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ORIGINAL ARTICLE

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Liver and/or kidney transplantation in amino and organic acid-related inborn errors of metabolism: An overview on European data

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Abstract

Background: This study provides a general overview on liver and/or kidney transplantation in patients with an amino and organic acid-related disorder (AOA) with the aim to investigate patient characteristics and global outcome in Europe. This study was an initiative of the E-IMD and the AOA subnetwork of MetabERN.

Methods: A questionnaire was sent to all clinically active European Society for the Study of Inborn Errors of Metabolism (SSIEM) members. The questionnaire focused on transplanted individuals with methylmalonic acidemia (MMA), propionic acidemia (PA), maple syrup urine disease (MSUD), and urea-cycle disorders (UCDs).

Results: We identified 280 transplanted AOA patients (liver transplantation in 20 MMA, 37 PA, 47 MSUD, and 111 UCD patients, kidney or combined liver

Abbreviations: AOA, amino and organic acid related disorder; Arg1-D, arginase 1 deficiency; ASL-D, argininosuccinate lyase deficiency; ASS-D, argininosuccinate synthetase deficiency; CPS1-D, carbamylphosphate synthetase 1 deficiency; HHH, hyperammonemia-hyperornithinemia-homocitrullinemia; IEM, inborn errors of metabolism; IVA, isovaleric acidemia; MELD, model for end-stage liver disease; MMA, methylmalonic acidemia; MSUD, maple syrup disorder; NAGS, N-acetylglutamate synthase deficiency; OAD, organic acidemia; OTC-D, ornithine transcarbamylase deficiency; PA, propionic acidemia; UCD, urea-cycle disorder; UNOS, united network for organ sharing.

Additional individual contributors of MetabERN are provided in Appendix.

and kidney transplantation in 57 MMA patients and undefined transplantation type in 8 MMA patients), followed by 51 metabolic centers. At a median follow-up of 3.5 years, posttransplant survival ranged between 78% and 100%, being the lowest in PA patients. Overall, the risk of mortality was highest within 14 days posttransplantation. Neurological complications were mainly reported in Mut^0 type MMA ($n = 8$). Nonneurological complications occurred in MMA ($n = 28$), PA ($n = 7$), and UCD ($n = 14$) patients, while it was virtually absent in MSUD patients. Only 116/280 patients were psychologically tested. In all, except MSUD patients, the intelligence quotient (IQ) remained unchanged in the majority (76/94, 81%). Forty-one percentage (9/22) of MSUD patient showed improved IQ.

Conclusion: The survival in AOA individuals receiving liver and/or kidney transplantation seems satisfactory. Evidence-based guidelines, systematic data collection, and improved cooperation between transplantation centers and European Reference Networks are indispensable to improve patient care and outcomes.

KEYWORDS

amino acid and organic acid diseases, development, inborn errors of metabolism, MetabERN, morbidity, mortality, quality of life, solid organ transplantation

1 | INTRODUCTION

Methylmalonic acidemia (MMA), propionic acidemia (PA), maple syrup urine disease (MSUD), and urea-cycle disorders (UCDs) are inborn errors of metabolism (IEM) belonging to the group of amino and organic acid-related disorder (AOA) that cause noncirrhotic extrahepatic disease.[1] Patients often present with severe neonatal onset. Despite increasing awareness and evidence-based recommendations for metabolic management using dietary treatment and pharmacotherapy, the long-term clinical outcomes of affected individuals are often poor. This is due to the fact that available conservative therapies do not reliably prevent recurrent metabolic decompensations and disease progression.[2]

Since the late 1980s, liver and/or kidney transplantation has been considered as alternative therapy in some IEM.[3] It has been applied with the aim of permanent enzyme replacement and hence rescue (UCDs)[4-6] or partial correction (eg, PA, MMA, MSUD)[7,8] of the deficient metabolic pathway with the transplanted organ.[9-11] Organ transplantation aims to (a) improve patient's metabolic control (reduce the occurrence of metabolic decompensations), (b) improve quality of life (QOL), and (c) ameliorate/prevent the occurrence of long-term complications (in MMA and PA patients).

In the United States, MMA, PA, and UCD patients per default receive a (pediatric) model for end-stage liver disease (MELD/PELD) score of 30, exclusively based on their IEM diagnosis[1,12] and thus a high priority on the transplant waiting list. In Europe, however, patients need to be placed on the transplant waiting list based on guidance by their clinician after discussion in a multidisciplinary transplantation team. Practice regarding transplantation and guideline advice (often being a-specific) in these disorders are based on single case reports, small cohort studies, United States or Japanese population cohorts (with different indications and methods compared to Europe), and expert opinions.

