Original article JOURNAL OF CLINICAL AND EXPERIMENTAL HEPATOLOGY

The Renal Histological Correlates of Refractory Renal Dysfunction After Liver Transplantation

Narendra S. Choudhary [*], Swapnil Dhampalwar [*], Neeraj Saraf [*], Shyam B. Bansal [†], Ashwini Gadde [†], Amit Rastogi [*], Prashant Bhangui [*], Abhyuday Rana [†], Alka Rana [‡], Arvinder S. Soin [*]

[*] *Institute of Liver Transplantation and Regenerative Medicine, Medanta the Medicity, Gurgaon, Delhi (NCR), India,* [†] *Institute of Nephrology, Medanta the Medicity, Gurgaon, Delhi (NCR), India and* [‡] *Department of Pathology, Medanta the Medicity, Gurgaon, Delhi (NCR), India*

Background: **Kidney dysfunction is common after liver transplantation (LT) and is often attributed to calcineurin inhibitors (CNIs). Very few studies have looked at histological causes.** ***Material and methods:*** **The study is a retrospective analysis of histological findings and diagnosis in all patients who underwent a kidney biopsy after LT from 2010 to 2020. Data are shown as mean ± standard deviation or medians (25–75 interquartile range).** ***Results:*** **The study cohort consisted of 26 patients (25 males, 1 female), aged 55 ± 7 years at the time of the kidney biopsy. Kidney biopsies were done at 27.5 (6.7–60.7) months after LT. At the time of the kidney biopsy, the median serum creatinine was 2.10 (1.50–2.86) mg/dl and proteinuria was 3.8 (1.8–5.9) gm/day. Twenty-four (92%) patients were on CNIs. The diagnoses on kidney biopsies were diabetic nephropathy (n = 7), focal segmental glomerulosclerosis (n = 4), CNI nephrotoxicity (n = 3), IgA nephropathy (n = 4), chronic glomerulonephritis (n = 3), hypertensive nephropathy (n = 1), membranous glomerulonephritis (n = 1), acute on chronic interstitial nephritis (n = 1), and C1q nephropathy (n = 1), and the sample was inadequate in one patient. A total of sixteen patients had progression of kidney disease. The kidney function remained stable/improved in 6 (23%) patients, follow-up data were not available for 4 patients. Fourteen (53.8%) patients (including one with CNI nephrotoxicity) required hemodialysis at 13.5 (5.7–29) months after the kidney biopsy.** ***Conclusion:*** **Although the kidney biopsy diagnosed the cause of unexplained renal insufficiency in LT recipients, the majority of patients progressed to end-stage renal disease despite treatment modifications. The use of CNIs was an uncommon cause of renal impairment. (J Clin Exp Hepatol xxxx;xxx:xxx)**

Chronic kidney disease (CKD) is one of the common causes of morbidity and mortality in the long term after liver transplantation (LT).[1–4] The problem of CKD after LT has become more important after a model for end-stage liver disease (MELD)-based organ allocation as creatinine is reflected in MELD score and patients with renal dysfunction get more MELD points.[5] The onset of CKD after LT is multifactorial, with immunosuppression, diabetes mellitus (DM), hypertension, and other contributory factors.[6–8] It is important to find out the cause of renal dysfunction in LT recipients to arrest the progression of kidney disease; however, data on kidney biopsy are limited to a few small series. While the authors of earlier studies considered calcineurin inhibitors (CNIs), i.e., cyclosporine and tacrolimus, to be the main causes of CKD in LT recipients,[9,10] later kidney biopsy-based studies have shown that CNI-related nephropathy accounts for only a minority of cases, with other diagnoses being more common.[11,12] In the current study, we aimed to study the kidney biopsy findings in LT recipients at our center.

