Received: 1 March 2020 | Revised: 2 August 2020 | Accepted: 15 August 2020

DOI: 10.1111/ctr.14082

Clinical TRANSPLANTATION
The Journal of Clinical and Translational Research
WILEY

REVIEW ARTICLE

Acute and chronic kidney disease after pediatric liver transplantation: An underestimated problem

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Abstract

Acute and chronic kidney injuries represent critical issues after liver transplantation (LTx), but whereas renal dysfunction in adult transplant patients is well documented, little is known about its prevalence in childhood. It is a challenge to accurately evaluate renal function in patients with liver disease, due to several confounding factors. Creatinine-based equations estimating glomerular filtration rate, validated in nephropathic patients without hepatic issues, are frequently inaccurate in end-stage liver disease, underestimating the real impact of renal disease. Moreover, whereas renal issues observed within 1 year from LTx were often related to acute injuries, kidney damage observed after 5-7 years from LTx, is due to chronic, irreversible mechanisms. Most immunosuppression protocols are based on calcineurin inhibitors (CNIs) and corticosteroids, but mycophenolate mofetil or sirolimus could play significant roles, also in children. Early diagnosis and personalized treatment represent the bases of kidney disease management, in order to minimize its close relation with increased mortality. This review analyzed acute and chronic kidney damage after pediatric LTx, also discussing the impact of pre-existent renal disease. The main immunosuppressant strategies have been reviewed, highlighting their impact on kidney function. Different methods assessing renal function were reported, with the potential application of new renal biomarkers.

KEYWORDS
calcineurin inhibitors, chronic kidney disease, nephrotoxicity, pediatric liver transplantation, renal biomarkers, renal function estimation

1 | INTRODUCTION

Liver transplantation (LTx) has revolutionized outcomes of children with end-stage liver disease (ESLD) and many patients with liver-based metabolic defects are now enjoying improved quality of life and increased life spans. Continuous advances in surgery, anesthesia and better selection criteria have led to an improvement of patient and graft survival, but the necessity to minimize posttransplant complications is crucial.[1]

Acute and chronic kidney injuries represent critical issues after liver transplantation (LTx),[2] but whereas renal dysfunction in adult transplant patients is well documented, little is known about its prevalence, absolutely underestimated, in childhood.

In pediatric LTx, several studies showed a prevalence of chronic kidney disease (CKD) ranging from 0% to 32%.[3] This wide range is related to individual immunosuppressive regimes of different centers and, more importantly, to varying applied methods used to evaluate renal function.

The gold standard to measure kidney performance is the inulin clearance, but is not widely used, due to its complexity and costs. Usually, estimated (e) glomerular filtration rate (GFR), based on serum creatinine levels is used, but, unfortunately, formulas are inaccurate and insensitive, especially in children.[4,5]

Furthermore, it was demonstrated an age-related difference in tacrolimus bio-disposition, with different metabolite formation with direct effects on developing kidneys.[6] In fact, younger children need, on average, high tacrolimus doses to achieve target levels and may consequently be exposed to higher levels of potential nephrotoxic tacrolimus metabolites.[7]

The genetic predisposition could play an important etiological role, considering the relationship between calcineurin inhibitor (CNI) nephrotoxic effects and polymorphisms of the enzymes involved in their metabolism, such as MDR1 and CYP3A.[8]

Over the past years, many studies have shown that an overall minimization of immunosuppression was possible, especially in pediatric LTx patients, with significant advantage for long-term quality of life.[9,10]

This review aimed to analyze the physiopathological mechanisms of kidney damage in pediatric LTx recipients. Moreover, different methods, used in clinical practice to evaluate renal function, were reported, highlighting the potential application of new renal biomarkers.

2 | THE LIVER-KIDNEY CONNECTION BEFORE LTX

Kidney disease represents a not negligible comorbidity in pediatric patients who suffered from hepatic disease and waiting for LTx, being a strong predictor of posttransplant mortality.

Renal failure often occurs before LTx, with different mechanisms of damage, according to the primary liver disease.

Hepatitis C virus-related kidney disease does not usually involve pediatric population, considering that glomerulonephritis develops many years, often decades, after initial infection. The most common HCV-related nephropathy is a membranoproliferative glomerulonephritis, usually in the context of cryoglobulinemia.[11]

A close association between chronic liver disease and immunoglobulin A nephropathy (IgAN) has been revealed, more often reported in adults with liver alcoholic cirrhosis and portal hypertension.