The AOA subnetwork of the MetabERN discussed the lack of uniformity regarding use of transplantation as a treatment option in Europe and clearly identified that there is a lack of a systematic overview/database of and uniform protocol regarding treatment of all European transplanted AOA patients. Despite this, the frequency of transplantation in these inherited metabolic disorders is increasing in Europe without sufficient documentation. Recently a review on the literature on MMA and PA transplanted patients showed 373 transplanted patients and a mortality rate of 11% and 14%, respectively.[13] This gives a first insight of the worldwide (reported) frequency of transplantation within these specific disorders. The aim of this study was to provide an overview of all known transplanted MMA, PA, MSUD, and UCD patients in Europe in order to describe patient characteristics and global outcome (mortality at the time of the evaluation—questionnaire, frequency of peri-/postoperative complications, and whether or not cognitive development and

QOL improved after transplantation) after liver and/or kidney transplantation was evaluated structurally. Besides increasing awareness, it will guide decision-making and the development of optimized guidelines for indication of transplantation.

2 | PATIENTS AND METHODS

2.1 | Data collection

Data collection started at the 11th of Match 2019 by a questionnaire—provided through LimeSurvey—to all health care professionals who were members of the Society for the Study of Inborn Errors of Metabolism (SSIEM). On September 20, 2019, the data collection through LimeSurvey was finalized. In total, 405 invitations were sent to a total of 216 hospitals, including metabolic as well as nonmetabolic centers. The three topics addressed in the questionnaire were: (a) description of the cohort: demographics, patient characteristics, and transplantation characteristics; (b) treatment: whether or not a transplantation protocol was used and whether or not dietary treatment was continued posttransplantation; and (c) clinical outcome: patient survival, whether complications had occurred, and if cognitive development and the QOL declined/stabilized or improved posttransplantation. We included patients currently alive or deceased, having received a liver and/or kidney transplantation and affected by the following disorders: classical OAD—MMA, PA, and isovaleric acidemia (IVA)—MSUD, and UCDs—carbamylphosphate synthetase 1 deficiency (CPS1-D), ornithine transcarbamylase deficiency (OTC-D), argininosuccinate synthetase deficiency (ASS-D), argininosuccinate lyase deficiency (ASL-D), or hyperammonemia-hyperornithinemia-homocitrullinemia (HHH) syndrome. No patients' identifiers were accessed by investigators. Questions addressed the whole subgroup of AOA transplanted patients, the disease-specific group, or the specific patient (Table S1). In OTC-D, a distinction was made between females and males, and in MMA between Mut^0 type MMA as well as other types (Mut^-, CblB, and undefined subtypes).

2.2 | Statistical analysis

SPSS (IBM SPSS Statistics 24.0, IBM Corp., Armonk, New York) was used for descriptive statistics. Normality was examined using the Kolmogorov-Smirnov test and quantile-quantile (Q-Q) plots.

Wilcoxon rank sum test (Ws) (comparison of two groups) and the Kruskal Wallis H-test (comparison of more than two groups) were performed if distribution was nonnormal. Chi-square test was performed to test age-dependent mortality risk and mortality risk within compared to after 14 days after transplantation. A *P*-value (a-level) of 0.05 or less, 2-tailed, was understood to indicate statistical significance. Crude patient survival was calculated using Kaplan-Meier survival method (curves were made by using GraphPad Prism 5).

3 | RESULTS

3.1 | European cohort of transplanted patients

Of 405 invited health care professionals, a total of 168 (43%) completed the survey. They reported 280 transplanted AOA patients: including 215 AOA patients with liver transplantation (20 MMA, 37 PA, 47 MSUD, and 111 UCD patients), and 48 MMA patients with either kidney or combined liver and kidney transplantation, and 8 MMA patients with unknown type of transplantation (Tables 1 and S1). The median follow-up time after transplantation was more than 1 year in 79% and more than 5 years in 47% (Figure S1). Fifty-one medical centers (representing 17 countries) performed one (n = 9) or more (2-23) transplantations (n = 42) (Table S2, Figures 1 and S2). Transplantations had been performed between 1987 and 2019. Nine centers performed transplantations before the year 2000. The main indication for transplantation reported was frequent metabolic decompensations. Waiting time for transplantation was between 0 and 48 months. A standardized protocol for transplantation in IEM (26/44 [59%]) and a multidisciplinary team for transplantation in IEM (34/45 [76%]) were available in more than half of reporting hospitals.

