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ORIGINAL ARTICLE

Key role of renal biopsy in management of progressive chronic kidney disease in liver graft recipients

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Abstract

Aims Chronic kidney disease (CKD) is a common complication after liver transplantation (LT). The etiology of CKD is broad and may only be assessed accurately by renal histology. The current study aimed to analyze the safety of renal biopsy in daily clinical practice as well as its usefulness regarding management of CKD after LT.

Methods We performed a retrospective analysis of clinical data and renal biopsies obtained from patients with severe renal impairment (overt proteinuria, progressive deterioration of renal function) after LT with respect to safety, etiology of renal disease, and therapeutic consequences.

Results Renal biopsies were obtained from 14 patients at median (minimum–maximum) 3 (0.2–12) years after LT. No major complications associated with renal biopsy were observed. Histomorphological alterations were varied (nephrosclerosis, n = 5; IgA-glomerulonephritis, n = 4; tenofovir-associated nephropathy, membranoproliferative glomerulonephritis type 1, membranous glomerulonephritis, amyloid A amyloidosis, and calcineurin inhibitor nephropathy, n = 1, respectively). The diagnosis of specific renal diseases other than calcineurin-inhibitor nephrotoxicity facilitated specific treaments and avoided unnecessary modification of immunosuppression in the majority of patients.

Conclusions Renal biopsy in patients with CKD after LT seems safe and may offer specific therapeutic options. Furthermore, unnecessary changes of immunosuppression can be avoided in a considerable number of patients.

Keywords Chronic kidney disease · Liver transplantation · Biopsy · Etiology

Abbreviations

ALT	Alanine transaminase
AST	Aspartate transaminase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CKD	Chronic kidney disease
CMV	Cytomegalovirus
CNI	Calcineurin inhibitor(s)
CsA	Cyclosporine A
DN	Diabetic nephropathy
eGFR	Estimated glomerular filtration rate
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus

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Maximum	Max.
MELD	Model of end stage liver disease
Minimum	Min.
MMF	Mycophenolate mofetil
mTOR	Mechanistic target of rapamycine
LT	Liver transplantation
SIR	Sirolimus
SD	Standard deviation
sec	Seconds
TAC	Tacrolimus
ULN	Upper limit of normal

Introduction

Chronic kidney disease (CKD) is common after liver transplantation (LT) and the mortality rate correlates with severity of renal impairment [1–3]. Early renal dysfunction after LT has been associated with the use of the calcineurin inhibitors (CNI) cyclosporine A (CsA) and tacrolimus (TAC) [4]. Notably, all approved immunosuppression regimens to prevent liver graft rejection contain either CsA or TAC. Nevertheless, the etiology of CKD after LT may be multifactorial and even independent from CNI nephrotoxicity as independent risk factors for CKD such as arterial hypertension and diabetes mellitus are common after LT [3, 5, 6]. Remarkably, the majority of studies addressing therapeutic interventions in patients with renal failure after LT focus on modification of immunosuppression without prior histological proof of CNI nephrotoxicity [7–26]. The sum of patients investigated in these studies, mainly without renal biopsy, markedly outnumbers the reported histological-based analyses of renal disease after LT [27–30].

Although improvement of kidney function in patients with CKD after LT has been observed following CNI withdrawal or reduction in general, the effect was of only doubtful clinical significance in some studies, and was more pronounced the earlier the immunosuppression was commenced after LT modification [13–25]. On the other hand, low exposure to CNI as well as conversion from a CNI to a mammalian target of rapamycin (mTOR) inhibitor has recently been associated with antibody-mediated liver graft rejection [31]. Therefore, modification of immunosuppression without histological confirmation of CNI nephropathy could harm the patient and, moreover, the existence of concurrent specific renal diseases and thereby the chance to administer specific treatment options may be missed. Thus, renal biopsy could guide further therapeutic approaches with regard to preservation or improvement of renal function, but it is performed only infrequently both in daily clinical practice and clinical studies, presumably because of its invasive nature and uncertainty of the clinical consequences.