MATERIAL AND METHODS

The study was conducted at a predominately living donor LT (LDLT) center in North India after approval by the Institutional Ethics Committee. Only adult patients (aged >18 years) at the time of LT were included. The data of LT recipients (LT from 2010 to 2020), who underwent a kidney biopsy, were retrospectively analyzed. A kidney biopsy was done in whom the correction of pre-renal factors and potential drug (including CNI reduction) nephrotoxicity was unsuccessful or in the presence of significant proteinuria/active urinary sediment. We use the following for immunosuppression: tacrolimus, mycophenolate mofetil (MMF, generally stopped at 2 years, unless kidney impairment or metabolic syndrome), and short-term prednisolone (for 3 months). Follow-up investigations include kidney function tests at the following intervals: weekly for the first 3 months, every 2 weeks in the next 3 months, monthly from 6 months to 2 years,

Keywords: Liver transplantation, immunosuppressant, calcineurin inhibitor, tacrolimus, complication
Received: 7.10.2022; *Accepted:* 21.1.2023; *Available online:* xxx
Address for correspondence: Dr Neeraj Saraf, Medanta Institute of Liver Transplantation and Regenerative Medicine, Medanta The Medicity hospital, sector 38, Gurgaon, Delhi (NCR), India Tel.: +919899077795.
E-mail: neerajsaraf@hotmail.com
Abbreviations: CKD: chronic kidney disease; CNI: calcineurin inhibitors; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; LDLT: living donor liver transplantation; LT: liver transplantation; MELD: model for end-stage liver disease; MMF: mycophenolate mofetil; mTORi: mammalian target of rapamycin inhibitors
https://doi.org/10.1016/j.jceh.2023.01.010

Please cite this article as: Choudhary et al., The Renal Histological Correlates of Refractory Renal Dysfunction After Liver Transplantation, Journal of Clinical and Experimental Hepatology, https://doi.org/10.1016/j.jceh.2023.01.010

and every 2 months thereafter. A proteinuria measurement was done at the baseline, 3 months, and 6 months thereafter. The following patients were considered for a kidney biopsy: proteinuria of more than 500 mg/day or the presence of active urinary sediments in a routine sample (red blood cells >5/high-power field and white blood cells> 5/high-power field) or in the presence of the rapid worsening of kidney functions. In patients with DM, a kidney biopsy was performed in the presence of the rapid worsening of kidney functions. A kidney biopsy was performed by nephrologists under real-time ultrasound guidance. All patients were informed about the need and indication of a kidney biopsy, and a written consent was taken before the procedure.

STATISTICAL METHODS

Categorical variables are shown as numbers and percentages and continuous variables are shown as means with standard deviation (parametric data) or median with a 25–75 interquartile range (non-parametric data). Fisher's exact test or chi-squared test was used for comparing categorical data. Continuous parametric variables are compared using a Student's t-test.

RESULTS

A total of 2114 adult (age >18 years at transplant) patients underwent LDLT in the study period. The study cohort included 26 patients (25 males, 1 female), aged 52.3 ± 7.5 years at the time of LT. The etiology of liver disease before LT was the following: alcoholic liver disease (n = 10), hepatitis C (n = 6), hepatitis B (n = 2), and non-alcoholic steatohepatitis or cryptogenic (n = 8). Pretransplant Child's score was 9.6 ± 1.9 and the MELD score was 16.1 ± 4.8. The study cohort aged 55.1 ± 7.5 years at the time of the kidney biopsy. A total of eighteen patients (69.2%) suffered from pretransplant acute kidney injury/hepatorenal syndrome. Pretransplant proteinuria was present in 8 (30.8%) patients. Pretransplant comorbidities were: DM in 11 (42.3%), hypertension in 6 (23.1%), and CKD in 4 (15.4%) patients. At the time of the kidney biopsy, the patients were on the following immunosuppression: CNIs and MMF (n = 23, 88.5%), mammalian target of rapamycin inhibitors (mTORi) + MMF (n = 2), and mTORi + CNI + MMF (n = 1). Post-transplant new-onset DM was present in 5 (19.2%) and new onset hypertension was present in 15 (57.7%) patients. The kidney biopsy was done at a mean of 27.5 (IQR 6.7–60.7, range 3–121) months after LT. The severity of CKD at the time of the biopsy was stage 2 in 4 (15.4%), stage 3 in 12 (46.2%), stage 4 in 6 (23.1%), and stage 5 in 4 (15.4%) patients. Active sediments in urine were present in 8 (30.8%) patients. The mean serum creatinine at LT was 1 ± 0.34 mg/dl, which increased to 2.1 (1.5–2.8) mg/dl at the time of the kidney biopsy. The corresponding estimated glomerular filtration rate (eGFR) was 85 (61–116) ml/min. at LT, which decreased to 34 (21–51) ml/min at the time of the kidney biopsy. The median 24-h proteinuria (data available in 24 patients) was 3.8 (1.8–5.9) grams before the kidney biopsy.

