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Renal Outcomes in Patients With IgA Nephropathy Undergoing Liver Transplant: A Retrospective Cohort Study

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Background. End-stage liver disease (ESLD) is the most common cause of secondary immunoglobulin A nephropathy (IgAN). Multiple mechanisms have been proposed to explain the association between liver disease and IgAN. Although some mechanisms are expected to reverse in patients after liver transplant, the long-term renal prognosis is unclear for these patients. **Methods.** This observational retrospective cohort study examined the renal outcomes of 14 patients who had IgAN with end-stage liver disease and subsequently underwent either liver transplant alone or combined liver and kidney transplant at a single tertiary care center. **Results.** Of the 7 patients who underwent liver transplant alone, hematuria persisted in 2, 4 had progressive loss of kidney function with worsening proteinuria in 3 but only 1 reached end-stage renal disease 5 years posttransplant. Among 7 combined liver and kidney transplant recipients, 1 had histologic and 1 had histologic and clinical recurrence of IgAN without kidney allograft loss. **Conclusions.** IgAN in patients with advanced liver disease does not necessarily resolve after liver transplant but has overall favorable renal outcomes.

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End-stage liver disease (ESLD) is commonly complicated by kidney dysfunction, which in turn leads to a worse prognosis.^{1,2} The kidney dysfunction can be functional or structural, ranging from prerenal azotemia and hepatorenal syndrome causing acute kidney injury to immunoglobulin A (IgA) nephropathy (IgAN) and membranoproliferative glomerulonephritis causing chronic kidney disease.² Each condition carries a different presentation, treatment, prognosis, and risk of recurrence. Therefore, when ESLD patients undergo evaluation for liver transplant, it is critical to assess their kidney function and understand the cause of any underlying kidney dysfunction. Patients who are not expected to

recover their kidney function after liver transplant usually benefit from combined liver and kidney transplant (CLKT). Others may need modified immunosuppressive regimens that minimize or avoid use of calcineurin inhibitors to preserve the remaining kidney function.³⁻⁵

IgAN is a common glomerular lesion that can occur in patients with liver disease.⁶⁻⁸ Historically, it was categorized as a *hepatic glomerulonephritis*.⁹ It is characterized by the deposition of IgA-containing immunocomplexes (IgA-ICs) in the glomerular mesangium, resulting in variable degrees of mesangial expansion and proliferation.¹⁰ When IgAN occurs in patients with liver disease, it is usually called *secondary IgAN*. Liver disease is the most common cause of secondary IgAN.¹¹ In a study of 60 patients with ESLD who underwent transjugular renal biopsy at liver transplant, 12 (25%) of 48 patients who had adequate biopsies had IgAN, and 3 (6%) other patients had IgAN along with another glomerular lesion.⁷ Pathogenesis of secondary IgAN in ESLD patients is not well understood. Multiple mechanisms have been proposed to explain the association between IgAN and ESLD. The main focus has been on impaired clearance of IgA and IgA-ICs by the failing liver.¹¹⁻¹³ The prognosis for patients with this glomerular lesion is also not clear. Reports describing renal outcomes for ESLD patients with IgAN are sparse and conflicting. For example, a few reports suggested that this condition tends to remain stable and rarely progresses to end-stage renal disease (ESRD).^{7,14} In contrast, Pouria et al¹¹ reported outcomes for 8 patients with liver disease and biopsy-proven IgAN, 4 of whom progressed to ESRD.

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The present study examined the renal outcomes of ESLD patients with biopsy-proven IgAN who underwent liver transplant at our institution. Our goal was to inform all healthcare providers caring for these patients about the long-term prognosis for patients with this condition after liver transplant. Based on the proposed mechanism of impaired clearance of IgA by the failing liver, we hypothesized that IgAN has a benign course and may even resolve after a new functioning liver is transplanted. It should also not recur in kidney allografts in patients undergoing CLKT.