Exact determination of CKD may be of special importance in patients with rapid and severe deterioration of renal function, and renal biopsy may be justified particularly under these conditions. The aim of the present study was therefore to focus on patients with progressive and severe CKD after LT and evaluate whether renal biopsy in liver graft recipients is a safe procedure in daily clinical practice and whether the histological results are of importance for further treatment of renal disease.

Methods

Study design

Renal biopsy in general is indicated in patients with clinically significant renal disease and presumable therapeutic consequences [32]. The present retrospective study was performed between 2011 and 2015 in liver graft recipients attending the LT follow-up clinic at a German tertiary center. Renal function was assessed by use of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula in ml/min/1.73 m^2 [33]. According to our center's protocol, all patients with new onset of overt proteinuria or progressive renal failure defined by a persistent (at least 3 months) decline of estimated glomerular filtration rate (eGFR) of at least 30 ml/min/1.73 m^2, or both, were considered for a renal biopsy.

Study approval was obtained by the local Ethics Committees for Medical Research in accordance with the 1975 Declaration of Helsinki. Main exclusion criteria were prior kidney transplantation or age < 18 years. Medical history, clinical, and biochemical data as well as immunosuppressant trough levels were assessed at the time of renal biopsy, as well as 6 and 12 months after renal biopsy. Concomittant risk factors for CKD such as arterial hypertension, diabetes mellitus, dyslipoproteinemia, and nicotine consumption were recorded. All patients received optimized treatment of comorbidities with a known influence on renal function, e.g. arterial hypertension, diabetes mellitus, and dyslipidemia, independently of the renal biopsy according to current international guidelines [34–36].

Immunosuppression

The standard immunosuppression protocol at our center during the study phase included intraoperative induction therapy with the interleukin (IL)-2 receptor antagonist basiliximab and 500 mg methylprednisolone i.v. A second dosage of basiliximab was applied on day 4 after LT. Initial immunosuppression consisted of mycophenolate mofetil at a daily dose of 2 g, and CNIs were not introduced before day 3 after LT. All but one patient included in the current study were

transplanted at our center. Maintenance immunosuppression contained CNI alone or in combination with mycophenolate mofetil and occationally prednisolone. An mTor containing regime was possible to be chosen in individual cases.

Renal biopsy

Preparation of renal biopsy included physical and ultrasound examination, a biochemical profile, blood and platelet count, prothrombin time, partial thromboplastin time and in-vitro bleeding time. Per protocol renal biopsy was done only as an inpatient procedure. Percutaneous renal biopsy itself was performed in the prone position under local anesthesia with a 14 gauge spring-loaded needle (CR Bard GmbH, Karlsruhe, Germany) under real-time ultrasonic guidance into the lower pole of the left kidney. Post-biopsy patients had to remain at bed rest overnight. To detect bleeding and other complications, vital functions such as heart rhythm and blood pressure were monitored for at least 24 h. Additionally, urine analysis, complete blood count as well as ultrasound examinations were obtained at least 4 and 16 h post intervention.

Histological assessment of kidney biopsies

Histology of kidney biopsies was read by specialized pathologists as described previously [37]. All renal biopsy specimens were submitted for diagnostic purposes (light microscopy, immune histology, electron microscopy) and processed using a standardized routine protocol. For most renal diseases and classification schemes, an adequate biopsy has to contain at least ten glomeruli. In the current study, adequacy of sample size was determined by the specialized renal pathologist. Briefly, formalin-fixed and paraffin-embedded kidney biopsy specimens were sectioned into 2 µm thick paraffin sections with at least 8 serial sections stained either by periodic acid-Schiff (PAS) or hematoxylin–eosin (HE) stainings. Additionally, a Congo red staining as well as immunohistochemical stainings with antisera specific for immunoglobulin (Ig)A (1:150,000), IgG (1:100,000), IgM (1:75,000), C1q (1:75,000) and C3c (1:75,000, all polyclonal rabbit antisera, Dako Cytomation, Hamburg, Germany) were performed in all cases. In Congo red positive cases, additional stainings with antibodies specific for the kappa (1:50,000) and lambda (1:100,000) light chains (both polyclonal rabbit antisera, Dako) and for amyloid A (1:500, monoclonal, mouse, clone mc-1, Dako) for differentiation of the amyloid deposits were initiated.

