

## ORIGINAL ARTICLE



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# The impact of liver transplantation on health-related quality of life in (acute) intoxication-type inborn errors of metabolism

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## Abstract

Organic acidurias (OAs), urea-cycle disorders (UCDs), and maple syrup urine disease (MSUD) belong to the category of intoxication-type inborn errors of metabolism (IT-IEM). Liver transplantation (LTx) is increasingly utilized in IT-IEM. However, its impact has been mainly focused on clinical outcome measures and rarely on health-related quality of life (HRQoL). Aim of the study was to investigate the impact of LTx on HrQoL in IT-IEMs. This single center prospective study involved 32 patients (15 OA, 11 UCD, 6 MSUD; median age at LTx 3.0 years, range 0.8–26.0). HRQoL was assessed pre/post transplantation by PedsQL-General Module 4.0 and by MetabQoL 1.0, a specifically designed tool for IT-IEM. PedsQL highlighted significant post-LTx improvements in total and physical functioning in both patients' and parents' scores. According to age at transplantation ( $\leq 3$  vs.  $> 3$  years), younger patients showed higher post-LTx scores on Physical ( $p = 0.03$ ), Social ( $p < 0.001$ ), and Total ( $p = 0.007$ ) functioning. MetabQoL confirmed significant post-LTx changes in Total and Physical functioning in both patients and parents scores ( $p \leq 0.009$ ). Differently from PedsQL, MetabQoL Mental (patients  $p = 0.013$ , parents  $p = 0.03$ ) and Social scores (patients  $p = 0.02$ , parents  $p = 0.012$ ) were significantly higher post-LTx. Significant improvements ( $p = 0.001$ – $0.04$ ) were also detected both in self- and proxy-reports for almost all MetabQoL subscales. This study shows the importance of assessing the impact of transplantation on HrQoL, a meaningful outcome reflecting patients' wellbeing. LTx is associated with significant improvements of HrQoL in both self- and parent-reports. The comparison between PedsQL-GM and MetabQoL highlighted that MetabQoL demonstrated higher sensitivity in the assessment of disease-specific domains than the generic PedsQL tool.

**Abbreviations:** HrQoL, health-related quality of life; IT-IEM, intoxication-type inborn errors of metabolism; LTx, liver transplantation; MSUD, maple syrup urine disease; OA, organic acidurias; UCD, urea-cycle disorders.

**KEYWORDS**

health-related quality of life, intoxication-type inborn errors of metabolism, maple syrup urine disease, MetabQoL, organic acidurias, PedsQL, urea-cycle disorders

## 1 | INTRODUCTION

Organic acidurias (OAs), urea-cycle disorders (UCDs), and maple syrup urine disease (MSUD) belong to the category of intoxication-type inborn errors of metabolism (IT-IEM). The main treatment for these diseases is a life-long protein-restricted diet combined with the supplementation of special amino acid mixtures, which substantially limits the consumption of natural foods.<sup>1–3</sup> Moreover, in OAs and UCDs chronic administration of pharmacotherapy is also needed.<sup>1,2</sup> Despite adequate treatment adherence, patients are at permanent risk of acute events of metabolic decompensation causing potentially irreversible neurological damage, or even death. Moreover, neurodevelopmental impairment and behavioral problems may also occur due to the progression of chronic central nervous system alterations.<sup>4</sup> Regular highly specialized medical follow-up visits are essential for the long-term management and prolonged or repeated hospitalizations may often become necessary in phases of treatment readjustment or deterioration. Taken together, all these factors considerably contribute to the high disease burden faced by patients and their families and may consequently result in an impaired health-related quality of life (HrQoL). HrQoL is a multidimensional construct, which includes the impact of disease on patients' physical, psychological, and social functioning.<sup>5,6</sup> Studies investigating HrQoL in IT-IEM are still scarce and often have methodological limitations, such as the small sample size, the use of generic assessment tools, or the use of questionnaire based exclusively on parent or on self-reports.<sup>7,8</sup> To overcome some of these limitations, a recent analysis involving a large sample of pediatric IT-IEM patients from six international reference metabolic centers was conducted. The study showed considerably impaired HrQoL and identified the strict diet regimen as a risk factor for lower scores in HrQoL questionnaires.<sup>7</sup> Research to ameliorate treatment and care in the field of IT-IEM has resulted in improved long-term outcome and patients' survival. Therefore, the improvement of the HrQoL of patients and families becomes an increasingly fundamental focus of comprehensive healthcare.<sup>8,9</sup> Beside dietary treatment and pharmacotherapy, liver transplantation (LTx) is increasingly used in IT-IEM<sup>10,11</sup> to reduce the risk of metabolic decompensation, prevent long-term complications, diminish disease burden, and improve patient's HrQoL.<sup>12</sup> However, although LTx in

