Humanistic and Economic Burden of Methylmalonic Acidemia – a Systematic Literature Review

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Background

- Methylmalonic acidemia (MMA) is an autosomal recessive disorder of amino acid metabolism that is characterized by impaired propionate metabolism
- Disease management relies on dietary restrictions, medications to manage symptoms, and ultimately, liver and kidney transplantation
- Prognosis is generally poor, especially in B12-unresponsive forms of MMA. Patients may die in the newborn period or during a later episode of metabolic decompensation. Those who survive often have significant neurodevelopmental delays. Renal disease, which may result in chronic renal failure, can also occur[1]

Objectives

- The objective of this systematic literature review (SLR) was to collect and synthesize the published evidence on the humanistic and economic burden of MMA, with a special focus on pre- and post-transplant results
- The scope of the review was restricted to the more severe, B12-unresponsive MMA subtypes, namely:
  - complete methylmalonyl-coenzyme A mutase deficiency (mut^0)
  - partial methylmalonyl-coenzyme A mutase deficiency (mut$^-$)
  - adenosyl-cobalamin B (cblB) defect
  - methylmalonyl-CoA epimerase deficiency (MCEE)

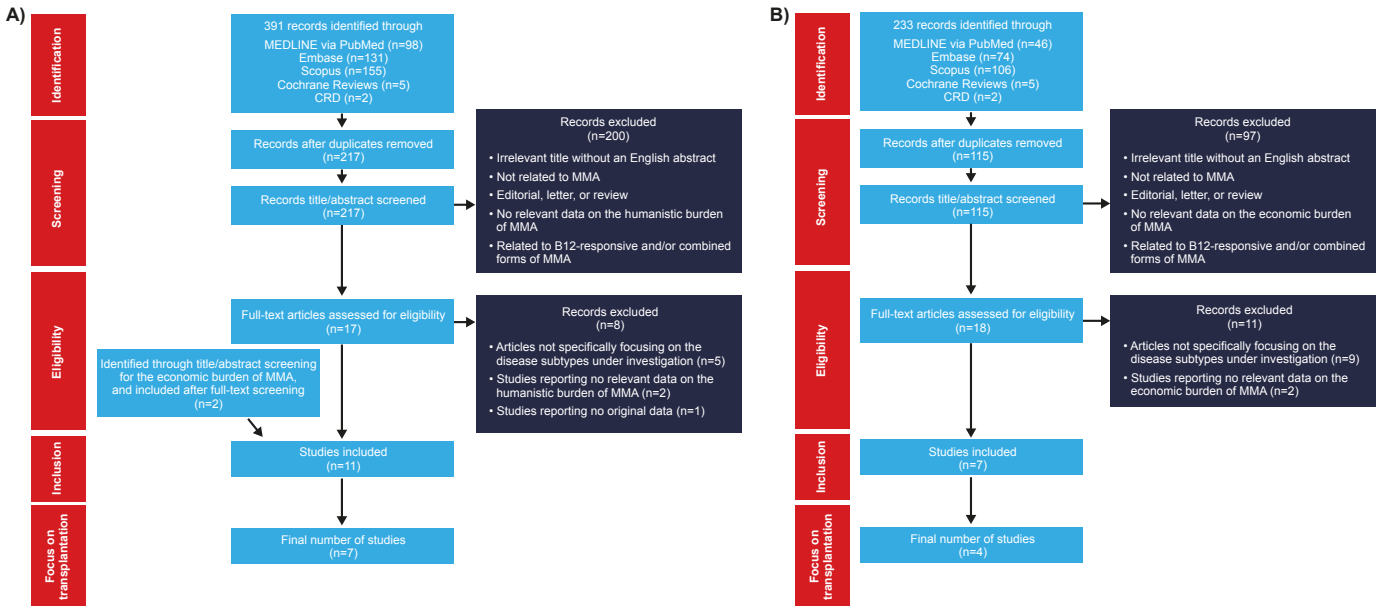
Methods

- The SLR was conducted and reported in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 statement[2] (**Figure 1A**, **Figure 1B**)
- Articles were searched in MEDLINE via PubMed, Embase, Scopus, Cochrane Reviews, and PROSPERO (only for methods) and the Centre for Reviews and Dissemination database at the University of York, on December 14, 2022
- The search strategy was built as a combination of search strings, allowing the capture of all relevant keywords that may have appeared in the papers
- Study eligibility criteria were set according to the Populations, Interventions, Comparators, Outcomes, Study (PICOS) design framework. No time or geographical limits were applied, but only full-text studies written in English were eligible for data extraction
- Search hits were screened by two independent researchers, with eventual conflicts solved via the involvement of a third researcher
- A backward and forward snowball search was conducted for additional results
- Data were extracted by two independent researchers. As the scales and measures used in the studies were heterogeneous, narrative synthesis of findings was provided
- The risk of bias of case report, cross-sectional, and cohort studies was assessed using the Joanna Briggs Institute Critical Appraisal Checklist for Case Reports,[3] the Joanna Briggs Institute Critical Appraisal Checklist for Analytical Cross-Sectional Studies,[3] and the Critical Appraisal Skills Programme checklist for Cohort Study,[4] respectively

Results

- A limited number of studies were identified that presented relevant pre- and post-transplant data on B12-unresponsive patients with MMA
- Seven studies presented information on humanistic burden[5–11] (**Table 1**) and four studies on economic burden[11–14] (**Table 2**) in the context of transplantation
- Studies showed stagnation[6,9] or improvement[5,7,8] in cognitive function after transplantation
- Case reports showed patients feeling more energetic, with muscle tone and improved strength,[7] while another study found that the development quotient did not change significantly with live-donor liver transplantation in children with MMA[9]
- One study found decreased anxiety among caregivers: level of 33.4 (mild anxiety) on the Beck Anxiety Inventory scale (Chinese Version) before transplant and 27.2 (minimal level of anxiety) post-transplant[11]