The pathogenesis remains uncertain, but an altered mucosal integrity, an impaired hepatic immune function, an increased bacterial products in the circulation, represent the principal mechanisms which induce an over-production of IgA and a concomitant reduced clearance, with consequent deposition of IgA-containing immune complexes in renal mesangium and glomeruli.[12]

This secondary glomerulonephritis often induces microscopic hematuria, nephritic or nephrotic proteinuria, and, in some cases, mild renal impairment.[13]

However, case reports of a similar illness have also been described in children,[14] but, considering the teen age of patients, it is possible that two separate entities have been diagnosed.

Harambat confirmed the great importance to investigate the underlying liver disease due to the potential renal involvement, revealing the association between CKD progression, Alagille syndrome and hepatic fibrosis, independently of arterial hypertension and cyclosporine effects.[15]

Autosomal recessive polycystic kidney disease (ARPKD), a rare hepato-renal disorder most frequently presenting during early childhood, is characterized by early-onset disease with bilateral enlargement of the kidneys and impairment of renal function, as well as congenital hepatic fibrosis with subsequent portal hypertension.[16]

It represents one of the leading causes of pediatric dialysis dependency and pediatric kidney-, liver-, or combined liver and kidney transplantation.[17]

While renal involvement typically presents early in life or even prenatally, liver involvement tends to manifest later, in late adolescence or even in adulthood, with a substantial number of patients who reaches adulthood.[18]

3 | EVALUATION OF RENAL FUNCTION IN PEDIATRIC LTX

It is a challenge to evaluate the exact renal function in patients with liver disease, behind age.

It was clearly demonstrated that creatinine-based equations estimating GFR, validated in nephropatic patients without hepatic issues, are frequently inaccurate in the ESLD populations.[19]

These patients have, in fact, low serum creatinine levels, due to lower muscle mass, decreased production of creatine by the liver and its increased tubular secretion, potentially related to medications, commonly prescribed in this setting.[20]

Most studies assessed a low (20%-40%) diagnostic accuracy of eGFR formulae, especially if GFR was near to normal values.[21]

Other issue derives from analytical point of view. In particular, there is no universal standardized creatinine assay or readily available isotope dilution mass spectroscopy (IDMS)-traceable standards for patients with liver dysfunction or cirrhosis. The colorimetric Jaffe assay is prone to errors not only due to non-renal patient factors (age, sex, muscle mass, diet) but also due to interference from bilirubin and other compounds.[22]

Enzymatic methods have been reported to be more accurate than Jaffe-based assays, but they are generally more expensive.[23]

Starting from the assumption, novel biomarkers are needed in order to detect kidney damage with high accuracy, precociously in the first months after LTx and in the long-term follow-up.

3.1 | Measured GFR, creatinine-related formulas, and renal biomarkers in LTx

Calculated GFR by Schwartz formula, from serum creatinine, is widely used to monitor renal function in pediatric LTx recipients, although this method has been revealed inaccurate, even in patients with mildly reduced kidney function.[24]

Schwartz formula, in fact, overestimating GFR, could not reveal several patients with CKD.

The gold standard to evaluate kidney function in children is the GFR measurements (mGFR), using radioactive tracers. These techniques cannot be applied routinely, due to the high cost and for biological implications in children. However, according to clear epidemiological data of the onset of renal damage after LTx, mGFR could be performed after the first year posttransplant and annually after the fifth year, as renal damage screening.

This management could achieve a correct and prompt diagnosis of renal insufficiency, helping to uncover an underestimated problem.

The confirmation of this strategy needs to be find in the large discrepancies existing between the correct diagnosis of CKD using mGFR and the underestimation of renal injury obtained by serum creatinine and/or its related formulas, leading to delayed introduction of nephroprotective immunosuppression protocols.

In the last years, a noninvasive determination of renal function by measurement of serum cystatin C has been revealed as feasible and repeatedly correlated with the gold standards of GFR measurements.