MATERIALS AND METHODS

We identified all adults who underwent liver transplant alone ($n = 2354$) or CLKT ($n = 151$) at Mayo Clinic in Rochester, MN, between January 1, 1992, and January 1, 2016. Pathology reports were searched to identify patients who underwent native or allograft kidney biopsy on or before the transplant date. Patients were included in the study if the kidney biopsy showed IgAN. Medical records review was completed for patients meeting the inclusion criteria. Demographics, comorbidities, the cause of ESLD, and the presence of other diagnoses on kidney biopsies were abstracted. Laboratory study results were collected, including serum creatinine, measured glomerular filtration rate (GFR), estimated GFR, and the presence of hematuria and proteinuria at transplant and at 12 and 60 months after transplant.

At our institution, GFR is measured with a short iohalamate clearance test.¹⁵ For patients who did not have a measured GFR, estimated GFR based on the Modification of Diet in Renal Disease study equation was used instead.¹⁶ Hematuria was defined as more than 3 erythrocytes per high-power field on urine microscopy. Proteinuria was quantified in milligrams per day from a 24-hour urine collection. If 24-hour urine collection was not available, the ratio of protein to osmolality or protein to creatinine was used to predict 24-hour proteinuria.¹⁷

At our institution, patients who undergo CLKT have follow-up protocol kidney biopsies at 4, 12, and 24 months and at 5 and 10 years after transplant. Biopsy findings were reviewed when available to identify any recurrent IgA deposition. The dates of diagnosis of ESRD, IgA recurrence in the allograft, and death were noted when applicable. All results were reported descriptively for each patient. The study protocol was approved by the Mayo Clinic Institutional Review Board.

RESULTS

After excluding 1 patient who died soon after transplant, 14 patients were included in the analysis (0.6% of all 2505 liver transplant recipients). Of those, 7 underwent liver transplant alone and 7 (4.6% of all CLKT) underwent CLKT.

Liver Transplant Alone Recipients

Data for liver transplant alone recipients are summarized in Table 1. Median age (range) at transplant was 47 (30-59) years. Causes of ESLD included α_1 -antitrypsin deficiency, alcoholic liver disease, hepatitis C cirrhosis, cholangiocarcinoma, and cryptogenic cirrhosis. All patients had IgAN on kidney biopsy, and the pathologic findings are summarized in Table 2. Median GFR (range) at transplant was 66 (31-120) mL/min per 1.73 m², and median 24-hour proteinuria was 302 (91-855) mg. All patients had microscopic

TABLE 1.

Summary of clinical data for liver transplant patients

Patient no.	Age at Tx, y	Sex	Cause of ESLD	Other diagnoses on kidney biopsy	Immunosuppression post-Tx	ESRD by year 5 post-Tx	Treatment with ACEI or ARB post-Tx
1	45	M	α_1 -ATD	—	Tac and MMF	No	None
2	30	M	α_1 -ATD	—	Tac	No	Lisinopril 5 mg
3 ^a	49	F	Cryptogenic	—	Tac, AZA, and Pred	No	None
4 ^b	41	M	ETOH and HCV	Arteriosclerosis ATN	Sirolimus, Pred, and MMF	NA	None
5	47	M	CCA	None	Tac and MMF	No	None
6	51	M	ETOH and α_1 -ATD	Mild osmotic nephrosis	Tac and MMF	No	None
7	59	M	Cryptogenic	Moderate arteriosclerosis	Tac	Yes	None

^a Patient 3 transferred care after 3 years.

^b Patient 4 died 3 years posttransplant.

ACEI, angiotensin-converting enzyme inhibitor; α_1 -ATD, α_1 -antitrypsin deficiency; ARB, angiotensin receptor blocker; ATN, acute tubular necrosis; AZA, azathioprine; CCA, cholangiocarcinoma; ESRD, end-stage liver disease; ETOH, alcoholic liver disease; HCV, hepatitis C virus infection; MMF, mycophenolate mofetil; NA, not applicable; Pred, prednisone; Tac, tacrolimus; Tx, transplant; M, male; F, female.