IT-IEM has become a more frequent therapeutical option,<sup>10,13</sup> to date little is known about its impact on HrQoL at follow-up. Improvements in HrQoL post transplantation have been reported, however outcomes were mainly assessed by generic tools,<sup>14</sup> qualitative analysis and as physician's descriptions<sup>13,15</sup> or assessed by unvalidated questionnaires.<sup>12</sup> Moreover, the limited data from quantitative studies often originate from heterogeneous patient cohorts with different diseases, in which IT-IEMs are under-represented,<sup>16–19</sup> highlighting the need of more structured evaluations.

Aim of our study was to quantify the impact of LTx in HrQoL in a cohort of 32 IT-IEM patients treated by LTx at the Bambino Gesù Children's Hospital, including both parents' and patients' perspectives. To obtain a broader view of the changes induced by transplantation, HrQoL was assessed with the generic PedsQL<sup>6</sup> and with the disease specific MetabQoL,<sup>20</sup> a tool recently developed to evaluate HrQoL in IT-IEM patients, and so far never utilized for transplant-related evaluations.

## 2 | METHODS

### 2.1 | Sample and procedure

Thirty-two study participants undergoing LTx were recruited from 36 IT-IEM patients listed for LTx regularly followed or referred to the Division of Metabolism of Bambino Gesù Children's Hospital in Rome (Italy). Eligible participants for the study were parents/caregivers of LTx candidates with IT-IEM and patients from age 7 years. To form the study group, parents and patients were enrolled from 2011 to 2021. One patient with propionic acidemia and severe cardiac disease died at the age of 17 years, 3 months after LTx.

The study was approved by the Bambino Gesù Children's Hospital ethical committee (2937\_OPBG-2022).

Data were collected by the psychologist of the patient's healthcare team, after explaining to patients and their families the purpose of the study and the content of the questionnaires used. To reduce hospital admissions, pre- and post-LTx evaluations were carried out during regular medical follow-up visits. Assessment was completed before the inclusion in the transplant list and repeated every 6 months until LTx. Post-LTx assessment were completed at least 2 months post-LTx and repeated

every 6 months. To the aim of our study, we considered at pre-LTx assessment the closest evaluation to LTx and at post-LTx the latest available follow-up data.

## 2.2 | Outcome measures

HRQoL was assessed pre- and post-LTx by the generic PedsQL-GM4.0<sup>6</sup> and by the IT-IEM-specific MetabQoL 1.0.<sup>20</sup>

## 2.3 | PedsQL

Parents completed the PedsQL-GM–parent version, a validated instrument, available in Italian, widely used to detect the perception of the impact of disease and its treatment on patient's HrQoL, assessing functioning in Physical, Emotional, Social, and School/Work domains.<sup>6</sup> Scores range from 0 to 100, with higher scores indicating a better HrQoL.<sup>6</sup> There are several versions of the tool, covering a wide age range from the first months of life to adulthood. To ensure the homogeneity and comparability of the results within the sample used, only the domains common to each age were considered (Physical, Emotional, and Social). Patients completed a self-report version of the PedsQL that replicates the parent-report version, with sentences adjustments to reduce the complexity and adapt the questionnaire to the respondent age.