3.2 | Disease-specific characteristics regarding organ transplantation and global outcome

3.3 | Total cohort

Age at transplantation was reported in 232 patients. Overall, mortality risk was significantly higher within the 14 days after transplantation than thereafter (χ^2 [1], $P < .001$). There was no association between year in which the patient was transplanted and mortality (Table S3). Graft failure was reported in 16 patients, graft rejection in 15 patients, and 11 patients underwent re-

TABLE 1 Baseline characteristics and follow-up period

Disease	Total patients treated (n=) (nbs, n=)	Total patients transplanted (n=)		Type transplantation (n=)	Age transplantation mentioned in (n=)	Age transplantation (years) (median; min-max)	Follow-up (years) (median; min-max)
MMA Mut^0	155 (25)	49	Classical OAD: 122	14KT, 18LT, 14 KLT	46	8.0; 0.0-29.0	*2.1; 0.0-26.0*
MMA Mut^-	63 (12)	3		2KT, 1LT	3	16.0; 0.5-17.0	*1.5; 0.0-13.0*
MMA CblB	64 (15)	5		3KT, 2KLT	4	12.5; 11.0-15.0	*1.5; 0.0-6.0*
MMA	47 (8)	28		16KT, 1LT, 6 KLT	14	17.0;2.5-35.0	*3.0; 0.0-13.0*
Undefined MMA total	*329 (60)*	85		35KT, 20LT, 22KLT	67	10.0; 0.0-35.0	2.1; 0.0-26.0
PA	255 (37)	37		LT	37	2.7; 0.6-23.0	2.2; 0.0-25.0
IVA	*111 (45)*	0		-		-	
MSUD	286 (99)	47		LT	31	4.0; 0.9-28.2	2.9; 0.0-11.0
CPS1-D	40 (3)	18	UCD: 111	LT	17	1.4; 0.4-11.5	6.0; 0.0-17.0
OTC-D male	135 (10)	32		LT	22	2.4; 0.3-23.0	4.4; 0.0-17.0
OTC-D female	167 (0)	19		LT	17	12.0; 2.0-38.0	6.1; 0.8-13.0
ASS-D	154 (32)	25		LT	25	2.0; 1.0-10.0	4.5; 0.0-19.0
ASL-D	136 (22)	11		LT	11	4.5; 1.3-15.0	7.0; 0.3-15.0
Arg1-D	45 (6)	5		LT	5	6.0; 1.0-10.0	2.0-0.0-19.0
HHH syndrome	28 (1)	1		LT	0		
Total	705 (315)	280			232	4.0; 0.0-38.0	3.5; 0.0-26.0

Abbreviations: KT, kidney transplant; LKT, liver and kidney transplant; LT, liver transplant; n, number of patients; nbs, newborn screening.

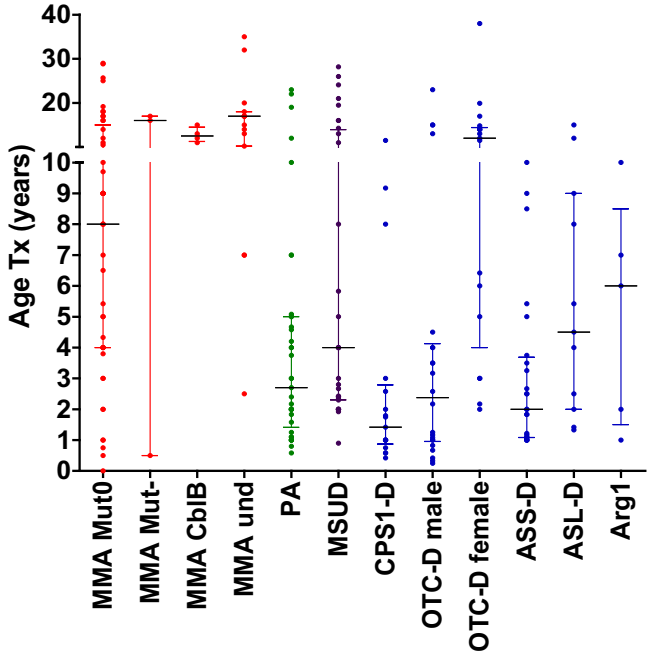

FIGURE 1 Age at transplantation broken down for type of disease. Horizontal stripes indicate median and IQ range, dots represent single patients

transplantation (Table 2). Cognitive development was evaluated in 116 patients by age-adapted intelligence quotient (IQ) tests, mainly by the Wechsler Intelligence Scale for Children. QOL was mainly assessed by the PedsQL and was decreased in the majority of patients before transplantation and improved thereafter in almost all (Table S5b).