Cystatin C is a 13.3 kDa low-molecular-weight member of the cystatin superfamily of cysteine protease inhibitors which is synthesized by all nucleated cells at a constant production rate. It is freely filtered at the glomerulus and is not reabsorbed, although it is metabolized by the renal tubules, which limits the utility of urinary measurement. However, it is not secreted by the tubules and its concentration in urine in normal states is remarkably lower and approximately 0.1 mg/L. Although it was supposed to be unaffected by gender, age, or muscle mass, recent work denied these data.[25] Furthermore, a possible drawback of cystatin C was related to its influenced levels by steroid and cyclosporine in asthmatic patients.[26] However, several data did not confirm this observation in children after transplantation, as well as standard high dose corticosteroid therapies, in children with corticosteroid-sensitive nephrotic syndrome, did not significantly affect cystatin C levels.[27]

In pediatric LTx, Samyn compared this biomarker to mGFR values, prior and after the transplantation, demonstrating a great diagnostic accuracy of Cystatin C in the identification of reduced renal function, in the short term.[28]

Moreover, Cystatin C-based equation was applied for the assessment of renal function in 15 years follow-up period, after pediatric LTx, comparing it with Schwartz formula. In particular, whereas Cystatin C equation detected 20% of patients with renal insufficiency, Schwartz formula identified only three patients (1.8%) who had a slightly reduced kidney function, confirming the well-known overestimation of kidney function by this formula.[29]

Recently, 59 children have been screened by eGFR formulas compared to mGFR. In particular, Filler (serum cystatin C), mSchwartz (serum creatinine), and CKiD (serum cystatin C, creatinine, urea, and height) formulas were used. The mean GFR value obtained by all formulas differed significantly from mGFR, overestimating it. Nevertheless, the CKiD was the only formula to achieve 91.1% accuracy, followed by Filler formula, representing a noninvasive and adequate method to monitor renal function.[30]

Moreover, these formulas have been related to another promising renal biomarker, such as neutrophil gelatinase-associated lipocalin (NGAL). It is a small 25 kDa protein, composed of 8 β-strands that form a β-barrel enclosing a calyx which binds and transports low-molecular-weight substances. Originally it was known as an innate immunity antibacterial factor released by activated neutrophils, also produced by renal tubular cells in response to different types of injury.[31]

In kidneys, circulating NGAL is filtered in the glomerulus and completely reabsorbed in the proximal tubule by a megalin-dependent pathway. Hence, only traces of NGAL are detectable in urine. During injury or inflammatory processes, NGAL is massively released from activated neutrophils and the urinary levels correlate with serum levels, independently of the cause of increased NGAL production.

NGAL is now widely considered an excellent predictor of acute kidney injury (AKI); its levels, both in plasma and urine, rise before any increase occurs in creatinine levels in response to treatments that are potentially harmful to the kidney, thus facilitating a more reliable prediction of AKI.[32]

Several studies, not conducted in children, have analyzed the diagnostic accuracy of this peptide for AKI after LTx, revealing a sensitive biomarker to predict precocious renal damage, with high levels detected in AKI within the first 24 hours following LTx.[33,34]

Although conducted in heart transplanted pediatric patients, a research conducted by Abraham, who compared NGAL to serum cystatin C, CKiD formula and revised Schwartz formula, deserves mention. It was again demonstrated that the prevalence of mild and moderate CKD was 2- to 3-fold higher using novel methods compared to Schwartz formula. Furthermore, NGAL levels were significantly high in patients with CKD and closely related to eGFR.[35]

4 | ACUTE KIDNEY INJURY AFTER PEDIATRIC LTX

In pediatric population, AKI incidence after LTx is relatively unknown. The definitions used currently for children are the pediatric Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) criteria, based on percentage decrease in eGFR, the Acute Kidney Injury Network (AKIN) and Kidney Disease Improving Global Outcomes (KDIGO) criteria, both based on percentage increase in serum creatinine from a baseline value.[36,37]

Furthermore, in the first week posttransplant, there were many fluctuations in creatinine levels, possibly due to volume status, representing a significant issue in terms of sensitivity and specificity of the exam, with inaccurate estimation of renal function.[38,39]

Wide and different ranges of AKI prevalence were reported in several studies, ranging from 17% and 50%, with small patients cohorts, often included in retrospective studies and using different methods to evaluate GFR.[40-42]

Seventy-seven children, who underwent LTx, were enrolled to evaluate AKI prevalence, comparing the three standardized definitions of AKI based on serum creatinine values, Pediatric RIFLE (pRIFLE), AKIN, and KDIGO criteria. In particular, pRIFLE detected AKI in 57% of patients, whereas AKIN and KDIGO criteria in only 43% of them. A good correlation among the three criteria was assessed with a close relation between kidney failure, duration of mechanical ventilation, and Intensive Care Unit (ICU) stay.[43] Immunosuppressant use, blood loss, blood product transfusion during surgery and hemodynamic instability represented the main clinical factors influencing AKI development.[44,45]

