplantation [51]. Infection, particularly CMV and EBV viremia, was also commonly reported, particularly in liver transplantation patients. Infection was a predominant cause of post-transplantation death, particularly in patients with MMA, and graft rejection/dysfunction leading to death was also reported. The most common reason reported for retransplantation in both patients with PA and MMA was HAT. Other complications which limited post-transplantation survival included cardiac failure and metabolic stroke. Of note, children with organic acidemias appear to be at higher risk of complications from transplantation than other metabolic disorders [52].

When considering the type of liver transplantation, SIGN guidelines recommended OLT, as this appears to be associated with fewer complications compared with auxiliary liver transplantation [1, 36]. However, any benefits of transplantation must always be weighed against the risks associated with organ transplantation along with the need for long-term immunosuppression [1, 36]. Toxicity associated with the use of post-transplantation immunosuppressive agents does occur, e.g. cyclosporine A and tacrolimus-induced leukoencephalopathy is a significant complication which may occur at therapeutic levels [53].

The findings from the current narrative review are in line with preliminary findings from a recent systematic review of the use of transplantation in patients with PA and MMA. This also demonstrated that while liver and/or kidney transplantation can improve patient outcome, the potential for increased mortality risk and a high risk of complications also need to be considered [54].

This review has a number of limitations. The search strategy used for this review identified 70 suitable references comprising both abstracts and full papers, although the available level of patient information, assessed clinical parameters, and clinical outcomes varied between them. All references were cross-checked to avoid any possible duplication of data between abstracts and full papers, although this was limited by the lack of patient information and clinical data provided in some of the abstracts meaning that the total number of transplants performed was actually lower than that reported. A number of these references were pooled studies of metabolic disease wherein only a few patients had PA or MMA. In addition, duration of follow-up varied substantially between studies, with some studies not providing timings of follow-up or complications, and some clinical outcomes of baseline parameters were not reported. For deaths related to transplantation, some references, particularly abstracts, failed to provide full details of the cause of these deaths, which was typically compounded by a lack of specific patient information. Likewise, for complications of transplantation surgery, some studies specifically defined and assessed complications, while others failed to do so, or failed to provide specific patient details, leaving the reader to subjectively interpret any issues related to the transplantation procedure. For this reason, the overall data included in this review should simply be used as a guide to the current issues related to transplantation in patients with PA and MMA.

## CONCLUSIONS

In summary, while the use of liver transplantation and combined liver–kidney transplantation appears to benefit some patients with PA or MMA, respectively, this approach does not provide a metabolic cure and patients remain at risk from disease-related and transplantation-related complications. Any transplantation procedure also has an associated mortality risk. Thus, all treatment avenues should ideally be exhausted for PA/MMA before selecting transplantation. If liver and/or kidney transplantation remains a viable option, the benefits of this approach must be individually and meticulously weighed against the risk of perioperative complications, including renal and neurological progressive impairment in the post-transplant period.

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***Data Availability.*** All data generated or analysed during this study are included in this published article/as supplementary information files.



## APPENDIX

See Tables 4 and 5.

**Table 4** Overview of data from PA studies/case studies (abstracts only)

| References | *n* | Transplant type[a] | Median (range) transplant age (years) | Post-transplant metabolic control | Post-transplant neurological health | Complications | Median (range) duration of follow-up (years) | Deaths (cause and number) |
|---|---|---|---|---|---|---|---|---|
| Alvarez-Elias et al. [7] | 1 | LDL/DDK | Liver transplant: 2 (n/s)<br>Kidney transplant: 4.9 (n/s) | Not reported | Not reported | Nephrotic syndrome (8 mo post-liver transplantation) with progression to ESRD necessitating renal transplant ($n$ = 1) | 3 (n/a) | None reported |
| Celik et al. [55] | 64 | LT [segmental ($n$ = 30), whole ($n$ = 34)] | 2.3 (0.25–13) | Not reported | Not reported | Graft loss ($n$ = 17) | ≤ 10 | Graft loss ($n$ = 12; incl. 3 after retransplantation)<br>Stroke ($n$ = 1)<br>Multiple organ failure/sepsis ($n$ = 2)<br>Unknown causes ($n$ = 1) |
| Celik et al. [56] | 1 | LT | Not specified | No further metabolic crises reported | Not reported | None | 0.6 (0.1–1.1) | None reported |