3.4 | MMA and PA patients

In MMA patients, combined liver and kidney transplantation (n = 22), and liver (n = 20) or kidney (n = 35) transplantation were performed. In eight MMA patients, the type of transplantation was not reported. MMA patients who received a liver transplant were younger (median 3.0 years, min-max: 0.0-10.0) than those receiving either a combined liver/kidney (median 13.5 years, min-max: 4.0-29.0) or kidney transplant (median 14.0 years, min-max: 4.0-35.0) ($H(3) = 32.758$, $P < .001$). Within the MMA subtypes, Mut^0 type MMA patients (n = 46) were transplanted at the youngest median age (median 8.0, min-max: 0.0-29.0; $H(3) = 9.613$, $P = .022$) (Figure 1). The type of transplantation performed did not differ between MMA subtypes. PA patients were transplanted at a median age of 2.7 years (min-max: 0.6-23.0). The age at liver transplantation did not differ between MMA and PA patients.

The patient survival rate was 87% in MMA at a median follow-up of 2.1 years and 78% in PA patients at a median follow-up of 2.2 years. Patient survival in MMA patients did not differ between kidney, liver, and combined liver and kidney transplantation (Figure 2). In Mut^0 type MMA, three patients received a liver transplant before the age of 1 year of whom 2 patients died, both having been transplanted in 1995.

In PA, patients having received a liver transplant before 4 years of age had a higher mortality risk than those transplanted at a later age ($\chi^2(1)$, $P = .019$). Half of the deceased MMA and PA patients died within 14 days after transplantation. The others died within 3 months up to 5 years after transplantation.

Nonneurological complications after transplantation were reported for 35 of the MMA and PA patients. Neurological complications were reported in 8 Mut^0 type MMA patients (Table 2). The type of transplantation did not apparently influence the risk of posttransplant neurological complications. In MMA and PA patients, the majority of patients had unchanged cognitive function after transplantation (Table S5a). The majority of PA patients had a liberalized diet, while a third of MMA patients continued a protein-restricted diet after transplantation (Table S4). In MMA, patients receiving a kidney transplant less often had a liberalized diet (33%; 6/18) compared to recipients of liver or combined liver and kidney transplant (63%; 15/24) (Table S4).

3.5 | MSUD

The median age at transplantation was 4.0 years of age (min-max: 0.9-28.2) in MSUD patients and the survival rate was 88% at a median follow-up of 2.9 years. All deceased patients (n = 4) died within 7 days after transplantation. Nonneurological complications were reported for 3 patients. Almost half of transplanted MSUD patients who survived had improved cognitive development (Table S5a), and all of them discontinued dietary treatment.

3.6 | Urea-cycle disorders

The median age at transplantation was 2.7 years of age (min-max: 0.3-38.0) in UCD patients; OTC-D females received liver transplantation at a later age (Ws 3389.5, $z = -4.246$, $P < .001$) (Figure 1). In UCDs, 6% of all the patients were transplanted in the first year of life. Overall survival was 93% at a median follow-up of 5.0 years. In OTC-D females and in ASL-D patients, all patients survived during the follow-up period (Table 2, Figure 2). In