TABLE 2.
Summary of native kidney biopsy findings for liver transplant alone recipients^a

Patient no.	Mesangial hypercellularity	Endocapillary hypercellularity	Segmental glomerulosclerosis	IFTA	Crescents	IFA		
						IgA	IgG	IgM
1	1	0	0	0	0	2+	Trace	1+
2	1	0	0	0	0	3+	Trace	2+
3	1	0	0	1	0	3+	1+	3+
4	1	0	0	1	0	2+	Trace	—
5	1	0	1	0	0	Pos ^b
6	1	0	1	0	0	2+	1+	1+
7	1	1	0	0	0	2+	—	1+

^a Biopsy findings follow the Oxford classification of IgA nephropathy.¹⁸

^b Report of IFA results was limited.

IFTA, interstitial fibrosis and tubular atrophy; IFA, immunofluorescence assay; Ig, immunoglobulin; Pos, positive.

hematuria before transplant. GFR and hematuria trends and proteinuria trends for liver transplant patients are summarized in Figures 1 and 2, respectively. Hematuria resolved in all but 2 recipients and proteinuria worsened over time in 3 recipients. Three patients (43%) had stable or improved GFR over the 5 years after transplant (Figure 1). In 1 patient (patient 4), acute kidney injury developed perioperatively and resulted in chronic kidney disease; the patient received sirolimus. No other patients had acute kidney injury in the perioperative time. Three (43%) other patients had progressive and sustained loss of kidney function over 5 years despite resolution of microscopic hematuria in 2 of them. In 1 patient (patient 7), ESRD developed 5 years after liver transplant. Liver allograft function was satisfactory and for recipients on calcineurin inhibitors, the level was typically maintained within goal (Tacrolimus between 4 and 6 ng/mL). None of these patients had a kidney biopsy after liver transplant, so the exact cause of chronic kidney disease was not confirmed histologically and remained unknown.

CLKT Recipients

Data for the patients who underwent CLKT are summarized in Table 3. All the patients had ESRD due to IgAN (1 had previous kidney transplant for reflux nephropathy, and IgAN developed in the allograft). The median age (range) at CLKT was 56 (30-68) years. One patient (patient 7T) had a histologic recurrence of IgA on protocol biopsy 5 months posttransplant but did not have any clinical features of IgAN.

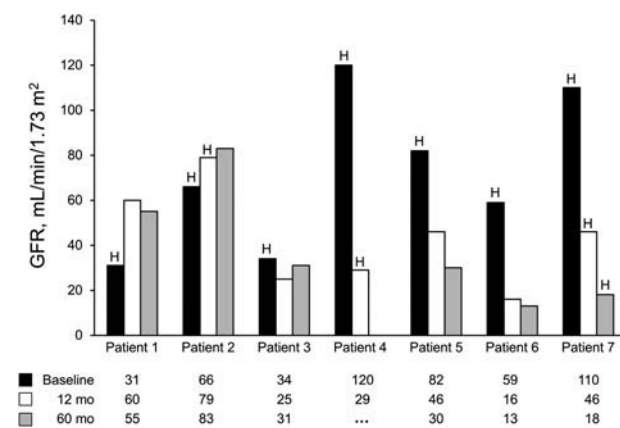


FIGURE 1. GFR and hematuria trends for liver transplant patients. Patient 4 had acute kidney injury peritransplant and died 3 years posttransplant. The letter H indicates hematuria.

His kidney function remained stable afterward. One patient (patient 4T) had a histologic recurrence of IgA on the 10-year protocol biopsy that also showed chronic glomerulopathy. At that time, liver allograft function was normal. One patient (patient 1T) had histologic and clinical recurrence of IgAN 2 months posttransplant associated with mild cellular rejection. He presented with microscopic hematuria and peak 24-hour proteinuria of 2400 mg. After he was treated with methylprednisolone and antithymocyte globulin, his proteinuria resolved. Later, after enalapril was added to his regimen, his kidney function stabilized.