The diagnoses on kidney biopsies were as follows (after excluding one patient with an inadequate sample): diabetic nephropathy (n = 7, 28%), focal segmental glomerulosclerosis (n = 4, 16%), IgA nephropathy (n = 4, 16%), CNI nephrotoxicity (n = 3 out of 24 patients on CNIs, 12%), chronic glomerulonephritis (n = 3, 12%), hypertensive nephrosclerosis (n = 1), membranous glomerulonephritis (n = 1), acute on chronic interstitial nephritis (n = 1), and C1q nephropathy (n = 1). The liver function was stable at the time of the kidney biopsy; the median parameters were as follows: serum bilirubin 0.5 (0.2–0.6) mg/dl, aspartate transaminase 24 (18–29) IU/L,and alanine transaminase 22 (15–38) IU/L. The serum albumin was 2.9 ± 0.69 g/dl at the time of the biopsy. The study cohort was followed up until October 2021, with a median follow-up of 13.5 (5.7–29) months. A total of 16 (61.5%) patients had progression of kidney disease despite treatment modification, and fourteen (53.8%) patients required hemodialysis during the follow-up. Serum creatinine improved in three patients, while kidney function remained stable in three patients. Follow-up data were not available for four patients (Table 1). A total of fourteen (53.8%) patients (including one with CNI nephrotoxicity) required hemodialysis at 13.5 (5.7–29) months after the kidney biopsy. There was a history of biopsy-proven T-cell mediated acute cellular rejection in four (15.4%) patients; none of these episodes happened after the kidney biopsy (immunosuppression modification). The diagnoses in these patients were CNI nephropathy (n = 1), diabetic nephropathy (n = 1), chronic glomerulonephritis (n = 1), and IgA nephropathy (n = 1). The first two of the patients with acute T cell-mediated-rejection also had a history of cytomegalovirus viremia.

Proteinuria was present in four patients before LT. The serum creatinine at the baseline was 1.1 mg/dl in these patients, with median proteinuria of 1.5 gm/day. The kidney biopsy after LT showed diabetic nephropathy in two and focal segmental glomerulosclerosis in two patients. Three of these patients progressed to end-stage renal disease (ESRD) during follow-up. The following changes were made in the immunosuppression: CNI was stopped in six and reduced in four patients, steroids were added in 14, a low dose CNI was added in the place of everolimus in six patients, and mTORi was added to immunosuppression in two patients. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers were added in 13 patients. Althoughwe compared patients who had stable disease or improvement (n = 6) with patients who had

Please cite this article as: Choudhary et al., The Renal Histological Correlates of Refractory Renal Dysfunction After Liver Transplantation, Journal of Clinical and Experimental Hepatology, https://doi.org/10.1016/j.jceh.2023.01.010

Table 1 Individual Characteristics of the Study Cohort.