TABLE 2 Posttransplant complications and mortality of transplanted patients

Disease	Total transplanted (n=)	Graft failure reported (n=)	Graft rejection reported (n=)	Neurological complications reported (n=)	Other than neurological complications reported (n=)	Re-transplantation reported (n=)	Age follow-up documented	Mortality (n=, %)
MMA *Mut*^{0}	*49*	*2*	*3*	*8*	*18*	*1*	*46*	*5 (11%)*
MMA *Mut*$^{-}$	*3*	*0*	*1*	*0*	*1*	*0*	*3*	*1 (33%)*
MMA *CblB*	*5*	*0*	*1*	*0*	*1*	*0*	*4*	*0 (0%)*
MMA *Undefined*	*14*	*1*	*1*	*0*	*8*	*0*	*14*	*3 (20%)*
MMA total	85	3	6	8	28	1	67	9 (13%)
PA	37	5	2	1	7	4	37	8 (22%)
IVA	0	-	-	-	-	-	-	-
MSUD	47	2	3	0	3	0	31	4 (12%)
CPS1-D	18	2	0	2	2	1	17	1 (6%)
OTC-D male	32	0	1	2	6	1	22	1 (4%)
OTC-D female	19	1	0	1	2	1	17	0 (0%)
ASS-D	25	2	2	1	3	1	25	4 (16%)
ASL-D	11	0	0	0	0	0	11	0 (0%)
Arg1-D	5	1	1	0	1	2	5	1 (20%)
HHH syndrome	1	0	0	0	0	0	0	-
Total	280	16	15	15	52	11	232	28 (12%)

Note: n = number of patients with reported outcome.

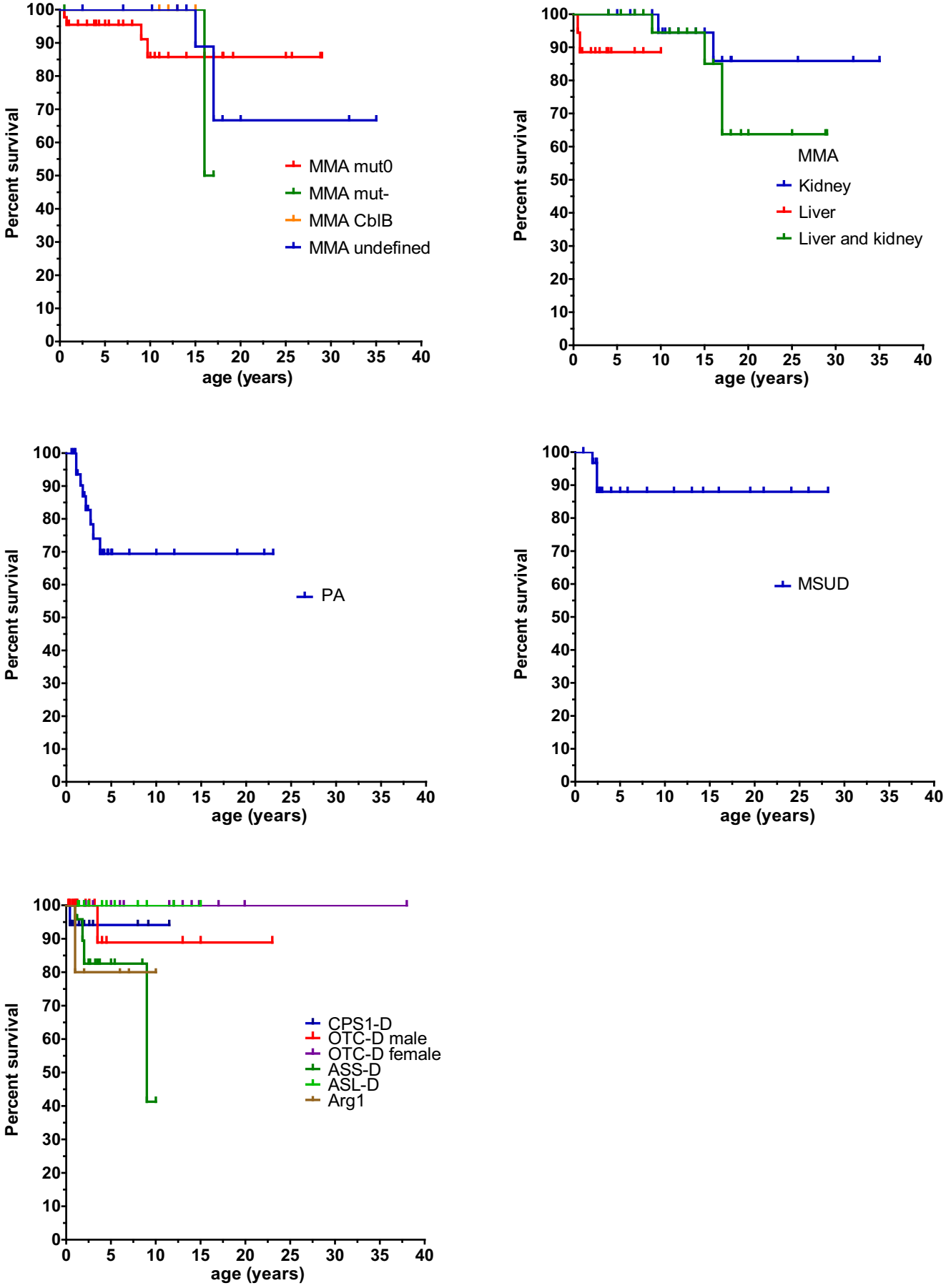

FIGURE 2 Survival curves per disease. Disease indicated by color, vertical stripes indicate patients