DISCUSSION

In this select cohort of ESRD patients with biopsy-proven IgAN, kidney outcomes were overall favorable after liver transplant. However, in 3 patients (43%), GFR decreased by more than 40% by year 5 posttransplant, and in 1 patient, the disease progressed to ESRD, although the exact cause of ESRD cannot be attributed to IgA without kidney biopsy. CLKT did not prevent recurrence of IgAN in kidney allografts. Two patients (29%) had evidence of recurrent IgA in the allograft within 6 months posttransplant; 1 of these patients had clinical features of IgAN. Despite that, overall kidney allograft survival was excellent with no graft lost from recurrent IgA at last follow-up.

Chronic liver disease is commonly associated with secondary IgAN. In fact, among all patients with secondary IgAN,

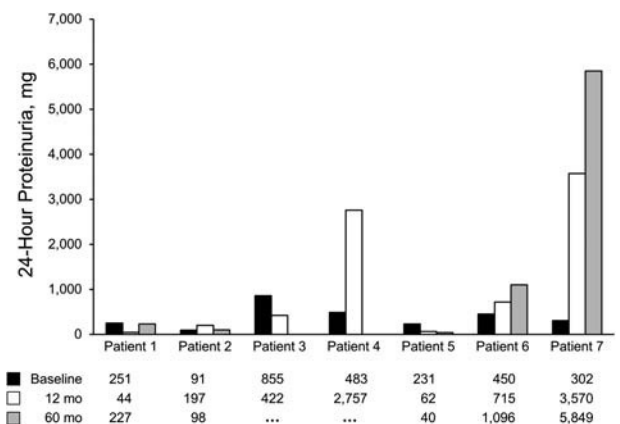


FIGURE 2. Proteinuria trends for liver transplant patients. Patient 3 transferred care after 3 years. Patient 4 died 3 years posttransplant.

TABLE 3.**Summary of clinical data for CLKT recipients**

Patient no.	Age at transplant, y	Sex	ESLD cause	ESRD cause	Immunosuppression post-Tx	Recurrence of IgA	Kidney allograft status
1T	67	M	ETOH	IgAN	CSA, AZA, and Pred	Present (histologic and clinical recurrence 2 mo post-Tx)	Death with functioning graft after 15 years
2T	30	M	HBV	IgAN ^a	Tac, MMF, and Pred	Absent	Functioning at 5 years
3T	56	M	ETOH	IgAN	Tac and Pred	Absent	Functioning at 13 years
4T	57	M	NASH	IgAN	Tac, Pred, and MMF	Present (histologic recurrence 10 y post-Tx)	Functioning at 13 years
5T	68	M	ETOH	IgAN	Tac and MMF	Absent	Functioning at 12 years
6T	53	M	HCV	IgAN	CSA, MMF, and Pred	Absent	Functioning at 1 year
7T	44	M	ETOH	IgAN	Tac, MMF, and Pred	Present (histologic recurrence 6 mo post-Tx)	Functioning at 2 years

^a Original disease was reflux nephropathy. IgAN developed in the allograft. CSA, cyclosporine A; HBV, hepatitis B virus; NASH, nonalcoholic steatohepatitis.

liver disease is the most common cause.¹² Secondary IgAN is a pathologic diagnosis with findings like what is observed with primary IgAN. The main characteristic is the presence of mesangial deposits that are predominantly IgA. These deposits can be associated with variable degrees of mesangial expansion and hypercellularity. Although immunofluorescence studies are predominantly positive for mesangial IgA staining, IgG, IgM, or C3 can also be present to a lesser degree.^{10,12,14} In studies that performed immunofluorescence assay on kidney tissue from ESLD patients, 30% to 90% of the samples had predominantly IgA staining.¹⁴ However, not all patients with mesangial IgA staining have other features of IgAN. For example, in 1 study in which ESLD patients underwent renal biopsy at liver transplant, 5 patients had mesangial IgA staining, but only 2 had other features of IgAN.⁶

In our cohort, all patients had clinical features of IgAN, which reflects the criteria we used to include them in this study. All patients had mesangial expansion and proliferation, but the degree of tubulointerstitial disease varied from minimal to mild.