Diagnosis	Patient number	Age at biopsy/gender	eGFR at biopsy (mL/min/1.73 m^2)	Proteinuria (gm/day)	Duration from LT (month)	Follow-up duration (month)	Course
Diabetic nephropathy (n = 7)	1	52/M	6	2.9	121	11	ESRD
	2	56/M	21	5.6	63	21	ESRD
	3	54/M	45	7.6	15	24	[a]
	4	51/M	63	3.5	6	35	ESRD
	5	45/M	51	4.9	7	12	ESRD
	6	57/M	38	0.8	34	10	ESRD
	7	59/F	36	8.3	5	4	Improvement
Focal segmental glomerulosclerosis (n = 4)	8	55/M	31	8.5	13	19	ESRD
	9	58/M	17	1.8	41	5	ESRD
	10	67/M	75	3.8	26	6	Improvement
	11	64/M	51	4.1	15	42	Stable
IgA nephropathy (n = 4)	12	53/M	45	7.9	3	59	ESRD
	13	64/M	22	4.8	84	27	ESRD
	14	52/M	53	[a]	4	44	ESRD
	15	58/M	32	5.5	3	1	[a]
CNI nephrotoxicity (n = 3)	16	40/M	52	2.2	29	6	Stable
	17	54/M	33	1.1	72	8	Improvement
	18	70/M	23	3.9	37	36	ESRD
Chronic glomerulonephritis (n = 3)	19	60/M	23	2.9	70	4	Stable
	20	43/M	40	1.2	16	116	ESRD
	21	56/M	14	2.7	38	18	ESRD
Hypertensive nephrosclerosis (n = 1)	22	62/M	29	1.6	25	2	[a]
C1q nephropathy (n = 1)	23	62/M	13	1.7	85	5	ESRD
Acute tubulointerstitial nephritis (n = 1)	24	42/M	10	[a]	45	7	ESRD
Membranous glomerulonephritis (n = 1)	25	52/M	78	6.1	60	15	[a]
Inadequate sample (n = 1)	26	48/M	71	8.6	3	24	ESRD

Abbreviations: CNI, calcineurin inhibitors; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease.
[a]Data not available.

progressive disease (n = 16) as shown in Table 2, none of the factors were statistically significant except for the follow-up duration, which was significantly longer in the group that progressed to ESRD. eGFR was better in the stable/improved group (45 ml/min vs. 32 ml/min), but this difference did not reach statistical significance. Also, time to the kidney biopsy was early in the stable/improved group (Table 2) that did not reach statistical significance.

A total of nine patients died during the follow-up. All mortalities were in the dialysis group, with sepsis and multiorgan failure being the common causes. One patient died due to COVID-19. Two patients are listed for kidney transplantation, while the one who received kidney transplant is doing well. Other patients on dialysis may also require kidney transplantation.

Complications of Kidney Biopsy

One patient developed perinephric hematoma, which was managed conservatively. There were no complications in rest of the patients.

DISCUSSION

CKD is common after LT and results in significant morbidity and mortality in the long term.[1,4] As the MELD score is heavily influenced by serum creatinine values, patients with some form of kidney disease often undergo LT but remain at a higher risk of CKD after LT. Sharma *et al.* found that CKD was 15% higher in the MELD era.[5] Ojo *et al.* performed an analysis of the Scientific Registry of Transplant Recipients data of solid (non-renal) organ transplantation. The cumulative incidence

Please cite this article as: Choudhary et al., The Renal Histological Correlates of Refractory Renal Dysfunction After Liver Transplantation, Journal of Clinical and Experimental Hepatology, https://doi.org/10.1016/j.jceh.2023.01.010

Table 2 Comparison of Patients With Progressive (n = 16) Versus Improvement or Stable Disease (n = 6)[a].

Parameter	Progressive (n = 16) decline of eGFR	Stable or improvement in eGFR (n = 6)	*P* value
Age at liver transplant (years)	51.0 ± 7.0	54.1 ± 10.2	0.42
Age at time of kidney biopsy (years)	54.0 ± 7.5	57.3 ± 9.5	0.40
MELD at liver transplant	16.5 ± 5.1	15.5 ± 5.9	0.68
Creatinine at liver transplant mg/dl	1.08 ± 0.37	0.83 ± 0.28	0.16
eGFR at the time of transplant (by MDRD 4, ml/min)	82.1 ± 30.7	98.5 ± 33.4	0.29
Pretransplant proteinuria	6 (37.5%)	1 (16.6%)	0.61
Diabetes mellitus Total (before transplant + new onset)	11 (7 + 4)	3 (2 + 1)	All *P* values are not significant
Hypertension Total (before transplant + new onset)	14 (3 + 11)	5 (2 + 3)	All *P* values are not significant
Chronic kidney stage at the time of kidney biopsy 2:3:4:5	2:6:4:4	1:4:1:0	0.47
Time to kidney biopsy from liver transplant (months)	35 (6–58)	27 (12–70)	0.94
Proteinuria at the time of kidney biopsy (grams/24 h)	4.2 ± 2.4 (n = 14 patients)	3.7 ± 2.4	0.70
Active sediments in urine	0	7	0.12
Creatinine at the time of kidney biopsy	3.1 ± 2.2	1.7 ± 0.6	0.14
eGFR at the time of kidney biopsy (by MDRD 4, ml/min)	32.3 ± 19.8	45.0 ± 18.4	0.19
Follow-up after kidney biopsy (months)	20 (10–35)	6 (4–16)	0.039