## 2.4 | MetabQoL

MetabQoL is a newly developed IT-IEM-specific tool, designed to assess HrQoL.<sup>8,20</sup> It evaluates the impact of IT-IEM on the patient's life both from his point of view and from parents' perspective. Different versions are available to adapt to the patient's age and type of self or parent-report. Patients completed a self-report version of the MetabQoL that replicates the parent-report version, with sentences adjustments to reduce the complexity and adapt the questionnaire to the respondent age. Outcome data can be summarized to obtain a HrQoL total score and, similarly to PedsQL, the best HrQoL was indicated by values of 100, worst by 0. In the MetabQoL version created for patients older than 7 years, item scores can be also aggregated to scale scores: Physical, Mental (corresponding to PedsQL Emotional scale), and Social. Further information can be obtained through 7 subscales: Diet, Drugs, Hospitalization, Living with the disease (belonging to Physical domain), Emotions about the disease (belonging to Mental Domain), Social relations, Stigma (belonging to Social Domain), and an additional subscale, not included in the total score, assessing disease severity during the last

12 month. For the present study, the questionnaire was translated into Italian by a professional translator supervised by a metabolic physician of the center.

## 3 | STATISTICAL ANALYSIS

All statistical analyses were performed using STATA, Statistical Software: Release 13 (StataCorp LP, College Station, TX). The statistical significance was set at  $p < 0.05$ . The Shapiro–Wilk test was used to assess the normality of the data. Categorical variables were summarized by absolute frequencies and percentages, and continuous variables by median and interquartile range (IQR). To determine statistical differences between pre-LTx and post-LTx for PedsQL and MetabQoL, Wilcoxon signed rank test was used. A Kruskal–Wallis test was used to determine the significance of differences between groups. Mann–Whitney test was used to compare patients according to the two age groups. Pearson correlation coefficients were calculated in a subgroup of 10 parent–child dyads to analyze self and parent-report relations.

## 4 | RESULTS

This single-center study involved parents of 32 LTx recipients with IT-IEM, between 2011 and 2021 (Table 1): 15 OAs, 11 UCDs, and 6 MSUD. Three out of 6 patients with methylmalonic aciduria were treated by combined liver and kidney transplantation. Median age at transplantation was 3 years (range, 8 months to 26 years).

Assessment was completed pre-LTx (time from pre-test to LTx: median 3 months, range: 0–11 months) and post-LTx (time from LTx to post-test; median 2.5 years, range: 0.2–10 years).

Ten out of 32 patients (6 OA, 3 UCD, 1 MSUD; median age at LTx: 16.5 years, range: 9–26 years) (Table S1) were able to independently complete the self-report version of the questionnaires administered to their parents (parent–child dyads). Assessment was completed pre-LTx (time from pre-test to LTx: median 4 months, range: 0–11 months) and post-LTx (time from LTx to post-test; median 1.5 years, range: 0.2–9 years).

### 4.1 | PedsQL

#### 4.1.1 | HrQoL of children reported by parents

A Wilcoxon signed rank test showed significant post-LTx improvement of Total, Physical, and Emotional

TABLE 1 Participants characteristics ( $N = 32$ ).

	Median	Range
Age at LTx, years	3	0.8–26
Months between pre-LTx assessment and LTx	3	0–11
Years between LTx and post-LTx assessment	2.5	0.2–10
<b>Sex</b>	<b>N</b>	<b>%</b>
Male	19	59
Female	13	41
<b>Diagnosis</b>	<b>N</b>	<b>%</b>
Organic acidurias (OA)	15	47
Age at LTx, years	4	0.8–26
Propionic aciduria (PA)	9	28
Methylmalonic aciduria (MMA)	6	19
Urea cycle disorders (UCD)	11	34
Age at LTx, years	4	1–11
Carbamoyl phosphate synthetase I deficiency (CPS)	3	9
Ornithine transcarbamylase deficiency (OTC)	2	6
Argininosuccinic aciduria (ASA)	6	19
Maple syrup urine disease (MSUD)	6	19
Age at LTx, years	2	0.9–16

functioning Scales compared with pre-LTx. Post-LTx improvement of Social Scales was not statistically significant (Table 2).

To detect an at-risk status for impaired HrQoL, one standard deviation below the population mean was defined as meaningful cut-off point score.<sup>21</sup> Total scores pre-LTx showed that 41% of patients were in the “at-risk status for impaired HrQoL” compared with only 19% at post-LTx assessment. Regarding the specific domains, Physical functioning was the most impaired pre-LTx subscale and showed the highest post-LTx improvement (44% vs. 13% of patients below the cut-off). Also in Emotional and Social functioning subscales the percentage of patients below the cut-off decreased from pre to post-LTx (respectively, 25% vs. 16%; 34% vs. 28%).