Biopsy serial sections were evaluated according to standard nephropathological protocols, which includes (1) analysis of percentage of cortical and medullary tissue, (2) quantitative and qualitative glomeruli assessment with special respect to globally or segmentally sclerosis, and (3) reporting of any intra- or extracapillary proliferation. Within the tubulointerstitium acute or chronic damage, interstitial fibrosis and inflammation were reported and quantified if possible. Intrarenal arteries and arterioles were evaluated in terms of wall thickening, hyalinosis, inflammation as well as acute or chronic thrombosis. In electron micropscopy, glomerular ultrastructure was analyzed with respect to changes of the glomerular basement membrane, podocyte foot process effacement, endothelial cell damage, and osmiophilic or fibrillary deposits.

A special focus was placed on signs of acute and chronic CNI nephrotoxicity. Acute CNI effects are considered mostly hemodynamically-mediated and may comprise any morphological lesion. The corresponding histopathological lesions comprise acute tubular damage with characteristic isovolumetric vacuolisation of the cytoplasm of tubular epithelial cells being the most common morphological feature. In contrast, chronic CNI-nephrotoxicity comprises patchy or striped tubular atrophy and fibrosis, tubular microcalcification and most typically a nodular type of arteriolar hyalinosis [38].

Statistical analyses

Clinical and biochemical characteristics of patients were expressed as mean ± standard deviation (SD) or median [minimum (min.)–maximum (max.)] as appropriate. Correlations between two variables were calculated by the Friedman test. Unless indicated otherwise, all tests were two tailed and p values < 0.05 were considered significant.

Results

Patients' characteristics

Overall, 102/221 (46%) liver graft recipients attending the post LT surveillance program had impaired renal function. Criteria for renal biopsy were fulfilled in 14 patients within the respective study period. The median (range) age at time of renal biopsy was 53 (32–63) years, and renal biopsy was performed at a median (range) interval after LT of 3 (0.2–12) years. Detailed patients' characteristics at renal biopsy are reported in Table 1. At the time of renal biopsy, 12/14 patients were receiving a CNI-based immunosuppression protocol, while the other two patients were on an mTOR-inhibitor and a mycophenolate mofetil monoimmunosuppression regimen, respectively. Co-medication with mycophenolate mofetil or low dose prednisolone was administered in ten and three patients, respectively. No patient received a CNI/mTOR inhibitor combination protocol at the time point of renal biopsy (Table 2).

Table 1 Clinical characteristics of patients with renal biopsy after liver transplantation

Parameter	Patients (n = 14)
Demography	
Age, years; median (min.–max.)	56 (34.4–75.4)
Gender distribution, male/female	11/3
Ethnicity	
Caucasian, n (%)	14 (100)
General and transplant specific medical data	
Etiology of liver disease prior LT	
Autoimmune, n (%)	1 (7)
HBV, n (%)	2 (14)
HCV, n (%)	5 (36)
Alcohol, n (%)	4 (29)
Cryptogenic, n (%)	1 (7)
Adenomatosis, n (%)	1(7)
Bilirubin at LT, mg/dl; median (min.–max.)	2.65 (0.3–54.7)
Creatinine at LT, mg/dl; median (min.–max.)[a]	1.02 (0.67–3.39)
CKD-EPI at LT, ml/min/1.73 m^2; median (min.–max.) [a]	75 (18–108)
MELD-score at LT, median (min.–max.)	28 (6–40)
CMV reactivation after LT	2 (14)
HBV liver graft infection, n (%)	2 (14)
HCV liver graft infection, n (%)	4 (29)
HIV coinfection, n (%)	1 (7)
HCC prior to LT, n (%)	5 (36)
Recurrent HCC after LT, n (%)	2 (14)
Biochemistry at time of renal biopsy	
aPTT, sec; median (min.–max.)	34 (24–37)
Bilirubin, mg/dl; median (min.–max.)	0.4 (0.2–2.7)
ALT, /ULN; median (min.–max.)	0.5 (0.2–3.0)
INR median (min.–max.)	1.00 (0.85–1.26)
Creatinine, mg/dl; median (min.–max.)	1.83 (1.00–5.32)
Platelets, nl; median (min.–max.)	139 (78–242)
Proteinuria, mg/day; median (min.–max.)	1244 (160–9241)
CKD-EPI, ml/min/1.73 m^2; median (min–max)	39.84 (8.49–64.02)