Furthermore, it was revealed that patients with biliary atresia, increased time of anhepatic phase and a lower postoperative jaundice clearance had an increased risk of AKI too.[46] Kidney function, in the first year after LTx, may be a more important indicator for long-term kidney function than in the perioperative period of the transplant.[47]

In fact, if AKI occurred in the perioperative period only, it was not associated with the development of CKD. Instead, if AKI persisted after the first week and up to 3 months posttransplant, it was significantly associated with 2.5 times greater risk of developing CKD, over a median follow-up of 3.4 years.[48]

Understanding when AKI occurs and how it may impact future kidney function is of paramount importance in the solid organ transplant population as it can aid in identifying the patients at risk for CKD, allowing for earlier implementation of kidney-sparing strategies to prevent kidney disease progression. Moreover, an early diagnosis of AKI will enable physicians to better inform families of risk for kidney injury after transplant and associated morbidity and mortality.

5 | IMMUNOSUPPRESSIVE REGIMEN CHOICE AND RENAL EFFECTS

It is crucial to personalize immunosuppressant strategies according to individual need, minimizing long-term undesired side effects and avoiding rejection.

Yet, up to date, appropriate tools are missing to determine the optimal level of immunosuppression, due to great differences between individuals, as well as within the same individual over time.

In particular, cytochrome P450-related genetic polymorphisms, body weight changes, hematocrit level, behavioral factors, such as non-adherence to treatment, especially during adolescence, represent covariates that may influence the variability in tacrolimus exposure in pediatric patients, with close relationships to poor graft and survival outcomes.[49,50]

Over the past 2 decades, newer immunosuppressive agents have been introduced to achieve better patient and graft survival. However, only few clinical studies have produced robust data that can rationalize the use of these agents in children.

Most current immunosuppression protocols are based on CNI and corticosteroids, but if complications occur, other immunosuppressive agents, such as mycophenolate mofetil (MMF) or sirolimus, could play significant roles, also in children. Often, CNI dosage was drastically reduced, with simultaneous introduction of these new drugs, obtaining a significant improvement in GFR.[51]

Although both cyclosporine and tacrolimus act by inhibiting calcineurin, the precise molecular mechanism causing CKD remains unclear.[52-54]

Acute and chronic renal damage are induced by CNI. In particular, profound alterations in vascular flow, involving afferent arterioles, are based on increased vasoconstrictor factors, activation of the renin-angiotensin system, as well as a reduction of vasodilator factors, like nitric oxide. The final effect is a decrease in GFR and an intra-renal ischemia with consequent free radical formation and toxic tubulopathy.[55]

Moreover, a direct toxic effect of CNI on the renal tubules was assessed, especially on proximal tubules, with cell apoptosis and free oxygen radicals and lipid peroxidation, inducing electrolytes abnormalities, such as loss of magnesium in urine and hypercalciuria.[56]

While acute nephrotoxicity can be clinically asymptomatic, it induces an increase in serum creatinine and blood pressure, with potential reversibility only if a precocious interruption of the drug occurs.[57]

Conversely, chronic nephrotoxicity is characterized by an irreversible, not dose dependent, loss of kidney function.

CNI stimulates pro-fibrotic cytokine transforming growth factor beta 1 (TGF-β1) synthesis, through the protein kinase C beta (PKC-β) pathway, promoting the development of tubule-interstitial fibrosis by inhibiting extracellular matrix (ECM) degradation, stimulating its production and inducing the epithelial-mesenchymal transition. This latter process contributes significantly to renal failure through the accumulation of ECM and loss of epithelial cells, leading to reduced tubular integrity and function Figure 1.

Kidney biopsy is required for diagnose this complication, revealing arteriopathy with nodular hyalinosis of the renal arterioles, glomerulosclerosis, interstitial fibrosis or tubular atrophy, even though these findings do not represent pathognomonic diagnostic elements.[58]

However, kidney biopsy is not frequently performed in LTx patients, especially in children. CKD diagnosis is obtained by clinical and laboratory examinations, without biopsy confirmation.

Literature data are very limited, almost always involving adults, with observations that cannot be used to make generalized statements of incidence or prevalence or to assess the relative frequencies of one disease vs another.

