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MINIREVIEWS

Outcomes of pediatric liver transplant recipients who reach adulthood: Current perspectives and unmet needs

Alberto Ferrarese, Mara Cananzi, Luca Bosa, Marco Senzolo, Giacomo Germani, Laura Marta Vivian, Claudia Mescoli, Annalisa Dolcet, Enrico Gringeri, Lorenzo D'Antiga, Marco Spada, Jorge Amil Dias, Umberto Cillo, Patrizia Burra

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Alberto Ferrarese, Giacomo Germani, Multivisceral Transplant Unit, Department of Surgery, Oncology and Gastroenterology, Padova University Hospital, Padova 35122, Veneto, Italy

Mara Cananzi, Luca Bosa, Department of Pediatric Hepatology, Padova University Hospital, Padova 35122, Veneto, Italy

Marco Senzolo, Laura Marta Vivian, Patrizia Burra, Department of Surgery, Oncology and Gastroenterology, Padova University Hospital, Padova 35122, Veneto, Italy

Claudia Mescoli, Pathology Unit, Padova University Hospital, Padova 35122, Veneto, Italy

Annalisa Dolcet, Enrico Gringeri, Umberto Cillo, Hepatobiliary Surgery and Liver Transplant Center, Department of Surgery, Oncology and Gastroenterology, Padova University Hospital, Padova 35122, Veneto, Italy

Lorenzo D'Antiga, Department of Pediatric Hepatology, Gastroenterology and Transplantation, Hospital Papa Giovanni XXIII, Bergamo 24127, Italy

Marco Spada, Division of Hepatobiliopancreatic Surgery, Liver and Kidney Transplantation, "Bambino Gesù" Children's Hospital, IRCCS, Rome 00165, Italy

Jorge Amil Dias, Department of Gastroenterology, Hospital Lusiadas, Porto 4000-008, Portugal

ORCID number: Alberto Ferrarese 0000-0002-3248-2038; Marco Senzolo 0000-0002-7261-6520; Enrico Gringeri 0000-0002-3459-7306; Lorenzo D'Antiga 0000-0001-7150-3148; Marco Spada 0000-0003-0796-6847; Umberto Cillo 0000-0002-2310-0245; Patrizia Burra 0000-0002-8791-191X.

Co-corresponding authors: Alberto Ferrarese and Patrizia Burra.

Corresponding author: Alberto Ferrarese, Multivisceral Transplant Unit, Department of Surgery, Oncology and Gastroenterology, Padova University Hospital, Via Giustiniani 2, Padova 35122, Veneto, Italy. alberto.ferrarese@unipd.it

Abstract

Pediatric liver transplantation (pLT) has evolved from a purely life-saving intervention into a therapeutic strategy associated with excellent long-term survival, with the majority of recipients now reaching adulthood. As survival outcomes have improved, the focus has progressively shifted from post-transplant survival

alone to the pursuit of overall health. This concept encompasses optimal graft function, the absence of significant medical comorbidities, psychological well-being, social integration, and good quality of life, and should be regarded as the ideal long-term outcome after pLT. However, only a minority of patients currently achieve this goal, mainly due to liver-related, often immune-mediated, or extrahepatic medical complications, as well as psychosocial challenges. This minireview summarizes the key factors that limit the attainment of such an endpoint, critically discussing the limitations of currently used diagnostic parameters, and highlights existing challenges and unmet needs. Finally, potential multilevel strategies are proposed, including the implementation of structured and universal transition processes, the incorporation of novel diagnostic and prognostic biomarkers of graft function, and the prevention and early treatment of modifiable risk factors for extrahepatic complications, aimed at enabling the achievement of overall health in the majority of pLT recipients reaching adulthood in the near future.