**Table 4** continued

| References | *n* | Transplant type[a] | Median (range) transplant age (years) | Post-transplant metabolic control | Post-transplant neurological health | Complications | Median (range) duration of follow-up (years) | Deaths (cause and number) |
|---|---|---|---|---|---|---|---|---|
| Curnock et al. [57] | 14 | Cadaveric graft LT ($n$ = 13, including 4 auxiliary)<br>Live-related donor LT ($n$ = 1) | 2 (0.8–8.0) | No further metabolic decompensations reported | Developmental progress ($n$ = 11) | $\geq$ 1 episode of acute cellular rejection ($n$ = 5)<br>Metabolic stroke ($n$ = 2)<br>Cardiomyopathy ($n$ = 3) | 4 (2–22) | Biliary peritonitis ($n$ = 1)<br>Acute or chronic rejection ($n$ = 1)<br>PTLD ($n$ = 1) |
| Duckworth et al. [58] | 6 | LT | 3.5 ± 2.3[b] | Not specified | Not reported | Post-LT rejection ($n$ = 2; one mild and one severe) | > 1 | None reported |
| Longo [59] | 3 | OLT | n/s (0.75–13) | No further metabolic crises | Patients had improvements of developmental milestones (no further data) | None specified | n/s (1.6–3.9) | None reported |
| Molera et al. [60] | 4 | LT [whole liver graft ($n$ = 2), LDLT ($n$ = 2)] | 5.2 (2.9–7.5)[b] | No further metabolic crises reported | Stable or improved neurological status at 1-year post LT ($n$ = 4) | HAT ($n$ = 2) | 2.1 (0.31–3.2) | None reported |
| Nassogne et al. [61] | 1 | LDLT | 12.5 | No further metabolic crises | Not specified | Late-onset cardiac failure ($n$ = 1) | 4.5 (n/a) | None reported |
| Nguyen et al. [62] | 7 | OLT | Not specified | Not specified | Not specified | Not specified | > 3 (n/s) | Cause not specified ($n$ = 1) |
| Ovchinsky et al. [63] | 1 | DDLT | 4 | No further metabolic crises | Not specified | None reported | 0.8 (n/a) | None reported |

**Table 4** continued

| References | *n* | Transplant type[a] | Median (range) transplant age (years) | Post-transplant metabolic control | Post-transplant neurological health | Complications | Median (range) duration of follow-up (years) | Deaths (cause and number) |
|---|---|---|---|---|---|---|---|---|
| Quintero et al. [64] | 5 | LT [whole liver graft ($n$ = 3), LDLT ($n$ = 2)] | 5.2 (2.9–7.5)[b] | No further metabolic decompensations | Stable or improved neurological status ($n$ = 5) | HAT ($n$ = 3) | 2.1 (0.31–3.2) | None reported |
| Reddy et al. [65] | 4 | APOLT | n/s (0.75–31) | No further metabolic crises | Not specified | HAT ($n$ = 1)<br>Recurrence of symptoms secondary to portal steal ($n$ = 1) | n/s (0–6.3) | None reported |
| Valamparampil et al. [66] | 5 | APOLT (all left auxiliary liver transplants) | 2.7 (n/s) | No metabolic episodes following transplantation | Progressive improvement in development ($n$ = 5) | None reported | 1.8 (n/s) | None reported |

**Table 4** continued

| References | *n* | Transplant type[a] | Median (range) transplant age (years) | Post-transplant metabolic control | Post-transplant neurological health | Complications | Median (range) duration of follow-up (years) | Deaths (cause and number) |
|---|---|---|---|---|---|---|---|---|
| Vara et al. [67] | 5 | LT [auxiliary LT (*n* = 1), orthotopic left lateral segment graft (*n* = 4)] | 1.5 (0.8–7) | No further metabolic decompensations reported | Moderate learning difficulties (*n* = 2)<br>Mild learning difficulties (*n* = 2)<br>Developmental delay with a probable metabolic stroke (resulting in mild hemiplegia and focal seizures) (*n* = 1) | Recurrent herpes simplex virus infection (*n* = 2)<br>EBV-positive PTLD (*n* = 1)<br>Probable metabolic stroke resulting in mild hemiplegia and focal seizures (*n* = 1) | 5.8 (1–14) | None reported |