The major indication to proceed with renal biopsy could be an increased creatinine level, heavy proteinuria, or protracted AKI.[59]

Moreover, behind CNI toxicity primary, glomerular diseases, such as IgA nephropathy or immune complex glomerulonephritis, and thrombotic microangiopathy could often involved patients after LTx.[60]

The timing of CNI withdrawal is important, as nephrotoxicity from CNI is not reversible when performed too late, but the chances of successful withdrawal are improved if undertaken later after transplantation.[61] Furthermore, starting a “renal sparing” approach,

before the onset of renal dysfunction, has no validity and may be harmful to the patient. This choice could induce an increased acute rejection, possible increased mortality in stable renal function patients.

Tacrolimus represents the main component of immunosuppressive regimens after LTx, as reported in an annual transplant registry in 2012, where 96% of pediatric LTx received tacrolimus as part of their initial immunosuppressive regimen, while 89%, 47%, and 1% received steroids, MMF and mammalian target of rapamycin (mTOR) inhibitors, respectively.[62]

According to the 2018 American transplant registry report, the volume of pediatric LTx was relatively unchanged associated with an improved graft and patient survival over time.

The most commonly used initial immunosuppression regimens were tacrolimus and steroids (42.2%) and tacrolimus, MMF, and steroids (35.3%).[63]

Several studies revealed that the insertion of MMF in LTx children allowed CNI dosage reduction with a consequent improvement in GFR,[64-66] with some protocols obtaining the CNI discontinuation.[67]

Moreover, only few episodes of acute rejection were revealed after CNI reduction when MMF was introduced as immunosuppressant agent, with main results observed in renal transplanted patients.[68]

Few pharmacokinetic data are available for MMF when used in combination with cyclosporine. A MMF dose of 740 mg twice daily would be recommended in pediatric LTx recipients, even though these findings should be confirmed by prospective trials.[69]

However, MMF has been related to an increased risk for trimester pregnancy loss and congenital malformations with specific embryopathy,[70] with clear implications when administered to young patients.

Alternatives could be found in prolonged-release tacrolimus formulations. A randomized study compared, in pediatric LTx, immediate- and prolonged-release tacrolimus effects, demonstrating good transplant outcomes over 1 year when prolonged-release tacrolimus was administered.[71]

It is well known that the prolonged-release formulation has been associated with reduced intra-patient variability in tacrolimus exposure in adults, improving adherence to treatment and long-term transplant outcomes.[72-74] There are limited clinical data in pediatric LTX and reported data are generally from small patient numbers.[75-77]

However, it is possible that pediatric LTx de novo treated with prolonged-release tacrolimus could achieve an optimized immunosuppression, reducing chronic side effects, such as nephrotoxicity.

Food and Drug Administration (FDA) recommended sirolimus therapy in patients aged 13 years or older receiving kidney transplants, whereas safety and efficacy as immunosuppressant in LTx patients have not well been established,[78] due to reported association with hepatic artery thrombosis.[79,80]

Subsequent studies, using sirolimus as primary immunosuppressive agent in LTx, have not confirmed these findings, showing an incidence of hepatic artery thrombosis with rapamycin similar to that seen with CNI.[81,82]

However, it is difficult to ignore FDA recommendations notified through a black box warning.

Everolimus, an mTOR inhibitor, was developed to improve the pharmacokinetic profile of sirolimus.[83] Several data have been obtained in the last decade about everolimus safety and efficacy in de novo LTx patients and after conversion from CNI,[84,85] with its approval by FDA as immunosuppressive agent in LTx, in combination with reduced dose of tacrolimus and steroids.

However, it is important to underline that mTOR inhibitor treatment is associated with a net increase in urinary protein excretion. In the H2304 study, higher incidence of proteinuria was reported, representing the leading cause of study drug discontinuation.[86]

Nielsen reported a single center experience, in which everolimus was given in 18 pediatric liver transplant recipients, as "rescue therapy" due to chronic graft dysfunction, CNI toxicity, hepatoblastoma, or recurrence of primary sclerosing cholangitis. An increase in GFR was noted in one of the three patients with suspected CNI nephrotoxicity.[87]

In the prospective trial H2305, GFR change has been evaluated after 12 months in 56 pediatric LTx who were added everolimus, reducing starting CNI dosage. This strategy improved renal function, but safety outcomes suggested over-immunosuppression, due to the high incidence of posttransplant lymphoproliferative disorder (PTLD) and serious infections.[88]