From our cohort findings, it is difficult to comment on the prevalence of IgAN among ESLD patients undergoing liver transplant because all included patients underwent kidney biopsy for a reason. The true prevalence is likely higher for multiple reasons. First, not all ESLD patients undergo kidney biopsy, even when they have clear evidence of kidney disease. With the increased risk of bleeding and the low likelihood of changing management, many nephrologists do not perform kidney biopsies on such patients. Second, having normal kidney function does not rule out the presence of pathologic changes. A few studies reported the presence of glomerular lesions even in patients with normal kidney function,^{7,9} although the meaning of this finding is unclear.

Clinically, patients with secondary IgAN present similarly to patients with primary IgAN. Patients can be asymptomatic, and the most common abnormality is microscopic hematuria. Fewer patients may have nephrotic syndrome and progressive kidney disease, likely indicating primary IgAN.¹¹ In our cohort, all patients had microscopic hematuria at transplant. Median 24-hour proteinuria was about 300 mg, and none of the patients had nephrotic proteinuria (Figure 2). It is important to pay close attention to urinary proteinuria and urine microscopic findings during evaluation of ESLD patients. This laboratory data may help clarify the main cause of kidney dysfunction because ESLD patients are prone to many conditions that can result in kidney disease. Some of these conditions are reversible and others are chronic and progressive. For example, the use of diuretics to control ascites and the need for recurrent paracentesis procedures in the setting of low systemic arterial pressure put ESLD patients at risk of prerenal kidney injury. This prerenal state can progress to acute tubular necrosis. Liver failure and concomitant viral hepatitis increase risk of glomerular diseases including membranoproliferative glomerulonephritis, cryoglobulinemia and membranous nephropathy. Treatment with nephrotoxic medications and exposure to contrast during imaging may result in tubulointerstitial injury. Some of these conditions can be present concomitantly, making the diagnostic process more challenging. In the posttransplant period, recurrence of primary disease, calcineurin inhibitors toxicity, and opportunistic infections can result in kidney disease as well.

The pathogenesis of IgAN in liver disease is not completely understood. ESKD patients have increased circulating levels of IgA-IC. Woodroffe et al¹⁹ showed that 100% of liver cirrhosis patients had circulating immunocomplexes, and 80% of the complexes were IgA-ICs. Unlike in primary IgAN patients who had an intermittent appearance of immunocomplexes, these complexes were constantly present in liver cirrhosis patients. These circulating immunocomplexes have been shown to be deposited in other organs, such as skin and jejunal capillaries.²⁰ Multiple mechanisms have been proposed for the increase in circulating IgA-ICs. First, an increase in exposure to antigen resulting from compromised gastrointestinal mucosal integrity and shunting across a failing liver may lead to formation of more IgA-ICs.¹¹ Second, the clearance of IgA and IgA-ICs appears to be decreased in patients with cirrhosis of the liver.^{13,21} This decrease could be related to a loss of hepatocytes, an altered position of Fc receptors on hepatocytes, and changes in the IgA molecule itself.^{13,21-23} Third, it is plausible that shunting of blood into systemic circulation and bypassing the liver could reduce the clearance of these immunocomplexes by the liver. A more detailed review of these mechanisms has been written by Pouria et al.¹¹ IgA molecules were shown to have abnormal glycosylation in patients with alcoholic liver disease, like in primary IgAN, and in the same study, soluble CD89-IgA (which is a feature of primary IgAN) was also present in patients with alcoholic cirrhosis.²⁴ This may be an additional mechanism of IgAN in this subgroup of patients and may explain the stronger association between alcoholic liver disease and IgAN.