LT liver transplantation, *CKD-EPI* Chronic Kidney Disease Epidemiology Collaboration, *MELD* Model for End-Stage Liver Disease, *CMV* cytomegalovirus, *HBV* hepatitis B virus, *HIV* human immunodeficiency virus, *HCC* hepatocellular carcinoma, *HCV* hepatitis C virus, *aPTT* activated partial thromboplastin time, *sec* seconds, *ALT* alanine transaminase, *ULN* upper limit of normal, *INR* international normalized ratio

[a]Except 2 patients on dialysis

Assessment of risk factors and histological changes of kidney disease

Detailed information on risk factors of renal disease, immunosuppression, and histological assessment of renal biopsies is presented in Table 2. In particular, diabetes mellitus and arterial hypertension were present in 6/14 and 11/14 patients, respectively. Pre- and post-transplant dialysis was documented in 2 and 5 patients. Histological assessment of CKD showed a broad spectrum of underlying diseases with nephrosclerosis (n = 5) and mesangioproliferative IgA-glomerulonephritis (n = 4) being the most frequent forms. Tubular atrophy and interstitial fibrosis was present in all patients ranging from 5 to 70%. Of note, CNI pathognomonic changes, such as isometric vacuolization of proximal tubular cells, arteriolar hyalinosis with medial/peripheral nodules and striped pattern of tubular atrophy/interstitial fibrosis, were found in only 1 of 14 patients (Table 2).

Assessment of complications after renal biopsy, therapeutic consequences of kidney histology, and clinical course

Renal biopsy was a safe procedure in our cohort as no major complication was observed. A peri-renal hematoma without subsequent interventions was documented in 4/14 (29%)

Table 2 Correlation of risk factors for kidney disease, immunosuppression and histologial alterations in patients with kidney biopsy after liver transplantation

Patient	Gender	Duration of dialysis prior to LT (days)	Duration of dialysis after LT (days)	Interval between LT and kidney biopsy (years, months)	CNI/mTOR inhibitor[a]	Respective trough level (ng/ml)[a]	MMF (daily dose in mg)[a]	Prednisolone (daily dose in mg)[a]	Nicotine consumption (pack years)[a]	HTN[a]	Medical treatment of HTN[a]
1	Male	–	–	3, 1	TAC	5.10	1000	–	No	No	n.a.
2	Male	–	102	2, 1	TAC	4.50	720	–	No	Yes	–[b]
3	Male	–	–	2, 6	TAC	6.10	1500	–	Yes (> 100)	Yes	Lercandipin, valsartan
4	Female	–	178	0, 8	TAC	5.60	1000	–	Yes (30)	Yes	Carvedilol, ramipril, torasemide
5	Male	–	–	12, 2	n.a.	n.a.	1440	–	No	Yes	Candesartan, metoprolol, torasemide
6	Female	–	–	0, 2	TAC	7.30	1000	–	No	No	n.a.
7[d]	Female	12	7	1, 2	EVR	7.90	1000	–	No	No	Ramipril[c]
8	Male	–	88	4, 2	TAC	6.40	1000	–	Yes (20)	Yes	Valsartan
9	Male	–	–	3, 1	TAC	4.90	–	–	No	Yes	Ramipril
10	Male	154	–	3, 2	TAC	4.20	1000	–	Yes (27)	Yes	Amlodipin
11	Male	–	–	4, 9	TAC	4.20	–	–	Yes (20)	Yes	Hydrochlorothiazide Metoprolol, ramipril
12	Male	–	–	9, 0	TAC	4.10	1000	5	No	Yes	Amlodipine, bisoprolol, doxazosin, ramipril
13	Male	–	67	0, 5	TAC	5.50	1000	–	No	Yes	Carvedilol, lercanadipin, ramipril, torasemide
14	Male	–	–	11, 7	SIR	4.70	–	100[a]	No	No	n.a.

