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Research paper

Outcomes of adults who received liver transplant as young children

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ABSTRACT

Background: Patient and graft survival 20-years after pediatric liver transplantation (pLT) are excellent. In children, attainment of normal growth, education and social adaptation to be an independent adult are equally important. This is particularly relevant for children who receive liver transplant at a young age, where infantile-onset liver disease, surgery and immunosuppression can adversely affect growth and neuro-development. The aim of this study was to evaluate the long-term physical and psychosocial outcomes of pLT recipients with normal graft function. We coin the term 'meaningful survival'.

Methods: We performed a cross-sectional study of pLT recipients who received transplants between 1985 and 2004. A 20-year evaluation of physical health (growth, renal function), mental wellbeing and social outcomes (substance abuse, adherence, education, employment) was performed. All patients included were considered to have normal graft function.

Findings: Eighty-four patients met study criteria. Median age at transplantation was 1.3 years (IQR 0·7−3·3 years), with median duration of follow-up of 20.2 years (18·0−23·5). At median of 20-years, 19 patients (23%) had chronic renal dysfunction and 3 patients (4%) had a BMI of >30 (mean 20·4). Evaluation of long-term psychosocial outcomes demonstrated 22 patients (26%) with mental health disorders. Substance abuse was lower than national average. 62 patients (74%) were in education, employment or training. Overall, only 26% of our cohort achieved a composite outcome of 'meaningful survival'.

Interpretation: This is the largest reported long-term study of biopsychosocial outcomes of pLT recipients with normal liver biochemistry, with follow-up upon completion of physical growth and senior school education. Importantly, despite normal liver function, many patients did not demonstrate 'meaningful survival'. We must refocus our efforts towards better understanding the long-term outcomes of children. A 'meaningful survival' rather than mere survival should be our goal.

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1. Introduction

Pediatric liver transplantation (pLT) is the standard of care for children with end stage liver disease and liver-based metabolic defects. Patient survival at 20 years is >80% [1]. As our survival rates consistently improve into adulthood, it is important that we ensure not only physical wellbeing but also preserve mental health, school performance and ultimately employment, so post-transplant recipients are able to lead a 'meaningful' and socially inclusive life [2]. The 'meaningful survival' we should strive for our pLT recipients is one where recipients are in a state of reasonable physical, mental and social wellbeing, and not merely the absence of disease.

We should be mindful that long-term complications might become more evident as patient survival approaches over 20 years. Some of this is possibly secondary to the early post-transplant period, whilst some are cumulative side effects of immunosuppression and sub-optimal adherence to treatment [3]. Individual genetic make-up and background health can affect long-term outcomes as well [4].

Research in context

Evidence before this study

A search of peer-reviewed papers on PubMed, ScienceDirect and Google Scholar using the keywords "liver transplant", "pediatric", "long-term", "psychosocial", "physical" and similar terms up to May 1, 2021, revealed that the question of long-term biopsychosocial outcomes after liver transplantation in children still remains one that needs answering. Whilst a number of papers have recently addressed 20-year pediatric liver transplant survivors, very few have focused on the physical and psychosocial outcomes of these survivors.

Added value of this study

We performed a study of long-term outcomes of pediatric liver transplant recipients. A 20-year cross-sectional evaluation of their physical health, mental wellbeing and social outcomes was performed in a cohort of patients with normal graft function. Some of the highlights of our findings include: (1) 23% with chronic renal dysfunction, (2) 19% with depression and anxiety, (3) 26% who were not in education or employment and (4) 13% with issues of substance abuse. We coin the term "meaningful survival" and show that only 26% of our cohort achieved a composite profile of meaningful survival.

Implications of all the available evidence

This study is the first to show, in a relatively large cohort of patients, that good graft function post-transplantation does not preclude the significant long-term psychosocial and physical impact of transplantation. Despite favorable survival outcomes, only a limited number of recipients achieved an overall composite profile of "meaningful survival". The onus is on us, as clinicians, to improve our understanding of these complications, through earlier detection and collaborative multi-center efforts.