The prognosis for patients with IgAN in liver disease is under debate. One proposal is that IgAN in ESKD patients has a benign and limited course. Calmus et al⁷ reported that outcomes from 5 patients with IgAN undergoing liver transplant were like the outcomes from patients with normal kidney biopsy findings. However, not all studies have reported similar findings. Pouria et al¹¹ reported 8 biopsy-proven cases of hepatic IgAN. Over 4 years, half the patients had ESKD and 25% had progressive CKD. It is plausible that many of the proposed pathogenic mechanisms leading to IgAN reverse after liver transplant, leading to IgAN stabilization or improvement (or both).²⁵ The resolution of hematuria, improvement in proteinuria, and stabilization of GFR are all signs of resolving disease. In our subgroup of patients undergoing liver transplant alone, 4 (57%) patients had resolution of hematuria by the first year posttransplant. However, this did not correlate with other markers of kidney disease. Patient 6, for example, had an increase in proteinuria and a decrease in GFR despite resolution of the hematuria, but in patient 2, GFR and proteinuria remained stable despite persistent hematuria. In this cohort, the degree of proteinuria correlated better than hematuria with progression of kidney disease. This finding is like what is reported with primary IgAN. Patient 6 progressed to ESKD even though he had a normal GFR at transplant. Although we do not have follow-up biopsies to confirm the persistence of IgAN, the ongoing glomerular hematuria suggests that IgAN at least contributed to this progression. These findings argue against the notion that IgAN has a benign course in ESKD patients and could reflect our inability to differentiate primary and secondary IgAN if we consider secondary IgAN to be benign. It is also possible that the presence of IgAN at time of liver transplant increased the likelihood of other risk factors (eg, calcineurin inhibitors

toxicity) to cause progressive kidney disease. Each of the 3 patients whose disease progressed had low-risk features at transplant: near-normal GFR, 24-hour proteinuria less than 1 g, normal blood pressure, and no significant tubulointerstitial disease.

Patients undergoing CLKT provide a unique opportunity to understand the pathogenesis of IgAN. In the presence of a new healthy liver, the risk of recurrence of secondary IgAN should be minimal or absent. Because these patients undergo protocol kidney biopsy at our institution, we had the opportunity to detect both histologic and clinical recurrence. Two patients (29%) had histologic recurrence within the first 6 months, and 1 patient (patient 1T) had signs of clinical recurrence as well. Both patients had satisfactory liver allograft function at time of IgA recurrence. These data suggest the presence of another pathogenic mechanism for IgAN besides impaired IgA clearance by the failing liver. Another explanation is heterogeneity of IgAN in ESKD patients, with some having primary IgAN and others having true secondary IgAN.

This study has important strengths. We included only patients who had biopsy-proven IgAN rather than relying on clinical presentation. The follow-up time exceeded 5 years for most patients, allowing reasonable time to detect the progression of IgAN. We also had the opportunity to review protocol biopsies for CLKT patients to detect early and asymptomatic recurrence of IgAN.

Our study has limitations. First, because we did not have follow-up biopsies for patients with native kidney IgAN, we could not evaluate what happened to the mesangial deposits after liver transplant. Second, we did not have histologic data for patients who had progressive kidney disease after liver transplant. These patients may have had another reason for the worsening kidney function, including calcineurin inhibitor toxicity. Third, patients who underwent CLKT may represent a population with skewed data because they have more severe IgAN at baseline and thus are more likely to have primary IgAN rather than secondary disease. This may explain the early recurrence in our small cohort.

In conclusion, IgAN in patients with advanced liver disease does not necessarily resolve after liver transplant. Some patients have progressive kidney disease after liver transplant alone and others have recurrence of IgAN in the kidney allograft after CLKT but their overall outcome is satisfactory. This suggests IgAN heterogeneity in this group of patients and possibly the presence of more than 1 pathogenic mechanism. These possibilities must be considered when evaluating patients with ESKD and IgAN rather than if all patients have benign secondary IgAN. Further research is needed to understand the pathogenesis of IgAN in ESKD and to differentiate primary IgAN from secondary IgAN.

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