the overall UCD group, four of seven deceased patients died within 7 days after transplantation, while the other three patients died at 1.5, 2.0, and 19 years, respectively, after transplantation. Nonneurological complications were reported in 14 UCD patients (Table 2). Cognitive development was virtually unchanged in the majority and improved in some (Table S5a). Protein restriction was liberalized or discontinued after transplantation in the majority of patients (Table S4).

4 | DISCUSSION

The aim of this study was to provide an overview of all known transplanted MMA, PA, MSUD, and UCD patients in Europe in order to investigate the patient characteristics and global clinical outcomes of AOA transplanted patients. This study was an initiative of the E-IMD and the AOA subnetwork of MetabERN, to increase awareness and make a first step toward (uniform) guideline development. We collected data with the use of a questionnaire and received information on a total of 280 transplanted patients with MMA, PA, MSUD, and UCDs in Europe.

The survival rate of transplanted MMA and PA, MSUD, and UCD patients in this study was similar to (a) nontransplanted patients,[14-16,17-19] (b) transplanted patients in the United States/UNOS database,[8,20] and to (c) patients receiving transplantation for other indications than an IEM (such as biliary atresia).[21] The mortality risk of AOA patients was highest within 14 days after transplantation. This can be due to complications arising from the disease itself, such as metabolic derangement, due to surgical difficulties (mainly in younger patients) or due to other common posttransplant complications such as infection/sepsis, multiorgan failure, graft failure, vascular thrombosis, biliary complications, and acute rejection.[12,20,22,23] These common posttransplant complications are also observed and associated with a higher mortality risk in patients transplanted for other reasons than IEM.[21] In our view, to decrease the mortality risk, (a) metabolic stability at time of transplantation is necessary, (b) the transplantation needs to be performed by an experienced transplantation team and (c) improved peri-surgical management is essential, this includes evaluation of cognitive outcome and QOL evaluation.

Newborn screening (NBS) programs for AOA are emerging.[23-25] The upcoming NBS prompts the need to determine whether to perform early transplantation in these patients. In the UNOS cohort, 33% of the UCD/OAD patients were transplanted before the age of 1 year, while in the European cohort this proportion was only 6%. In MSUD and UCD patients, early transplantation might be beneficial for this patient group.[26] In the other disease groups, early transplantation might be beneficial,[27,28] but others reported that early transplantation was associated with an increased frequency of peri-operative (as a consequence of large transplant size) and postoperative complications.[12]

The need of immunosuppressive therapies after transplantation should be taken into account when considering a patient for transplantation. In this study, immunosuppressive schemes were not evaluated since this study was performed to provide a first overview of the transplanted AOA patients in Europe. It is hypothesized that in MMA patients, liver transplantation may potentially delay chronic kidney disease (CKD) due to a decrease of (nephro-) toxic metabolites by liver transplantation. The use of calcineurin inhibitors (CNIs) as part of the immunosuppressive protocol[21] is a risk factor for CKD. CNI can also be neurotoxic and caution regarding its use is essential, especially in MMA Mut^0 patients, since these patients have an increased risk on posttransplant neurological complications.[29] The accumulation of neurotoxic metabolites in the brain compartment is unlikely to be reliably prevented by this therapeutic intervention.[30-32]