End-organ damage is an important aspect to consider as patient survival improves. Renal disease tends to be the main cause of morbidity and mortality after liver transplantation in adults [5]. The long-term impact of numerous low-grade, sustained insults including use of different immunosuppressants such as calcineurin-inhibitors has a significant effect on renal health in the pLT population [6].

Liver transplantation also has a profound impact on the psychological status of the recipient [7]. Young adults, who undergo liver transplantation in childhood, are faced with multiple challenges compared to their peers. The state of chronic physical illness present from a young age may lead to a distorted psychosocial experience of normality and perception of quality of life [8,9]

The long-term functional outcome of these children is increasingly more important. Studies have shown that children who undergo liver transplantation tend to show low average or abnormal scores on cognitive and behavioral tests [10] The child's neurodevelopment is likely affected by the underlying disease and long waitlist time, but transplantation does not always correct this impairment [11]. Alongside this, the poor health-related quality of life and prevalence of mental health disorders can lead to an ongoing burden of disease despite transplantation [1].

The United States Society of Pediatric Liver Transplantation (SPLIT) registry evaluated the health status of children alive at 10-years post-liver transplantation [12]. 167 survivors were examined with only 32% achieving an "ideal profile" which was defined by first allograft, stable monotherapy immunosuppression, adequate growth and absence of secondary side effects of immunosuppression. Growth was affected in 23% of patients, whilst 9% had developed Stage 2

chronic kidney disease. Patients had a lower quality of life score, with 14% reporting a generic health-related quality of life value of >2 standard deviations below that of a matched health population.

Whilst long-term outcomes may vary across different geographical locations, the general themes remain the same [13,14] These long-term issues include graft disease, side effects of immunosuppression, poor growth and metabolic syndrome, and the psychosocial impact of transplantation as they transition to adult care. Few reports have addressed 20-year pLT survivors, and even fewer have focused on the biopsychosocial outcomes of these survivors [13,15,16]. The aim of this study therefore is to assess the renal function, growth and psychosocial outcomes including mental health, education and employment, substance abuse and adherence in a cohort of children with a median follow-up of 20 years post-transplantation.

2. Methods

A single-center study, based at King's College London, United Kingdom was performed to evaluate 20-year pLT survivors. The study group consisted of patients who underwent pLT under the age of five, between 1985 and 2004 and survived up to at least 10 years post-transplantation with normal liver biochemistry. We chose this subset of patients with normal graft function at 10 years, to demonstrate the impact of transplantation on the psychological outcomes, growth and end-organ health of these recipients a further 10 years on.

Data was entered into a centralized database on a password-encrypted computer. Data collection of pre-transplant demographics included indications for transplant, age of recipient at liver transplantation, gender; post-transplant details explored included biliary complications, hepatic artery and portal vein complications and immunosuppression regimens used. Data was retrieved from medical records (both paper and electronic records). A structured proforma was used to aid systematic data collection. Study received institutional regulatory approval.

Behavioral and mental health data was obtained from the Integrating Mental and Physical Healthcare: Research, Training and Services (IMPARTS) questionnaire [17]. The IMPARTS questionnaire is a web-based screening system, routinely used by a multidisciplinary team in the transition clinics to collate data on mental health. As part of clinical practice, all young people who then screened positive for possible major depressive disorders or generalized anxiety disorders were offered referral to a clinical psychologist. The IMPARTS system comprises of customized measures for the adolescent population, including Patient Health Questionnaire (PHQ9) and Generalized Anxiety Questionnaire (GAD7) [17]. Data on behavioral and mental health issues was also extracted from electronic patient letters from the multidisciplinary team. Data on substance use, education and work status and adherence in the sample was retrieved from electronic patient notes and clinical letters. Heavy alcohol consumption was defined as drinking twice the recommended daily limit on the heaviest drinking day [18].