Similar conclusion was achieved in 56 pediatric LTx patients in which standard CNI therapy (± MMF) was converted to everolimus. Recruitment was stopped prematurely due to high rates of PTLD even though an increased eGFR from baseline (+6.2 mL/min/1.73 m^2) was observed.[89]

In clinical practice, main indications for mTOR inhibitors are limited to pre-existing liver malignancy, CNI nephrotoxicity or rejection. The main adverse events included hyperlipidemia, proteinuria, PTLD, dermatitis, and mucitis, with mean discontinuation rate about 25%.[90]

A new immunosuppressive agent, recently approved by the FDA, was the co-stimulatory inhibitor belatacept. In the phase 3 trial BENEFIT, adult transplant recipients prescribed belatacept with CNI avoidance exhibited better GFRs at 3 years posttransplantation.[91]

However, patients who are Epstein-Barr Virus naive are contraindicated for this treatment because of the higher rate of PTLD, which would exclude a large number of pediatric patients.

Another strategy that could be applied to pediatric LTx is based on several studies revealing that, especially in patients who are transplanted early in life or receive a parental living liver donation, a certain extent of immune tolerance toward the transplanted graft could be developed.

Single center experiences, in which patients were withdrawn from immunosuppression because of medical reasons, such as CKD, suggest that approximately 20% of LTx become operationally tolerant toward the graft, with a possible complete withdrawal of immunosuppressant drugs.[92,93]

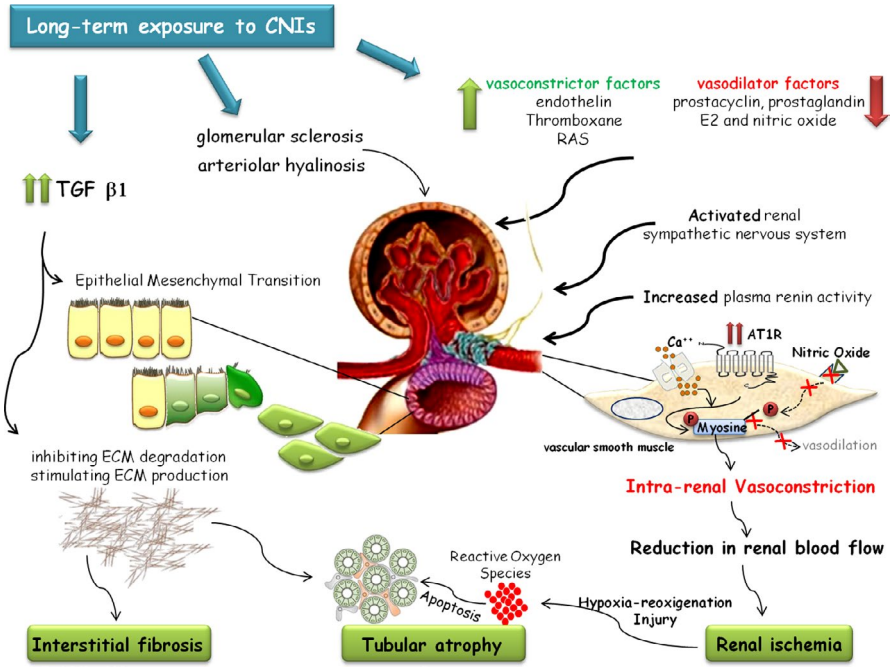

FIGURE 1 Nephrotoxic mechanisms of long-term calcineurin inhibitor exposure. CNIs, calcineurin inhibitor; RAS, renin-angiotensin system; TGF-β1, transforming growth factor beta 1; PKC-β, protein kinase C beta; ECM, extracellular matrix

However, no reliable markers are available to assess in which patient tolerance has been developed.

Two research groups, one studying children and the other evaluating adults, have reported that functionally tolerant LTx recipients have increased proportion and absolute numbers of circulating γδ T cells when compared to immunosuppression dependent LTx patients and healthy controls. Moreover, functionally tolerant subjects show a predominance of $V\gamma\delta1^+$ over $V\gamma\delta2^+$ cells, suggesting that the expression patterns of as few as 22 genes can accurately predict the outcome of withdrawal.[94,95]

This new immuno-genetic approach could identify patients with different risk profiles, obtaining a personalized immunosuppression until the interruption of the therapy, with obvious positive consequences.