The subgroup analyses of the three disease groups (OA, UCD, MSUD), showed significant post-LTx improvement of Total Score in all subgroups. Physical functioning improved significantly in OA and UCD but not in MSUD (Table 2). No statistically significant difference between the three disease groups were detected by Kruskal–Wallis test in both pre- (Total score  $p = 0.319$ ; Physical functioning  $p = 0.177$ ; Emotional functioning  $p = 0.601$ ; Social functioning  $p = 0.302$ ) and post-LTx

TABLE 2 Pre- and post-LTx PedsQL and MetabQoL parent-report scores.

Patients	N	PedsQL				MetabQoL			
		Physical functioning		Emotional functioning		Social functioning		Total score	
		Median (IQR)	p value	Median (IQR)	p value	Median (IQR)	p value	Median (IQR)	p value
Total sample	32	72.0 (52.8, 80.0)	<0.001	84.0 (40.1, 81.8)	<0.001	72.5 (63.8, 85.6)	0.02	52.3 (40.0, 60.8)	<0.001
OA	15	57.0 (50.0, 73.5)	0.004	78.0 (69.0, 89.0)	0.001	65.0 (44.5, 87.5)	0.109	49.0 (37.5, 61.5)	<0.001
UCD	11	78.0 (52.5, 82.0)	0.011	84.0 (70.5, 90.0)	0.006	75.0 (62.5, 92.5)	0.283	52.5 (45.0, 58.8)	0.006
MSUD	6	74.5 (72.5, 76.5)	0.03	89.5 (84.3, 96.3)	0.281	92.5 (58.8, 100)	0.400	52.5 (48.4, 63.8)	0.03
≤3 years at LTx	17	75.0 (55.0, 83.0)	<0.001	87.0 (80.0, 92.0)	0.002	85.0 (65.0, 90.0)	0.003	52.5 (37.5, 60.0)	>0.001
>3 years at LTx	15	57.0 (48.0, 76.5)	0.007	75.0 (59.0, 80.0)	0.002	75.0 (55.0, 90.0)	0.833	49.0 (45.0, 64.0)	0.001

Abbreviations: IQR, interquartile range; MSUD, maple syrup urine disease; OA, organic acidurias; UCD, urea cycle disorders.

(Total score  $p = 0.281$ ; Physical functioning  $p = 0.426$ ; Emotional functioning  $p = 0.744$ ; Social functioning  $p = 0.172$ ) comparison.

According to the median-split method, we divided the patients' sample into two groups based on the median age at transplantation ( $\leq 3$  and  $> 3$  years). As reported in Table 2, Total and Physical functioning scores were significantly improved post-LTx in both age categories, while Emotional functioning was significantly improved by LTx only in younger patients. No significant improvements were recorded in Social functioning scale in both age categories.

Between group comparisons using Mann–Whitney test showed, at pre-LTx significantly lower Social functioning scores in patients  $> 3$  years versus patients  $\leq 3$  years (55.0 vs. 85.0,  $p = 0.012$ ). No other significant differences were recorded in Total score (57.0 vs. 75.0,  $p = 0.104$ ), Physical functioning (62.5 vs. 69.0,  $p = 0.364$ ), and Emotional functioning (70.0 vs. 79.0,  $p = 0.895$ ) subscales. At post-LTx evaluation, the highest scores were recorded in younger patients ( $\leq 3$  years): Total score (87.0 vs. 71.0,  $p = 0.007$ ), Physical (94.0 vs. 75.0,  $p = 0.03$ ), and Social functioning (90.0 vs. 60.0,  $p < 0.001$ ), with no significant difference in Emotional functioning scale (85.0 vs. 75.0,  $p = 0.123$ ).

#### 4.1.2 | Self-reported HrQoL of children versus parent-report

Positive changes post-LTx in Total and Physical functioning were recorded for both patient- and parent-report, with no significant improvements in Emotional and Social functioning (Table 3).

According to meaningful PedsQL cut-off point scores,<sup>21</sup> 60% of patient reports showed an at-risk status for impaired HrQoL in the Total score at the pre-LTx evaluation, a percentage reduced to 20% at post-LTx. Regarding the specific domains, Physical functioning was the most impaired pre-LTx subscale with 80% of patients below the cut-off versus only 30% at post-LTx. Also in Emotional and Social functioning subscales the percentage of patients below the cut-off decreased from pre to post-LTx (respectively, 20% vs. 10%; 40% vs. 20%).