Data on renal function was obtained from laboratory tests. Values of cystatin-C and creatinine were documented in a pre-specified proforma. Estimated Glomerular Filtration Rate (eGFR) was calculated using the Creatinine-based "bedside Schwartz" equation and the Grubb formula for cystatin-C based equation. Both the formulas are validated by the National Kidney Foundation for pediatric patients. Weight and height measurements were collected from electronic health records as part of routine screening during follow-up. BMI was calculated as the weight (in kilograms) divided by the height squared (in meters).

We collected data on medication adherence based on ratings given by the attending physician after consultation with the patient. We defined good adherence as medications taken >80% of the time, moderate adherence as 50−80% of the time and poor adherence when medication was taken <50% of the time.
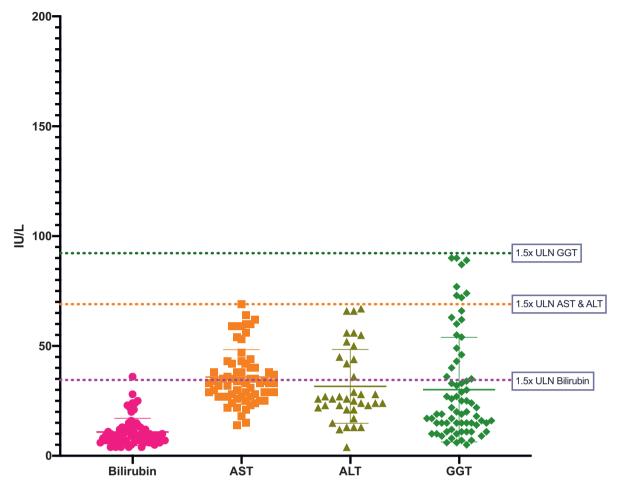
Fig. 1. Liver Biochemistry of each patient included in the study. All patients had normal graft function, with liver enzymes within 1.5x of the upper limit of normal. Vertical lines represent mean with standard deviation. Horizontal lines represent the 1.5x upper limit of normal for each measure.

Institutional ethical approval was granted by the National Research Ethics Committee (REC: 15-LO-1258). The Institutional Audit Committee also permitted data collection of the surgical and medical outcomes of the patients at this institution and review of our current practice compared to the national standards. As part of the IMPARTS study, we received research ethical approval for data collection on the psychosocial outcomes of patients through the screening interface (REC: 12-SC-0422).

Data was analyzed using SPSS Statistics software for MAC (IBM Analytics, Florida, USA) and Prism (GraphPad, LaJolla, California, USA). Demographic data was analyzed using descriptive statistics, including absolute numbers (n), percentages, mean, median, standard deviation (SD), and 25 and 75% interquartile range. Data was tested for normality using the Shapiro-Wilk test. Indications for transplant, pre and post-transplant complications, psychosocial outcomes and adherence were expressed as percentages of a whole. All variables assumed Gaussian distribution and t-tests were used to analyze difference between mean eGFR based on cystatin-C and creatinine values. Bland and Altman analysis was used to identify any systematic difference between the formulas used for calculation of eGFR. A two-tailed p-value of <0.05 was considered statistically significant.

4. Results

Between 1985 and 2004, 585 pediatric patients received liver transplants in our center. The study cohort was selected from patients who had liver transplant before five years of age and survived to 10 years with normal graft function (liver enzymes up to 1.5 times of the normal value) (Fig. 1) and consented for a liver biopsy as part of the study. Eighty-four patients met the study criteria and were included in this study.

The median age at transplantation was 1·3 years (IQR 0·7−3·3 years) and 44% (37/84) were female (Table 1). The median follow-up duration of these patients was 20·2 years (18·0−23·5). Of our patient cohort, 31% (26/84) are now in transition clinics and 50% (42/84) in adult follow-up clinics.

The most common indication for pLT was biliary atresia 51% (43/84) (Table 2). Results of main post-operative complications are shown in Table 3. We report 19% (16/84) vascular complications; 7% (6/84) with hepatic artery thrombosis and 12% (10/84) with portal vein thrombosis. Until 1998, all patients were commenced on cyclosporine and were converted to tacrolimus if they had an episode of allograft rejection. Thereafter, tacrolimus became the first line drug. 33% (28/84) of patients had acute rejection episodes and 21% (18/84) had chronic rejection (Table 3). Two deaths (2%) occurred in the late transplant phase (>10 years). Late graft loss occurred in 7% (6/84), 10 years or more after the initial transplantation.