Table 2 (continued)

(Patient)	Treatment with statin	HbA1c (mmol/mol)	DM[a]	Medical treatment of DM	Serum creatinine (mg/dl)[a]	Hematuria[a]	Proteinuria (g/24 h)[a]	Main histological finding	IFTA
1	No	31.15	No	n.a.	1.5	Yes	0.2	TDF	5–10
2	No	n.a.	No	n.a.	2.2	Yes	3.9	Nephrosclerosis	50
3	Yes	34.43	No	n.a.	1.8	No	0.4	Nephrosclerosis	35–40
4	No	38.80	Yes	Insulin	4.5	No	1.2	DN, CNI toxicity	70
5	Yes	38.80	No	n.a.	2.1	Yes	9.2	IgA-glomerulonephritis	n.q.
6	No	34.43	No	n.a.	1.6	No	1.3	Nephrosclerosis	15–20
7[d]	Yes	58.47	Yes	Insulin, metformin	1.5	No	0.8	IgA-glomerulonephritis	15
8	No	31.15	No	n.a.	1,6	Yes	0.3	IgA-glomerulonephritis	15–30
9	No	44.26	Yes	Repagalinide	1.7	Yes	1.9	MGPN type 1	25–30
10	No	27.87	No	n.a.	1.4	No	1.4	Membranous GN	5–10
11	No	47.54	Yes	Insulin, vildagliptin	1.5	Yes	0.5	IgA-glomerulonephritis	25–30
12	No	53.77	Yes	Insulin	2.6	No	1.1	Nephrosclerosis	25
13	No	35.30	No	n.a.	2.4	No	0.4	Nephrosclerosis	40
14	No	31.04	No	n.a.	2.1	No	8.6	AA amyloidosis	n.q.

AA serum amyloid A, *CNI* calcineurin inhibitor, *CSA* cyclosporine A, *DM* diabetes mellitus, *DN* diabetic nephropathy, *EVR* everolimus, *GN* glomerulonephritis, *HTN* arterial hypertension, *IgA* immunoglobulin A, *IFTA* interstitial fibrosis and tubular atrophy, *MGPN* membranoproliferative glomerulonephritis, MMF mycophenolate mofetil, *mTOR* mammalian target of rapamycin, *n.a.* not applicable/available, *n.q.* not quantifiable, *SIR* sirolimus, *TAC* tacrolimus, *TDV* tenofovir associated nephrotoxicity

[a]At time of renal biopsy

[b]Diagnosis of arterial hypertension isochronic with rapid deterioration and renal biopsy

[c]Indication, renin–angiotensin–aldosteron-system inhibition to treat proteinuria

[d]This was the only patient with proteinuria prior to liver transplantation

patients by routine ultrasound 1 day after biopsy, whereas a complete uncomplicated course was observed in the remaining 10 patients.

In one patient with histological features of CNI nephrotoxicity, immunosuppression was changed from TAC to everolimus (EVR). However, renal function did not improve significantly, and TAC was reinitiated because of planned surgery. Of note, this patient received hemodialysis peri-transplant, and renal biopsy also demonstrated signs of diabetic nephropathy as the predominant underlying chronic renal disease. In the remaining 13 patients, modification of immunosuppression was not done in the knowledge of respective histological changes, whereas antiviral medication to target hepatitis B virus was changed in one patient with tenofovir nephropathy. In the remaining patients, CNI-independent nephropathy was treated according to specific nephrologic recommendations.