Key Words: Adherence; Allograft rejection; Chronic kidney disease; Transition; Long-term outcomes

Core Tip: Pediatric liver transplantation has progressed from a life-saving procedure to one offering excellent long-term survival, with most recipients reaching adulthood. The focus has shifted from survival to global health, encompassing medical outcomes, psychological well-being, social integration, quality of life, and long-term functional and developmental success. However, only a minority achieve the ideal outcome, largely due to medical complications. Graft-related issues (such as persistent liver function test abnormalities) and extrahepatic complications, including chronic kidney disease, and metabolic disorders, and *de novo* cancers, often result from long-term immunosuppression. This minireview highlights determinants of long-term outcomes and proposes refinements to better assess the ideal outcome.

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INTRODUCTION

Liver transplantation (LT) remains a life-saving therapy for a wide range of inherited and acquired pediatric diseases. Over recent decades, pediatric LT (pLT) programs have expanded worldwide, alongside the harmonization of organ allocation policies[1,2]. Two factors underpin the transplant benefit at pediatric age. First, pharmacological therapies for many pediatric conditions, including neoplastic, metabolic and cholestatic disorders, remain limited[3,4]. Second, outcomes after pLT have improved markedly, largely due to advances in surgical techniques and a reduction in immunosuppression-related toxicity. Multicenter studies consistently report excellent patient and graft survival beyond 5 and 10 years[5,6], with some cohorts extending follow-up to 20 years[7,8]. Therefore, the focus of long-term post-transplant care has progressively shifted from survival alone to the achievement of overall health, which has now emerged as the optimal endpoint, or the ideal outcome, to be achieved after pLT. This condition is fulfilled in the presence of psychosocial well-being and in the absence of clinically significant medical comorbidities. Non-medical factors, including mental health, educational attainment, social and occupational integration, and parenthood, are beyond the scope of this minireview. Medical factors, in turn, can be broadly categorized into graft-related issues and extrahepatic complications, with chronic kidney disease (CKD), *de novo* cancer (DNC), metabolic disorders being the most impactful (Figure 1).

In light of these considerations, there has been a growing need to develop composite scores capable of adequately measuring overall health during long-term follow-up, and enabling comparisons between cohorts. Analyzing a retrospective cohort of North-American pLT recipients, Ng *et al*[9] proposed a 13-item score made of clinical and biochemical variables to measure overall health 10 years after pLT (Table 1). Notably, only 32% of patients fulfilled this endpoint. In a subsequent study from Germany, a revised version of this score (including arterial hypertension and solid post-transplant cancers, and excluding isolated bilirubin elevation and early re-transplantation) was applied to assess overall health at longer timepoints[8]. Again, the proportion of patients achieving overall health was only 54%, 42% and 25% at 10, 15 and 20 years after pLT, respectively.

Reaching long post-transplant follow-up often coincides with adolescence or young adulthood (AYA), a life phase characterized by increased vulnerability to non-adherence and significant changes in patients' perceptions, behaviors, and priorities[10]. This period frequently overlaps with the transfer of care from pediatric to adult healthcare services, a critical phase marked by the loss of established relationships with pediatric healthcare professionals and the need to develop new therapeutic alliances within adult care settings[11]. A structured transition process may provide a safe framework to address both medical and non-medical challenges, thereby facilitating the achievement of overall health.

The primary aim of this narrative minireview is to describe the prevalence and risk factors of medical complications, both graft-related and extrahepatic, that may hinder the attainment of an ideal outcome after pLT, with particular attention to issues relevant to adult transplant hepatologists. A secondary aim is to highlight current challenges and future perspectives for each of these complications. To this end, all relevant manuscripts indexed in PubMed were

Table 1 Predictors of ideal long-term outcome after pediatric liver transplantation