- Studies on economic burden showed that the average length-of-stay was reduced (78.8–90.6 days per year before and 7.4–28.2 days per year after transplantation),[11,12] and the number of hospitalizations decreased significantly after transplantation, both to the general ward and to the intensive care unit[13,14]

Figure 1. (A) PRISMA flowchart of humanistic burden results and (B) PRISMA flowchart of economic burden results



CRD, Centre for Reviews and Dissemination; MMA, methylmalonic acidemia; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Table 1. Humanistic burden measures of patients with MMA with a transplant

Study	Population and sample size	Measurement	Value
Niemi (2015)[5]	1 child with MMA, undergoing LT	Wechsler Intelligence Scale	• Pre-transplant: performance IQ=55 (1st percentile); verbal IQ=87, (19th percentile) • Post-transplant: performance IQ=82 (12th percentile); verbal IQ=89, (23rd percentile)
Molema (2020)[6]	41 children (MMA mut^0, mut$^-$, and cblB), before and after LT	Wechsler Intelligence Scale	• mut^0: 8% had decreased cognitive function after transplantation, 82% stable, 10% improved • mut$^-$: 100% stable • cblB: 50% stable, 50% improved
		Dietary restrictions	• Pre-transplant: data were available for 44 patients, 43 of whom (98%) had dietary restrictions, and 1 patient (2%) who did not • Post-transplant: data were available for 41 patients, 18 of whom (44%) had continued restrictions, 22 (54%) who were liberated from restrictions and 1 (2%) who continued not to have them at all
Nagarajan (2005)[7]	2 MMA mut^0 cases	Need for special education	• Patient 1: needed special education before combined kidney and liver transplantation (transplantation only in adulthood) • Patient 2: unable to attend school regularly before transplantation; regularly attended school 2 years post-transplantation
		Physical impairment	• Patient 1: developed progressive neurological decompensation, with a shuffling gait, dystonia of the extremities, and mild difficulties with writing and spatial organization before combined liver and kidney transplantation. 2 years after transplantation, they felt more energetic • Patient 2: quality of life improved significantly with the transplantation: 6 months post-transplantation, their energy levels, muscle tone, and strength improved further, and they ambulated increasingly with their walker
Spada (2015)[8]	2 cases of cobalamin unresponsive MMA, with early LT	Case 1: Bayley-III scale	• Adequate development: cognitive functions composite score of 90 (95% CI 83–99) at the age of 2.5 years
		Case 2: Marioka's Standard	• Excellent quality of life
Sakamoto (2016)[9]	13 patients with MMA (9 mut^0, 2 mut$^-$, and 2 cases of unknown phenotype)	Denver Developmental Screening Test and Kyoto Scale of Psychological Development-2000	• The development quotient did not change significantly with live-donor liver transplantation: its mean value before transplantation was 51 ± 9, while its mean value post-transplantation was 50 ± 5
Splinter (2016)[10]	35 MMA mut^0 children (aged 8 ± 4.7 years) undergoing LT, and their caregivers	PedsQL scale	• Children with MMA mut^0 had a lower score (mean=64.5) than healthy children (mean=80.9) and children on the PedsQL Transplant Module (mean=77.3) • The mean score of families affected by MMA mut^0 (62.0) was comparable with the mean score of families with children with chronic conditions living at home (62.5)
Chu (2019)[11]	Caregivers of 19 patients with MMA mut^0/mut$^-$ and cblB	Beck Anxiety Inventory scale (Chinese version)	• Pre-transplant: 33.4 (mild anxiety) • Post-transplant: 27.2 (minimal level of anxiety)