To further determine dynamics of renal function, eGFR was assessed 6 and 12 months after renal biopsy. Follow-up data were available in 13/14 patients after 24 weeks and after median (range) 361 (303–381) days, respectively. Dynamics of eGFR estimated by CKD-EPI formula are given in Fig. 1. In detail, mean ± SD eGFR was 39.49 ± 16.88 ml/min/1.73 m^2 at renal biopsy, and 38.17 ± 15.16 ml/min/1.73 m^2 12 months thereafter (p = n.s.), while mean ± SD TAC trough levels were comparable between time point of biopsy (5.26 ± 1.03 ng/ml) and follow-up after 12 months (4.81 ± 2.08, p = n.s.).

Discussion

Determination of correct diagnosis and optimal treatment of renal impairment after LT is challenging. The etiological spectrum is broad and the clinical course ranges from mild

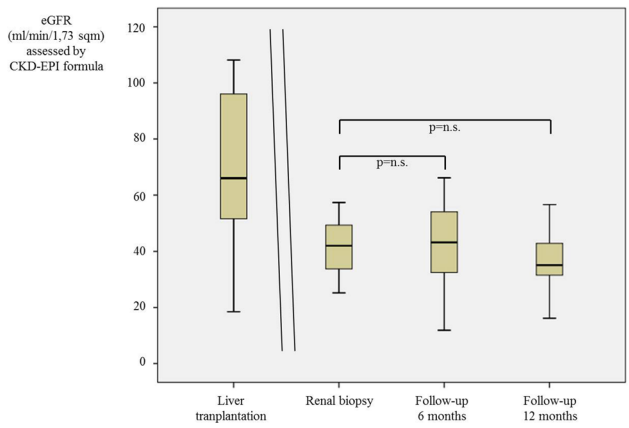

Fig. 1 Fig. 1 shows renal function at liver transplantation in comparison to renal function at time point of kidney biopsy and follow-up at 6 and 12 months thereafter, given as mean ± SD eGFR assessed by the CKD-EPI formula

and stable CKD to rapid deterioration of renal function [2, 3]. Although renal biopsy is considered indicated in patients with clinically significant renal disease and presumable therapeutic consequences based on the histological finding in general [32], data about histological changes in patients with CKD after LT are scarce [27–30]. In this study, we analyzed whether renal biopsy is safe after LT under daily clinical conditions and justified by the therapeutic consequences.

Our current data strongly encourage to perform kidney biopsies more frequently in patients with CKD after LT. The procedure was found to be safe and histological assessment revealed etiologies of CKD which would not have been established otherwise. Thus, results of renal biopsies enabled specific nephrologic treatment and helped to avoid unnecessary modification of immunosuppression. According to current data, kidney biopsy is a safe procedure [39]. In line with this study, we observed no severe complications in our case series of renal biopsy in liver transplant recipients. Thus, we suggest that renal biopsy may be considered more often in liver graft recipients developing renal impairment, including patients with preserved renal function and before development of proteinuria. Moreover, histologically-proven CNI nephrotoxicity was rare in our study, although the majority of patients received a CNI-based immunosuppression. In general, CNI-associated histomorphological changes are considered irreversible despite occasional reports of reversibility [40, 41]. However, it cannot be excluded that CNI nephrotoxicity contributed at least in part to the nephrosclerotic alterations observed in our study. Bearing this in mind, our data, although based on a limited number of patients, nevertheless indicate that CNI nephrotoxicity may not play the etiologic key role for CKD in long-term liver graft recipients as suggested by the high numbers of studies investigating reduction of CNI exposure to improve renal function after LT [13–25]. As low exposure to CNI has been associated with rejection and an unfavorable course after LT [31], CNI reduction or withdrawal without histologically-proven CNI nephropathy may not be recommended in patients with CKD after LT in general.