Variables associated with ideal outcome at 10 years follow-up[9]	Prevalence[1] (%)	Variables associated with AYA-ideal outcome at long term follow-up[8]	Prevalence (%)
Graft related issues			
No re-transplantation	88	No late re-transplantation[2]	76.7
No chronic rejection	91	No chronic rejection	93.3
Normal liver enzymes (alanine aminotransferase)	89	Normal liver enzymes (alanine aminotransferase)	66.7
Normal liver enzymes (gamma-glutamyl transpeptidase)	85	Normal liver enzymes (gamma glutamyl transpeptidase)	74.2
Normal liver function (albumin)	98	Normal liver function (albumin)	87.5
Normal liver function (total bilirubin)	99		
Immunosuppression-induced issues			
No post-transplant lymphoproliferative disease	94	No malignancy[2]	95
No renal dysfunction (*i.e.*, GFR < 90 mL/minute/1.73 m^2)	91	No renal dysfunction (*i.e.*, GFR < 90 mL/minute/1.73 m^2)	61.7
Acceptable linear growth	93	No arterial hypertension[2]	68.3
No diabetes	99	No diabetes	99.2
Additional medications			
No ongoing use of prednisone	81	No antiseizure medication	97.5
No use of antihypertensive agents	87	No treatment with steroids	80.8
No use of antiseizure medication	100		

[1]Prevalence of ideal outcome has been calculated from patients with all available data (n = 106/167; of these, 53 fulfilled criteria of ideal outcome since they fulfilled all the above-mentioned items).
[2]Differences between the two scores.
GFR: Glomerular filtration rate; AYA: Adolescent and young adult.

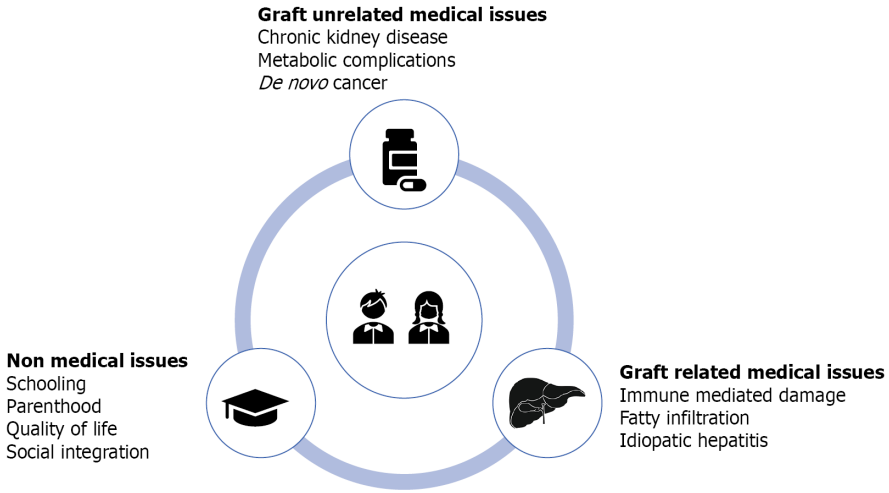

Figure 1 Main factors influencing overall health in pediatric liver transplant recipients.

reviewed, prioritizing multicenter, prospective studies published within the last 15 years, in order to provide an up-to-date overview of the available evidence.

GRAFT RELATED ISSUES

Epidemiology and risk factors

In the long-term follow-up after pLT, the trajectories of patient and graft survival may diverge, indicating that a subset of recipients, particularly in AYA, may require late re-transplantation (re-LT). The leading indications of re-LT differ from those observed in adult LT recipients and are predominantly related to immune-mediated mechanisms. Consequently, the overarching goal of long-term follow-up is the preservation of graft function through the early identification of subclinical (immune-mediated) injury, and the prevention of its progression. Studies have shown that elevations of transaminases and γ-glutamyl transferase tests occur in approximately 15% of pLT recipients at 10 years post-transplant, doubling at 20 years[8,9,12,13]. This chronic increase also predicts graft fibrosis, which may in turn determine graft loss [14-17]. Persistent elevations of transaminases and γ-glutamyl transferase have therefore been incorporated among the items defining ideal outcome (Table 1).

Although elevations in liver function tests may reflect a variety of conditions, including fatty infiltration, *de novo* idiopathic or viral hepatitis, immune-mediated complications remain the most prevalent and clinically concerning. Among modifiable risk factors associated with the development of immune-mediated graft injury, non-adherence to immunosuppressive therapy plays a particularly critical role and is more prevalent among AYA recipients than in older LT populations. Fluctuations in immunosuppressive drug trough levels have been associated with both acute and chronic immune-mediated liver injury, further underscoring the importance of adherence monitoring[18].