This cohort demonstrated a mean serum creatinine of 59·6 μmol/L (SD 21·6), and mean cystatin-C of 0·9 mg/l (SD 0·6). When using

Table 1
Demographic of Study Population.

	n = 84
Age at Transplant (range)	1.3 (0.7−3.3)
Duration of follow-up (range)	20.2 (18.0−23.5)
Male/Female	47/37

Table 2
Indications for Transplantation.

Indications for Transplantation	Number, n	%
Biliary atresia	43	51.2
Progressive Familial Intrahepatic Cholestasis	7	8.3
Acute Hepatic Failure (Indeterminate Aetiology)	4	4.8
Autoimmune liver disease	4	4.8
Hepatoblastoma	4	4.8
Idiopathic Neonatal Hepatitis	1	1.2
Metabolic disorders	3	3.6
Alpha 1-antitrysin Deficiency	2	2.4
Delta 3-oxosteroid 5-beta Reductase deficiency	2	2.4
Wilson's Disease	14	16.7
Others		

Table 3
Post-operative Complications.

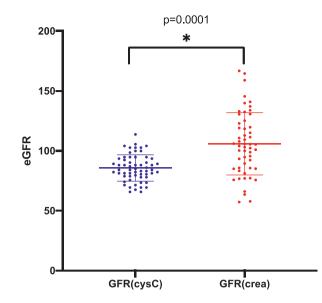| Post-operative Complications		
	Number	%
Biliary and Vascular Complications		
Biliary Complication	9	10.7
Hepatic Artery Thrombosis	6	7.1
Portal Vein Thrombosis	10	12.0
Medical Complications		
Acute Rejection	28	33.3
Chronic Rejection	18	21.4
Denovo hepatitis	13	15.5

Fig. 2. Renal function of the patients based on estimated glomerular filtration rate based on creatinine, eGFR(crea) and cystatin-C, eGFR(cysC). Significant difference in mean eGFR based on cystatin C compared to creatinine. Vertical lines represent mean with standard deviation. * Represents a *p*-value that is significant.

Cystatin C for eGFR calculation, renal impairment (defined as eGFR <90 ml/min/1.73m2) was more prevalent (23%, 19/84) compared to eGFR using serum creatinine (11%, 9/84) ($p = 0.0001$) (Fig. 2). All other patients had eGFR above 90 ml/min/1.73 m^2. None of the patients were on dialysis or received kidney transplants. Bland and

Altman analysis test agreement between the Schwartz formula for creatinine and Grubb formula for cystatin-C demonstrated sufficient bias with a mean difference of +25% with a trend in overestimation of the eGFR by Schwartz formula. Analysis using t-tests of the immuno-suppressive treatments for eGFR (cysC) showed no significant difference between cyclosporin based immunosuppresion versus patients with a tacrolimus based regime in our patient cohort ($p = 0.07$) as shown in Fig. 3.

We also evaluated body mass index (BMI) at median 20 years post-transplantation. The mean BMI was 20.4 (SD +/- 5.0). 8% (7/84) patients had a BMI of >25, three of whom had a BMI of >30. None of our patients were on antihypertensive medications. None of the patients had a diagnosis of diabetes mellitus.