Abbreviations: eGFR, estimated glomerular filtration rate; MDRD, modification of diet in renal disease , MELD, model for end-stage liver disease
[a]Four patients with no follow-up data were excluded from this table.

of CKD (defined as eGFR <29 ml per minute per 1.73 M^2 of the body-surface area) was 18% at 5 years in LT recipients. The risk of CKD was more in the recipients of intestinal transplants, followed by liver, heart, or lung transplants (combined or isolated).[1] Guisto *et al.* found CKD (defined as eGFR <60 ml/min) in 45% of patients at 5 years in a cohort of 179 patients. The estimated GFR at LT, the development of hypertension, and episodes of severe infection were prognostic factors in Cox regression time-dependent analysis.[2]

Watt *et al.* analyzed data from 798 liver transplant recipients. In their series, renal failure contributed to 6% of the deaths. Patients with older age, diabetes, and renal insufficiency were at the highest risk of poor survival.[3] In a long-term follow-up study of 1,211 LT recipients, 9% underwent kidney transplantation, while 21% and 18% had mGFR 59–30 and < 30 ml/min, respectively. The risk of death increased when measured GFR (by iothalamate clearance) decreased <30 ml/min (HR = 2.67 or < 15 ml/min (HR = 5.47).[4]

The kidney dysfunction in LT recipients is multifactorial and related to pre-existing renal impairment, pre- and peri-transplant acute kidney injury events, the nephrotoxic effect of immunosuppressive medications, and comorbid conditions like DM and hypertension. It is important to identify kidney impairment early as it is difficult to prevent progression once serum creatinine is significantly elevated.[6,7]

CNIs (Tacrolimus and Cyclosporine)-induced nephrotoxicity contributes to both short- and long-term renal function deterioration. The acute component is mediated by afferent arteriolar vasoconstriction, which is caused by an imbalance of vasoconstrictors and vasodilators. This afferent arteriolar vasoconstriction causes a dose-related acute and reversible decrease in GFR, renal blood flow, and urine output. Chronic CNI exposure affects renal vessels (arteriolar hyalinosis), tubulointerstitium (the presence of tubular atrophy and interstitial fibrosis), and glomeruli (the thickening and fibrosis of Bowman's capsule and glomerular sclerosis). The mechanisms of chronic CNI nephrotoxicity include hemodynamic changes and possible direct effects on tubular epithelial cells.[7,13]

The use of CNIs was considered a major cause of kidney dysfunction in LT recipients. Gonwa *et al.* concluded that kidney dysfunction was due to CNIs in the majority (73.3%) of patients, however, this study was based on clinical impression. The authors attributed kidney disease to CNIs in the absence of other known diseases, and biopsies were available in only a few patients.[9] Another old series also showed the changes of CNI nephrotoxicity on a kidney biopsy in nine cases.[10] Later studies showed that other risk factors for CKD (perioperative acute kidney injury, diabetes mellitus, and hypertension) also play a significant role. Pillebout *et al.* examined the renal biopsies of 26 recipients with chronic renal failure, at a mean of 5 years after

Please cite this article as: Choudhary et al., The Renal Histological Correlates of Refractory Renal Dysfunction After Liver Transplantation, Journal of Clinical and Experimental Hepatology, https://doi.org/10.1016/j.jceh.2023.01.010