cblB, adenosyl-cobalamin B; CI, confidence interval; IQ, intelligence quotient; LT, liver transplantation; MMA, methylmalonic acidemia; mut^0, complete methylmalonyl-coenzyme A mutase deficiency; mut$^-$, partial methylmalonyl-coenzyme A mutase deficiency; PedsQL, Pediatric Quality of Life Inventory

Table 2. Hospital admissions and length of stay related to MMA

Study	Population	Measurement	Value
Chu (2019)[11]	19 patients with MMA (mut^0, mut$^-$, cblB) and 2 patients with PA	Annual admission length: 1 year pre-LT	90.6 ± 52.8 days
		Annual admission length: 1 year post-LT	28.2 ± 20.4 days
		Annual admission length: 2 years post-LT	18.4 ± 14.4 days
		Annual admission length: 3 years post-LT	5.3 ± 14.3 days
		Annual admission length: 4 years post-LT	7.7 ± 9.2 days
		Annual admission length: 5 years post-LT	6.2 ± 4.7 days
Lin (2022)[12]	11 patients with MMA (10 mut^0 and 1 mut$^-$)	Hospital stay pre-LT	Mean: 78.8 ± 74.5 days
		Hospital stay post-LT	Mean: 7.4 ± 7.0 days
Pillai (2019)[13]	3 patients with MMA and 8 patients with PA who underwent LT	Number of hospitalizations to the ICU in the 6 months pre-LT, 0–6 months post-LT, and 6–12 months post-LT	Significant decrease in ICU admissions between pre-LT or 0–6 months post-LT, vs 6–12 months post-LT
		Number of hospitalizations to the general floor in the 6 months pre-LT, 0–6 months post-LT, and 6–12 months post-LT	Significant decrease in hospital admissions to the general floor between pre-LT or 0–6 months post-LT, vs 6–12 months post-LT
		Total number of hospitalizations in the 6 months pre-LT, 0–6 months post-LT, and 6–12 months post-LT	Significant decrease in total hospital admissions between pre-LT or 0–6 months post-LT, vs 6–12 months post-LT
McGuire (2008)[14]	Case report of a 5-year-old boy who underwent combined liver–kidney transplant for MMA mut^0	Qualitative description	Besides a single episode of iatrogenic decompensation, this case has not been hospitalized for metabolic acidosis since the transplantation, reflecting the beneficial effect of the combined kidney and liver transplantation

cblB, adenosyl-cobalamin B; ICU, intensive care unit; LT, liver transplantation; MMA, methylmalonic acidemia; mut^0, complete methylmalonyl-coenzyme A mutase deficiency; mut$^-$, partial methylmalonyl-coenzyme A mutase deficiency; PA, propionic acidemia

Conclusions

- Although very limited data are available, transplantation seems to decrease humanistic and economic burden of severe MMA
- The results clearly indicate that both areas are under-researched, and the scarcity of studies currently limits the possibility of a detailed description of the disease burden in the context of transplantation

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Disclosures

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