Future challenges

A major priority is the development of internationally shared protocols for the assessment of graft function in the long-term follow-up, with the aim of enabling earlier detection of graft injury[19-21]. Although serum transaminases currently represent the main indicators used in routine clinical practice to monitor graft function, growing evidence indicates that a substantial proportion of liver allografts may harbor immune-mediated injury, such as subclinical acute cellular rejection, even in the presence of normal transaminase levels. In this setting, the application of biomarkers already used in adult transplantation, including donor-specific antibodies, may improve the diagnostic accuracy for silent graft injury and facilitate earlier diagnosis[22,23]. Moreover, the adoption of innovative approaches, such as genome-wide analyses and artificial intelligence-based platforms, may allow the identification of new patient-tailored biomarkers, both serological and histological, which could complement or potentially replace transaminases as indicators of allograft health in future composite scores of overall health[24,25].

Another aim for the near future will be to identify the true prevalence of fibrosis during fixed follow-up endpoints, and its prognostic impact. Although liver biopsy remains the gold standard for fibrosis assessment, serum biomarkers, transient elastography, and/or the combination thereof, could improve the longitudinal evaluation of fibrosis progression [26-29]. Furthermore, elucidating the relationship between the phenotype of the inflammatory tissue infiltrate and the concomitant presence of fibrosis could enable the identification of specific immunological therapeutic targets[30].

Another key question will be to assess the influence of immunosuppression minimization (up to its complete withdrawal) on graft injury, using dedicated tools that extend beyond conventional transaminase measurements. Pending the identification and validation of such biomarkers, close surveillance of allograft function remains essential, including the use of protocol liver biopsies in dedicated settings, which may guide timely and appropriate modulation of immunosuppressive therapy[31-33].

CKD

Prevalence and risk factors

Incidence of post-pLT CKD is expected to rise with extended follow-up, affecting the long-term outcome, especially at deeper stages. Stage III CKD has been reported in 1%-3% of patients after pLT in recent studies. Liver disease etiology (*e.g.*, Alagille syndrome, Wilson's disease), pre-transplant renal impairment, older age at pLT and cyclosporine-based immunosuppression have been identified as associated risk factors[34-36]. Two studies specifically addressed the incidence of end-stage renal disease after pLT. In the study by Ruebner *et al*[37] on pLTs performed between 1990 and 2010, 2% of recipients developed this condition, after a median follow-up of 7.8 years. Notably, male gender, older age, viral hepatitis, late re-LT were the independent predictors of this condition, which significantly correlated with mortality. In another retrospective observational study, Umemura *et al*[38] showed a progressive decrease of renal function over time, highlighting a prevalence of end-stage renal disease up to 5.9% in subjects surviving more than 20 years after pLT.

Prevention, therapeutic options, unmet needs

The risk of CKD development during the long-term follow-up is largely due to calcineurin inhibitors (CNI) toxicity. To slow CKD progression while preserving graft function, protocols that minimize CNI exposure have been considered, including the off-label use of everolimus and minimization strategies with mycophenolic acid[39-41]. In a prospective study, 56 pLT recipients who started everolimus within 6 months post-transplant demonstrated a modest improvement of renal function (glomerular filtration rate increase of 6.2 mL/minute/1.73 m^2 from baseline to month 12). However, 44% discontinued treatment due to adverse events[42]. A multicenter retrospective study evaluated everolimus or sirolimus use in various settings (*e.g.*, nephrotoxicity, neoplasms, rejection) at a longer interval after pLT (median 3 years); in that study, the overall discontinuation rate was 23.3%. Although no significant renal benefit was observed in the whole cohort,