LT. Twelve patients were diabetic and 25 were hypertensive. Histology revealed interstitial fibrosis and glomerular sclerosis (mean 45%) and severe arteriosclerosis in all biopsies. There were four main diagnoses: chronic CNI arteriolopathy, typical diabetic nephropathy, acute or chronic thrombotic microangiopathy (attributed to CNI or alpha-IFN), and tubular changes due to the administration of hydroxyethyl starch.[14]

Later studies (after 2010) with more than 10 kidney biopsies have reported CNI-related changes on histopathology in only 7.1%–30% of the patients.[11,12,15–17] This fact may be related to the lower doses of CNIs in the current era. Lee *et al.* reported CNI-related changes in 3/10 LT recipients at a median of 24.5 months. Eight of the 10 patients showed improvement on follow-up after treatment modification.[15] Welker *et al.* reported CNI nephropathy in 1 of 14 patients at a median of 3 years after LT. The main diagnoses of the kidney biopsy were nephrosclerosis (n = 5) and IgA glomerulonephritis (n = 4).[16] Similar to this study, Chan *et al.* showed that one of the 10 biopsies revealed CNI-related changes. DN and IgA nephropathy were the most common etiologies.[17] In a series by Tsapenko *et al.*, 23 recipients underwent a kidney biopsy at a median of 6.9 years after LT. The median serum creatinine was 2.2 mg/dl at the time of the kidney biopsy. The main diagnoses were focal segmental and global glomerulosclerosis in eight patients and glomerular diseases in seven patients. The features of diabetic nephropathy and CNI toxicity were present in 2 and 2 patients (8.7%), respectively. More than half of the patients developed ESRD during the follow-up with mortality being more common in patients with ESRD.[11] In the largest study by Kim *et al.*, 81 LT recipients with impaired kidney function or new proteinuria underwent a kidney biopsy at a mean of 4.8 years after transplant. The baseline parameters at the time of the biopsy were as follows: mean serum creatinine 2.0 mg/dl, eGFR 38.7 mL/min (by MDRD-4 formula), and 24-h urine protein 1.37 g. A total of 42% of biopsies showed primary glomerular diseases, and 16% had the evidence of CNI toxicity. Eight of these patients progressed to ESRD at a mean follow-up of 20 months.[12]

It is important to identify renal dysfunction early as treatment modification can prevent progression. Various immunosuppression modification strategies used are the minimization of CNIs, the addition of MMF (generally with the minimization of CNIs), or mTOR inhibitors. A late change may not help.[18–22]

It is possible that some of the changes/diseases in a kidney biopsy might be there before the liver transplant, and a temporal relation with the transplant cannot be established in all cases (other than in patients with diabetes and hypertension). Some studies have looked at pre-liver transplant kidney biopsies. McGuire *et al.* performed 30 kidney biopsies in patients with hepatitis C at the time of liver transplant. A total of 25 patients had immune-complex glomerulonephritis.[23] Wadei *et al.* performed a kidney biopsy in 44 LT candidates. IgA nephropathy was the most common finding (45%) case, followed by membranoproliferative glomerulonephritis in 14% and diabetic nephropathy in 11% of patients. Some biopsies also revealed more than one finding.[24] Calmus *et al.* observed a 55.3% diagnosis of renal disease in 60 patients. The common diagnoses were IgA nephropathy (n = 15) and diabetic nephropathy (n = 7). At 5 years after LT, renal functions were worse in patients with diabetic lesions as compared to normal histology or IgA nephropathy alone.[25] Pichler et al. found that common pathological diagnoses on kidney biopsies were membranoproliferative glomerulonephritis (23%), IgA nephropathy (19%), and acute tubular injury (19%).[26] In a study, systemic hypertension at the time of LT evaluation correlated with the kidney histology.[27]