Mental health disorders were common, occurring in 26% (22/84) (Fig. 4). Depression was seen in 12% (10/84) of patients, whilst
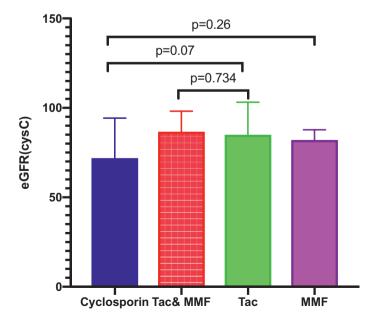

Fig. 3. Immunosuppressive treatments and impact on estimated glomerular filtration rate based on cystatin-C, eGFR (cysC). No significant difference found between different immunosuppresive regimes. Each bar represents mean, with vertical lines representing standard deviation.
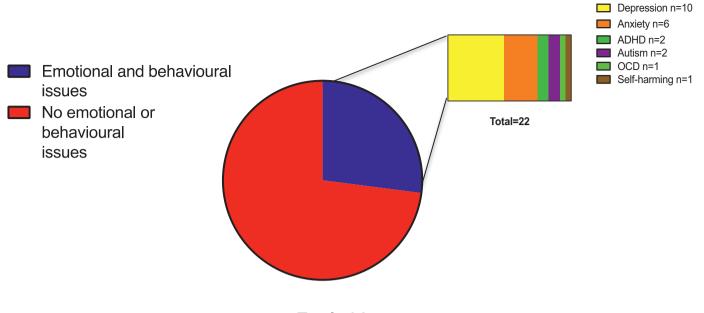
Fig. 4. Mental Health Outcomes in the study cohort. Twenty-two patients had mental health disorders.

anxiety including social anxiety and panic attacks occurred in 7% (6/84). Two patients had both depression and anxiety. Attention deficit hyperactivity disorder and autism were present in two patients respectively, whilst one patient suffered from obsessive-compulsive disorder and self-harming behavior. Learning difficulties were common, occurring in 13% (11/84); a further 11% (10/84) were unable to work or continue studies due to health concerns. In this cohort, 29% (24/84) were employed (full time/ part time), 38% (32/84) in higher education and 7% (6/84) were still in school.

Incidence of tobacco smoking was 10% (8/84) – lower than the UK national average of 17% for an age-matched cohort [19]. Excessive

alcohol consumption was 4% (3/84) - lower than the national average of 20% [18]. From our patient cohort, 7% (6/84) were married and 4% (3/84) had successful pregnancies. One patient had an early miscarriage at 10 weeks.

Adherence was reported to be good in 67% (56/84) followed by moderate adherence in 17% (14/84) and poor adherence in 8% (7/84) (Fig. 5).

In our patient cohort, only 26% (22/84) had a composite profile of "meaningful survival" (Table 4). This was characterized by survival to median of 20-years, presence of normal liver biochemistry, no renal dysfunction, normal BMI, no mental health disorder and were in education or employment and had good adherence of >80%.
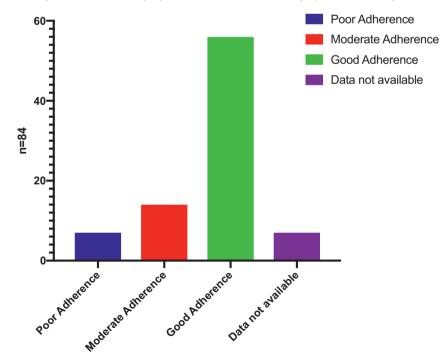

Fig. 5. Adherence rates in study cohort. Adherence was reported to be good in 56 patients (67%), followed by moderate adherence in 14 patients (17%) and poor adherence in 7 patients (8%).

Table 4
Composite Analysis Strategy Approach at 20-years.

Variable	Number of patients, n (%)
Survival to median 20-years	82 (97.6)
Normal renal function (according to Cystatin-C eGFR)	65 (77.4)
Normal BMI	77 (91.7)
No mental health disorder	62 (73.8)
In education or employment	62 (73.8)
Good adherence	56 (66.7)

5. Discussion

Advances in the field of pLT mean that short-term complications have decreased and survival rates have improved [20]. However, a correlate of this success is that long-term effects of transplantation are more evident as our pre-school age recipients approach over 20-years post-transplantation. This age group is especially important, as the first couple of years of life are crucial to a child's brain development for the formation of cognitive, social and emotional health [21]. The impact of severe disease, surgical intervention, anesthesia and medications on neurocognitive functioning and physical health at this age cannot be overstated [22,23]. In this study, we reviewed some of the long-term outcome metrics of pLT.