**Table 4** continued

| References | *n* | Transplant type[a] | Median (range) transplant age (years) | Post-transplant metabolic control | Post-transplant neurological health | Complications | Median (range) duration of follow-up (years) | Deaths (cause and number) |
|---|---|---|---|---|---|---|---|---|
| Vara et al. [68] | 13 | LT [left lateral segment grafts (*n* = 7), left lateral segment (*n* = 2), right lobe auxiliary grafts (*n* = 2), whole graft (*n* = 1), live related donor (*n* = 1)] | 2 (1–7) | No metabolic decompensations reported in 9 surviving patients | No evidence of cardiomyopathy in 9 surviving patients | HAT requiring retransplantation (*n* = 1)<br>Chronic cholangiopathy requiring retransplantation (*n* = 1)<br>Pulmonary haemorrhage (*n* = 1)<br>Biliary sepsis (*n* = 1) | 4 (0.6–20.5) | Pulmonary haemorrhage (*n* = 1; 29 days post LT)<br>Biliary sepsis (*n* = 1; 42 days post LT)<br>Lymphoproliferative disorder (*n* = 1; 14 years post LT) |
| Walker et al. [69] | 5 | LT | 1.8 (0.75–7.0) | Not reported | Not reported | Impaired systolic function (*n* = 1) | 4.25 (0–10.5) | None reported |

*APOLT* auxiliary partial orthotopic liver transplantation, *DDLT* deceased-donor liver transplantation, *EBV* Epstein–Barr virus, *ESRD* end-stage renal disease, *HAT* hepatic artery stenosis, *KT* kidney transplantation, *LDL/DDK* living-donor liver/deceased-donor kidney, *LDLT* living-donor liver transplantation, *LT* liver transplantation, *OLT* orthotopic liver transplantation, *PTLD* post-transplant lymphoproliferative disease, *n/a* not available, *n/s* not specified

[a] Various types of liver transplantation used

[b] Mean (range) transplant age shown

**Table 5** Overview of data from MMA studies/case studies (abstracts only)

| References | *n* | Transplant type[a] | Median (range) transplant age (years) | Post-transplant metabolic control | Post-transplant neurological health | Complications | Median (range) duration of follow-up (years) | Deaths (cause and number) |
|---|---|---|---|---|---|---|---|---|
| Almeida et al. [70] | 1 | LT | 10 (n/a) | Not reported | Post-LT VIQ, PIQ and FSIQ scores displayed a positive change (VIQ = 91; PIQ = 84; FSIQ = 84) | None reported | 1 (n/a) | None reported |
| Barshop et al. [71] | 1 | DLT | 28 (n/a) | No metabolic decompensations | Not specified | None reported | 0.75 (n/a) | None reported |
| Boyer et al. [72] | 4 | DDKT | 5.7 (5–10) | Number per year dramatically decreased (no data specified) | Neurological complications stabilised (no further deterioration) | Hepatocarcinoma ($n$ = 1) | n/s (0.5–3.0) | Hepatocarcinoma ($n$ = 1) |
| Corno et al. [47] | 1 | LT | 9 (n/a) | Fatal metabolic crisis ($n$ = 1) | Not reported | Fatal metabolic crisis ($n$ = 1) | Not reported | Fatal metabolic crisis ($n$ = 1) |
| Fukuda et al. [73] | 10 | LDLT | n/s (0.6–7) | Severe metabolic acidosis ($n$ = 2)<br>No further metabolic decompensations in surviving patients ($n$ = 9) | No significant improvement in patient IQ | Viral infection ($n$ = 6)<br>Severe metabolic acidosis ($n$ = 2) | 3.5 (n/s) | Severe metabolic acidosis following rejection and sepsis ($n$ = 2) |
| Jiang and Sun [74] | 7 | LDLT ($n$ = 3)<br>DDLT ($n$ = 4) | Not specified | No further metabolic crises | Not specified | None reported | Not specified | None reported |