The limitations of the current study include its retrospective nature and the presence of significant proteinuria (possibility of a selection bias against CNIs) in the majority of patients. The study lacks a number of patients with kidney dysfunction (or total number of patients with eGFR <30) from this period, so we do not have a comparator group (without a kidney biopsy or all patients with a pre-transplant kidney injury). Not all patients with kidney dysfunction or CNI dose reduction because of rising creatinine underwent a biopsy in the case of improvement as a kidney biopsy can result in severe complications. Also, the follow-up after the kidney biopsy is relatively short. However, it should be noted that a kidney biopsy is an invasive procedure with a significant risk of complications, and cannot be done in all patients without good indication. Although 26 patients were included, it is a relatively large cohort considering the nature of the study, data from LDLT setting, and the recent era are other strengths of the study. The study showed that there were several causes of kidney dysfunction in LT recipients, among which CNI contributed to only a minority (12%) of the cases. It may be related to the lower doses of tacrolimus used in Indian patients or in the LDLT setting. Diabetic nephropathy was the most common cause (slightly more than one-fourth of the patients). DM and hypertension were very common, and all efforts should be made to control these comorbid conditions. The study suggests that although the cause of kidney dysfunction was ascertained by a kidney biopsy, it did not change the progressive decline of the kidney function in the majority of patients. Also, patients in the improved/stable group had less follow-up duration, hence long-term results are not known. The majority of patients progressed to ESRD despite treatment modification as the biopsy was done late in the course (median eGFR was 34 ml/min). The patients with stable or improved disease had better eGFR at the time of the kidney biopsy (a difference of 13 ml/min, although not significant statistically) and the biopsy was done relatively earlier in them. This

Please cite this article as: Choudhary et al., The Renal Histological Correlates of Refractory Renal Dysfunction After Liver Transplantation, Journal of Clinical and Experimental Hepatology, https://doi.org/10.1016/j.jceh.2023.01.010

finding raises an interesting and important question. Could a kidney biopsy help in stabilizing or improving renal dysfunction if done early in the course of unexplained kidney dysfunction not improving with general management? Doing a kidney biopsy in the late course of kidney disease (eGFR <30) was not largely beneficial (and can be avoided) as it did not change the progression of the kidney disease.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

NSC, NS, SB: Conceptualization, writing - original draft. SW, AG, AR, PB, AR, AR: writing draft, data collection. SB, ASS: critical revision.

CONFLICTS OF INTEREST

All authors have none to declare.

ACKNOWLEDGMENTS

None.

FUNDING

None.