creatinine levels remained stable in patients with pre-existing renal impairment[43]. Additional long-term strategies for preserving renal function include the early management of metabolic complications, such as hypertension, diabetes and obesity, which can themselves adversely impact kidney health. These complications may be overlooked more often in the pediatric population compared with adults, underscoring the need for vigilant long-term follow-up. Furthermore, the implementation of biomarkers such as cystatin C may be of help in diagnosis of CKD, alongside indirect formulas for estimating glomerular filtration rate that appropriately account for patient age. Once CKD develops, a nephrological assessment becomes essential to evaluate the degree of renal dysfunction and proteinuria, and to initiate targeted pharmacological therapies (*e.g.*, angiotensin-converting enzyme inhibitors, or newer drugs such as sodium-glucose cotransporter-2 inhibitors) aimed at slowing disease progression[44]. Kidney transplantation in adolescence, young adulthood, or adulthood should be pursued for patients who develop ESRD following a previous pLT, while promoting organ-allocation strategies that do not disadvantage these patients compared with those without a history of transplantation[45].

DNC IN AYA PLT RECIPIENTS

Prevalence and comparison with adult LT recipients

The onset of DNC and its consequences have a significant impact on overall health, affecting long-term ideal outcomes after pLT[46]. Considering available epidemiological data, and comparing pLT recipients with age-matched non-transplanted controls, these patients exhibit a markedly higher prevalence of DNC, which justifies the implementation of dedicated surveillance policies for this at-risk population. Moreover, the relationship between DNC and time is crucial, as prevalence increases from 2%-5% to 15%-22% at 10 and 25 years after LT, respectively[47-49]. Therefore, it is likely that the development of DNC will be identified once patients have transitioned to the adult healthcare setting. When comparing pediatric and adult LT recipients, cancer types and outcomes differ substantially: Pediatric/AYA recipients exhibit a higher prevalence of lymphoproliferative disorders, whereas other cancers that are more typical of adults, such as gastrointestinal and lung cancers, are rare. Risk factors are less well characterized in pediatric recipients; however, long-term immunosuppression, Epstein-Barr virus serostatus, and age at transplant have been identified as key contributors[50]. In contrast, the impact of modifiable adult risk factors, such as smoking and alcohol use, is less pronounced in pediatric or AYA recipients. Nevertheless, metabolic disorders are increasing among adolescents and may play a significant role in the future.

Challenges for the future

Future challenges require larger datasets to better stratify oncological risk, particularly according to types of immunosuppression, and to personalize surveillance, especially in patients with comorbidities (*e.g.*, primary sclerosing cholangitis, inflammatory bowel disease) or modifiable risk factors (such as smoking, alcohol intake and sexually transmitted infections)[51]. Such surveillance should target cancer types different from those seen in adult LT recipients and should be implemented especially during transition to adult healthcare, given that the risk of DNC increases over time. Regarding composite surveillance strategies, the field of biomarkers, including liquid biopsy and circulating tumor cells, holds significant potential in terms of diagnosis and prognosis[52]. Appropriate long-term immunosuppression management aimed at reducing excessive toxic exposures may help lower the risk of DNC. The antiproliferative effects of mammalian target of rapamycin inhibitors remain poorly characterized in the pLT/AYA setting and warrant further investigation. Moreover, the impact of immunosuppression withdrawal on the reduction of DNC cumulative incidence remains to be fully elucidated[33].

METABOLIC COMPLICATIONS

Epidemiology and risk factors

Metabolic complications are increasingly encountered in AYA pLT recipients. A systematic review reported a prevalence of diabetes, hypertriglyceridemia, hypertension and obesity in approximately 10%, 16%-50%, 4%-100%, 10%-60% of pLT recipients, respectively[53]. Overall, the wide heterogeneity in prevalence can be attributed to several factors, including study design, variability in diagnostic criteria, approaches to case identification (direct diagnosis *vs* inference from chronic medication use), and differences in the timing of assessment according to age at transplantation.