The results of our study must not be misinterpreted as implying that CNI nephrotoxicity is to be neglected as an important cause of CKD after LT. Of note, improvement or preservation of renal function has been shown in studies investigating CNI minimizing or avoiding strategies in the early period after LT [8–12, 26]. Histologically, CNI nephrotoxicity has been attributed to putative irreversible renal vessels injury, tubular atrophy and interstitial fibrosis [38]. However, the CNI target trough level in current immunosuppression regimens after LT is lower even in the first year after LT in comparison to the time shortly after introducing CNI in transplantation medicine, and this may have also influenced severity and verifiability of CNI nephrotoxicity over a longer time period. It has to be stressed that studies

investigating modification of immunosuppression in patients with established CKD after LT predominantly did not provide histological data to characterize CKD [7–26]. Clinically significant improvement of renal function after CNI reduction or withdrawal was not shown convincing and conclusive in all the respective studies in liver graft recipients with established CKD [7–26]. This could be explained by irreversible CNI-associated renal damage as well as concurrent etiologies. Given the low percentage of histologically-proven CNI in patients with CKD after LT in our and other studies [27–30], it seems reasonable that further interventional trials on this topic may use renal biopsy as an inclusion criterion.

Finally, it should be stressed that the results of our study must be taken with caution. The number of patients with renal biopsy was limited. This, however, is a common problem in studies investigating renal biopsy after LT [27–30]. Lee et al., for example, reported histological data in 10 of 544 liver graft recipients with CKD. Nevertheless, our results are reliable as the histological patterns found in our study are in line even with other studies investigating histologic alterations in patients with CKD after LT [27–30]. Furthermore, the spectrum of underlying renal diseases observed in the current study may have been influenced by the biopsy selection criteria. Although the criteria used seem reasonable because in these constellations the putative consequences can be considered to outweigh putative risks of the invasive procedure, it is likely that the results of the biopsies are not representive of the complete etiological spectrum of CKD after LT.

In conclusion, the findings of the current study indicate that renal biopsy after LT is safe and that the etiology of CKD after LT is varied including rare renal diseases. Without renal biopsy, the appropriate specific nephrological treatment could be missed. Thus, we suggest that patients with renal impairment after LT should be offered a thorough nephrological diagnostic workup including renal biopsy to explore other diagnoses than CNI toxicity with potential for specific treatment options.

Compliance with ethical standards

Conflict of interest Martin-Walter Welker, Consultancies/speaker's fees: AbbVie, Amgen, Bayer, BMS, Gilead, Novartis, Roche, Sequana Medical. Travel Support: AbbVie, Astellas, Bayer, BMS, Novartis, Janssen, Roche. Nina Weiler, Consultancies/speaker´s bureau for Astellas, Novartis. Wolf Otto Bechstein, Consultancies/speaker's fees: Astellas, Celgene, Gilead, Integra, Medupdate, MerckSerono, Novartis, Teva. Eva Herrmann, nothing to report. Christoph Betz, noting to report. Mark Schöffauer, nothing to report. Stefan Zeuzem, Consultancies/speaker's bureau for Abbvie, BMS, Gilead, Janssen, Merck. Christoph Sarrazin, Consultancies/Advisory boards: Abbott, BMS, Gilead, Janssen, Merck/MSD, Roche. Research support: Abbott, Gilead, Janssen, Siemens. Speaker: Abbott, BMS, Gilead, Janssen, Merck/MSD, Qiagen, Roche, Siemens. Kerstin Amann, Speaker/Advisory boards: Alexion, Böhringer Ingelheim. Oliver Jung, nothing to report. On behalf of the remaining authors, no financial, personal, or professional interests that could be construed to have influenced the paper have to be reported.

Ethical statement Study approval was obtained by the local Ethics Committee for Medical Research in accordance with the 1975 Declaration of Helsinki.

Informed consent For this type of study formal consent is not required.

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