As for the reports of their parents, Total scores pre-LTx showed that 61% of patients were in the “at-risk status for impaired HrQoL” compared with 30% at post-LTx assessment. Also in Physical functioning the percentage of patients below the cut-off decreased from 60% at pre-LTx to 30% at post-LTx. Differently from what reported by their children, parents showed fewer positive changes at post-LTx in other subscales: Emotional functioning slightly worsened (30% vs. 40%) and Social domain remained below cut-off in 60% of patients as at pre-LTx.

TABLE 3 Pre- and post-LTx PedsQL and MetabQoL self and parent-report scores of 10 parent–child dyads.

	Parent report											
	PedsQL						MetabQoL					
	Total score Median (IQR)	Physical Median (IQR)	Emotional Median (IQR)	Social Median (IQR)	Mental Median (IQR)	Physical Median (IQR)	Total score Median (IQR)	Physical Median (IQR)	Emotional Median (IQR)	Social Median (IQR)	Mental Median (IQR)	Physical Median (IQR)
Pre	67.3 (60.8, 71.5)	62.5 (50.0, 70.5)	70.0 (66.3, 78.8)	70.0 (50.0, 82.5)	56.0 (39.6, 61.4)	56.3 (42.5, 71.3)	54.8 (47.5, 70.8)	54.8 (47.5, 70.8)	70.0 (62.5, 75.0)	50.0 (41.3, 68.8)	54.0 (46.0, 65.9)	58.0 (51.0, 79.0)
Post	83.3 (72.3, 86.8)	84.3 (75.8, 92.4)	80.0 (80.0, 83.8)	80.0 (70.0, 88.8)	75.0 (75.0, 89.8)	75.0 (55.5, 83.3)	70.0 (59.3, 75.3)	72.0 (69.5, 82.5)	72.5 (48.8, 87.5)	52.5 (42.5, 68.8)	71.0 (62.5, 82.0)	81.0 (74.5, 89.1)
<i>p</i> value	0.05	0.02	0.152	0.312	0.013	0.009	0.02	0.009	1.000	0.490	0.03	0.009

As regards parent-child agreement, at pre-LTx evaluation the Pearson correlation coefficient showed a statistically significant strong relationship between patients and parents reports in Physical functioning ( $r = 0.681$ ,  $p = 0.030$ ). No significant patient-parents reports correlations were detected in Total score ( $r = 0.540$ ,  $p = 0.107$ ), Emotional functioning ( $r = 0.609$ ,  $p = 0.061$ ), and Social functioning ( $r = 0.206$ ,  $p = 0.568$ ) scales. At post-LTx, a strong correlation was observed in Total score ( $r = 0.804$ ,  $p = 0.005$ ), Physical ( $r = 0.792$ ,  $p = 0.006$ ), and Emotional functioning ( $r = 0.821$ ,  $p = 0.004$ ). No significant correlation was detected in Social functioning scale ( $r = 0.387$ ,  $p = 0.270$ ).

## 4.2 | MetabQoL

### 4.2.1 | HrQoL of children reported by parents

The MetabQoL Total score significantly improved after LTx (Table 2). The analysis of Total scores within the three disease sub-groups highlighted a better post-LTx HrQoL in each sub-group (Table 2). No statistically significant difference between the three sub-groups (OA, UCD, MSUD) were detected by Kruskal Wallis test in both pre- (Total score  $p = 0.772$ ) and post-LTx (Total score  $p = 0.099$ ) comparison. The analysis of patients' sample in the two groups according to median age at transplantation, showed a significantly improved Total score in both age groups (Table 2). Between group comparisons using Mann-Whitney test showed no significant differences between the two groups ( $\leq 3$  years and  $> 3$  years) in both pre- ( $p = 0.570$ ) and post-LTx ( $p = 0.374$ ) Total scores.

### 4.2.2 | Self-reported HrQoL of children versus parent-report

MetabQoL highlighted significantly improved post-LTx scores, for both self- and parent-report, in all scales (Table 3).