Chronic renal failure is an important long-term complication post-transplantation. The main contributors are nephrotoxic effects of the calcineurin inhibitors; namely cyclosporine and tacrolimus, as well as a primarily renal pathology of the underlying liver diagnosis and the use of nephrotoxic antibiotics. Several pediatric studies have shown rates of renal failure ranging from 0% to 32% [6,24,25]. This wide range is likely due to the individual immunosuppressive regimens and the different methods used to determine renal function in these studies. Most studies use a calculated eGFR based on serum creatinine, but these methods have been shown to be inaccurate and tend to overestimate renal function in children [26]. Cystatin-C has been increasingly used as an easy and reliable marker of renal function to determine deterioration of kidney function. Our center has shown good correlation between cystatin-C levels and measured eGFR, especially in children after liver transplantation in the short term [27]. We show a significant discrepancy of a cystatin C-based equation compared to creatinine-based equation in the calculation of eGFR and identification of patients with renal failure.

Our data comprises of a large 20-year follow-up study of pLT patients who received liver transplant before school age and these results are consistent with other published studies which report roughly 30% of patients with chronic renal failure >10 years post-liver transplant [6]. We demonstrate a prevalence of 23% of patients with renal dysfunction with standard immunosuppression protocols and therefore the need to closely monitor these children with a reliable method to determine eGFR.

Although we did not show significant difference between immunosuppressive protocols, the numbers in each cohort were small with only ten patients on cyclosporine-based regimes. Guidelines on how to modify immunosuppression drugs once renal dysfunction is

Table 5
20-year outcomes compared to national data (16−24 year olds).

Outcomes	20-years post-transplantation	National Data (16−24 year olds)
BMI >25	8.3%	37.0%
Anxiety and depression	19.1%	19.7%
Not in education or employment	26.2%	11.3%
Learning difficulties	13.1%	3.4%
Smoking	9.5%	16.8%
Heavy alcohol consumption	3.6%	18.0%

detected are needed. There is contradictory evidence on the impact of cyclosporine compared to tacrolimus treated patients on renal dysfunction. Exposure to immunosuppressive treatments over time also matters [25]. Newer strategies through randomized studies using less nephrotoxic drugs are still needed.

The Health Survey for England 2019, showed that 37% of 16−24 years olds were overweight or obese, compared to the 8% in our cohort (Table 5). After transplantation, children with adequate graft function tend to recover their weight gain in spite of prior malnutrition. Linear growth tends to improve, but catch-up growth can be variable depending on the underlying etiology of the pre-transplant state and accumulative steroid use. Whilst we did not analyze specific risk factors for obesity, studies have suggested the following as risk factors including: patient's BMI before transplantation, higher accumulative dose of prednisolone and episodes of acute rejection [28]. With this in mind, adequate nutritional management is important with the increased success of pLT programs.

Following successful transplantation, many children and families experience a sense of elation. The role of parents as carers whilst their child awaits the transplant is relinquished to the liver team and intensive care staff once the transplant occurs. This period of "cease-fire" is then quickly diminished by the child's first episode of complication with infection or rejection [29]. Up to 30% of our cohort of patients experienced acute rejection whilst surgical and vascular complications occurred in 1 in 5 of our patient cohort. The post-transplant period is a roller coaster of emotions for both the parent and child.

The Mental Health Report in 2014 reported that 19.7% of people in the UK aged 16 and older showed symptoms of anxiety and depression [30]. We report a similar proportion with anxiety and depression (Table 5). The emotional reaction brought about by the frustration of not being "cured" by the transplant is well known [31]. For children and their families, accepting the limitation that the transplant does not always signify a cure, instead it is another form of a chronic illness, which may be easier to manage, can be a significant challenge.