4.1 | Strengths and limitations of the study

This is the first overview of current practice on liver and/or kidney transplantation in individuals with AOA in Europe. In comparison to the UNOS database, this study provides information on specific disorders within a broad spectrum of OADs and UCDs. Furthermore, compared to literature reviews this study gained information specifically of the European transplantation patients, with a follow-up up to finalization date of the survey, unless the patient died. This study has some limitations due to its design. First, to improve the response rate and hence to include patient data from the majority of European metabolic centers we designed a basic questionnaire that could be filled in a reasonable time. To achieve this goal, the questionnaire answers on topic concerning treatment and outcome gave insufficient answers to come up with specific advices on how to improve this treatment and how to improve outcome after transplantation. However, this lack of knowledge highlights the need for more protocolled care. Furthermore, we were not able to correlate outcome data, other than mortality, to potential predictive factors. Additionally, in the majority of patients the year in which transplantation was performed was not known. Lastly, immunosuppressive therapies

and particular adverse effects could not be evaluated. A registry with prospective data seems essential. Furthermore, some aspects such as the cause of death and whether it differs to other transplanted patients remained unknown. Secondly, we have received a response from more than 50 metabolic centers following (transplanted) AOA patients. While this is a representative number of centers, it might be that nonresponders differed from responders. Thirdly, we did not focus on the reduction of metabolic decompensations after transplantation (if any), since this has already been described in previous studies.[6,33-36] Lastly, in this study we did not investigate in detail the various postoperative complications, but decided to focus on neurological complications, considering the large effect of neurological complications on mortality, IQ, QOL, and costs. It could well be that organ transplantation prevents further decline of cognitive impairment and thereby organ transplantation can be beneficial.

4.2 | Future perspectives

In order to provide more specific guidelines and identify risk groups of mortality, we need to perform a prospective study. This requires a strong collaboration and effort of all transplantation centers within Europe and a prospective follow-up. For now, it remains unanswered which patients need to be transplanted. If patients are considered for transplantation it is important to acknowledge that "pre- and perioperative morbidity and nutritional status are correlated with the outcome after transplantation."[21] In some OAD patients, reason to perform transplantation is elective management. To date, however, it is not known if transplantation of liver and/or kidney can prevent the occurrence of long-term complications. Several long-term complications in OAD occur due to mitochondrial dysfunction[37] and FGF-21 seems a good biomarker for the occurrence of long-term mitochondrial complications.[38] Transplantation can potentially (partially) reverse this mitochondrial dysfunction, shown by a decrease in FGF-21 levels after transplantation.[29,39] The potential role of FGF-21 in decision making on transplantation needs further study and discussion.

Considering the access to transplants, we need to determine if the number of available organs meet the transplantation need for these specific disease groups. The role of living related donors, including disease carriers, in patients with an IEM is evolving and common practice in Japan[22,40] and associated with a comparable patient and graft survival as those receiving deceased donor transplantation.[1] The use of living related donors is increasing in Europe[21] and needs to be discussed and protocolled. Furthermore, the outcome in patients with disease carriers as donors must be evaluated. It is also important to further explore the option of domino liver transplantation in these disorders.[41-43]

Once a patient is considered for transplantation, we should decide what the best center for transplantation of these patients will be. We suggest to discuss the potential role of designated centers with sufficient experience of transplantation in IEM.[21] The AOA subnetwork of the MetabERN together with other European Reference Networks can foster to achieving more cooperation between centers. Furthermore, protocolled follow-up is necessary, also since the use of transplantation is expected to continue to grow and (more detailed) outcome needs to be prospectively evaluated and data should be stored in a European registry. To improve patients care and for a better understanding of the impact of organ transplant on the long-term disease course, we strongly recommend to involve metabolic clinicians in the multidisciplinary team managing the (life-long) post-transplant follow-up.

5 | CONCLUSION

Liver and/or kidney transplantation was performed in 280 MMA, PA, MSUD, and UCD patients in Europe, in 51 centers, with a survival ranging from 78% to 100% (within the different disorders) at a median follow-up of 3.5 years. Mortality risk was highest within 14 days after transplantation. Neurological complications after transplantation warrant attention. Protocolled pre- and post-operative follow-up with detailed data collection is essential. Clear guidelines need to be established and cooperation between transplantation centers and ERNs seems necessary within Europe to optimize outcome in patients with these metabolic disorders.

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CONFLICT OF INTEREST

This research was performed independent of all financial sponsors other than Erasmus MC, University Medical Center. The project was initiated by the E-IMD and AOA subnetwork of MetabERN, the Europe Reference Network for Hereditary Metabolic Disorders.

ETHICS STATEMENT

The study was approved by the local ethics committee. No patients' identifiers were accessed by investigators. All

the procedures followed were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national) and with the Helsinki Declaration of 1975 as revised in 2000. Data were collected by LimeSurvey (an approved data system by the Erasmus Medical Center Rotterdam and will be stored in Heidelberg University Medical Center.

Animal rights: This article contains no studies with animal subjects performed by any of the authors.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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APPENDIX

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