Moreover, patients and their parents reported significantly positive changes ( $p$  range 0.001–0.037) in most subscales: Diet, Living with a disease, Emotion about the disease, Stigma, and Disease severity (Figure 1). Although showing a positive post-LTx trend, Social relation in patient- and Drugs subscales in parent-reports did not reach statistical significance. No significant changes in the Hospitalization subscale both by patient- and parent-reports were recorded.

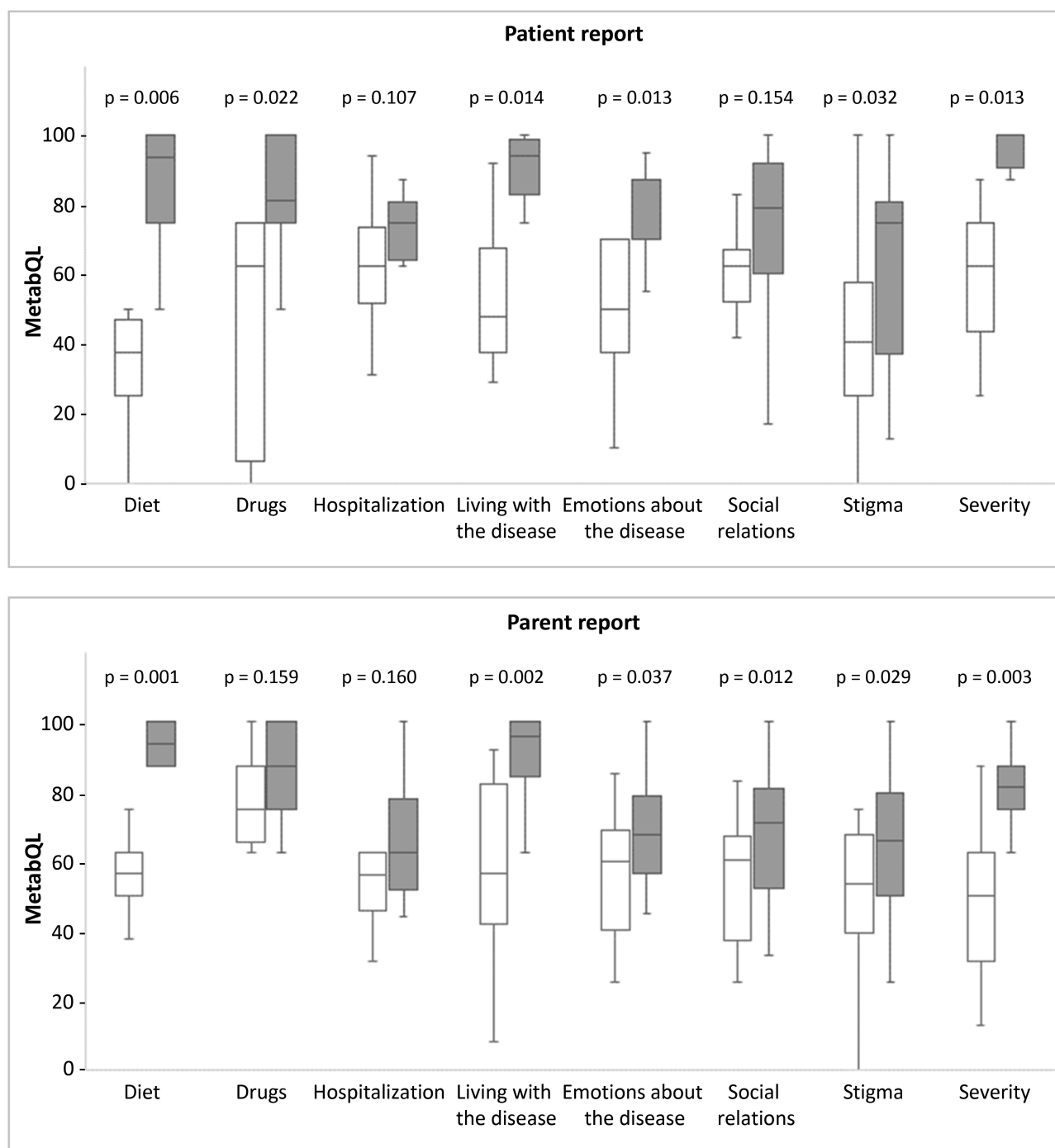
As regards parent-child agreement, at pre-LTx evaluation, no significant correlations were detected by Pearson correlation coefficients in Total score ( $r = 0.256$ ,  $p = 0.476$ ), Physical ( $r = 0.189$ ,  $p = 0.601$ ), Mental ( $r = 0.145$ ,  $p = 0.690$ ), and Social ( $r = 0.461$ ,  $p = 0.180$ ) scales. At post-LTx, a strong correlation was observed in Mental scale ( $r = 0.870$ ,  $p = 0.001$ ), while no significant correlations were detected in Total score ( $r = 0.442$ ,  $p = 0.201$ ), Physical ( $r = 0.014$ ,  $p = 0.969$ ), and Social ( $r = 0.427$ ,  $p = 0.218$ ) scales. Compared with PedsQL, MetabQoL raw scores showed smallest differences between patients and their parents' reports.