That said, growing evidence underscores that the prevalence of many of these complications is higher in pLT recipients compared with age- and sex-matched non-transplanted controls[54,55]. Risk factors for post-pLT metabolic complications include long-term immunosuppressive therapy, in particular CNI and corticosteroids. Notably, the prevalence of impaired fasting glucose has been shown to double approximately every 7.5 years of CNI therapy, suggesting mechanisms of hyperglycemia that are not entirely explained by insulin resistance associated with overweight or obesity[56]. Discontinuation of CNI following the achievement of operational tolerance does not consistently result in significant long-term metabolic improvement, implying the involvement of additional, potentially irreversible pathways[57]. Other important contributors include older age at transplant, genetic background, and underlying diseases such as cystic fibrosis or primary sclerosing cholangitis[58-60]. If inadequately managed, metabolic complications can contribute to the development of cardiovascular events during long-term follow-up, mirroring patterns already observed among adult LT recipients[61].

Future perspectives

The significant clinical implications of these metabolic complications underscore the need for regular monitoring, early lifestyle interventions, and careful immunosuppressive management. Routine screening of metabolic complications to enable early diagnosis, even in the absence of risk factors commonly seen in adult LT recipients, is a crucial action, particularly during the transition phase. The self-monitoring of selected parameters may represent an effective strategy, although it requires dedicated structures and algorithms[62].

Preventive strategies could include those already implemented in the general adolescent population to reduce modifiable risk factors, such as dietary patterns, physical activity levels, and limiting sedentary behaviors related to technology use[63]. In the whole pediatric population, obesity prevalence tends to be higher in pre-school and school-age children than in adolescents, likely due to differences in hormonal changes during puberty and greater psychological attention to weight control during adolescence[64]. More data on AYA pLT recipients are needed to understand whether long-term immunosuppressive therapy may alter this pattern, maintaining a rising trend also during adolescence.

Considering therapeutic approaches, a major challenge for the future will be to apply novel therapies for metabolic conditions, particularly diabetes and obesity, to AYA pLT recipients. Studies in both transplanted patients and adolescent populations have demonstrated the safety and effectiveness of novel molecules, paving the way for their potential large-scale use in patients who share both conditions[65-68].

A final aspect concerns adherence to chronic therapy, which often declines during adolescence. This can affect both immunosuppressive regimens and other long-term treatments, such as for diabetes. Fostering adherence through a multidimensional approach, including reducing the number of daily tablets, simplifying therapeutic algorithms, and providing psychological support, may represent an additional effective therapeutic strategy.

NEUROLOGICAL COMPLICATIONS

Neurological complications are a significant cause of morbidity and mortality early after pLT, and are reported in 8%-46% of patients. Seizures and encephalopathy are the most common, typically occurring in the early post-transplant period, whereas tremor, headaches, ataxia, and neuropathy usually develop later[69-72]. Common causes of seizures include metabolic derangements (electrolyte, hepatic, or renal abnormalities) and the use of immunosuppressive agents (such as cyclosporine and tacrolimus)[73]. Although often transient, these conditions may leave sequelae that require long-term chronic medications, for example anticonvulsants. Moreover, certain types of drug-resistant epilepsy may lead, even years later, to complications related to polypharmacy, interactions with immunosuppressive medications, reduced neurocognitive development, and a significant impairment in quality of life[74]. In the previously proposed scores of ideal outcome, the need for antiseizure medications was an important but uncommon factor. Indeed, in the study by Lund *et al*[8], only 2.5% of patients were still receiving such chronic therapy at the last follow-up, whereas in the study by Ng *et al*[9], none of the patients continued anticonvulsants. An important goal for the future will be to complement, or even replace, antiseizure medications with other indicators of chronic polypharmacy (hypertension, CKD, diabetes, dyslipidemia, insomnia, or depression), better suited to capturing the achievement of an ideal outcome in AYA pLT recipients. In this context, the number of agents used for each class, and the total number of daily medications could serve as a useful indicator of the patient's overall health, potentially guiding future therapy simplification to improve adherence when feasible.

CONCLUSION

Good short- and long-term survival after pLT is well established; accordingly, the focus of long-term follow-up has progressively shifted from survival to optimal long-term functioning[75]. Increased awareness of the specific needs of AYA pLT recipients among parents, healthcare professionals, and policymakers has contributed to improved outcomes; nevertheless, several unmet needs and challenges persist.