REFERENCES

1. Ojo AO, Held PJ, Port FK, et al. Chronic renal failure after transplantation of a nonrenal organ. *N Engl J Med*. 2003;349:931–940.
2. Giusto M, Berenguer M, Merkel C, et al. Chronic kidney disease after liver transplantation: pretransplantation risk factors and predictors during follow-up. *Transplantation*. 2013;95:1148–1153.
3. Watt KD, Pedersen RA, Kremers WK, Heimbach JK, Charlton MR. Evolution of causes and risk factors for mortality post-liver transplant: results of the NIDDK long-term follow-up study. *Am J Transplant*. 2010;10:1420–1427.
4. Allen A, Kim WR, Therneau TM, Larson JJ, Heimbach JK, Rule AD. Chronic kidney disease and associated mortality after liver transplantation – a time-dependent analysis using measured glomerular filtration rate. *J Hepatol*. 2014;61:286–292.
5. Sharma P, Schaubel DE, Guidinger MK, Goodrich NP, Ojo AO, Merion RM. Impact of MELD-based allocation on the end-stage renal disease after liver transplantation. *Am J Transplant*. 2011;11:2372–2378.
6. Choudhary NS, Saraf N, Saigal S, Soin AS. Long-term management of the adult liver transplant recipients. *J Clin Exp Hepatol*. 2021;11:239–253.
7. Duvoux C, Pageaux GP. Immunosuppression in liver transplant recipients with renal impairment. *J Hepatol*. 2011;54:1041–1054.
8. Choudhary NS, Saigal S, Shukla R, Kotecha H, Saraf N, Soin AS. Current status of immunosuppression in liver transplantation. *J Clin Exp Hepatol*. 2013:1–9.
9. Gonwa TA, Mai ML, Melton LB, et al. End-stage renal disease (ESRD) after orthotopic liver transplantation (OLTX) using calcineurin-based immunotherapy: risk of development and treatment. *Transplantation*. 2001;27:1934–1939.
10. Neau-Cransac M, Morel D, Bernard PH, et al. Renal failure after liver transplantation: outcome after calcineurin inhibitor withdrawal. *Clin Transplant*. 2002;16:368–373.
11. Tsapenko M, El-Zoghby ZM, Sethi S. Renal histological lesions and outcome in liver transplant recipients. *Clin Transplant*. 2012;26:E48–E54.
12. Kim JY, Akalin E, Dikman S, et al. The variable pathology of kidney disease after liver transplantation. *Transplantation*. 2010;89:215–221.
13. Pallet N. Calcineurin inhibitors nephrotoxicity revisited. *Am J Transplant*. 2021;21:2929–2930.
14. Pillebout E, Nochy D, Hill G, et al. Renal histopathological lesions after orthotopic liver transplantation (OLT). *Am J Transplant*. 2005;5:1120–1129.
15. Lee JH, Cho YH, Ryu SJ, et al. Clinical usefulness of kidney biopsy in liver transplant recipients with renal impairment. *Kidney Res Clin Pract*. 2013 Dec;32:153–157.
16. Welker MW, Weiler N, Bechstein WO, et al. Key role of renal biopsy in the management of progressive chronic kidney disease in liver graft recipients. *J Nephrol*. 2019;32:129–137.
17. Chan GS, Lam MF, Kwan L, Fung SH, Chan SC, Chan KW. Clinicopathological study of renal biopsies after liver transplantation. *Hong Kong Med J*. 2013;19:27–32.
18. Kornberg A, Kupper B, Thrum K, et al. Sustained renal response to mycophenolate mofetil and CNI taper promotes survival in liver transplant patients with CNI-related renal dysfunction. *Dig Dis Sci*. 2011;56:244–251.
19. De Simone P, Nevens F, De Carlis L, et al. Everolimus with reduced tacrolimus improves renal function in de novo liver transplant recipients: a randomized controlled trial. *Am J Transplant*. 2012;12:3008–3020.
20. Abdelmalek MF, Humar A, Stickel F, et al. Sirolimus conversion regimen versus continued calcineurin inhibitors in liver allograft recipients: a randomized trial. *Am J Transplant*. 2012;12:694–705.
21. De Simone P, Metselaar HJ, Fischer L, et al. *Conversion from a Calcineurin Inhibitor to Everolimus Therapy in Maintenance Liver Transplant Recipients: A Prospective, Randomized, Multicenter Trial. Liver Transplantation*. vol. 15. Official Publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society; 2009:1262–1269.
22. Levitsky J, O'Leary JG, Asrani S, et al. Protecting the kidney in liver transplant recipients: practice-based recommendations from the American society of transplantation liver and intestine community of practice. *Am J Transplant*. 2016;16:2532–2544.
23. McGuire BM, Julian BA, Bynon Jr JS, et al. Brief communication: glomerulonephritis in patients with hepatitis C cirrhosis undergoing liver transplantation. *Ann Intern Med*. 2006;144:735–741.
24. Wadei HM, Geiger XJ, Cortese C, et al. Kidney allocation to liver transplant candidates with renal failure of undetermined etiology: role of percutaneous renal biopsy. *Am J Transplant*. 2008;8:2618–2626.
25. Calmus Y, Conti F, Cluzel P, et al. Prospective assessment of renal histopathological lesions in patients with end-stage liver disease: effects on long-term renal function after liver transplantation. *J Hepatol*. 2012;57:572–576.
26. Pichler RH, Huskey J, Kowalewska J, et al. Kidney biopsies may help predict renal function after liver transplantation. *Transplantation*. 2016;100:2122–2128.
27. Wadei HM, Abader P, Alsaad AA, et al. Arterial blood pressure at liver transplant evaluation predicts renal histology in candidates with renal dysfunction. *Liver Transpl*. 2019;25:1756–1767.

Please cite this article as: Choudhary et al., The Renal Histological Correlates of Refractory Renal Dysfunction After Liver Transplantation, Journal of Clinical and Experimental Hepatology, https://doi.org/10.1016/j.jceh.2023.01.010