However, these data are referred to very few patients and do not draw definitive conclusions. Multicentric studies are needed, analyzing GFR correctly and allowing to solve therapeutic doubts through valid guidelines inherent fist and second lines of treatment, according to renal function. Moreover, the required pediatric clinical trials, at the licensing stage for newer agents, could improve this situation in the future.

6 | CHRONIC KIDNEY DISEASE AFTER PEDIATRIC LIVER TRANSPLANT

Survival rates after pediatric LTx have been improved, but kidney disease impacts survival of children after transplantation.[96,97]

In the early posttransplant period, acute renal damage is often described and, after some years from the transplant, a not negligible prevalence of CKD, between 25% and 38%, is reported.[3,15,98]

One of the main determinant of this percentage is the presence of pre-transplant renal disease. Consequently, assessing accurately the renal function in the presence of advanced liver disease could predict, after LTx, AKI events, closely related to high risk for CKD development.[48,99]

However, early diagnosis and personalized treatment represent the bases of CKD management, in order to minimize its close relation with increased mortality.[100]

Consequently, all pediatric LTx recipients require mandatory and planned nephrologic evaluation to early detect renal impairment, considering that the development of end-stage renal disease after LTx increases patient mortality more than 40%.[101]

Mention studied renal outcomes in 12 children, transplanted at a median age of 7 years, evaluating their kidney function through serum creatinine, calculated GFR according to Schwartz formula and measured GFR through isotopic Cr-51-EDTA scintigraphy. Two peaks of renal worsening have been revealed, 2 years after the transplant and between the 7th and 10th year.[102]

This study, despite the not be entirely negligible small cohort, highlighted the risk to underestimate renal dysfunction, if the evaluation was based only on serum creatinine levels and related formulas. Another study prospectively analyzed the long-term renal function in pediatric LTx recipients, highlighting a significant reduction of renal filtration function only within the first year after transplantation.[51] However, whereas the authors concluded that no patients experienced a progression of CKD, it is also important to highlight the relative short follow-up period of 3 years.

If measuring GFR could be considered a not common procedure, according to these data, it is obvious to increase the renal surveillance at least after 5 years after LTx, when GFR started to

deteriorate. Another study, recording a progressive reduction of GFR from 5 to 7 years after LTx in 57 pediatric patients, strengthens this strategy.[103]

The largest study included 117 pediatric recipients of primary, solitary liver transplant, in which GFR was measured. After a mean follow-up of 7.6 years, 37 patients (31.6%) had a mGFR < 70 mL/min per 1.73 m^2, corresponding to stage ≥ 2 CKD.[104]

These studies clearly demonstrated a latent period after which renal damage has been revealed. Whereas renal issues observed within 1-2 years from LTx were often related to acute injuries, the physiopathology of renal damage observed in the late "crucial period," after 5-7 years from LTx, is based on chronic, irreversible mechanisms. Probably nephrotoxic comorbidities, related to immunosuppressant drug nephrotoxicity and/or other emerging diseases, such as diabetes, hypertension and/or cardiovascular disease, could explain why renal disease involves these patients only after a latent period.

In particular, arterial hypertension (HTN) is common among patients who have undergone LTx, representing a major contributor to cardiovascular events. However, few studies have studied the risk factors post-LTx in children. The principal etiologies are related to CNI use, stimulation of renin release, up-regulation of angiotensin II receptor, decreased GFR, enhanced sodium reabsorption, sympathetic over activity, use of corticosteroids, and impaired vasodilation system, due to reduced production of prostacyclin and nitric oxide.[105]

Moreover, HTN has been associated with tacrolimus predose concentration, with the need of amore intensive blood pressure surveillance in patients with high tacrolimus target to achieve.[106]

Given the high prevalence of masked hypertension, it is recommended to perform the ambulatory blood pressure measurement on all liver transplanted children, not to under-diagnose HTN.[107]

However, referrals to a pediatric nephrologist should be early made for patients with repeated blood pressures > 95th percentile, especially if associated with microalbumin/creatinine ratio > 32.5 mg/g.

In fact, proteinuria is not only a marker of kidney damage but also is responsible for progression of kidney injury, due to its direct toxic effect on glomerular capillary wall and tubular cells, leading to interstitial fibrosis and glomerulosclerosis.[108]

Moreover, high pre-transplant proteinuria or new onset after LTx has been related to renal dysfunction and mortality.[109]

However, we are evaluating young patients with a median age of 3 and 14 years, with potential nephrotoxic comorbidities that probably will be developed only during the adulthood, when the renal disease will arise.