**Table 5** continued

| References | *n* | Transplant type[a] | Median (range) transplant age (years) | Post-transplant metabolic control | Post-transplant neurological health | Complications | Median (range) duration of follow-up (years) | Deaths (cause and number) |
|---|---|---|---|---|---|---|---|---|
| Matsumoto et al. [75] | 1 | LDKT | 26 (n/a) | No further metabolic crises | Not specified | None reported | 0.5 (n/a) | None reported |
| Nakajima et al. [76] | 1 | LDLT | 5.3 (n/a) | Marked reduction of metabolic decompensation (no additional data) | Leigh's encephalopathy ($n = 1$) | Leigh's encephalopathy ($n = 1$) | > 1.5 (n/a) | None reported |
| Shenoy et al. [77] | 5 | KT | 10.8 (5.8–17.8) | No episodes of metabolic decompensation reported in the immediate perioperative period | Neurological deterioration ($n = 1$) | Severe haemorrhagic pancreatitis ($n = 1$)<br>Bacterial endocarditis ($n = 1$)<br>Progressive deterioration in graft function ($n = 1$)<br>Pancreatitis ($n = 1$)<br>Neurological deterioration ($n = 1$) | ≤ 6 | Severe haemorrhagic pancreatitis leading to death ($n = 1$)<br>Bacterial endocarditis, progressive deterioration in graft function, pancreatitis, and neurological deterioration ($n = 1$) |

**Table 5** continued

| References | *n* | Transplant type[a] | Median (range) transplant age (years) | Post-transplant metabolic control | Post-transplant neurological health | Complications | Median (range) duration of follow-up (years) | Deaths (cause and number) |
|---|---|---|---|---|---|---|---|---|
| Sissaoui et al. [78] | 13 | KT (*n* = 7)<br>Combined LT/KT (*n* = 5)<br>LT (*n* = 1) | KT: 9.7 (5–17)<br>Combined LT/KT: 14 (6–19)<br>LT: n/s (n/a) | Not specified | LT/KT:<br>Axonal neuropathy (*n* = 1)<br>Myoclonus (*n* = 1) | KT: renal failure recurrence (*n* = 4)<br>Combined LT/KT: graft rejection (*n* = 1)<br>Biliary problems (*n* = 1)<br>Axonal neuropathy (*n* = 1)<br>Myoclonus (*n* = 1)<br>LT: none reported | KT: 5 (n/s)<br>Combined LT/KT: 1.5 (n/s)<br>LT: 0.5 (n/a) | None reported |
| Yamamoto et al. [79] | 1 | KT | 26 (n/a) | No further episodes of metabolic decompensation reported | No further neurological deterioration (at 10 months post-transplant) | None reported | 0.8 (n/a) | None reported |

**Table 5** continued

| References | *n* | Transplant type[a] | Median (range) transplant age (years) | Post-transplant metabolic control | Post-transplant neurological health | Complications | Median (range) duration of follow-up (years) | Deaths (cause and number) |
|---|---|---|---|---|---|---|---|---|
| Yoshino et al. [80] | 2 | LT | 6.3 (5.2–7.3) | Not specified | Episodes of quick torsional movements of the head ($n = 1$)<br>Tonic seizure ($n = 1$) | Episodes of quick torsional movements of the head ($n = 1$)<br>Tonic seizure ($n = 1$)<br>Weakness of the right extremities and flexion of the right upper extremity ($n = 1$) | 2.3 (2–2.6) | None reported |

*ALT* auxiliary liver transplantation, *CMV* cytomegalovirus, *KT* kidney transplantation, *LDLT* living-donor liver transplantation, *LT* liver transplantation, *LT/KT* liver/kidney transplantation, *OLT* orthotopic liver transplantation, *n/a* not available, *n/s* not specified

[a] Various types of liver transplantation used

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