## 5 | DISCUSSION

Improving HrQoL is one of the major aims of liver transplantation in pediatric patients with IT-IEM.<sup>12</sup> However, to date, little is known about the impact of transplantation on these patients' HrQoL at follow-up. Our study aimed to provide an in depth understanding on this topic by evaluating the impact of LTx on HrQoL, including both the generic PedsQL and the IT-IEM specific MetabQoL tools. The design of this work did not include the evaluation of post-LTx long-term complication.

In our study, all baseline (i.e., pre-LTx) PedsQL scores were lower than those reported by Bösch et al.<sup>7</sup> in a cohort of non-transplanted IT-IEM patients, and lowest when compared with chronically and acutely ill children affected by other diseases than IT-IEM.<sup>6</sup> Similarly, also the baseline evaluation by MetabQoL indicated lower scores in both patient and parent assessments.<sup>20</sup> Compared with pre-LTx, post-LTx assessment showed significant HrQoL improvements with both tools, regardless of individual disease categories. Our data are consistent with the improved post-LTx HrQoL in a cohort of IT-IEM patients qualitatively evaluated by an ad-hoc designed questionnaire.<sup>12</sup>

The ideal timing of liver transplantation is a main and debated issue in pediatric IT-IEM patients. Recent data reported that in Europe 6% of OA and UCD patients were transplanted before 1 year of age, while in the United States this percentage was to 33%.<sup>12</sup> In general, existing studies have shown that early liver transplantation improves long term neurological and developmental outcome, prevents morbidity from recurrent metabolic decompensation and relieves patients from restrictive diets.<sup>13,15,22</sup> In our sample, both age-related groups reported a higher post transplantation HrQoL but patients transplanted before the age of 3 years showed more improvements than those transplanted later. Thus, early transplantation in IT-IEM patients should be considered as the preferable option.<sup>23,24</sup>



**FIGURE 1** MetabQoL subscales assessment pre-LTx, white bars, and post-LTx, gray bars, in patient (top panel) and in parent (bottom panel) reports. Diet, Drugs, Hospitalization, and Living with the disease subscales belong to Physical domain; Emotions about the disease subscale belongs to Mental domain; Social relations and Stigma subscales belong to Social domain.

Regarding the specific HrQoL domains, Physical functioning scores assessed by PedsQL showed the greatest impairment pre-LTx and the most improvement post-LTx in both patients- and parent-reports. The impact of transplantation on Emotional and Social domains was also positive with differences between parents' and patients' reports and between earlier and later

transplanted individuals. A possible explanation could be that positive changes in the Physical domain are easier recognized and quantifiable in shorter post-operative intervals than Social and Mental functioning.<sup>20,25</sup> Another variable could be the specifics of HrQoL evaluation in a pediatric cohort. At the time of transplantation, the majority of patients were too young to answer a

questionnaire, so their HrQoL was assessed by parents' report. It is known that parents' proxy scorings are influenced by factors related to parents' own HrQoL.<sup>26,27</sup> This impact might be even stronger in IT-IEMs, in which the high complexity of diseases and treatment combined with an often unpredictable disease courses may have a significant negative impact on parents' experience and HrQoL.<sup>28</sup> Since disease-specific tools show higher responsiveness to HrQoL changes over time and are more sensitive,<sup>4,29</sup> for a better understanding of these aspects, we utilized in our study the MetabQoL, specifically designed for IT-IEM category.<sup>20</sup>