The ability to return to a near normal life is an important gauge for the success of a medical intervention [13]. Our data suggests 74% of our cohort were in age-appropriate education or in employment. Twelve percent were unable to work or study despite ongoing good graft function. When compared to data from the Office of National Statistics, 11.3% of the UK population (aged 16−24 years) were not in education, employment or training in 2018 (Table 5) [32]. Public Health England reported that in 2018, 33.9 per 1000 (3.4%) of the UK population of children had learning difficulties [33]. This was significantly lower than the described number of children with learning disabilities, which was reported to be as high as 13% (Table 5). A number of studies have investigated the cognitive abilities of children pre- and post-transplantation [34,35]. These studies have suggested that as a group, children post-transplantation do not show much change in their Intelligence Quotient as compared to pre-transplant.

Risk-taking behavior is a common theme in the adolescent population but may be easily brushed aside during the late post-transplant stage, when substance abuse tends to begin. According to the Office for National Statistics the number of 18 to 24 year olds who were smokers in 2018 was 16·8% [19]. We report smoking in roughly 10% of our patient cohort, lower than that of the UK national average (Table 5). Similarly with heavy alcohol consumption, the UK data suggests a reduction in number of young people between 16 and 24 years who are heavy drinkers, but the numbers are still as high as 18% in this cohort [18]. We report a significantly lower proportion of heavy drinking of only 3·6% (Table 5). Substance abuse is generally lower in our patient cohort, which may be secondary to our transition clinics (31% in transition clinics), where risk-taking behavior is reviewed and discussed.

Only a quarter of our cohort had achieved a composite profile of 'meaningful survival'. For our survivors to achieve a normal life span

and quality of life, we must address the challenges of side effects of medication, long-term graft failure and the adverse behavioral, emotional and social effects of chronic illness. The early identification of these potential health hazards through transition clinics provides a concerted and coordinated effort to managing these recipients.

This study shows that even in this relatively large cohort of patients with good graft function post-transplantation, the impact of transplantation on psychosocial and physical health is significant. Though we did not use specific questionnaires for education and employment and substance abuse, there was clear documentation in patient notes by clinicians to extract this data. Medication adherence was assessed through a structured consultation with the clinician, which was convenient and efficient. However, we recognize that this may be subject to recall and response bias, which may decrease accuracy and validity. The lack of standardization of data input, may however limit comparability of our findings.

Whilst we still have much ground to cover in the scientific and medical understanding of pLT, some existing issues of care remain: improve current treatment modalities to reduce toxicity, address the psychosocial impact and reduce the economic burden secondary to the reduced long-term quality of life in these childhood survivors.

Our data suggests that late mortality and late graft loss are uncommon, possibly secondary to better surgical techniques and multidisciplinary long-term follow up in our center. However, pLT recipients continue to face multiple challenges affecting their long-term physical health. The impact of lifelong immunosuppression on renal health and nutrition are pertinent issues that require emphasis as these children transition from pediatric to adult services. We show a comparable but alarming number of children with renal dysfunction on standard immunosuppression protocols 20-years post-transplantation and the immediate need to address these issues.

In children, optimizing quality of life post-transplantation is crucial, as their potential life span following liver transplantation continues to improve. Our cohort shows relatively good psychological outcomes post-transplantation. The integration of psychosocial evaluation through IMPARTS to our routine practice has been an important step in assessing the health status of these children.

Therefore, in conclusion, despite favorable survival outcomes, based on a long post-transplantation follow- up period, only a limited number of recipients achieve an overall composite profile of 'meaningful survival'. In facing the future, the onus is on us, as clinicians, to improve our current understanding of these complications, through early detection and collaborative multi-center efforts, so our patients can have a meaningful survival.

Statement of contribution

SV contributed to the research design, writing the paper, performance of the research and data analysis. SV, LNS, MD and AD had full access to the data. MD, JD and LNS contributed to data acquisition and writing the paper. MD, MS, AV, HVM, MR and NH contributed to revising the draft. AD contributed to the conception and design of the work, data analysis, writing the paper and final approval of the paper.

Declaration of Competing Interest

LNS received a PhD grant from CAPES- Brazil. All other authors declare no conflicts of interest.

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Data sharing statement

The data that support the findings of this study are available on request from the corresponding author, AD.

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