The prognostic significance of these data about the evolution to end-stage renal disease remains unknown. The principal target is avoiding future renal transplant recipients.

Nevertheless, CKD may ultimately result in the need for dialysis. In a retrospective study involving more than eight thousands of LTx children, end-stage renal disease requiring dialysis, was observed in 2% of patients, characterized by a twofold increased risk of mortality.[110]

This rate is absolutely lower than adult patients, but renal function was evaluated in children with a median age of 3 years, in which renal plasticity probably compensates for function decline. In fact, subjects older than 15 years were characterized by the highest risk for dialysis. Moreover, the follow-up time in this study underestimates lifetime burden of end-stage renal disease, probably diagnosed and treated during the adulthood.

7 | NEPHROPROTECTIVE STRATEGIES IN LTX PEDIATRIC PATIENTS

The first step to optimizing post-LTx renal outcomes is to manage risk factors, identifying modifiable preoperative, perioperative, and postoperative factors that may affect kidney function.

In pre-transplant period, it is imperative evaluating the correct renal function through a staging flow-chart that must not be exclusively based on serum creatinine, especially if patients suffer from liver diseases, which are typically characterized by concomitant renal involvement.

If renal function cannot be established through measured GFR, cystatin C equation is a noninvasive and sensitive diagnostic tool to reveal renal dysfunction in LTx children, obtaining a better diagnostic data than Schwartz formula or other creatinine-related calculations. However, creatinine is inexpensive and noninvasive and often it represents the only biomarker available in clinical practice for renal function monitoring. Enzymatic method could help to reduce sensitivity and specificity of the test.

The accurate measurement of the drug level is important to be protected from immunosuppression and its side effects.

Cyclosporine levels can be measured from plasma or from whole blood to be able to follow toxic complications. At first, C0 (the time right before taking the drug) levels were used. However, time length to reach the high concentrations after the cyclosporine application ranges between 0 and 4 hours. It reaches to its highest level in the 2nd hour. For this reason, it was attempted to foresee the drug exposure and clinic outcome by following the plasma levels in the C2 after having taken the drug.[111,112]

Moreover, analyze the link between therapeutic effects of immunosuppressant drugs and single nucleotide polymorphisms could play a central role for personalizing immunosuppressant therapy, especially for CNI, whose high hematic levels are related to nephrotoxicity.

While standard immunosuppressant protocols, based frequently on tacrolimus, MMF, and steroids, provide best guarantee for rejection outcomes, dynamic protocols based on CNI sparing regimens are necessary in children to minimize the well-known side effects.

A representative study reports the experience with a CNI-free regimen of mycophenolate mofetil, steroids and basiliximab induction with delayed introduction of sirolimus in 27 adult patients with a median preoperative GFR of 24 mL/minute. Over the 1-year

follow-up, these patients experienced no rejection and marked GFR improvements.[113]

Favorable renal effects, obtained by different immunosuppressant, such as sirolimus or MMF, have been supposed, but, to date, little data are available in LTx pediatric recipients. Prolonged-release tacrolimus formulations should be considered.

Finally, when renal dysfunction emerges post-LTx, an optimal control of arterial hypertension and proteinuria, through angiotensin converting enzyme inhibitors, could exert nephroprotective effects, even in pediatric patients.

8 | CONCLUSIONS

Kidney function can be highly preserved following LTx even in patients with CKD, providing that LTx is not contraindicated in patients with renal involvement, but receiving optimal immunosuppressive management.

Recommendations for closer monitoring of kidney function include frequent assessment of serum creatinine and potentially adding cystatin C, monitoring of proteinuria and microalbuminuria, calculation of GFR using modified Schwartz equation, and monitoring of blood pressure with referrals to a nephrologist as appropriate.

CONFLICT OF INTEREST

The authors have no conflict of interest to disclose that could be perceived as prejudicing the impartiality of the research reported.

AUTHOR CONTRIBUTIONS

Lacquaniti A designed, drafted, and revised the article. Campo S, Casuscelli Di Tocco T, Rovito S, Bucca M, and Ragusa A revised and approved the article. Monardo P designed, revised and approved the article.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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How to cite this article: Lacquaniti A, Campo S, Casuscelli Di Tocco T, et al. Acute and chronic kidney disease after pediatric liver transplantation: An underestimated problem. *Clin. Transplant*.2020;34:e14082. https://doi.org/10.1111/ctr.14082