Assessment by MetabQoL confirmed a significant post-LTx improvement in the Physical Domain. Unlike PedsQL-GM, MetabQoL allowed to evaluate this dimension on IT-IEM patients more specifically by referring to characteristic symptoms and treatments. The MetabQoL considers the restrictive diet and the taste of special low-protein food, the tightly scheduled intake of food and drugs, need of tube feeding, frequent nausea/vomiting, limited exercise tolerance, and the risk of life-threatening metabolic decompensations that may cause constant fear of crises and potential neurological sequelae.<sup>25,30–32</sup> From our patients' perspective, liver transplantation had a significant impact on their HrQoL mainly through a liberalized dietary regimen, reduced pharmacotherapy burden, less physical complaints, reduced risk of metabolic crises and tube feeding. Parents confirmed the point of view of their children, reporting positive changes in HrQoL as reported in other studies.<sup>11,14,33,34</sup> Interestingly no significant changes were reported in the "hospitalization" dimension, both by patients and parents. This likely reflects the need of post-LTx hospitalization (also in ICU) and, after discharge, of frequent scheduled evaluations and procedures, especially in the early post-operative period. Hospital stays reduce leisure times and interfere with everyday life, blood sampling and other necessary invasive procedures (e.g., liver biopsy) can be very stressful and frightening.<sup>8</sup> Moreover, fear of liver rejection and the threat of re-transplantation may intensify the emotional burden. Taken together, these issues highlight that a tailored psychological support is necessary to help patients and their parents to develop coping strategies to manage stress and anxiety better.<sup>35,36</sup>

Regarding Emotional and Social functioning subscales, no significant changes were recorded both by patient and parents PedsQL reports. In particular, from the parents' perspective the majority of patients remained within the at-risk status for impaired HrQoL also after transplantation. In contrast, the MetabQoL Mental dimension which evaluates patient's emotions about their disease (e.g., concern for the future), showed significant improvements post-LTx in both self- and parent-reports.

Similarly, also the Social dimension which analyses the impact of the disease on relationship with peers and family members and on social stigma showed significant improvements. Nevertheless, post-LTx scores on the stigma dimension were still the lowest when compared with other subscales both by parents and patients' reports. Experiences of social exclusion and the difficulty to explain the clinical complexity of a rare disease in a simple and comprehensive way remains a major concern from patients' and parents' perspective.<sup>25</sup>

The partial agreement between parents and patients' reports in our study is not surprising. Previous studies<sup>26,27,37,38</sup> showed that in families with a child with a chronic disease, parent-child agreement is higher for visible characteristics evaluated by the Physical domain than for non-visible characteristics evaluated with Emotional or Social subscales. Furthermore, when patients grow older they could experience more difficulties to verbalize their feelings, or choose not to share their concerns and personal burdens with their caregiver.<sup>39</sup> Our results are consistent with these findings, and the better parent-child agreement—with the smallest differences in raw scores—by MetabQoL, could be explained by the greater relevance and sensitivity of this tool which utilizes information collected by focus group of parents and patients with IT-IEMs, interviewed as content experts.<sup>25</sup>

## 6 | CONCLUSION

Aim of the study was to investigate the impact of LTx on HrQoL in IT-IEMs. Results showed that patients' HrQoL significantly improved post-LTx, in both self- and parent-reports.

The combined use of two tools—the generic PedsQL and the IT-IEM-specific MetabQoL—allowed to perform a complete assessment of patients' HrQoL and highlighted that MetabQoL added specific disease-related content. Our results support the importance to consider HrQoL evaluation as a meaningful LTx outcome and encourage to include this aspect into transplant decision making, as a parameter and indication for transplantation itself, as recently recommended by the European Association for the Study of the Liver.<sup>40</sup>

Lastly, although the present study clearly demonstrates a positive impact of LTx in improving HrQoL, families should be informed that after LTx patients may be not eligible for novel gene-related therapies which are fast arriving for those conditions.

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## CONFLICT OF INTEREST STATEMENT

All authors state that they have no competing interests to declare.

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## SUPPORTING INFORMATION

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

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