This minireview underscores that currently available parameters for outcome assessment remain suboptimal, both because they fail to comprehensively capture the concept of overall health and because they require updating in light of advances in medical knowledge. Proposed actions for implementation of overall health assessment within three domains (graft-related issues, medical complications, and non-medical parameters such as social integration, parenthood, and patient-reported outcomes) are summarized in Table 2. Adaptation to different socio-economic contexts and their periodic updates could be subsequent steps to ensure broad applicability of these scores and long-term relevance.

Finally, particular emphasis should be placed on the transition process from pediatric to adult care, which has been demonstrated to be effective in supporting AYA during this vulnerable life phase. Favorable long-term outcomes associated with structured transition programs have been reported in both retrospective and prospective studies, as recently summarized by Kosmach-Park *et al*[76]. Transition represents a key opportunity to "grasp" global health, as it reduces the risk of non-adherence, closely associated with immune-mediated graft injury, ensures continuity of follow-up aimed at preventing and promptly treating extrahepatic complications, and improves health-related quality of life[18,77,78]. In recent years, structured transition models have been proposed, based on multidisciplinary and multistep approaches and on close collaboration between pediatric and adult hepatologists; additionally, multiple endpoints have been well defined, including transition readiness, the active involvement of parents and healthcare professionals, and the desirable timing of transfer of care[79]. Future challenges will include the identification of robust post-transitional long-term

Table 2 Progress on the management of paediatric liver transplant recipients reaching adulthood and future actions

Topic	Progress on the management of paediatric LT recipients reaching adulthood	Future actions
pLT overall health during and beyond transition	Recognition of overall health as the ideal outcome to be achieved in the long-term follow-up	Change of current scores or development of novel composite scores, preferably derived from multicenter studies, capable of capturing overall health from both medical and psychosocial perspectives
Long-term allograft health	Increased awareness of importance of monitoring allograft health, especially beyond transition; lack of universal association between normal transaminases and absence of graft inflammation/immune-mediated injury; variable degree of histologically proven fibrosis after pLT without significant rates of progression over time, according to studies in paired biopsies	Identification of novel biomarkers capable of enabling early detection of immune-mediated graft injury and fibrosis, as well as predicting long-term clinical outcomes; integration of graft function-related biomarkers into algorithms for the assessment of overall health during long-term follow-up, either alongside or as a replacement for conventional transaminase measurements
Extrahepatic complications affecting long-term overall health	Implementation of CNI sparing/minimization strategies to reduce the risk of long-term CKD development; increased awareness of metabolic syndrome as a potentially dangerous complication after pediatric LT; increased awareness about reproductive health (including sexual dysfunction, infertility, contraception) as a key topic to address in the long-term follow-up	Prevention and aggressive correction of modifiable risk factors for CKD development; development of tailored (universal) surveillance algorithms for *de novo* cancer; evaluation of safety and effectiveness of available drugs for the general population of young adult LT recipients with metabolic syndrome; evaluation of effectiveness and safety of artificial reproductive technologies even in the setting of young adult LT recipients
Transition	Increased awareness of the importance of transition among many pediatric and adult transplant hepatologists; development and validation of tools to assess readiness for transition; development of structured transition pathways in many transplant centers, managed by qualified healthcare professionals	Development of a universal transition protocol applicable in all LT centers, to be tailored according to local expertise and needs; greater integration of psychosocial support into transition programs; systematic application of reliable endpoints to evaluate the quality and effectiveness of the transition process; long-term, multicenter data on the outcomes of structured transition programs to guide best practices

LT: Liver transplant; pLT: Pediatric liver transplantation; CNI: Calcineurin inhibitors; CKD: Chronic kidney disease.

indicators, such as retention rate, prevention of chronic graft injury, educational attainment, and social integration. Large-scale confirmation of the favorable impact of transition may ultimately support its incorporation as a core component in future models aimed at defining and achieving overall health after pLT.

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